JAMA Oncology | Original Investigation

Dissection of Progressive Disease Patterns for a Modified Classification for Immunotherapy

Jonas Saal, MD; Markus Eckstein, MD; Manuel Ritter, MD; Peter Brossart, MD; Julian Luetkens, MD; Jörg Ellinger, MD; Viktor Grünwald, MD; Michael Hölzel, MD; Niklas Klümper, MD

IMPORTANCE Progressive disease (PD) in patients treated with immune checkpoint inhibitors (ICIs) varies widely in outcomes according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Efforts to modify RECIST for ICI treatment have not resolved the heterogeneity in PD patterns, posing a clinical challenge.

OBJECTIVE To develop and validate a modified PD classification based on PD patterns and evaluate its association with postprogression survival (PPOS) in patients treated with the programmed cell death protein ligand 1 antibody atezolizumab across various solid tumors.

DESIGN, SETTING, AND PARTICIPANTS This study analyzed data from 5 phase 3 trials (IMmotion151, IMvigor211, OAK, Impower133, and IMspire150) involving patients treated with atezolizumab for renal cell carcinoma (RCC), urothelial carcinoma, small cell lung cancer, non–small cell lung cancer, and melanoma. This post hoc analysis was conducted from March to September 2024.

EXPOSURE Treatment with atezolizumab.

MAIN OUTCOMES AND MEASURES The primary outcome was the association of PD patterns with PPOS. Seven PD patterns were identified based on the enlargement of target and nontarget lesions or new lesions and their combinations.

RESULTS A total of 1377 patients were analyzed across the 5 trials. In RCC, 7 PD patterns significantly affected prognosis. The 6-month PPOS probability ranged from 26% for progression in target and nontarget lesions plus new lesions to 90% for progression in either target or nontarget lesions alone. A modified PD classification was developed that categorized PD into 3 risk levels: low risk (progression of existing lesions), intermediate risk (new lesions without progression of existing lesions), and high risk (progression of existing lesions plus new lesions). This score was associated with PPOS in ICI-treated RCC, with hazard ratios of 0.23 (95% CI, 0.13-0.41; $P < .001$) and 0.39 (95% CI, 0.23-0.66; $P < .001$) for low-risk and intermediate-risk PD compared with high-risk PD, respectively. Validation in additional trials confirmed the score's applicability across various tumors.

CONCLUSIONS AND RELEVANCE In this study, a survival score was developed based on PD patterns. The risk classification was associated with PPOS across various solid tumors treated with immunotherapy and may therefore enhance prognostication and clinical decision-making, potentially providing a valuable tool for treating patients with PD who are receiving immunotherapy.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Niklas Klümper, MD, Department of Urology and Pediatric Urology, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany (niklas.kluemper@ukbonn.de).

JAMA Oncol. doi:10.1001/jamaoncol.2024.5672
Published online December 26, 2024.

The Response Evaluation Criteria in Solid Tumors (RECIST) are the standard for evaluating responses and progression-free survival (PFS) for clinical trials.[1] They were introduced in the era of conventional chemotherapy, during which efficacy was primarily measured by tumor shrinkage. However, with the advent of immune checkpoint inhibition (ICI), the shortcomings of RECIST have become apparent, especially as novel patterns of response and progression were observed.[2-5]

RECIST defines progressive disease (PD) as an increase in the combined diameters of up to 5 specified target lesions (with a maximum of 2 lesions per organ) by at least 20%, for which the reference is the smallest sum on study, and an absolute lesion enlargement of at least 5 mm or the appearance of new lesions.[1] Because of this complicated approach, which was developed for response assessment in clinical trials only, RECIST is generally not evaluated in daily clinical practice, for which the physician's assessment of tumor response is decisive.

