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Application of Exhaustive Method in Deriving Confirmed Best Overall Response

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ABSTRACT

In oncology studies for solid tumor, the revised RECIST guideline (version 1.1) [1] is considered as the golden standard for response evaluation. In non-randomized trials, where primary object is to evaluate the efficacy of investigation product, confirmation of Complete Response (CR) and Partial Response (PR) is required and essential to efficacy endpoints. The derivation rule of confirmed response from revised RECIST 1.1 seems simple and straightforward, but it poses great challenge even for experienced programmer to handle various cases comprehensively. The paper introduces a novel approach of adopting exhaustive method in deriving confirmed Best Overall Response (cBOR). It starts with construct all possible combination of three consecutive tumor response, apply exclusion criteria to limit options, then gradually convergence to 7 conditions. Finally, using simple data step to derive cBOR and date of first confirmed response simultaneously. The underlying logic of this approach is easy to understand, the code is user friendly, easy for quality control and flexible for different study designs.

INTRODUCTION

Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) is the most widely used standard guidance of solid tumor in industry. It provides clear definition of BOR, *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. Specifically, in non-randomised trails where response is the primary endpoint, confirmation of PR or CR is needed to deem either one of the 'best of response'.*

Confirmed BOR not only has important implication itself, but essential to other commonly used efficacy endpoint, such as Objective Overall Response, Duration of Response, etc. The derivation rule from revised RECIST 1.1 for confirmed response is shown in the table below.

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.

Although it seems straightforward in paper, we, as programmer, still face complex cases from time to time. Many papers have been written on the topic, with dazzling macro and complicated codes, which accomplish the goal, but difficult to understand and maintain the program. This paper provides an alternative approach with easily understandable logic and readable code. And it is also easy to perform quality control and flexible for different study design.

The Underlying Logic

There are 2 underlying logic of applying exhaustive method in deriving cBOR.

1. Although the derivation rule from revised RECIST 1.1 Table 3 only includes 2 consecutive overall responses when deriving cBOR, there are conditions written in the text that require an additional response to confirm the overall response from the first time point, for example CR-NE-CR. Therefore, it takes maximum 2 following tumor assessments to confirm the first.
2. The results of tumor response and their combinations are limited and in an acceptable amount. The available tumor responses in solid tumor includes CR, PR, Stable Disease (SD), Progressive Disease (PD) and Not Evaluable (NE). Considering participants discontinued after 1 or 2 tumor assessments, there are 155 combinations (=5+25+125) in total.
    a. Subject has only 1 tumor assessment: 5 possible results
    b. Subject has 2 tumor assessments: 25 possible results (5 x 5)
    c. Subject has more than 3 tumor assessments, but break down to group of 3: 125 possible results (5 x 5 x 5)

The Exception rules

Although, considering all possibilities, the total number of combinations is fixed and decidedly. There are study specific exception rules which can help impose restriction on the initial 155 combinations. The exception rules should be written in details in Statistical Analysis Plan (SAP) with reference or clear explanation. The possible restriction rule includes,

- Any tumor response after first PD should not be considered when deriving cBOR
- PR after CR is not allowed: if target lesion reappear, it should be considered as PD
- Others: such as CR-SD-CR is not allowed

Exception rules may vary from study to study due to pathology difference, study design, or data collection in Electronic Data Capture (EDC) system.

Time restrictions considered

Below listed several time restrictions, which should be taken into consideration deriving cBOR. Each time interval should reflect a duration of clinical relevance for the disease under study and should be pre-specified in SAP.

- Response confirmation required time difference: generally, 4 weeks = 28 days.
- SD too early: SD < Minimal required time interval should be considered as NE. Commonly used criteria is 6 weeks or the period of 2 tumor assessment minus time window of 7 days.
- PD too late: PD > Maximum required time interval should be considered as NE. commonly used criteria is 12 weeks or twice the period of tumor assessment minus time window of 7 days.
- Time restriction on the second tumor response: The second tumor assessment must after 70 days of treatment start to confirm the first.
- Others…

Real case scenario

Step 1. Prepare dataset

a. Delete Tumor assessments after date of first PD and New anti-cancer therapy

Tumor assessments after first PD and New anti-cancer therapy should not be considered when deriving cBOR. For convenience, delete those records before further data manipulation.

