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Introduction to iRECIST

Howard Tien, Sanofi, Beijing, China

ABSTRACT

In 2000, the Response Evaluation Criteria in Solid Tumours (RECIST) was proposed, later in 2009, RECIST was refined to version 1.1. Ever since, this criterion was used broadly in the solid tumours oncology clinical trial efficacy endpoint evaluation.

However, recently the emerging of the immunotherapies, tumours response differently compared to the chemotherapeutic drugs. The late but deep and durable response was one of the unique patterns.

Therefore, the immunotherapy RECIST, termed as iRECIST, was developed by the RECIST working group, which modified base on the RECIST 1.1, is the consensus guidelines to deal with this immunotherapy tumour response.

This paper discusses the key points of the difference between iRECIST and RECIST, statistical and protocol considerations, the difference of CRF collection and summary of the iRECIST criteria.

INTRODUCTION

In this paper, we summarized the information in iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics by Seymour et al, and the training slides from the iRECIST working group for the readers with following points: The difference between iRECIST and RECIST, statistical and protocol consideration, difference between data collection and a summary to the iRECIST criteria

WHAT IS RECIST?

Back in 1981, World Health Organization (WHO) published the first tumour response criteria. However, the specification documents were not so clear, causing inconsistent conclusions. In 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) were developed and published by an international collaboration including European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute (NCI) of the United States, and the National Cancer Institute of Canada Clinical Trials Group.

Ever since, many investigators, industry and government authorities adopted these criteria in the efficacy endpoints assessment of the oncology clinical trials, which including the changed in tumour size and disease progression. However, just like the guidance of WHO in 1981, number of questions and issues have arisen (for example, how to handle assessment of lymph nodes?) which based on separate papers, large data warehouse (EORTC, over 6500 patients), simulation studies and literature reviews, have led to the revision of the RECIST guideline (version 1.1).

Currently, RECIST 1.1 is the most used solid tumour assessment criteria in oncology clinical trials since it provide standardization, and the published rules and criteria are well established provide a framework for reproducible analysis and reporting of changes in tumour size. The set of rules that defined when cancer patients improve (“respond”), stay as the same (“stable”) or worsen (“progression”) during treatments. For more detail information of RECIST 1.1, reader can refer to New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) by E.A. Eisenhauer et al.

So, if RECIST can handle most of the solid tumour assessment, why do we need iRECIST?

IMMUNO-ONCOLOGY AND IRECIST

Recently, the emerging of immune oncology, including the modulators Cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) pathways are the most studied, and have been used for multiple type of cancers, which including melanoma, lung, bladder, renal and head and neck cancer, which is a major advancement in patient care.

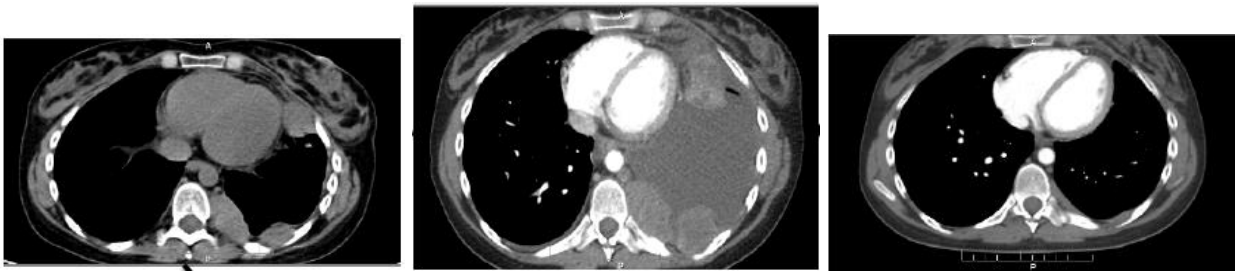
However, in early immune-based therapeutics in melanoma, investigators described unique response patterns, terms pseudoprogression. Some patients were noted to have late but deep and durable responses. In RECIST 1.1, these criteria, would met the criteria for disease progression in early stage, see Figure 1.

In 2009, based on the WHO criteria, a modified response criteria was proposed, which including collection of bidimensional measurements of target lesion, named as immune-related response criteria (irRC). In 2013, researchers revised the irRC using unidimensional measurement based on the original RECIST, and some published incorporate with RECIST 1.1. These modifications often referred to irRECIST. But, these assessment doesn’t applied

consistently, leading the concerns about the comparability of data and results across trials, difficulty with pooling databases and without a standardize and validate response criteria dealing with immune oncology tumour assessment. Few concerns also arisen, including may not be applicable to all tumour types, since these multiple variation of immune criteria were developed primarily in melanoma.

