A Phase 2, Single Arm, Two Period Study of Sodium Cridanimod in Conjunction with Progestin Therapy in Patients with Endometrial Carcinoma

Protocol Number:	VX-EC-2-02
Development Phase:	Phase 2
Investigational Product:	Sodium Cridanimod
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Sponsor:

Xenetic Biosciences, Inc.
99 Hayden Avenue, Suite 230
Lexington, MA 02421

Confidentiality Statement

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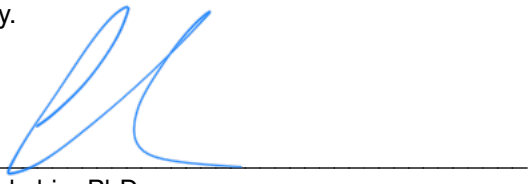
Appendix 1: New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)

A Phase 2, Single Arm, Two Period Study of Sodium Cridanimod in Conjunction with Progestin Therapy in Patients with Endometrial Carcinoma

Protocol No. VX-EC-2-02

The signature below constitutes the approval of this protocol by the signatory and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Signed: 

Curtis Lockshin, PhD
Chief Scientific Officer
Xenetic Biosciences, Inc.

Date: 02 Jan 2018

A Phase 2, Single Arm, Two Period Study of Sodium Cridanimod in Conjunction with Progestin Therapy in Patients with Endometrial Carcinoma

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The signature below constitutes acknowledgement of my review of this protocol as well as an agreement to abide by its terms and conditions set out herein.

I agree to recruit and treat patients in an ethical manner and conduct this trial strictly according to the protocol, applicable regulations and current Good Clinical Practices.

I have received an Investigator's Brochure for Sodium Cridanimod and have been informed about the pharmacology, toxicology and clinical findings related to the administration of this Investigational Medicinal Product (IMP).

I will ensure all Sub-Investigators and research personnel involved in this trial, will understand information regarding the IMP as well as the protocol and will conduct the trial in the manner described above.

Principal Investigator:

Signature: ----------

Date

Printed Name: ----------

Address: ----------

LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviation	Term
AE	Adverse event
ALT	Alanine transaminase
APrR	Activated progesterone receptor
AST	Aspartate transaminase
ß-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CI	Confidence interval
eGFR	Estimated Glomerular filtration rate
CR	Complete response
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
dL	Deciliter
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram, also Electrocardiography
EOS	End of Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IEC	Independent Ethics Committee
i.m.	Intramuscularly
IMP	Investigational medicinal product
IRB	Institutional Review Board
kg	Kilogram
LDH	Lactate dehydrogenase
MA	megestrol acetate
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
mL	Milliliter
MPA	Medroxyprogesterone acetate
MRI	Magnetic resonance imaging
NA	Not applicable

Abbreviation	Term
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ODCR	Overall Disease Control Rate
ORR	Objective Response Rate
OS	Overall Survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression-free survival
p.o.	Per os (per mouth)
PR	Partial response
PrR	Progesterone receptor
QTcB	QT ECG interval corrected for heart rate according to Bazett's formula
QTcF	QT ECG interval corrected for heart rate according to Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SFU	Safety Follow-up Visit
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TP1	Treatment Period 1
TP1-EXT	Treatment Period 1 Extension
TP2	Treatment Period 2
ULN	Upper limit of normal

SYNOPSIS

Investigational Medicinal Product	Sodium Cridanimod 125 mg/mL
Study Title	A Phase 2, Single Arm, Two Period Study of Sodium Cridanimod in Conjunction with Progestin Therapy in Patients with Endometrial Carcinoma
Study Code	VX-EC-2-02
Phase	2
Study Duration	Subjects determined to have progesterone receptor (PrR) positive status from an archival tumor tissue sample at Screening will participate in Treatment Period 1 receiving megestrol acetate (progestin monotherapy) for up to 24 weeks. Subjects determined to have disease progression within the 24 weeks of Treatment Period 1 will qualify to participate in Treatment Period 2. Subjects determined to continue to have disease control after 24 weeks of treatment will not be eligible for Treatment Period 2, and will return for an End of Study Visit within 2 weeks and be discontinued from the study. Subjects determined to have PrR negative status from an archival tumor tissue sample at Screening will enroll directly into Treatment Period 2 and will receive combination treatment (Sodium Cridanimod and megestrol acetate) until documented disease progression. Once disease progression is documented in Treatment Period 2, subjects will return for the Safety Follow-up Visit four (4) weeks following the last treatment and then continue to be followed for an additional 12-month period for overall survival. Considering the estimated accrual rate of 4-6 subjects per month, the total duration of the study after the first visit of the first subject is about 36 months.
Study Objectives	*Primary Objective:* To assess the antitumor activity of Sodium Cridanimod in conjunction with progestin therapy as measured by Overall Disease Control Rate (ODCR) in women with recurrent or persistent endometrial carcinoma not amenable to surgical treatment or radiotherapy who have either failed progestin monotherapy or who have been identified as PrR negative.
	Secondary Objectives: Efficacy: To assess Objective Response Rate (ORR), including partial response (PR) and complete response (CR), Progression-free Survival (PFS), Duration of Stable Disease (SD) and Overall Survival (OS) for subjects receiving Sodium Cridanimod, in conjunction with progestin therapy. Safety: To evaluate the safety and tolerability of Sodium Cridanimod, possibly in conjunction with progestin therapy, as measured by adverse events, laboratory safety parameters, and cardiac safety assessments (including QT prolongation potential).
	Translational Objective: To assess pharmacokinetics data of Sodium Cridanimod and megestrol acetate after a single dose and after multiple

	dose administrations and possible pharmaceutical interaction between Sodium Cridanimod and megestrol acetate.
Study Design	This is an open-label, multi-center, single-arm, two-period Phase 2 study. The study will investigate the efficacy of Sodium Cridanimod in conjunction with progestin therapy in a population of subjects with endometrial cancer who have failed progestin monotherapy or who have been identified as PrR negative. All patients must have endometrial cancer PrR status determined from an archival sample at Screening. The PrR status (positive or negative) will be determined by central laboratory by IHC testing. There are two treatment periods and a follow-up period within the study. **Treatment Period 1 (Progestin Monotherapy):** During Treatment Period 1, all eligible subjects determined to be PrR positive will receive progestin monotherapy (megestrol acetate 160 mg p.o. / day) for up to 24 weeks. Subjects will have a CT or MRI scan after 12 and 24 weeks of progestin monotherapy, with response to treatment being assessed according to RECIST 1.1 criteria. Subjects determined to have disease progression will qualify to enroll into Treatment Period 2. Subjects determined to have disease control (SD, PR or CR) by tumor assessment after 24 weeks in Treatment Period 1, will be ***ineligible*** to enter Treatment Period 2. The subject will be withdrawn from the study treatment and return for the End of Study Visit within 2 weeks to be discontinued from the study. Subjects withdrawn from Treatment Period 1 will be treated in accordance with local standards and clinical practice (which may include continuation of progestin therapy). A subject may be discontinued from Treatment Period 1 at any time if the subject experiences a change in symptoms and/or if disease progression is suspected by the Investigator. • Subjects who discontinue Treatment Period 1 prematurely (receiving < 4 weeks of progestin monotherapy) for any reason, will be excluded from the remainder of the study. Subjects determined to be PrR negative at Screening will not enroll into Treatment Period 1. These subjects will enroll directly into Treatment Period 2 (Visit 1, Day 0). **Treatment Period 2 (Combination Treatment):** All subjects determined to be PrR negative at Screening and those who received at least 4 weeks of progestin monotherapy and who experienced disease progression during Treatment Period 1 will enter Treatment Period 2 of the study (Visit 1, Day 0). During Treatment Period 2, subjects will receive Sodium Cridanimod (500 mg, 2 times / week, intramuscularly) in combination with continued progestin treatment (megestrol acetate 160 mg p.o. / day).

	• For those subjects who participated in Treatment Period 1, there should be no interruption of progestin therapy between Treatment Period 1 and Treatment Period 2. • Subjects will receive combination treatment until disease progression as defined according to RECIST 1.1 criteria, with response assessments performed at 12-week intervals. • Confirmation of objective responses in Treatment Period 2 will be performed at least 4 weeks after the criteria for response are first met. **Follow-up Period:** Once subjects progress during Treatment Period 2, they will return for the Safety Follow-up Visit four (4) weeks following the last treatment, and then continue to be followed for an additional 12-month period for overall survival.
Study Population	A total of 72 women with recurrent or persistent endometrial cancer not amenable to surgical treatment or radiotherapy but suitable to be treated with progestins will be enrolled in the study.
Eligibility Criteria	*Inclusion Criteria* 1. Female patients 18 years of age or older; 2. Histologically confirmed serous carcinoma or endometrioid type of endometrial carcinoma (histological documentation of recurrence is not required); 3. Recurrent or persistent progressive disease which is refractory to curative therapy or established treatments and cannot be treated with surgery or radiotherapy; 4. Measurable disease, as defined by RECIST 1.1 criteria; 5. At least one “target lesion” to be used to assess response, as defined by RECIST 1.1 criteria. Tumors within a previously irradiated field will be designated as “non-target” lesions unless previous progression is documented; 6. Availability of archived tumor tissue sample that can be used for assessment of PrR status by the central laboratory; 7. GOG performance status 0-2 (refer to Table 9 under Section 5.5.3); 8. Estimated Glomerular filtration rate ≥ 50 mL/min; 9. Total bilirubin ≤ 2.5 times upper limit of normal (ULN); 10. AST ≤ 2.5 times ULN (≤ 5 times ULN for patients with liver metastases); 11. Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 times ULN for patients with liver metastases); 12. Albumin ≥ 3.0 mg/dL; 13. Ability to take oral medication; 14. Patients able to understand the nature of the study and who are willing to give written informed consent;

	15. *And for Treatment Period 2 only: 1) Patients participating in Treatment Period 1 must have had disease progression after receiving at least 4 weeks of progestin therapy or 2) Patients must be determined as PrR negative status at Screening.*
	Exclusion Criteria 1. Mixed histology of the tumor or evidence of tumor histology other than serous carcinoma or endometrioid type of endometrial carcinoma; 2. Concurrent systemic corticosteroid therapy; 3. Concurrent oral contraceptive use / Women of childbearing potential not using highly effective means of contraception; 4. Pregnancy confirmed by pregnancy test / Lactating women (for women of childbearing potential); 5. Prior therapy with hormonal progestin agents; 6. Patients who are candidates for treatment with standard chemotherapy agents (there is no limit to the number of lines of prior chemotherapy); 7. History of blood clot; 8. History of known bleeding disorder (i.e. disseminated intravascular coagulation or clotting factor deficiency); 9. Major surgery within 4 weeks prior to the start of the study; 10. Patients with clinically significant illnesses which, according to the Investigator, could compromise participation in the study; 11. History of other clinically active malignancies within 5 years, except for carcinoma in situ of the cervix, basal cell carcinoma, or squamous carcinoma of the skin. 12. Known hypersensitivity or idiosyncratic reaction to any of the study drugs (Sodium Cridanimod, megestrol acetate, lidocaine) and excipients; 13. Patients with known brain metastases; 14. Patients currently receiving any other investigational agents; 15. Patients currently receiving any other anticancer therapies; 16. Participation in any other clinical study within the last 4 weeks prior to the start of the study;
Treatment	During Treatment Period 1, subjects who are PrR positive will receive megestrol acetate only. Megestrol acetate will be taken p.o. in a total daily dose of 160 mg. Subjects who are PrR negative will not participate in Treatment Period 1, but instead enroll directly into Treatment Period 2. During Treatment Period 2, subjects will receive megestrol acetate in combination with Sodium Cridanimod. • Megestrol acetate will be taken p.o. in a total daily dose of 160 mg.

	• Sodium Cridanimod (500 mg / 4 mL) is to be diluted with 1 mL of 2% lidocaine hydrochloride (5 mL total) and administered twice a week intramuscularly. For Sodium Cridanimod doses that do not correspond to a Study Visit, the drug may be administered either at the clinical site or at home by a medical service provider if feasible. Subjects will be provided a diary and instructed to record all doses of megestrol acetate.
Efficacy Assessments	A disease or tumor assessment will be performed by clinical examination for palpable or visual tumor lesions as well as by computerized tomography (CT) or magnetic resonance imaging (MRI). A CT or MRI scan with tumor assessments will be performed during Screening (baseline). During Treatment Period 1, a CT or MRI scan and tumor assessments will be performed following 12 weeks of treatment (at Visit -1), and again after 24 weeks of treatment (at Visit TP1-EXT) if the subject achieved disease control at the 12 Week scan. During Treatment Period 2, CT or MRI scans and tumor assessments will be performed every 12 weeks. RECIST 1.1 criteria will be used to interpret all scans. During Treatment Period 2, all objective responses must be confirmed with an additional scan performed at least four weeks after the criteria for response were initially met. For evaluating subject responses during Treatment Period 2, the measurements for determining progression in Treatment Period 1 will be used as the new baseline measurements.
Safety Assessments	Physical examinations, ECGs, adverse events and clinical laboratory assessments will be monitored. All laboratory testing for safety will be conducted by local laboratories. An independent Data and Safety Monitoring Board (DSMB) will monitor the study.
Electrocardiograms (ECG)	An ECG will be obtained during Screening. During Treatment Period 1, at Study Visit -3, an ECG will be obtained prior to first dose of megestrol acetate. An ECG will be obtained at each of the remaining study visits (prior to drug administration of megestrol acetate whenever possible). An ECG will be obtained at the End of Study Visit. During Treatment Period 2, at Study Visits 1 and 3, an ECG will be obtained 5 times: before administration of Sodium Cridanimod, and at 15, 60, 120 and 360 (±5) minutes after administration to evaluate study drug-induced QT prolongation potential. At all other study visits during Treatment Period 2, only one ECG will be obtained prior to Sodium Cridanimod administration. An ECG will be obtained at the Safety Follow-up Visit.
Optional Pharmacokinetic (PK) Sub-Study	An important objective of this study is to investigate the pharmacokinetics of megestrol acetate when administered alone (Treatment Period 1), and the

	possible pharmacokinetic drug-drug interactions of Sodium Cridanimod and megestrol acetate when administered together. For subjects who have consented to participate in the Pharmacokinetics (PK) Sub-Study, additional blood samples will be taken as follows: • Treatment Period 1 (at 10 timepoints): Study Visit -3, before administration of megestrol acetate, and 1, 2, 3, 4, 6, 24, 48, 72 and 96 hours after first administration of megestrol acetate. Subjects who are PrR negative will not participate in this portion of the PK Sub-Study. • Treatment Period 2 (at 15 timepoints): Study Visit 1, before administration of the study drugs and at 15, 30, 45, 60 and 90 minutes, 2, 3, 4 and 6 hours after administration. Blood samples will additionally be taken on Days 3, 7, 10, 56 (Visit 3) and 84 (Visit 4) of Treatment Period 2 prior to the administration of both Sodium Cridanimod and megestrol acetate. Blood samples will be analyzed at a central laboratory.
Efficacy Endpoints	1. Overall Disease Control Rate (ODCR) including SD, PR and CR, as defined by RECIST 1.1 criteria 2. Objective Response Rate (ORR) including CR and PR, as defined by RECIST 1.1 criteria 3. Progression-free survival (PFS) 4. Duration of Stable Disease (SD) 5. Overall survival (OS)
Statistics	Sample Size: The primary objective of the study is to evaluate the efficacy of the study drug by the frequency of subjects with overall disease control (including SD, PR, and CR). The null hypothesis specifies the probability of a subject experiencing disease control to <5%. A clinically significant difference is predefined as a 15% increase in the probability of the event (i.e., disease control rate of 20%). Using the Fleming's single stage procedure (in which a predetermined number of patients is recruited to the study and a decision about activity is obtained from the number of responses (including SD, PR, or CR) amongst these patients) with the probabilities of type I and type II errors of 5% (one-sided) and 10%, respectively, approximately 40 subjects are planned to be enrolled to Treatment Period 2. It is estimated that approximately 20-25% of subjects will be classified as PrR negative and go directly into Treatment Period 2. This group will represent 14-16 of the Treatment Period 2 subjects. The rate of subjects who will have progressive disease following treatment with megestrol acetate in Treatment Period 1 and then move on to Treatment Period 2 is estimated at 55-60%. These subjects will represent 30-32 of the Treatment Period 2 subjects (Approximately 24-25 subjects treated in Treatment Period 1 will not exhibit progressive disease and will not move into Treatment Period 2.) Estimating the rate of subjects who will be unavailable for disease assessment for various reasons at 10-15%, it is planned to enroll 72 total subjects. Analysis: A descriptive analysis approach will be used to analyze demographic and baseline characteristics, as well as safety and efficacy data (mean, standard deviation, median, minimum, maximum, range,

