Seymour et al: Supplementary Appendix to: iRECIST: Guidelines for response for use in trials testing immunotherapeutics

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***Table* S1: Participants/reviewers in the development of this guideline**

Scenario A						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	125	125	125	-	-
NT lesions	PRES	UC	UC	UNE	-	-
New lesions	-	ABS	ABS	ABS	-	-
TP response (R)	-	PD	PD	PD	-	-
TP response (iR)	-	iUPD	iUPD	iCPD	-	-
RECIST 1.1 has PD at TP1. iRECIST has iUPD at TP1, iCPD at TP3 and iBOR of iCPD. iPD date=TP1. iCPD is based on NEW RECIST 1.1 PD in NT disease. Follow up past iCPD is recommended at TP4 and TP5 unless other systemic or local treatment started.						

Scenario B						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	125	50	50	50	120
NT lesions	PRES	UC	UC	UC	UC	UC
New lesions		+	UC	UC	++	+*
TP response (R)		PD	PD	PD	PD	PD
TP response (iR)		iUPD	iPR**	iPR**	iUPD	iCPD
* some NLs resolve. ** iPR despite non-resolution of new lesions detected at TP2. RECIST 1.1 has PD at TP1. iRECIST has iUPD at TP1 and TP4, iCPD at TP5 and iBOR of iPR. iCPD is based on RECIST 1.1 defined PD in T disease. iPD date = TP4						

Scenario C						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	125	130	-	-	-
NT lesions	PRES	UC	UC	-	-	-
New lesions		ABS	ABS	-	-	-
TP response (R)		PD	PD	-	-	-
TP response (iR)		iUPD	iCPD	-	-	-
RECIST 1.1 has PD at TP1. iRECIST has iUPD at TP1, iCPD at TP2 and iBOR of iCPD. iUPD is based on RECIST 1.1 PD in T lesions and confirmed by a 5 mm increase in SOM. iPD date =TP1						

Scenario D						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	50	50	75	50	50
NT lesions	PRES	UC	UC	UC	UC	UC
New lesions		ABS	ABS	+	ABS	ABS
TP response (R)		PR	PR	PD	PD	PD
TP response (iR)		iPR	iPR	iUPD	iPR	iPR
RECIST 1.1 has PD at TP3. iRECIST has iUPD at TP3 and iBOR of iPR. iUPD is based on NLs (NLT or NLNT) which subsequently resolve. iPD date = not occurred						

Scenario E						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	50	50	75	NE	NE
NT lesions	PRES	UC	UC	UC	NE	NE
New lesions		ABS	ABS	+	NE	NE
TP response (R)		PR	PR	PD	NE	NE
TP response (iR)		iPR	iPR	iUPD	NE	NE
RECIST 1.1 has PD at TP3 and BOR of PR. iRECIST has iUPD at TP3 and iBOR of iPR. iUPD is based on RECIST 1.1 increase in T lesions as well as NL. iPD date = TP3 as defaults to last assessment when not re-evaluated. CRF should collect reason why not reassessed.						

Scenario F						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	50	50	50	NE	NE
NT lesions	PRES	UC	UC	UC	NE	NE
New lesions		ABS	+	UC	NE	NE
TP response (R)		PR	PD	PD	NE	NE
TP response (iR)		iPR	iUPD	iUPD	NE	NE
RECIST 1.1 has PD at TP2 and BOR of PR. iRECIST has iUPD (based on new lesions) at TP2 and iBOR of iPR. iPD date = TP2 even though never confirmed; CRF should collect reason why not reassessed.						

***Table S2*: Response scenarios**

PRES = present; TP = time-point; R = RECIST 1.1; iR = iRECIST; TPR = response at that time-point; BOR = best overall response; UNE = unequivocal increase in NT; NT = non-target, T = target; UC = unchanged; INC = increase but not meeting definition of unequivocal increase in NT; NL = new lesions; iUPD = unconfirmed immune PD; iCPD = confirmed immune PD; + = 1 or more NL; ++ = additional NL or increase in NL size; PD date = date used for RECIST 1.1 survival analyses; iPD date = date of PD to be used for exploratory iRECIST analyses; NE = not evaluable/evaluated; ABS = absent; SOM = sum of measures. iCR – immune complete response; iPR – immune partial response; iSD – immune stable disease

Appendix 1: Protocol criteria for measurement of study endpoint

1 Definitions

1.1 Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

1.2 Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below..

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria.

See section X for criteria for continuing treatment past RECIST 1.1 disease progression.

2 RECIST 1.1 Response and Evaluation Endpoints

2.1 *Measurable Disease*. Measurable tumour lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). *Malignant lymph nodes* must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

2.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

2.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥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 (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be

present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

2.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

2.5 *Response*.

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases[4] before CR can be accepted. Confirmation of response is only required in non-randomised studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomised studies.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category also Requires**
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				

No Target	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: 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". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see table 2.

