

Applying the New iRECIST Guidelines

Radiologic and Clinical Trial Considerations

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iRECIST¹: Guidelines for response criteria for use in trials testing immunotherapeutics

The RECIST (Response Evaluation Criteria in Solid Tumors) guidelines (RECIST 1.0 and RECIST 1.1) have been the standard for response evaluation in clinical trials and have supported myriad regulatory approvals in solid tumors. RECIST first published in 2000² (v1.0) and later revised in 2009³ as RECIST 1.1 provided a methodology for the consistent and reproducible evaluation of imaging and clinical data as a surrogate endpoint for survival and quality of life based endpoints.

The hallmark of RECIST is capturing a patient's disease extent beginning with a 'Baseline' tumor burden quantification and following a patient radiographically from one imaging exam to the next over time to evaluate the change in that tumor burden both quantitatively and qualitatively. This same concept has been widely applied to other standardized oncologic response criteria and a therapeutics' efficacy has been largely measured against the principle that a decrease from baseline indicates a response to treatment while an increase from nadir (lowest tumor burden value met since baseline) is consistent with a worsening of disease.

RECIST (both 1.0 and 1.1 variants) has been widely adopted for use in clinical trials for evaluating efficacy and has served as a defining methodology used by oncologists to guide clinical decision making for patient care in continuing, stopping or switching therapy. In immuno-therapy treatments, however, RECIST may not consistently provide the most accurate correlation of overall survival with response evaluation by evaluation of tumor burden with an increase in tumor burden being a definitive indicator of progression.

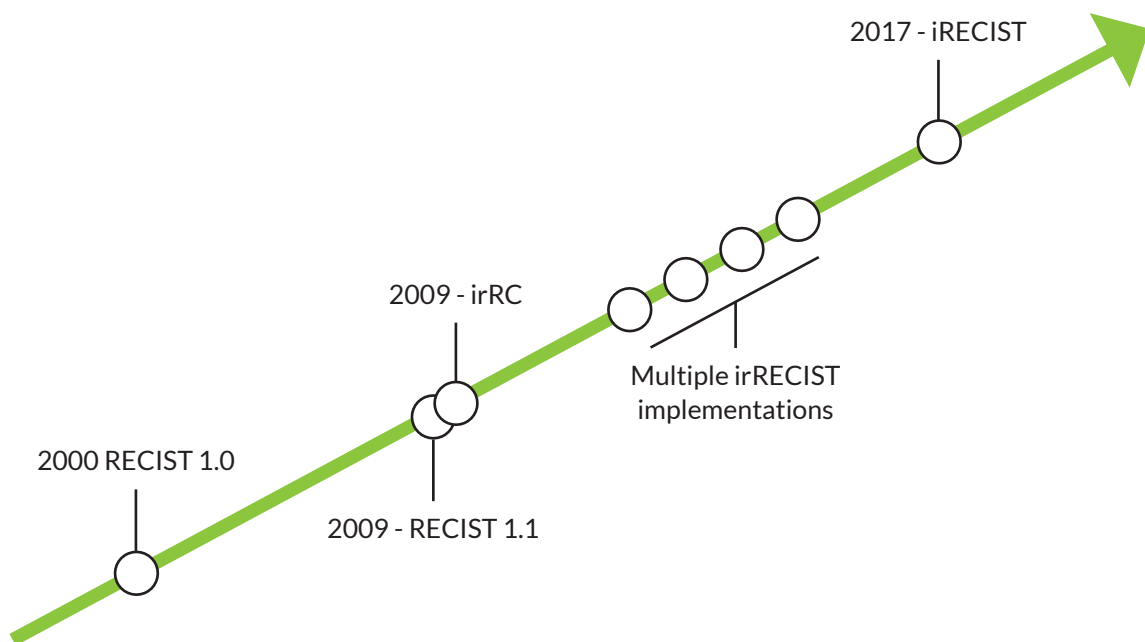
Immuno-therapies include monoclonal antibodies, check-point inhibitors, immunomodulatory agents, cytokines and antibody-drug conjugates. Patients on these therapies may demonstrate what has been termed 'pseudo-progression', with an initial increase in size of existing baseline lesions and/or the appearance of new disease with patients subsequently demonstrating a response, albeit delayed, to therapy. A confounding aspect also noted is the relative decrease in size of existing baseline disease with the appearance of new disease – a common pattern observed with immuno-therapies. This can occur as immune cells infiltrate disease sites simulating apparent growth. In other cases, as the body mounts an immune response following treatment, disease can initially worsen until an adaptive immune response can be achieved. Disease sites which are likely present at baseline but not visible on imaging appear as new disease on initial follow-up evaluations only to subsequently resolve. Even though worsening is transient, traditional response assessment (i.e., RECIST) would consider this evidence of treatment failure.

