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REVIEW

Novel patterns of response under immunotherapy

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Novel patterns of response and progression to immunotherapy have been reported that are not observed with conventional cytotoxic or targeted anticancer treatments. A major breakthrough with immunotherapy is its potential to achieve durable responses in a subset of patients with advanced cancer that can be maintained several years even after stopping the treatment. No standardized definition of durable response exists in the literature, and the optimal duration of treatment in case of durable response is not clearly established. However, the majority of patients do not respond to immunotherapy. Initially reported in advanced melanoma patients, pseudoprogression occurs when tumor index lesions regress after initial progression, supporting the concept of treating some patients beyond progression. Overall, reported rates of pseudoprogression never exceeded 10%, meaning that the large majority of patients who have a disease progression will not eventually respond to treatment. The decision to pursue treatment beyond progression must therefore only be taken in carefully selected patients with clinical benefit, who did not experience severe toxicities with immunotherapy. Conversely, rapid progressions, called hyperprogressions, were reported by several teams with rates ranging from 4% to 29%. These observations need to be confirmed from randomized trials. It is essential to interrupt the treatment in patients with hyperprogression, in order to switch to another potentially active treatment. Finally, some patients experience dissociated responses, with some lesions shrinking and others growing. Local treatment with surgery or radiotherapy for growing lesions may be considered. Several immune-specific-related response criteria were developed to better capture benefits of immunotherapy. These criteria only address the pseudoprogression pattern of response, and do not capture the other patterns of response such as hyperprogression and dissociated response. The classic RECIST remains a reasonable and meaningful method to assess response to immunotherapy in the clinic.

Key words: immunotherapy, pseudoprogression, treatment beyond progression, durable response, hyperprogression, response assessment

Introduction

Immune checkpoint inhibitors (ICIs) including agents targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its ligand represent a major breakthrough in oncology, demonstrating an improvement in overall survival (OS) across a broad range of advanced cancer types [1–6]. Because cancer cells can induce immune tolerance via engagement of inhibitory immune checkpoints like CTLA-4 or PD-1, leading to the escape from tumor-specific T-cell response and tumor progression, strategies to stimulate cancer-specific immune response were developed by inhibiting these specific inhibitory immune checkpoints with the development of ICIs such as anti-CTLA-4 or anti-PD-1/PD-L1 fully human antibodies [7].

Novel patterns of response, not previously seen with chemotherapy and targeted therapy, are observed with ICIs related to their unique mechanism of action. Durable responses that may persist even after treatment interruption, challenge the broadly

accepted concept of treatment until disease progression in patients with advanced cancer [8]. The second atypical pattern of response is pseudoprogression reported in patients with advanced melanoma with patients experiencing an objective response following disease progression, raising the question of continuing treatment beyond disease progression [9]. More recently, the concept of hyperprogression has been reported in the literature, suggesting that immunotherapy might do more harm than good in some patients, which has practical consequences for the clinic [10]. Finally, dissociated responses were reported in some patients with some lesions shrinking while others continued to grow [11]. This latter pattern of response raises the question of local treatments of growing lesions.

In this paper, we aim to review these novel patterns of response under immunotherapy and to discuss their clinical implications. We also summarize the different immune-related criteria that have been developed in order to take into account some of these patterns and discuss their relevance for clinical decision-making.

Durable responses

Since ICIs restore an active immune infiltrate of T cells and stimulate a cancer-specific immune response, responses to immunotherapy should be durable, even after stopping the treatment [12]. This concept, however, has been challenged by the description of resistance mutations in biopsy samples of melanoma patients experiencing delayed relapses reported long time after initial objective tumor regression despite continuous therapy, with a shift in the antigen repertoire of cancer cells under ICI treatment, or mutations leading to defects in interferon-receptor signaling and antigen presentation [13, 14]. In addition, in case of severe T-cell exhaustion, if tumor antigens persist, the PD-1 pathway blockade may be insufficient to mediate durable reinvigoration of exhausted T cells, which may acquire a distinct epigenetic profile than effector or memory T cells, thus leading to a minimal memory development [15].

No standard definition of durable response exists (Figure 1). In patients with advanced melanoma, the first long-term outcomes with ICIs were reported with ipilimumab, with OS curve plateauing at 21% at 3 years with a follow-up of up to 10 years [8]. A 36% OS rate at 4 years was reported with ipilimumab in the KEYNOTE-006 trial, whereas a 34% OS rate at 5 year and a 44% OS rate at 4 years were reported with nivolumab and pembrolizumab, respectively [16, 17]. In pretreated advanced non-small-cell lung cancer (NSCLC) patients treated with nivolumab, an estimated 5-year OS rate of 16% was reported [18]. A 44% OS rate at 3 years was reported in pretreated advanced renal cell carcinoma patients treated with nivolumab [19].