USUBJID	TRTSDT	NCTXSDT	PDDAT	SEQ	VISIT	VISITNUM	AVALC	ADT	ADY
1001	2023-08-22			1	END OF TREATMENT	30000	SD	2023-09-14	24
1002	2023-06-25	2023-10-12	2023-09-22	1	CYCLE 3 DAY 1	20301	SD	2023-08-16	53
1002	2023-06-25	2023-10-12	2023-09-22	2	END OF TREATMENT	30000	PD	2023-09-22	90
1003	2023-02-05		2024-01-13	1	CYCLE 3 DAY 1	20301	PR	2023-04-07	62
1003	2023-02-05		2024-01-13	2	CYCLE 5 DAY 1	20501	PR	2023-06-07	123
1003	2023-02-05		2024-01-13	3	CYCLE 7 DAY 1	20701	CR	2023-07-21	167
1003	2023-02-05		2024-01-13	4	CYCLE 9 DAY 1	20901	CR	2023-09-17	225
1003	2023-02-05		2024-01-13	5	CYCLE 11 DAY 1	21101	CR	2023-11-17	286
1003	2023-02-05		2024-01-13	6	CYCLE 13 DAY 1	21301	PD	2024-01-13	343

b. Merge the next 2 consecutive tumor response

The 2 subsequent tumor response is used to confirm the first, renaming to Tumor Assessment 1, 2, 3 to be more readable. And the number of records after the merger shall be the same as before.

c. Concatenate the tumor response to form a response list for each record

USUBJID	SEQ	VISIT	TA1	TA1_ADT	TA1_DY	TA2	TA2_ADT	TA2_DY	TA3	TA3_ADT	TA3_DY	RESP_LST
1001	1	EOT	SD	2023-09-14	24							**SD**
1002	1	C3D1	SD	2023-08-16	53	PD	2023-09-22	90				**SD-PD**
1002	2	EOT	PD	2023-09-22	90							**PD**
1003	1	C3D1	PR	2023-04-07	62	PR	2023-06-07	123	CR	2023-07-21	167	**PR-PR-CR**
1003	2	C5D1	PR	2023-06-07	123	CR	2023-07-21	167	CR	2023-09-17	225	**PR-CR-CR**
1003	3	C7D1	CR	2023-07-21	167	CR	2023-09-17	225	CR	2023-11-17	286	**CR-CR-CR**
1003	4	C9D1	CR	2023-09-17	225	CR	2023-11-17	286	PD	2024-01-13	343	**CR-CR-PD**
1003	5	C11D1	CR	2023-11-17	286	PD	2024-01-13	343				**CR-PD**
1003	6	C13D1	PD	2024-01-13	343							**PD**

Step 2. Applying format on response list

Construct format list of all possible combination of 155, and down-sizing to 93 based on study specific exclusion criteria. The exclusion rule used in this case is

1) No tumor response after PD,

2) No PR after CR.

The step can be done in EXCEL first, and read into SAS as format later. Also, it is better to discuss with statistician and relative party regarding the derivation logic.

