Objective tumor response and RECIST criteria in cancer clinical trials

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Abstract

Objective tumor response is one of primary endpoints for efficacy in cancer clinical trials, and has been widely utilized by clinicians in evaluation and guidance of cancer treatments as well as in prediction of clinical outcomes. To date, the most commonly used standard for determining the tumor response is a set of published rules called Response Evaluation Criteria in Solid Tumors (RECIST). According to RECIST, there are so many information need to be considered for estimating objective tumor responses, but usually no great detail instruction on how to appropriately apply them into practice. Thus, it is not easy and straightforward for SAS® programmers to incorporate RECIST criteria into the analyses for cancer trials with great confidence. Here the author will systematically summarize the general process for dealing with tumor response data in clinical trials, and use a SAS macro to demonstrate and simplify the whole process. The objective of this effort is to demonstrate how to handle tumor response data in cancer clinical trials easily and with less frustration.

RECIST introduction

RECIST criteria, which defines when cancer patients improve ("respond"), stay the same ("stable"), or get worsen ("progression") during antitumor treatments, was first published in February 2000 by an international collaboration group including the 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. It was widely adopted by cooperative groups, industries, and academia ever since. Revised RECIST guideline, published in January 2009, is an update to its original version. According to U.S. Food and Drug Administration 'Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics', objective tumor response rate has been the most commonly used surrogate endpoint in support of accelerated anticancer drug approval; up to date, the majority of clinical trials evaluating objective tumor response in solid tumors are using RECIST.

RECIST terminology

In order to clearly understand RECIST criteria before applying it in the clinical trials, it is important to understand some relevant terminologies. In RECIST criteria, "lesion" is generally used instead of "tumor". The following terminologies are based on the revised RECIST guideline (version 1.1):

Measurable lesions- lesions that can be accurately measured in at least one dimension with longest diameter ≥10 mm using CT scan for non-nodal lesions; the short axis>=15mm for lymph node.
Non-measurable lesions - all other lesions, including small lesions (longest diameter <10 mm with CT scan for non nodal lesion or the short axis length of lymph node is between 10-15 mm) and other truly non-measurable lesions, e.g., bone lesion, as cites, pleural/pericardial effusions etc.

Target lesions - lesions that have been specifically selected and measured. Lesion should be selected based on the largest in size and ease of measurement. Maximum of total 5 target lesions can be selected to represent the overall involved organs and maximum of 2 within one organ site.
Non-target Lesions- lesions whose presences have been noted but no measurement has been taken.

Evaluation summary

1. Target lesions

To assess response, it is essential to estimate the overall tumor burden at baseline to which subsequent measurements can be compared. CT and MRI are the best currently available and reproducible methods to measure target lesions.There are four evaluable categories of tumor response for target lesions:

- Complete Response (CR) –all target lesions have disappeared during the treatment. Lymph nodes selected must return to normal size (<10mm).
- Partial Response (PR) –at least 30% decrease from baseline sum of the longest diameter.
- Stable Disease (SD) –no significant decrease or increase in the size of target lesions.
- Progressive Disease (PD) – >=20% increase over the smallest sum of the longest diameter and with at least 5mm increase, or appearance of any new lesion.

2. Non-target lesions

Measurement of these lesions is not required, but the presence or absence of each should be noted. Evaluation results usually are provided on the study Case Report Form. There are only three categories to describe the status of non-target lesions.

- Complete Response (CR): complete disappearance of all non-target lesions and normalization of lymph node.
- Stable Disease (SD): persistence of one or more non-target lesions.
- Progressive Disease (PD): Appearance of any new lesion and/or unequivocal progression of existing non-target lesions.

If tumor markers are being used in cancer trials, the specific marker assessment guidelines for response need to be outlined in the protocol.

3. Time point overall response

The overall tumor response for each patient at certain time point will depend on the findings of both target and no-target lesions, and also will include the occurrence of any new lesion. The below is the summary table of overall response at certain time point per RECIST guideline.

Target Lesion	Non-Target	New Lesion(s)	Overall Response
CR	**CR**	**No**	**CR**
CR or PR	**SD or NE**	**No**	**PR**
SD	**No PD**	**No**	**SD**
NE	**No PD**	**No**	**NE**
PD	**Any**	**Yes or No**	**PD**
Any	**PD**	**Yes or No**	**PD**
Any	**Any**	**Yes**	**PD**

NE -- inevaluable.

4. Best overall response

Once the study is completed and time point overall response data is available, best overall response can be determined thereafter. The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). Note, tumor assessments performed after initiation of new anticancer treatment will be excluded from evaluating the best overall response. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. For trials where the response rate is the primary endpoint, the best tumor response needs to be confirmed according to RECIST; and it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's conclusion. Simultaneous review of the patients' files and radiological images is the best approach.

Data preparation

Usually there is tons of information related to objective tumor response, no matter what the data structure or protocol you may encounter, in order to derive the objective tumor response for each patient by applying RECIST criteria. The following variables are sufficient for SAS programmers to conduct the analysis and do the confirmation for best overall response.

