Imaging in immuno-oncology

Understanding novel response patterns of immunotherapies

Presented by Median Technologies, The Imaging Phenomics Company®

Contents

Immunotherapies display novel response patterns that affect the design of imaging based studies and the subsequent evaluation of imaging data.

Applying traditional chemotherapy-based response assumptions to immunotherapy trials can result in inaccurate interpretation of response, premature therapy termination, and unnecessary removal of subjects from a trial. Our unique solutions for medical image analysis and management and iBiopsy® for imaging phenotyping, together with our global team of experts, are advancing the development of new drugs and diagnostic tools to monitor disease and assess response to therapy.

Introduction

Researchers are actively developing strategies to harness the powerful human immune system (protecting us from bacteria, viruses, and our own diseased cells) in the fight against cancer. A relatively new class of drugs, known as immunotherapies, is revolutionizing how we treat patients with cancer. Unlike traditional chemotherapies that kill tumor cells directly, immunotherapies target one's own immune system, causing it to identify and remove tumor cells by increasing endogenous anti-tumor activities. There are different types of immunotherapies including vaccines, recombinant cytokines, and antibodies that modulate the adaptive immune response; however, it is the immunomodulatory antibodies (i.e., checkpoint-blocking antibodies) that are the center of current immunotherapeutic efforts, and as such will be the focus of this article.

Immune checkpoints

The genetic changes that induce cells to become cancerous produce unique protein antigens capable of eliciting an immune response. Cancer-cell antigens are presented on the surface of dendritic cells or macrophages (i.e., antigen–presenting cells) where they are recognized by naïve T cells, triggering T cell activation and response. Activated T cells proliferate, travel to the tumor site, and initiate death in tumor cells that express the antigen. CD8+ cytolytic T cells kill tumor cells directly, while CD4+ T helper cells secrete cytokines that recruit additional immune cells. Each step in the activation/response cycle is regulated by a balance of receptor-mediated stimulatory and inhibitory signals, called immune checkpoints, that control the magnitude of the response. Checkpoint receptor proteins, along with their corresponding ligands, are shown in Figure 1.