	quintiles, number of valid cases for continuous variables and n, frequency and percentage for categorical variables with 95% confidence limits, when appropriate). All subjects who received a full or partial dose of the study drug (in Treatment Period 2) on at least one occasion are considered evaluable subjects for safety analysis. All treated subjects in Treatment Period 2 who also undergo a CT or MRI scan with tumor assessment after 12 weeks, or who discontinue treatment prior to 12 weeks solely due to disease progression, will be included in the Full Analysis Set (FAS), which will be used for the efficacy evaluation. The Per Protocol population (all FAS subjects, excluding those for whom major protocol violations have been identified) will be used in the sensitivity analyses for all secondary efficacy endpoints. The ODCR will be determined as the proportion of treated subjects who have achieved SD, PR or CR. The ORR will be determined as the proportion of treated subjects who have achieved CR or PR. Estimates of the ORR and the ODCR will be presented with the corresponding 95% confidence interval. PFS, duration of stable disease, and OS will be analyzed using the Kaplan-Meier method. The Kaplan-Meier survival curves will be plotted. OS is defined as the time from the first dose of study drug (beginning of Treatment Period 2) until the date of death from any cause. Subjects who do not die will be censored for this analysis at the last documented date at which the subject is known to be alive. PFS is defined as the time from the first dose of study drug (beginning of Treatment Period 2) until objective tumor progression or death. Medians for time to event variables will be presented with the corresponding 95% confidence intervals.
Interim Analysis	Interim analysis will be performed for the primary efficacy endpoint (ODCR) once the first tumor assessment during Treatment Period 2 is completed for at least 20 enrolled subjects. An interim analysis of all efficacy endpoints (with the exclusion of overall survival) may also be performed once all enrolled subjects have entered the Follow-up Period and are being followed for overall survival. Analysis of all safety endpoints will also be included in any interim analyses.
Number of Study Centers (and Locations) Planned	Up to 50 study sites in the US and Europe are planned for enrollment.
Estimated Time Schedule	First subject enrolled: September 2017 Recruitment completed: September 2018 Last subject completed the study: January 2021

STUDY DESIGN AND ASSESSMENT SCHEDULE

Figure 1: Study Flow Chart

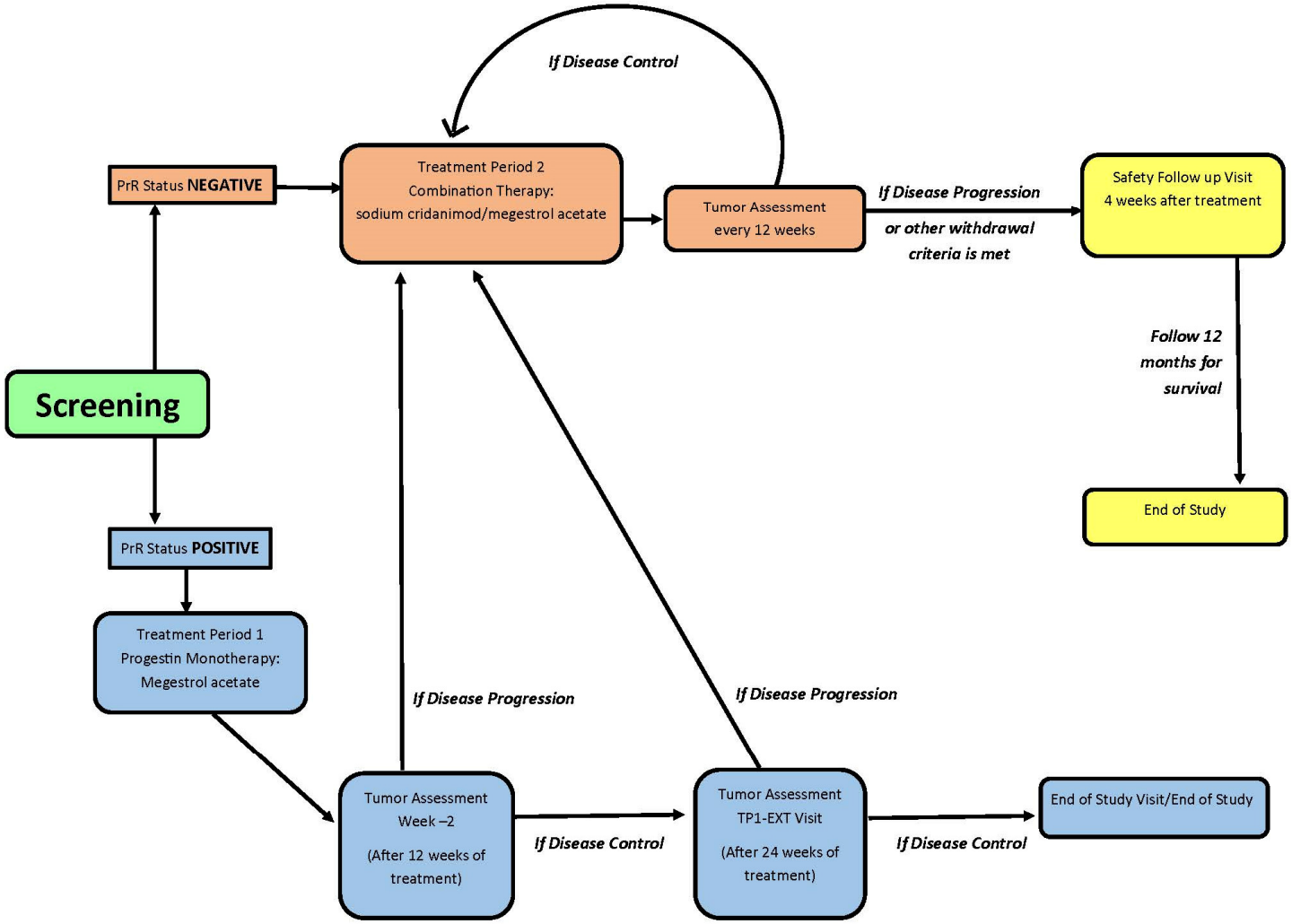

Table 1: Screening Schedule of Assessments

Screening	
Study Calendar (Weeks)	-18 to -15
Procedures and Assessments	
Informed consent	X
Eligibility Criteria	X
Demographics	X
Medical History	X
Concomitant Medication	X
Physical Exam	X
Vital Signs	X
Height	X
Weight	X
Performance Status	X
CBC w/ diff, platelets	X
Serum chemistry[A]	X
eGFR	X
Urinalysis	X
Serum Pregnancy Test (B-hCG) [B]	X
ECG	X
Assessment of Adverse Events	X
PrR status of archived tumor tissue determined by central lab	X
Imaging (CT/MRI) [E]	X
Tumor Assessment (using RECIST criteria) [E]	X

Footnotes
A - Phosphate, sodium, potassium, chloride, calcium, bicarbonate, creatinine, creatine kinase, glucose, blood urea nitrogen (BUN), total proteins, albumin, total bilirubin, alkaline phosphatase, LDH, SGOT/AST, SGPT/ALT.
B - For women of childbearing potential.
E - Screening tumor assessments must be performed <10 days before Visit -3.

Table 2: TP1 Schedule of Visits and Assessments

	Treatment Period 1 (PrR Positive Patients Only)				Subjects Ineligible to enter TP2 or who Withdraw Early
Study Visits	**-3**	**-2**	**-1**	**TP1-EXT**	**End of Study (EOS)**
Study Calendar (Weeks)	-14	-8	-2	+12 wks	+ 2 weeks
Treatments					
Progestin therapy (Megestrol acetate) Dispensing/Return[F]	D	R/D	R/D	R/D	R
Procedures and Assessments					
Eligibility Criteria	X				
Concomitant Medication	X	X	X	X	X
Physical Exam	X[C]	X	X	X	X
Vital Signs	X	X	X	X	X
Weight	X[C]	X	X	X	X
Performance Status	X[C]	X	X	X	X
CBC w/ diff, platelets	X[C]	X	X	X	X
Serum chemistry[A]	X[C]	X	X	X	X
eGFR	X[C]	X	X	X	X
Urinalysis					X
Urine Pregnancy Test[B]					X
ECG	X[H]	X[H]	X[H]	X[H]	X
Blood Draw (for PK sub-study)[G]	X[G]				
Assessment of Adverse Events	X	X	X	X	X
Imaging (CT/MRI)			X	X[D]	
Tumor Assessment (using RECIST criteria)			X	X[D]	
Patient Diary Issue/Collection[F]	I	I/C	I/C	I/C	C
Subject Compliance		X	X	X	X

Footnotes
A - Phosphate, sodium, potassium, chloride, calcium, bicarbonate, creatinine, creatine kinase, glucose, blood urea nitrogen (BUN), total proteins, albumin, total bilirubin, alkaline phosphatase, LDH, SGOT/AST, SGPT/ALT.
B - For women of childbearing potential.
C - These assessments on Visit -3 are only performed if more than 7 days have passed since the previous evaluation at Screening.
D - The tumor assessments near the conclusion of Treatment Period 1 are scheduled to take place within 2 weeks prior to TP1 EOS Visit or TP2 Visit 1 (Day 0) so as to allow adequate time to obtain tumor measurements prior to Treatment Period 2. This 2 week window can be shortened (and Visit 1 may occur) as soon as these tumor measurements are available.
F - D = Dispense, R = Return, I = Issue, C = Collect
G - For subjects who consent to participate in the PK sub-study, blood samples are taken before administration of megestrol acetate as well as 1, 2, 3, 4, 6, 24, 48, 72 and 96 hours after first administration of megestrol acetate during Visit -3.
H – ECGs to be performed prior to study drug administration whenever possible. Exception: ECG performed at End of Study Visit.

Table 3: TP2 Schedule of Visits and Assessments

Treatment Period 2															
Study Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 - ?**	**Safety Follow-up Visit[G]**	**Follow Up Period- OS**
Study Calendar (Weeks)	0	4	8	12	16	20	24	28	32	36	40	44	48, 60 etc.[F]		
Treatments															
Sodium Cridanimod	Sodium Cridanimod is administered twice a week on either Mondays and Thursdays or Tuesdays and Fridays for the duration of Treatment Period 2.														
Progestin therapy (Megestrol acetate) Dispensing/Return[J]	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D	R/D[H]	R	
Procedures and Assessments															
Eligibility Criteria	X														
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam	X		X		X		X		X		X		X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X		X		X		X		X		X		X	X	
Performance Status	X		X		X		X		X		X		X	X	
CBC w/ diff, platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry[A]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
eGFR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis							X						X	X	
Urine Pregnancy Test[C]							X							X	
ECG	X[E]	X	X[E]	X	X	X	X	X	X	X	X	X	X	X	
Blood Draw (for PK sub-study)	X[D]		X[D]	X[D]											
Assessment of Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Imaging (CT/MRI)				X			X			X			X	X[B]	
Tumor Assessments (using RECIST criteria)	Tumor assessments and radiologic imaging are repeated every 12 weeks during Treatment Period 2. In subjects with an objective response, an additional tumor assessment is performed 4 weeks later to confirm the presence of an objective response. Documentation (CT or MRI) must be provided for subjects removed from study for progressive disease.													X[B]	
Patient Diary Issue/Collection[J]	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C	I/C[H]	C	
Subject Compliance	X	X	X	X	X	X	X	X	X	X	X	X	X		
Phone or other contact to determine survival															X[I]

Footnotes

A - Phosphate, sodium, potassium, chloride, calcium, bicarbonate, creatinine, creatine kinase, glucose, blood urea nitrogen (BUN), total proteins, albumin, total bilirubin, alkaline phosphatase, LDH, SGOT/AST, SGPT/ALT.

B - Only performed on subjects discontinued for reasons other than disease progression (if not obtained within 4 weeks of withdrawal)

C - For women of childbearing potential.

D - For the subjects who consented to participate in the PK sub-study, blood samples are taken before administration of Sodium Cridanimod and megestrol acetate as well as 15 min, 30 min, 45 min, 60 min, 90 min, 2, 3, 4 and 6 hours (all times +/- 2 minutes) after administration at Visit 1. Blood samples are also taken on Days 3, 7, 10, 56 (Visit 3) and 84 (Visit 4), before Sodium Cridanimod and megestrol acetate administration.

E - ECG will be performed 5 times at Visits 1 and 3: before Sodium Cridanimod administration, 15, 60, 120 and 360 (±5) minutes after administration. At all other visits, ECG is only performed before administration. Exception: ECG performed at Safety Follow-up Visit.

F - Subjects with disease control (non-PD) after one year of treatment in Period 2 (Visit 13) will continue treatment and will switch to study visits every 12 weeks, until discontinuation of treatment.
G - Safety Follow-up Visit occurs four weeks following the discontinuation of treatment.
H - At the visit where treatment is discontinued, study drug will not be dispensed and a new patient diary will not be issued. The remaining drug will be returned and the final patient diary will be collected.
I – After subjects discontinue treatment and undergo the Safety Follow-up Visit, they will be followed for overall survival for an additional 12 months (from the date of treatment discontinuation) by phone call or other personal contact.
J - D = Dispense, R = Return, I = Issue, C = Collect

1. INTRODUCTION

1.1. Background

1.1.1. Endometrial Cancer

Endometrial cancer is ranked as the sixth most prevalent cancer among women and is the fourteenth most prevalent cancer overall.. There were 320,000 new cases of endometrial cancer diagnosed in 2012 and there will be an estimated 500,000 cases of endometrial cancer in the world by 2035. In the United States, the 5 year relative survival rate for all endometrial cancer cases is 69% (wcrf.org). Endometrial cancer is now the most common gynecological malignancy in Europe and North America. The median age of occurrence is 63 years; more than 90% of women diagnosed are older than 50.[1]

1.1.2. Progestins for the Treatment of Endometrial Cancer

Megestrol acetate is a synthetic derivative of the naturally occurring steroid hormone progesterone and has been studied extensively for the treatment of endometrial cancer[2–4]. The results from several clinical trials examining the efficacy of megestrol acetate at treating subjects with recurrent or persistent endometrial cancer are summarized in Table 4[4,5].

Table 4. Efficacy of megestrol acetate in patients with recurrent or persistent endometrial cancer.

Treatment	Overall response rate	Median progression free survival, months	Median overall survival, months	Reference
MA 800 mg/day	24%	2.5	7.6	[4]
MA	NA	NA	12	[5]
MA + Tamoxifen	NA	NA	8.6	[5]

It was found that subjects had increased progression-free and overall survival following treatment with megestrol acetate compared to placebo, leading to its FDA approval. It was also found that subjects whose tumors expressed the progesterone receptor (PrR) had a significantly higher response rate than those subjects who did not express PrR. For this reason, progestins are typically only used in patients with documented PrR-positive endometrial cancer. However, PrR-expression's predictive power is still limited, as the response rate even in these subjects is only approximately 25%.

