Molecular Imaging CRO Network

Micron's ViewPoint

iRECIST Overview

Contents

Disclaimer

Introduction

This white paper is a summary of iRECIST, the Immunotherapy Response Evaluation Criteria In Solid Tumors, published by EORTC (European Organization for Research and Treatment of Cancer) in 2017. This white paper has been published and reprinted with permission from EORTC.

What is iRECIST?

Changes in tumor burden are often used in clinical trials as response evaluation criteria surrogates of survival or quality of life. It is essential to develop global standard response evaluation criteria to appropriately express the therapeutic effect. In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) working group by EORTC published RECIST. In 2009, RECIST was refined to RECIST version 1.1., which is the most widely used therapeutic effect evaluation criteria in solid tumors. With the development of imaging technologies and new approaches to tumors, RECIST undergoes continuous updates.

Immunotherapy, as typified by immune checkpoint inhibitors (such as Nivolumab, Pembullizumab, and Atezolizumab), is a treatment of novel mechanisms of action targeting immunomodulators. Its tumor shrinkage pattern is different from known chemotherapy tumor shrinkage patterns, often mimics "flare effect." When this characteristic pattern is considered in RECIST 1.1, a transient increase in tumor burden may correspond to PD, leading to early discontinuation of the trial in patients with a therapeutic effect. The response evaluation criteria in immunotherapy require criteria to determine whether an increase in tumor burden is "true progression" or "pseudoprogression (PSPD)." The immune-related response criteria (irRC) in 2009 and irRECIST in 2014 have been published as criteria for response to immunotherapy. However, the irRC is based on WHO criteria and is not currently in compliance with RECIST 1.1, the most common response evaluation criteria for solid tumors. Although irRECIST is based on RECIST, it is currently "modified" for each clinical trial by the pharmaceutical company and may not be a standard response evaluation criteria due to the difficulty in interpreting clinical trial data.

Based on these findings, the RECIST Working Group led the publication of iRECIST in 2017 for the development of standard protocols and consistent study design in collaboration with pharmaceutical companies dealing with immune-related products, regulatory authorities, and academia. In addition, the pattern of tumor shrinkage in immunotherapy has not been fully understood. Therefore, collecting additional evidence and constructing a data warehouse are necessary. As RECIST may be revised based on the results of analyses of accumulated data, being familiar with iRECIST is needed, not only for conducting appropriate clinical trials but also for being a factor in the next generation of therapeutic response evaluation criteria. It should also be mentioned that, like RECSIT 1.1, this guideline is not intended to define or guide clinical practice or treatment decisions; instead, it is just intended to provide a consistent framework for the management of data collected in clinical trials of immune-based therapies. Treatment decisions rest on the patient and their healthcare team. The RECIST working group recommends using RECIST 1.1 as the primary endpoint and iRECIST as the exploratory endpoint in studies, which regard objective antitumor efficacy as the endpoints. It is also acceptable to use iRECIST as the primary endpoint in early phase studies.

(This page is a condensation of Ref. 1.)

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Comparison of Response Evaluation Criteria: irRC, irRECIST, RECIST 1.1, and iRECIST

	irRC	irRECIST	RECIST 1.1	iRECIST
Lesion Measurement	Bidimensional Measurement	Unidimensional Measurement	Unidimensional Measurement	Unidimensional Measurement
BL Target Lesion Size	5×5 or more	≥ 10 mm	≥ 10 mm	≥ 10 mm
Number of BL Lesions	10 lesions total, 5 per organ	5 lesions total, 2 per organ	5 lesions total, 2 per organ	5 lesions total, 2 per organ
Measurement of New Lesions	Included in TTB	Included in TTB	Not required	Not included in TTB
Response	CR: All lesions disappeared PR: ≥ 50% decrease from BL TTB SD: Neither PR nor PD PD: ≥ 25% increase in the nadir of TTB	CR: All lesions disappeared PR: ≥ 30% decrease from BL TTB SD: Neither PR nor PD PD: ≥ 20% increase in the nadir of TTB (should be plus ≥5 mm)	CR: All lesions disappeared PR: ≥ 30% decrease from BL TTB SD: Neither PR nor PD PD: ≥ 20% increase in the nadir of TTB (should be plus ≥5 mm)	CR: All lesions disappeared PR: ≥ 30% decrease from BL TTB SD: Neither PR nor PD PD: ≥ 20% increase in the nadir of TTB (should be plus ≥5 mm)
PD Confirmation	4 weeks	12 weeks	Not required	4 - 8 weeks