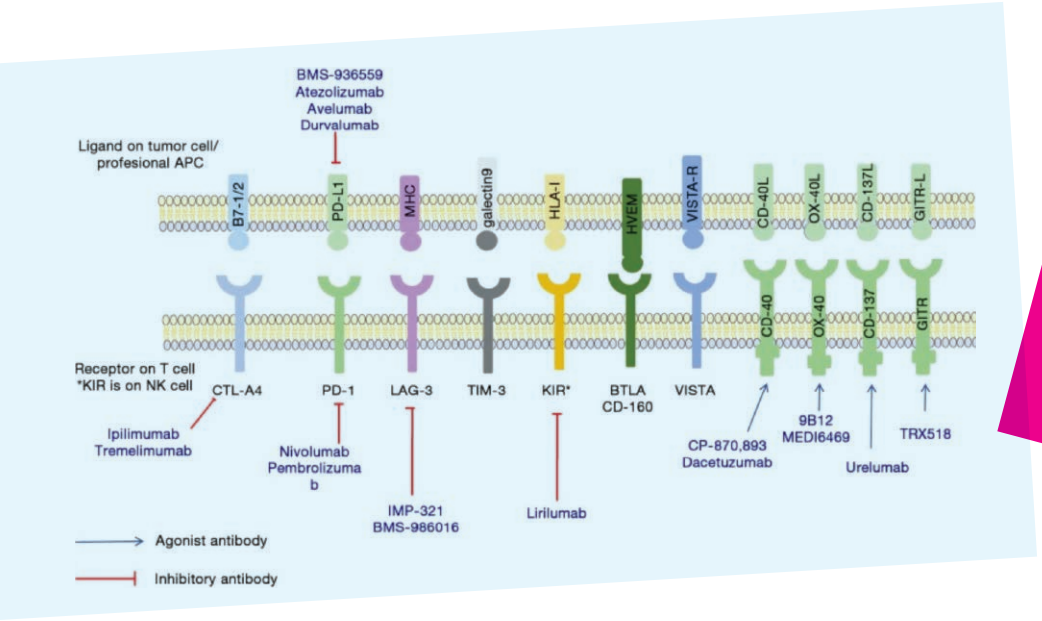


Figure 1
Checkpoint receptor proteins, along with their corresponding ligands

With such an elegant, self-regulating system in place, how does cancer develop? It's because cancer cells fight back by co-opting the immune checkpoint system to evade immune detection, either by downregulating activation signals or upregulating inhibitory signals. Two of the most commonly studied immune checkpoints are CTLA-4 and PD-1/ PD-L1, both of which participate in inhibitory signaling that limits T cell activation, dampens response, and enhances immunosuppressive activity, albeit at different points. *[Pardoll 2012; Freeman 2000]*

Blocking CTLA-4 and PD-1/PD-L1 checkpoint signaling through antibody binding relieves inhibition and increases antitumor immune response. *[Leach 1996; Iwai 2002]*

History of immunotherapy

The first immunomodulatory antibody developed for clinical use was ipilimumab (Bristol-Myers Squibb; BMS), which targets the CTLA-4 checkpoint protein. Ipilimumab was approved by the FDA in March 2011 for the treatment of metastatic melanoma. In a phase 3 study, ipilimumab increased overall survival (OS) in patients with melanoma, with a median OS of 10 months with ipilimumab treatment versus 6.4 months for patients treated with a glycoprotein 100 peptide vaccine. *[Hodi 2010]* **This was the first drug ever developed to increase OS for patients with this aggressive form of cancer.** *[Ribas 2012]*

The following immunomodulatory antibodies

Additional immunomodulatory antibodies quickly followed. Nivolumab (BMS) and pembrolizumab (Merck), which are both PD-1-targeting antibodies, received Breakthrough Therapy Designation by the FDA in 2014. Nivolumab was initially approved for the treatment of unresectable or metastatic melanoma refractory to ipilimumab, and later for use in patients with renal cell carcinoma and non-small cell lung cancer.

Similarly, pembrolizumab was initially approved in 2014 for patients with unresectable or metastatic melanoma refractory to ipilimumab, based on an overall response rate (ORR) of 24%.

[http://www.cancer.gov/ about-cancer/treatment/drugs/fda-pembrolizumab]

Later phase 3 studies demonstrated increased rates of 6-month progression-free survival (PFS) and OS (measured at the 12-month interim analysis point) with pembrolizumab treatment as well.

[Robert 2015]

In May 2016, atezolizumab (Genentech Oncology), a programmed death-ligand 1 (PD-L1) blocking antibody, received FDA accelerated approval for the treatment of locally advanced or metastatic urothelial carcinoma. In October, 2016, FDA approved atezolizumab for the treatment of patients with metastatic non-small cell lung cancer (NSCLC).

In March, 2017, Avelumab (EMD Serono, Inc) became the latest immunomodulatory antibody to be approved by the FDA. The drug was approved for the treatment of metastatic Merkel cell carcinoma (MCC). Avelumab is PD-L1 blocking human IgG1 lambda monoclonal antibody and is the first FDA-approved product to treat this type of cancer.

Combining further increases efficacy

Because CTLA-4 and PD-1 checkpoints work at different points in the T cell activation and response cycle, therapeutics targeting these molecules can be combined to further increase efficacy. A recent phase 3 trial comparing use of nivolumab alone or in combination with ipilimumab for patients with metastatic melanoma found that these immunotherapies have complementary activity: PFS was 11.5 months for patients treated with nivolumab plus ipilimumab, as opposed to either treatment alone (6.9 months for nivolumab alone and 2.9 months for ipilimumab alone). *[Larkin 2015]*

