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COMMENTARY ▌

When Progressive Disease Does Not Mean Treatment Failure: Reconsidering the Criteria for Progression

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Although progression-based endpoints, such as progression-free survival, are often key clinical trial endpoints for anticancer agents, the clinical meaning of "objective progression" is much less certain. As scrutiny of progression-based endpoints in clinical trials increases, it should be remembered that the Response Evaluation Criteria In Solid Tumors (RECIST) progression criteria were not developed as a surrogate for survival. Now that progression-free survival has come to be an increasingly important trial endpoint, the criteria that define progression deserve critical evaluation to determine whether alternate definitions of progression might facilitate the development of stronger surrogate endpoints and more meaningful trial results. In this commentary, we review the genesis of the criteria for progression, highlight recent data that question their value as a marker of treatment failure, and advocate for several research strategies that could lay the groundwork for a clinically validated definition of disease progression in solid tumor oncology.

Introduction

In the minds of most oncologists, "tumor response" and "disease progression" represent a fundamental dichotomy in solid tumor oncology. The former is a time-tested marker of therapeutic efficacy, whereas the latter is an essential sign of treatment failure. Response is a more intuitive construct, and as such has been a trial endpoint since the first randomized trial in solid tumor oncology in the year 1960 (1). Progression, as described in the World Health Organization (WHO) guidelines of 1981 (2), is akin to cancer recurrence but is "usually reserved for patients with advanced disease."

Because response and progression play two very different roles in solid tumor oncology, the two may be better conceptualized as distinct events rather than the two ends of a single spectrum (Figure 1). Response assessment generally occurs early in a treatment course and is used primarily to calculate a "response rate." This metric dichotomizes patients into responders and nonresponders; the proportion of responders is used to quantify the efficacy of a therapy in a particular patient population. For most patients, an objective response determined by imaging is not normally used to decide when to change therapies, although there is ongoing research into such response-guided treatment strategies (3). Even after a patient has been classified as a responder or nonresponder, progression continues to be assessed at intervals to determine when a change of therapy is needed. Unless a patient is cured or dying from other causes, both responders and nonresponders will develop disease progression at some subsequent time

point. The date of progression is then used in clinical trials to calculate time-to-event endpoints, such as time to progression (TTP, the time between treatment initiation and tumor progression) and progression-free survival (PFS, the time between treatment initiation and tumor progression or death from any cause).

Distinguishing response and progression as two distinct events rather than two ends of a spectrum emphasizes that the criteria for each can be studied (and critiqued) separately. The recent medical literature has explored a number of alternate strategies for defining response, including metrics such as minor response (4,5), "disease control" (6,7), response on positron emission tomography (3,8), and volumetric response (9,10). Yet these response metrics do not necessarily assist in accurately pinpointing when a treatment has failed or when resistance has developed. Although there has been recent literature debating the value of PFS as an endpoint for drug development and regulatory approval (particularly after the US Food and Drug Administration withdrew approval of bevacizumab for metastatic breast cancer) (11–13), this literature presumes there is no flexibility in how progression is defined. It is the relative paucity of literature studying the optimal definition for progression that spurs our commentary.

The Evolution of Progression Criteria

Criteria for progression remain loosely based on those outlined in the original WHO guidelines published in the year 1981 (2). This landmark set of guidelines also included recommendations

	Response	Progression
Timing of assessment:	Assessed early in treatment course	Assessed at intervals until change of therapy
Role in clinical practice:	Not normally used to determine whether to change therapy	Commonly used to determine when to change therapy
Role in clinical research:	Primarily used to calculate overall response rate	Primarily used to calculate time to progression endpoints

Figure 1. Response and progression as distinct events in solid tumor oncology care and research. Because response and progression play two very different roles, the two may be better conceptualized as distinct events rather than as the two ends of a single spectrum, and each can be studied and critiqued separately.

on performance status reporting and toxicity grading, although the recommendations were mostly based on a consensus agreement instead of data. The WHO criterion for partial response (a 50% decrease in the bidimensional measurement) was derived from an earlier study that quantified the variability of manual tumor measurement (14). In contrast, the definition of progressive disease (a 25% increase in the size of one or more measurable lesions or the appearance of new lesions) was an educated guess and not based on any specific published data.

