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Position Paper

Practical consensus recommendations - Current role of immune response evaluation criteria in solid tumors criteria in the management of cancer patients receiving immunotherapy

Purvish M. Parikh[1]*, T. P. Sahoo[2], Randeep Singh[3], Bahl Ankur[4], Talvar Vineet[5], G. S. Bhattacharyya[6], Babu Govind[7], Mehta Prashant[8]

[1]Department of Oncology, Shalby Cancer and Research Institute, Mumbai, Maharashtra, India, [2]Department of Medical Oncology, Silverline Hospital, Bhopal, Madhya Pradesh, India, [3]Department of Medical Oncology, Artemis Hospital, Gurugram, Haryana, India, [4]Department of Medical Oncology, Max Hospital, New Delhi, India, [5]Department of Medical Oncology, RGCI, Noida, Uttar Pradesh, India, [6]Department of Medical Oncology, Bhattacharyya Clinic, Kolkata, West Bengal, India, [7]Department of Medical Oncology, KMIO, Bengaluru, Karnataka, India, [8]Department of Medical Oncology, Asian Institute of Medical Sciences, Faridabad, Haryana, India

***Purvish M. Parikh**
Department of Oncology, Shalby Cancer and Research Institute, Mumbai, Maharashtra, India.

purvish1@gmail.com

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ABSTRACT

Response evaluation criteria in solid tumors (RECIST) are a method used to evaluate and document the response to cancer treatment in solid tumors. The availability of a new class of immuneoncology drugs has resulted in the need to modify RECIST criteria methodology. The first leadership immuno-oncology network (LION) master course brought together experts in oncology and immuno-oncology. Six questions were put to the experts and their opinion, supporting evidence, and experience were discussed to arrive at a practical consensus recommendation. n this nascent field, the availability of a practical consensus recommendation developed by experts in the field is of immense value to the community oncologist and other health-care consultants.

Keywords: RECIST, Solid tumors, Immunotherapy, Response criteria

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INTRODUCTION

Response evaluation criteria in solid tumors (RECIST) are a method used to evaluate and document the response to cancer treatment in solid tumors.[1] This has been developed by western countries (North America and Europe) essentially to allow regulatory authorities to objectively and transparently interpret the outcome of clinical trials by pharma companies - mainly for marketing approval and label indications for use. These criteria are constantly undergoing change to keep abreast with evolving methods treatment and novel classes of drugs. They are also subject to rigorous testing and validation.

The availability of a new class of immuno-oncology drugs has resulted in the need to modify RECIST criteria methodology. This has become especially important since these drugs are now recognized as one of the most important advances in cancer management in the past 5 years.[2]

Two important challenges made us realize that, perhaps, conventional RECIST criteria were not ideal for patients being treated with immunotherapy.[3] The first was that pattern of response to immunotherapy drugs was significantly different from what we were used to seeing with conventional chemotherapy. Moreover, using conventional response criteria (RC) led to misleading labeling of patients as having

progressive disease when they were, in fact, responding to immunotherapy agents. As a result, there were instances of premature termination of therapy and patients being removed from clinical trials even before the drug could demonstrate its beneficial effect.

This gave birth to the immune RECIST (iRECIST) criteria - which were first published on March 2, 2017 and specifically meant for immunotherapies.[4] In fact, iRECIST have been preceded by immune-related RC (irRC - 2009) and irRECIST (irRECIST - 2013).[5] The main change was the category of new overall response being defined as immune unconfirmed progressive disease (IUPD) unless it met iRECIST criteria at follow-up scanning after a fixed interval (4–8 weeks). Such patients in clinical trials were continued on ongoing treatment if clinically stable.

METHODOLOGY

The first leadership immuno-oncology network (LION) master course brought together experts in oncology and immuneoncology at Bhopal on May 5, 2018. These experts discussed specific topics in immuno-oncology in a structured and predetermined manner. One session during this, the first LION master course focused on the topic of response evaluation criteria for patients on immunotherapy was discussed and this consensus statement prepared. Six questions were put to the experts and their opinion, supporting evidence, and experience were discussed to arrive at a practical consensus recommendation. The six questions are shown in Table 1.

RESULTS

Q1: Is there a need to reanalyze RC for patients receiving immunotherapy? The discussion was based on the fact that patients on immune therapy drugs often have a response that is seen only after the time period of median survival is completed. This indicates that the response is slow. During this time, there have been reports of patients showing flare reaction, development of signs of disease at new sites that are not measurable, features commonly interpreted as progressive disease while their clinical symptoms are receding and general condition improving.[6] Hence, there seems to be a case of disconnect between clinical response and objective imaging response. For these reasons, there was consensus among experts that there are sufficient grounds to explore better RC for patients receiving immunotherapy.

Q2: Is pseudoprogression seen in significant number of patients to validate change in response measurement? There was general consensus that pseudoprogression has been well documented in international literature. Some of the experts had also identified its existence in their patients. However, its incidence seems to be small (generally perceived to be about 10%). Therefore, response measurement should be continued in the conventional manner as a rule of thumb. The consensus was that if the imaging showed progression was contradictory to the clinical response/benefit seen, pseudoprogression can be considered and appropriate imaging evaluation modified as per iRECIST criteria.

