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Response evaluation criteria practice for skin cancer by RECIST 1.1, or modified World Health Organization (WHO) criteria or composite criteria

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ABSTRACT

Skin cancer is one of the most common and active types of cancer with rapidly rising incidence worldwide in the present decade. The main types of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma. BCC is the most common skin cancer with less than 0.01% rate of metastases. SCC is the second most common skin cancer ranging from in situ tumors to invasive tumors and metastatic disease. Melanoma is much less common than the other types but much more likely to invade nearby tissue and spread to other parts of the body or even be fatal. Due to its extensiveness, high disease burden and a certain degree of lethality, it has spawned the establishment of an internationally accepted response evaluation criteria.

The WHO criteria was published in 1981 as the first standard tumor response criteria assessing treatment response. The modified WHO criteria is used for response evaluation for externally visible superficial lesions that can be measured using digital medical photography. While for the lesions that are not only superficial and have subdermal component that cannot be adequately assessed by digital medical photography, RECIST 1.1 is highly recommended to be used combined with modified WHO criteria to break the limitation and provide a holistic assessment of the patient's true condition, thereby to improve treatment effects. More and more clinical trials use this type of evaluation system by using multiple response criteria for tumor assessment including RECIST 1.1, or modified WHO or composite to meet current research needs.

This paper discusses the key difference points between RECIST 1.1 and modified WHO criteria and how composite criteria used when considering both RECIST 1.1 and modified WHO criteria in the practice, statistical and protocol considerations, the difference of CRF and summary of the modified WHO criteria and composite criteria.

INTRODUCTION

In this paper, we summarize the information about modified WHO criteria and composite criteria, guidelines for response criteria for use in trials for skin cancer, and the examples and scenarios for the readers with following points: How modified WHO criteria and composite criteria works, the difference between modified WHO criteria and RECIST 1.1, statistical and protocol consideration, difference between data collection and summary of the modified WHO criteria.

BACKGROUND

Skin cancer is one of the most common, malignant, and aggressive cancer across the globe. The main types of skin cancer are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. Although basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are common, they rarely spread/metastasize, to distant parts of the body. In more than 95% of patients, surgery can cure earlier stages of BCC and SCC. Melanoma is less common than BCC and SCC while more likely to dermal invasion and metastasis. Most deaths from skin cancer are due to melanoma. In the past, patients with metastatic or locally advanced skin cancer that were not candidates for surgery or radiation therapy, were considered for palliative systemic therapy which can be administered as part of routine clinical practice. Recently, with the rise of the immunotherapies including the Cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death ligand-1 (PD-L1) pathways, immunotherapies have been used for multiple cancer types, not only including lung, bladder, renal, head and neck cancer but also for metastatic or locally advanced skin cancer. Based on the characteristics of skin cancer and the rise of immunotherapies, single tumor response evaluation criteria cannot meet current clinical research

needs anymore, multiple tumor response evaluation criteria like RECIST 1.1, or modified WHO criteria or composite criteria or iRECIST used in parallel are becoming more and more popular and can fulfill current research needs.

WHAT ARE MODIFIED WHO CRITERIA AND COMPOSITE CRITERIA?

MODIFIED WHO CRITERIA

There has been a proliferation and divergence of imaging-based tumor-specific response criteria over the past 4 decades whose purpose are to achieve objective assessment of treatment response in oncologic clinical trials. The World Health Organization (WHO) criteria, published in 1981, was the first response criteria and used bidimensional measurements of tumors. The Response Evaluation Criteria in Solid Tumors (RECIST) was created in 2000 and revised in 2009. The RECIST criteria made use of unidimensional measurements and addressed several pitfalls and limitations of the original WHO criteria. Both the WHO and RECIST criteria were developed during the era of cytotoxic chemotherapeutic agents and are still widely used. However, treatment strategies changed over the past decade, more recent criteria that are used for targeted therapies, RECIST 1.1, or modified WHO criteria or composite criteria are used for skin cancer more and more along with iRECIST.

