iRECIST

A guideline for data management and data collection for trials testing immunotherapeutics

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On behalf of the RECIST Working Group (RWG) and Immunotherapy Subcommittee
I have no conflicts to declare
Response and Immunotherapy

- We know
  - Progression based endpoints are increasingly used for marketing approvals
  - Immune based therapies are a major advancement in patient care
  - Unusual response patterns well described especially in melanoma
- We don’t know
  - True frequency
  - Optimal response criteria or how to implement them
Unusual Response Patterns

Baseline

Time point 2

TP3
How should we assess response and progression for trials of immunotherapies?
Plan

• RECIST Working Group
• Overview of current criteria & concerns
• Development of iRECIST
• Overview of iRECIST with examples
• Using iRECIST in your trials
Create IPD Warehouse to Develop and Test Response Criteria

Publish Revised Criteria (if indicated)

Identify Next Question

Unidimensional measures → RECIST (2000)

Number of lesions to be measured, nodes? → RECIST 1.1 (2009)

Functional imaging

Targeted agents different? → No change

Immunotherapy
Initial plan (2012):

– Create a warehouse
– Validate RECIST 1.1 and / or publish new criteria

• Became apparent there were multiple similar, but distinct, interpretations of immune response criteria
Response and Immunotherapy

• irRC - consensus based recommendations (2009)
  – Based on WHO, bi-dimensional measures
  – New lesion measures included in sum of measures of target lesions

• Subsequent modifications proposed
  – Based on RECIST/RECIST 1.1

## Response Criteria

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

– Multiple variations used across trials
– Comparability
– Response data /measures not always collected after RECIST defined progression
– May not be applicable to other tumour types
True or Pseudoprogression?

IF **TRUE** PROGRESSION THEN THE START OF EFFECTIVE SALVAGE THERAPY DELAYED FOR MANY WEEKS
Revised plan

– Standardise data management and collection - develop consensus guidelines (termed iRECIST)

– Create IPD warehouse and validate criteria
  • If necessary publish updated RECIST (2?)
Development of iRECIST Guideline

**Fall 2015**
Initial meetings: RWG, pharma

**Agreement on plans**

**Spring 2016**
F2F - ASCO: RWG, groups, pharma, regulatory – clinicians, imagers and statisticians

**Agreement on key principles**

**Fall 2016**
Wide review

**Draft Manuscript**

**Summer 2016**
Draft White Paper

Data collection ongoing and validation planned in the coming 1-2 years
iRECIST Addresses

• Recommendations on
  – Terminology (“i” prefix)
  – Data to be collected after RECIST 1.1 defined PD
  – Definition of “events”
  – Primary endpoints versus exploratory endpoints

• They are not treatment decision guidelines
• These are not (yet) validated response criteria
• They are internationally agreed data recommendations from academia, pharma and regulatory authorities
<table>
<thead>
<tr>
<th>RECIST 1.1</th>
<th>iRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitions of measurable, non-measurable disease</td>
<td>✓</td>
</tr>
<tr>
<td>Definitions of target (T) and non target (NT) lesions</td>
<td>✓</td>
</tr>
<tr>
<td>Measurement and management of nodal disease</td>
<td>✓</td>
</tr>
<tr>
<td>Calculation of the sum of measurement (SOM)</td>
<td>✓</td>
</tr>
<tr>
<td>Definitions of CR, PR, SD and their duration</td>
<td>✓</td>
</tr>
<tr>
<td>Confirmation of CR and PR</td>
<td>✓</td>
</tr>
<tr>
<td>Definition of progression in T and NT (iRECIST terms i-unconfirmed progressions (iUPD))</td>
<td>✓</td>
</tr>
</tbody>
</table>
# iRECIST vs RECIST 1.1: Changes

<table>
<thead>
<tr>
<th>RECIST 1.1</th>
<th>iRECIST</th>
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</thead>
<tbody>
<tr>
<td>Management of new lesions</td>
<td><strong>NEW</strong></td>
</tr>
<tr>
<td>Time point response after RECIST 1.1 progression</td>
<td><strong>NEW</strong></td>
</tr>
<tr>
<td>Confirmation of progression required</td>
<td><strong>NEW</strong></td>
</tr>
<tr>
<td>Collection of reason why progression cannot be confirmed</td>
<td><strong>NEW</strong></td>
</tr>
<tr>
<td>Inclusion and recording of clinical status</td>
<td><strong>NEW</strong></td>
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iRECIST vs RECIST 1.1: Changes

• New lesions (NL) - assessed using RECIST 1.1 principles
  – Up to 5 (2 per site) measured (NL-T) are included in iSOM
    • Not included in SOM of target lesions identified at baseline
  – Other NLs (measurable/non-measurable) are recorded as non-target (NL-NT)

• Time point (TP) response after RECIST 1.1 PD.
  – Once a PD always a PD is no longer the case
  – First RECIST 1.1 PD is “unconfirmed” - iUPD
  – iUPD must be confirmed at the next assessment (4-8 weeks)

• TP response is dynamic and based on
  – Change from baseline (iCR, iPR, iSD) or change from nadir (PD)
  – The last i-response

Prior iUPD does not preclude subsequent iCR, iPR or iSD
iRECIST vs RECIST 1.1: Changes

• 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
**Summary**

**RECIST 1.1**

**iRECIST DESCRIBES DATA MANAGEMENT, COLLECTION AND USE**

- **PD:** progression
- **iSD:** stable disease
- **iPR:** partial disease
- **iUPD:** unconfirmed progression
- **TP:** timepoint

* iSD and iPR occur AFTER iUPD
* iUPD occurs again and must be confirmed
Confirming Progression (iCPD)