Table 5. Response rate to progestin therapy by PrR status

Characteristic	Overall response rate	Median overall survival, months
Histologic grade 1	37%	18.8
Histologic grade 2	23%	7.5
Histologic grade 3	9%	6.9
PrR level, ≥ 50 fmol/mg cytosol protein	37%	12.1
PrR level, < 50 fmol/mg cytosol protein	8%	6.8

1.2. Sodium Cridanimod

For the most complete and up-to-date information regarding Sodium Cridanimod, refer to the current version of the Investigator's Brochure.

Sodium Cridanimod (oxodihydroacridinylacetate sodium) is a synthetic interferon inducer that was developed in the 1970s-80s by Hoffman-La Roche Inc[6,7]. In preclinical models, Sodium Cridanimod was shown to protect against lethal Semliki Forest, Coxsackie Bi, Columbia SK, Western equine encephalitis, herpes simplex, and pseudorabies virus infections[8]. A number of clinical studies performed in the former Soviet Union and Russian Federation demonstrated its safety and efficacy in humans, and lead to its current approval in the Russian Federation and many Eastern European countries for the treatment of many viral infections. To date, no clinical trials with Sodium Cridanimod have been performed in the United States and Canada.

1.2.1. Nonclinical Data Relevant to Endometrial Cancer

An early animal study revealed that Sodium Cridanimod administration to rats for a 2-week period significantly increased the endometrial expression of PrR and that the magnitude of the effect was similar, and additive, to that of tamoxifen[8]. A subsequent animal study examined the efficacy of Sodium Cridanimod in combination with medroxyprogesterone acetate (a synthetic progestin, similar to megestrol acetate) on treating xenograft Hec50co endometrial tumors, a tumor line known to be PrR-negative. This study demonstrated that the addition of Sodium Cridanimod could significantly increase the anti-tumor efficacy of medroxyprogesterone acetate when targeting an otherwise PrR-negative endometrial cancer. Taken together, these findings suggest a mode of action for Sodium Cridanimod, namely that Sodium Cridanimod can increase the expression of PrR on endometrial tumors subsequently making them more amenable to treatment with traditional progestin therapy.

1.2.2. Clinical Data Relevant to Endometrial Cancer

An early clinical study conducted in the Russian Federation enrolled 50 subjects with untreated stage I-II endometrial cancer. Subjects were treated with either Sodium Cridanimod (250 mg every 3 days), medroxyprogesterone acetate (500 mg daily), or a combination of the two for three weeks prior to hysterectomy. The results of this study revealed that Sodium Cridanimod significantly increased the PrR levels in tumors that were negative for PrR prior to treatment.

A second clinical study, designed similarly to this study, enrolled 28 subjects and treated them initially with medroxyprogesterone acetate (250 mg daily). After these subjects progressed on progestin monotherapy, they then received a combination of Sodium Cridanimod (250 mg, twice weekly) and medroxyprogesterone acetate. In this study, the subjects who failed medroxyprogesterone acetate monotherapy had a 100% response rate to the combination therapy, whereas the subjects who initially had a response to medroxyprogesterone acetate and then later progressed only had a 33% response rate to the combination therapy.

Taken together, these studies demonstrate that Sodium Cridanimod can increase the levels of PrR expression in endometrial tumors and can make them more amenable to treatment with progestin therapy. These data also demonstrate that the effect of combining Sodium Cridanimod

with progestin therapy may be most pronounced in subjects for whom progestin monotherapy demonstrates no efficacy.

1.3. Summary of Key Safety Information for Study Drug

Acute toxicity of Sodium Cridanimod has been studied in mice, rats, hamsters and rabbits, with intramuscular administration not shown to cause deaths in any of these species. Repeated dose toxicity studies have been performed in rats, rabbits and dogs. These studies have not identified any target organ toxicity at doses as high as 31.3 mg/kg i.m. Sodium Cridanimod is known to be eliminated mostly by the kidney with a half-life of approximately 0.6 hours.

More than 750 subjects have been exposed to Sodium Cridanimod in clinical studies. The regimen of administration of Sodium Cridanimod was similar across clinical studies: study drug was administered at the dose of either 250 or 500 mg either two or three times a week intramuscularly, in some cases for as long as 2 years. All of these trials have demonstrated that Sodium Cridanimod is well tolerated, with mild to moderate adverse events (AEs) and no subjects ever permanently discontinuing study drug due to an AE related to administration of Sodium Cridanimod. The most frequently reported AE across the studies was moderate intensity pain at the site of injection. There have been no deaths associated with the administration of Sodium Cridanimod. Table 6 below summarizes the related, AEs observed in all subjects who were treated with Sodium Cridanimod in all studies to date.

Table 6. Adverse Events with causal relationship to Sodium Cridanimod

Adverse Event	Investigator Causality Assessment	AE Frequency per Study	Total Subjects with reported AE to date*	Frequency of AE based on total Subjects treated*
Burning pain at the injection site	Related	729 of 751 (97%)	730	96.18 %
Relative eosinophilia	Probably related	6 of 50 (12%)	6	0.79 %
Burning Lips	Probably related	1 of 8 (13%)	1	0.13 %
Fatigue and tired all the time	Probably related	1 of 8 (13%)	1	0.13 %
Hyperemia of the face	Probably related	1 of 8 (13%)	1	0.13 %
Pharyngalgia	Probably related	1 of 8 (13%)	1	0.13 %
Sleepiness	Probably related	1 of 8 (13%)	1	0.13 %
Headache	Possibly related	4 of 12 (33%), 1 of 8 (13%)	5	0.66 %
Sore throat	Possibly related	4 of 12 (33%), 1of 8 (13%)	5	0.66 %
Weakness	Possibly related	2 of 6 (33%), 1 of 8 (13%)	3	0.40 %
Dizziness	Possibly related	2 of 6 (33%)	2	0.26 %
Sleepiness	Possibly related	2 of 6 (33%)	2	0.26 %

**Data from 759 subjects in clinical trials through 1Sep2017*

All AEs determined by the Investigator to have an unrelated causality to Sodium Cridanimod occurred in a frequency less than 1% in all treated subjects.

Additionally, safety and tolerability of Sodium Cridanimod was assessed in a post-registration study in healthy subjects, where subjects were treated twice weekly with either Sodium Cridanimod (500 mg), Sodium Cridanimod (500 mg) + 2% lidocaine hydrochloride, or placebo. The main purpose of this study was to assess the safety and tolerability of Sodium Cridanimod at a dose of 500 mg and whether the injection site pain could be lessened by the addition of lidocaine hydrochloride solution to the injection. Overall, repeated intramuscular injections of 500 mg Sodium Cridanimod with or without lidocaine were well tolerated by these healthy volunteers, with no significant changes in blood pressure, heart rate, ECG, or physical or clinical laboratory parameters. Table 7 below summarizes the nature and frequency of all AEs experienced by subjects during the study. Four AEs of sore throat were rated as "probably related" to the use of study medication.

Table 7. Summary of AEs related to Sodium Cridanimod in post-registration safety and tolerability study in healthy subjects

Study treatment	Sodium Cridanimod 500 mg i.m. twice a week	Sodium Cridanimod 500 mg i.m. + 2% Lidocaine hydrochloride 1 mL twice a week	0.9%Sodium chloride 4 mL i.m. twice a week (placebo)
Number of subjects	12	12	12
Pain at the injection site	10	4	1
Sore throat	1	3	0

Sodium Cridanimod is approved for marketing in the Russian Federation, Republic of Belarus, Ukraine, Republic of Uzbekistan, Republic of Azerbaijan, Republic of Kazakhstan, Kyrgyz, Republic of Georgia and Republic of Armenia for the treatment of several viral infections including in immunodeficient patients. The data from marketing experience indicates treatment with Sodium Cridanimod is well tolerated, as more than 1.4 million doses have been sold to date and no SAEs have been reported as documented in periodic safety update reports.

1.3.1 Adverse Reactions Reported with Megestrol Acetate

Adverse events associated with the use of megestrol acetate as reported in the current, marketed package insert[9] include: Weight gain as a frequent side effect. Thromboembolic Phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal). Glucocorticoid effects, heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, glucose intolerance, alopecia, hypertension, carpal tunnel syndrome, mood changes, hot flashes, malaise, asthenia, lethargy, sweating and rash. The investigator should refer to the current prescribing information for complete information including contraindications, warnings and precaution information. A copy of the current package insert is included in the Pharmacy Manual for this study.

1.3.2 Adverse Reactions Reported with Lidocaine Hydrochloride

Lidocaine HCL is mixed with Sodium Cridanimod for each injection. Adverse events associated with the use of lidocaine HCL as reported in a current, marketed package insert[10] include those most commonly reported:

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized by lightheadedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest. Drowsiness following the administration of lidocaine HCl is usually an early sign of a high blood level of the drug and may occur as a consequence of rapid absorption.

Cardiovascular System: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, and cardiovascular collapse, which may lead to cardiac arrest.

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result of sensitivity either to local anesthetic agents or to the methylparaben used as a preservative in the multiple dose vials. Allergic reactions as result of sensitivity to lidocaine HCl are extremely rare and, if they occur, should be managed by conventional means. The detection of sensitivity by skin testing is of doubtful value.

Serious adverse experiences are generally systemic in nature. The investigator should refer to the current prescribing information for complete information including contraindications, warnings and precaution information. A copy of the current package insert is included in the Pharmacy Manual for this study.

1.4 Rationale for Study

Patients with recurrent or persistent endometrial cancer have limited treatment options. Although treatment with progestins provides some benefit and is routinely used to treat patients with PrR-positive recurrent or persistent tumors, only 25% of patients develop a response to these therapies, leaving a majority of the patients with few other options for treatment. Additionally, patients whose tumors do not express PrR are rarely treated with hormonal therapy as the response rate for these treatments in PrR-negative tumors is very low. As such, hormone resistant recurrent or persistent endometrial cancer represents a patient population for which new treatment options are greatly needed. Sodium Cridanimod has been shown to increase endometrial cancer expression of PrR and increase the efficacy of progestin therapy in at least a subset of these patients, which we believe provides a strong rationale for the combination of these agents for the treatment of recurrent or persistent endometrial cancer that has failed hormonal therapy. Additionally, combining progestin therapy with other agents known to increase tumor PrR expression (such as tamoxifen) has shown some success in other studies, supporting the rationale for this study[11,12].

1.5. Rationale for Study Population, Exclusion Criteria

This study will enroll patients with endometrioid histology of the tumor as endometrioid tumors have been shown to be the most sensitive to treatment with hormonal therapy. Additionally, the majority of the tumors previously treated with Sodium Cridanimod and progestins were of the endometrioid

histology. The efficacy of the study treatment in patients with other tumor histologies, or mixed histologies, is difficult to predict. For this reason, inclusion of patients with tumors of other histologies or mixed histology is prohibited with the exception of serous carcinoma[13]. Patients with serous carcinoma are eligible to enter this protocol as this histology was included in a prior trial of Sodium Cridanimod and progestin therapy in recurrent or persistent endometrial cancer with PrR negative tumors.

Endometrial cancer patients whose tumors do not express progesterone receptors are not considered candidates for progestin-based therapy. Patients therefore who have been identified as PrR negative from an archived tumor tissue sample will not be treated with progestin monotherapy and will enroll directly into the combination therapy portion of the trial.

As the main elimination route of Sodium Cridanimod is the kidney, patients with significant kidney disease and a diminished glomerular filtration rate (GFR < 50 mL/min) will not be enrolled in the study. eGFR will be monitored during the study for safety reasons. In the event of an observed renal toxicity, the decision to withdraw the treatment should be made by the Investigator.

1.6. Rationale for Selection of Dose of Study Drug

The dosage of Sodium Cridanimod (500 mg, twice weekly) was chosen because it was shown to be well tolerated in safety evaluations and evidence from preclinical models demonstrated this dosage (per kg) to have the best activity. Intramuscular administration was selected based on preclinical studies demonstrating other routes were not feasible or offered no advantage over i.m. administration. Oral bioavailability of Sodium Cridanimod was shown to be very low, and repeated intravenous administration of Sodium Cridanimod was shown to potentially induce phlebitis.

As the intramuscular injection of Sodium Cridanimod has been shown to cause moderate pain at the site of injection, this study will dilute the Sodium Cridanimod (4 mL, 500 mg) with 1 mL of 2% lidocaine hydrochloride, a local anesthetic solution. The resulting 5 mL dosage was shown to be well tolerated in the post-registration study noted above and was shown to decrease the frequency of injection site pain.

The dosage of megestrol acetate (160 mg / day) is in accordance with the most up-to-date prescribing information provided by the commercial vendor.

1.7. Rationale for Treatment Duration

Previous trials examining the efficacy of progestin monotherapy at treating advanced endometrial cancer demonstrated an objective response rate (ORR) of approximately 25% with disease stabilization (no progression) for an average duration of 9 months. Progestin therapies for endometrial cancer are administered for long periods of time in order to constantly expose the tumor cells to the progestins, and this prolonged exposure has been shown to be safe and well-tolerated.

However, prolonged exposure of tumor cells to progestins has been demonstrated to downregulate the expression of PrR in tumor tissue as the tumor cells become desensitized to the repressive signaling induced by the progestins. As such, we believe prolonged treatment with Sodium Cridanimod in conjunction with prolonged progestin treatment is a rational treatment approach. Sodium Cridanimod has been demonstrated to be safe when given 2-3 times per week for as long as 2 years of administration. A recent Gynecologic Oncology Group demonstrated the safety of prolonged treatment

of advanced endometrial cancer patients with megestrol acetate in combination with tamoxifen, a similar inducer of PrR expression. Therefore, we believe that the continuous treatment of hormone resistant recurrent or persistent endometrial cancer with megestrol acetate in combination with Sodium Cridanimod until documented disease progression will be well tolerated and provide the greatest chance at observing objective anti-tumor responses, disease stabilization, and increased overall survival.

2. STUDY OBJECTIVE(S), DESIGN AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

To assess the antitumor activity of Sodium Cridanimod in conjunction with progestin therapy as measured by Overall Disease Control Rate (ODCR) in women with recurrent or persistent endometrial carcinoma not amenable to surgical treatment or radiotherapy who have either failed progestin monotherapy or who have been identified as PrR negative.

2.1.2. Secondary Objective

Efficacy: To assess ORR including PR and CR, PFS, Duration of Stable Disease and OS for subjects receiving Sodium Cridanimod and possibly in conjunction with progestin therapy.

Safety: To evaluate the safety and tolerability of Sodium Cridanimod possibly in conjunction with progestin therapy as measured by adverse events, laboratory safety parameters, and cardiac safety assessments (including QT prolongation potential).

2.1.3. Translational Research Objective

To assess pharmacokinetics of Sodium Cridanimod and megestrol acetate after a single dose and after multiple dose administrations and possible drug-drug interactions between Sodium Cridanimod and megestrol acetate.

2.2. Study Design

This is an open-label, multi-center, single-arm, two-period Phase 2 study. The study will investigate the efficacy of Sodium Cridanimod in conjunction with progestin therapy in a population of patients with endometrial cancer who have either failed progestin monotherapy or who have been identified as PrR negative.

All patients must have endometrial cancer PrR status determined from an archival sample at Screening.

The tumor is considered to be PrR negative if the number of PrR positive cells is less than 1% determined by use of IHC. Conversely, the tumor is considered to be PrR positive if the number of PrR positive cells is 1% or greater as determined by IHC.

There are two treatment periods and a follow-up period within the study.

2.2.1 Treatment Period 1 (Progestin Monotherapy):

During Treatment Period 1, all eligible subjects determined to be PrR positive will receive progestin monotherapy (megestrol acetate 160 mg p.o. / day) for up to 24 weeks. Subjects will

have a CT or MRI scan after 12 and 24 weeks of progestin monotherapy, with response to treatment being assessed according to RECIST 1.1 criteria.