Therefore, the RECIST working group planned to create a large data warehouse from immunotherapeutics to test and validate RECIST 1.1 and suggest modification if needed. Working group also works closely with pharmaceutical company, regulatory authorities and academia to ensure the consistent design to facilitate the ongoing collection of clinical trial data.

A modified RECIST 1.1 for immune-based therapeutics, termed iRECIST was proposed on 2017, aiming to provide a guideline for data management and data collection for trials testing immunotherapeutics. As above, iRECIST is a data management approach, not yet validated response criteria, usually will be used as exploratory endpoints, and are not treatment decision guidelines.



Baseline | Time point 1, Progression per RECIST 1.1 | Time point 2, Complete Response

Figure 1 An example of pattern of immunotherapeutics tumour response from training slides by iRECIST working group

IRECIST

TERMINOLOGY

Prefix “i”, stands for immune, were added to the disease responses in iRECIST which based in RECIST 1.1 – eg, immune complete response (iCR), immune partial response (iPR), immune unconfirmed progressive disease (iUPD), immune stable disease (iSD) and immune confirmed progressive disease (iCPD) to distinct with the response assigned in RECIST 1.1. New lesions are assessed and categorized into target lesion (new lesion, target) or non-target lesions (new lesion, non-target).

COMPARE TO RECIST 1.1

The continued use of RECIST 1.1 is recommended to define whether tumour lesions, including lymph nodes, are measurable or non-measurable. Also, no changes have been made to the recommendation of the method of measurement. However, modern imaging techniques, e.g., CT scans and MRI are preferred. Most of the guideline of objective tumour assessment response is mainly unchanged compare to RECIST 1.1, including definitions of measurable, non-measurable disease, definitions of target and non-target lesions, calculation of sum of diameters, definitions of complete (CR), partial (PR) and stable (SD) disease and their duration, confirmation of CR and PR and when applicable and definition of progression in target and new target lesion. However, few significant changes for iRECIST were made. One is management of new lesions and one is the concept of resetting the bar, we will make an introduction of these two points below. Detail information for difference between RECIST 1.1 and iRECIST, reader can refer to iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics by Seymour et al, table 1: Comparison of RECIST 1.1 and iRECIST.

New Lesion

For new lesion, diameters now was measured for new lesion target, assessed using RECIST 1.1 principles, which including classified as measurable or non-measurable lesion and only up to five (two per site) was measure, and should not include in the sum of the original baseline target lesion measurement. As for other new lesions, are recorded as new lesion non-target. The response for new lesion non-target was quantitative responses, including unequivocal progression for example. See Figure 2 for case report form example for new lesion.

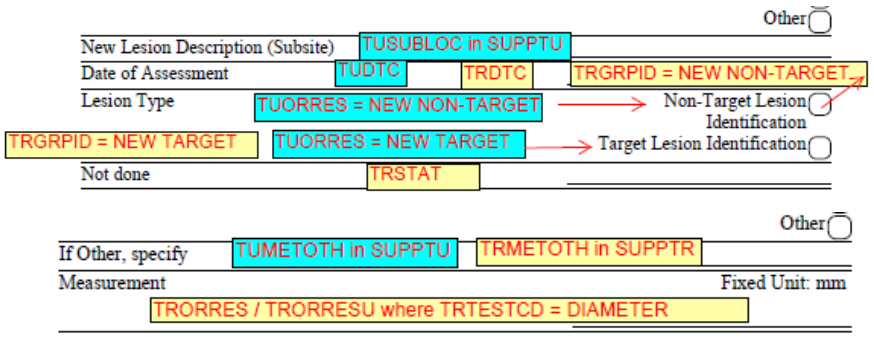


Figure 2 Case report form example for new lesion, where new lesion target diameter was measured.

