PharmaSUG 2020 - Paper DS-82

Implementation of Immune Response Evaluation Criteria in Solid Tumors (iRECIST) in Efficacy Analysis of Oncology Studies

Weiwei Guo, Merck & Co., Inc., Rahway, NJ, USA

ABSTRACT

In recent years the Immunotherapy have gained attention as being one of the most promising types cancer treatment on the horizon. Immunotherapy, also called biologic therapy, is a type of cancer treatment that boosts the body's natural defenses to fight cancer. While conventional RECIST criteria have served us well in evaluating chemotherapeutic agents, in immuno-oncology, a small percentage of patients manifest a new response pattern termed pseudoprogression, in which, after the initial increase in tumor burden or after the discovery of new lesions, a response or at least a prolonged stabilization of the disease can occur. Tumors respond differently to immunotherapies compared with chemotherapeutic drugs, raising questions about analysis of efficacy. Therefore, a novel set of anti-tumor assessment criteria iRECIST was published to standardize response assessment among immunotherapy clinical trials. In this paper, the difference between the RECIST and iRECIST criteria assessment is described first, then a step by step implementation of iRECIST in efficacy analysis in solid tumors oncology studies using investigator assessment (INV) will be provided starting from the data collection up to the final statistical analysis.

INTRODUCTION

In recent years cancer immunotherapy have gained attention as being one of the most promising types cancer treatment on the horizon. Immunotherapy, also called biologic therapy, is a type of cancer treatment that boosts the body's natural defenses to fight cancer. In March of 2011, first immune checkpoint inhibitor Yervoy from Bristol-Myers Squibb targeting CTLA-4 was approved by FDA for the treatment of late-stage Melanoma. Since 2015, Keytruda (pembrolizumab) from Merck targeting PD-1 ligands has been approved by FDA to treat various types of cancers like Advanced Melanoma, NSCLC, Head and Neck, Hodgkin's Lymphoma, Urothelial (Bladder) Carcinoma, Gastric (Stomach) Cancer, Cervical Cancer, HCC, RCC etc. Anticancer activity derived from chemotherapeutic agents traditionally has been assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. While these guidelines have served us well in evaluating chemotherapeutic agents, recent research experience in immuno-oncology has indicated that the clinical benefit from immunotherapy might extend beyond that of cytotoxic agents. For example, stable disease or responses to immunotherapy may occur after conventional PD due to clinically insignificant new lesions in the presence of other responsive lesions and reduction of the total tumor burden. Therefore, discontinuation of immunotherapy at the first sight of PD may not be appropriate in some cases. In addition, measurable antitumor activity may take longer for immunotherapies than for cytotoxic agents, and durable stable disease (SD) may represent meaningful antitumor activity. Therefore, a guideline iRECIST was developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data. In this paper, first I will introduce the background and evolving history of iRECIST, then compare the difference between the RECIST 1.1 and iRECIST, then use a specific example based on investigator assessment (INV) to show how to implement iRECIST in immune-oncology clinical trials.

BACKGROUND AND HISTORY

In 2000, the Response Evaluation Criteria in Solid Tumours (RECIST) working group simplified the 1981 WHO response criteria after validation in a large data warehouse. In 2009, RECIST was refined to RECIST version 1.1. In 2009, modified response criteria based on WHO criteria (which include the collection of bidimensional measurements of target lesions) were proposed—the immune-related response criteria (irRC). Later researchers published revised irRC using unidimensional measurements based on the original RECIST and subsequent recommendations and modifications are often referred to as irRECIST. However, the irRECIST was not applied consistently across all clinical trials and substantial difference in which criteria were used was seen across clinical trials within pharmaceutical companies and cooperative groups. These caused serious concerns about interpretation of pooled datasets. Additionally, most of the trials which need immune-modified criteria used independent review committees (IRC) data from a vendor, rather than investigator assessments (INV). Response criteria should be applicable across all cancer clinical trials, including those done in the academic sector, where costly independent review is not feasible. On the basis of these observations, the RECIST working group decided to develop a guideline for the use of a modified RECIST to ensure consistent design and data collection that would facilitate the ongoing collection of clinical trial data and ultimate validation, if indicated, of a modified RECIST 1.1 for immune-based therapeutics (termed iRECIST)[1]. For most of the phase 3 clinical trials which incorporate both RECIST 1.1 and iRECIST, RECIST 1.1 is used to define the primary efficacy outcomes and iRECIST is for the exploratory purpose and patient management.

Table 1. Comparison of RECIST 1.1 and iRECIST[1]

	RECIST 1.1	iRECIST
Definitions of measurable and nonmeasurable 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-randomized 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

Responses assigned using iRECIST have a prefix of "i" like complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. iRECIST have identical definitions of CR, PR and SD as RECIST 1.1 guidelines, but differ in cases of progression, the iRECIST guideline need confirmation for the PD.