SEQ	NO.	TA1	TA2	TA3	RESP_LST	CBOR_COND
1	1	CR			CR	SD*/NE
2	1	PR			PR	SD*/NE
3	1	SD			SD	SD*/NE
4	1	PD			PD	PD*/NE
5	1	NE			NE	NE
6	2	CR	CR		CR-CR	CR(TW2_1)/SD
7	2	CR	SD		CR-SD	SD*/NE
8	2	CR	PD		CR-PD	SD*/NE
9	2	CR	NE		CR-NE	SD*/NE
10	2	PR	CR		PR-CR	PR(TW2_1)/SD
11	2	PR	PR		PR-PR	PR(TW2_1)/SD
12	2	PR	SD		PR-SD	SD*/NE
13	2	PR	PD		PR-PD	SD*/NE
14	2	PR	NE		PR-NE	SD*/NE
15	2	SD	CR		SD-CR	SD*/NE
16	2	SD	PR		SD-PR	SD*/NE
17	2	SD	SD		SD-SD	SD*/NE
18	2	SD	PD		SD-PD	SD*/NE
19	2	SD	NE		SD-NE	SD*/NE
20	2	NE	CR		NE-CR	NE
21	2	NE	PR		NE-PR	NE
22	2	NE	SD		NE-SD	NE
23	2	NE	PD		NE-PD	NE
24	2	NE	NE		NE-NE	NE
25	3	CR	CR	CR	CR-CR-CR	CR(TW3_1)/SD
26	3	CR	CR	SD	CR-CR-SD	CR(TW2_1)/SD
27	3	CR	CR	PD	CR-CR-PD	CR(TW2_1)/SD
28	3	CR	CR	NE	CR-CR-NE	CR(TW2_1)/SD
29	3	CR	SD	CR	CR-SD-CR	CR(TW3_1)/SD
30	3	CR	SD	SD	CR-SD-SD	SD*/NE
31	3	CR	SD	PD	CR-SD-PD	SD*/NE
32	3	CR	SD	NE	CR-SD-NE	SD*/NE
33	3	CR	NE	CR	CR-NE-CR	CR(TW3_1)/SD
34	3	CR	NE	SD	CR-NE-SD	SD*/NE
35	3	CR	NE	PD	CR-NE-PD	SD*/NE
36	3	CR	NE	NE	CR-NE-NE	SD*/NE
37	3	PR	CR	CR	PR-CR-CR	PR(TW3_1)/SD
38	3	PR	CR	SD	PR-CR-SD	PR(TW2_1)/SD
39	3	PR	CR	PD	PR-CR-PD	PR(TW2_1)/SD
40	3	PR	CR	NE	PR-CR-NE	PR(TW2_1)/SD
41	3	PR	PR	CR	PR-PR-CR	PR(TW3_1)/SD
42	3	PR	PR	PR	PR-PR-PR	PR(TW3_1)/SD
43	3	PR	PR	SD	PR-PR-SD	PR(TW2_1)/SD
44	3	PR	PR	PD	PR-PR-PD	PR(TW2_1)/SD
45	3	PR	PR	NE	PR-PR-NE	PR(TW2_1)/SD
46	3	PR	SD	CR	PR-SD-CR	PR(TW3_1)/SD
47	3	PR	SD	PR	PR-SD-PR	PR(TW3_1)/SD
48	3	PR	SD	SD	PR-SD-SD	SD*/NE
49	3	PR	SD	PD	PR-SD-PD	SD*/NE
50	3	PR	SD	NE	PR-SD-NE	SD*/NE
51	3	PR	NE	CR	PR-NE-CR	PR(TW3_1)/SD
52	3	PR	NE	PR	PR-NE-PR	PR(TW3_1)/SD
53	3	PR	NE	SD	PR-NE-SD	SD*/NE
54	3	PR	NE	PD	PR-NE-PD	SD*/NE
55	3	PR	NE	NE	PR-NE-NE	SD*/NE
56	3	SD	CR	CR	SD-CR-CR	SD*/NE
57	3	SD	CR	SD	SD-CR-SD	SD*/NE
58	3	SD	CR	PD	SD-CR-PD	SD*/NE
59	3	SD	CR	NE	SD-CR-NE	SD*/NE
60	3	SD	PR	CR	SD-PR-CR	SD*/NE
61	3	SD	PR	PR	SD-PR-PR	SD*/NE
62	3	SD	PR	SD	SD-PR-SD	SD*/NE
63	3	SD	PR	PD	SD-PR-PD	SD*/NE
64	3	SD	PR	NE	SD-PR-NE	SD*/NE
65	3	SD	SD	CR	SD-SD-CR	SD*/NE
66	3	SD	SD	PR	SD-SD-PR	SD*/NE
67	3	SD	SD	SD	SD-SD-SD	SD*/NE
68	3	SD	SD	PD	SD-SD-PD	SD*/NE
69	3	SD	SD	NE	SD-SD-NE	SD*/NE
70	3	SD	NE	CR	SD-NE-CR	SD*/NE
71	3	SD	NE	PR	SD-NE-PR	SD*/NE
72	3	SD	NE	SD	SD-NE-SD	SD*/NE
73	3	SD	NE	PD	SD-NE-PD	SD*/NE
74	3	SD	NE	NE	SD-NE-NE	SD*/NE
75	3	NE	CR	CR	NE-CR-CR	NE
76	3	NE	CR	SD	NE-CR-SD	NE
77	3	NE	CR	PD	NE-CR-PD	NE
78	3	NE	CR	NE	NE-CR-NE	NE
79	3	NE	PR	CR	NE-PR-CR	NE
80	3	NE	PR	PR	NE-PR-PR	NE
81	3	NE	PR	SD	NE-PR-SD	NE
82	3	NE	PR	PD	NE-PR-PD	NE
83	3	NE	PR	NE	NE-PR-NE	NE
84	3	NE	SD	CR	NE-SD-CR	NE
85	3	NE	SD	PR	NE-SD-PR	NE
86	3	NE	SD	SD	NE-SD-SD	NE
87	3	NE	SD	PD	NE-SD-PD	NE
88	3	NE	SD	NE	NE-SD-NE	NE
89	3	NE	NE	CR	NE-NE-CR	NE
90	3	NE	NE	PR	NE-NE-PR	NE
91	3	NE	NE	SD	NE-NE-SD	NE
92	3	NE	NE	PD	NE-NE-PD	NE
93	3	NE	NE	NE	NE-NE-NE	NE

Use PROC FORMAT to format Response list into cBOR conditions (CBOR_COND). There are 7 Conditions in total.

