CISC 2021 Meeting
Harnessing Imaging Tools to Guide Immunotherapy Trials

Session 2 – Opportunities and Challenges

CT and MR (including iRECIST)

Michael V. Knopp, MD PhD

Knopp.16@osu.edu

The Ohio State University
Wexner Medical Center
Wright Center of Innovation in Biomedical Imaging

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Response Criteria Summarized

	RECIST 1.1	irRC (+ unidimensional variant)	"irRECIST /irRECIST1.1" variants
Bi/unidimen.?	Unidimensional	**Bidimensional**	Unidimensional
N Target	5	**15; (≥5 × 5mm)**	10 / 5 (≥10mm/ ≥10mm (15 for nodes))
New target lesions added to sum or measures (SOM)?	No	(≥5 × 5mm); **Yes** - does not automatically define PD	(RECIST or RECIST 1.1 rules) **Yes**
How many ?	NA	10 visceral, 5 cutaneous	10 / 5 (RECIST 1.1 rules)
Definition of progression (PD)	≥ 20% ↑ compared to nadir (≥ 5mm ↑)	≥ 25% ↑ compared to baseline (BL), nadir/**reset BL**	≥ 20% ↑ compared to nadir (≥ 5mm ↑)
Confirmation ?	No	Yes, required	Yes, recommended
How confirmed?	NA	**Not defined**	**Not defined;** not improved? Imager feels is worse?

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iRECIST vs RECIST 1.1: “Principles”

- Treatment past PD should only be considered if patient clinically stable*
  - No worsening of performance status.
  - No clinically relevant ↑in disease related symptoms
  - No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)
- Record the reason iUPD not confirmed
  - Not stable
  - Treatment stopped but patient not reassessed/imaging not performed
  - iCPD never occurs
  - Patient has died

* recommendation – may be protocol specific

iRECIST:

guidelines for response criteria for use in trials testing immunotherapeutics

***Lancet Oncol* 2017; 18: e143–52**

iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics

Lesley Seymour, Jan Bogaerts, Andrea Perrone, Robert Ford, Lawrence H Schwartz, Sumithra Mandrekar, Nancy U Lin, Saskia Litière, Janet Dancey, Alice Chen, F Stephen Hodi, Patrick Therasse, Otto S Hoekstra, Lalitha K Shankar, Jedd D Wolchok, Marcus Ballinger, Caroline Caramella, Elisabeth G E de Vries, on behalf of the RECIST working group

Tumours respond differently to immunotherapies compared with chemotherapeutic drugs, raising questions about the assessment of changes in tumour burden—a mainstay of evaluation of cancer therapeutics that provides key information about objective response and disease progression. A consensus guideline—iRECIST—was developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data, and ultimate validation of the guideline. This guideline describes a standard approach to solid tumour measurements and definitions for objective change in tumour size for use in trials in which an immunotherapy is used. Additionally, it defines the minimum datapoints required from future trials and those currently in development to facilitate the compilation of a data warehouse to use to later validate iRECIST. An unprecedented number of trials have been done, initiated, or are planned to test new immune modulators for cancer therapy using a variety of modified response criteria. This guideline will allow consistent conduct, interpretation, and analysis of trials of immunotherapies.

Lancet Oncol 2017; 18: e143–52

This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on April 30, 2019

Canadian Cancer Trials Group, Queen's University, Kingston, ON, Canada (Prof L Seymour MD, Prof J Dancey MD); **EORTC Headquarters, Brussels, Belgium** (J Bogaerts PhD, S Litière PhD); **Translational Medicine, Merck & Co, Kenilworth, NJ, USA** (A Perrone MD); **Clinical Trials Imaging Consulting, LLC, Belle Mead, NJ, USA** (R Ford MD); **Department of Radiology,**

Introduction

Changes in tumour burden (termed response) are often used as surrogates of survival or quality of life;[1] consequently, validated and consistent criteria for lesions) were proposed—the immune-related response criteria (irRC).[29] The major modification involved the inclusion of the measurements of new target lesions (each must be at least 5×5 mm in size; with a maximum

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 1: **Comparison of RECIST 1.1 and iRECIST**