COMPARISON TO RECIST 1.1

Comparing to RECIST 1.1, modified WHO criteria is different from the definition, data collection and evaluation of target lesion, new lesion, and the derivation of clinical overall response. For the composite criteria which use both RECIST 1.1 overall response and modified WHO criteria clinical overall response at each timepoint within specified time window, the derivation is also significant different for the derivation of the composite overall response. We will make an introduction of four key topics below for: target lesion, new lesion, clinical response, and composite response.

Target Lesion

The externally visible component of target lesion(s) is measured using bi-dimensional modified WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension at each tumor assessment and will be documented using standardized digital photography. In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

The target lesion is measured in the longest dimension (First Measurement of Lesion: TRTEST="Diameter" and TRSPID=1) and perpendicular second longest dimension (Second Measurement of Lesion: TRTEST="Diameter" and TRSPID=2). And the sum of the products (of individual target lesions) is derived as sum of the product of the longest dimension (First Measurement of Lesion) and perpendicular second longest dimension (Second Measurement of Lesion) of all individual target lesions, for example for the patient who have two target lesions, can refer the calculation of sum of product of as below. And the derivation of the Externally Visible Tumor Dimension will base on the sum of the products (of individual target lesions) for the percent change from baseline and percent change from nadir.

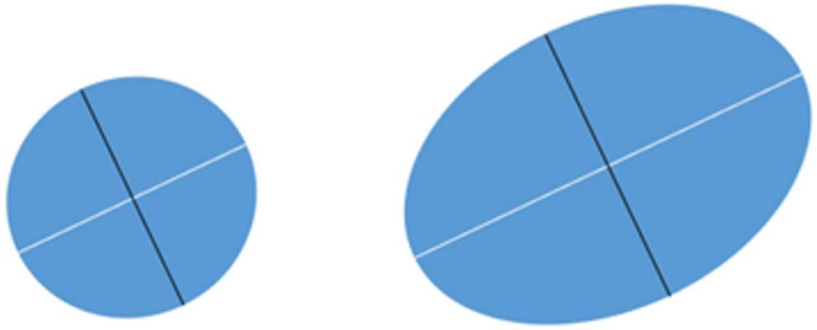

Figure 1. Example for the patient who have two target lesions and both longest dimension and perpendicular second longest dimension are measurable with same method at baseline

White lines = longest diameter (First Measurement of Lesion: TRTEST="Diameter" and TRSPID=1), black lines = longest perpendicular diameter(Second Measurement of Lesion: TRTEST="Diameter" and TRSPID=2).

	Target Lesion 1	Target Lesion 2
Longest diameter (First Measurement of Lesion: TRTEST="Diameter" and TRSPID=1)	15 mm	30 mm
Longest perpendicular diameter (Second Measurement of Lesion: TRTEST="Diameter" and TRSPID=2)	15 mm	20 mm
Target Lesion 1 Product	225 mm^2	
Target Lesion 2 Product		600 mm^2
Sum of the products of Target Lesion 1 and Target Lesion 2	825 mm^2	

Table 1. Example for the Sum of the products calculation for the patient who have two target lesions and both longest dimension and perpendicular second longest dimension are measurable with same method at baseline

