Rethinking RECIST 1.1 - iRECIST for Immuno-Therapies

Imaging Endpoints – Connecting Imaging to the Cure

Immunotherapies are changing the way tumor response is defined. These treatments are directed at the body’s own immune system to invoke a disease response and they are revealing novel changes on imaging including tumor growth and/or new lesions in the setting of clinical stability i.e. pseudoprogression. Over the past decade, many response criteria including modifications to RECIST and Immune-Related Response Criteria (irRC) have been used to assess disease response for immunotherapies leading to confusion due to a lack of consensus on response assessments and the inability to compare datasets across studies. To address this concern, Seymour et al published the iRECIST guidelines, which propose standardized criteria that account for the unique response patterns seen with immunotherapy.

Imaging Endpoints is an Imaging Research and Core Lab (iCRO) based in Scottsdale, Arizona and Waltham, Massachusetts. We specialize in providing the industry’s leading imaging experts, most advanced technology, exquisite service, and experience that extends from translational to phase 3 trials and every step in-between. Our capabilities go above and beyond the typical imaging core lab offering. We provide oncology assessments using criteria based upon RECIST 1.1, iRECIST, Choi, PERCIST, EORTC, IWG-NHL, IWCLL, Lugano, PCWG2, irRC, Macdonald, and RANO criteria, amongst others - and can apply many of these simultaneously across the same imaging time points. We also perform highly sophisticated, cutting-edge radiological evaluations of disease allowing you to capture the maximum value of data from acquired imaging.

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Rethinking RECIST 1.1 - iRECIST for Immuno-Therapies

Radiologic Evaluation of the Immune Response before iRECIST

In 2009, the Immune-Related Response Criteria (irRC)\(^1\) were published. These criteria describe the systemic approach used to assess response for advanced melanoma subjects taking part in the phase II clinical trial program with ipilimumab. At that time, this clinical trial program represented the most comprehensive data set available for an immunotherapeutic agent. These criteria were designed to characterize the different types of response patterns observed with ipilimumab monotherapy which include:

- Standard response: tumor shrinkage without new lesions
- Durable stable disease: initial tumor stability that sometimes was followed by slow steady tumor shrinkage
- Pseudoprogression: response after lesion growth and/or development of new lesions

As a result, irRC differs from RECIST\(^2,3\) and WHO\(^4\) response criteria, which were mainly designed in the era of cytotoxic agents for evaluating the standard response pattern. The key differences of irRC being:

- Requirement for confirmation of progressive disease by a consecutive assessment at least 4 weeks after first documentation
- New lesions do not always represent PD, instead irRC allows for response in the presence of new lesions
  - New lesions that meet measurability criteria are added to the baseline sum of the products of perpendicular diameters and only when this sum of baseline target lesions and new lesions increases to greater than 25% of baseline did it denote progression.

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New lesions that do not meet measurability criteria prevent an assessment of complete response and do not play a role in progression.

Since the publication of irRC in 2009, recommendations to align irRC with RECIST 1.1 have been made. In 2013 a group of researchers re-analyzed a subset of the phase II ipilimumab subjects using the irRC with one key difference: unidimensional longest diameter tumor measurements like RECIST 1.1 rather than bidimensional tumor measurements like irRC. This publication, often referred to as irRECIST, showed that irRC using unidimensional measurements was highly concordant with irRC assessments, with less measurement variability, while being easier to implement. Multiple other irRECIST-like criteria subsequently emerged, each providing valuable recommendations, but together leading to variations in the assessment of response in the setting of immunotherapy. As a result, a more standardized and universally accepted approach has been needed to simplify the assessment of immune response and maintain consistency across treatment regimens permitting comparison of radiologic response assessments across multiple trials and treatment regimens.

**The new iRECIST**

iRECIST provides a uniform approach to the evaluation of solid tumors in trials where an immunotherapy is used. A critical aspect to the success of iRECIST is the goal to collect data for future trials. A data warehouse has been developed with the intent of sharing anonymized, patient level data to formally validate iRECIST.

The authors of iRECIST advise 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. For more exploratory and earlier phase trials, iRECIST can be considered as the primary method of disease response evaluation. A benefit of iRECIST that Imaging Endpoints would like to highlight, is that iRECIST can easily be conducted in parallel with RECIST 1.1 on the same imaging timepoints. Thus, allowing trials to result in both RECIST 1.1 and iRECIST data sets without doubling work. Imaging

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Endpoints believes this will encourage the use of iRECIST in alignment with the authors’ recommendations.

**iRECIST in Practice**

An iRECIST response assessment begins with categorization of disease on the baseline imaging. Disease is categorized as target or non-target lesions per RECIST 1.1. Target lesions are measured identical to RECIST 1.1 in their longest diameter (or short axis for nodes) and a sum of measures (SOM) is calculated by summing the target lesions measurements. Follow-up time points are also assessed per RECIST 1.1 until progressive disease (PD), at which time point the unique rules of iRECIST begin to be applied. Cornerstone to these rules, is the categorization of new lesions as new target lesions (NTL) or new lesion non-targets (NLNT). NTLs must meet the RECIST 1.1 target lesion size requirements and are measured per RECIST 1.1. Up to 5 NTLs with a maximum of 2 in a single organ can be measured. A SOM of NTLs (separate from the SOM for target lesions) is calculated. Any new lesions not categorized as NTLs are categorized as NLNT and followed qualitatively.