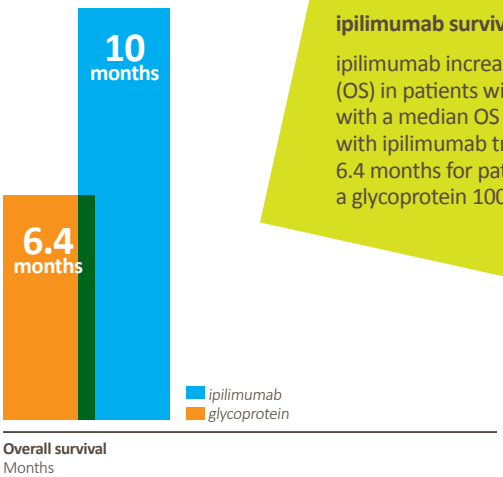
$35 bn

Market opportunity *checkpoint inhibitors*

Expected to peak at $35 billion per year

ipilimumab survival

ipilimumab increased overall survival (OS) in patients with melanoma, with a median OS of 10 months with ipilimumab treatment versus 6.4 months for patients treated with a glycoprotein 100 peptide vaccine



This is just the beginning

Ipilimumab, nivolumab, pembrolizumab, atezolizumab and avelumab are only the beginning. With the large number of immune checkpoint proteins and their various mechanisms for immune modulation, there is no doubt that many more checkpoint-targeting antibodies will soon be available. The market for checkpoint inhibitors is expected to peak at $35 billion per year. *[Garde 2014]* In fact, antibodies targeting LAG3, GITR, and CD40 are already under development.

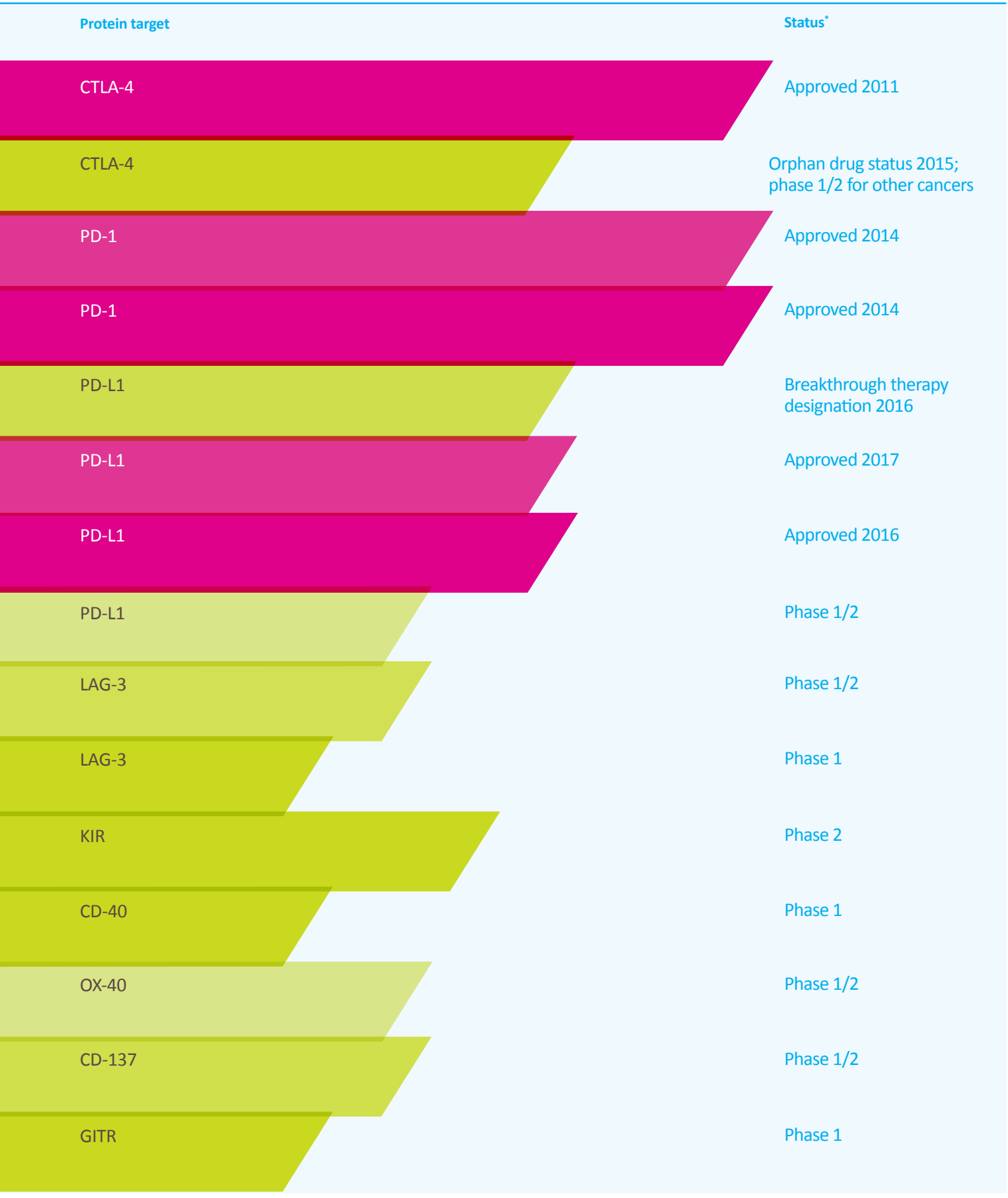
[Table 1; Ascierto 2014]