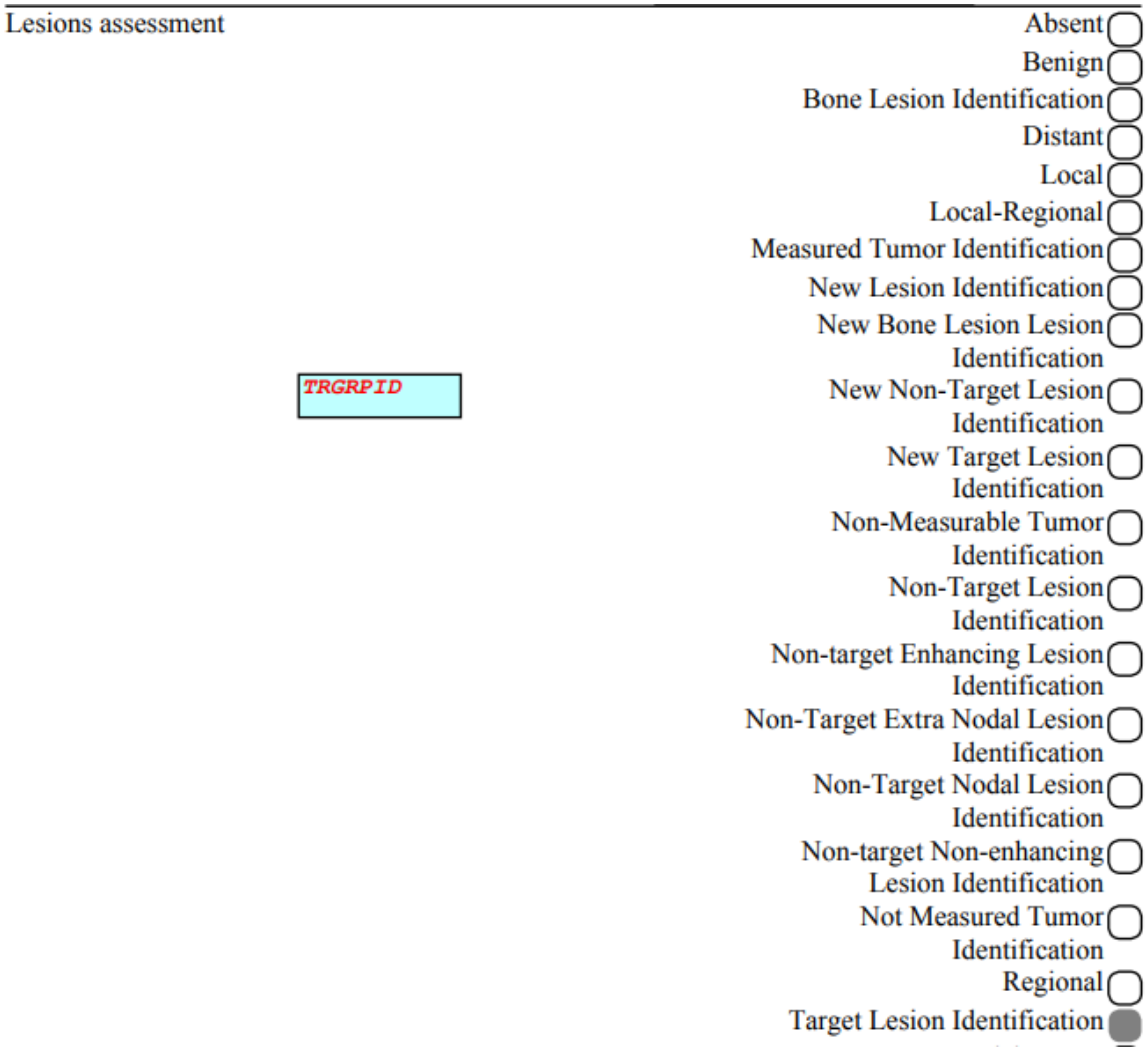

Figure 2. Case report form example for Target Lesion, where the Target Lesion Group ID