Immune unconfirmed progressive disease

As in Figure 1 described, if RECIST 1.1 were applied for this case, then at time point 2, would have been classified as progression disease. Furthermore, in RECIST 1.1, once a time point is PD, the response is always a PD. However, in iRECIST, this is no longer the case due to resetting the bar.

iRECIST introduced iUPD on the basis of RECIST 1.1, defined by RECIST 1.1 criteria for progressive disease, requires confirmation in the following assessment to get iCPD, due to the late but deep and durable responses by immunotherapeutics. Which is done by observing either a further increase in size or number of new lesions in the same lesion category where the progression was first identified (target lesion, non-target lesion or new lesion) (low bar, see Figure 3), or progression (defined by RECIST 1.1) on where the lesion categories that had not met progression (defined as well by RECIST 1.1) previously (see Figure 4), then the following assessment is considered as iCPD.

One thing to note, iUPD must be confirmed at the next assessment within 4 to 8 weeks, and iUPD can be assigned multiple times as long as iCPD is not confirmed in the next assessment. In the other hands, RECIST 1.1, in which any progression precludes the following CR, PR and SD.

However, if the iUPD is not confirmed, but the tumour shrinkage appears, which meets the criteria of iCR, iPR or iSD (change from baseline), then the bar is reset so that iUPD need to occur and to be confirmed at the next assessment for iCPD again. If no change in tumour size or increase of lesion number from iUPD occurs, then next time point would be iUPD as well. If confirmatory scans not done must document the reason why.

As shown, the algorism with no previous iUPD is identical between RECIST 1.1 and iRECIST. However, if iUPD appears in any time point, the following next assessment response is dependent on the status of target lesion, non-target lesion, new lesion target, new lesion non-target and whether any new lesion appears.

Assessment for Target lesion

iUPD is defined by RECIST 1.1 target lesion progression disease, and iCR, iPR and iSD can all be assigned after iUPD been recorded, as long as not confirmed. The confirmation of iUPD (in target lesion category), is done by a further increase in sum of diameter of the target lesion greater than 5 mm in the next assessment within 4 to 8 weeks.

The confirmations of iUPD are not considered done if iCR, iPR or iSD criteria were met in the next assessment. The status is reset, as we mentioned above. Moreover, if no changed is detected, nor iCPD, iCR, iPR or iSD, then the time point response for target lesion is iUPD.

Assessment for Non-target lesion

The assessment for non-target lesion follows similar principles, iUPD is defined by RECIST 1.1 non-target lesion progression disease and can be recorded before iCR or non-iCPD/non-iUPD (when the criteria for neither CR nor PD have been met) with multiple times. The confirmation of iUPD (in non-target lesion category) must be done in the next assessment within 4 to 8 weeks if any further increase in the size of non-target disease.

Assessment for New lesion

In iRECIST, new lesions are now measured by new lesion target and new lesion non-target. For new lesion target, sum diameters are collected, but should not include with the baseline target lesion sum of diameter. If any new lesion appears (target or non-target), then the time point response for new lesion is considered as iUPD. The confirmation of iUPD (in new lesion category) must be done in the next assessment within 4 to 8 weeks if any additional new lesions appear or sum of diameters of new lesion target increase by more than 5 mm.