* *Clinical testing conducted as monotherapy or in combination with other therapies. www.clinicaltrials.gov*

AML = acute myeloid leukemia; CLL = chronic lymphocytic leukemia
MCC = Merkel cell carcinoma; mUC = metastatic urothelial carcinoma
NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma

Approved
Clinical development

Immunotherapy Type of cancer
Ipilimumab Melanoma
Tremelimumab Mesothelioma
Nivolumab Melanoma, RCC, NSCLC
Pembrolizumab Melanoma, NSCLC
Durvalumab mUC
Avelumab MCC
Atezolizumab mUC and NSCLC
BMS-936559 Melanoma and other advanced cancers
IMP-321 RCC, breast cancer, melanoma
BMS-986016 Solid tumors, lymphomas
Lirilumab AML, select solid and hematologic tumors
CP-870, 893 Melanoma
MEDI6469 Colorectal, breast, head & neck cancer
Urelumab Colorectal, head & neck, metastatic solid tumors, CLL
TRX518 Melanoma


Protein target
Status*
CTLA-4
Approved 2011
CTLA-4
Orphan drug status 2015; phase 1/2 for other cancers
PD-1
Approved 2014
PD-1
Approved 2014
PD-L1
Breakthrough therapy designation 2016
PD-L1
Approved 2017
PD-L1
Approved 2016
PD-L1
Phase 1/2
LAG-3
Phase 1/2
LAG-3
Phase 1
KIR
Phase 2
CD-40
Phase 1
OX-40
Phase 1/2
CD-137
Phase 1/2
GITR
Phase 1

The Challenge

Accurate evaluation of clinical response

Immunotherapies are completely unlike traditional chemotherapies or molecularly targeted drugs because they target and enhance endogenous immune system functions instead of directly targeting and killing cancer cells. Given this alternate mechanism of action, it is not surprising that immunotherapies demonstrate novel patterns of clinical response. Applying chemotherapy-based response assumptions to immunotherapy trials could result in inaccurate interpretation of response, premature therapy termination, and unnecessary removal of subjects from a trial. Therefore, a thorough understanding of immunotherapy response patterns is critical for effective evaluation of efficacy.

Patterns of response

Immunotherapy treatment is a 3-stage process:

1

Administration of drug activates the immune system, creating a cellular response.

2

The cellular response begins to attack tumor cells, translating into an anti-tumor response.