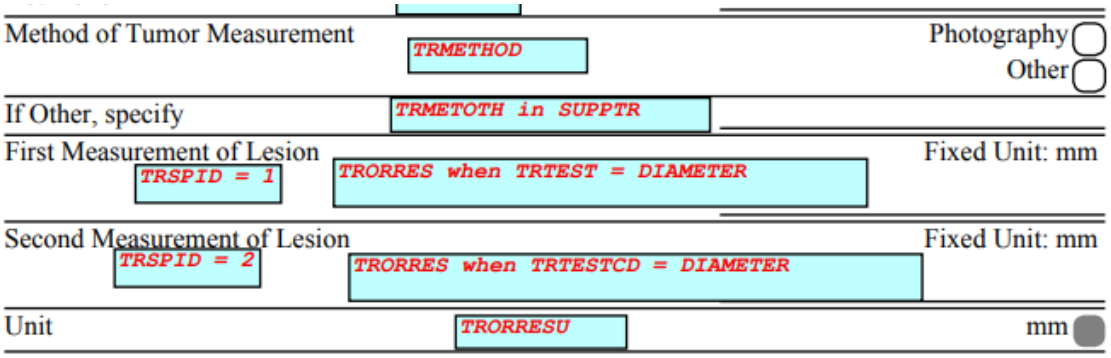

Figure 3. Case report form example for Target Lesion, where the longest dimension (First Measurement of Lesion) and perpendicular second longest dimension (Second Measurement of Lesion) is measured

Biopsy is needed for the confirmation of complete response of externally visible disease, if the investigator Interpretation of Result is Normal and all target lesion(s) are no longer visible then the Externally Visible Tumor Disease can be considered as vCR; else not.

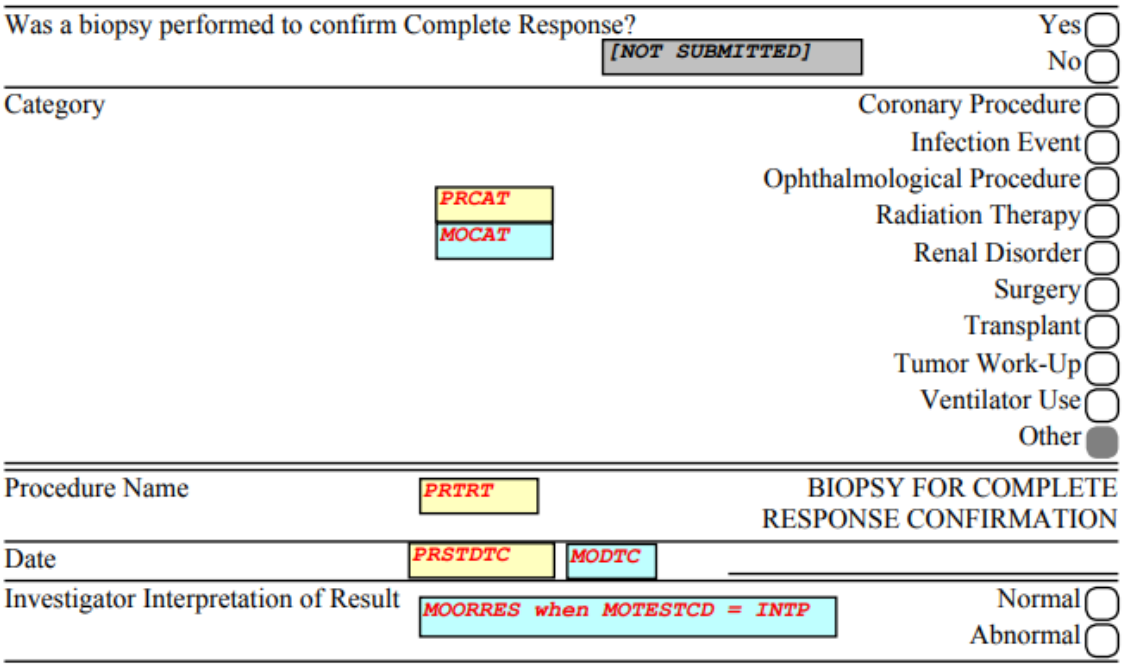

Figure 4. Case report form example for Biopsy for Complete Response confirmation

For the response evaluation of Target Lesions for the Complete Response, Partial Response, Progressive Disease and Stable Disease, below table present the detail of the difference between RECIST 1.1 and modified WHO criteria.