The Southwest Oncology Group (SWOG) later proposed a larger criterion for progression (a 50% increase in the sum of tumor measurements) because of concern about the poor reproducibility of the WHO criterion for progression (15,16). In the year 2000, the Response Evaluation Criteria in Solid Tumors (RECIST) group (17) then established the current criterion for progression—a 20% increase in unidimensional measurement or appearance of new lesions. Mathematically, the RECIST criterion is equivalent to a 73% increase in the volume of a spherical tumor

mass (Table 1), which is somewhat less than the SWOG criterion (a 84% increase in volume) and greater than the WHO criterion (a 40% increase in volume) (18). The waxing and waning criteria for progression over the past decades contrasts with the criteria for response, which have consistently represented a 65% decrease in volume of a spherical tumor mass despite changes in the measurement technique.

Reviewing the evolution of response and progression criteria since the landmark publication by Zubrod et al. (1) in the year 1960, it is striking how the "confirmed response rate" has remained a consistent trial endpoint while the time-to-event endpoints have changed (Table 1). The date of disease progression was originally used in clinical trials to calculate the "duration of response" (2). Of note, a critical analysis of trial endpoints from 61 published reports published in the year 1985 included no mention of TTP or PFS (19). The SWOG guidelines were the first to formally define PFS: SWOG preferred PFS to duration of response because it can be quantified in all patients rather than just in responders (15). Despite this precedent, even the latest version of RECIST is intended to "[focus] primarily on the use of objective response endpoints." Whereas RECIST formally defines duration of response, the guidelines discuss PFS only briefly (17, 20). In other words, PFS is a recent and sparsely defined endpoint in oncology, whose value as a surrogate for overall survival may not have been the primary consideration when the current progression criteria were developed.

Although progression-based endpoints play an increasingly important role in clinical trial analysis and regulatory drug approval, their value in clinical practice is uncertain. The published criteria for objective progression were developed to guide clinical trial analyses and are not intended to influence the care of individual patients. The WHO guidelines state that a finding of 25% tumor growth "should not necessarily be regarded as influencing the

Table 1. The evolution of criteria for determining response and progression in solid tumor oncology

Criteria	Study and year published				
	Zubrod et al. (1), 1960	WHO (2), 1980	SWOG (15), 1992	RECIST 1.0 (17), 2000	RECIST 1.1 (20), 2009
Response characteristics					
Measurement method	Not described	Bidimensional	Bidimensional	Unidimensional	Unidimensional
Response criteria, % change	Investigator consensus	50	50	30	30
Equivalent % volume change*	NA	65	65	66	66
Response confirmation required	Yes	Yes	Yes	Yes†	Yes†
Considers "clinical response"	Yes	Yes	No	No	No
Progression characteristics					
Progression criteria, % change	Two consecutive increases	25	50	20	20
Equivalent % volume change*	NA	40	84	73	73
New lesions count as progression	Yes	Yes	Yes	Yes	Yes
Trial endpoints discussed					
Response rate	Yes	Yes	Yes	Yes	Yes
Duration of response	Yes	Yes	Yes	Yes	Yes
Time to progression and progression-free survival	No	No	Yes	Yes‡	Yes‡

* This calculation assumes a spherical tumor mass. NA = not applicable.

† Note that response confirmation is not always required, such as when response is a secondary endpoint or for randomized trials.

‡ The criteria were mentioned but not defined.

management of the patient" (2). RECIST similarly states that "it is not intended these RECIST guidelines play a role in [clinical] decision making, except if determined appropriate by the treating oncologist" (20). In clinical practice, decisions about changing therapy must weigh a number of factors, including tumor burden, cancer-related symptoms, and drug toxicity. This uncertain value of RECIST progression in clinical practice contributes to the debated validity of progression as a trial endpoint, and may result in trial results that are not easily translatable into clinical practice. We propose that objective progression criteria that are developed to be clearly indicative of treatment failure and are closely associated with poorer survival would be the most valuable foundation for clinical trial endpoints. Furthermore, the development of such criteria could also have an important impact on the treatment of individual cancer patients.

The Weaknesses of Current Progression Criteria

The growing number of clinical settings in which "objective progression" does not necessarily indicate treatment failure or a need to change therapy supports the need for a reassessment of criteria for progression. These scenarios can generally be classified into four groups: tumor marker progression, focal progression amenable to local therapy, indolent or asymptomatic progression, and progression while on immunotherapy. Reviewing these separately provides insight into how the criteria for objective progression could potentially be revised to improve their value in clinical trial evaluation.

