Endpoint evaluation in Immunotherapy Clinical Trials: Focus on irRECIST

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Current methods for endpoint evaluations in Immunotherapy Trials

Historically, most solid tumor responses to cytotoxic agents have been radiologically assessed through use of the modified World Health Organization (mWHO) and the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The recognition that tumor activity response patterns to Immuno-Oncology agents may be different compared to cytotoxic agents, led to the development of the immune-related response criteria (irRC). These criteria, released in 2009, were derived from the mWHO criteria and based on response patterns seen with ipilimumab.

Need for the more uniform and harmonized method of Evaluation

Unlike chemotherapy, which acts directly on the tumor, cancer immunotherapies exert their effects on the immune system and demonstrate new kinetics that involve building a cellular immune response, followed by changes in tumor burden or patient survival. Thus, adequate design and evaluation of immunotherapy clinical trials require a new development paradigm that includes reconsideration of evaluation of established endpoints.

irRC has its own pitfall like erroneous consideration of pseudo progression and reset of baseline. Compared to RECIST, irRC is bidimensional and evaluates greater number of lesions. Studies have demonstrated that irRC unidimensional measurements, when compared to bidimensional measurements, are more reproducible, have less measurement variability and result in lower misclassification rates for response assessment.

irRECIST and its advantages

irRECIST is an innovative step which is expected to be simpler, more reproducible and less ambiguous to assess efficacy and effectiveness of immunotherapeutic agents, and provide response assessment that can be directly compared with the results from clinical trials in the past decade. It overcomes shortcomings of both the criteria including unidimensional measurements, inclusion and assessment of all detected lesions and avoiding early declaration of progressive disease. Few studies have been carried out to validate the criteria compared to irRC and RECIST 1.1. Currently 39 clinical trials are listed on *ClinicalTrials.gov* that uses irRECIST criteria for response evaluation.

References:

1. Bohnsack O, Hoos A, Ludajic K. Adaptation of the immune related response criteria: irRECIST. Ann Oncol 25:iv369, 2014 (suppl 4; abstr 1070P)
2. Nishino M, Gargano M, Suda M, et al. Optimizing immune-related tumor response assessment: Does reducing the number of lesions impact response assessment in melanoma patients treated with ipilimumab? J Immunother Cancer. 2014;2:17.

Original irRC, Including WHO criteria References	irRECIST: Modifications and clarifications
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.	Baseline: Measurable Lesion Definitions and Target Lesion Selection Follow the definitions from RECIST 1.1.
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.	Baseline: Non-measurable Lesion Definitions Follow the definitions from RECIST 1.1
At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (⩾5×5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden: SPDindex lesions + SPDnew measured lesion	Follow-up: Recording of Target and New Measureable Lesion Measurements The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.
Non-index lesions at follow-up timepoints contribute to defining irCR (complete disappearance required).	Follow-up: Non-Target Lesion Assessment The RECIST 1.1 definitions for the 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.
New, non-measurable lesions at follow-up timepoints do not define progression, they only preclude irCR.	Follow-up: Non-Target Lesion Assessment The RECIST 1.1 definitions for the 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.
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	**irRECIST 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.

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