1 Seymour, L, et al; iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.*18(3):e143-e152. (iRECIST).

2 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; 92:205-16. (RECIST 1.0).

3 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45:228-47. (RECIST 1.1).

A well-known example was seen in patients receiving Ipilimumab for melanoma where nearly 10% of subjects with clinical responses would have met progression by traditional WHO⁴ criteria (WHO being an earlier measure of tumor response than RECIST 1.0)⁵. Further reports of Ipilimumab in melanoma have also shown similar findings⁶. Other immuno-therapy agents as well as other indications aside from melanoma (e.g., breast, bladder, colorectal, gastric, lung, sarcoma) have reported few relative incidents of this immune-related response, with some reporting only a few more subjects who would be considered progressions by RECIST⁷.



Criteria publication over time with focus on criteria for Immuno-Therapy Agents

4 WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization Offset Publication No. 48, 1979. (WHO criteria)

5 Wolchok JD, et al: Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clin Cancer Res 15:7412-7420, 2009. (irRC)

6 Hodi FS, et al: Evaluation of immune-related response criteria (irRC) in patients (pts) with advanced melanoma (MEL) treated with the anti-PD-1 monoclonal antibody MK-3475. J Clin Oncol 32, 2014 (suppl 15s; abstr 3006) 10.

7 Chiou L, Burotto M; Pseudoprogession and Immune-Related Response in Solid Tumors. J. Clin Oncol 33: 31, 3531-3543.

Criteria for Immuno-Therapy Agents

Even with the somewhat lower incidence of pseudo-progression overall related to immuno-therapies, it remains a known possibility that must be accounted for in clinical trials and when evaluating patient care decisions with these agents. A first approach to evaluating response with immuno-therapy agents evolved in 2009 from Ipilimumab treatment with the Immune-Related Response Criteria (irRC) which has been widely applied. Melanoma patients treated with Ipilimumab who were followed with traditional WHO criteria appeared to progress but later went on to demonstrate a response to therapy. A different approach was explored since these traditional response criteria failed to accurately correlate with treatment response observations.

Based on the original WHO guidelines which utilized bi-dimensional measurements of tumors and with slightly different response and progression thresholds from RECIST 1.0, irRC incorporated a new concept in clinical trials: *New or worsening disease observed on imaging does not always correlate with a lack of response to treatment.*

In 2009, RECIST 1.1 was published bringing further refinement to the widely-utilized criteria for solid tumors. As RECIST 1.1 and irRC emerged around the same time, other iterations of response criteria naturally developed merging the principles of RECIST 1.1 with irRC. However, while multiple interpretations and iterations of 'immune-RECIST' were used in clinical trials, no singular publication was referenced. Rather the approach was subject to the user's interpretation. Some approaches simply used irRC with unidimensional measurements and the response/progression thresholds of RECIST 1.1. Other implementations utilized a confirmatory progression evaluation which required further worsening of disease to establish a progression event.

Since the publication of irRC in 2009, there has been a growing approach to standardization of the criteria with RECIST 1.1 based concepts. The 2017 publication of iRECIST provides an opportunity for this standardization of response assessment and an approach to utilizing the principles established by RECIST 1.1 while considering the evolving therapeutic effects of immuno-therapy agents.