BL : baseline
TTB : total tumor burden
iUPD : immune unconfirmed PD

Comparison of RECIST 1.1 and iRECIST

Common Points

Details	RECIST 1.1 and iRECIST
Definition of measurable and non-measurable lesions	Same
Definition of target and non-target lesions	
Measurement and management of lymph nodes	
SUM of tumor diameter calculation	
Definition of CR, PR, and SD	
Confirmation of CR and PR in Best Overall Response	
Definition of PD for target and non-target lesions	

Differences

Details	RECIST 1.1	iRECIST
New Lesion	-	New target lesions and new non-target lesions
Overall Response After PD	PD after PD	Consider pseudoprogression
Confirmation of PD	-	New definitions (iUPD and iCPD)
Date of Progression	The first date of PD	If iCPD is confirmed, the first date of iUPD that is confirmed a progression date. Also, in case, iCPD can't be determined and iUPD date is used as progression date, need to gather reasons. (See page 9 for details)

iUPD : immune unconfirmed PD
iCPD : immune confirmed PD

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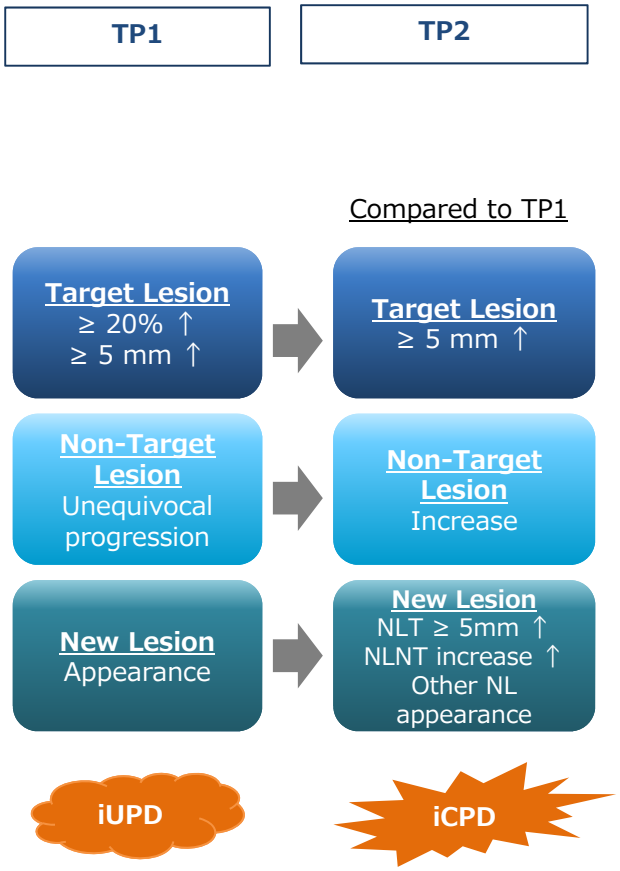
iCPD Criteria Patterns

iCPD is determined via 2 main patterns: “Progression within the same lesion category" and “Progression in different lesion categories".

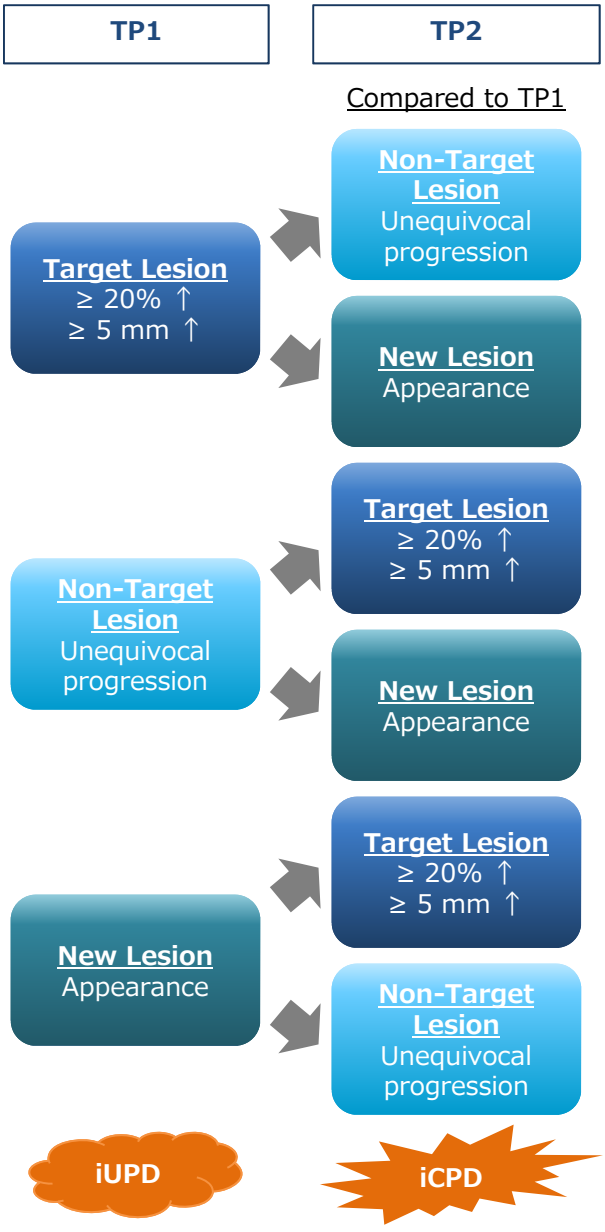
Progression patterns within the same lesion category