At Visit -1 (After 12 weeks of treatment):

- Subjects determined to have disease progression will be eligible to enter Treatment Period 2.
- Subjects who maintain disease control (SD, PR or CR) may continue progestin monotherapy for an additional 12 weeks. These subjects will be re-assessed after 24 weeks of treatment (TP1-EXT Visit).
    - Subjects determined to have disease progression will be eligible to enter Treatment Period 2.
    - Subjects who maintain disease control will be ***ineligible*** to enter Treatment Period 2. These subjects will return 2 weeks following the TP1-EXT Visit for the End of Study Visit.

A subject may be discontinued from Treatment Period 1 at any time if the subject experiences a change in symptoms and/or if disease progression is suspected by the Investigator.

- Subjects who discontinue Treatment Period 1 prematurely (receiving < 4 weeks of progestin monotherapy) for any reason will be excluded from the remainder of the study.
- Subjects who have had ≥ 4 weeks of progestin monotherapy and have documented disease progression may enter Treatment Period 2 at Visit 1, Day 0.

Subjects who terminate study participation at the end of Treatment Period 1 due to disease control will be treated in accordance with local standards and clinical practice (which can include continuation of progestin therapy).

Subjects determined to be PrR negative at Screening will not enroll into Treatment Period 1. These subjects will enroll directly into Treatment Period 2.

2.2.2 Treatment Period 2 (Combination Therapy):

All subjects determined to be PrR negative at Screening and those who received at least 4 weeks of progestin monotherapy and who experienced disease progression during Treatment Period 1 will enter Treatment Period 2 of the study (Visit 1, Day 0).

During Treatment Period 2, subjects will receive Sodium Cridanimod (500 mg, 2 times / week, intramuscularly) in combination with continued progestin treatment (megestrol acetate 160 mg p.o. / day).

- For those subjects who participated in Treatment Period 1, there should be no interruption of progestin therapy between Treatment Period 1 and Treatment Period 2.
- Subjects will receive treatment until disease progression as defined according to RECIST 1.1 Criteria, with response assessments performed at 12-week intervals.

- Confirmation of objective responses in Treatment Period 2 will be performed at least 4 weeks after the criteria for response are first met.

2.2.3 Follow-up Period:

Once subjects progress in Treatment Period 2, treatment will be stopped and the subjects will return for the Safety Follow-up Visit four (4) weeks following the last treatment, and then continue to be followed for a 12-month period for overall survival.

2.3. Endpoints

Subjects will be discontinued from the study (during Treatment Period 2) at the time of radiographic (CT/MRI) disease progression, relative to baseline measurements from the scan that determined the subject was eligible to participate in Treatment Period 2 of the study (i.e. scan typically taken at Week -1 or at TP1-EXT). Subjects will also be discontinued from the study when, at the discretion of the subject or treating physician, continuing treatment is not in their best interest and/or that other standard therapies for endometrial cancer are warranted.

2.3.1. Primary Endpoint

The primary endpoint of the trial is overall disease control (SD, CR or PR) as determined by radiographic measurements. All subjects in Treatment Period 1 will undergo radiographic imaging (CT or MRI scan of chest, abdomen and pelvis) prior to treatment, after 12 weeks of progestin monotherapy (at Visit -1), and if disease control is maintained, again after an additional 12 weeks of progestin monotherapy (at Visit TP1-EXT). During Treatment Period 2, subjects will undergo a CT or MRI scan at 12-week intervals. Subjects may also be assessed at any point when the Investigator determines radiographic imaging is indicated. Radiographic disease progression and responses will be defined using RECIST 1.1 criteria as detailed in Section 5.5, and the ODCR will be determined as described in Section 7.4.

2.3.2. Secondary Endpoints

The secondary endpoints of the trial include safety and other efficacy parameters. As before, radiographic imaging will be used to assess the ORR, PFS, duration of stable disease, and OS. A more detailed description of how these will be calculated is included in Section 7.4. Safety will be assessed as described in Sections 5.7 and 5.9.

3. STUDY POPULATION

3.1. Selection of Study Population

This study will enroll subjects with recurrent or persistent endometrial cancer.

3.2. Informed Consent

Before any study-related screening procedure is performed, each potential subject will be informed of the study's objectives and requirements. The Investigator or his/her designee will explain the study fully to the subject using the Informed Consent Form (or Patient Information Sheet, as applicable in some countries). If the subject is willing to participate in the study, written informed consent will be requested after sufficient time to consider participation and the opportunity to ask further questions has been

given. The Informed Consent Form will be signed and personally dated by both the subject and the person obtaining the consent. The person obtaining consent must be the Investigator or his/her designee who is also medically qualified. The subject will be provided a copy of the signed and dated Informed Consent Form. The original signed and dated Informed Consent Form will be retained with the source documents.

3.3. Screening

Following the receipt of informed consent, potential subjects will be assigned a subject identification number and undergo screening procedures to determine eligibility for the study. Screening procedures will be conducted according to the Visit and Assessment Schedule described in Section 5.4.

3.4. Inclusion Criteria

1. Female patients 18 years of age or older;
2. Histologically confirmed serous carcinoma or endometrioid type of endometrial carcinoma (histological documentation of recurrence is not required);
3. Recurrent or persistent progressive disease which is refractory to curative therapy or established treatments and cannot be treated with surgery or radiotherapy;
4. Measurable disease, as defined by RECIST 1.1 criteria;
5. At least one “target lesion” to be used to assess response, as defined by RECIST 1.1 criteria. Tumors within a previously irradiated field will be designated as “non-target” lesions unless previous progression is documented;
6. Availability of archived tumor tissue sample that can be used for assessment of PrR status by the central laboratory;
7. GOG performance status 0-2 (refer to Table 9 under Section 5.5.3);
8. eGFR ≥ 50 mL/min;
9. Total bilirubin ≤ 2.5 times upper limit of normal (ULN);
10. AST ≤ 2.5 ULN (≤ 5 times ULN for patients with liver metastases);
11. Alkaline phosphatase ≤ 2.5 ULN (≤ 5 times ULN for patients with liver metastases);
12. Albumin ≥ 3.0 mg/dL;
13. Ability to take oral medication
14. Patients able to understand the nature of the study and who are willing to give written informed consent;
15. *And or Treatment Period 2 only,* Patients participating in Treatment Period 1 must have had disease progression after receiving at least 4 weeks of progestin therapy or 2) Patients must be determined as PrR negative status at Screening.

Waivers to the inclusion criteria will **NOT** be allowed.

3.5. Exclusion Criteria

1. Mixed histology of the tumor or evidence of tumor histology other than serous carcinoma or endometrioid type of endometrial carcinoma;
2. Concurrent systemic corticosteroid therapy;
3. Concurrent oral contraceptive use / Women of childbearing potential not using highly effective means of contraception;
4. Pregnancy confirmed by pregnancy test / Lactating women (for women of childbearing potential);
5. Prior therapy with hormonal progestin agents;
6. Patients who are candidates for treatment with standard chemotherapy agents (there is no limit to the number of lines of prior chemotherapy);
7. History of blood clot;
8. History of known bleeding disorder (i.e. disseminated intravascular coagulation or clotting factor deficiency);
9. Major surgery within 4 weeks prior to the start of the study;
10. Patients with clinically significant illnesses which, according to the Investigator, could compromise participation in the study;
11. History of other clinically active malignancies within 5 years, except for carcinoma in situ of the cervix, basal cell carcinoma, or squamous carcinoma of the skin.
12. Known hypersensitivity or idiosyncratic reaction to any of the study drugs (Sodium Cridanimod, megestrol acetate, lidocaine) and excipients;
13. Patients with known brain metastases;
14. Patients currently receiving any other investigational agents;
15. Patients currently receiving any other anticancer therapies;
16. Participation in any other clinical study within the last 4 weeks prior to the start of the study;

Waivers to the exclusion criteria will **NOT** be allowed.

3.6. Discontinuation Criteria for Individual Subjects

Treatment may continue until one of the following criteria applies:

- Disease progression (during Treatment Period 2 only),
- A Grade 3 or higher AE (according to NCI-CTCAE Version 4 criteria) is observed and is determined to be related to either the Sodium Cridanimod or progestin therapy.
- Concurrent illness that prevents further administration of treatment,
- Unacceptable AE(s),

- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator.

3.7. Patient Requirements

The following patient requirements apply from screening through completion or withdrawal of the study:

- Patients must have the availability to attend visits according to the protocol;
- Patients must not participate in any other clinical study;
- Patients of childbearing potential must use highly effective barrier contraception;
- Patients must keep a diary of megestrol acetate doses as described in Section 5.7.7.

3.8. Subject Identification

Subjects in this study will be identified only by the subject number (CCC-SS-XX), which consists of a 3-digit country code (CCC), a 2-digit site number (SS) followed by 2-digit consecutive enrollment number (XX) of subjects enrolled at the specific clinical site.

4. STUDY DRUG

4.1. Description of Study Drugs

For the most recent, detailed pharmaceutical information on Sodium Cridanimod and megestrol acetate, refer to the Sodium Cridanimod Investigator's Brochure and the Prescribing Information for megestrol acetate.

4.1.1 Sodium Cridanimod is a synthetic interferon inducer that has been extensively studied and is approved for many indications (mainly viral infections) in the Russian Federation and other Eastern European countries. Sodium Cridanimod (125 mg/mL) will be supplied to the investigational sites as a ready-to-use solution in ampules. One ampoule contains 2 mL, or 250 mg, of Sodium Cridanimod.

4.1.2 Megestrol acetate is a synthetic derivative of the naturally occurring hormone progesterone and is FDA approved for the treatment of advanced endometrial cancer. Megestrol acetate will be supplied in tablet form in doses of either 40 or 160 mg (depending on approved dosage forms in the applicable country).

4.1.3 Lidocaine Hydrochloride is a local anesthetic that is commonly used in clinical settings. It will be provided by the Investigator's pharmacy as a 2% (w/v) aqueous solution. As described in detail below, lidocaine will be mixed with Sodium Cridanimod to increase tolerability of the intramuscular injection.

4.2. Preparation of Sodium Cridanimod

To administer Sodium Cridanimod, the contents of 2 ampules (4 mL of solution equal to 500 mg of Sodium Cridanimod) and 1 mL of 2% lidocaine hydrochloride solution (for a total administration volume of 5 mL) should be withdrawn with a syringe. After the contents of the syringe are mixed, and all air

and air bubbles are removed from the syringe, the resulting solution is administered intramuscularly. It is preferable to rotate injection sites with each dose.

4.3. Study Drug Handling

Sodium Cridanimod may be requested by the Principal Investigator (or authorized designee) at each participating institution and will be shipped directly to the institution where the subject is to be treated.

The Investigator/pharmacist is responsible for safe and proper handling and storage of the study drugs at the investigational site. The study drugs must be stored in a secure area. Access to and administration of study drugs will be limited to the Investigator and authorized site personnel. The Investigator must ensure that study drugs are administered or dispensed only to subjects enrolled in this study and in accordance with the protocol. The study drugs must be stored at room temperature. Temperature logs should be kept updated by the Investigator, pharmacist or designated site personnel to document adequate storage during the course of the study.

It is the responsibility of the Investigator or, if applicable, pharmacist or designated site personnel to ensure that records of receipt, use by each subject, return, loss, or other disposition of study drugs are maintained at each study site. These records will include dates, quantities, batch numbers, and the unique subject numbers assigned to subjects. The Investigator must maintain records documenting that the subjects were provided with the doses specified in the protocol. Furthermore, they should reconcile all study drugs received from the Sponsor. It is the responsibility of the Investigator to give reasons for any discrepancies in study drug accountability and inventory. Study related forms and logs will be provided by the Sponsor to enhance drug accountability and inventory. All remaining study drugs shall be collected and disposed of according to the Sponsor's directions at the end of the study.

5. TREATMENTS AND EVALUATION

5.1. Dosing and Administration of Study Drugs and Other Medications

5.1.1. Dose/Dose Regimen and Administration

5.1.1.1 Megestrol acetate is supplied as either 40 mg (US) or 160 mg (Europe) tablets. For 40 mg tablets, two tablets are administered orally, twice daily, for a total daily dose of 160 mg. For 160 mg tablets, one tablet is administered orally, once daily, for a total daily dose of 160 mg.

At Study Visits when both megestrol acetate and Sodium Cridanimod are to be administered, the dose of megestrol acetate should be administered prior to Sodium Cridanimod. Whenever possible, the a.m. or p.m. dose of megestrol acetate should be taken in the clinic during the Study Visit.

5.1.1.2 Sodium Cridanimod solution is administered twice weekly according to either Schedule 1 (Mondays and Thursdays) or Schedule 2 (Tuesdays and Fridays) until documented disease progression, according to Table 8. For scheduled Sodium Cridanimod administrations that do not coincide with Study Visits, the Sodium Cridanimod can be administered either at the study site or at a subject's home by a medical service provider.

Table 8: Schedule of Sodium Cridanimod Administration

	Weekly until Disease Progression						
	Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
Schedule 1	500 mg i.m.			500 mg i.m.			
Schedule 2		500 mg i.m.			500 mg i.m.		

5.1.2. Dose Modifications

There will be no allowed modifications to the dosage, including dose reduction, of either megestrol acetate or Sodium Cridanimod during the trial.

If injection of Sodium Cridanimod was not administered on the scheduled dosing date, this can be done during the next two days but not later than 1 day before the next scheduled dose. The subsequent injection of Sodium Cridanimod should be given according to the study drug administration schedule.

If a subject misses a dose of megestrol acetate, the next dose should be taken at the regularly scheduled time.

Sodium Cridanimod and megestrol acetate combination therapy should be discontinued if an AE of Grade 3 or higher (according to NCI-CTCAE Version 4 criteria) is observed and determined to be potentially related to either medication**.** When combination treatment is discontinued, both Sodium Cridanimod and megestrol acetate are to be discontinued. Monotherapy in Treatment Period 2 is not permitted. The treatment will not be re-started and the subject will be withdrawn from Treatment Period 2. The subject will then enter the Follow-up Period as described in Section 5.1.4.

5.1.3. Duration of Therapy

5.1.3.1 Treatment Period 1*:* Subjects will participate in Treatment Period 1 for up to 24 weeks, during which time they are receiving only megestrol acetate. If a subject terminates therapy early in Treatment Period 1 for reasons outlined in Section 3.6, they will not be eligible to enter Treatment Period 2. They will have an End of Study Visit, and then be treated in accordance with local standards of clinical practice.

5.1.3.2 Treatment Period 2*:* Subjects who qualify to participate in Treatment Period 2 will receive both megestrol acetate and Sodium Cridanimod until documented disease progression. If a subject terminates therapy early in Treatment Period 2 for reasons outlined in Section 3.6, they will enter the Follow-up Period and then be treated in accordance with local standards of clinical practice.

5.1.4. Duration of Follow-up

There is no follow-up period for subjects exiting the study during or at the end of Treatment Period 1; they will continue to be treated in accordance with local standards of clinical practice.

Subjects who have participated in Treatment Period 2 and exit the study for any reason will enter the Follow-up Period. These subjects will return to the site 4 weeks following the discontinuation of treatment for the Safety Follow-up Visit. Subjects will then be followed for a 12-month period to determine overall survival. No additional visits are required after the Safety Follow-up Visit. Study staff will confirm survival status via telephone, personal contact or through clinic records, once, at the end of the 12 month period. This outcome is to be recorded in the eCRF.

5.1.5. Subject Compliance

Treatment compliance will be monitored by the review of study drug accountability, inventory records by study personnel, and patient diaries. Subject compliance (for each study drug individually) lower than 80% or higher than 120% will be considered a major protocol violation. In the case of poor compliance, the reason for the discrepancy will be documented in the eCRF and the Investigator, together with the Sponsor, will decide on a clinical basis as to whether the subject may remain in the study.

5.2. Demographics and Baseline Characteristics

5.2.1. Demographics

Year and month of birth, weight, height, and ethnic origin will be recorded.