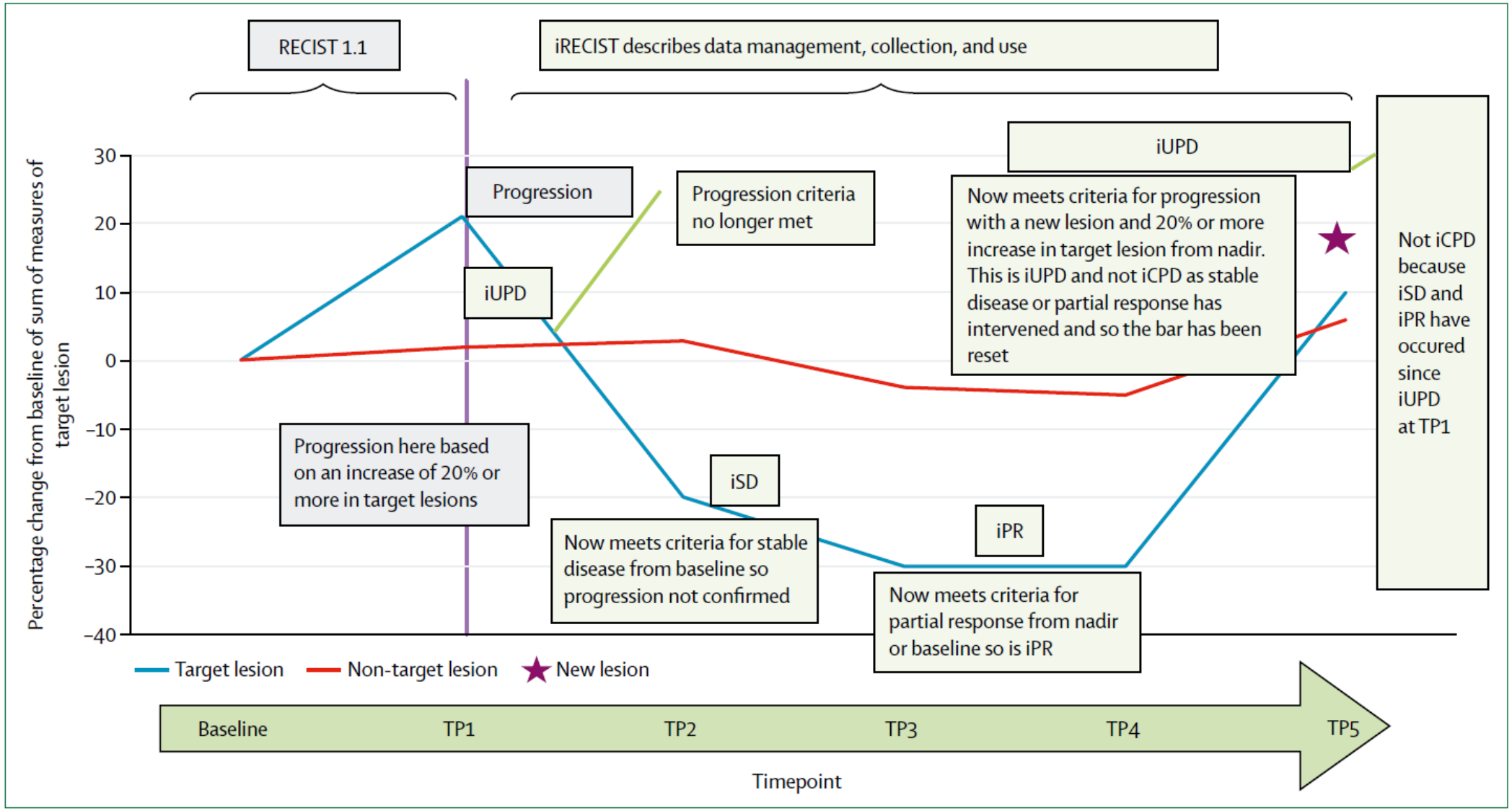

Figure 2: **RECIST 1.1 and iRECIST: an example of assessment**

Prefix "i" indicates immune responses assigned using iRECIST; others without "i" are confirmed by RECIST 1.1. RECIST=Response Evaluation Criteria in Solid Tumours. iCR=complete response. iCPD=complete progression. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. TP=timepoint.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Seymour L, Bogaerts J, Perrone A, et al, on behalf of the RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 2017; **18:** e143–52.

Appendix 2. Sample RECIST 1.1 and i-RECIST CRFs

Baseline

TARGET LESIONS AT BASELINE – QUESTION
Does the patient have any target lesions? O Yes O 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? O Yes O 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

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.

- ○ No further treatment is planned
- ○ 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.