Immune-Related Response Criteria (irRC)

In irRC, new lesions that meet the criteria for measurability are added to the Sum of the Products of Perpendicular Diameters (SPPD) of Target Lesions.

If Target Lesion + New Measurable Lesion SPPD meets the threshold for progression, the subject is considered progressed. Any new lesions which do not meet the minimum measurable lesion size at baseline do not trigger progression but do prevent a complete response.

“ New or worsening disease observed on imaging does not always correlate with a lack of response to treatment.

New Immuno-Therapy Response Criteria – iRECIST

iRECIST is intended to provide a standard approach to the evaluation of solid tumors with measurements and assessment of the disease burden in trials where an immunotherapy is used. iRECIST also strives to collect data for future trials so that a data warehouse can be subsequently utilized to validate iRECIST.

iRECIST follows similar recommendations provided by RECIST 1.1 on a lesion level in terms of methods of measurement, size criteria, disease selection and categorization. The methodology of determining response is also comparable between iRECIST and RECIST 1.1.

A primary difference between iRECIST and RECIST 1.1 is the concept of ‘status reset’ if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage or disappearance, thus confirmation of progression is a requirement in iRECIST. Additionally, new lesions are categorized differently from RECIST 1.1 as Target or Non-Target New Lesions in iRECIST. Perhaps the most distinguishing aspect of iRECIST is that the Overall Response is designated with a prefix of “i” (i.e., iCR, iPR, iSD, iUPD, iCPD). Furthermore, the time point response and best overall response is to be recorded separately from RECIST 1.1.

Concepts and Lexicon

iRECIST is based on RECIST 1.1. To differentiate responses by iRECIST from RECIST 1.1, a prefix of “i” (for immune response) is appended to the front of the time point designation (iCR, iPR, iSD). The progression category is additionally sub-divided into unconfirmed and confirmed progression (iUPD and iCPD respectively). Another variation is the treatment of new lesions which are sub-divided into Target New Lesions (New Lesion Target (NLT)) and Non-Target New Lesions (New Lesion Non-Target (NLNT)).

Table 1 further demonstrates these differences. *(on the next page)*

iCR	immune Complete Response
iPR	immune Partial Response
iSD	immune Stable Disease
iUPD	immune unconfirmed Progression
iCPD	immune confirmed Progression
iNN	immune Non-iCR/Non-iUPD
NLT	New Lesion Target
NLNT	New Lesion Non-Target
NE	Not Evaluable
TPR	Time Point Response
iBOR	immune Best Overall Response
iPFS	Immune Progression Free Survival
PSPD	Pseudo-progression
SOM	Sum of Measures

iCR - iPR - iSD - iUPD - iCPD

RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	
Measurable lesions are 10 mm or more in long diameter (15 mm for nodal lesions); Maximum of 5 lesions (2 per organ); All other disease considered non-target (must be 10 mm or longer in short axis for nodal disease)	No change; however, NEW lesions are evaluated as per RECIST 1.1 but are recorded separately on the case report form (CRF) (but not included in the sum of lesions for target lesions identified at baseline)
CR, PR or SD	
Cannot have met criteria for PD prior to CR, PR or SD	May have had iUPD (1 or more instances), but not iCPD, prior to iCR, iPR or iSD
Confirmation of CR, PR	
Only required for non-randomized trials	
Confirmation of SD	
Not Required	
New Lesions (unequivocal)	
Results in PD. Recorded but not measured.	Results in iUPD but iCPD is only assigned based on this category if at next assessment: <ul style="list-style-type: none"> • Additional NL appear or • Increase in size of NLs (≥ 5 mm for sum of NLT or any increase in NLNT) The appearance of New Lesions can also confirm progression first observed at the prior timepoint in the Target or Non-Target Category.
Independent blinded review and central collection of scans	
Recommended in some circumstances	Collection of scans (but not independent review) recommended for all trials
Confirmation of PD	
Not required (unless equivocal)	Required
Consideration of clinical status	
Not included in assessment	Clinical stability is considered in whether treatment is continued after iUPD

Table 1. RECIST 1.1 compared to iRECIST⁸

⁸ Seymour, L, et al; iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol.18(3):e143-e152. (iRECIST).

iRECIST Principles

iRECIST considers the categories of Target Lesions, Non-Target Lesions and New Lesions. Each category has a categorical response assessment that drives the overall response assessment.