***Table* S2: Integration of target, non-target and new lesions into response assessment**

3 iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

3.1 Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumour burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

3.2 New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified

Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on ○ increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

***Table* S3: Time-point (TP) iResponse**

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomised study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

***Table S*4:iRECIST Best Overall Response (iBOR)**

5 Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

6 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). 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. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

6.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm 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 recommended. If feasible, imaging is preferred.

6.2 *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 ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

6.3 *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. 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). Other specialized imaging or other techniques may also be appropriate for individual case.[4] For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

6.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

6.5 *Endoscopy, Laparoscopy*. The utilization 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.

6.6 *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 normalize for a patient to be considered in complete response.

6.7 *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 when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease

Appendix 2. Sample RECIST 1.1 and i-RECIST CRFs

Baseline

TARGET LESIONS AT BASELINE – QUESTION
Does the patient have any target lesions? ○ Yes ○ No Measurable *tumour lesions* must be measurable in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest x-ray, and as ≥10 mm with CT scan or clinical examination (calipers must be used). Bone lesions are measurable only if soft tissue components as assessed by CT scan meet these requirements. *Malignant lymph nodes* must be ≥15 mm in the short axis to be measurable (short axis to be measured / followed). Record in millimetres (or decimal fractions of centimetres). Identify a maximum of 5 measurable lesions (maximum of 2 lesions per organ) as **target lesions**: select based on size, representation of all involved organs and *reproducibility for repeated measurements.* Note: Lymph nodes are considered an organ, and no more than two should be recorded.

NON-TARGET LESIONS AT BASELINE QUESTION
Does the patient have any non-target lesions? ○ Yes ○ No **Non-target lesions** include **all** OTHER lesions (measurable lesions not selected as target and non-measurable lesions). Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin, abdominal masses followed by clinical examination and pathological nodes whose short axis is ≥10 mm but <15 mm are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

TARGET LESIONS AT BASELINE

Note: All target lesions listed at baseline must appear on each subsequent report in the same order and must be assessed using the same techniques as at baseline.

For Site of Disease please be sure to select the affected organ for each target lesion. For example: 'Lymph node' should be selected for site of disease instead of 'mediastinum'. 'Liver' should be selected instead of 'abdomen'.

Site of disease (e.g. lung) *(Drop down)*	Site (detailed description) (e.g. left upper lobe)	Radiation given before protocol treatment started? *(Y/N Drop-down)*	Test *(Drop down)*	Specify *(if Test=other)*	Date of Test	Baseline Measurements(?) *(mm)*
		O Yes O No				mm
		O Yes O No				mm
		O Yes O No				mm
		O Yes O No				mm
		O Yes O No				mm
			Sum of measurements *[calculated field]*			

(?) Please submit copies of source documents (radiology reports, clinic notes, tumour measurement worksheets) to confirm tumour measurements recorded.

NON-TARGET LESIONS AT BASELINE

Note: All non-target lesions listed at baseline must appear on each subsequent report in the same order and must be assessed using the same techniques as at baseline. Multiple lesions in the same organ may be recorded as a single lesion (e.g. multiple bone metastases).
For Site of Disease please be sure to select the affected organ for each non-target lesion. For example: 'Lymph node' should be selected for site of disease instead of 'mediastinum'. 'Liver' should be selected instead of 'abdomen'.

Site of disease (e.g. liver) *(Drop down)*	Site (detailed description) (e.g. multiple other liver metastases)	Radiation given before protocol treatment started? *(Y/N Drop-down)*	Test *(Drop down)*	Specify *(it Test=other)*	Date of Test

If a paper CRF, add in additional rows up to 20.

Time Point Response for RECIST 1.1 and iRECIST

RESPONSE ASSESSMENT - QUESTION
Required <u>every xx weeks</u> (± 1 week) from date of randomisation. Maintain schedule even if cycles are delayed. Was disease assessed this reporting period? O Yes O No If no, reason disease was not assessed: _____ Specify: _____ Note: If PD, load and complete the Relapse/Progression Folder.

NEW LESIONS (iRECIST) – QUESTION
Have any **<u>new</u>** malignant lesions been identified since baseline (i.e. in a previous or current reporting period)? O Yes O No Note: Please complete the New Lesions iRECIST form.

TARGET LESIONS (RECIST1.1)

Tumour measurements reported here must be from the end of this **reporting period**. All target lesions listed at baseline must appear on each subsequent report in the same order and must be assessed using the same techniques as at baseline.

- NEW malignant lesions must be entered on the New Lesions form.
- Use the longest diameter for tumour lesions; malignant nodes must be measured in the short axis.
- If a target lesion is present, but too small to measure, enter default measurement as "5 mm"; if a target lesion is considered absent, enter measurement as "0 mm".
- Lymph nodes recorded on the Baseline Target lesions table, should continue to be entered in this table even if they shrink to less than 10 mm in their short axis.
- If two target lesions coalesce (join together), pick one to follow and select 'coalesced' in the 'Reason Measurement Not Provided' field to document the other lesion. Please identify which lesions have joined in the 'Comments' field.
- If a target lesion splits, add the measurements for the two or more lesions/nodes and document the sum in the measurement field for the original lesion. In the 'Comments' field indicate that the lesion has split.