- Patient (PAT)
- Cycle (VISIT)
- Tumor measurement date(VISDT)
- Sum of longest diameters for target lesions(LSSUM)
- Response evaluation for non-target lesions(RESP_NONT):
- Treatment start date(FIRSTDT)
- New lesion flag(NEWLESION)

For the illustration purpose, the below is the artificial data for this paper. The data is displayed in vertical layout and the above needed information can be easily gathered by either SAS DATA step or SQL procedure. When objective tumor response is the primary endpoint, patients must have measurable disease at baseline (lssum is not missing); In addition, usually the codes have been provided on the Case Report Form for non-target lesions, just select one code per lesion that best describes the status of each non-measurable lesion(CR, SD or PD, etc).

	Subject	Cycle	Tumor measurement date	Sum of longest diameters for target lesions	Non-target lesion response	New lesion flag(1=yes)	Treatment start date
1	1	0	26FEB2009	2.5		.	02MAR2009
2	1	1	10APR2009	2	SD	0	02MAR2009
3	1	2	28MAY2009	2.7	SD	0	02MAR2009
4	1	801	08JUL2009	2.5	PD	1	02MAR2009
5	2	0	19APR2009	2		.	22APR2009
6	2	1	02JUN2009	2.4	SD	0	22APR2009
7	2	2	17JUL2009	5	PD	0	22APR2009
8	3	0	13OCT2009	4.6		.	20OCT2009
9	3	1	28NOV2009	3	SD	0	20OCT2009
10	3	2	03JAN2010	2	SD	0	20OCT2009
11	3	3	17FEB2010	1.5	SD	0	20OCT2009
12	3	4	01APR2010	2.2	PD	1	20OCT2009
13	4	0	05JUN2009	6.5		.	16JUN2009
14	4	1	20JUL2009	2.7	SD	0	16JUN2009
15	4	2	03SEP2009	1	NE	0	16JUN2009
16	4	3	17OCT2009	0	CR	0	16JUN2009
17	4	801	15NOV2009	0	CR	0	16JUN2009
18	5	0	17OCT2009	1.2		0	17SEP2009
19	5	1	15NOV2009	.	SD	0	17SEP2009

Macro for deriving the time point tumor response

Here is the macro can be used to derive the time point tumor response based on the available data.

```
%macro resp;
      proc sort data=lesion;
            by pat visit;
      run;

      Data cycle_resp;
            set lesion;
            by pat visit;
            retain  baselsum leastsum;
            if first.pat then do;
                baselsum=lssum;
                leastsum=lssum;
            end;
            if .<lssum<leastsum then leastsum=lssum;

            ** target lesion response **;
            *  determine order PD->NE->CR->PR->SD *;
```

```
            if visit> 0 then do;
            if (leastsum >0  and (lssum-leastsum)>=0.5 and
            (lssum-leastsum)/leastsum>=0.2 )or newlesion=1 then resp_t="PD";
                  else if lssum=. or baselsum=. then resp_t="NE";
                  else if lssum=0 then resp_t="CR";
                  else if baselsum >. and (baselsum-lssum)/baselsum >=0.3
                  then resp_t="PR";
                  else resp_t="SD";

            ** time point tumor response **;
            *  determine order PD->NE->CR->PR->SD *;

            if newlesion=1 or resp_t="PD" or resp_nont="PD" then resp="PD";
            else if resp_t  in ("NE", " ", "NA") and resp_nont ne "PD"
            then resp="NE";
            else if resp_t="CR" and resp_nont="CR" then resp="CR";
            else if resp_t in ("CR", "PR") and resp_nont ne "PD" then
            resp="PR";
            else if resp_t="SD" and resp_nont ne "PD" then resp="SD";
            end;
            label resp_t="Target lesion response"
                  resp="cycle based overall response";
            keep pat visit resp resp_t resp_nont visdt firstdt;
      run;
%mend resp;
%resp;
```

After running the above macro and the time point tumor response data being derived, for the studies with best response as the primary study endpoint, the best oval response need to be confirmed according to RECIST criteria. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. After the confirmation analysis, the below data table demonstrates that unconfirmed best response for each patient may be different than the confirmed response data, the latter is more conservative.

	Subject	Unconfirmed Best response	Confirmed best response
1	1	SD	PD
2	2	SD	SD
3	3	PR	PR
4	4	CR	CR
5	5	NE	NE

Conclusion

Oncology studies are increasing complexities and the RECIST guidelines are highly dependent upon measurement of tumor size, different clinicians may vary in their approaches of performing these measurements. Consistency in following the imaging requirements and rules is even more challenging. When investigators vary in how they follow RECIST as a trial endpoint, the significant variability may place the jeopardy in study results. During the process of analysis of those tumor response data, SAS programmers also have to rigidly follow the guidelines and be consistent at the interpretation of the study results. Here the author provides the general instruction on

tumor response evaluation in cancer trials, which may need to be modified by different protocols. The objective of this effort is to demonstrate how to systematically handle tumor response data in cancer clinical trials, hopefully with less frustration and more confidence.

Reference

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf
Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). J Natl Cancer Inst 2000;92:205–16.
Eisenhauer EA, Threasse P , Boagerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), EUROPEAN JOURNAL OF CANCER 4 5 (2 0 0 9) 2 2 8 –2 4 7

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