modified WHO criteria Externally Visible Tumor Dimension		**RECIST 1.1** Response of Target Lesions	
vCR	All target lesion(s) no longer visible maintained for at least 4 weeks. Confirmation by biopsy of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy.	CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm)
vPR	Decrease of 50% or greater in the sum the products of perpendicular longest dimensions of target lesion(s) from baseline, maintained for at least 4 weeks.	PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
vPD	Increase of ⩾25% in the sum of the products of perpendicular longest dimensions of target lesion(s), taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest).	PD	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions)

modified WHO criteria		RECIST 1.1	
vSD	Not meeting criteria for vCR, vPR, or progressive disease.	SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters

Table 2. modified WHO criteria and RECIST 1.1 criteria for response assessment

New lesion

For the Phase I and II clinical trials, the biopsy confirmation for new lesion is not mandatory. The new lesion present will be considered as cPD if the lesion is ⩾10 mm in both maximal perpendicular diameters (First Measurement of Lesion and Second Measurement of Lesion) and can be clearly documented as not being previously present. Below is new lesion CRF Form as an example for Phase I, II and III clinical trials. The CRF will be completed if the biopsy is done. For the Phase III clinical trial, the biopsy confirmation for new lesion is highly recommended.

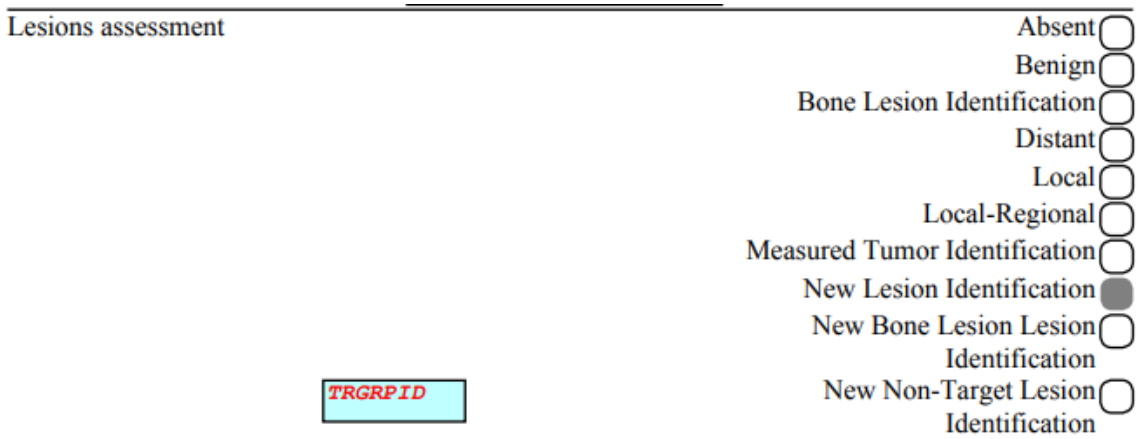

Figure 5. Case report form example for New Lesion, where the New Lesion Group ID

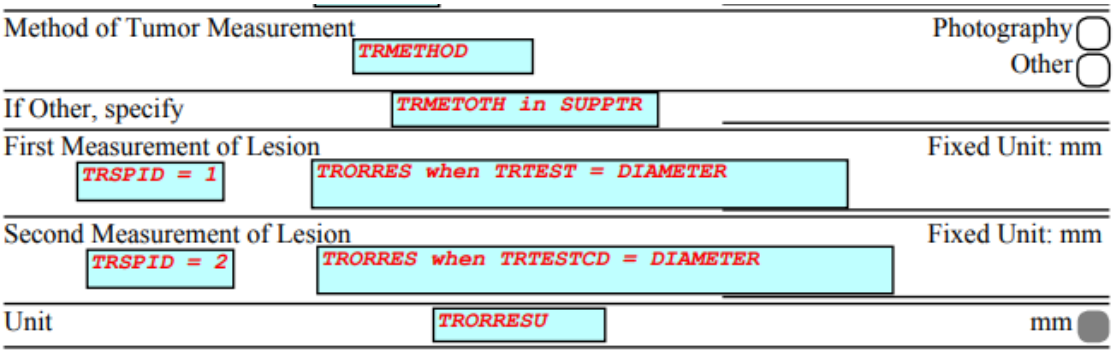

Figure 6. Case report form example for New Lesion, where the longest dimension (First Measurement of Lesion) and perpendicular second longest dimension (Second Measurement of Lesion) is measured

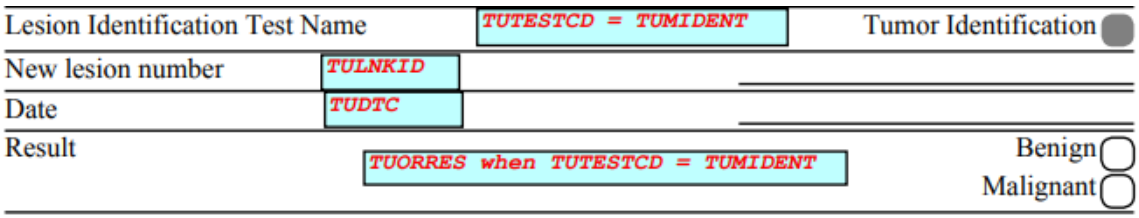

Figure 7. Case report form example for biopsy for New Lesion confirmation

Clinical Response

Components of the derivation for clinical response are:

1. New lesions presence.
2. Externally visible tumor dimension if target lesions are identified at baseline.

The computation of the clinical response will follow below rules at each timepoint.

Externally Visible Tumor Dimension	New Lesions	Clinical Response
vCR	No	cCR[a]
vPR	No	cPR[b]
vSD	No	cSD[c]
vPD	Yes or No	cPD[d]
Any	Yes	cPD[d]