**Table 1: iRECIST Disease Categories**

<table>
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<tr>
<th>iRECIST Lesion Categories</th>
<th>Definition</th>
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</table>
| **Target Lesions**        | Per RECIST 1.1:  
  - Identified at baseline  
  - ≥10 mm in long diameter (15 mm for nodal lesions)  
  - Maximum of 5 target lesions, 2 per organ |
| **Non-Target Lesions**    | Per RECIST 1.1:  
  - Identified at baseline  
  - All baseline disease that is not categorized as a target lesion  
  - Nodes must be ≥10 mm in short axis |
| **New Target Lesions (NTL)** | Unique to iRECIST:  
  - Identified at follow-up  
  - ≥10 mm in long diameter (15 mm for nodal lesions)  
  - Maximum of 5 target lesions, 2 per organ |
| **New Lesion Non-Targets (NLNT)** | Unique to iRECIST:  
  - Identified at follow-up  
  - All new lesions not categorized as new target lesions |

iRECIST diverges from RECIST at PD, at which time point the response assessment becomes immune unconfirmed PD (iUPD) by iRECIST criteria ([Figure 1](#)). After iUPD, subsequent time points can either confirm PD or “reset the bar” for another response to apply per iRECIST ([Table 2](#)).
**Figure 1: Exemplar Response Assessments: iRECIST diverges from RECIST 1.1 at PD**

**Example 1: progression immediately confirmed**

**RECIST 1.1 Response Assessments**
- Baseline
- Follow-up 1: SD
- Follow-up 2: PD

**iRECIST Response Assessments**
- Follow-up 2: iUPD
- Follow-up 3: iCPD

**Example 2: confirmed response after iUPD; pseudoprogression**

**RECIST 1.1 Response Assessments**
- Baseline
- Follow-up 1: SD
- Follow-up 2: PD

**iRECIST Response Assessments**
- Follow-up 2: iUPD
- Follow-up 3: iPR
- Follow-up 4: iPR

**Example 3: bar is reset and progression is later confirmed**

**RECIST 1.1 Response Assessments**
- Baseline
- Follow-up 1: SD
- Follow-up 2: PD

**iRECIST Response Assessments**
- Follow-up 2: iUPD
- Follow-up 3: iSD
- Follow-up 4: iUPD
- Follow-up 5: iCPD
### Table 2: iRECIST Response Assessment Definitions

<table>
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<tr>
<th>iRECIST Responses</th>
<th>Definition</th>
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| Complete Response (CR) | **Defined per RECIST 1.1:**  
  • All lesions resolve (lymph nodes normalize to <10mm in short axis) and  
  • No new lesions |
| Partial Response (PR) | **Defined per RECIST 1.1:**  
  • A ≥30% decrease in SOM of target lesions when compared to baseline and  
  • No new lesions |
| Stable Disease (SD) | **Defined per RECIST 1.1:**  
  • A <30% decrease in SOM of target lesions when compared to baseline (not meeting PR) and a <20% increase in SOM of target lesions when compared to nadir (not meeting PD)  
  • No new lesions |
| Progressive Disease (PD) | **Defined per RECIST 1.1:**  
  • A ≥20% increase in SOM of target lesions when compared to nadir and an increase in SOM of ≥5mm OR  
  • Unequivocal progression of non-target lesions OR  
  • Any new lesions  

**Note:** The response assessment of PD is converted to iUPD in an iRECIST data set.

| Immune Unconfirmed Progressive Disease (iUPD) | • Always the first iRECIST time point assessment (corresponds to the RECIST 1.1 PD time point as defined above)  
  • There can be multiple iUPD assessments with no iCPD when the original cause of iUPD still exists and no other causes of progression appear |
| Immune Confirmed Progressive Disease (iCPD) | • Can only be reported immediately following iUPD  
  • Requires any original cause of iUPD to worsen or for another cause of progression to appear (see Figure 2) |
| Immune Complete Response (iCR) | • Can only occur after an assessment of iUPD (does not need to be immediately after iUPD)  
  • All lesions resolve (lymph nodes normalized) |
| Immune Partial Response (iPR) | • Can only occur after an assessment of iUPD (does not need to be immediately after iUPD)  
  • A ≥30% decrease in SOM of target lesions when compared to baseline SOM  
  • Can occur in the presence of new lesions |
| Immune Stable Disease (ISD) | • Can only occur after an assessment of iUPD (does not need to be immediately after iUPD)  
  • <20% increase in SOM when compared to nadir and a <30% decrease in SOM when compared to baseline  
  • Can occur in the presence of new lesions |
Reseting the bar and confirmation of PD are imperative concepts that differentiate iRECIST from RECIST 1.1.