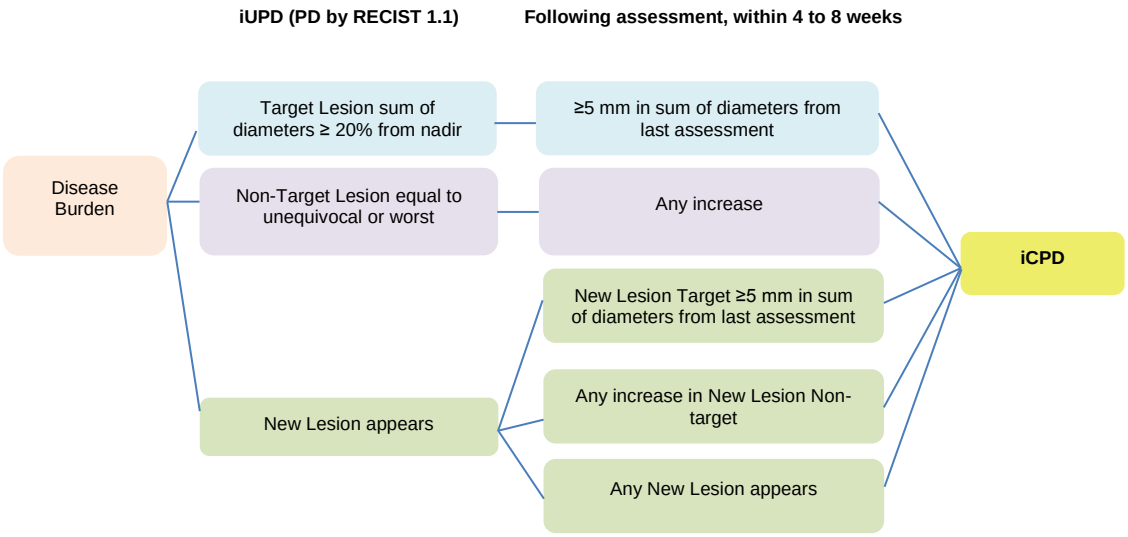


Figure 3 Existing iUPD gets worse, where iCPD in lesion category with iUPD ("Low bar")

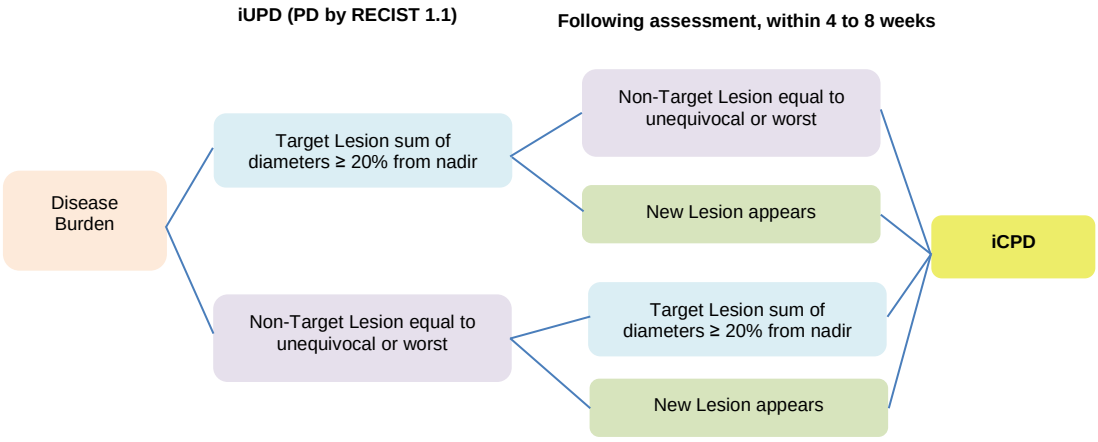


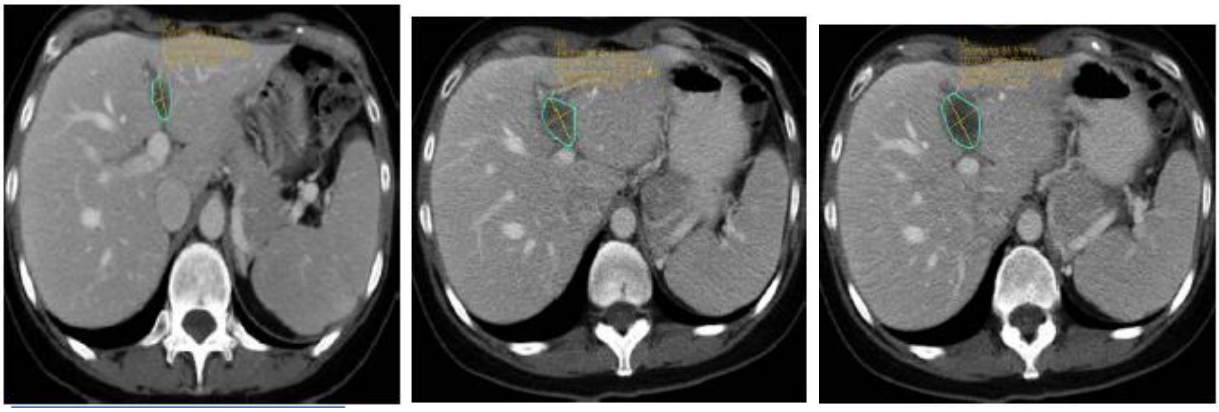
Figure 4 Another RECIST 1.1 PD in another Lesion category without prior iUPD

TIME POINT AND BEST OVERALL RESPONSE

Although the time point assessment is similar to RECIST 1.1, but the presence of new lesions, pseudoprogression and iUPD increase the complexity of the assessment. In iRECIST, results of last time point for target, non-target, new lesion target and new lesion non-target, whether any increase in size has occurred or any additional new lesions should be all take into consideration. If there is no prior iUPD appears in any lesion category (target, non-target and new lesion), then the time point response is identical with the RECIST 1.1 results. However, if iUPD have been met, the next time point response could be iCPD if disease burden worsen (in target lesion, non-target lesion or new lesion). The response could also be iSD, iPD and iCR (the reset bar), or iUPD if no changes noted in any lesion category. For more detail information, reader can refer to Supplementary Appendix to iRECIST: Guidelines for response for use in trials testing immunotherapeutics by Seymour et al., table S2: Integration of target, non-target and new lesions into response assessment.