5.2.2. Medical History

All current medical conditions, including endometrial cancer and any significant past conditions, surgeries, tobacco and alcohol consumption, previous therapeutic or diagnostic procedures, and all concomitant medications will be recorded.

5.3. Assessment of PrR Status at Screening

The PrR status of the endometrial cancer is determined at screening, through the assessment of an archived tumor sample. The archived sample should preferably be provided within Formalin-fixed Paraffin Embedded (FFPE) Block, but slides are acceptable. For confirmation of PrR status, the patient's tumor sample is sent to the central laboratory. Levels of PrR are determined with the use of semi-quantitative IHC. The tumor is considered to be PrR negative if the number of PrR positive cells is less than 1% determined by IHC. Conversely, the tumor is considered to be PrR positive if the number of PrR positive cells is 1% or greater as determined by IHC.

It is preferable to send the most recently obtained tumor sample whenever possible. Patients who cannot have PrR status confirmed by the central lab will be excluded from study participation.

5.4. Visit Schedule and Required Study Procedures

5.4.1. Screening (Time Frame: ≤ 4 weeks from the start of Treatment Period 1, Week -18 to -15)

- Informed consent
- Eligibility criteria
- Demographics
- Medical history
- Concomitant medication review
- Physical exam
- Vital signs

- Height
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- Urinalysis
- Serum pregnancy test (for women of childbearing potential)
- ECG
- AE evaluation
- Confirmation of PrR status in central laboratory of archived tumor sample *(Specimen should be sent to central lab during Screening Weeks -18 and -16 to ensure results are received prior to Study Visit -3).*
- CT/MRI Scan
- Tumor assessment and measurements *(Radiologic evaluation must be obtained within 10 days of Visit -3).*

5.4.2. Treatment

Treatment Period 1 – Patients determined to have PrR Positive Status Only

Visit -3 (Week -14, ± 3 days) *

- Eligibility criteria
- Concomitant medication review
- Vital signs
- ECG
- For optional PK Sub-Study Participants:
  - Collection of blood samples for optional PK sub-study, at 10 timepoints: 0 (before administration of megestrol acetate), and 1, 2, 3, 4, 6, 24, 48, 72 and 96 hours (all times +/- 2 minutes) after administration).
- AE evaluation
- Administration of megestrol acetate
- Dispense supply of megestrol acetate
- Issue patient diaries

*** If Visit -3 occurs > 7 days after the Screening visit, the following assessments should also be performed:**

- Physical exam
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR

Visit -2 (Week -8, ± 3 days)

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG
- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diary(ies) and issue new diary(ies)
- Administration of megestrol acetate
- Collect any empty bottle(s) of megestrol acetate and dispense new supply

Visit -1 (Week -2, ± 3 days)

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG
- AE evaluation
- CT/MRI Scan
- Tumor assessment and measurements
- Assess subject dosing compliance
- Administration of megestrol acetate
- Collect completed patient diary(ies) and issue new diary(ies)
- Collect any empty bottle(s) of megestrol acetate

Visit TP1-EXT (Week +12, ± 3 days)

This treatment extension and visit is only for those subjects assessed to have disease control at Visit -1.

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status

- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG
- AE evaluation
- CT/MRI Scan
- Tumor assessment and measurements
- Assess subject dosing compliance
- Administration of megestrol acetate
- Collect completed patient diary(ies) and issue new diary(ies)
- Collect any empty bottle(s) of megestrol acetate

Subjects determined to have disease control (SD, PR or CR) confirmed by tumor assessment after 24 weeks in Treatment Period 1, will be ***ineligible*** to enter Treatment Period 2. The subject will be withdrawn from the study treatment and return for the End of Study Visit within 2 weeks to be discontinued from the study.

END OF STUDY VISIT (2 weeks after TP1-EXT, +/- 7 days)

For subjects who discontinue during TP1 for any reason (refer to Section 3.6) and those assessed to have disease control at Visit TP1-EXT:

Subjects to be discontinued from TP1 should complete the EOS as soon as withdrawal is determined.

Subjects assessed to have disease control at TP1-EXT should attend the EOS within 2 weeks of TP1-EXT Visit.

Subjects should continue their megestrol acetate dosing until the EOS unless the Investigator determines this is contraindicated.

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- Urinalysis
- Urine Pregnancy Test (for women of childbearing potential)
- ECG
- AE evaluation
- Collect any outstanding patient diaries
- Collect all remaining megestrol acetate supplies

Subjects determined to have PrR negative status and subjects with documented disease progression after completing Treatment Period 1, will be eligible to enter Treatment Period 2.

Treatment Period 2

Visit 1, Day 0 (+/- 3 days) (Combination Treatment Start)

- Eligibility criteria
- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG (before administration of Sodium Cridanimod and megestrol acetate, and 15, 60, 120, and 360 (± 5) minutes after administration of Sodium Cridanimod)
- For optional PK Sub-Study Participants:
    - Collection of blood samples for optional PK sub-study, at 10 timepoints: 0 min (before administration of Sodium Cridanimod and megestrol acetate), and 15 min, 30 min, 45 min, 60 min, 90 min, 2 hr, 3 hr, 4 hr, and 6 hr (all times +/- 2 minutes) after administration. Note additional PK draws below**
- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diaries and remaining megestrol acetate for subjects completing Treatment Period 1
- Issue patient diaries
- Dispense supply of megestrol acetate
- Administration of megestrol acetate
- First administration of Sodium Cridanimod – The subject's condition will be monitored closely for a one-hour period after this first administration.

**** Days 3, 7, and 10 for optional PK Sub-Study Participants:**
Blood samples will be taken on Days 3, 7 and 10 (before administration of Sodium Cridanimod and megestrol acetate).

Visits 2, 6, 8, and 12 (Weeks 4, 20, 28, and 44; all ± 3 days)

- Concomitant medication review
- Vital signs
- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG

- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diaries and issue new diaries
- Collect any empty bottle(s) of megestrol acetate and dispense new supply
- Continued dosing of Sodium Cridanimod and megestrol acetate

Visit 3 (Week 8, ± 3 days)

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG (before administration of Sodium Cridanimod and megestrol acetate, and 15, 60, 120, and 360 (± 5) minutes after administration of Sodium Cridanimod)
- For optional PK Sub-Study Participants:
    - Collection of Day 56 blood sample for optional PK sub-study (before administration of Sodium Cridanimod and megestrol acetate)
- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diaries and issue new diaries
- Collect any empty bottle(s) of megestrol acetate and dispense new supply
- Continued dosing of Sodium Cridanimod and megestrol acetate

Visits 4 and 10 (Weeks 12 and 36; both ± 3 days)

- Concomitant medication review
- Vital signs
- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG
- Visit 4 only - for optional PK Sub-Study Participants:
    - Collection of Day 84 blood sample for optional PK sub-study (before administration of Sodium Cridanimod and megestrol acetate) at Visit 4 only. Does not occur at Visit 10.
- CT/MRI Scan
- Tumor assessment and measurements
- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diaries and issue new diaries
- Collect any empty bottle(s) of megestrol acetate and dispense new supply

- Continued dosing of Sodium Cridanimod and megestrol acetate

Visits 5, 9, and 11 (Weeks 16, 32, and 40; all ± 3 days)

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- ECG
- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diaries and issue new diaries
- Collect any empty bottle(s) of megestrol acetate and dispense new supply
- Continued dosing of Sodium Cridanimod and megestrol acetate

Visit 7 (Week 24, ± 3 days)

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- Urinalysis
- Urine Pregnancy Test (for women of childbearing potential)
- ECG
- CT/MRI Scan
- Tumor assessment and measurements
- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diaries and issue new diaries
- Collect any empty bottle(s) of megestrol acetate and dispense new supply
- Continued dosing of Sodium Cridanimod and megestrol acetate

Beginning with Visit 13 (Week 48), study visits will occur every 12 weeks instead of every 4 weeks.

Visit 13, 14, 15, and continuing every 12 weeks until disease progression or other reason for withdrawal* (Weeks 48, 60, 72 etc.; all ± 7 days)

- Concomitant medication review

- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- Urinalysis
- ECG
- CT/MRI Scan
- Tumor assessment and measurements
- AE evaluation
- Assess subject dosing compliance
- Collect completed patient diaries and issue new diaries
- Collect any empty bottle(s) of megestrol acetate and dispense new supply
- Continued dosing of Sodium Cridanimod and megestrol acetate

* Subjects continue administration of both Sodium Cridanimod and megestrol acetate until documented disease progression. If subjects have no evidence of progressive disease at Visit 13, they continue treatment as before, with visits to the Study Site continuing every 12 weeks thereafter until disease progression. At the visit where disease progression is documented, a new patient diary is not issued and no megestrol acetate is dispensed.

Subjects who discontinue from the study during Treatment Period 2 for reasons other than disease progression will enter the Follow-up Period and return for the Safety Follow-up Visit.

5.4.3. Follow-up Period *(Subjects participating in Treatment Period 2 only)*

Safety Follow-up Visit (Four [4] weeks following the last treatment of Sodium Cridanimod, ± 3 days)

- Concomitant medication review
- Physical exam
- Vital signs
- Weight
- Performance status
- CBC with differential, platelets
- Serum chemistry
- eGFR
- Urinalysis
- Urine Pregnancy Test (for women of childbearing potential)
- ECG
- AE evaluation
- CT/MRI Scan

- Tumor assessment and measurements should be obtained whenever possible for subjects discontinuing for reasons other than disease progression *(unless a scan has been done within 4 weeks of withdrawal).*
- Collect any outstanding patient diaries
- Collect all remaining megestrol acetate supplies

Overall Survival Assessment (for 12 months after discontinuation of Treatment Period 2)

- Confirm survival status of subject via telephone, personal contact or through clinic records once, at the end of the 12 month period. No Study Visits are required. This outcome is to be recorded in the eCRF.

5.5. Efficacy Assessments

5.5.1. Visual Tumor Examination

The subject will undergo a clinical disease assessment for all palpable or visible lesions at the Screening Visit, and at Visits -1, TP1-EXT, and every 12 weeks in Treatment Period 2 to correlate with radiologic assessments.

5.5.2. Tumor Imaging and Measurement (CT/MRI)

Radiologic imaging with assessment and measurement of disease (CT or MRI scan of chest, abdomen, and pelvis) will be performed at the Screening, during Treatment Period 1 following 12 weeks of treatment (at Visit -1), and if disease control is achieved, after an additional 12 weeks of treatment (at Visit TP1-EXT), during Treatment Period 2 every 12 weeks (± 7 day window) until disease progression is documented.

In subjects with an objective response during Treatment Period 2, an additional radiologic assessment will be performed at least 4 weeks later to confirm the presence of an objective response. Response criteria is further outlined in Section 5.5.

Radiographic imaging may also be performed at any point during the trial the Investigator determines this is indicated. If disease progression is observed at an unscheduled scan during TP1, the subject is eligible to enter TP2 if she has received > 4 weeks of treatment, otherwise the subject must return for an End of Study Visit and be discontinued from the trial. If disease progression is observed at an unscheduled scan during TP2, the subject must be withdrawn from treatment, enter the Follow-up Period and return for the Safety Follow-up Visit. An Unscheduled scan eCRF is to be completed.

5.5.3. Gynecologic Oncology Group (GOG) Performance Status

A subject will be assigned a GOG Performance Status at the Screening Visit and at Visits -3, -2, -1, TP1-EXT, EOS, 1, 3, 5, 7, 9, 11, 13, all subsequent quarterly Study Visits, and at the Safety Follow-up Visit, according to the following table:

Table 9. Performance Status Criteria

Gynecologic Oncology Group (GOG) Status Scale	
GOG Score	**Descriptions**
0	Fully active, unrestricted activities of daily living.
1	Ambulatory, but restricted in strenuous activity.
2	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours.
3	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance.
4	Completely disabled, and no self care.
5	Dead.

5.6. Assessment of Response

Tumor measurements will be collected by CT or MRI scan, as noted in Section 5.5.2. CT or MRI scan of chest, abdomen, and pelvis are appropriate, but all scans for an individual subject must use the same procedure as was performed at baseline. Conventional CT and MRI should be performed with contiguous cuts of 10mm or less in slice thickness. Spiral CT should be performed by use of a 5 mm contiguous reconstruction algorithm. Ultrasound should not be used for measurement. Clinically detected lesions will only be considered measurable if they are superficial (e.g. skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a tool to estimate size of the lesion, is recommended. Photographs should be retained with all other study documents at the study site.

In subjects with an objective response (as defined below), an additional CT/MRI scan and tumor assessment will be performed at least four weeks later to confirm the presence of objective response.

If a subject discontinues Treatment Period 2 for any reason other than disease progression (i.e. intolerable AE), every reasonable effort should be taken to encourage subjects to continue receiving regular CT/MRI scans and tumor assessments until disease progression is documented, with the date of disease progression still recorded in the eCRF.

5.6.1. Measurable Disease Definitions

Important inclusion criteria for this trial include the presence of measurable disease with at least one target lesion to use for all disease assessments.

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$20 mm by chest x-ray or as $\geq$10 mm with CT or MRI scan, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). For a lymph node to be considered pathologically enlarged and measurable, it must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion before study entry.

Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

5.6.2. Definitions of Response

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements.

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 of diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum.

Table 10. Target Lesion Evaluation

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

Non-Target Lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

Table 11. Non-Target Lesion Evaluation

Response	Definition
Complete Response (CR)	Disappearance of all extranodal non-target lesions. 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)

Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression

Symptomatic Deterioration: Subjects with a global deterioration of health status requiring discontinuation of treatment in Treatment Period 2 without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Reasonable efforts should be taken to obtain radiographic evidence to confirm disease progression. Subjects experiencing symptomatic deterioration during Treatment Period 1 are ineligible to enter Treatment Period 2 (as they do not meet the inclusion criteria requiring radiographic evidence of progression).

The baseline sum of diameters (from the Screening Visit) will be used as reference to further characterize disease control in the measurable dimension of the disease to determine the eligibility to continue participation in Treatment Period 2 of the study. From that point onward, the scan that led to those subjects' termination of Treatment Period 1 and eligibility to enter Treatment Period 2 will serve as a subject's new "baseline" measurements, with that sum of diameters used as reference to characterize the objective tumor response. CR and PR are defined as Objective Responses and must be confirmed by repeat assessment performed at least four weeks after the criteria for response are first met.

Table 12. Evaluation of Time Point Response: Patients with target (+/– non-target) disease*

Target Lesions	Non Target Lesions	New Lesions	Overall Response	Confirmation Scan (Treatment Period 2 only)
CR	CR	No	CR	Yes
CR	Non CR/Non PD	No	PR	Yes
CR	Not Evaluated	No	PR	Yes
PR	Non CR/Non PD/Not Evaluated	No	PR	Yes
SD	Non CR/Non PD	No	SD	No
PD	Any	Yes or No	PD	No
Any	PD	Yes or No	PD	No
Any	Any	Yes	PD	No

Derived from New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1),* ***Table 1, 2 & 3*

5.6.3. Evaluations of a Subject's Best Overall Response

The best overall response is the best response recorded from the start of Treatment Period 2 until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 13. 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
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

**Derived from New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1), Table 5*

First Documentation of Response: The time between the initiation of Treatment Period 2 and the first documentation of PR or CR.

Confirmation of Response: To be assigned a status of CR or PR, tumor measurements must be confirmed by repeat assessment performed at least four weeks after the criteria for response are first met.

Duration of Response: The period of time from the disease assessment at which measurement criteria are first met for CR or PR (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented.

Duration of Complete Response (CR): The period of time from the disease assessment at which criteria for CR are met until the first date that recurrent disease is objectively documented.

Duration of Stable Disease: The time from the initiation of combination therapy on Study Visit 1 in Treatment Period 2 until the criteria for disease progression are first met.

Disease Control: Disease control is defined as all Best Overall Responses that are not progressive disease (i.e. SD, PR or CR).