3

The anti-tumor response reduces tumor burden and impacts a patient's survival. *[Hoos 2012]*

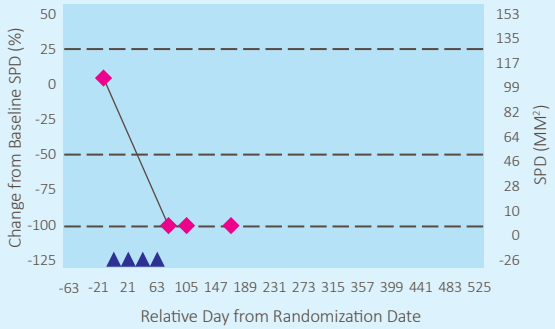
This 3-step process takes time. As a result, it can be many weeks or months before an anti-tumor response can be identified, and even longer to see an impact on patient health. In melanoma patients treated with ipilimumab, it took 30 months to achieve complete response. *[Prieto 2012]* This is very unlike traditional chemotherapies that can initiate tumor shrinking almost immediately.

Thorough understanding of immunotherapy response patterns is critical for effective evaluation of efficacy

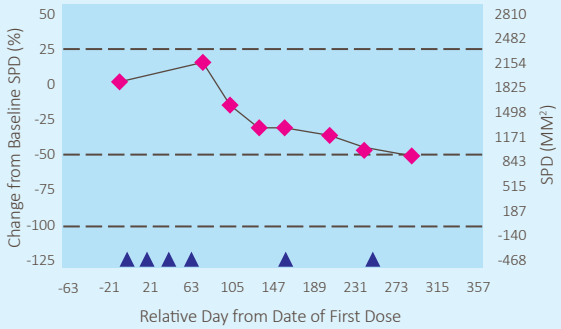
Four distinct patterns of clinical response for immunotherapies were mapped out using ipilimumab data:

[Wolchok 2009]

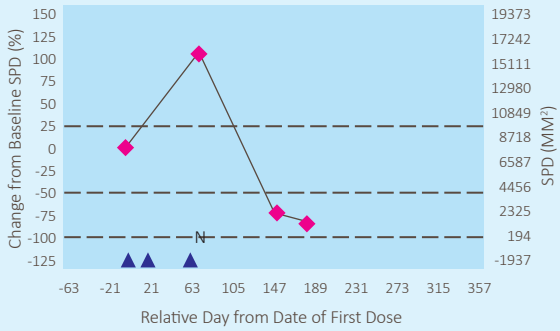
A. Immediate response, no new lesions



B. Stable disease with slow decline in tumor volume



C. Response after initial tumor volume increase



D. Response with new lesions

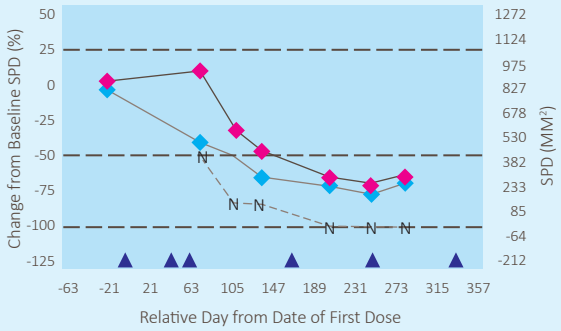


Figure 2
Novel Response Patterns for Immunotherapy Using Ipilimumab
Response pattern A is similar to a traditional chemotherapy. However, the remaining response patterns illustrate the two defining features of immunotherapy: 1) delayed response compared with chemotherapy, and 2) the presence of flare, in which an initial increase in tumor size or tumor number is followed by clinically significant reduction and stabilization of disease.

[Reproduced with permission Wolchok, 2009]

Figure 3. Complete response preceded by flare
Axial contrast-enhanced CT image of the chest showing lymph node metastasis (arrow) before (A), 3 weeks after (B), and 26 months after (C) treatment with ipilimumab. Note the enlargement of the nodule after initiation of therapy, prior to complete response. *[Reproduced with permission, Kwak 2015]*

Immunotherapies can also result in long-term stabilization of disease. Studies with ipilimumab found that long-term stabilization of disease (in patients categorized as having progressive disease [PD]) resulted in increased overall survival. *[Di Giacomo 2013]*