Tumor Marker Progression

Although the identification of progression based on tumor markers has an uncertain role in much of solid tumor oncology, the assessment of treatment-related alterations in serum concentrations of prostate-specific antigen (PSA) has been a cornerstone of prostate cancer drug development because patients often have nonmeasurable bone disease. However, a change in PSA is not an accepted surrogate for survival or other measures of clinical benefit. Indeed, the degree to which PSA alterations explain a treatment-induced alteration in survival remains a matter of debate and investigation (21,22). For example, the drug sipuleucel-T improves survival, when compared with the placebo, in minimally symptomatic metastatic prostate cancer patients who are progressing despite testosterone-lowering agents (23). Although sipuleucel-T reduces the risk of death by 23%, PSA levels continued to increase in treated patients at a rate similar to that of placebo-treated patients (23). In another trial of cabozantinib (XL184) in advanced prostate cancer patients, treatment induced objective radiographic responses despite the fact that the patients' PSA levels sometimes increased (24,25). The Prostate Cancer Working Group 2 (PCWG2) has now recommended that although an increase in PSA levels can be analyzed as an endpoint in clinical trials, it should not be used as a criterion to discontinue treatment (26). This decision rule minimizes the chance of an oncologist withdrawing an effective treatment too early based on PSA levels alone, a practice that can confound clinical trial analysis and may deny a patient a potentially beneficial treatment. More reliable objective markers

of progression are being studied in patients with prostate cancer, including quantification of disease burden observed by bone imaging and quantification of circulating tumor cells (27,28).

Focal Progression Amenable to Local Therapy

Progression confined to a single site of disease and amenable to a local therapy may indicate a favorable biology and may not always necessitate a change in systemic therapy. Under the "therapeutic stress" of tyrosine kinase–inhibitor therapy for solid tumors, such as gastrointestinal stromal tumors, epidermal growth factor (*EGFR*)–mutant lung cancers, and anaplastic lymphoma kinase (*ALK*)-positive lung cancers, a subset of cancer cells can develop resistance while the remainder of the cancer burden remains controlled. In such circumstances, a patient may stay on the same systemic therapy and undergo an appropriate local therapy delivered to the area of progression, despite the fact that the objective criteria for progression have been met (29). In a recent single-institution series of patients with imatinib-treated gastrointestinal stromal tumors, 31 patients who underwent resection of an isolated site of progressive disease achieved a median of 8 months of additional PFS beyond the median 15-month TTP while on initial imatinib therapy (30). Three patients were able to continue on imatinib for more than 2 years following resection of the progressing disease. These results suggest that, in gastrointestinal stromal tumors, local therapy can prolong the utility of an effective targeted therapy and stave off treatment failure despite objective progression.

Some parallel results have been observed in patients with *EGFR*-mutant lung cancers who received erlotinib or in those with *ALK*-positive lung cancers who received crizotinib. In these patients, isolated progression may be seen in the central nervous system (CNS), a resistance mechanism thought to be attributable to limited passage of drug into the CNS (termed "pharmacokinetic failure") (31). In *EGFR*-mutant lung cancers, a tyrosine kinase inhibitor given weekly at a high dose has been reported to elevate drug levels in the CNS and control disease at that site (32,33). Another strategy in patients with a prior response to tyrosine kinase inhibitors has been the use of brain irradiation to control isolated CNS progression and reinstitution of erlotinib or crizotinib afterward. This therapeutic strategy often results in another durable period without progression (34). Patients with such CNS-only progression meet the criteria for objective progression but would be expected to have better postprogression survival than patients who develop multifocal systemic progression.

Indolent or Asymptomatic Progression

Slow growth of a cancer represents a unique challenge in drug development. A small magnitude of interval growth could reflect indolent tumor biology, but it could also be caused by a cytostatic therapeutic effect on a more aggressive cancer, and differentiating these two can be challenging. Complicating these issues further is the fact that, by RECIST criteria, a 20% increase in the size of an indicator lesion constitutes progression even if there is still major improvement compared with the baseline measurement. For example, if a 7-cm tumor that had shrunk to 2 cm grows to 3 cm, RECIST progression has occurred even if no new lesions have appeared and the patient remains asymptomatic. Small changes

in tumor measurement can be seen in the setting of measurement variability alone (35).