Q3: For patients receiving immunotherapy, is iRECIST better than other guidelines available today? The discussion was around the use of RC in clinical trials for regulatory approval of new drugs. Various modifications of RECIST criteria for immunotherapy recipient patients have been proposed since 2009. This included irRC, irRECIST, and iRECIST. The consensus was that for clinical trials, current evidence indicates that iRECIST is better than other available guidelines.

Q4: Is iRECIST ready to be currently used in routine clinical practice? While iRECIST is considered as important for clinical trials, its application in routine clinical practice is not yet clear. The main reason for the same is the fact that the new criteria have become available only recently, have not been compared to the gold standard (RECIST 1.1) in a prospective manner and its value has not been subject to the test of time.[7] After intense discussion, the consensus recommendation was that RC using iRECIST may be prospectively collected even in routine clinical practices - however, its use for routine treatment decisions should be done only on case-to-case basis.

Q5: Should we continue immunotherapy beyond progressive disease as identified by conventional RECIST criteria? This question also led to intense debate and close scrutiny of the available published data as well as personal experience of experts. Important discussion points included the cost of immunotherapy drugs, their availability, their response rates, lag time in demonstrating response, unique toxicities, and the need to optimize patient benefit. Finally, the consensus recommendation was to continue immunotherapy for clinically responding patients beyond progressive disease using conventional RECIST criteria on case-to-case basis only.

Q6: Under what circumstances should a patient of IUPD or immune confirmed progressive disease (ICPD) be continued

Table 1: Questions discussed during RC session of the first LION master course

Question No.	Question
1	Is there a need to reanalyze RC for patients receiving immunotherapy?
2	Is pseudoprogression seen in significant number of patients to validate change in response measurement?
3	For patients receiving immunotherapy, is iRECIST better than other guidelines available today?
4	Is iRECIST ready to be currently used in routine clinical practice?
5	Should we continue immunotherapy beyond progressive disease as identified by conventional RECIST criteria?
6	Under what circumstances should a patient of IUPD or ICPD be continued on ongoing immunotherapy?

IUPD: Immune unconfirmed progressive disease, ICPD: Immune confirmed progressive disease, RC: Response criteria, LION: Leadership immuno-oncology network, iRECIST: Immune response evaluation criteria in solid tumors

Table 2: Take-home messages regarding the use of RC in patients receiving immunotherapy (practical consensus recommendations of the first LION master course)

Question No.	Question
1	There is a need to explore better criteria for evaluating patients receiving immunotherapy?
2	Pseudoprogression is seen in a small but significant number of patients on immunotherapy. If the imaging showing progression was contradictory to the clinical response/benefit seen, pseudoprogression can be considered and appropriate imaging evaluation modified as per iRECIST criteria on case-to-case basis
3	For clinical trials in patients receiving immunotherapy, current evidence indicates that iRECIST is better than other available guidelines
4	Attempts may be taken to collect data on response using iRECIST criteria even in routine clinical practices - however, its use for routine treatment decisions should be done only on case-to-case basis
5	Continue immunotherapy for clinically responding patients beyond progressive disease using conventional RECIST criteria on case-to-case basis only
6	For patient on immunotherapy who deteriorates clinically who also shows imaging progression (irrespective of whether the disease progression is documented using RECIST 1.1, iUPD, or ICPD), further treatment with ongoing immunotherapy should be discontinued. On the other hand, those whose clinical condition was stable or improving (in spite of progression on imaging) were considered to currently lie in the controversial gray area and no consensus existed on how to manage their further treatment

ICPD: Immune confirmed progressive disease, RC: Response criteria, LION: Leadership immuno-oncology network, iRECIST: Immune response evaluation criteria in solid tumors

on ongoing immunotherapy? Consensus was clear, if the patient was clinically deteriorating, irrespective of whether the disease progression is documented using RECIST 1.1, iUPD, or ICPD - treatment of such patients should be changed to subsequent line(s) of therapy. On the other hand, controversial gray area existed in the field of immuneoncology for those whose clinical condition was stable or improving. There is a small but significant chance that such patients might remain in good quality of life. It was, therefore, not surprising that the experts were equally divided on what is the best course of action under such circumstances.

CONCLUSIONS

Immuno-oncology is a recent breakthrough. It has been recognized as an important advance with a new class of drugs in cancer management. As data are being generated, we are constantly learning finer points about their appropriate use and benefit. Documenting response of the disease in cancer patients treated with immunotherapy is following suit. With emerging insights, criteria for assessing response in an objective manner are also becoming available. However, several questions remain unanswered. In this nascent field, the availability of a practical consensus recommendation developed by experts in the field is of immense value to the community oncologist and other health-care consultants. We expect the answers to the six questions and the take-home messages (Table 2) will give clarity in specific circumstances while managing patients with cancer treated with immunotherapy drugs. They also clearly state where gray areas exist and where decisions are to be taken on a case-to-case basis.

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