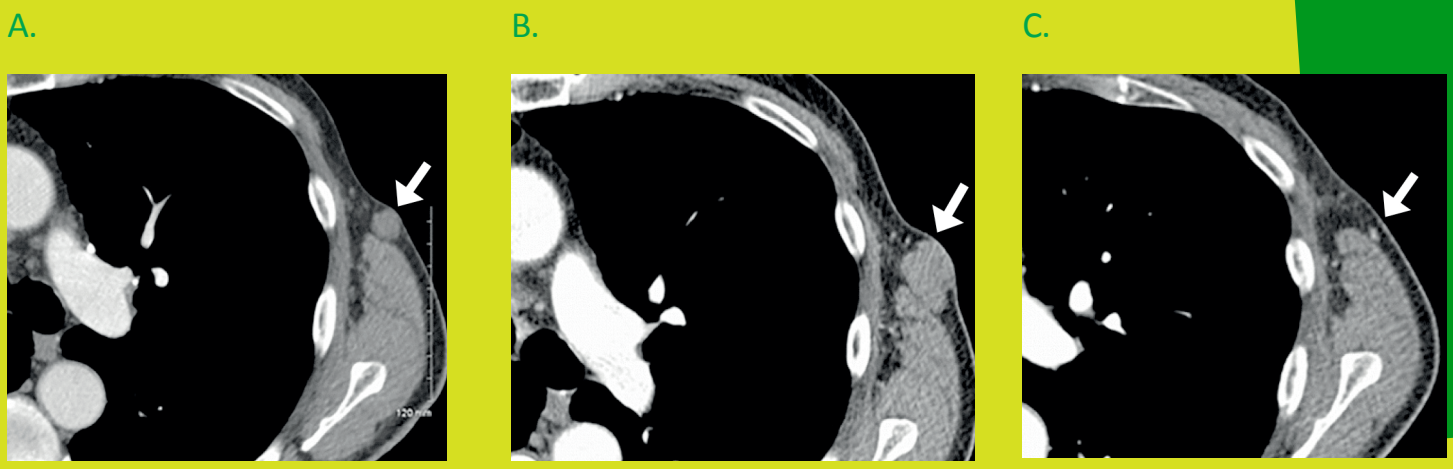


Figure 3
Complete response preceded by flare
[Reproduced with permission, Kwak 2015]

