Assigning response after the appearance of new lesion/s: must the new lesion/s resolve completely before an iPR or iCR can be assigned?

A number of questions have been received regarding the impact of new lesions on subsequent i-response assignment. The key principle is that the 'new lesion' may have resulted from immune infiltration rather than tumour growth. Therefore the continued presence of a 'new lesion', providing it does not increase further in size (using the 5mm rule), does not preclude subsequent cycles being assigned iSD, iPR or iCR*. This is demonstrated in *supplementary materials*.

- In scenario B
- In scenario D, there is iUPD after PR/iPR, with a 20% increase in target SOM, plus a new lesion; at the next assessment the target lesion SOM no longer meets the criteria for PD and has shrunk sufficiently to qualify for iPR (from baseline) and the new lesion disappears - note that this would be iPR even if the new lesion remained visible as long as not had not increased (by 5mm or more for target NLs or any increase if non target).
- In scenario F, PR/iPR criteria are met at TP1, but at TP2 a new lesion develops, which remains unchanged at the next assessment. TP3 therefore remains iUPD as iCPD cannot be confirmed; it is not iPR as no further change in target SOM has occurred from TP1.

* Note: ideally iCR should not be assigned until the residual new lesion has been confirmed to be non-malignant pathologically or with functional imaging.

If iUPD is driven by non-target disease, how is progression confirmed at the next assessment?

Per RECIST 1.1, in exceptional circumstances, unequivocal progression in non-target disease may result in RECIST 1.1 PD / iRECIST iUPD. Any increase in non-target tumour burden at the next assessment would allow iCPD to be confirmed; the increase does NOT have to be unequivocal (per RECIST 1.1) again.

The same is true for new lesions. A new lesion results in iUPD; if the new lesions are non-target, any increase in size at the next assessment allows iCPD to be assigned- the increase does not need to be unequivocal as defined by a RECIST 1.1

Lesions designated as non-target disease should be categorised on the case record form as for example

- no change from baseline or nadir (NC)
- increased from baseline or nadir (INC)
- no change from last assessment (NCLA)
- further increase from last assessment (INCLA)
- unequivocal increase (UNE)

Assessments with NC, UNE, NCLA can then be differentiated in the database from NC, UNE, INCLA with the former being iUPD/iUPD and the latter iUPD/iCPD

'New' progression in other disease categories such as target disease, or another new lesion can of course also confirm progression.

If iUPD is driven by target disease, how is progression confirmed at the next assessment?

Progression can be confirmed by a 5mm or more increase* in the SOM of target lesions as follows

- if the iUPD was assigned based on RECIST 1.1 defined increase in target SOM (from baseline or nadir) then a 5mm more increase in the SOM → iCPD
- if the iUPD was assigned based on new lesions which meet the criteria for target lesions, then a 5mm more increase in the SOM → iCPD

'New' progression in other disease categories such as non-target disease, or another new lesion can of course also confirm progression.

* Note: sequential increases are additive; thus a 4mm increase at one assessment, followed at the next assessment by a further 2mm increase meets the criteria for iCPD.

How do new lesions define progression?

New lesions by themselves may define iUPD (when they appear), or iCPD when they increase in size (5mm or more if they are target, or any increase if non target), or another lesion appears.

However, as noted, the rules of RECIST1.1 always apply – if new lesions appear but then decrease in size or stay stable there are 2 scenarios possible

- each subsequent TP response remains iUPD. Here, any subsequent increase in size of the new lesions (5mm or more* for target or any for non-target new lesions) would allow ICPD to be defined. The TPR would be iUPD, iUPD, iUPD, iCPD for example
- Subsequent TP response is iSD, iPR. Here, the new lesions would result in a new iUPD in the following circumstances
    - Further new lesions develop
    - The NLT meet RECIST 1.1 criteria for PD (20% or more increase in SOM from 'baseline' or nadir)
    - The NLNT meet RECIST 1.1 criteria for PD (unequivocal increase equating to a 73% overall increase in tumour burden)

* Note: sequential increases are additive; thus a 4mm increase at one assessment, followed at the next assessment by a further 2mm increase meets the criteria for iCPD.

Duration of i-response (iDOR).

iDOR is defined as the time from the date of the first response iCR/iPR (whichever is first recorded) to the date of PD (iUPD confirmed as iCPD. iDOR is only defined for subjects who have best overall response of iCR or iPR. If a patient has iPR (#1) followed by a iUPD (#1) which is not confirmed, then a iPR (#2) followed by a iUPD (#2) which is confirmed at the next assessment, then the iDOR is from iPR1→ iUPD2.

Managing assessments where one or more lesions were not assessed, or not evaluable.

RECIST 1.1 principles should be followed. In general, when a lesion cannot be assessed the entire timepoint assessment should be considered to be not evaluable (NE). RECIST 1.1 describes how to manage lesions that have become so small they cannot be measured.

iRECIST adds an additional element, as progression is only confirmed at the "next assessment", and so the question arises of whether iCPD can be assigned If there is an intervening NE between iUPD and what would be iCPD. iRECIST recommends that the NE TP assessments be disregarded, and the next evaluable assessment be considered the 'next assessment'. Clearly, this does not apply to scenarios where lesions are NE because of massive increases in size, the development of large effusions, are an increase in size leading to lobar collapse (for lung lesions).

Managing PR when TP measurements change slightly over time.

In RECIST 1.1 the usual principle used is that once a PR has been assigned, and confirmed (if required), then the best response is always PR even is subsequent TP measurements no longer quite meet the criteria (providing that the criteria for PD are not met). The same principles hold for iRECIST as shown below.

	Baseline	TP1	TP2	TP3	TP4	TP5
T lesions (sum)	100	70	70	80	80	80
NT lesions	Pres	No change	No change	No change	No change	No change
New lesions		-	-	-	-	-
TP response (R)		PR	PR	PR	PR	PR
TP response (iR)		iPR	iPR	iPR	iPR	iPR