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Confirmation of Best Overall Tumor Response in Oncology Clinical Trials per RECIST 1.1

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ABSTRACT

In oncology clinical trials for solid tumor, the revised RECIST guideline (version 1.1) [1] is the standard guidance for response evaluation. In non-randomized trials where response is the primary endpoint, confirmation of partial response (PR) or complete response (CR) is required and handled in response analysis datasets. Instruction in RECIST v1.1 guideline does not provide the logic to handle response scenarios for all data. In this paper overall logic from RECIST 1.1 is explained, clarification of the confirmation logic to use for specific scenarios based on RECIST v1.1 is presented. Subsequent time requirements and minimum durations for stable disease (SD) is addressed. Finally, handling of intervening responses of SD or not evaluable (NE) between two CR or PR response time points is explained.

INTRODUCTION

In revised RECIST guideline (version 1.1) [1], "the best overall response is defined as the best response recorded across all time points from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error".

In below Table 3 from RECIST 1.1, logic for best overall response confirmation is defined.

CR: Complete Response

PR: Partial Response

SD: Stable Disease

PD: Progressive Disease

NE: Not Evaluable

SD duration is the key to implement the confirmation logic, SD requirement should be at least 6-8 weeks from study entry depends on the study protocol for response assessments.

Table A: Table 3 from RECIST 1.1 [1]

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

RESPONSE ANLYSIS DATASETS

Timepoint response analysis dataset (ADRS) is first created based on timepoint response data collected at each response assessment visits. In ADRS, response of subsequent visit, number of days between the visits are derived to support the confirmation needed.

Best overall response analysis dataset is then created based on ADRS. In this analysis dataset, below variables are derived on subject level. New anti-cancer therapy date, date of death, end of study date, first PD date and data cut-off date are used to determine cut-off date for subject best overall response derivation.

Table B: Key Derived Date Variables to Support Best Overall Response Confirmation

FPDDT	First PD Date
EOSDT	End of Study Date
DTHDT	Date of Death
NWTHERDT	New Anti-Cancer Therapy Date
CUTOFFDT	Cut off Date for BOR Derivation
FCRDT	First CR Date
FPRDT	First PR Date

BEST OVERALL RESPONSE CONFIRMATION

Best overall response (BOR) is derived for responses reported across all visits from subject treatment start till subject first disease progression, it's defined in the order of CR, PR, SD, PD and NE. A patient who has SD at first assessment, PR at second assessment and PD on last assessment has a BOR of PR.

In best overall response analysis dataset, all response data from ADRS on or prior to BOR cut-off date are included. If best response is either CR or PR, then proceed with response confirmation logic.

It's required there are assessments at screening/baseline and at least one follow-up visit, otherwise BOR will be reported as NE [1].

"CR or PR confirmation needs to be assessed based on responses at least 4 weeks apart" [1].

Minimum requirement for SD duration is defined if subject had the first response of CR/PR/SD at least 42 days from treatment start to the date of the response without PD prior to day 42.

For confirmed CR/PR, first CR/PR response date is confirmed best overall response date. Confirmed best overall response date is used to support duration of response analysis (DOR).

If subject had no CR or PR, then first SD/PD/NE will be used to derive subject best overall response, no response confirmation needed. If SD duration criteria met, then BOR for the subject will be SD, otherwise PD or NE.

Table C: Implementation of response confirmation logic per RECIST 1.1

1	First Response	Next Response	Days between responses	SD Duration	Confirmed Best Overall Response
2	CR	CR	>=28		CR
3	CR	PR	>=28		PR
4	CR	PR	<28	Y	SD
5	CR	PR	<28	N	PD
6	CR	SD/PD/NE		Y	SD
7	CR	SD/PD		N	PD
8	CR	NE		N	NE
9	PR	CR/PR	>=28		PR
10	PR	PR	<28	Y	SD
11	PR	PR	<28	N	PD
12	PR	SD/PD/NE		Y	SD
13	PR	SD/PD		N	PD
14	PR	NE		N	NE

OTHER SCENARIOS

"In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response" [1].

Follows above guidance from RECIST 1.1, a confirmed BOR of CR or PR can be achieved when the initial and confirmatory timepoint responses with intervening response reported in between. If there is a single intervening timepoint response of SD or NE, we will look at next response as confirmatory response. For example, responses of PR, SD and PR can lead to BOR of PR, responses of PR, NE and PR can lead to BOR of PR.

A single intervening timepoint response of SD or NE will not prevent the subject from having confirmed BOR of CR/PR, however only one intervening timepoint is allow between the initial and confirmatory timepoint responses of PR or CR. In the situation that there are multiple intervening NE or SD timepoints, CR or PR cannot be confirmed. If there is a later CR or PR, this later assessment will be used as initial response, confirmation logic will be applied using subsequent responses as defined in Table C.

The date of first confirmed response is the first date at which the response is observed. For example, if a response is seen at Week 4 and confirmed at Week 8, Week 4 is the first confirmed response date.

Table D List of Different Scenarios

Timepoint Response					Confirmed Best Overall Response
Week 4	**Week 8**	**Week 12**	**Week 16**	**Week 20**	
PR*	PR	SD	PR	NE	PR
PR*	SD	PR	PD	PD	PR
PR*	NE	PR	SD	SD	PR
PR	SD	SD	PR	PD	SD
CR	SD	SD	PR*	PR	PR
* Date of first confirmed response					

CONCLUSION

This short paper focuses on response confirmation logic of CR/PR per RECIST 1.1 [1] to provide more clarification to programmers.

For studies with only 2 or 3 post-baseline timepoint responses reported, above guidance should provide solid programming guidance to support response confirmation work.

Scenarios with intervening response for CR/PR confirmation is not specified in RECIST 1.1, the discussed approach is based on study team recommendation. This approach may be handled differently by different statisticians and clinicians.

If there are more than 5-6 post baseline response assessments, the logic can be trickier to handle the intervening results. Study team needs to make study-based decision on how to handle these data scenarios.

REFERENCES

[1] New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1) October 2008

CONTACT INFORMATION

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