TIMEPOINT AND OVERALL RESPONSES

iRECIST criteria starts from when the initial PD is accessed per RECIST. For example, the patient 001 (table 2) at the beginning the responses were evaluated by RECIST 1.1 category until the appearance of the first PD (visit 4). With the appearance of the first PD based on RECIST 1.1, the responses will start to be evaluated by the iRECIST, the first visit (visit 4) showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD in iRECIST category, regardless of which factors caused the progression, as seen in the highlighted visit in table 2. In next visit, if an increase in size is observed, or the number of new lesions appear in the lesion category in which progression was first identified in (ie, target or non-target disease), then the progression will be confirmed as iCPD (patient 002, visit 5). However, if progression is not confirmed, but instead tumor shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the response will be called iSD (patient 001, visit 5) or iPR (patient 001, visit 6). In the next visit (patient 001, visit 7), for example the tumor size increased to meet the progression criteria, the bar will be reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment (patient 001, visit 8) for iCPD to be assigned.

Table 2. Example of Patient 001

Patient ID	visit	Date	RECIST Category	Response
001	1	05/12/2016	RECIST 1.1	SD
001	2	07/14/2016	RECIST 1.1	PR
001	3	09/15/2016	RECIST 1.1	PR
001	4	11/17/2016	RECIST 1.1	PD
001	4	11/17/2016	iRECIST	iUPD
001	5	01/17/2017	iRECIST	iPR
001	6	03/23/2017	iRECIST	iPR
001	7	05/25/2017	iRECIST	iUPD
001	8	06/25/2017	iRECIST	iCPD

Table 3. Example of Patient 002

Patient ID	visit	Date	RECIST Category	Response
002	1	05/12/2016	RECIST 1.1	SD
002	2	07/14/2016	RECIST 1.1	PR
002	3	09/15/2016	RECIST 1.1	PR
002	4	11/17/2016	RECIST 1.1	PD
002	4	11/17/2016	iRECIST	iUPD
002	5	01/17/2017	iRECIST	iCPD

After the appearance of the first PD, if no change in tumor size or extent from iUPD occurs, then the timepoint response would again be iUPD (patient 003, visit 5). This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterized.

Table 4. Example of Patient 003

Patient ID	visit	Date	RECIST Category	Response
003	1	05/12/2016	RECIST 1.1	SD
003	2	07/14/2016	RECIST 1.1	PR
003	3	09/15/2016	RECIST 1.1	PR
003	4	11/17/2016	RECIST 1.1	PD
003	4	11/17/2016	iRECIST	iUPD
003	5	01/17/2017	iRECIST	iUPD
003	6	03/23/2017	iRECIST	iCPD

BEST OVERALL RESPONSES

Although the principles of the assignment of the timepoint response and best overall response closely follow RECIST 1.1, the possibility of pseudoprogression adds complexity. According to iRECIST guideline 'For iRECIST, the best overall response (iBOR) is the best timepoint response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation.' Since the criteria before the initial progression is based on RECIST 1.1, the iRECIST criteria starts from when the initial PD is accessed per RECIST, naming the best overall response across the whole treatment period as iBOR maybe causing confusion, in this paper I will use 'BOR' for the best overall response from the start of the study treatment to the end of treatment. I will use the iBOR for the best overall response recorded during the iRECIST criteria period. As shown in the table 5, patient 001, the iBOR is iPR, the BOR from the start of the study treatment to the end of treatment is PR. For patient 002 and patient 003 the iBOR is iCPD, the BOR is PR.

