Derivation of Efficacy Endpoints by iRECIST Criteria: A Practical Approach

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ABSTRACT

Immune-checkpoint inhibitors represent one of the most important therapy advancements in modern oncology. They are currently used for treatment of multiple malignant diseases, especially at advanced metastatic stages. A challenging aspect of these immunotherapies is that they may show atypical therapy response patterns such as pseudoprogression. In 2017, the RECIST working group published a modified set of response criteria, iRECIST, for immunotherapy, based on RECIST 1.1, which was initially developed for cytotoxic therapies and adapted for targeted agents. This document provides rules and examples for how to derive most common endpoints (like Best Overall Response or Progression-Free Survival Time) for clinical studies according to iRECIST criteria. When a Clinical Study Report is produced, it is developed from Analysis (ADaM) Data Sets created under CDISC guidelines. This article provides recommendations for creating ADaM data sets and deriving needed endpoints by iRECIST criteria from these ADaM data sets.

HISTORY OF RESPONSE EVALUATION CRITERIA

The WHO (World Health Organization) published a bulletin in 1979, in which they said that "During the last few decades there has been a rapid and continuous increase in the number of investigations of cancer therapy carried out in many parts of the world. However, these investigations are frequently reported in a way which makes it difficult for investigators to compare their results with those of others. It has become necessary to develop a "common language" to describe cancer treatment and to agree on internationally acceptable general principles for evaluation data." In 1981, the WHO published the first tumor response criteria. Since the early 1980s, the WHO response criteria have been adopted as the standard method for evaluating tumor response. Response evaluation criteria in solid tumors (RECIST) were developed by an international collaboration including the European Organization for Research and Treatment of Cancer (EORTC), National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group. These criteria were published in February 2000 (Version 1.0), and subsequently updated in 2009 (Version 1.1).

For cytotoxic agents, WHO and RECIST guidelines assumed that an early increase in tumor size or the appearance of new lesions signaled progressive disease, resulting in discontinuation of treatment. Chemotherapy drugs are designed to kill all rapidly growing cells, including normal cells in the body that divide rapidly. However, not all drugs used to treat cancer are cytotoxic. Some of the newer types of cancer drugs, such as targeted therapies and immunotherapies, are not considered cytotoxic. These drugs work either to interfere with a particular pathway in the growth of cancer cells, or to stimulate or use the immune system in some way to fight cancer. In studies with immunotherapeutic agents, clinical experience showed that complete response, partial response, or stable disease status could still be achieved after an increase in overall tumor burden after an initial progression, which may turn out to be pseudoprogression. Pseudoprogression is a phenomenon in which an initial increase in tumor size is observed or new lesions appear, followed by a decrease in tumor burden; this phenomenon can benefit patients receiving immunotherapy. Therefore, conventional response criteria may not allow adequate assessment of the activity of immunotherapeutic agents. Patients whose performance status is stable and whose laboratory values have not significantly deteriorated should be considered for repeat confirmation imaging before true progressive disease status is declared and the immunotherapeutic agent is withdrawn. The RECIST criteria present problems for immunotherapies, so around 2009, the immune-related response criteria (irRECIST) were developed and used in some immunotherapy clinical trials. In 2017, the official RECIST Working Group (http://www.eortc.org/recist) published the new iRECIST (immune based therapeutics RECIST) guideline for assessing response to immunotherapy in clinical trials. This new criterion was proposed to accurately evaluate the response to immunotherapy. RECIST 1.1 should continue to be used as the primary criteria for response-based endpoints for randomized

studies planned for licensing applications; iRECIST could be considered exploratory in such trials, although earlier phase trials may consider using primarily iRECIST.

OVERALL TIME-POINT RESPONSES; MAPPING INTO SDTM AND CREATING ADAM DATA SET FOR TIME-POINT RESPONSES

RECIST 1.1 has five response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE). If subject is without target lesions at baseline, another category, non-CR/non-PD, is in use as a sort of substitute for Stable Disease, but in derivation of efficacy endpoints it usually handles the same way as Stable Disease (SD). For simplicity, this paper will not consider RECIST 1.1 cases of non-CR/non-PD for overall time-point results and their equivalency in iRECIST. iRECIST requires additional follow-up imaging (4-8 weeks) for the confirmation of an assessment of progressive disease and has additional response categories. iRECIST response assessments have the prefix "i." The categories are: Complete Response (iCR), Partial Response (iPR), Stable Disease (iSD), Unconfirmed Progressive Disease (iUPD), Confirmed Progressive Disease (iCPD), and Not Evaluable (NE). Below we summarize some key points regarding confirmation of progression in iRECIST.