Site of disease **(e.g. lung)**	**Site (detailed description)** **(e.g. left upper lobe)**	**Radiation given since last response assessment**	**Test** ***(Drop down)***	**Specify** ***(it Test=other)***	**Date of Test**	**End of Reporting Period Measurements (?-3)**	**Reason Measurement Not Provided** ***(Drop down)***	**Comments**
		O Yes O No				mm	– *Not assessed* – *Obscured, cannot be evaluated* – *Coalesced*	
		O Yes O No				mm	– *Not assessed* – *Obscured, cannot be evaluated* – *Coalesced*	
		O Yes O No				mm	– *Not assessed* – *Obscured, cannot be evaluated* – *Coalesced*	
		O Yes O No				mm	– *Not assessed* – *Obscured, cannot be evaluated* – *Coalesced*	

		O Yes O No				mm	– *Not assessed* – *Obscured, cannot be evaluated* – *Coalesced*	
			Sum of measurements *[calculated field**]* mm					
Site of disease must match baseline report ; If radiation was given during protocol treatment, irradiated site should not be included in the disease assessment.; Please submit copies of source documents (radiology reports, clinic notes, tumour measurement worksheets) to confirm tumour measurements recorded.								

NON- TARGET LESIONS

Non-target lesions reported here must be from the end of this **reporting period**. All non-target lesions listed at baseline must appear on each subsequent report in the same order and must be assessed using the same techniques as at baseline.

Note: NEW lesions must be entered on the New Lesions – Table

Site of disease (e.g. liver) *(Drop down)*	**Site (detailed description)** **(e.g. multiple other liver metastases)**	**Radiation given since last response assessment?** *(Y/N)*	**Test** *(Drop down)*	**Specify** *(it Test=other)*	**Date of Test**	**End of Reporting Period Non-Target Lesion Status** *(Drop down**)*
		O Yes O No				*- Absent* *- Present* *- Increase* *- Unequivocal increase* *- Not Assessed* *- Obscured, cannot be evaluated*

If a paper CRF, add in additional rows up to 20.

NEW LESIONS – RECIST1.1 and iRECIST

Please record all new sites of disease. Follow RECIST 1.1 rules for defining measurable and non-measurable lesions recording a maximum of 5 measurable lesions (max. 2 per organ) and **all** OTHER lesions (measurable lesions not selected as target and non-measurable lesions).

Note: iUPD, including the appearance of new lesions must be confirmed at least 4 weeks (but no more than 8 weeks) after first documentation. New lesions reported in previous reporting period(s) should be entered here again and marked as "Previously Reported" in the table below.

New lesions which have not been previously reported must be entered here. If the new lesion was identified in a previous reporting period, but was not reported, please correct in the Folder for THAT reporting period.

Site of disease (e.g. liver)	**Site (detailed description)** **(e.g. right lobe)**	**Test (this reporting period)** ***(Drop down)***	**Specify** ***(it Test=other)***	**Date of Test (this reporting period)**	**Lesion Type**	**Measurement (mm)**	**Previously Reported?** ***(Y/N)***
					Target Non-target		
					Target Non-target		
					Target Non-target		
					Target Non-target		
					Target Non-target		
			Sum of measurements: *[calculated field**]*			mm	

Investigator Response Assessment – iRECIST
Response this reporting period: □ Patient has stable or responding disease and continues on treatment. □ Patient has unconfirmed disease progression (iUPD) as per iRECIST BUT is clinically stable AND patient will continue on treatment until the next assessment. □ Patient has unconfirmed progression (iUPD) as per iRECIST AND is not clinically stable; protocol treatment will be discontinued. o No further treatment is planned o Further systemic treatment or radiation is planned □ Patient has confirmed progression (iCPD) by iRECIST AND protocol treatment will be discontinued Note: Do not record the date of progression in the iRECIST Relapse/Progression folder until progression has been confirmed. When confirmed, the date of progression to be used is the iUPD date providing confirmed by iCPD at the next assessment. Consult protocol / CCTG for other scenarios.

Best Overall Response

BEST OBJECTIVE RESPONSE – RECIST 1.1

What was the patient's best RECIST 1.1 response to protocol treatment? (CR, PR, SD, PD, inevaluable)

If CR, PR, the following field must be entered:
Date Response first documented: _____

If PD, the following field must be entered (can be entered for other values too)
Date of relapse/progression _____

If IN, the following field must be entered:
Reason inevaluable: *drop down*

If Other, the following field must be entered:
Specify _____

Comments: _____

BEST OBJECTIVE RESPONSE – iRECIST

Best objective response (iRECIST) to protocol therapy _____
(iCR, iPR, iSD, iUPD, iCPD, inevaluable)

If iCR or iPR, date response first documented: _____

If iUPD, date first documented: ____
Reason not confirmed:
Specify: _____

If iCPD, date progression first documented: _____

Reason inevaluable: _____
Specify: _____