Reseting the bar occurs when iUPD is not confirmed and instead there is tumor shrinkage. This is when the assessments of iCR, iPR, and iSD are applied, thus resetting the bar so that iUPD must occur again. It is important to note that the comparator for iUPD is always the nadir values and iUPD can be assessed multiple times in a row if progression is not confirmed.

iRECIST manuscript makes it clear that confirmation of progression requires worsening disease defined within a lesion category, or for another cause of progression to appear (Figure 2). Confirmation of disease progression must occur at least 4 weeks and no more than 8 weeks after initial disease progress. Figure 3 provides an example application of iRECIST and includes the scenario of iUPD followed by iCPD.
Figure 2: Ways to confirm progression using iRECIST (iCPD)

iCPD requires any original cause of iUPD to worsen
OR another cause of progression to appear

Original Cause of iUPD

Target lesion progression: A ≥20% increase in SOM of target lesions when compared to nadir and an increase in SOM of ≥5mm

Further increase in SOM of target lesions, with an increase of at least 5mm

Non-target lesion progression: Unequivocal progression in non-targets

Any additional growth of non-target lesions

Appearance of New Lesions: A ≥5mm increase in the SOM of NTL since iUPD OR Any growth in NTNL OR Additional new lesions

Worsening of original cause of iUPD

Target lesion progression: A ≥20% increase in SOM of target lesions when compared to nadir and an increase in SOM of ≥5mm

Non-target lesion progression: Unequivocal progression in non-targets

Appearance of New Lesions

Another Cause of progression appears

Target lesion progression: Non-target lesion progression OR appearance of new lesions

Non-target lesion progression: Target lesion progression OR appearance of new lesions

Appearance of New Lesions: Target lesion progression OR non-target lesion progression

New cause
Figure 3: Applying iRECIST

Applying iRECIST

There are 3 target lesions at baseline with a Sum of Measures of 60 mm.

At Follow-up 1, target lesion SOM is 85, an increase of 41.7%, which is more than 20% and there is a 5 mm increase in SOM meeting criteria for PD by RECIST 1.1

By iRECIST this meets criteria for iUPD.

At Follow-up 2, target lesion SOM is 95, which is a further increase with a greater than 5mm increase in SOM since iUPD, meeting criteria for iCPD.

The Time Point of Progression is Follow-up 1 (with confirmation at Follow-up 2).
**Time Point of Progression**

When using iRECIST to determine PFS, the date of progression is the first date that progression is met (i.e. the iUPD time point) if it is subsequently confirmed. iUPD is not considered progression when not confirmed. Furthermore, in trials with cross-over treatment, the protocol must clearly state if a iUPD or iCPD is the trigger for cross-over though iRECIST suggest iCPD be considered.

**Best Overall Response**

In iRECIST, the Best Overall Response (iBOR) is the best overall time point overall response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. As with RECIST 1.1, iRECIST recommends confirmation of response only be required for non-randomized trials. When confirmation of response is required by the study protocol, iRECIST recommends the confirmation be at least 4 weeks after the initial response.

Unlike RECIST 1.1, the iRECIST BOR can occur after initial progression (i.e. after an assessment of iUPD). Therefore, iSD, iPR, and iCR are valid BOR assessments. The duration of response for iCR and iPR is considered from the time the criterion is first met and the duration of stable disease is calculated from baseline.

**Cutting Edge Experience in Immunotherapy — The Imaging Endpoints Difference**

Imaging Endpoints has maintained a leadership role in the immunotherapy imaging field. Our scientific and operational leadership team has hands-on experience with multiple immune response criteria as well as other single or composite endpoint analysis. At Imaging Endpoints, we go beyond what other imaging core labs have to offer when it comes to image analysis. This is driven by our belief that images are rich sources of high-content data that can be utilized in unique ways to highlight new insights into tumor biology, treatment responses and predictive/prognostic imaging biomarkers. Our approach to imaging analysis beyond RECIST is unique amongst imaging core labs and can help accelerate clinical trials by deepening the understanding of how new drugs, devices and products can be applied in clinical trials. As an example, we have developed an immune response signature based on a radiogenomic approach using CT textural analysis on standard-of-care images to determine whether patients will respond to PD-L1 therapy by interrogating their baseline scans only. With this information, we have been collaborating with some of the most well-known investigators in the immunotherapy arena to better identify with imaging what makes one person likely to respond to therapy while another person will not. Imaging Endpoints has also been very active providing services to a multitude of sponsors in their Phase 1-3 clinical trials that focus on single immunotherapy treatments or combination therapies.
Imaging Endpoints - Exceptional Scientific Guidance

At Imaging Endpoints, we excel in dedicating expert and nimble project teams that adapt to meet the changing needs of your trials. We routinely work with our sponsors to not only design their central review plan but to assist in protocol development, CRF development, and assessment criteria utilization, ensuring a robust final data set. We will assist you by providing guidance, expertise and planning for your product pipeline and ensure that every aspect of radiology science has been considered to the fullest extent possible. As your partner, we will take the lead in developing imaging protocols/techniques that will take advantage of the latest imaging discoveries in oncology and immunology and successfully integrate them into the multicenter environment that will focus on the needs of your clinical trial.