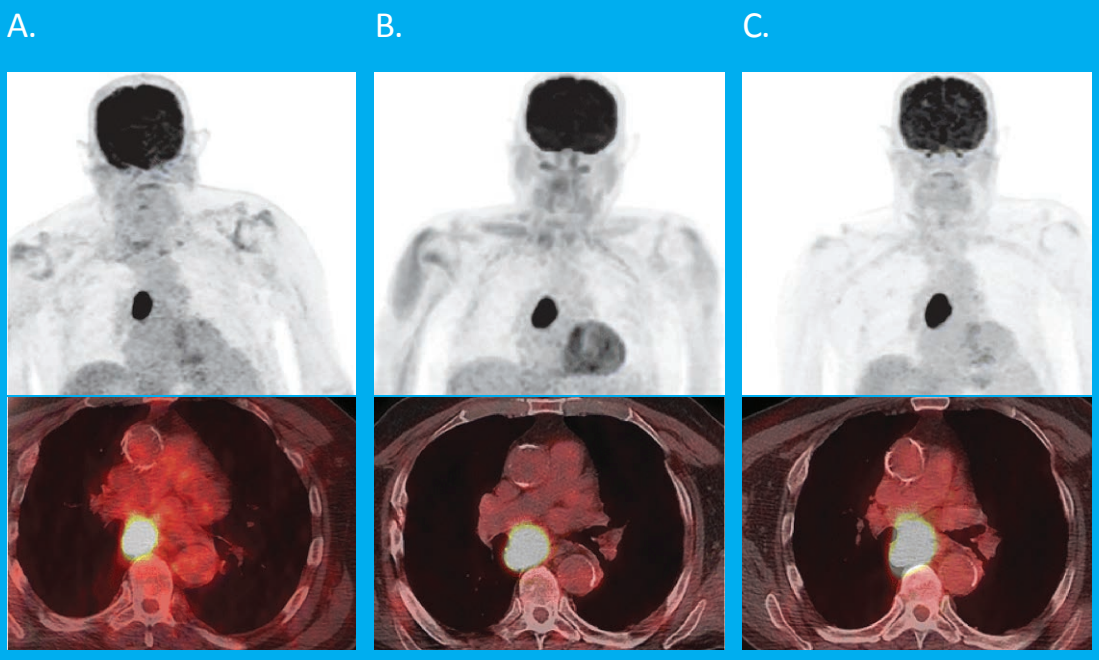


Figure 4
Clinically significant stability
[Reproduced with permission, Kwak 2015]

Figure 4. Clinically significant stability
Axial contrast-enhanced CT image of the chest showing lymph node metastasis (arrow) PET (upper panels) and fused PET/CT (lower panels) images of the chest at 2 months (A), 4 months (B), and 7 months (C) after ipilimumab treatment in a patient with metastatic melanoma. Tumor size is stabilized long beyond the 2-3 month survival period that is typically observed with chemotherapy, and there is no evidence of new disease. *[Reproduced with permission, Kwak 2015]*

Immunotherapies often induce autoimmunity and inflammation, resulting in immune-related adverse events (irAEs). irAEs can appear on imaging scans and must be correctly recognized and interpreted by clinical staff for proper patient treatment and maintaining patients in the trial. *[Kwak 2015]*

Therefore, clinical researchers who perform imaging studies in support of immunotherapies should consider delayed response (i.e., repeat imaging after a 12-week wait period), flare, and irAEs when designing trials and choosing the appropriate response criteria.

Choice of response criteria

Impact on trial design

Measuring tumor size is a well-established method for evaluating clinical benefit, and the RECIST criteria is the gold standard for assessing response in solid tumors. RECIST is an acceptable imaging marker for phase 3 approval by the FDA. However, some of the novel response patterns observed with immunotherapies would not be appropriately captured using RECIST. In fact, early tumor enlargement (due to flare) would be inaccurately marked as progressive disease and treatment would be prematurely terminated. A recent study performed in advanced melanoma patients treated with pembrolizumab found that assessing response using RECIST criteria may underestimate the benefit of treatment in approximately 15% of patients. *[Hodi 2016]*

Researchers quickly realized that new response criteria were needed. The immune-related response criteria (irRC), based on WHO criteria, were published in 2009, irRECIST criteria, which combine elements of irRC with RECIST, appeared in 2013. and iRECIST was published in 2017 by the RECIST working group. Both irRC and irRECIST make predictions on response by calculating the overall tumor burden, as compared with the individual lesion assessment seen in WHO and RECIST. irRC and irRECIST account for flare by assessing new lesions as part of the overall tumor burden, whereas the appearance of new lesions using RECIST would represent progressive disease. *[Wolchok 2009]* iRECIST defines a new overall response called iUPD at first RECIST progressive disease waiting for confirmation by a subsequent evaluation. iRECIST accounts also for flare by calculating separately the sum of new lesions (iSoD). A comparison of irRC, irRECIST, iRECIST, and RECIST1.1 is found in Table 2.