Non-target lesions at TP2 do not need to meet the RECIST 1.1 criteria for “unequivocal progression".

TP : time point
NL : new lesion
NLT : new lesion target
NLNT : new lesion non-target

Progression patterns in different lesion categories



TP2 must meet the RECIST 1.1 criteria:

- Target lesion increased more than 20% and 5mm compared to nadir.
- Unequivocal progression of non-target lesion, and new lesion appeared.

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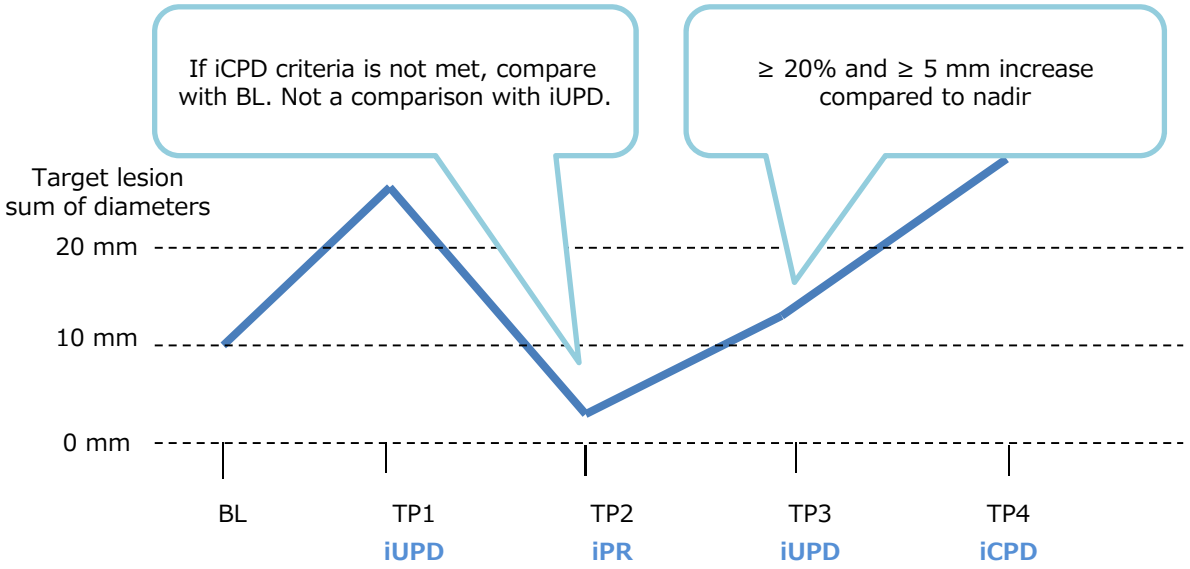
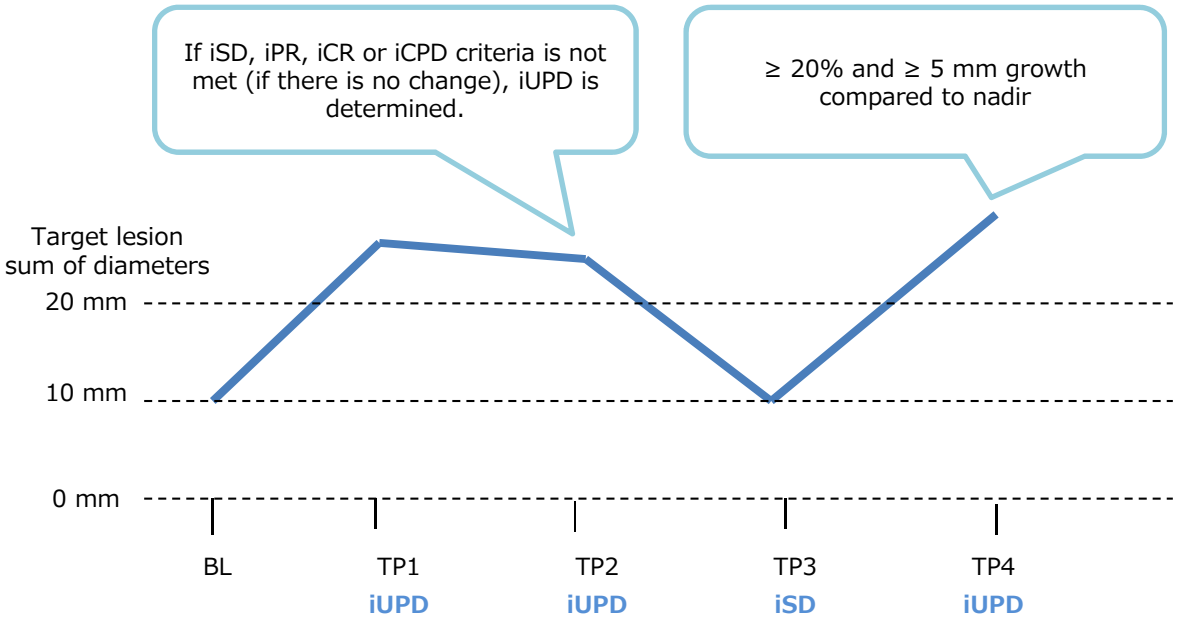
Reset iUPD