-   iRECIST is different from RECIST 1.1 only after the first progression is observed. The first PD per RECIST 1.1 is an "unconfirmed" progression for iRECIST and termed as "iUPD." Progression must be confirmed in the next scan between 4-8 weeks.

-   If   progression is confirmed in the subsequent assessment(s), without of intervening iCR, iPR, or iSD, then it becomes a "confirmed" PD, termed "iCPD" in iRECIST with the date of progression being the date of the initial iUPD record. Subject may have several time-point responses resulting in iUPD before progression becomes confirmed (before overall time-point evaluation resulting in iCPD) - iUPD can be assigned multiple times as long as iCPD is not confirmed at the next assessment.

-   If iUPD is not confirmed in the subsequent assessment, i.e., if it is followed by an iSD, iPR, or iCR, then the bar is reset for iUPD. In other words, the original iUPD will be ignored and it must occur again and be confirmed at the subsequent assessment to be assigned as iCPD.

When iBOR (Best Overall Response) and other efficacy endpoints are derived by iRECIST criteria, the results of **all** overall time-point evaluations from the start of treatment contribute to the derived study endpoints. However, the data collection and SDTM mapping may be organized in such a way that, until a subject has progressed by RECIST 1.1 criteria, only time-point responses by RECIST 1.1 criteria are collected and mapped into SDTM. Starting from progression by RECIST 1.1, results of time-point evaluations should be collected by iRECIST criteria only.

In the ADaM data set, we strongly recommend having 2 Categories for Parameters (values of variable PARCAT1):

-   by RECIST 1.1 criteria (starting from Baseline till subject progressed by RECIST 1.1)

-   by iRECIST criteria (starting from Baseline and continued after progression by RECIST 1.1 till subject progressed by iRECIST or till the end of the study in case of absence confirmed progression by iRECIST)

This indicates that, until a subject progresses by RECIST 1.1, some kind of duplication will be present in ADaM: all records by RECIST 1.1 will be duplicated with records by iRECIST with the prefix "i" in front of the result of overall time-point assessment. This approach makes derivation of efficacy endpoints straightforward and easy to implement. After a subject progress by RECIST 1.1, he/she may continue to be evaluated by iRECIST criteria alone, and only records with Parameter Category "iRECIST" will be placed in ADaM after progression by RECIST 1.1. It is possible that a subject may not have recorded progression by RECIST 1.1 criteria; in this case, all records in ADaM for overall time-point responses by RECIST 1.1 will be duplicated with similar records by iRECIST with one minor difference: the presence of the prefix "i" in front of the results of time-point adequate assessments.

ANALYSIS DATASET FOR TIME-POINT RESPONSES

This Analysis dataset for time-point responses contains time-point level results. It has one observation per subject per time-point per parameter per response assessment criteria per evaluator. Possible parameters should cover:

- Time-point Sum of Target Lesion Diameters: Lymph Nodes (mm)

- Time-point Sum of Target Lesion Diameters: Non-Lymph Nodes (mm)

- Time-point Sum of all Target Lesion Diameters (mm)

- Time-point Target Lesions Response

- Time-point Non-Target Lesions Response

- Initial Appearance of New Lesions

- Sum of Diameters for New Target Lesions (iRECIST-specific requirement)

- Time-point status for New Non-Target Lesions (iRECIST-specific requirement)

- Time-point Overall Response

Because qualifiers (like information about applied Response criteria) are not allowed in the ADaM BDS structure, this information is now part of the parameters. For example, we should have 2 separate parameters:

- 'Time-point Overall Response – RECIST 1.1' with possible values of AVALC: 'CR', 'PR', 'SD', 'PD', 'NE'

- 'Time-point Overall Response – iRECIST' with possible values of AVALC: 'iCR', 'iPR', 'iSD', 'iUPD', 'iCPD', 'NE'

These 2 parameters belong to two different Parameter Categories ('RECIST 1.1' and 'iRECIST'). Records with parameter 'Time-point Overall Response – RECIST 1.1' are expected to be present in the analysis data set starting from baseline till progression by RECIST 1.1 criteria; records with parameter 'Time-point Overall Response – iRECIST' are expected to be present in the data set starting from baseline till last available evaluation by iRECIST criteria (till subject progresses by iRECIST or till the end of follow-up in case of absence confirmed progression by iRECIST).