Table 2

	irRC	irRECIST	iRECIST	RECIST1.1
Lesion Measurement	Bidimensional	Unidimensional	Unidimensional	Unidimensional
Baseline Lesion Size	5 mm X 5 mm	≥ 10 mm	≥ 10 mm	≥ 10 mm
Baseline Lesion Number	10 lesions total, 5 per organ	5 lesions total, 2 per organ	5 lesions total, 2 per organ	5 lesions total, 2 per organ
Appearance of New Lesions	Incorporated into TTB	Incorporated into TTB	iUPD, iSoD (sum of diameters of new lesions target, if any)	Always represents PD
Response	CR = disappearance of all lesions PR ≥50% decrease from baseline TTB SD = when neither PR nor PD can be established PD ≥25% increase in the nadir of TTB	CR = disappearance of all lesions PR ≥30% decrease from baseline TTB SD = when neither PR nor PD can be established PD ≥20% increase in nadir of TTB (minimum 5 mm)	CR = disappearance of all lesions PR ≥ 30% decrease from baseline SoD = when neither PR nor PD can be established PD ≥ 20% increase in the nadir of SoD (minimum 5 mm)	CR = disappearance of all lesions PR ≥30% decrease from baseline SoD SD = when neither PR nor PD can be established PD ≥20% increase in nadir of SoD (minimum 5 mm)
Confirmation 4 weeks after first assessment	Yes	Yes, wait up to 12 weeks to confirm PD to account for flare	Yes 4-8 weeks	Yes, if response is primary endpoint

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; TTB = total tumor burden (sum of target lesions plus new lesions, if any) ; SoD = sum of diameters for all target lesions

[Nishino 2013; Wolchok 2009]

So which response criteria should you use?

Overall, irRC, irRECIST and iRECIST are similar—they include two consecutive imaging assessments to account for delayed response with modified definitions of progression. Due to its bidimensional definition, irRC is likely to be more accurate for assessing tumor growth. However, tumor assessment using RECIST unidimensional measurements showed less variability than with other measurements. *[Nishino 2013]*

In addition, the unidimensional defined immune criteria irRECIST and iRECIST have thresholds for PD and partial response (PR) that are aligned with RECIST 1.1, allowing for comparisons with prior and ongoing trials and studies. Furthermore the rules to confirm a progression are clearly and best defined in iRECIST. As mentioned by the RECIST working group in their guidelines, new early-phase trials might even consider using primarily iRECIST. However, iRECIST should still be regarded as an exploratory criterion for most trials and recommendation for the design of studies planned for licensing applications is to make a dual assessment with both RECIST 1.1 and iRECIST; RECIST 1.1 remaining the primary criteria for response-based endpoints.

Given the rapid growth of this drug class (i.e., increasing number of indications) and the increased complexity of experimental design (e.g., immunotherapy combined with traditional chemotherapies or targeted small-molecule inhibitors), choosing the appropriate response criteria can be challenging. Researchers must carefully consider indication-specific criteria (e.g., RANO) and drug type- specific criteria (e.g., iRECIST) when designing oncology trials. However, RECIST 1.1 still remains the gold standard for FDA approval.

Centralized imaging

Given the complexity of immunotherapy response patterns, potential for irAEs, and the multiple response criteria (RECIST, irRECIST, iRECIST), centralized imaging may be needed or required for immunotherapy-based studies in order to accurately and reliability assess response across clinical sites.

Regulatory perspective

Overall survival remains the gold standard endpoint for oncology trials, and the first immunecheckpointtargeting antibody, ipilimumab, was granted FDA approval using this endpoint. However, OS is not always attainable due to the high participant numbers and extended time periods necessary to achieve this endpoint, which is why many trials assess response rate or PFS. Both nivolumab and pembrolizumab were granted approval using ORR. For studies that use PFS or response endpoints, the FDA requires use of RECIST, either alone or in combination with irRECIST/ irRC /iRECIST, and all imaging modifications should be documented in the protocol and independent review charter.

Good imaging practices

Given its complex nature, medical imaging is prone to variability that can prevent proper evaluation of therapeutic efficacy. General variability issues that are associated with all imaging studies, such as inter-reader differences in interpretation, may become even more important in the context of immunotherapies since the reader must be fluent in the new response patterns and response criteria to correctly evaluate images. Proper training of radiologists in these areas, both before and during the trial, is critical for minimizing variability and ensuring consistency of results. In addition, the use of technology for automated lesion identification, measurement, and tracking can greatly enhance the reliability of quantitative measurements, particularly when dealing with flare or the appearance of new lesions. Technology platforms can also simplify tumor assessment by evaluating many parameters (e.g., diameter, volume, density), allowing the user to select multiple response criteria and assess them on a common platform.

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