5.7. Safety Assessments

5.7.1. Concomitant Medication

Concomitant medication is defined as any medication, other than the investigational medicinal product (Sodium Cridanimod) and megestrol acetate, taken at any point in the duration from the Screening Visit until the End of Study Visit or the Safety Follow-up Visit. This includes all prescription medications, over-the-counter medications, and herbal remedies. All concomitant medications will be recorded.

5.7.2. Vital Signs

The subject will undergo an assessment of vital signs (systolic and diastolic blood pressure, heart rate and body temperature) after 5 minutes in a supine position at the Screening Visit, at all Study Visits, at the End of Study Visit, and at the Safety Follow-up Visit.

5.7.3. Laboratory Assessments

Hematology, biochemistry, and urinalysis samples will be analyzed by the local laboratory using standard methods.

5.7.3.1. Hematology

Blood samples (5 mL) will be taken at the Screening Visit, at each Study Visit, at the End of Study Visit, and at the Safety Follow-up Visit and used for routine hematology analysis.

Hematology profile will include:

- Hemoglobin value
- Hematocrit
- Mean corpuscular volume (MCV)
- Mean corpuscular hemoglobin concentration (MCHC)
- Erythrocytes
- Leucocytes
- Differential leukocyte count (neutrophils, lymphocytes, monocytes, eosinophils and basophils)
- Platelet count

5.7.3.2. Serum Chemistry

Blood samples (5 mL) will be taken at the Screening Visit, at each Study Visit, at the End of Study Visit, and at the Safety Follow-up Visit and used for routine serum chemistry analysis.

Chemistry profile will include:

- Phosphate
- Sodium
- Potassium
- Chloride
- Calcium
- Bicarbonate
- Creatinine
- Creatine kinase
- Glucose
- Blood urea nitrogen (BUN)
- Total proteins
- Albumin

- Total bilirubin
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)
- Serum glutamic oxaloacetic transaminase (SGOT) / Aspartate aminotransferase (AST)
- Serum glutamic pyruvic transaminase (SGPT) / Alanine aminotransferase (ALT)

Estimated Glomerular Filtration Rate (eGFR) will be calculated based on blood creatinine levels and subject demographics using the CKD Epidemiology Collaboration (CKD-EPI method[14].

5.7.3.3. Urinalysis

Urine samples are taken at the Screening Visit, at the End of Study Visit, at Visit 7, at Visit 13 and every 12 weeks thereafter until disease progression, and at the Safety Follow-up Visit.

Urine analysis will include:

- Blood
- Protein
- Glucose
- Ketones
- pH

5.7.4. Pregnancy Test

Pregnancy tests are applicable to all subjects of childbearing potential (i.e. excluding those who are anatomically sterile or are post-menopausal). A serum pregnancy test (measuring β-human chorionic gonadotropin [β-hCG]) will be performed at the Screening Visit, and a urine pregnancy test will be performed at Visit 7 at the End of Study Visit, and at the Safety Follow-up Visit.

5.7.5. Physical Examination

The subject will undergo an evaluation of all major body systems, including the measurement of height and weight. Physical examinations will be performed at the Screening Visit and at Visits -3, -2, -1, TP1-EXT, EOS, 1, 3, 5, 7, 9, 11, 13, at all subsequent quarterly Study Visits, and at the Safety Follow-up Visit.

5.7.6. Electrocardiogram

A 12-lead Electrocardiogram (ECG) will be performed to evaluate potential study drug-induced QT prolongation potential at the Screening Visit, at all Study Visits, at the End of Study Visit, and at the Safety Follow-up Visit. At Visits 1 and 3, ECG will be performed 5 times: before administration of both Sodium Cridanimod and megestrol acetate, and at 15, 60, 120, and 360 (± 5) minutes after administration of Sodium Cridanimod. ECGs at all other visits will be performed only once, prior to administration of both Sodium Cridanimod and megestrol acetate.

For all ECGs performed after the first dose of Sodium Cridanimod, any clinically significant changes compared with the ECG recorded at the Screening Visit must be reported as an AE. All ECG intervals (QT, QTcB, QTcF, PR, QRS, and RR) will be reported in the eCRF.

5.7.7. Patient Diary

At all visits following the Screening Visit, the subject will be provided with Patient Diaries and asked to record their daily doses of megestrol acetate (including those taken in clinic during a study visit). In addition, subjects are to record any AEs and concomitant medications in the diary. Diaries will be completed by the subjects until they exit the study at the End of Study Visit or the Safety Follow-up Visit. Subjects will be instructed to return their completed diaries at each Study Visit and new diaries will be provided to the subject.

5.8. Optional Sub-Study Procedures

To address an important translational objective, subjects will have the ability to consent to participate in an optional sub-study. Participation in this sub-study is completely voluntary and will not affect the subject's ability to participate in the study. Participation in this study will undergo additional study procedures as outlined below.

5.8.1. Optional Pharmacokinetic (PK) Sub-Study

An important objective of this study is to investigate the possible pharmacokinetics of megestrol acetate when administered alone (Treatment Period 1), and the pharmacokinetic drug-drug interactions of Sodium Cridanimod and megestrol acetate when administered together (Treatment Period 2). To accomplish this objective, certain subjects will be enrolled to participate in an optional Pharmacokinetic Sub-Study.

For these subjects, additional blood samples will be taken as follows:

- Treatment Period 1: Study Visit -3, before administration of megestrol acetate, and 1, 2, 3, 4, 6, 24, 48, 72 and 96 hours (all times +/- 2 minutes) after administration. ***Subjects who are PrR negative will not participate in this portion of the PK Sub-Study.***
- Treatment Period 2: Study Visit 1, before administration of both Sodium Cridanimod and megestrol acetate and at 15, 30, 45, 60 and 90 minutes, 2, 3, 4 and 6 hours (all times +/- 2 minutes) after administration. Blood samples will additionally be taken on Days 3, 7, 10, 56 (Visit 3) and Day 84 (Visit 4) prior to the administration of both Sodium Cridanimod and megestrol acetate. Administration of the study drugs should be timed as close as possible on PK days, preferably within 5 minutes or less. Timing of the post dose PK blood sample collection should be based on the Sodium Cridanimod dose.

Blood samples will be analyzed in a central laboratory using standard analysis methods.

5.9. Adverse Events and Other Safety Aspects

5.9.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with treatment in Treatment Period 1, 2 through either the End of Study Visit or the Safety Follow-up Visit. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or

disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

For the purposes of this protocol, an AE is any undesirable sign(s), symptom(s) or worsening of pre-existing condition(s) occurring after the signing of the informed consent through the final study visit, even if the event is not considered to be related to the study drug. No AEs information will be collected following the End of Study Visit/Safety Follow-up Visit.

AEs do not include the following:

- The disease being studied, or the expected progression, signs or symptoms (including laboratory values) of the disease being studied, unless it is more severe than expected for the subject's condition. Disease progression or symptoms related to disease progression will not be considered AEs.
- Pre-existing disease or medical conditions that does not worsen from those reported at Screening.
- Hospitalizations for elective surgery unless the event meets other criteria as an SAE such as "prolonged hospitalization".
- Hospital admissions for social or convenience reasons where an AE does not occur.
- Medical or surgical procedures such as surgeries and transfusions. These are treatments for an AE resulting in the procedure. The underlying AE should be reported as the event, not the procedure.
- Elective treatment of a pre-existing disease or medical condition that did not worsen or result in AEs, e.g., hospitalization for chemotherapy for cancer.
- Overdose of either study drug or any concomitant medication without any signs or symptoms.

Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- is considered by the Investigator to be of clinical significance
- results in study withdrawal
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests

An AE is "unexpected" when the nature, severity, specificity, or outcome is not consistent with the term or description used in protocol related documents including the Investigator brochure, product labeling (e.g. Package Insert or Summary of Product Characteristics), protocol and IEC/IRB approved informed consent form. If an Investigator is uncertain whether an AE is expected or unexpected, the AE should be reported as unexpected.

The outcome of each AE should be assessed as follows:

- Fatal: Subject has died due to AE
- Not Recovered/Not Resolved: AE is ongoing
- Recovered/Resolved: AE is no longer present
- Recovered/Resolved with sequelae: AE has resolved but the subject retains a condition that is the consequence of the AE

- Recovered/Resolving: AE is in the process of recovering
- Unknown: Outcome of the AE is not known because the subject did not return for follow-up and attempts to obtain follow-up were unsuccessful

The Investigator will assess subjects for AEs at each study visit through the End of Study Visit/Safety Follow-up Visit. All AEs observed or reported after the subject has provided informed consent must be recorded in the source data and reported on the eCRF regardless of causal relationship. The nature of each AE, date of onset, outcome, severity, actions taken with respect to dosage, and relationship to study drug should be assessed and recorded. Any changes to study drug dosing or any medical treatment should be recorded in the source and appropriate eCRFs. AEs documented at a previous assessment as 'ongoing' should be reviewed at subsequent visits as necessary until resolved.

All related signs, symptoms, and abnormal diagnostic procedures results should be grouped as a diagnosis whenever possible. All AEs will be assessed for severity, seriousness and causality by the Investigator.

AEs that do not meet the criteria for expedited reporting will be documented in the eCRF and reported in the final clinical study report.

5.9.2. Definition of Serious Adverse Events

An SAE is defined as any untoward medical occurrence or effect that, at any dose:

- Results in death;
- Is life-threatening*;
- Requires hospitalization or prolongation of hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;
- Other medically important event

Medical judgment should be exercised in deciding whether an AE/reaction is serious in other situations. Important AEs/reactions that are not immediately life-threatening, or do not result in death or hospitalization but may jeopardize a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

** "Life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

5.9.3. Criteria for Causal Relationship

Table 14. The causality of each AE should be assessed using one of the following terms:

Causal Relationship* to the Study Drug	Criteria for Causal Relationship
Related	AE occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals.
Possibly Related	AE occurring with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals.
Unlikely Related	AE occurring with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Not Related	AE with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

**Definitions with basis in Clinical Data Acquisition Standards Harmonization (CDASH), ICH E2B.*

For data analysis and SAE reporting purposes, any AEs classified as 'unlikely related" will be regarded as 'not related' to study drug. AEs classified as 'possibly related" will be regarded as 'related' to the study drug.

5.9.4. Criteria for Defining the Severity of an Adverse Event

Table 15. The severity of all AEs should be graded according to the NCI-CTCAE Version 4:

Grade	Assessment Standard
1 – Mild	Does not hamper daily activities
2 – Moderate	Hampers daily activities
3 – Severe	Makes daily activities impossible
4 – Life-Threatening	Imminent risk of death
5 – Death	Death

5.9.5. Reporting of Serious Adverse Events (SAEs)

AEs meeting the criteria as an SAE must be reported to ProductLife Pharmacovigilance within 24 hours of becoming aware of its occurrence even if the SAE does not appear to be study drug-related. An SAE Form and any related eCRFs must also be completed by the Investigator and faxed or emailed to ProductLife Pharmacovigilance within 24 hours:

SAFETY REPORTING Contact: ProductLife Pharmacovigilance

- Email: safety@productlife-group.com
- Fax: 1-800-963-0353

Within the following 48 hours, the Investigator shall provide further any additional information regarding the SAE and a written narrative of the event. Follow-up including additional information,

complications or worsening of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the information. Any SAEs experienced up to 60 days after last administration of study drug should be reported if the Investigator suspects a causal relationship to the study drug. Deaths or congenital abnormalities brought to the attention of the Investigator at any time after administration of study drug and considered by the Investigator to be possibly related to study drug, should be reported to the Sponsor.

The Investigator must also notify the reviewing IEC/IRB in writing as soon as possible but no later than 72 hours of knowledge of an SAE. Documentation of IEC/IRB notification and receipt will be kept in the Investigator's study file.

Expedited regulatory reports will be submitted by Xenetic or designee to the regulatory authorities in accordance with specific country requirements.

5.9.6. Reporting of Deaths

The death of any subject during the study, regardless of the cause, must be reported within 24 hours of the Investigator or the study site personnel becoming aware of the occurrence.

Death cases are to be captured in the SAE and Mortality pages of the eCRF. If an autopsy is performed, the report must also be provided.

Depending on country specific requirements, death cases will be submitted to the appropriate Regulatory Authorities, as well as IEC/IRB(s), as applicable.

5.9.7. Procedure in Case of Pregnancy

If a subject becomes pregnant at any time during the trial, the subject must be withdrawn from the trial and Safety Follow-up procedures should be completed. The Investigator should report the pregnancy to ProductLife Pharmacovigilance within 24 hours of becoming aware of event.

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify ProductLife Pharmacovigilance.

At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for notification of SAEs.

6. TERMINATION OF THE CLINICAL STUDY

The Sponsor reserves the right to discontinue the study for safety, ethical or administrative reasons.

Any concerned regulatory authorities also have the authority to discontinue this trial.

All Investigators will be notified in writing, outlining the reasons for the discontinuation of the study at their site. Instructions will be provided if assessments beyond the regular per protocol procedures should be necessary.

If a study is prematurely terminated, the Sponsor will promptly inform the IEC/IRB and competent authorities of the termination and its reason(s).

7. STATISTICAL METHODOLOGY

7.1. Sample Size

The primary objective of the study is to evaluate the efficacy of the study drug by the frequency of subjects with overall disease control (including SD, PR, and CR).

The null hypothesis assumes an historical disease control rate of <5%, given that these subjects have already failed progestin therapy. A clinically significant difference is predefined as a 15% increase (i.e. disease control rate of 20%). Using the Fleming's single stage procedure (in which a predetermined number of patients is recruited to the study and a decision about activity is obtained from the number of responses (including SD, PR, or CR) amongst these patients) with the probabilities of type I and type II errors of 5% (one-sided) and 10%, respectively, approximately 40 subjects are planned to be enrolled to Treatment Period 2. It is estimated that approximately 20-25% of subjects will be classified as PrR negative and go directly into Treatment Period 2. This group will represent 14-16 of the Treatment Period 2 subjects. The rate of subjects who will have progressive disease following treatment with megestrol acetate in Treatment Period 1 and then move on to Treatment Period 2 is estimated at 55-60%. These subjects will represent 30-32 of the Treatment Period 2 subjects (estimating that approximately 24-25 subjects treated in Treatment Period 1 will not exhibit progressive disease and will not move into Treatment Period 2.) Estimating the rate of subjects who will be unavailable for disease assessment for various reasons at10-15%, it is planned to enroll 72 total subjects. An estimated 20% screen failure rate will require up to 90 screened patients to allow for enrollment of 72 subjects.

7.2. Analysis Sets

7.2.1. Safety Population

The Safety Population will consist of all subjects who receive at least one full or partial dose of study treatment (all treated subjects) in Treatment Period 2. This population will be used for all safety reporting. Safety data will be reported separately for subjects in Treatment Period 1 who do not go on to Treatment Period 2, and for those subjects in Treatment Period 1 who are treated in both periods.

7.2.2. Full Analysis Set (FAS)

The FAS will consist of all subjects treated in Period 2 who either undergo a CT or MRI scan with tumor assessment at Visit 4 (i.e. they have not discontinued treatment prior to Visit 4) or those who have discontinued Treatment Period 2 prior to Visit 4 solely due to documented disease progression. This population will be used for efficacy evaluation.

7.2.3. Per Protocol Set (PPS)

The Per Protocol Set will consist of all FAS subjects, excluding those for whom major protocol deviations have been identified. This population will be used for supportive analysis of the response rate and other efficacy parameters.

7.3. Demographics and Other Baseline Characteristics

A descriptive analysis approach will be used to analyze all demographic and baseline characteristics and will be presented using appropriate summary statistics (mean, standard deviation, median, minimum, maximum, range, quintiles, frequency and percentage for categorical variables with 95% confidence limits etc., when appropriate). The Safety Population will be used to present all demographic and baseline characteristics.