iCPD is always determined at the next assessment after iUPD. If tumor shrinkage occurs following iUPD (iSD, iPR, or iCR is determined), then iUPD is reset so that iUPD needs to occur again.





Best Overall Response: iBOR

- The general rules for Overall and Best Overall Response follow RECIST 1.1.
- Confirmation of iCR/iPR, as in RECIST 1.1, is necessary for nonrandomized trials but not for randomized trials. The definitive duration for iCR/iPR should be specified in the protocol.
- The protocol should specify what to do if assessments are not performed or cannot be assessed following iUPD: NE included in the assessment or not.
  NE excluded from iBOR calculations or not.

Order of Best Overall Response

iCR > iPR > iSD = Non-iCR/non-iUPD >iCPD > iUPD > NE

	TP1	TP2	TP3	TP4	TP5	**iBOR**
Example 1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	**iCR**
Example 2	iUPD	iPR, iSD or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD or NE	**iCR**
Example 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE or iCPD	iPR, iSD, iUPD, NE or iCPD	**iPR**
Example 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD or NE	iPR, iSD, iUPD, iCPD or NE	**iPR**
Example 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD or NE	iSD, iUPD, iCPD or NE	**iSD**
Example 6	iUPD	iCPD	Any	Any	Any	**iCPD**
Example 7	iUPD	iUPD	iCPD	Any	Any	**iCPD**
Example 8	iUPD	NE	NE	NE	NE	**iUPD**

Note:
Randomized controlled trials with no iCR or iPR determinations are assumed in this table.
For patients with only non-target lesions at baseline, only iCR or Non-iCR/Non-iUPD is assigned at each time point.

iBOR : immune best overall response

(Cited from Ref. 1)

Date of Progressive Disease: iPD Date

- The date of progressive disease (iPD date) is the event date used to calculate progression-free survival (iPFS).
- If progression is confirmed (iCPD) after iUPD, the date of first iUPD is considered as the progression date. (Example 1 and 2).
- If iUPD occurs but subsequently becomes iSD, iPR, or iCR, that iUPD date is not used as the event date for progression (Example 3).
- If iUPD occurs but progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios (should be specified in the protocol): (Example 4).
  - ✓ Withdrawal of protocol therapy because patient is not clinically stable (deterioration of PS, onset or increase of disease-related clinical symptoms such as dyspnea & cancer pain, etc.)
  - ✓ Continuous iUPD and no iCPD
  - ✓ Death of the patient

	TP1	TP2	TP3
Example 1	**iUPD**	iCPD	-
	Since iUPD is followed by iCPD, the date of the first iUPD (TP1) is the date of progression.		
Example 2	**iUPD**	iUPD	iCPD
	If a series of iUPDs occurs before iCPD, the date of the first iUPD (TP1) is the date of progression.		
Example 3	iUPD	iSD, iPR or iCR	iSD, iPR or iCR
	If the next assessment after iUPD is determined as iSD, iPR, or iCR, and there is no iUPD thereafter (pseudoprogression), the first iUPD does not represent the progression date. (No date of progression)		
Example 4	**iUPD**	-	-
	Reasons for not imaging at TP2 and TP3 should be recorded. The date of iUPD is the date of progression according to the protocol.		