**Disease Burden**

- iUPD (T)
  - ≥ 5mm ↑ in SOM

- iUPD (NT)
  - Any ↑
  - NLT ≥ 5mm ↑ in iSOM
  - NLNT - Any increase

- iUPD (NLs)

**Worsening in lesion category with prior iUPD**

**OR**

- New lesion
- ≥ 20 %↑ in nadir SOM
- UNE ↑ in NT

**NEW RECIST 1.1 PD in lesion category without prior iUPD**
iCPD in Lesion Category with iUPD

If only

- **Target** ≥ 20% ↑
- **Non Target** Unequiv. ↑
- **New lesion**

Then

- ≥5mm ↑
- Any in size ↑
- NLT ≥5mm ↑ NLNT Any ↑ Another NL

Next assessment

= iCPD

= iCPD

= iCPD
New RECIST PD in another Lesion Category

If only

- Target $\geq 20\%$ ↑

Then

- OR

- Non Target Uneq. ↑

Next assessment

= iCPD

OR

- New Lesion

= iCPD
New RECIST PD in another Lesion Category

iUPD

Next assessment

If only Non Target Uneq.↑ Then Target ≥ 20% ↑ OR New Lesion

\[\text{iCPD}\]

\[\text{iCPD}\]
Notes: assigning PD in iRECIST:

• Must be the NEXT assessment – if iSD, iPR or iCR intervenes then bar is reset and iUPD must occur again and be confirmed.

• Two ways to confirm
  – Existing iUPD gets worse – “low bar”
  – Lesion category without prior iUPD now meet RECIST 1.1 criteria for PD – “RECIST PD”

• If confirmatory scans not done must document reason why
Summary: iUPD – T and NL

iRECIST describes data management, collection and use.

PD: progression
iSD: stable disease
iPR: partial disease
iUPD: unconfirmed progression
TP: timepoint

Target vs. Non Target
New lesion
Confirming Progression (iCPD)

Disease Burden

iUPD (T)

≥ 5mm ↑ in SOM

iUPD (NT)

Any ↑ in SOM

iUPD (NLs)

NLT ≥ 5mm ↑ in iSOM

NLNT - Any increase

Worsening in lesion category with prior iUPD

New lesion

NEW RECIST 1.1 PD in lesion category without prior iUPD

OR

UNE ↑ in NT

iUPD

iCPD
Summary

iRECIST describes data management, collection, and use.

PD

iUPD

iCPD

iSD

iPR

Baseline

TP1

TP2

TP3

TP4

TP5

TP6

Target

Non Target

New lesion

TREATMENT
iCPD: Target PD followed by ≥ 5mm↑

**Baseline**

**TP 1:**
- ≥20% ↑ in SOM = PD by RECIST 1.1
- iUPD by iRECIST
- Clinically stable

**TP 2 (4 wks later):**
- SOM ↑ ≥ 5mm above iUPD
- iCPD
**iCPD:** NL then $\geq 5\text{mm} \uparrow$ iSOM

**Baseline:**
Target - para aortic mass

**TP1:**
- T lesion stable ;
- New node = PD / iUPD
- Clinically stable.

**TP2 (+ 4 w):**
- T stable,
- NLT $\uparrow \geq 5\text{mm}$
- iCPD
iCPD: NL then additional NL

Baseline: T - liver

TP1:
- New Lesion
- PD / iUPD
- Clinically stable.

TP 2 (+ 4w)
- TL and NLT no change
- Additional NL
- iCPD
• RECIST 1.1 should remain primary criteria
  – iRECIST exploratory
• iRECIST Event (progression)
  – iUPD date which has been subsequently confirmed
  – If iUPD never confirmed
    • If a subsequent iSD, iPR or iCR is seen with no later iUPD or iCPD then the initial iUPD is ignored
    • Otherwise the iUPD date is used
      – Patient not considered to be clinically stable, stops protocol treatment and no further response assessments are done
      – The next TPRs are all iUPD, and iCPD never occurs.
      – The patient dies of cancer
Investigator/site assessment is the primary method of evaluation for RECIST and iRECIST in keeping with RWG principles.

- Record time-point and best overall response for both RECIST 1.1 and iRECIST.
- Record reasons:
  - Treatment discontinued when iUPD
  - iCPD not confirmed

Independent imaging review can occur in parallel if indicated.
iRECIST in a Nutshell

• RECIST 1.1 – primary criteria
• Progression must be confirmed
  – Consider treatment past progression only in carefully defined scenarios
  – Confirmation requires some worsening of disease bulk
• New lesions
  – Managed using RECIST 1.1 principles
  – NOT added to SOM (but included in separate iSOM)
• Unconfirmed progression does not preclude a later i-response
Conclusions

• Recommendations on terminology, collection and response definitions for trials including immunotherapeutics

• They are not recommendations for treatment decisions
  – How to manage the clinical trial data if treatment is continued past RECIST 1.1 progression

• RECIST 1.1 should continue to be used to define response based endpoints for late stage trials planned for marketing authorisations

• Data collection for testing and validation is ongoing
  – May result in a formal update to RECIST

• The RWG is always happy to address any questions

http://www.eortc.org/recist/contact-us/
RECIST (Response Evaluation Criteria in Solid Tumours) provides a simple and pragmatic methodology to evaluate the activity and efficacy of new cancer therapeutics in solid tumors, using validated and consistent criteria to assess changes in tumor burden. The RECIST Working Group comprises representatives of the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States and Canadian Cancer Trials Group (CCTG), as well as several pharmaceutical companies. Its mission is to ensure that RECIST undergoes
In Press

THE LANCET Oncology

http://www.eortc.org/recist

- This presentation
- Protocol sections
- CRF examples
- FAQ
- A WORD version of the manuscript (after publication)
## Acknowledgments

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*RECIST Working Group Member ** Currently Parker Institute
We also received written comments from:

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