Category 1: Target Lesions

iCR, iPR and iSD can be assigned after iUPD has been documented provided iCPD was not confirmed. iUPD is defined by RECIST 1.1 criteria for PD and can be reported multiple times as long as iCPD is not met.

PD is confirmed in the target lesion category if the next imaging assessment (4 weeks but no more than 8 weeks later after iUPD) confirms further increase in the sum of measures (SOM) of target disease from iUPD, with an increase of at least 5 mm.

iCPD is not met if iCR, iPR or iSD criteria (compared to baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is 'reset' and iUPD must be met again followed by a iCPD to confirm progression.

Category 2: Non-Target Lesions

iUPD (not iCPD) may have been documented prior to iCR or Non-iCR/Non-iUPD and may be assigned multiple times provided iCPD is not met.

Progression in the non-target lesion category is confirmed if subsequent imaging, (conducted at least 4 weeks but no more than 8 weeks after iUPD) shows further increase from iUPD.

If iCR or non-iCR/non-iUPD criteria is met after iUPD, the status is 'reset' and iUPD must be met again followed by iCPD to confirm progression.

Category 3: New Lesions

New lesions in iRECIST are categorized as Target (measurable) or Non-Target (non-measurable) in accordance with RECIST 1.1 principles. Five new lesions, no more than two per organ, should be measured and recorded as New Lesions Target (NLT), but are NOT to be included in SOM of the original target lesions identified at baseline. Other new lesions are recorded as New Lesion Non-Target (NLNT).

NLT and NLNT can drive a iUPD and iCPD. Progression is confirmed (iCPD) in the New Lesion category if the next imaging assessment (conducted at least 4 weeks but no more than 8 weeks after iUPD), confirms additional new lesions or further increase in new lesion size from iUPD (SOM increase in NLT \geq 5 mm, any increase for NLNT).

Achieving iCPD

At the confirmatory time point, an overall assessment of **iCPD** can be met by:
iUPD in a lesion category followed by **iCPD** in the same lesion category **AND/OR** **iUPD** in a different lesion category



Incorporating iRECIST with RECIST 1.1

iRECIST recommends that clinical trials which allow continued treatment following a RECIST 1.1 based progression event should only do so provided the patient is clinically stable. Following progression by RECIST 1.1, the next imaging assessment to evaluate tumor burden status should not be longer than 8 weeks later unless evidence exist that pseudo-progression is a known occurrence. It is always the decision of the patient and treating physician to continue or discontinue therapy.

As with RECIST 1.1, the protocol must define how iRECIST will be incorporated into a trial, in particular, how the study endpoints will be supported (RECIST 1.1 or iRECIST). For the purpose of evaluating potential pseudo-progression events, conducting a trial where both RECIST 1.1 and iRECIST response assessment is collected may provide useful data on the efficacy of the therapeutic under investigation. Furthermore, when defining criteria for a given protocol using RECIST 1.1 and iRECIST, the following parameters should also be considered:

When to apply iRECIST

iRECIST recommends that RECIST 1.1 should continue to be used as the primary criteria for response based endpoints in randomized trials intended for registration with iRECIST considered exploratory.

Confirmation of Response

- Is confirmation of a iCR or iPR required? (Confirmation of response by RECIST 1.1 is typically only a requirement in non-randomized trials.)
- What is the minimum time in days between two responses to consider confirmation met (i.e., 28 days)? Is there a window (i.e., + or - 5 days)?