Table 3. Overall clinical responses for all possible combinations of clinical tumor responses

a Clinical Complete Response

b Clinical Partial Response

c Clinical Stable Disease

d Clinical Progression of Disease

COMPOSITE CRITERIA

For participants who have disease that is measurable by BOTH modified WHO criteria by digital medical photography and RECIST 1.1 using radiologic imaging. The investigator will decide on using RECIST 1.1 only or modified WHO criteria only or composite criteria i.e. use both RECIST 1.1 and modified WHO criteria.

Normally the patients who have disease that is measurable by BOTH modified WHO criteria by digital medical photography and RECIST 1.1 using radiologic imaging at baseline will undergo tumor assessment by both criteria, and then investigator decides how to follow the tumors i.e. use both criteria or only RECIST 1.1 or only modified WHO criteria. If it is decided by investigator to use both criteria, then the composite response will be derived based on clinical response using digital medical photography and RECIST 1.1 overall response using radiologic imaging at each timepoint. The tumor assessment for both criteria at each timepoint should be done within specified time window, for example, 7 days' time window. Why use composite criteria with both modified WHO criteria and RECIST 1.1? The reason is that modified WHO criteria is more used for response evaluation for externally visible superficial lesions that can be measured using digital medical photography. While the lesions that are not only superficial and also have subdermal component that cannot be adequately assessed by digital medical photography, under this situation RECIST 1.1 is highly recommended to be used combined with modified WHO criteria to achieve objective and precise assessment of treatment response. An increasing number of clinical trials are adopting this evaluation system to address the current research needs.

Composite Response

The derivation of Composite Response which both the Clinical Response using digital medical photography and RECIST 1.1 Overall Response using radiologic imaging evaluated within specified time window (for example, 7 days) at each timepoint needs the components listed as below:

1. Clinical Response by modified WHO criteria by digital medical photography.
2. Overall Response by RECIST 1.1 using radiologic imaging.
3. Clinical Response and Overall Response should be evaluated within a specified time window for each timepoint, for example 7 days.