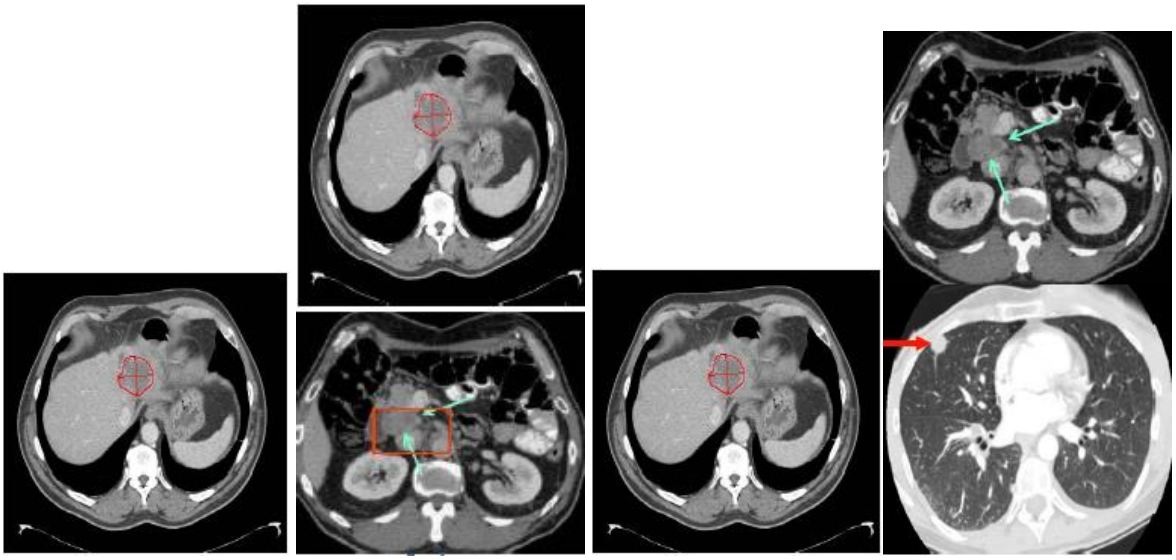
EXAMPLES AND SCENARIOS

Few examples and scenarios were provided by iRECIST working group.



Baseline	Time point 1	Time point 2
RECIST 1.1	PD	PD
iRECIST	iUPD, target lesion sum of diameter ≥ 20% from nadir	iCPD, target lesion sum of diameter ≥ 5 mm from last assessment

Figure 5 iCPD confirmed by target lesion sum of diameter increase by more than 5 mm



Baseline	Time point 1	Time point 2
RECIST 1.1	PD	PD
iRECIST	iUPD, new lesion target appears	iCPD, target lesion and new lesion target no change, another new lesion appears

Figure 6 iCPD confirmed by additional new lesion

	Baseline	Time point 1	Time point 2	Time point 3	Time point 4	Time point 5
Target lesion sum of diameter	100	130	105	115	120	125
% Change from baseline		30%	5%	15%	20%	25%
Nadir		100	100	100	100	100
% Change from nadir		30%	5%	15%	20%	25%
RECIST 1.1		PD	PD	PD	PD	PD
iRECIST		iUPD, ≥ 20% from nadir	iSD, by change from baseline ("Reset")	iSD	iUPD, ≥ 20% from nadir	iCPD, ≥ 5mm increase from last assessment

Table 1 Example of resetting, then iUPD occurs again. Last, confirmed by increase of diameter of target lesion sum of diameter