ASSIGNING ANALYSIS FLAGS TO SUPPORT ENDPOINT DERIVATIONS

It is important to identify whether specific observations are used in or excluded from the future analysis. The ADaM methodology is to use analysis flags (ANLzzFL, where zz is a two digits numeral assigned sequentially to cover different analyses) to indicate observations that fulfill specific requirements for one or more analyses. Assigning of these flags is based on methodology provided by the SAP (Statistical Analysis Plan). For example, based on SAP instruction about censoring rules, the following time-point evaluations may not be taken into consideration for derivation of PFS (Progression-Free Survival) and other endpoints by RECIST 1.1:

- if they are after a new anti-cancer treatment started

- if they are after a certain number of days post last dose date (specified by the SAP)

- if they are after more than one missing adequate assessment.

Different sets of flags may support different selections. Of course, selection of records used for derivation of efficacy endpoints by iRECIST should follow different rules compared to selection of records used for derivation of efficacy endpoints by RECIST 1.1. In this article, we going to use Analysis flags ANL11FL, ANL12FL, and ANL13FL to select the records needed to support derivation of efficacy endpoint by iRECIST. Such selection should be done according to study-specific protocol and Statistical Analysis Plan. For simplicity, let's consider a protocol in which confirmation of response is not required. In many

studies the confirmation of response is not required when using RECIST 1.1 and iRECIST (should be specified in study protocol).

Let's use the **ANL11FL** flag to select the overall time-point evaluations participating in making the decisions for iRECIST criteria. Only the records in Analysis data set for Time-point Responses that are related to iRECIST criteria are qualified to have ANL11FL. The possible restrictions (rules) for marking overall time-point assessment with ANL11FL are below (**all** criteria must be met):

a) iRECIST overall time-point assessment is not resulted in NE.

b) iRECIST overall time-point assessment is conducted before new anti-cancer treatment/procedures started (see if protocol / SAP has such requirements).

c) There are no cases of more than one missing assessment (Use value provided in protocol / SAP as a criterion) (see if protocol / SAP has such requirements and how to apply this criterion)

Example: the provided value as a criterion is equal to 97 days. The subject has the following overall time-point assessments:

Day 40:   iSD

Day 80:   iSD

Day 120: NE

Day 160: iSD

Day 200: NE

Day 280: iUPD

Day 320: iPR

As we can see, the adequate overall time-point assessments were conducted at Days 40, 80, 160, 280, and 320. The gap between Day 160 and Day 280 exceeds the required number of days used in criterion provided by protocol (120 days > required 97 days). In this case, all assessments conducted after the first occurrence of more than one missing assessment (after Day 160) are not qualified to be marked with ANL11FL.

d) If the protocol / SAP has restrictions regarding whether the assessments collected after the end of treatment can contribute to the derivation of efficacy endpoints by iRECIST criteria, then apply this restriction (For example, if the protocol specifies that that assessments should be excluded from analysis after if they we done in more than particular number of days after last dose, then every overall time-point assessment conducted in more than this number of days after last dose will not be marked with ANL11FL).

e) All overall time-point assessments reported chronologically after the first occurrence of iCPD are not qualified to be marked with ANL11FL (sometimes the protocol allows subjects to stay on treatment after progression if the investigator sees clinical benefits in treatment continuation).

Another flag, **ANL12FL**, is needed to identify overall time-point evaluations where progression per iRECIST has started (one record per subject for overall time-point responses). Records marked with this flag will be used in derivation of Progression Free Survival Time per iRECIST. This flag is derived only for iRECIST criteria if the most recent overall time-point evaluation marked with ANL11FL is iUPD or iCPD. In these cases, we should look back from the most recent assessment to figure out when the progression started. This process should take into consideration only adequate assessments and go back assessment by assessment, starting from the latest one marked with ANL11FL while adequate assessments result in iUPD. The chronologically earliest among this latest group of iUPDs will indicate when progression per iRECIST started, and record about this examination should be marked with ANL12FL. In the examples below we define pseudoprogression as cases with a time-point response of iCR, or iPR, or iSD following iUPD without iCPD.