A recent meta-analysis of randomized phase III trials evaluating ICIs estimated rates of durable responses according to drug classes [20]. The authors arbitrarily defined a patient with a durable response as a patient having a progression-free survival (PFS) exceeding three times the median PFS of the whole population of patients treated with the same drug(s) in the same trial. This method is an elegant way to overcome patient population bias, especially in terms of tumor type and lines of treatment. It remains to be demonstrated whether this measure correlates with

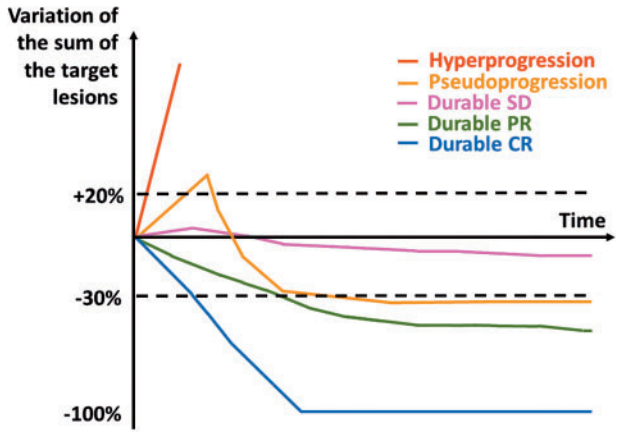

Figure 1. Patterns of response and progression under immunotherapy. SD, stable disease; PR, partial response; CR, complete response.

OS. The mean proportion of patients experiencing a durable response was 2.3 times higher in patients treated with ICIs in comparison to patients treated in the control arms with chemotherapy or targeted therapy (25% versus 11%). In multivariate analysis, the proportion of durable responses was higher in patients treated in first-line metastatic setting. This study also underlines that durable responses are not specific to ICIs.

Several studies attempted to identify predictors of durable responses. In NSCLC patients treated with nivolumab, durable responses, defined by being alive at 5 years following nivolumab initiation, were more frequent in current or former smokers in comparison to never smokers (88% versus 6%), in patients whose tumors expressed PD-L1 in $\geq$1% of tumor cells at baseline in comparison to PD-L1 <1% (70% versus 30%), and in those who achieved at least a partial response according to response evaluation criteria in solid tumors (RECIST) in comparison to those who progressed (75% versus 12%) [18]. Nevertheless, PD-L1 expression does not seem to be a reliable predictor of durable response, since durable responses were also reported in patients with PD-L1 negative tumors [21, 22]. In a retrospective study of melanoma patients treated with anti-PD-1 therapy alone or in combination with ipilimumab, a complete metabolic response on ^{18}F fludeoxyglucose positron emission tomography at 1 year of treatment predicted a durable response [23]. Seventy-five of the 78 patients (96%) who had a complete metabolic response at 1 year and who stopped treatment had an ongoing response with a median postdiscontinuation follow-up of 14.5 months.

The observation of durable responses raises the question of treatment duration. The schedule of administration of ipilimumab is four injections given every 3 weeks. Conversely, ICIs targeting PD1/PD-L1 were evaluated for a longer period of time, ranging from 1 year to until disease progression, depending on the clinical trial designs. In some clinical trials, patients were allowed to be rechallenged with the same ICI in case patients had completed 1 or 2 years of treatment without disease progression, at the time of disease progression.

Few studies reported the efficacy of rechallenging patients with the same ICI following progression during treatment interruption (Table 1) [16, 21, 24–29]. Overall, <25% of patients subsequently responded to treatment in these studies. Only one trial

Table 1. Rates and outcomes of patients who stopped immunotherapy after treatment completion or complete response

Study drugs	Rate of patients who stopped immunotherapy agent after treatment completion or CR	Outcomes of patients who stopped immunotherapy agent after treatment completion or CR	Outcomes following drug rechallenge because of disease progression	References
Melanoma				
Pembrolizumab	19% of patients (103/556) completed 2 years of pembrolizumab	86% of patients (89/103) were progression-free at 20.3 months after pembrolizumab completion	8 patients were rechallenged Median duration of second-course pembrolizumab was 9.7 months with 1 CR, 1 PR, 5 SD, and 1 PD	[16, 24]
Pembrolizumab	10% of patients (67/655) among the 105 patients who achieved a CR stopped treatment	90% of patients (60/67) were disease-free at 24 months	–	[21]
Ipilimumab[a]	–	34% of patients (13/38) with an objective response maintained an objective response for at least 2 years	31 patients were rechallenged 19% of patients (6/31) had an objective response	[25]
Ipilimumab[a]	–	–	51 patients were rechallenged 55% of patients (28/51) had irCR (2), irPR (4), or irSD (22)	[26]
Ipilimumab[a]	–	–	122 patients were rechallenged 23% of patients (28/122) had an objective response	[27]
NSCLC				
Nivolumab	16% of patients (218/1375) completed 1-year treatment	–	–	[28]
Phase I patient population				
Anti-PD1/PD-L1 agents	13 patients discontinued treatment per protocol	Median time free-treatment after discontinuation was 12.6 months	8 patients were rechallenged 25% of patients (2/8) had a PR	[29]

[a]Patients received four injections.

CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; irSD, immune-related SD; irPR, immune-related PR; irCR, immune-related CR; irDCR, immune-related DCR; ORR, overall response rate; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival.

randomized NSCLC patients who were not progressing after 1 year of nivolumab between continuing nivolumab until disease progression or to interrupt nivolumab [28]. The hazard ratio for PFS was 0.43 [95% confidence interval (CI) 0.25–0.76] with a trend toward an improved OS with a hazard ratio of 0.63 (95% CI 0.33–1.20), suggesting that interrupting nivolumab at 1 year in NSCLC patients is too early.