1. CR(TW2_1)/SD
2. CR(TW3_1)/SD
3. PR(TW2_1)/SD
4. PR(TW3_1)/SD
5. SD*/NE
6. PD*/NE
7. NE

USUBJID	SEQ	VISIT	TA1	TA1_ADT	TA1_DY	TA2	TA2_ADT	TA2_DY	TA3	TA3_ADT	TA3_DY	RESP_LST	CBOR_COND
1001	1	EOT	SD	2023-09-14	24							SD	**SD*/NE**
1002	1	C3D1	SD	2023-08-16	53	PD	2023-09-22	90				SD-PD	**SD*/NE**
1002	2	EOT	PD	2023-09-22	90							PD	**PD*/NE**
1003	1	C3D1	PR	2023-04-07	62	PR	2023-06-07	123	CR	2023-07-21	167	PR-PR-CR	**PR(TW3_1)/SD**
1003	2	C5D1	PR	2023-06-07	123	CR	2023-07-21	167	CR	2023-09-17	225	PR-CR-CR	**PR(TW3_1)/SD**
1003	3	C7D1	CR	2023-07-21	167	CR	2023-09-17	225	CR	2023-11-17	286	CR-CR-CR	**CR(TW3_1)/SD**
1003	4	C9D1	CR	2023-09-17	225	CR	2023-11-17	286	PD	2024-01-13	343	CR-CR-PD	**CR(TW2_1)/SD**
1003	5	C11D1	CR	2023-11-17	286	PD	2024-01-13	343				CR-PD	**SD*/NE**
1003	6	C13D1	PD	2024-01-13	343							PD	**PD*/NE**

Step 3. SAS data step to generate _CBOR (temporary cBOR) and its corresponding numeric variable (_CBORN)

Calculate Time interval variables:

- TW2_1: the time interval of TA2_ADT and TA1_ADT
- TW3_1: the time interval of TA3_ADT and TA1_ADT

There are 3 time window used which can be written into macro variables.

- respc_tw: CR/PR required confirmation time window is 28 days
- sd_min_tw: the minimal time requirement for SD confirmation is 49 days: 2 cycles (28 days) minus 7 days
- pd_max_tw: the maximum time limit for PD too late is 112 days

Use IF-THEN/ELSE statement for each condition.

1. CR(TW2_1)/SD: if the TW2_1>=&respc_tw. then _CBOR = CR，else _CBOR = SD
2. CR(TW3_1)/SD: if the TW3_1>=&respc_tw. then _CBOR = CR，else _CBOR = SD
3. PR(TW2_1)/SD: if the TW2_1>=&respc_tw. then _CBOR = PR，else _CBOR = SD
4. PR(TW3_1)/SD: if the TW3_1>=&respc_tw. then _CBOR = PR，else _CBOR = SD

5. SD*/NE: TA1_DY>=&sd_min_tw. then _CBOR = SD, else _CBOR = NE (SD too early)
6. PD*/NE: TA1_DY<=&pd_max_tw then _CBOR = PD, else _CBOR = NE (PD too late)
7. NE

USUBJID	SEQ	VISIT	TA1	TA1_ADT	TA1_DY	TA2	TA2_ADT	TA2_DY	TA3	TA3_ADT	TA3_DY
1001	1	EOT	SD	2023-09-14	24						
1002	1	C3D1	SD	2023-08-16	53	PD	2023-09-22	90			
1002	2	EOT	PD	2023-09-22	90						
1003	1	C3D1	PR	2023-04-07	62	PR	2023-06-07	123	CR	2023-07-21	167
1003	2	C5D1	PR	2023-06-07	123	CR	2023-07-21	167	CR	2023-09-17	225
1003	3	C7D1	CR	2023-07-21	167	CR	2023-09-17	225	CR	2023-11-17	286
1003	4	C9D1	CR	2023-09-17	225	CR	2023-11-17	286	PD	2024-01-13	343
1003	5	C11D1	CR	2023-11-17	286	PD	2024-01-13	343			
1003	6	C13D1	PD	2024-01-13	343						