Missing and Not Evaluable Assessments

- How will missing response assessments be handled?
- How many gaps are allowed between responses and what assessments are allowed in order to consider a response confirmed?
- Are multiple Not Evaluable assessments between responses allowed in order to consider a response confirmed? For example, is iPR-NE-iPR a confirmed iPR? iCR-NE-iCR? iPR-NE-NE-iPR?
- Is an assessment of iSD allowed between two responses for confirmation to be met? For example, is iPR-iSD-iPR a confirmed iPR? How does iUPD factor into the confirmation of response? For example, iPR-iUPD-iPR?

Confirmation of Progression Time

- What is the minimum time for confirmation to report iCPD (e.g., 28 days)?

Example Case 1

	Baseline	Follow-Up 1	Follow-Up 2
Target Lesion	SOD = 100 mm	SOD = 130 mm (30% Increase - Nadir)	SOD = 147 mm (≥ 5 mm Increase - from iUPD)
Non-Target Lesions	None	None	None
New Lesions		None	None
Overall Response by iRECIST		iUPD	iCPD

Explanation: At Follow-up 2, iCPD confirms the iUPD at Follow-up 1 with a ≥ 5 mm Increase from iUPD and the threshold for progression (≥ 20 % increase from nadir) is still met.

Example Case 2

	Baseline	Follow-Up 1	Follow-Up 2
Target Lesion	SOD = 100 mm	SOD = 130 mm (30% Increase - Nadir)	SOD = 131 mm (< 5 mm Increase - from iUPD)
Non-Target Lesions	None	None	None
New Lesions		None	None
Overall Response by iRECIST		iUPD	iUPD

Explanation: At Follow-up 2, there is **NOT** a ≥ 5 mm Increase from iUPD even though the threshold for progression (≥ 20 % increase from nadir) is still met; iUPD is reported again for Follow-up 2. Confirmed Progression is not met.

Example Case 3

	Baseline	Follow-Up 1	Follow-Up 2
Target Lesion	SOD = 100 mm	SOD = 130 mm (30% Increase - Nadir)	SOD = 70 mm (30% Decrease - Baseline)
Non-Target Lesions	None	None	None
New Lesions		None	None
Overall Response by iRECIST		iUPD	iPR

Explanation: At Follow-up 2, progression is not confirmed. The SOD decreases and meets criteria for Partial Response ($\geq 30\%$ decrease from baseline). iUPD must again be met before iCPD can be met and the case considered confirmed progression.

Example Case 4

	Baseline	Follow-Up 1	Follow-Up 2
Target Lesion	SOD = 100 mm	SOD = 130 mm (30% Increase - Nadir)	SOD = 120 mm (20% increase - Nadir; 5 mm minimum not met)
Non-Target Lesions		Non-iCR/Non-iUPD	iUPD
New Lesions		None	None
Overall Response by iRECIST		iUPD	iCPD

Explanation: At Follow-up 1, iUPD is met by Target Lesions. Target lesions remain iUPD at Follow-up 2 but do not meet minimum 5 mm absolute increase. However, Non-Target Lesions have unequivocally progressed meeting iUPD. Confirmed Progression is met since Non-Target iUPD confirms Target Lesion iUPD at Follow-up 1.

Example Case 5

	Baseline	Follow-Up 1	Follow-Up 2
Target Lesion	SOD = 100 mm	SOD = 100 mm (No Change)	SOD = 100 mm (No Change)
Non-Target Lesions		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New Lesions		New Liver Lesion - 17 mm (New Lesion Target)	New Liver Lesion - 19 mm (from Follow-up 1)
Overall Response by iRECIST		iUPD	iSD

Explanation: At Follow-up 1, iUPD is met by the New Target Liver Lesion. This new lesion remains present but does not increase by the 5mm minimum needed for a iCPD thus progression is not confirmed and response is based on other disease findings which meet criteria for iSD.