The question of rechallenging patients after serious immune-related adverse events (iAEs), leading to ICI discontinuation, and resolution of the toxicity remains also unresolved. In a retrospective study, subsequent treatment with anti-PD1 antibody could be safely started in melanoma patients who experienced a serious ipilimumab-related iAEs requiring immunosuppression, showing low rate of recurrent iAEs (3%) [30]. Another study evaluated ICI rechallenge in NSCLC patients treated with anti-PD-1/PD-L1 antibody who already experienced iAEs [31]. Among 38 patients who experienced a serious iAE and who were retreated, 48% had no further iAE, 26% had a recurrence of the initial event, and 26% had a new event. Regarding efficacy, data from melanoma patients suggested similar outcomes between patients who discontinued nivolumab plus ipilimumab treatment because of iAE during the induction phase and those who did not discontinue treatment due to toxicity [32]. Prospective data from clinical trials are still limited to clearly answer this question and decision to restart ICI needs to take into account severity of prior iAEs, performance status of the patient, availability of alternative treatments and initial response observed under ICI treatment, but is contraindicated in case of initial life-threatening iAEs.

Sustained responses after treatment interruption for many metastatic solid tumors is an outstanding goal that seemed unachievable until the era of immunotherapy. However, no consensus exists regarding the optimal duration of treatment and the kind of response that should be achieved (complete or partial) and for how long to support stopping treatment. In the absence of randomized data, the decision to stop immunotherapy should be carefully discussed between the physician and the patient. In case of disease progression after treatment completion, it remains to be determined whether patients should be rechallenged with the same drug or not (Table 2). These questions should be addressed in clinical trials.

Table 2. Novel patterns of response and progression under immunotherapy and clinical implications

Patterns of response	Clinical implications
Durable response	• No standardized definition exists • It remains to be determined whether immunotherapy should be given until disease progression or whether the treatment should be interrupted after a certain treatment duration and/or after achieving a certain type of response (CR or PR) • In case of treatment interruption without disease progression, it remains to be determined whether patients should be rechallenged with the same drug or not
Pseudoprogression	• Pseudoprogression remains a rare event and the majority of patients who have disease progression have a real progression • Decision of treatment beyond progression should be only taken in carefully selected patients who experience a clinical benefit and who have not experienced severe toxicities
Hyperprogression	• Hyperprogression were reported in 4%–29% of patients treated with immunotherapy • In case of rapid progression, an early clinical and imaging assessment should be carried out in order to rapidly switch to another potential effective treatment
Dissociated response	• Dissociated response was reported in 7.5% of patients in one study • In case of oligometastatic disease progression, local treatments of the growing lesions might be discussed in tumor boards, while pursing the immunotherapy treatment

CR, complete response; PR, partial response.

Pseudoprogression

Active cytotoxic agents produce immediate tumor shrinkage that correlates with survival [33]. The increase in size of the lesions and the appearance of new lesions have therefore been defined as disease progression with RECIST [34]. Some targeted therapies do not produce tumor shrinkage but still improve survival. This is particularly true with antiangiogenic agents that produce tumor necrosis without modifying the size of tumor lesions, such as sorafenib in hepatocellular carcinoma [35].

A new pattern of response has been initially described in advanced melanoma patients receiving ipilimumab with patients experiencing an objective response after having an initial disease progression (Figure 1). Possible biologic explanations for this atypical pattern of response include continued tumor growth until an efficient antitumor immune response occurs, and a transient immune-cell infiltrate in the tumor bed leading to an artificial increase of the tumor burden. This latter hypothesis has been confirmed by tumor biopsies from melanoma patients treated with ipilimumab showing acute inflammatory reactions [36]. Based on these first clinical observations in advanced melanoma, the possibility to pursue immunotherapy after an RECIST-defined disease progression was rapidly adopted in the majority of trials evaluating ICIs and extended to other tumor types, allowing treatment beyond progression in patients who derived clinical benefit.

Pseudoprogression was reported across tumor types (Table 3). When evaluating the rate of pseudoprogression, it is important to use as a denominator all patients who started immunotherapy and not only the subgroup of patients who continued on treatment beyond progression. Rates of pseudoprogression never exceeded 10%, independent of tumor type, which is far below the rate of patients who have disease progression at first tumor evaluation, meaning that pseudoprogression is rare [11, 37–54]. In other words, in a majority of scenarios, radiographic progression at the first response assessment is reflective of true disease progression.

Another differential to be considered with new or progressive lesions in the setting of ICI therapy is immune-mediated sarcoid reaction. There have been reports of enlarging nodal, pulmonary or other visceral lesions, which were biopsied to show granulomas without malignancy, and may occur early as following one to two doses of immunotherapy [55].

No clear predictors of pseudoprogression exist. The early assessment of circulating tumor DNA (ctDNA) might help distinguishing pseudoprogression from real progression [56–58]. In one study, all nine patients among 125 melanoma patients who experienced a pseudoprogression on anti-PD-1 therapy alone or in combination with ipilimumab had undetectable ctDNA at baseline or detectable ctDNA at baseline followed by a >10-fold decrease [57]. Sensitivity of ctDNA for predicting pseudoprogression was 90% and specificity 100%. Real-time assessment of ctDNA might help distinguishing pseudoprogression from true progression, but this needs to be validated in larger cohorts of patients.

Given that pseudoprogression is rare, the decision to continue immunotherapy beyond progression is disputable and should be taken with caution and considered in selected patients who (i) do not experience severe toxicity from these agents and (ii) whose disease-related symptoms has improved (or stabilized in those with rapid progressive disease) on treatment (Table 2).