The slow growth kinetics of pancreatic neuroendocrine cancer has complicated drug development for years. In the year 2009, a placebo-controlled trial in 85 patients with treatment-naïve midgut neuroendocrine carcinoma found that octreotide long-acting release statistically significantly prolonged median TTP (14 vs 6 months, hazard ratio [HR] = 0.34, 95% confidence interval [CI] = 0.20 to 0.59, $P < .001$) without prolonging survival (HR = 0.81, 95% CI = 0.30 to 2.18, $P = .77$) (36). A subset analysis suggested that the improvement in TTP was largely restricted to patients with a low tumor burden, leading some to question whether this finding had clinical meaning in this population (37). In comparison, a more recent placebo-controlled study of sunitinib in pancreatic neuroendocrine tumors showed an improvement both in PFS (HR = 0.42, 95% CI = 0.26 to 0.66) and survival (HR = 0.41, 95% CI = 0.19 to 0.89) (38). Although both trials studied well-differentiated neuroendocrine carcinomas, only the sunitinib study required prior disease progression as part of the eligibility criteria (38). By selecting for more aggressive cancers, the investigators identified a setting in which a delay of objective progression would have greater clinical meaning, even in a cancer that often can exhibit an indolent behavior.

Slow growth of a cancer after an initial major response to targeted therapy is another setting in which there may be different prognostic implications to different rates of progression. For example, patients with *EGFR*-mutant lung cancers, who have had a durable response to erlotinib, can at times experience slow regrowth of their tumors over the course of many months (39). This pattern can be replicated in *EGFR*-mutant cell lines that acquire the T790M resistance mutation (40). Despite having objective progression based on a 20% or greater increase in tumor diameter, these tumors often have persistent oncogene addiction to EGFR signaling and can exhibit growth acceleration or "flare" when the tyrosine kinase inhibitor is discontinued (41,42). In one series, 19% of patients were able to delay the use of an alternate systemic therapy for more than 12 months by receiving continued erlotinib after RECIST progression (43). This phenomenon may also occur in renal cell carcinoma: in a study of the tumor growth kinetics of patients receiving sunitinib for advanced disease (described further below) (44), the authors suggested that discontinuation of sunitinib in patients who exhibited indolent RECIST progression led to an acceleration of growth and a shorter survival than if sunitinib had been continued longer.

Progression on Immunotherapy

When ipilimumab, a monoclonal antibody against CTLA4, was given to patients with advanced melanoma, tumor growth followed by a clinically significant response—termed "pseudoprogression"—was observed in a subset of patients (45). Such transient progression before a response has also now been described in non–small cell lung cancer after treatment with BMS-936558, an antibody against programmed death 1 (PD-1) (46), and has led many researchers to reconsider the meaning of progression while on immunotherapy. Ipilimumab increased median survival by 4 months in a randomized trial vs a vaccine therapy in patients

with advanced melanoma (47). Although this trial found a statistically significant reduction in the risk of progression (HR = 0.64, $P < .001$), there was no difference in median PFS, and the progression curves separated after more than 60% of patients met criteria for progression—results that are atypical for a therapy that prolongs median survival. This paradoxical finding has been attributed to the delayed development of an immune response, which can occur after initial growth of an indicator lesion or the appearance of new lesions (48). Clinical observations of pseudoprogression have prompted investigators to propose a set of immune-related response criteria (49). Using these criteria, both tumor growth followed by response and new lesions in the presence of response are not necessarily considered disease progression—both phenomena were associated with a better prognosis than sustained progression without any response.

Recommendations for Developing Improved Criteria for Progression

With a growing body of literature suggesting that RECIST-defined progression may not indicate treatment failure in some clinical settings, a critical analysis of progression criteria is needed. We hypothesize that more effective time-to-event endpoints could be developed through a more comprehensive study of the phenomenon of progression, which could potentially lead to the identification of criteria more clearly indicative of treatment failure and poor outcome. However, study of progression is made difficult by the chain of events triggered when the endpoint of progression is reached. For most patients participating in clinical trials, objective progression results in discontinuation of the study drug as well as a sizeable reduction in data collection (eg, cessation of imaging at set intervals). This impedes the study of a later definition of progression because the treatment has changed and the collection of data has ceased. Such challenges are not encountered when performing a critical analysis of alternative criteria for response: because the lack of response to a therapy does not generally lead to a treatment change, the prognostic values of different response criteria met at different times while on study can be compared (5,6).