Table 5. BOR and Progression Free Date with iRECIST

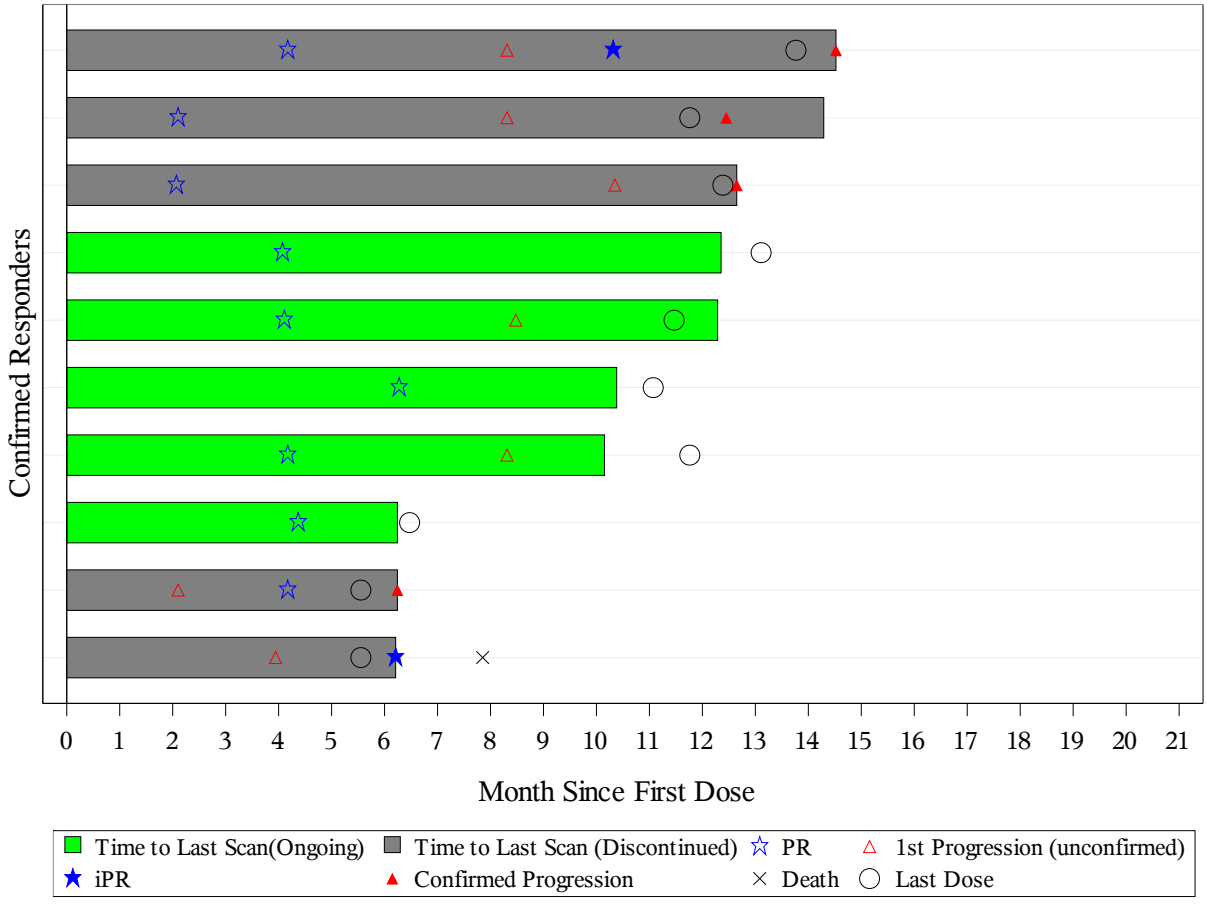
Patient ID	iBOR	BOR	iPDDT
001	iPR	PR	05/25/2017
002	iCPD	PR	11/17/2016
003	iCPD	PR	11/17/2016

PROGRESSION-FREE SURVIAL

With iRECIST, the calculation of the progression free date is also becoming complexed. The immune progression free survival (iPFS) would be based on the PD that is ultimately confirmed. The progression date (iPDDT) to be used for calculation of progression-free survival (iPFS) should be the first date (Patient 002, 11/17/2016) at which progression criteria are met (ie, the date of iUPD) if that iUPD is confirmed at the next assessment. However for patient 001, if iUPD occurs, but followed by iSD, iPR, or iCR, the initial iUPD date (visit 4, 11/17/2016) that was not confirmed should not be used as the progression event date, and the later iUPD date (visit 7, 05/25/2017) that was subsequently confirmed would be the progression date for iPFS (table 5).

Next I will use the swimlane plot, one of the common graphs used in oncology clinical trial analysis to explain how the iRECIST is used. The following swimplot graph is based on the INV data per iRECIST and the first bar is the patient 001. The length of the bar represents the time from the initial treatment to the last CT scan. The bar with grey color indicates the patient is discontinued the treatment, the bar with green color indicates the patient is still on-going with the treatment. The non-filled star symbol represents the first response per RECIST 1.1 assessment, the filled star symbol represents the first response per iRECIST. We still use patient 001 as the example, as shown in the first bar, the patient 001 first have the response PR at about 4 months after the initial treatment. The initial progression (iUPD) appears at 8-9 months after the treatment. This progression is not real progression according to the following assessment per iRECIST, the response iPR appears after the initial progression. As I mentioned earlier, for immunotherapy, the treatment will not be discontinued at the sight of the first progression. As we can see from the example patient 001, the treatment is still on-going after initial progression (the circle symbol) and no more treatments are administered after the confirmation of the progression.

Error! Reference source not found. **Swimlane Plot for Responders Based on Investigator Assessment per iRECIST**



CONCLUSION

In conclusion, this paper first introduced why the iRECIST is needed and the development history of iRECIST , then compared the difference between the RECIST 1.1 and iRECIST, then use several cases to explain how is the

progression confirmed in different scenarios and how to derive the best overall response and progression free date for clinical trials incorporating both the RECIST 1.1 and the iRECIST criteria.

REFERENCES

[1] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. 2017. "iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics." *Lancet Oncol.* 18:e143-e152.

ACKNOWLEDGMENTS

Thanks Nicole(Xiaoyun) Li, Jeff Xia and Christine Teng for review the paper and useful suggestions.

CONTACT INFORMATION

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

Weiwei Guo
Merck & Co., Inc.,
Rahway, NJ, 07065
Phone: 732-594-6356
E-mail: weiwei.guo@merck.com