Hyperprogression

The concept of hyperprogression was first reported in retrospective studies of patients treated with ICIs based on clinical observations of patients whose disease seemed to grow faster after the initiation of immunotherapy (Figure 1) [10, 59]. This concept was supported by OS data from randomized trials that showed curves crossing at 3 months, meaning that immunotherapy did worse than standard treatment in a subgroup of patients [5, 41].

To address this question, several teams compared tumor growth kinetics before and during immunotherapy (Figure 2).

Table 3. Rates of pseudoprogressions in patients receiving PD1/PD-L1 inhibitors in selected phase II/III clinical trials

Study drugs	Assessment of pseudoprogression	Rates of pseudoprogressions	References
Melanoma			
Nivolumab	PR according to RECIST following a PD	8.1% (17/210)	[37]
Nivolumab	PR according to RECIST following a PD	8.3% (10/120)	[38]
Pooled retrospective study of two multicenter phase III trials evaluating anti-PD1 antibodies	PR according to RECIST following a PD	4.6% (24/526)	[39]
Non-small-cell lung cancer			
Nivolumab	Tumor burden reduction or No further progression for at least two tumor assessments after initial PD according to RECIST	3.4% (4/117)	[40]
Nivolumab	Appearance of a new lesion followed by a decrease from baseline of at least 10% in the sum of target lesions or Initial increase from nadir ≥20% in the sum of target lesions followed by a reduction from baseline of at least 30% or Initial increase from nadir ≥20% in the sum of target lesions or Appearance of new lesions followed by at least two tumor assessments showing no further progression defined as >10% additional increase in the sum of target lesions and new lesions	5.5% (16/292)	[41]
Nivolumab	Appearance of a new lesion followed by a decrease from baseline of at least 10% in the sum of target lesions or Initial increase from nadir ≥20% in the sum of target lesions followed by a reduction from baseline of at least 30% or Initial increase from nadir ≥20% in the sum of target lesions followed by at least two tumor assessments showing no further progression defined as >10% additional increase in the sum of target lesions and new lesions	6.9% (9/131)	[42]
Atezolizumab	PR according to RECIST following a PD	3.6% (12/332)	[43]
Pooled retrospective study of three multicenter open-label trials evaluating anti-PD1 antibodies	PR according to RECIST following a PD	1.9% (10/535)	[44]
Monocentric retrospective study of consecutive patients treated with anti-PD1 antibodies	PR according to RECIST following a PD	1.8% (3/166)	[45]
Monocentric retrospective study of consecutive patients treated with anti-PD1/PD-L1 antibodies	PR according to RECIST following a PD	5% (8/160)	[11]
Head and neck squamous cell carcinoma			
Nivolumab	PR according to RECIST following a PD	1.3% (3/240)	[46]
Renal cell carcinoma			
Nivolumab	PR according to RECIST following a PD	7.1% (12/168)	[47]
Nivolumab	PR according to RECIST following a PD	4.9% (20/406)	[48]
Urothelial carcinoma			
Nivolumab	PR according to RECIST following a PD	9.1% (24/265)	[49]
Atezolizumab	PR according to RECIST following a PD	1.6% (5/310)	[50]

PR, partial response; PD, progressive disease.

Several studies reported on hyperprogression using different methods of assessing tumor growth (Table 4). Some studies evaluated the sum of the largest diameters according to RECIST over time [59, 61–63], whereas others evaluated the evolution of tumor volume [10, 60, 64]. The increase in size or volume per unit of time used thresholds ranging from 1.2 to 2 to define hyperprogression [10, 59, 60, 62–64]. In some studies, time to treatment failure of <2 months was also considered as hyperprogression [61, 62]. Kato et al. [61] included a >2-fold increase in pace of progression as part of the criteria for diagnosing hyperprogression. Some studies were carried out in phase I patient populations [10, 60–62], whereas others were cancer-specific [59, 63, 64]. Rates of hyperprogression ranged from 4% to 29%.