Accepting the need for an improved understanding of progression, there are a number of specific strategies that could facilitate future analysis of different criteria for progression if incorporated into prospective trials:

1. *Better collection of progression characteristics*. A key difficulty in the critical analysis of this endpoint is that most studies collect few details about progression other than the date at which it occurred. Given the clinical heterogeneity of progression, we believe there are a number of additional progression characteristics that must be documented prospectively to allow subsequent correlative analyses. First, clinical trials should collect data about the absence or presence of new distant metastases because development of a new site of metastasis (eg, new CNS metastases) may represent an important change in the biology of the patient's disease. Second, documentation of the magnitude of measurement increase between the date of "best response" and the date of RECIST progression

would be important for the calculation of a cancer's growth kinetics or "progression rate," which may have prognostic meaning. Third, documentation of performance status and cancer-related symptoms at the time of progression could allow differentiation of symptomatic vs asymptomatic progression; it is possible that small changes in size have more prognostic significance if associated with a recurrence of cancer-related symptoms. Such data are not routinely collected during the course of prospective trials, making correlative analysis challenging. Some cooperative groups are now working to prospectively collect these types of progression characteristics as a standard part of new clinical trials.

2. *Study of "treatment beyond progression."* A simple strategy that has been incorporated into some early-stage trials of targeted therapies has allowed clinicians to continue an experimental agent after RECIST progression if they feel the patient is deriving a clinical benefit (50). In these trials, objective criteria for progression are met and used for the TTP calculation, but treatment while on the protocol may temporarily continue. This achieves two important goals— patients who may be benefitting from a therapy can continue to receive a drug that may be unavailable outside of the clinical trial, and investigators can learn about the course of the disease following RECIST progression. Importantly, this practice allows the study of 1) progression characteristics that are associated with successful treatment continuation beyond objective progression and 2) progression characteristics that are associated with earlier clinical deterioration. Through incorporation of such a "treatment beyond progression" approach, clinical trials may be able to more closely emulate clinical practice, in which a number of critical factors, such as availability of alternate therapies, are factored into the decision to change therapy. This strategy was successfully used in the phase I trial of crizotinib for *ALK*-positive lung cancers (34, 51) and is being prospectively studied in subsequent crizotinib trials.

3. *Prospective study of alternate progression endpoints.* Perhaps the most important step to improve the definition of progression is for investigators to recognize the potential weaknesses of existing criteria and to incorporate the exploration of alternate progression endpoints into prospective trials. Alternate endpoints have already begun to emerge in the oncology literature, yet they require prospective validation to determine their value as clinical trial endpoints. These progression metrics may not yet be well established for use as primary endpoints, but incorporating them into protocols as secondary and exploratory endpoints would facilitate the correlative analyses needed to improve on the weaknesses of the RECIST progression criteria.

Alternate Progression Endpoints

We review some of these alternate progression endpoints that have recently been studied in a number of different disease settings below. Although some of these metrics may be specific to one disease or treatment modality, others are more broadly applicable to a number of clinical settings and each provides a better understanding of how an investigator could critically assess the RECIST progression criteria.

Time to New Metastasis

The development of new metastases in the brain, bones, or viscera can lead to morbidity and may represent a major change in the biology of a cancer. Sequist et al. (52) studied this phenomenon in an ad hoc analysis of the randomized phase II trial of erlotinib with or without tivantinib in patients whohad advanced non–small cell lung cancer. The investigators quantified the time from treatment initiation "until the appearance of a new site of disease" (52). The median time to new metastasis (TTM) was 7.3 months for patients who were administered erlotinib with tivantinib vs 3.6 months for those who were administered erlotinib with the placebo ($P < .01$). These results supported the investigators' hypothesis that tivantinib may specifically impair metastatic spread. The TTM endpoint has also been explored in a correlative analysis of outcomes of patients diagnosed with *EGFR*-mutant lung cancer who acquired resistance to erlotinib; presence of the T790M EGFR mutation in postprogression biopsies was associated with a later TTM, perhaps indicating a favorable biology to this resistance mechanism (39). TTM is challenging to study prospectively because it requires continued assessment of metastatic spread even after developing RECIST progression. Yet, TTM could be more easily incorporated as an endpoint in protocols that use the "treatment beyond progression" approach discussed earlier.