The computation of the composite response will adhere to the following incremental procedure:

- If any progression disease in a). Clinical Response is observed on this assessment, b). Overall Response is observed on this assessment then composite response will take a value of PD.
- If Clinical Response is cCR and Overall Response is CR then composite response will take a value of CR.
- If Clinical Response is cCR and Overall Response is PR/SD, then composite response will take a value of PR.
- If Clinical Response is cPR and Overall Response is CR/PR/SD, then composite response will take a value of PR.
- If Clinical Response is cSD and Overall Response is CR/PR, then composite response will take a value of PR.
- If Clinical Response is cSD and Overall Response is SD, then composite response will take a value of SD.

Clinical Response (Digital Medical Photography)	RECIST 1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
cCR	CR	CR
cCR	PR or SD	PR
cPR	CR, PR, or SD	PR
cSD	CR or PR	PR
cSD	SD	SD
cPD	Any	PD
Any	PD	PD

Table 4. Overall Composite Responses for both clinical response criteria and RECIST 1.1 criteria

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response to investigational medicinal product, the Sponsor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the Sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

RESPONSE-BASED ENDPOINTS

BEST OVERALL RESPONSE

The derivation of best overall response is similar like RECIST 1.1 for the participants only used modified WHO criteria and the subsequently confirmation at least 4 weeks (⩾28 days) is needed while it is complex for the derivation for composite participants who used both RECIST 1.1 and modified WHO criteria. The most challenge part is for the practice in the same timepoint, the tumor assessment for RECIST 1.1 and the tumor assessment for modified WHO criteria sometimes will be done not on the same date, the ranges of these two tumor assessments are different and sometimes it is close and sometimes it is very far even in the same cycle. So, the time window for these two tumor assessments will be used to facilitate the practice of the derivation of the composite response. If the two tumor assessments are not done in the time window, the composite overall response will not be derived at this timepoint. The best overall response will be derived based on the available composite overall response. The derivation is same as RECIST 1.1.

Objective Response Rate, Disease Control Rate, Clinical Benefit Rate

Often used for skin cancer.

Best Relative Tumor Change

The best relative change selection is same as RECIST 1.1 to choose the best relative change, the only difference, is that the relative change for modified WHO only patient is based on the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension. And for the composite patients will

use sum of the diameter based on RECIST 1.1 in the presentation of typical efficacy plots for waterfall plot or spider plot.

TIME-TO-EVENT ENDPOINTS

Except Progression Free Survival (PFS), Duration of Response (DOR) and Time to Response (TTR), the Time to Complete Response (TTCR) often used for skin cancer.

EXAMPLES AND SCENARIOS CONCLUSION

Few examples and scenarios were provided as below based on the clinical trial practice.

		Baseline	Time point 1
Target Lesion 1	Longest dimension	15 mm	15 mm
	Perpendicular second longest dimension	15 mm	15 mm
Target Lesion 2	Longest dimension	20 mm	30
	Perpendicular second longest dimension	20 mm	25
	Sum of the products (of individual target lesions)	625 mm^2	975 mm^2
	Nadir		625 mm^2
	Change from Nadir		350 mm^2
	Percent Change from Nadir		56
	Externally Visible Tumor Dimension		vPD

Table 5. Example for the modified WHO criteria for Externally Visible Tumor Dimension