7.4. Analysis of Efficacy

The Full Analysis Set will be used for all efficacy analysis. The Per Protocol Set will be used for supportive analysis of all efficacy parameters.

7.4.1. Analysis of Primary Objective

The primary objective of this study is to evaluate the efficacy of the study drug by the frequency of subjects with overall disease control (including SD, PR, and CR).

The ODCR will be determined as the proportion of subjects who achieved SD, PR and CR during Treatment Period 2. The ODCR will be estimated and presented with the corresponding 95% confidence interval.

7.4.2. Analysis of Secondary and Translational Objectives

The secondary efficacy objective is to assess the ORR, PFS, duration of Stable Disease, and OS.

The Objective Response Rate (ORR) is defined as the proportion of subjects who achieved CR or PR during Treatment Period 2. The ORR will be estimated and presented with the corresponding 95% confidence interval.

Progression-free Survival (PFS) is defined as the duration of time from initiation of Treatment Period 2 (Day 0) until disease progression or death from any cause, whichever occurs first. For the purpose of analysis of PFS, subjects with an unknown response will be censored.

Duration of Stable Disease is defined as the duration of time from initiation of Treatment Period 2 (Day 0) until the criteria for disease progression are first met. For the purpose of analysis of Duration of SD, subjects who die before documented progressive disease will be censored.

Overall Survival (OS) is defined as the duration of time from initiation of Treatment Period 2 (Day 0) until the subject's death from any cause. For the purpose of analysis of OS, if a subject is alive at the date of last contact the subject will be censored at that date of contact.

OS, Duration of Stable Disease, and OS will be analyzed by the Kaplan-Meier method, and the Kaplan-Meier survival curves will be plotted.

7.5. Analysis of Safety

7.5.1. Adverse Events

AEs developed after informed consent and before administration of the study drug will be rendered as AEs occurred before the treatment. AEs developed after the first administration of the study drug will be rendered as AEs occurred during the treatment.

Information about AEs will be coded with the use of medical dictionary MedDRA in the current revision. The frequency of occurrence of AEs during the treatment will be calculated for each system organ class and each main diagnosis. The information will be presented as absolute number of subjects with AE and relative frequency. Summary data for the severity of AEs and their relationship with the study treatment will be presented for each system organ class and each main diagnosis.

Summary data about withdrawal of subjects from the study due to the development of AEs will be presented for each system organ class and each main diagnosis.

SAEs will be presented as listings and as summaries for each system organ class and each main diagnosis.

7.5.2. Clinical Laboratory Evaluations

Results of laboratory evaluations (hematology, serum chemistry, and urinalysis) will be presented as listings and summaries for each measurement point. Values of laboratory tests outside the normal range (i.e. abnormal values) will be determined based on each labs specification of normal ranges and will be indicated in listings. Shift tables for laboratory tests will contain information about change of distribution of values below, inside and outside of normal range from the screening period to the date of the End of Study Visit/Safety Follow-up Visit.

7.5.3. Physical Examination

Results of physical examinations will be presented for each measurement point.

7.5.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate and body temperature) will be presented as a listings and summaries for each measurement point. Statistical significance of changes relative to baseline values will be analyzed with applicable statistical methods.

7.5.5. Electrocardiogram

Results of ECG (“normal”, “with clinically non-significant deviations from normal”, and “with clinically significant deviations from normal”) will be presented as listings and as summaries for each measurement point.

ECG intervals (QT and QT intervals adjusted by an appropriate correction [QTcB and QTcF; Bazett and Fridericia], PR, QRS, and RR) will be summarized at each scheduled timepoint, along with mean change from baseline to each post treatment timepoint.

ECG intervals (QTcB and QTcF; Bazett and Fridericia) recorded at Visits 1 and 3 will be presented both as analyses of central tendency and categorical analyses.

7.5.6. Gynecologic Oncology Group (GOG)

Performance Status Results of GOG performance status assessment will be presented as listings and as summaries for each measurement point.

7.6. Analysis of Pharmacokinetics

For each subject, the following PK parameters after a single dose and multiple doses will be calculated, whenever possible, based on the plasma concentrations of Sodium Cridanimod and progestins, using non-compartmental methods:

Table 16. Pharmacokinetics Analysis Parameters

C_{max}	Maximum observed concentration.
t_{max}	Time to maximum concentration.
AUC0-t	Area under the concentration-time curve from time 0 to the time of the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.
$AUC_{0-\infty}$	Area under the concentration-time curve extrapolated to infinity, calculated using the formula: $$\mathbf{AUC0_{0-\infty} = AUC0\text{-}t + C_t/ \lambda_z}$$ where C_t is the last measurable concentration and λ_z is the apparent terminal elimination rate constant.
$t_{1/2}$	Apparent terminal elimination half-life (whenever possible), where $$\mathbf{t_{1/2} = (ln2)/ \lambda_z}$$
CL/F	Total clearance for extravascular administration
Vz/F	Volume of distribution based on the terminal phase

Other parameters may be calculated as appropriate. Obtained pharmacokinetics data will also be used as a part of data for population pharmacokinetics analysis, assessment of effect of body weight and body surface area on pharmacokinetics of study drug and evaluation the potential for a pharmacokinetic interaction between Sodium Cridanimod and progestins used in the study.

Pharmacokinetic analysis will use actual times as recorded on the eCRF.

7.7. Protocol Deviations

Any violations of the inclusion or exclusion criteria or subject compliance outside of the 80-120% acceptable range will be considered major protocol violations. These (and any other) protocol deviations will be clearly documented in the eCRF. Subjects for whom major protocol deviations were recorded will not be included in the Per Protocol Set.

7.8. Handling of Missing Data, Outliers, Visit Windows, and Other Information

7.8.1. Missing Data

Statistical analysis will be performed using available data only; missing values will not be imputed.

7.8.2. Visit Windows

Each Study Visit has an acceptable window for when it must occur (see Section 5.4). Any visit that falls outside of the acceptable window must be clearly documented as a protocol deviation. Data collected at such a visit may still be used for analysis of all safety and efficacy objectives, using the date for when the data was collected (as recorded in the eCRF).

8. OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1. Procedure for Clinical Study Quality Control

8.1.1. Clinical Study Monitoring

The study will be supervised by a monitor from the Sponsor or CRO. The study monitor will contact the Investigator regularly to discuss the progress of the study and to check the study documents including the informed consent forms for completeness and consistency.

It is understood that monitors, and any authorized personnel contracted to the Sponsor or CRO may contact and visit the Investigator, and that they will be allowed to inspect the various records of the study on request (eCRFs and other pertinent data), provided that subject confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

It is the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to regulatory requirements and ICH GCP guidelines.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

8.1.2. Source Data

Where source documents (such as laboratory reports, medical records, or ECG reports) or laboratory databases exist, all relevant data will be transcribed into the eCRF, transferred electronically to the study database, or entered into the study database directly from source documents. Where no source documents exist, data will be written directly into the eCRF

The Investigator/institution will permit study-related monitoring, audits/inspections, IEC/IRB review and regulatory inspections to directly access source documents.

8.1.3. Language

eCRFs will be developed in the English language for all subjects at all study sites. All recordings in the eCRF will be in English. Generic names for concomitant medications should be recorded in the eCRF wherever possible. All written material to be used by subjects must use vocabulary that is clearly understood and be in the language appropriate for the subjects participating at the study site.

8.1.4. Data Collection

All of the clinical data will be captured via a web-based electronic data capture (EDC) tool.

The Investigator site staff will enter and edit the data via a secure network with secure access features (i.e. username and password). A complete electronic audit trail will be maintained. The Investigator will approve the data using an electronic signature, and this approval is used to confirm the accuracy of the data recorded.

eCRFs will be used for all subjects. The Investigator's data will be accessible from the Investigator's site throughout the trial. The eCRFs must be kept current to reflect subject status at each phase during the course of the trial. A screening number will identify the subjects on the eCRF. The Investigator must make a separate confidential record of personalized details (name and initials) on the subject identification log. All changes to data are done by the Investigator through the EDC system. If a change is necessary once the Investigator has no further access to the database, a request for change will be sent to the Investigator for confirmation of the change.

It is the responsibility of the Principal Investigator of each site to ensure that all subject discontinuations or changes in study or other changes in subject health entered on the subject's eCRF are also documented on the subject's medical records.

The eCRFs for any subject leaving the study should be completed at the time of the final visit or shortly thereafter. Data reported in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

All laboratory reports (if applicable) will be reviewed, signed and dated by the Investigator.

8.1.5. Data Management

Data management will be coordinated by the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. eCRF correction process will be referenced in the eCRF instructions. Coding of medical terms will be performed using MedDRA.

The study database will be soft-locked when all data that are specified in the study protocol to be collected have been received and cleaned. It will be hard-locked when a data review meeting has been held, and all data related decisions have been made and reflected in the database.

8.1.6. Protocol Deviations

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator should not implement any deviation from, or changes of, the protocol without the agreement by the Sponsor and prior review and documented approval/favorable opinion of the IEC/IRB of an amendment, except where necessary to eliminate an immediate hazard to trial subjects. The Investigator must document all protocol deviations in the subject's source documents and applicable eCRFs or deviation forms. The process for reporting deviations will be communicated to the site by the Sponsor. For the purposes of this protocol, deviations requiring notification to Sponsor are defined as:

- Subject entered into the study even though they did not satisfy entry criteria.
- Subject who developed withdrawal criteria during the study and was not withdrawn.
- Subject who received an incorrect dose.

- Subject who received excluded concomitant treatment as noted

NOTE: Other deviations outside of the categories defined above that are required by the IEC/IRB in accordance with local requirements will be reported, as applicable.

8.1.7. End of Trial

The end of trial for all participating countries is defined as the date of the last subject's last visit or date of last follow-up contact, whichever is later.

8.2. Ethics and Protection of Subject Confidentiality

8.2.1. Independent Ethics Committee / Institutional Review Board (IRB) / Competent Authorities (CA)

The trial will be conducted under the auspices of an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) as required by the local regulations, ICH GCP and in accordance with ethical principles. The Investigator will ensure the IEC/IRB is appropriately constituted according to regulatory requirements and ICH GCP. Prior to the initiation of the trial, the Investigator will ensure the protocol. Informed consent form, investigator Brochure, Investigators qualifications, any advertisement and if applicable, any other subject related documents are provided to the IEC/IRB for review and approval. Before initiating the trial, the Investigator must receive written and dated full approval from the IEC/IRB responsible for the trial. The Sponsor may not provide IMP or authorize the initiation of the trial activities until this approval is received.

During the course of the trial, the Investigator will ensure any amendments to the protocol, revised consent forms, updates to the Investigator Brochures, suspected unexpected serious adverse reactions (SUSARs) are provided to the IEC/IRB for their review and approval. The Investigator will also promptly notify the IEC/IRB of any unanticipated problems involving risks to human subject or others, and any protocol deviations, to eliminate the immediate hazards to subjects. The Investigator will not make any change in the trial or trial conduct without the IEC/IRB approval except where necessary to eliminate the apparent immediate hazards to subjects. In the event this occurs, the IEC/IRB and Xenetic must be notified of the changes as soon as possible.

The Investigator is responsible for submitting period progress reports as required to the IEC/IRB but not less than once per year. At the end of the study, the Investigator must provide a final report and notify the IEC/IRB of the study completion.

8.2.2. Ethical Conduct of the Study

This protocol will be conducted according the US code of Federal Regulations, ICH E6 GCP, and ethical principles that have their origins in the Declaration of Helsinki.

8.2.3. Informed Consent of Subjects

Subject written informed consent will be obtained in accordance with local regulations, ICH GCP requirements and ethical principles that have their origin in the Declaration of Helsinki. Prior to obtaining consent, information should be provided by the Investigator or designee in the language and level understandable to the subject. The purpose, procedures, anticipated benefits, and potential hazards of the study should be included in the consent discussion and the

subject should be allowed ample time to ask questions. Prior to any study procedure, the Informed Consent Form must be signed and personally dated by both the subject (or subject's legal representative if applicable) and the person obtaining the consent. The person obtaining consent must be the Investigator or his/her designee who is also medically qualified. The subject will be provided a copy of the signed and dated consent form. The original signed and dated consent form must be retained in the Investigator's files. The consent form should be updated for any new information that is relevant to the subject. The subject should sign the revised consent form.

8.2.4. Subject Confidentiality

It is the Investigator's responsibility to inform the subject General Practitioner/Primary Care Physician (where applicable) by letter that the subject is taking part in the study provided the subject agrees to this, and information to this effect is included in the Informed Consent form. A copy of the letter should be filed in the Investigator Site File.

The investigators will make every effort to keep samples and data confidential at all times. However, absolute confidentiality cannot be guaranteed. There is a slight risk of breach of confidentiality, which could be embarrassing or stigmatizing.

8.2.5. Financial Disclosure of Investigators

According to US regulations 21 CFR Part 54, the Sponsor will obtain a financial disclosure form from the Investigator(s) and sub-Investigator(s) to whom the Investigator delegates significant study-related responsibilities (i.e., individuals listed in Form FDA 1572).

8.3. Administrative Matters

8.3.1. Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical Investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

The Sponsor intends to publish the results of the study as a whole once all subjects have completed the study and the results have been analyzed. The Investigator may not publish the results of their cohort of subjects until the fully study has been accepted for publication. The Investigator may not submit for publication or present the results of this study without allowing the Sponsor 30 days in which to review and comment on the pre-publication manuscript or

content. The Investigator may not submit the results of the study for publication with the prior, written consent of the Sponsor.

8.3.2. Regulatory Authority Approval

The Sponsor is responsible for all regulatory aspects of the trial with regard to regulatory submissions.

8.3.3. Protocol Amendment and/or Revision

Any changes to the study which arise after approval of the protocol must be documented as protocol amendments/substantial amendments and/or administrative changes/non-substantial amendments. Depending on the nature of the amendment, either IEC/IRB approval or notification is required. The changes will become effective only after the approval of the Sponsor, the Investigator, the regulatory authority, and the IEC/IRB (if applicable).

Amendments to this protocol must be agreed upon in writing between the Investigator and the Sponsor. Written verification of IEC/IRB approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IEC/IRB approval, but will be submitted to the IEC/IRB for their information.

If there are changes to the Informed Consent, written verification of IEC/IRB approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4. Study Documentation and Storage

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the Sponsor and representatives of appropriate Regulatory Authorities.

The Investigator must retain essential documents until notified by the Sponsor, and at least for five years after study completion, as per Directive 2005/28/EC Article 17. Subject files and other source data (including copies of protocols, eCRFs, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

8.3.5. Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and European Agency for the Evaluation of Medicinal Products (EMEA) Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the coordinating Investigator(s) or the (principal) Investigator(s). The representative for the principal Investigator will have the

responsibility to review the final study results to confirm to the best of his/her knowledge that it accurately describes the conduct and results of the study.

9. QUALITY ASSURANCE

Quality control (QC) will be performed according to Sponsor or CRO internal procedures. The study will be audited by a quality assurance (QA) representative of the Sponsor or authorized personnel contracted to Sponsor. All necessary data and documents will be made available for inspection.

10. STUDY ORGANIZATION

10.1. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be used to evaluate safety as needed during the trial and to review results of interim efficacy and safety analyses. The DSMB will consist of at least 2 clinicians (who are not Investigators for this trial) and 1 biostatistician with expertise in oncology trials. The DSMB will make recommendations to the Sponsor regarding the conduct of the study, including possible early discontinuation of the study for excessive toxicity or extreme efficacy. A separate DSMB Charter document will specify the procedures governing the conduct of the DSMB. Qualified individuals not affiliated with the Sponsor, including a statistician, will be responsible for preparing reports for the DSMB.

11. REFERENCES

1. Colombo et al., 2011; lataniotis and Catiglione, 2010.

2. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol. 1999;17(6):1736-1744.