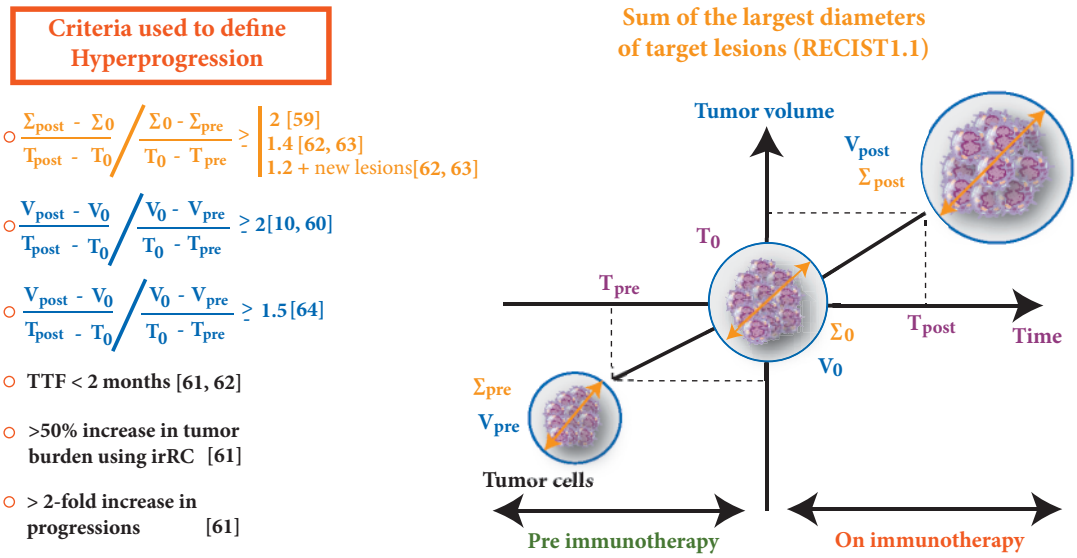

Figure 2. Criteria used in the literature to define hyperprogression. Σ_{pre}, sum of the largest diameters of the target lesions on baseline imaging before starting last prior treatment; Σ_{post}, sum of the largest diameters of the target lesions on imaging postimmunotherapy; V_{pre}, sum of the volumes of the target lesions on baseline imaging before starting last prior treatment; V_{post}, sum of the volumes of the target lesions on imaging postimmunotherapy; T_{pre}, time of baseline imaging before starting last prior treatment; T_{post}, time of imaging postimmunotherapy; TTF, time to treatment failure.

Table 4. Rates of hyperprogressions in patients receiving immune checkpoint inhibitors

Study drugs	Cancer types	Assessment of hyperprogression	Rates of hyperprogression	References
Anti-PD1/PD-L1 antibodies	All	TGR >2 according to tumor volume	9.1% (12/131)	[10]
ICIs and/or costimulatory molecules	All	TGR >2 according to tumor volume	7.1% (13/182)	[60]
Anti-PD1/PD-L1 antibodies	All	TTF <2 months or >50% increase in tumor burden according to irRC or >2-fold increase in progression pace	3.8% (6/155)	[61]
Anti-PD1/PD-L1 antibodies or ICI combinations in phase I trials	All	TTF <2 months and minimum increase in measurable lesions of 10 mm and Increase of ≥40% in target tumor burden compared with baseline or increase of ≥20% plus the appearance of multiple new lesions	15.4% (33/214)	[62]
Anti-PD1/PD-L1 antibodies	HNSCC	TGK > 2 according to RECIST1.1	29.4% (10/34)	[59]
ICIs in phase I/II trials	Gynecological cancers	≥40% tumor burden increase or ≥20% tumor burden increase plus multiple new lesions	23.3% (14/60)	[63]
Anti-PD1/PD-L1 antibodies	NSCLC	Variation of TGR >1.5 according to tumor volume	16.2% (54/333)	[64]

ICI, immune checkpoint inhibitor; TGR, tumor growth rate; TTF, time to treatment failure; TGK, tumor growth kinetics; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer.

Hyperprogression correlated with a worse survival in several studies [10, 59, 64]. While an older age predicted hyperprogression in one study [10], this was not confirmed in other studies [60, 62, 64]. Hyperprogression was found to be more frequent in patients who had a higher number of metastatic sites in one study [64], but not in another [10]. Tumor burden never correlated with hyperprogression [10, 60, 62, 64]. In the head and neck squamous cell carcinoma (HNSCC) patient population, hyperprogression was more frequent in patients with a locoregional recurrence in the radiation field [59]. One study identified *MDM2/MDM4* amplifications and *EGFR* alterations as potential predictors of hyperprogression [61]. This result was confirmed in an independent series [65].

Few data exist describing the biological rationale underlying this phenomenon. The potential role of innate immunity has

been advocated [66]. Anti-PD1 antibody could interact with tumor-associated macrophages via the fragment crystallizable domain of the ICI, engendering reprogramming into M2-like macrophages that are immunosuppressive and promote tumor growth, and eventually inducing disease spread [66].

Recently, chromosomal instability using next-generation sequencing on plasma/serum-derived cell-free DNA (cfDNA) was evaluated in patients with multiple solid tumors receiving immunotherapy and in control patients [67]. The aim was to assess the changes in genomic copy number instability (CNI) score during the first therapeutic cycle and assess the potential early prediction of tumor response under immunotherapy. The authors were able to accurately predict progression based on chromosomal instability quantification in plasma cfDNA, with a risk of progression over 90% in patients not having a substantial decrease in the CNI score. Interestingly, in five out of the six patients who experienced hyperprogression, progression was predicted using the CNI score early. Larger prospective studies will be needed to validate pharmacodynamics monitoring of systemic cancer therapies using cfDNA.

The concept of hyperprogression is controversial since most of the studies mentioned above did not use a control arm. It is not possible to confirm that the acceleration of growth kinetics was induced by immunotherapy, or that similar growth kinetics simply reflects the natural history of the cancer. The NSCLC series, however, assessed the tumor growth rate (TGR) in chemotherapy-treated patients as a comparator to immunotherapy-treated patients. This informed that the phenomenon of hyperprogression is more common with immunotherapy than chemotherapy (13.8% versus 5.1%) [64]. However, this analysis cannot definitively conclude whether hyperprogression was driven by underlying tumor biology or the effect of drug treatment. An opportunity to compare change in TGR in matched patient populations receiving ICI and no treatment would provide the most convincing evidence for hyperprogression, but such data are lacking. Retrospective review of randomized trials would provide larger datasets to validate or not the phenomenon of hyperprogression by quantitative analysis of tumor growth kinetics in progressive patients in ICI and control arms, although assessment of the preimmunotherapy TGR may be limited by availability of imaging immediately preceding the baseline assessment. Collaboration from the pharmaceutical industry in analyzing data from phase III registration trials would be vital for the analysis to be possible.