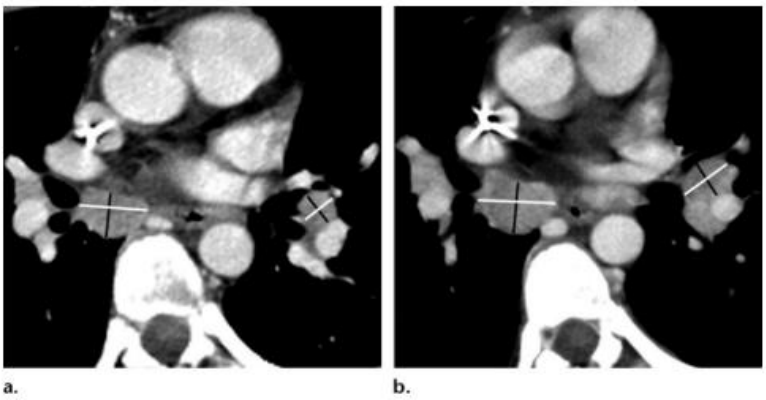

Figure 8. Example for comparison of treatment response according to modified WHO criteria and RECIST 1.1

White lines = longest diameter, black lines = longest perpendicular diameter.

(a) Axial CT image shows two metastatic lymph nodes. The modified WHO criteria make use of the SPD; and RECIST 1.1 uses the shortest diameters of the lymph nodes and the longest diameter of the target lesion. In this baseline study, SPD = 455, and RECIST 1.1 SLD = 28 mm. (b) Follow-up CT image shows an increase of a few millimeters in the size of the lymph nodes. SPD increased to 569 (25% increase), and RECIST 1.1 SLD increased to 33 mm (18% change). On the basis of these measurements, treatment response would be categorized as progressive disease by the modified WHO criteria and as stable disease by RECIST 1.1. Because the size of the lymph nodes increased in short diameter more than in long diameter. As seen in this example, the treatment response category can vary depending on which criteria are used. Because the modified WHO criteria make use of the product of the diameters, they have been criticized as yielding results that are overly sensitive to small changes in tumor size or possible measurement errors. RECIST 1.1 added the requirement that target lymph nodes be at least 15 mm in short-axis diameter.

STATISTICAL AND PROTOCOL CONSIDERATION

The efficacy criteria the patient use if RECIST 1.1 only or modified WHO criteria only or composite criteria whether to be collected in CRF by investigator or other rules should be clarified.

For modified WHO criteria, the following key points should be clarified:

- Only the target lesion or both target lesion and non-target lesion information need to be collected.
- Biopsy confirmation for new lesion or complete response of externally visible disease is needed or not.
- Maintenance at least for 4 weeks for vCR or vPR if need or not.
- Target lesion response derivation take as reference the baseline or nadir.

For composite criteria, the time window needs to be identified when using both RECIST 1.1 and modified WHO criteria at same timepoint. And the analysis date or visit rules are recommended to follow the analysis date or visit derivation for RECIST 1.1 overall response derivation.

Presentation of multiple criteria in table, listing and plots, attention to be given to the composite criterion, as this criterion is response based, there are relative changes available for both RECIST 1.1 and modified WHO criteria, RECIST 1.1 sum of diameter are recommended to be used when presenting in the same table, listing and plots or separately.

Modified WHO criteria or composite criteria could be used for the primary efficacy outcome. For early phase and late phase clinical trials, modified WHO criteria or composite criteria can be considered as primary endpoint criteria.

CONCLUSION

For specific indication for metastatic or locally advanced skin cancer which are not suitable for surgery or radiation therapy, the use of multiple response evaluation criteria for RECIST 1.1, or modified WHO criteria or composite criteria will offset pitfalls and limitation for the use of single response evaluation criteria and therefore to provide a holistic assessment of the patient's true condition and improve treatment effects. More and more clinical trials use this kind of evaluation system to meet current research needs based on the treatment strategies' changes.

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RECOMMENDED READING

- *New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1)*
- *WHO handbook for reporting results of cancer treatment, available at* WHO handbook for reporting results of cancer treatment
- *Reporting Results of Cancer Treatment, available at* Reporting results of cancer treatment - Miller - 1981 - Cancer - Wiley Online Library

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