Example Case 6

	Baseline	Follow-Up 1	Follow-Up 2
Target Lesion	SOD = 100 mm	SOD = 120 mm (20% Increase - Nadir)	SOD = 122 mm (20% increase - Nadir; 5 mm minimum not met)
Non-Target Lesions		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New Lesions		None	New Lung Lesion - present (New Lesion Non-Target)
Overall Response by iRECIST		iUPD	iCPD

Explanation: At Follow-up 1, iUPD is met by Target Lesions. Target lesions remain iUPD at Follow-up 2 but do not meet minimum 5 mm absolute increase. However, a new Non-Target lung lesion appears at Follow-up 2 meeting iUPD in the New Lesion category. Confirmed Progression is met since the New Lesion iUPD confirms iUPD by Target Lesions at Follow-up 1 even though Target lesions did not meet confirmed progression (iCPD) independently.

About **mintLesion™**

mintLesion™ image analysis software streamlines imaging and clinical data evaluation for clinical trials and research in accordance with standardized response criteria comparing medical images from multiple modalities across time points. Multiple workflow options are available in **mintLesion™** including Single and Double Reads, Adjudication, Eligibility, and Consensus Review.



Software screenshot of **mintLesion™**

mintLesion™ is designed to facilitate research in clinical trials with imaging endpoints. This includes the transfer and storage of clinical trial DICOM data, a workflow optimized for consistent interpretation and reviewing of image findings, the review of image meta-data, and the simplified provision of results to physicians and other clinical systems, e.g. PACS and Clinical Trial Management Systems.

The **mintLesion™** software is a 510(k) – cleared, Class II medical device which conforms to the European Medical Devices Act and bears the CE mark. **mintLesion™** utilizes strict user authorization, passwords, user permissions, clinical trial creation and assignment, data entry logging, audit trail management, electronic signature, and post-approval revision tracking and identification.

mintLesion™ facilitates radiological assessment with automatic response classification. Standardized response criteria are inherent to the **mintLesion™** software with conformance by criteria-based edit-checks. Novel criteria configurations are also supported based on trial and therapeutic specific needs. Radiologists and other physician specialists utilize **mintLesion™** to access subject images, catalog disease findings, annotate findings, for qualitative and quantitative analysis, evaluating clinical data, and storing measurement values.

The screenshots illustrate the software's capabilities in providing structured reporting, visual lesion tracking, and graphical response analysis.

Sample report - multiple visualisations from one trial

mintLesion™ offers configurability with flexibility to meet trial specific requirements. The oncologic response assessment analysis facilitated by **mintLesion** is further enhanced by the structured reporting templates that provide an organized, consistent, and reproducible display of the analysis criteria evaluation required for clinical trials.

- Multi-modality analysis including CT, MRI, PET, X-ray, Bone Scan, DCE-MRI and other DICOM series.
- Quantitative measurement tools including density, texture and volume with image correlation and lesion matching.
- Structured reporting with diagrams, graphs, and lesion measurement snapshots.
- Multi-criteria analysis on the same imaging data.
- Real-time reporting of results.
- Data change functionality with original read data preservation.
- Trial Dashboard for read monitoring and data mining.

Currently available reading profiles in **mintLesion™**

Therapy response evaluation

in line with ...

Cheson / Lugano	Choi	irRC	iRECIST
irRECIST	mRECIST HCC	mRECIST Mesothelioma	PCWG2
RANO	RECIST 1.1	RECIST 1.0	WHO

Oncological Screening & Staging

Liver LI-RADS	Lung Lung-RADS	Prostate PI-RADS	Mamma BI-RADS
Colon Staging	Kidney Staging	Liver Staging	Lung Staging
Lymphoma Staging	Pancreas Staging	Pharynx/Larynx Staging	Rectum Staging

and much more to come.

Mint Medical was founded by researchers of the German Cancer Research Center (DKFZ). It is based on the innovation and experience from more than 20 years of research work in the area of medical imaging.

Mint Medical aims to provide a new quality in clinical trial imaging and improves reproducibility and objectiveness in day-to-day clinical routine.

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