In any case, we strongly recommend in case of rapid clinical progression to interrupt immunotherapy, especially if it is associated with a clinical deterioration (Table 2). Patients should be reassessed clinically and imaging carried out rapidly to accurately choose the best therapeutic strategy. This might allow switching to another treatment in patients with a still good clinical condition. Several retrospective studies in NSCLC and HNSCC patients reported higher overall response rates with salvage chemotherapy than in historical controls [68–72]. These preliminary data suggest that chemotherapy is a valuable option that should not be underestimated as salvage therapy in case of true progression under immunotherapy.

From a clinical point of view, we do not need to know whether a rapid progression is a hyperprogression or not. However, we believe that the concept of hyperprogression is worth being evaluated, especially if it is eventually demonstrated that immunotherapy can cause harm in some cancer patients.

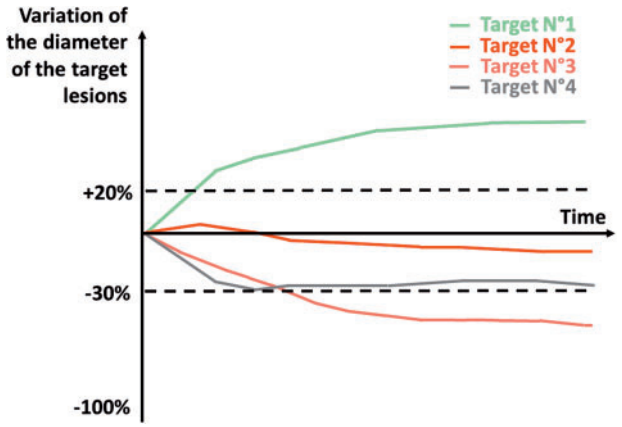

Figure 3. Illustration of a dissociated response to immunotherapy.

Dissociated responses

Dissociated responses are present when some tumors grow and others regress. This response pattern is analogous to mixed responses seen with chemotherapy and targeted therapy (Figure 3). Only one study to our knowledge reported on dissociated responses in 7.5% of NSCLC patients treated with anti-PD1/PD-L1 agents [11]. This atypical pattern of response was associated with a better survival than true progressions. No predictor of dissociated response was identified.

Liniker et al. [73] reported data of patients who received salvage extracranial radiotherapy and/or intracranial stereotactic radiosurgery for progressive disease under anti-PD-1 therapy of 15 patients with advanced melanoma, who continued immunotherapy after radiotherapy. An overall response rate of 45% was reported in the 30 progressing lesions that underwent radiotherapy. This study illustrates the feasibility of a local treatment during immunotherapy. While no clear recommendations exist in case of dissociated response, we believe that local treatments of progressing lesions should be discussed in selected patients with a good clinical condition if possible (Table 2).

Assessment of response to immunotherapy

Disease stabilization can be an indicator of a significant therapeutic effect of immunotherapy, and initial disease progression according to RECIST1.1 does not necessarily reflect a treatment failure. In this context, specific immune-related response criteria were developed beyond RECIST (Figure 4) [74–77].

Immune-related response criteria (irRC) were the first immune-specific criteria established based on evolved WHO criteria adapted for assessment of response to immunotherapy [74]. The irRC were elaborated based on data coming from clinical trials of ipilimumab in patients with advanced melanoma showing delayed but durable clinical responses in a subset of patients. One of the major points of the irRC allowed for the continuation of immunotherapy at first documented progression, but required the need for the confirmation of progression at least 4 weeks after

