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Adaptation of the immune-related response criteria: irRECIST

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AIM

RECIST 1.1 has its shortcomings for targeted immunotherapy in oncology. Using RECIST 1.1 in immunotherapy trials would lead to declaration of progressive disease (PD) too early, when the treatment effect is not yet fully evident. RECIST also neglects the importance of the 'flare effect' - pseudo-progression effect within the so-called flare time window. Immune related Response Criteria (irRC) based on WHO criteria were published with an aim to provide better assessment of the effect of immunotherapeutic agents. With this poster we introduce irRECIST based on RECIST 1.1, irRC and Nishino et al., 2013 findings. Our aim is to define criteria that better capture antitumor activity and reduce irRC criteria ambiguity. Consistent implementation of irRECIST by both investigators and blinded independent readers will help reduce site: central discordance.

ORIGINAL IRRC, INCLUDING WHO CRITERIA REFERENCES	IRRECIST MODIFICATIONS AND CLARIFICATIONS	RATIONALE FOR MODIFICATION
At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.	**1. 0 Baseline: Measurable Lesion Definitions and Target Lesion Selection** Follow the definitions from RECIST 1.1. Measurable lesions must be accurately measured in at least one dimension with a minimum size of: – 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for nonnodal lesions and ≥15 mm in short axis for nodal lesions – 10 mm caliper measurement byclinical exam – 20 mm by chest X-ray	Up to 5 target lesions may be selected at baseline. Lesions will be measured unidimensionally. The minimum target lesion size at baseline in irRECIST is aligned with RECIST 1.1, as outlined in Nishino et al., 2013.
WHO 5.1.2 Unmeasurable Disease There are many forms of unmeasurable disease, and only a few are mentioned as examples: Lymphangitic pulmonary metastases. Skin involvement in breast cancer. Abdominal masses that can be palpated but not measured	**1.1. Baseline: Non-measurable Lesion Definitions** Non-target lesions will include: – Measurable lesions not selected as target lesions – All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest per-pendicular diameter is ≥10 and < 15 mm. – Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/ pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.	Although irRC does not specifically define non-target lesions, irRC is derived from WHO criteria and indicates accordance with the same for the purposes of definitions of non-target lesions. Further clarifications in alignment with RECIST 1.1 are provided.
Not specified.	**1.2 Baseline: Target and Non-Target Lymph Node Lesion Definitions** Follow the definitions from RECIST 1.1	No change in definition of target and non-target lymph nodes from RECIST 1.1.
Not specified.	**1.3 Baseline: Non-Target Lesion Selection** All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.	In alignment with RECIST 1.1, all malignant lesions have to be selected at baseline. The excess of measurable lesions and all true non-measurable lesions will be selected as non-target lesions at baseline and followed at subsequent timepoints.
Not specified.	**1.4 Baseline: Bone Lesions** Follow the definitions from RECIST 1.1. Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.	Bone lesions are to be handled the same as in RECIST 1.1.
Not specified.	**1.5 Baseline: Brain Lesions** detected on brain scans can be considered as both target or non-target lesions.	Brain lesions can be selected as target or non-target lesions at baseline, depending on the protocol definition, indication, and study design.

Methods

The adaptations from irRC and WHO criteria, as applicable in immunotherapy clinical studies, are documented in the "irRECIST Modifications and Clarifications" column in a comparative table format within our Blinded Independent Central Review (BICR) Charter. The modifications we introduce represent adaptations of published criteria based on radiology practice and clinical trial experience, and they provide more objective and reproducible response assessments for investigators and for the central independent image review.

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Results

irRECIST criteria are based on irRC criteria adapted for unidimensional measurements, as outlined in Nishino et al., 2013. To further align the criteria with RECIST 1.1 we outline the approach for the assessment of baselineselected non-target lesions and new non-measurable lesions, and discuss the impact of those lesions on the overall tumor response assessment.

Guidelines for the evaluation of patients with non-target disease only and patients in adjuvant setting is provided.

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Non-index lesions at follow-up timepoints contribute to defining irCR (complete disappearance required).	**2.2 Follow-up: Non-Target Lesion Assessment** The RECIST 1.1 definitions forthe assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.	Non-target lesions have a subordinate function. In the event that non-target lesions massively progress one cannot ignore such worsening and in these rare cases irPD based only on non-target lesions will be a valid assessment option.
New, non-measurable lesions at follow-up timepoints do not define progression, they only preclude irCR.	**2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment** All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new nonmeasurable lesions prevent irCR.:	When new non-measurable lesions substantially worsen in these rare cases irPD based only on new non-measurable lesions will be an assessment option.
irRC Overall Tumor Assessments **irCR,** complete disappearance of all lesions (whether measurable or not, and no new lesions) – Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented **irPR,** decrease in tumor burden ≥50% relative to baseline – Confirmed by a consecutive assessment at least 4 weeks after first documentation **irSD,** not meeting criteria for irCR or irPR, in absence of irPD **irPD,** increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) – Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented	**2.4 irRC Overall Tumor Assessments** **irCR,** complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory. **irPR,** decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. **irSD,** failure to meet criteria for irCR or irPR in the absence of irPD. **irNN,** no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD. **irPD,** minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. **irNE,** used in exceptional cases where insufficient data exists. **irND,** in adjuvant setting when no disease is detected.	The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions. The thresholds for irPR and irPD assessment are aligned with RECIST 1.1, and confirmation of response is not required. An irPD confirmation scan may be recommended for patients with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response.