Example 1 of a group of assessments with ANL11FL:

Day 40:   iSD

Day 80:   iUPD

Day 120:   iPR

Day 160:   iUPD

Day 200:   iUPD

Day 240:   iCPD

The most recent assessment marked with ANL11FL is at Day 240; this assessment is resulted in iCPD. If we go backwards from this assessment toward baseline, taking into consideration only adequate assessments, we need to stop at the Day 160 assessment and mark it with ANL12FL .

Example 2 of a group of assessments with ANL11FL:

Day 40:   iSD

Day 80:   iUPD

The most recent assessment marked with ANL11FL is at Day 80; this assessment is resulted in iUPD. If we go backwards from this assessment toward baseline, taking into consideration only adequate assessments, we need to stop at the same assessment at Day 80 and mark it with ANL12FL.

Example 3 of a group of assessments with ANL11FL:

Day 40:   iUPD

Day 80:   iUPD

Day 120:   iUPD

The most recent assessment marked with ANL11FL is at Day 120; this assessment is resulted in iUPD. If we go backwards from this assessment toward baseline, taking into consideration only adequate assessments, we need to stop at the Day 40 assessment and mark it with ANL12FL.

Example 4 of a group of assessments with ANL11FL:

Day 40:   iUPD

Day 80:   iUPD

Day 120:   iSD

The most recent assessment marked with ANL11FL is resulted in iSD. This indicates that previous assessments resulted in iUPD, are indicating pseudoprogression and has been reset by iSD at Day 120. In this case, there would not be any assessments marked with ANL12FL.

An additional Analysis Flag, **ANL13FL**, is needed to indicate when a subject became a responder and to be used in time to response analysis or duration of response analysis. It is likely that only some subjects (if any) will have an overall time-point response record marked with ANL13FL.

In our case, the study protocol does not require confirmation of response. Assign ANL13FL to the chronologically earliest overall time-point response marked with ANL11FL and resulting in iCR or iPR. If the protocol requires confirmation of response, assign ANL13FL to the chronologically earliest confirmed response (iCR or iPR) already marked with ANL11FL according to the protocol or SAP.

BEST OVERALL RESPONSE

Let's consider a step-by-step iRECIST-specific algorithm for derivation of Best Overall Response. For simplicity, let's consider cases where the protocol does not require confirmation of response (if such confirmation is needed, the derivation rule should be adjusted in the same way as it was adjusted for derivation of BOR by RECIST 1.1 criteria when the protocol requires confirmation of response). The possible values of iBOR can be iCR, iPR, iSD, iUPD, iCPD, Unknown, and NE. Note that values of iBOR

start with the prefix "i" (except cases of Unknown and/or NE). As mentioned above, for simplicity, this paper will not consider iRECIST cases of overall response of non-iCR/non-iPD. These cases should be handled the same way as cases of non-CR/non-PD are handled in derivation of BOR by RECIST 1.1 criteria.

Case 1: No baseline assessment

iBOR = Unknown

If not the previous case, Case 2: At least one overall time-point assessment is resulted in iCR and was marked with ANL11FL

iBOR = iCR

If not the previous cases, Case 3: At least one overall time-point assessment is resulted in iPR and was marked with ANL11FL

iBOR = iPR

If not the previous cases, Case 4: At least one overall time-point assessment is resulted in iSD and was marked with ANL11FL, and is conducted after an essential period of time specified by protocol since randomization date (randomized study) or baseline (non-randomized study)

iBOR = iSD

If not the previous cases, Case 5: At least one overall time-point assessment is resulted in iCPD and was marked with ANL11FL

iBOR = iCPD

If not the previous cases, Case 6: At least one overall time-point assessment is resulted in iUPD and was marked with ANL11FL

iBOR = iUPD

If not the previous cases, Case 7: No post-baseline overall assessments marked with ANL11FL

iBOR = NE

If not the previous cases, Case 8: Has overall time-point assessment that is resulted in iSD and was marked with ANL11FL, and was conducted within an essential period of time specified by protocol since randomization date (randomized study) or baseline (non-randomized study)

iBOR = NE

PROGRESSION-FREE SURVIVAL TIME (IN DAYS)

The ADTTE (Analysis Dataset for Time-to-Event Analysis) variables of interest for this paper are:

- STARTDT (Time to Event Origin Date for Subject). This is usually date of randomization (for randomized study) or date of first dose (for non-randomized study).
- ADT (Analysis Date). In this case ADT is the date of progression; the value can be observed or censored.
- AVAL (Analysis Value). In this case, AVAL = iPFS time (in days) and is always derived as AVAL = ADT – STARTDT + 1; the value can be observed or censored.
- CNSR (Censor). This is a required variable for time-to-event analysis. CNSR = 0 for observed events; CNSR > 0 for censored records (in this paper, for the purpose of simplicity, we will always use CNSR = 1 for censored records).