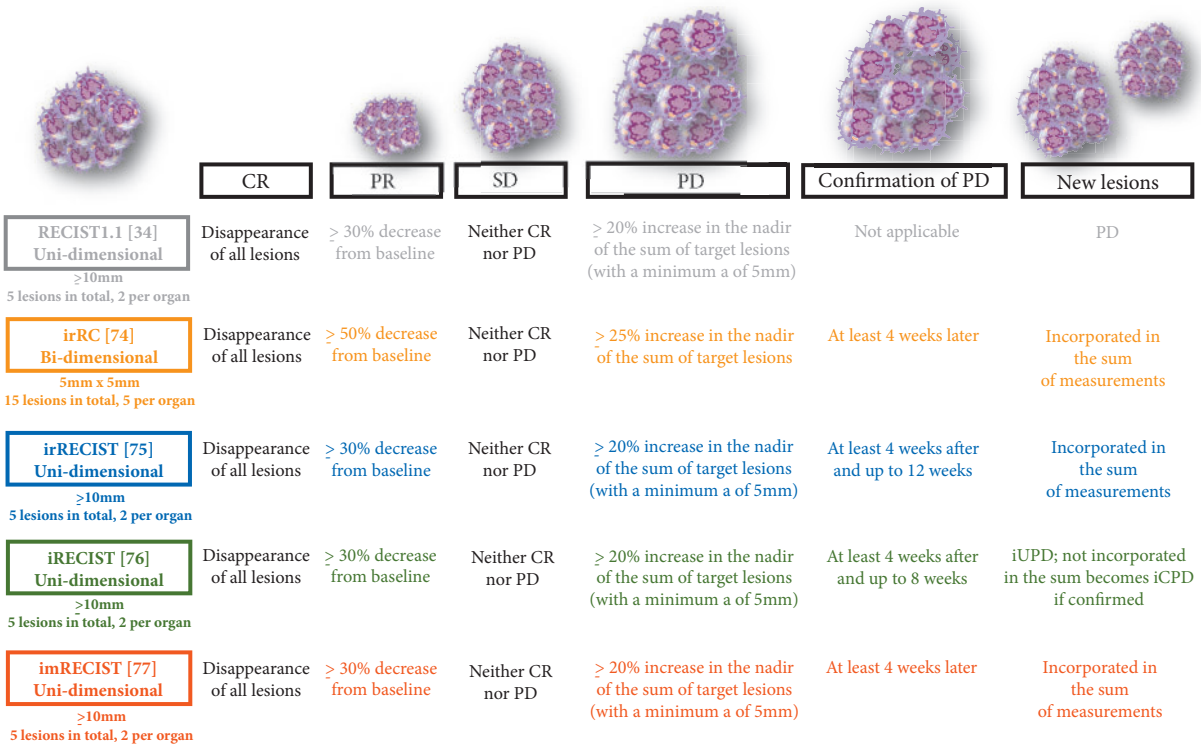

Figure 4. Overview of immune-specific related response criteria reported in the literature. RECIST, response evaluation criteria in solid tumors; irRC, immune-related response criteria; irRECIST, immune-related RECIST; iRECIST, immune RECIST; imRECIST, immune-modified RECIST; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; iUPD, immune unconfirmed progressive disease; iCPD, immune confirmed progressive disease.

initial assessment with a repeat imaging. Another important point is that irRC allowed for the appearance of new lesions, no longer considered as disease progression but incorporated into the sum of measurements of the total tumor burden. At baseline tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions (five lesions per organ—up to 15 in total) is calculated, and at each subsequent tumor assessment, index lesions and new measurable lesions ($\geq$5 mm$\times$ 5 mm) are added into the total tumor burden. Data coming from patients treated beyond RECIST1.1-defined progression but not irRC showed that these patients had better survival than patients showing progression per both criteria, therefore suggesting that irRC could prevent premature discontinuation of effective immunotherapy in a subset of patients [78]. The main caveats with irRC were that these criteria are based on bi-dimensional measurements of tumor lesions, as WHO criteria are, increasing variability in assessments in comparison to uni-dimensional measurements with RECIST, and that the majority of initial immunotherapy trials already used the uni-dimensional measurements according to RECIST, rendering comparisons difficult between trials [79].

Specific immune-related criteria were further redefined with the immune-related RECIST (irRECIST), based on the uni-dimensional measurements of RECIST [75]. In irRECIST, measurable lesion is defined as non-nodal metastases $\geq$10 mm in long axis and nodal lesions $\geq$15 mm in short axis, which are included in the sum of the total tumor burden. The responses in irRECIST are defined as followed: complete response if there is disappearance of all the target and nontarget lesions while the nodal lesions are $<$10 mm in short axis with no appearance of new lesions, and partial response if there is a $\geq$30% decrease in the tumor burden when compared with the baseline, and no unequivocal progression (UEP) in the nontarget lesions, with no appearance of new lesions. An increase of $\geq$20% in the total measurable tumor burden from nadir with a minimum of 5 mm, progression of nontarget lesions or the appearance of a new lesion is defined as irPD. An important aspect of these immune-related response criteria is that the irPD must also be confirmed, as per irRC, with a repeat assessment at least 4 weeks later, and if the repeat assessment shows a new UEP from the prior imaging assessments, or the appearance of another new lesion, this defines a confirmed disease progression [75].

To harmonize interpretation of data between different trials assessing immunotherapy agents, a consensus guideline was published by the RECIST working group along with immunotherapy subcommittees and created a modified version of RECIST1.1 for immunotherapy, the immune RECIST (iRECIST) [76]. The iRECIST defined a standard terminology including immune CR (iCR), SD (iSD), PR (iPR), and unconfirmed PD (iUPD) or confirmed PD (iCPD) (Figure 5). The main points in iRECIST are that iUPD must be confirmed by a repeat imaging assessment at least 4 weeks after first assessment, but no more than 8 weeks from iUPD and that a patient can be assigned iUPD multiples times under immunotherapy, until there is a iCPD. The iRECIST differs from irRECIST in the definition of disease progression. After a first observed iUPD, subsequent response can be