3. Miyake T, Ueda Y, Egawa-Takata T, et al. Recurrent endometrial carcinoma: prognosis for patients with recurrence within 6 to 12 months is worse relative to those relapsing at 12 months or later. Am J Obstet Gynecol. 2011;204(6):535.e1-e5. doi:10.1016/j.ajog.2011.02.034.

4. Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 1996;14(2):357-361.

5. Pandya KJ, Yeap BY, Weiner LM, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). Am J Clin Oncol. 2001;24(1):43-46.

6. Taylor JL, Schoenherr CK, Grossberg SE. High-yield interferon induction by 10-carboxymethyl-9-acridanone in mice and hamsters. Antimicrob Agents Chemother. 1980;18(1):20-26.

7. Kramer MJ, Cleeland R, Grunberg E. Antiviral activity of 10-carboxymethyl-9-acridanone. Antimicrob Agents Chemother. 1976;9(2):233-238.

8. Surkov KG, Tsyrlina EV, Konstantinova MM, Bersteĭn LM. [Neovir, an interferon inductor, modifies expression of steroid hormone receptors in hormone-dependent tissues and restores sensitivity to tamoxifen in patients with inoperable breast cancer]. Vopr Onkol. 1996;42(6):28-32.

9. Megestrol Acetate Tablets, USP, Rx only, PAR PHARMACEUTICAL, Chestnut Ridge, NY 10977 Revised: 04/16.

10. Xylocaine (lidocaine HCl Injection, USP), Rx only, APP Pharmaceuticals, LLC, Schaumburg, IL 60173, 451175A, Revised: Feb 2010. Clinical sites are to provide the 2% lidocaine HCL so manufacturer may vary. Package insert information from the manufacturer APP Pharmaceuticals is provided for reference.

11. Whitney CW, Brunetto VL, Zaino RJ, et al. Phase 2 study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(1):4-9.

12. Yang S, Jia Y, Liu X, et al. Systematic dissection of the mechanisms underlying progesterone receptor downregulation in endometrial cancer. Oncotarget. 2014;5(20):9783-9797.

13. Tavassoli, FA., Devilee, P. (Eds) World Health Organization Classification of Tumours , International Agency for Research on Cancer (IARC) Pathology and Genetics of Tumours of the Breast and Female Genital Organs

14. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-612.

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

E.A. Eisenhauer[a,], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]*

[a]*National Cancer Institute of Canada – Clinical Trials Group, 10 Stuart Street, Queen's University, Kingston, ON, Canada*
[b]*GlaxoSmithKline Biologicals, Rixensart, Belgium*
[c]*European Organisation for Research and Treatment of Cancer, Data Centre, Brussels, Belgium*
[d]*Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[e]*Mayo Clinic, Rochester, MN, USA*
[f]*RadPharm, Princeton, NJ, USA*
[g]*Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA*
[h]*Schering-Plough, Kenilworth, NJ, USA*
[i]*East Surrey Hospital, Redhill, Surrey, UK*
[j]*National Cancer Research Network, Leeds, UK*
[k]*Erasmus University Medical Center, Rotterdam, The Netherlands*

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ABSTRACT

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

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

* *Corresponding author:* Tel.: +1 613 533 6430; fax: +1 613 533 2411.
E-mail address: eeisenhauer@ctg.queensu.ca (E.A. Eisenhauer).
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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progression' of non-measurable/non-target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG-PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assessment of lesions.

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

1. Background

1.1. History of RECIST criteria

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

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

1.2. Why update RECIST?

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

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

1.3. *Process of RECIST 1.1 development*

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

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

1.4. *What about volumetric or functional assessment?*

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

2. Purpose of this guideline

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

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

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

3. Measurability of tumour at baseline

3.1. *Definitions*

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

3.1.1. *Measurable*

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

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

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

3.1.2. *Non-measurable*

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

3.1.3. *Special considerations regarding lesion measurability*

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

Bone lesions:.

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

Cystic lesions:.

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

Lesions with prior local treatment:

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

3.2. *Specifications by methods of measurements*

3.2.1. *Measurement of lesions*

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

3.2.2. *Method of assessment*

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

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

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

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

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

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

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

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

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

4. Tumour response evaluation

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

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

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

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

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

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

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

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

4.3. *Response criteria*

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

4.3.1. *Evaluation of target lesions*

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

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

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

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

4.3.2. Special notes on the assessment of target lesions

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

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

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

4.3.3. Evaluation of non-target lesions

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

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

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

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

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

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

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

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

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

4.3.5. *New lesions*

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

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

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

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

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

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

4.4. *Evaluation of best overall response*

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

4.4.1. *Time point response*

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

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

4.4.2. *Missing assessments and inevaluable designation*

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

4.4.3. *Best overall response: all time points*

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

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

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

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

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

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

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

4.4.4. *Special notes on response assessment*

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

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

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

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

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

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

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

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

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

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

4.5. *Frequency of tumour re-evaluation*

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

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

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

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

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

4.6.2. *Duration of overall response*

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

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

4.6.3. *Duration of stable disease*

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

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

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

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

4.7.1. *Phase II trials*

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

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

4.7.2. *Phase III trials*

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

4.8. *Independent review of response and progression*

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

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

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

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

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

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

4.9.2. *Phase III trials*

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

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

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

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

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

APPENDIX 1
Xenetic Biosciences Protocol No. VX-EC-2-02

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

Conflict of interest statement

None declared.

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Appendix II. Specifications for standard anatomical radiological imaging

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

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

Specific notes

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

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

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

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

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

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

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

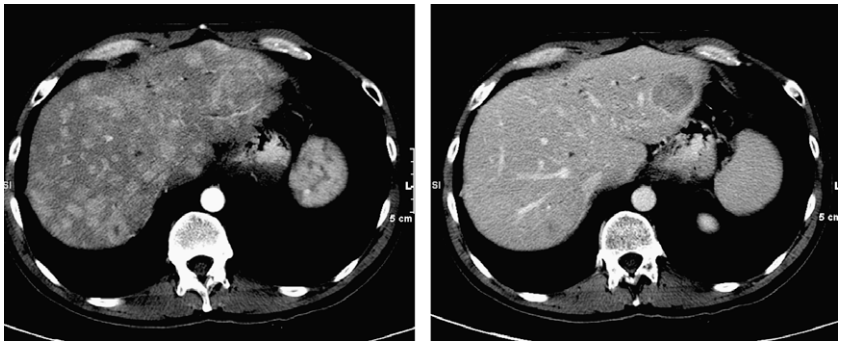

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration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

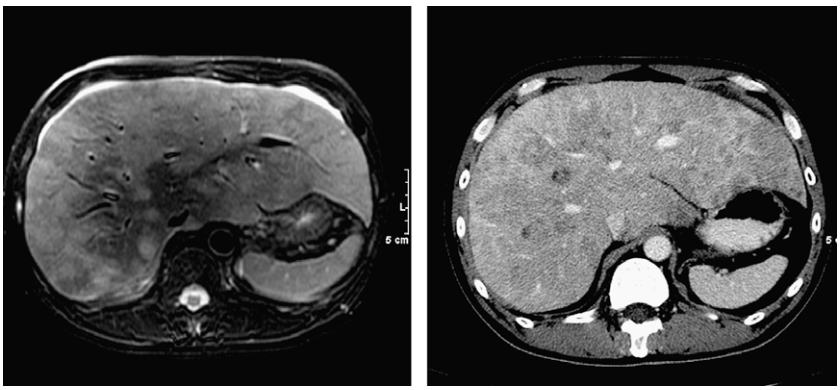

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

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

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

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

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

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

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

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

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

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

Measurement of lesions

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

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

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

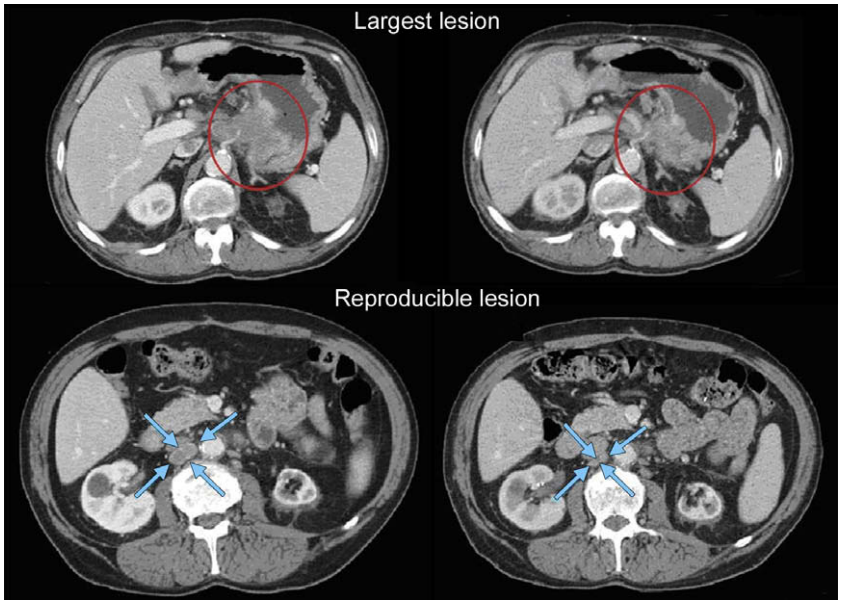

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention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

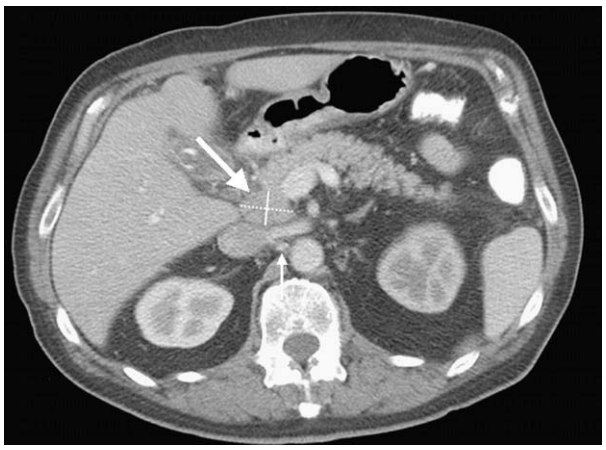

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

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

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

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

Progression of non-target lesions

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

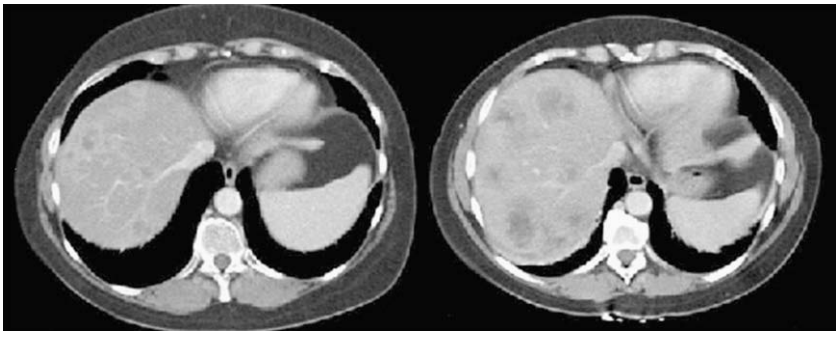

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

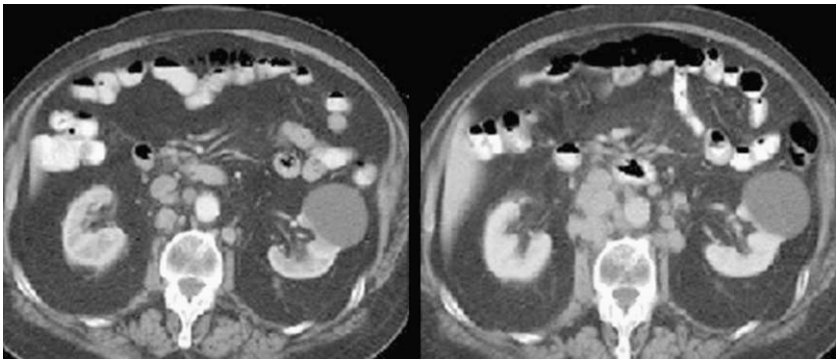

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

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

(*continued on next page*)

Appendix III – *continued*

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

REFERENCES

1. Paesmans M, Sculier JP, Libert P, et al. Response to chemotherapy has predictive value for further survival of patients with advanced non-small cell lung cancer: 10 years experience of the European Lung Cancer Working Party. *Eur J Cancer* 1997;**33**:2326–32.
2. Buyse M, Thirion P, Carlson RW, et al. Relation between tumor response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Meta-analysis group in Cancer. *Lancet* 2000;**356**:373–8.
3. Goffin J, Baral S, Tu D, et al. Objective responses in patients with malignant melanoma or renal cell cancer in early clinical studies do not predict regulatory approval. *Clin Cancer Res* 2005;**15**:5928–34.
4. El-Maraghi RH, Eisenhauer EA. Review of phase II trial designs used in studies of molecular targeted agents: outcomes and predictors of success in phase III. *J Clin Oncol* 2008;**10**:1346–54.
5. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;**47**:207–14.
6. Tonkin K, Tritchler D, Tannock I. Criteria of tumor response used in clinical trials of chemotherapy. *J Clin Oncol* 1985;**3**:870–5.
7. Baar J, Tannock I. Analyzing the same data in two ways: a demonstration model to illustrate the reporting and misreporting of clinical trials. *J Clin Oncol* 1989;**7**:969–78.
8. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). *J Natl Cancer Inst* 2000;**92**:205–16.
9. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 2006;**42**:1031–9.
10. Bogaerts J, Ford R, Sargent D, et al. Individual patient data analysis to assess modifications to the RECIST criteria. *Eur J Cancer* 2009;**45**:248–60.
11. Moskowitz CS, Jia X, Schwartz LH, Gönen M. A simulation study to evaluate the impact of the number of lesions measured on response assessment. *Eur J Cancer* 2009;**45**:300–10.
12. Sargent D, Rubinstein L, Schwartz L, et al. Validation of novel imaging methodologies for use as cancer clinical trials end-points. *Eur J Cancer* 2009;**45**:290–9.

13. Macdonald DR, Cascino TL, Schold Jr SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;**8**:1277–80.
14. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007;**10**:579–86.
15. Schwartz LH, Bogaerts J, Ford R, et al. Evaluation of lymph nodes with RECIST 1.1. *Eur J Cancer* 2009;**45**:261–7.
16. Rustin GJ, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst* 2004;**96**:487–8.
17. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999;**17**:3461–7.
18. Scher H, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol* 2008;**26**:1148–59.
19. Vergote I, Rustin GJ, Eisenhauer EA, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. *J Natl Cancer Inst* 2000;**92**:1534–5.
20. Van Glabbeke M, Verweij J, Judson I, Nielsen OS. EORTC Soft Tissue and Bone Sarcoma Group: Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. *Eur J Cancer* 2002;**38**:543–9.
21. Dancey JE, Dodd LE, Ford R, et al. Recommendations for the assessment of progression in randomised cancer treatment trials. *Eur J Cancer* 2009;**45**:281–9.
22. Ford R, Schwartz L, Dancey J, et al. Lessons learned from independent central review. *Eur J Cancer* 2009;**45**: 268–74.
23. Catalano C, Francone M, Ascarelli A, Mangia M, Iacucci I, Passariello R. Optimizing radiation dose and image quality. *Eur Radiol* 2007;**17**(Suppl 6):F26–32.
24. Low RN. Abdominal MRI advances in the detection of liver tumours and characterization. *Lancet Oncol* 2007;**8**(6):525–35.
25. Barrett T, Choyke PL, Kobayashi H. Imaging of the lymphatic system: new horizons. *Contrast Media Mol Imaging* 2006;**1**(6):230–45.
26. Shankar LK, Hoffman JM, Bacharach S, et al. National Cancer Institute. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med* 2006;**47**(6):1059–66.