USUBJID	SEQ	VISIT	RESP_LST	CBOR_COND	TW2_1	TW3_1	_CBOR	_CBORN
1001	1	EOT	SD	SD*/NE			**NE**	5
1002	1	C3D1	SD-PD	SD*/NE	37		**SD**	3
1002	2	EOT	PD	PD*/NE			**PD**	4
1003	1	C3D1	PR-PR-CR	PR(TW3_1)/SD	61	105	**PR**	2
1003	2	C5D1	PR-CR-CR	PR(TW3_1)/SD	44	102	**PR**	2
1003	3	C7D1	CR-CR-CR	CR(TW3_1)/SD	58	119	**CR**	1
1003	4	C9D1	CR-CR-PD	CR(TW2_1)/SD	61	118	**CR**	1
1003	5	C11D1	CR-PD	SD*/NE	57		**SD**	3
1003	6	C13D1	PD	PD*/NE			**NE**	5

Step 4. Flag cBOR and first response record

- RESP_FL (Response flag): flag record which _CBOR is CR or PR as response record.
- CBOR_FL (Records identifies cBOR): sort by _CBORN and date, flag out the best and earliest _CBOR, one record per subject

- FIRST_RESP_FL (First confirmed response flag): Select the earliest record from all response records (CR or PR). The flag is later used to derive first confirmed response date.

USUBJID	SEQ	VISIT	RESP_LST	CBOR_COND	TW2_1	TW3_1	_CBOR	_CBORN	RESP_FL	CBOR_FL	FIRST_RESP_FL
1001	1	EOT	SD	SD*/NE			NE	5		Y	
1002	1	C3D1	SD-PD	SD*/NE	37		SD	3		Y	
1002	2	EOT	PD	PD*/NE			PD	4			
1003	1	C3D1	PR-PR-CR	PR(TW3_1)/SD	61	105	PR	2	Y		Y
1003	2	C5D1	PR-CR-CR	PR(TW3_1)/SD	44	102	PR	2	Y		
1003	3	C7D1	CR-CR-CR	CR(TW3_1)/SD	58	119	CR	1	Y	Y	
1003	4	C9D1	CR-CR-PD	CR(TW2_1)/SD	61	118	CR	1	Y		
1003	5	C11D1	CR-PD	SD*/NE	57		SD	3			
1003	6	C13D1	PD	PD*/NE			NE	5			

Subject 1001 has only 1 tumor assessment at End of Treatment visit, with Tumor response of SD. The CBOR condition is categorized into SD*/NE. The assessment happened on day 24, which doesn't meet the minimal time requirement for SD confirmation of 49 days. So, the temporary cBOR of the record is NE. Since this is the only record, the cBOR of the subject is NE and the record is flagged as cBOR. NE is not considered as response, so the response flag and first confirmed response flag are NULL.

Subject 1002 has 2 tumor assessments at Cycle 3 Day 1 and End of Treatment visit. The record of C3D1 is categorized into SD*/NE. It happened on day 53, which meet the 49 days of SD confirmation requirement. So, the temporary cBOR of the record is SD. It ranks higher than PD, so it is flagged as cBOR of the subject. SD is not considered as response, so the response flag and first confirmed response flag are NULL.

Subject 1003 has 6 tumor assessments from Cycle 3 Day 1 to End of Treatment visit. The First tumor response is PR and it's next 2 consecutive assessments is PR-CR. The time difference between TA3 and TA1 is greater than CR/PR required confirmation time window of 28 days. So, the temporary cBOR of the record is PR. There are 4 records with temporary cBOR in CR or PR flagged as response record. Among which, the first record of C3D1 is flagged as first confirmed response and its date will be outputted as date of first confirmed response later. Sorting the response records by ranking and date, the record of C7D1 is selected as the cBOR among all records.

CONCLUSION

In clinical trials using RECIST as response evaluation criteria, cBOR is of great importance of efficacy endpoints. The paper presents an approach using exhaustive method in the derivation of cBOR. Compared with other methods, it is easy to understand, simple to use and convenient to perform quality control. It is also flexible to adapt for different study design, by using format to converge to conditions and using macro variables to control pre-specified time restrictions.

REFERENCE

[1] Cheson, B. D., Pfistner, B., Juweid, M. E., Gascoyne, R. D., Specht, L., Horning, S. J., ... & Diehl, V. (2007). Revised response criteria for malignant lymphoma. *Journal of clinical oncology*, *25*(5), 579-586.
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