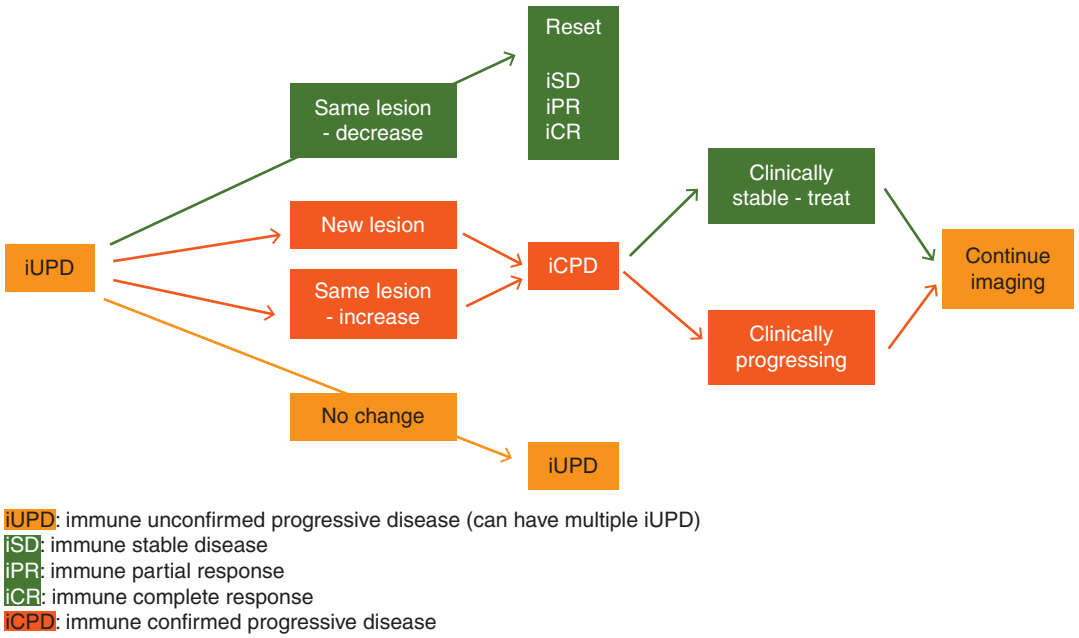

Figure 5. Illustration of immune unconfirmed progressive disease (iUPD) in iRECIST.

categorized as iCR, iPR, or iSD. The iUPD is defined when there is an increase of ≥20% of the sum of the longest diameters with nadir, with a minimum of 5 mm, or progression of nontarget lesions or appearance of new lesion. Regarding new lesions, any of them should be identified as measurable or nonmeasurable according to RECIST1.1, new target lesions should be evaluated separately and not be included in the sum of measures of the baseline target lesions, by opposition to irRC or irRECIST. If a new lesion is identified, considered as an iUPD, it can be proposed to the patient to pursue the ongoing immunotherapy if the patient is considered asymptomatic or at least does not clinically deteriorate. After an iUPD, appearance of another new lesion in a subsequent scan, increase in size of target or nontarget lesions, an increase in the sum of measurements of new target lesions >5 mm, or any progression of new nontarget lesions, the case will be categorized as iCPD (Figure 5). Recently, new criteria were evaluated based on atezolizumab data in NSCLC, the immune-modified RECIST (imRECIST), requiring a confirmation of disease progression at least 4 weeks after initial assessment, but it is unclear if these criteria offer any benefit beyond irRECIST or iRECIST [77].

The main goals of these immune-specific criteria with incorporation in clinical trials assessment are to standardize interpretation and analysis between different trials evaluating immunotherapy, and to integrate the atypical patterns of response to immunotherapy. However, the emergence of these many different immune-related criteria can lead to confusion, and some of them are not as simple to use in clinical practice, such as irRC (with bi-dimensional measurement) for example. Furthermore, these immune-related criteria do not take into account all the particular cases of atypical patterns of response and progression under immunotherapy, such as hyperprogression or dissociated responses. None of these criteria have actually been uniformly adopted in routine [80], and RECIST1.1 should remain the standard of patient management and decision-making in clinical trials and immune-related criteria kept as secondary end points. This is especially important in randomized trials versus chemotherapy or targeted therapy where RECIST1.1 is standard.

Discussion

Conclusions

Novel patterns of response and progression have been observed under immunotherapy that differ from those seen with conventional therapeutic agents. This is especially true for the assessment of disease progression, for which RECIST1.1 might underestimate the benefit of immunotherapy and lead to premature arrest of a potential effective treatment in a proportion of patients with pseudoprogression. However, pseudoprogression is rare and most initial radiographic progressions under immunotherapy reflect true disease progression. No predictive factor of pseudoprogression has been identified to date, although encouraging results were obtained with the sequential assessment of ctDNA. Treatment beyond progression, consistent with novel immune-related response criteria, should therefore only be considered for carefully selected patients whose clinical condition has improved (or stabilized in patients who were rapidly progressing before starting treatment) on immunotherapy, and who have not experienced severe toxicities. In case of rapid progression or suspected hyperprogression, treatment should be interrupted in order to reassess radiologically the situation, and to be able to carry out an early switch of the patient to another treatment. This is all the more important given the preliminary data suggesting that some patients may have higher responses to subsequent therapies such as chemotherapy. The decision to pursue the immunotherapy in case of dissociated response should be also carefully taken, and

proposed only in patients with true clinical benefit, for whom a locoregional treatment of a limited number of progressive lesions is feasible. In case of durable response, the questions of treatment duration, along with the possibility to rechallenge patients with the same treatment at disease progression have to be assessed in randomized trials. Some patients experiencing a durable response and who have stopped treatment might be cured from their metastatic cancer, which is something that was almost impossible to achieve with conventional chemotherapy and targeted therapy. However these impressive responses only occur in a small subset of patients.

The occurrence of atypical patterns of response and progression under immunotherapy has led to the development of specific immune-related response criteria to better capture the therapeutic effect of immunotherapy. It is our opinion that classical RECIST criteria are still practical, efficient, and relevant criteria for the assessment of response and progression to immunotherapy in the vast majority of patients, to continue to have access to comparable data between clinical trials. Although there is an urgent need to identify predictive factors of (durable) response to immunotherapy, it seems equally important to identify predictive biomarkers of progression or possible hyperprogression that is even more clinically relevant. Translational research will help decipher mechanisms of the antitumor immune response, to better understand and predict these novel patterns of response and progression to immunotherapy, and to better understand resistance mechanisms to immunotherapy.

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