	Baseline	Time point 1	Time point 2	Time point 3	Time point 4	Time point 5
Target lesion sum of diameter	100	130	80	70	110	120
% Change from baseline		30%	-20%	-30%	10%	20%
Nadir		100	100	80	70	70
% Change from nadir		30%	-20%	-12.5%	57%	71%
New lesion					Non-target +	Non-target ++
RECIST 1.1		PD	PD	PD	PD	PD
iRECIST		iUPD, ≥ 20% from nadir	iSD, by change from baseline ("Reset")	iPR, by change from baseline	iUPD, ≥ 20% from nadir and new lesion appears	iCPD, ≥ 5mm increase from last assessment and additional new lesion appears

Table 2 Example of resetting, then iUPD occurs again. Last, confirmed by increase of diameter of target lesion sum of diameter and additional new lesion appears

	Baseline	Time point 1	Time point 2	Time point 3	Time point 4	Time point 5
Target lesion sum of diameter	100	130	60	71	75	78
% Change from baseline		30%	-40%	-29%	-25%	-22%
Nadir		100	100	60	60	60
% Change from nadir		30%	-40%	18%	25%	30%
Target lesion response		iUPD, ≥ 20% from nadir	iPR, ≤ -30% from baseline ("Reset")	iSD, >-30% from baseline, and <20% from nadir	iUPD, ≥ 20% from nadir	iUPD, cannot confirm since only increase by 3 mm
Non-target lesion		Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD	Non-CR/Non-PD
New lesion		Target + (14mm)	Target + (12mm)	Target + (10mm)	Target + (14mm)/ Non-target +	Target + (14mm)/ Non-target ++
RECIST 1.1		PD	PD	PD	PD	PD
iRECIST		iUPD, ≥ 20% from nadir and one new target lesion appears	iPR, since target lesion response became iPR and non-target lesion is stable, and no increase on new lesion	iSD, since target lesion response became iSD and non-target lesion is stable, and no increase on new lesion	iUPD, since target lesion became iUPD and we have one new non-target lesion appears	iCPD, since we have another new lesion non-target appears, which confirmed the previously iUPD

Table 3 Example of resetting, then iUPD occurs again. Last, confirmed by different lesion category

STATISTICAL AND PROTOCOL CONSIDERATION

The event date for progression free survival in iRECIST should be the first date of the progression appears and confirmed in the following assessment. If iSD, iPR or iCR occurs after the iUPD (not confirmed), then we should not consider this iUPD date as our event date. In some cases, if we have consecutive iUPD and confirmed, then the first iUPD date in the sequence should be used. If the confirmation (iCPD) never occurs, the event date will not occur.

If progression is not confirmed and no subsequent iSD, iPR or iCR, then the date of the iUPD should still be used in below cases: if patients were not clinically stable to stops protocol treatment, no further assessment (due to below reasons: patients refusal, protocol non-compliance or death), or all following time point are all iUPD, and iCPD never occurs.

Both iRECIST and RECIST 1.1 recommended for phase 3 clinical trials and RECIST 1.1 should be used for primary efficacy outcome. iRECIST should be used for exploratory analysis and in early phase trials, iRECIST can consider being used for primary endpoint criteria.

CONCLUSION

Immunotherapeutics is a new emerging treatment and a significant advantage for cancer patient. RECIST 1.1 may not always adequately capture the unique response of the disease response. iRECIST introduce the confirmation of progression to rule out or confirm pseudoprogression and collect more information for the new lesion. The iRECIST working group is now underway of the creation of the data warehouse, and update is available from EORTC when available. The implementation and the validation of iRECIST provide robust guidance to improve treatments for the patients.

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- Supplementary Appendix to: iRECIST: Guidelines for response for use in trials testing immunotherapeutics
- Presentation EORTC-NCI-AACR meeting (December 1, 2016), available at http://recist.eortc.org/irecist/
- iRECIST training set of slides, available at http://recist.eortc.org/irecist/

ACKNOWLEDGMENTS

I would like to acknowledge Sufang Huang, for introducing me to the concept of the iRECIST. Moreover, I would especially like to thank my wife, Cassie has been incredibly supportive, and our sweetest newborn daughter, Sheena.

RECOMMENDED READING

- New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)
- iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics
- Presentation EORTC-NCI-AACR meeting (December 1, 2016), available at http://recist.eortc.org/irecist/
- iRECIST training set of slides, available at http://recist.eortc.org/irecist/

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Name: Howard Tien
Enterprise: Sanofi
Address: 2/F, HNA Building, No. 110, Jianguo Road, Chaoyang District
City, State ZIP: Beijing, 100022, China
E-mail: howard.tien@sanofi.com

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