Progression Confirmation

Trial design in prostate cancer has historically relied upon PSA measurement and bone scans for efficacy assessment; however, these two metrics can be vulnerable to fluctuations that may not represent actual changes in the tumor. To overcome the problem of progression incorrectly being identified too early, the PCWG2 has recommended that progression be confirmed with a repeat assessment according to a standardized set of criteria (26). Because of the variable course of prostate cancer, they discourage the consideration of any changes before 12 weeks as an indication of treatment failure. Confirmation of progression is mandated if new lesions are documented on the first posttreatment scan, to control for the "flare" phenomenon that can be observed in patients who are responding but whose bone scans worsen because the bone is healing. The PCWG2 criteria therefore serve as a semiquantitative indicator of progression, control for pseudoprogression, and standardize the termination of treatment for patients who are participating in the study. Although the PCWG2 progression criteria may reduce the number of patients who discontinue use of the study drug early, the criteria are still undergoing clinical qualification in three prospective randomized studies (28). Confirmation of progression was also a component of the landmark trial by Zubrod et al. (1), which was published in 1960; but this practice was not incorporated into subsequent response criteria (Table 1). Separately, the bone scan index, a more quantitative measure of bone scan burden, is under development as a trial endpoint in prostate cancer (28). Changes in bone scan index are more closely associated with survival than changes in PSA in patients with castrate-resistant prostate cancer although a bone scan index–based definition of progression has not yet been proposed.

Immune-Related Response Criteria

Studies have shown that response after initial progression on immunotherapy in melanoma can still portend a favorable prognosis, which has led to the proposal of immune-related response criteria (49). O'Day et al. (53) applied these criteria to a phase II trial of ipilimumab in previously treated advanced melanoma patients and reported that 8% of patients had a reduction or stabilization of their total tumor burden after an initial objective progression. This subset of patients had a similar survival to patients who had stable disease or response per the WHO criteria. Reclassifying the patients in this study using immune-related response criteria increased the disease control rate from 27% to 35%, which may better represent the efficacy of this agent. These alternate criteria are now being studied prospectively, in parallel with conventional RECIST assessments, in trials of novel immune-modulating agents such as PD-1 antibodies (46) and could potentially lead to PFS results that are a better surrogate for survival.

Tumor Growth Kinetics

Aiming to better characterize therapeutic effect in renal cell cancer, Stein et al. (44) used mathematical models to calculate constants that describe the exponential decrease and growth of the tumor burden for each patient treated on the phase III study of sunitinib vs interferon-α. They found that the median tumor growth constant of patients receiving sunitinib was statistically significantly lower than for those receiving interferon-α, which is consistent with the observation that patients who received sunitinib had a longer median survival compared with patients who received interferon (54). The investigators suggest that calculation of a tumor growth constant, available potentially well before progression is seen, could be an effective clinical trial endpoint and surrogate for overall survival. Tumor growth modeling has also been studied in lung cancer (55) and has led to the proposal of a randomized trial design that uses early tumor growth, rather than PFS, as a primary endpoint (56). The strategy of studying tumor growth kinetics circumvents one weakness of "progression criteria," which is that they inherently dichotomize a complex biological process that may be better characterized using a continuous function.

Conclusions

The determination of progression is an essential part of the treatment and study of patients with solid tumors because it allows the calculation of clinical trial endpoints and also assists in determining clinical treatment failure. Yet a growing body of literature suggests that our current objective criteria for progression may not always indicate treatment failure and do not adequately capture disease biology, potentially limiting their value in clinical trial analysis. We encourage three changes to clinical trial design to facilitate the development of more meaningful criteria for objective progression: more detailed collection of progression characteristics, further prospective study of treatment beyond progression, and exploration of alternate progression endpoints in prospective trials. In this way, the value of progression-based endpoints in clinical trial evaluation can be strengthened and the relevance of objective progression in the care of individual patients can be validated.

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