Conclusions

irRECIST criteria as outlined here introduce the needed clarifications and adjustments to irRC criteria and Nishino et al., 2013 publication to allow for treatment evaluations that better meet both investigators' and patients' needs and with that better reflect sponsors' demands for more reliable and reproducible study data in targeted immunotherapy in oncology studies. The main adaptation of the existing immune-response criteira lies in the assessment of all detected lesions. Unequivocal and substantial increase of non-target and new non-measurable lesions prevents irCR and may also lead to irPD. Reduction of the tumor burden in patients in an adjuvant setting may lead to irPR and such patients may therefore be enrolled in studies with response endpoints.

Clinical relevance of these adaptations needs to be confirmed.

Summary and Additional Guidance

1. TMTB: Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the Total Measured Tumor Burden (TMTB), and one combined assessment provided.

2. New Measurable Lesions: According to irRC a measurable new lesion has to be at least 5 mm x 5 mm to be selected as an index lesion. For bidimensional measurements this threshold was acceptable. In irRECIST, criteria for unidimensional lesion measurment apply to both target and new measurable lesions: a minimum 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in short axis for lymph nodes. Smaller lesions contribute to the non-target or new nonmeasurable tumor burden, but do not get measured.

3. irPR if no Target Lesions: If new measurable lesions appear in patients with no target lesions at baseline, irPD will be assessed. That irPD timepoint will be considered a new baseline, and all subsequent timepoints will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation.

4. irPR in Adjuvant Studies: irRECIST can be used in the adjuvant setting, in patients with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These patients can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response.

   Considering 3 and 4, sponsors may consider enrolling patients with no measurable disease and/or patients with no visible disease at all in studies with response related endpoints.

5. Non-Target Lesions: In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become measurable. Only true new lesions can be measured and contribute to the TMTB.

6. Example: A patient has multiple lung metastases, all smaller than 10 mm and selected as non-target lesions at baseline. If, at a subsequent timepoint some of these non-target lesions increase and become > 10 mm, and one new lesion >10 mm appears, only the new measurable lesion will contribute to the TMTB, and not the baseline selected non-target lesion that increased in size. Otherwise such an increase would make persisting non-target lesions switch into the new measurable lesion category which would be inaccurate, as the lesion existed at baseline.

7. irPD Based on Non-Target Lesions: Unlike irRC that neglect non-target lesions for the assessment of irPD, in irRECIST a substantial and unequivocal increase of non-target lesions is indicative of progression.

8. irPD Based on New Non-Measurable Lesions: According to irRC, a patient with multiple new lesions of 9 mm would be considered non-PD, whereas a patient with just one new lesion of 10 mm may be assessed as irPD if the TMTB of such a patient increases ≥ 20% compared to nadir. According to irRECIST, the reviewer may assign irPD for the patient with multiple new lesions of 9 mm if they are considered to be a sign of unequivocal, massive worsening (see 2.3)

9. irPD Confirmation: Progression confirmation no less than 4 weeks after the initial irPD assessment is recommended especially in case of marginal disease growth and if the first irPD assessment is within the compound-specific tumor flare window.

References

1. JD Wolchok, A Hoos, O Bohnsack, et.al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria, Clin Cancer Res 2009;15(23) December 1, 2009

2. Nishino M et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43

3. Therasse P, Arbuck SG, et al.: New Guidelines to Evaluate the Response to Treatment in Solid Tumors. Journal of the National Cancer Institute 2000 92(3):205-216]

4. Eisenhauer EA, Therasse P, Bogaerts J, et al.: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). In: Eur. J. Cancer. 45, Nr. 2, Januar 2009, S. 228–47.

5. Therasse P, Eisenhauer EA, Verweij J: RECIST revisited: a review of validation studies on tumour assessment. In: Eur. J. Cancer. 42, Nr. 8, Mai 2006, S. 1031–9.

6. WHO handbook for reporting results of cancer treatment. Geneva (Switzerland): World Health Organization Offset Publication No. 48; 1979.

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