*The date of progression is indicated in red.

iPFS : immune progression free survival

Response Evaluation Examples

Case 1		BL	TP1	TP2	TP3
Sum of Diameters (mm)		100	130	125	120
Target Response		-	iUPD	iUPD	iUPD
Non-Target Response		-	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	iUPD
New Lesion	Target	-	-	-	-
	Non-Target	-	-	-	-
Overall Response		-	iUPD	iUPD	iCPD
iPD Date		-	✓	-	-
iBOR		iCPD			

iUPD is confirmed by the target lesion at TP2.
Unequivocal progression is determined due to the non-target lesion at TP3, confirming iCPD.

Case 2		BL	TP1	TP2
Sum of Diameters (mm)		100	130	100
Target Response		-	iUPD	iSD
Non-Target Response		-	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New Lesion	Target	-	-	24 mm
	Non-Target	-	-	Appears
Overall Response		-	iUPD	iCPD
iPD Date		-	✓	-
iBOR		iCPD		

iUPD is determined by the target lesion at TP1 and iSD determined due to target lesion reduction at TP2. iCPD is confirmed due to the appearance of a new lesion.

Response Evaluation Examples

Case 3		BL	TP1	TP2
Sum of Diameters (mm)		100	130	110
Target Response		-	iUPD	iSD
Non-Target Response		-	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New Lesion	Target	-	14 mm	24 mm
	Non-Target	-	-	-
Overall Response		-	iUPD	iCPD
iPD Date		-	✓	-
iBOR		iCPD		

iUPD determined at TP1 due to appearance of a new target lesion.
iCPD confirmed at TP2 due to a minimum 5mm increase of the new target lesion compared to TP1.

Case 4		BL	TP1	TP2	TP3	TP4
Sum of Diameters (mm)		100	50	50	75	NE
Target Response		-	iPR	iPR	iUPD	NE
Non-Target Response		-	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	NE
New Lesion	Target	-	-	-	-	NE
	Non-Target	-	-	-	Appears	NE
Overall Response		-	iPR	iPR	iUPD	NE
iPD Date		-	-	-	✓	-
iBOR		iPR				

Reason for NE at TP4 should be recorded. The progression date is set as TP3 according to the protocol.

Response Evaluation Examples

Case 5		BL	TP1	TP2	TP3	TP4	TP5
Sum of Diameters (mm)		100	130	60	71	75	78
Target Response		-	iUPD	iPR	iSD	iUPD	iUPD
Non-Target Response		-	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New Lesion	Target	-	14 mm	12 mm	10 mm	14 mm	14 mm
	Non-Target	-	-	-	-	Appears	No change Appears
Overall Response		-	iUPD	iPR	iSD	iUPD	iCPD
iPD Date		-	-	-	-	✓	-
iBOR		iPR					

At TP1, iUPD was determined.
At TP2, the target lesion decreased in size and did not meet PD criteria, resulting in iPR.
At TP4, iUPD was determined again in target lesion.
At TP5, iCPD was confirmed due to the appearance of a new lesion.
TP4 is considered the iPD date due to lack of progression at TP2 following the initial iUPD at TP1.

Summary

- ✓ Fundamental principles of iRECIST are similar to those of RECIST 1.1. To distinguish between true progression or pseudoprogression, classifications were added for new lesions (new lesion target, new lesion non-target) and confirmed/unconfirmed PD (iCPD/iUPD).
- ✓ To determine iCPD overall response, there must be progression of the same or different lesion category.
- ✓ iRECIST defines data collection in immunotherapy clinical trials but is not a guideline for deciding treatment.
- ✓ RECIST 1.1 will continue to be used as the primary endpoint, and iRECIST will be used as the exploratory endpoint. In early phase trials, iRECIST may also be used as the primary endpoint.

Reference

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Final Words

Micron provides image analysis support for the development of anticancer drugs with emphasis on the oncology field. We have experienced not only RECIST 1.1 but also various other Response Evaluation Criteria, such as irRC and irRECIST. Based on this wealth of experience and know-how, we are currently building a new system that can support iRECIST assessment. We are also working closely with EORTC to expand our knowledge of iRECIST.

If you have any questions about iRECIST, please contact us.

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