Let's consider a step-by-step iRECIST-specific algorithm for derivation of Progression-Free Survival Time (in days) (iPFS) values.

Case 1: Analysis set for time-point responses by iRECIST has record marked with ANL12FL (as a reminder – this flag identifies start of progression):

- ADT = Date associated with this record

- CNSR = 0 (event observed)

If not the previous case, <u>Case 2a</u>: No baseline assessment and subject died within period of time specified in the protocol / SAP since randomization (for randomized studies) or baseline (for non-randomized study) without starting a new anti-cancer treatment:

- ADT = Date of death

- CNSR = 0 (event observed)

If not the previous case, <u>Case 2b</u>: No baseline assessment and subject started new anti-cancer treatment or did not die within period of time specified in protocol / SAP since randomization (for randomized studies) or baseline (for non-randomized studies):

- ADT = Date of randomization (for randomized studies) / Date of baseline (for non-randomized studies)

- CNSR = 1 (event censored)

If not the previous cases, <u>Case 3a</u>: Subject does not have any post-baseline assessments marked with ANL11FL and subject died within predefined by protocol / SAP number of days from date of randomization (for randomized studies) / date of baseline (for non-randomized studies) without starting new-anti-cancer treatment:

- ADT = Date of death

- CNSR = 0 (event observed)

If not the previous cases, <u>Case 3b</u>: Subject does not have any post-baseline assessments marked with ANL11FL and subject did not die within predefined by protocol / SAP number of days from date of randomization (for randomized studies) / date of baseline (for non-randomized studies) or new-anti-cancer treatment started:

- ADT = Date of randomization (for randomized studies) / Date of baseline (for non-randomized studies)

- CNSR = 1 (event censored)

If not the previous cases, <u>Case 4a</u>: Subject has at least one post-baseline assessment marked with ANL11FL, and subject died within predefined by protocol / SAP number of days from date of last adequate assessment marked with ANL11FL without starting new-anti-cancer treatment:

- ADT = Date of death

- CNSR = 0 (event observed)

If not the previous cases, <u>Case 4b</u>: Subject has at least one post-baseline assessment marked with ANL11FL, and subject did not die within predefined by protocol / SAP number of days from date of last adequate assessment marked with ANL11FL or new-anti-cancer treatment started:

- ADT = Date of last adequate assessment marked with ANL11FL

- CNSR = 1 (event censored)

DURATION OF RESPONSE (IN DAYS)

Duration of Response (iDOR) should be derived only for responders (only for subjects having iBOR of iCR or iPR). This endpoint can be observed or censored. Response starts with the date associated with the record identified with ANL13FL and continues to the ADT of Progression Free Survival Date (iPFS date). If the value of iPFS is censored, then the value of Duration of Response by iRECIST criteria is censored; if the value of iPFS is observed, then the value of Duration of Response by iRECIST criteria is observed.

CONCLUSION

By applying the techniques described in this paper and referencing source documents such as iRECIST guidelines, study protocol, Statistical Analysis Plan, and CDISC ADaM Guidance, all required subject-level efficacy parameters in oncology clinical trials can be derived and stored. Using this approach can lead to the standardization of the process of derivation of efficacy endpoints by iRECIST criteria, and thus saving time and resources. It is very important to follow the order proposed in this paper:

1. Creating Analysis records by iRECIST criteria according to the data collection method. These records should be created starting with first post-baseline evaluation. Until a subject progresses by RECIST criteria, these records may somehow duplicate corresponding records by RECIST criteria in the Analysis dataset

2. Assigning iRECIST-specific Analysis Flags in Analysis dataset for overall time-point responses (in this article: flag ANL11FL to identify the adequate records contributing to making decisions by iRECIST; flag ANL12FL to identify the records pointing to the start of progression by iRECIST; and flag ANL13FL to identify the record pointing to the start of response by iRECIST)

3. Derivation of iBOR (Best Overall Response by iRECIST) in proposed order

4. Derivation of iPFS (Progression Free Survival Time by iRECIST) in proposed order

5. Derivation of iDOR (Duration of Response by iRECIST) for responders only

6. Other efficacy-related statistics by iRECIST can be derived as well if required by the protocol or SAP

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