PD as per RECIST is frequent yet associated with diverse outcomes among patients undergoing treatment with ICI. A unique feature of ICI is the ability to deliver durable benefits even in patients with PD[6] who receive treatment beyond progression, which is usually based on clinical benefit as defined by the treating physician.[4,6]

Several studies have aimed at deciphering ICI treatment responses on a lesion level.[5,7-9] They demonstrated a marked heterogeneity in responses, with most patients showing mixed responses (ie, some lesions increasing and others decreasing in size).[5] A different study found that focal progression occurred in approximately 50% of non-small cell lung cancer (NSCLC) or microsatellite instability high tumors and was associated with improved overall survival (OS) compared with systemic progression. This study showed more uniform lesion-level growth patterns in patients who responded to treatment.[7]

The most prevalent reason for primary PD in melanoma and NSCLC is new metastatic lesions. However, about 50% of the individual target lesions are nonprogressive in the context of primary PD.[5] This implies that many patients with documented PD as assessed via RECIST version 1.1 may have ICI-induced tumor control in a substantial proportion of the overall tumor burden.[5]

Deepening our understanding of the differential PD patterns is relevant for prognostication, therapy management, and development of novel therapeutic concepts, such as metastasis-directed therapy (MDT), in the era of targeted therapies and especially immunotherapy. As RECIST-based end points are common in drug development,[3] the optimization or fine-tuning of response, but also the exact assessment of disease progression and dynamics, is crucial for assessing efficacy within clinical trials but also patient counselling for shared decision-making regarding individual therapeutic concepts. This study aimed to delineate the characteristics of PD in ICI-treated metastatic renal cell carcinoma (RCC) within the phase 3 IMmotion151 trial (NCT02420821)[10] and validate our intuitive and easily implemented modified PD classification across ICI-treated solid entities.

Key Points

Question Is a modified classification of progressive disease (PD) patterns associated with improved prognostication of postprogression survival in patients treated with immune checkpoint inhibitors?

Findings In this study of 5 phase 3 randomized clinical trials of 1377 patients with PD treated with atezolizumab, a new PD classification was developed. This classification stratified patients into 3 risk levels (low, intermediate, and high) based on the progression of existing lesions and the presence of new lesions; the score was associated with postprogression survival, and its validity was confirmed across multiple tumor types.

Meaning The study results suggest that the modified PD classification enhances the prediction of survival in patients treated with immune checkpoint inhibitors and is associated with improved clinical decision-making for managing PD.

Methods

Data from the phase 3 studies IMmotion151 (NCT02420821; RCC[10]), IMvigor211 (NCT02302807; urothelial carcinoma [UC][11]), OAK (NCT02008227; NSCLC[12]), Impower133 (NCT02763579; small cell lung carcinoma [SCLC][13]), and IMspire150 (NCT02908672; melanoma[14]) was made available through vivli.org. The post hoc analysis was approved by the data provider Roche and an independent review panel comprising ethical experts and was conducted from March to September 2024. The trial protocols for all trials have been previously published.

The number of patients experiencing PD while receiving treatment in the immunotherapy arm was 484 in the OAK trial, 253 in IMmotion151, 349 in IMvigor211 131 in IMspire150, and 160 in Impower133 (eFigure 1 in Supplement 1). A total of 1377 patients were analyzed.

Patterns of PD were analyzed at the time of the first PD within the trial according to investigator-assessed RECIST, version 1.1. Postprogression survival (PPOS) was calculated as the difference between PFS and OS (ie, the time from first PD to death or censoring).

PD patterns were based on lesion-level tumor measurements on imaging that was performed as part of the trial protocols. Target lesions were defined by expert radiologists at each participating center. For each staging scan, progression (defined as a growth of the tumor diameter of 20% or more from baseline or the smallest measurement on trial, according to RECIST, version 1.1) was reported for target lesions and nontarget lesions separately. Additionally, the appearance of new lesions was reported if applicable.

The modified PD classification was derived from these data for any patient who experienced PD while participating in a trial for the point of first PD. Patients without documented PD while they were participating in a trial were excluded from analysis. PD patterns were classified as follows (eTable 1 in Supplement 1): 20% or more growth from baseline or lowest measurement during the trial (referred to

as PD) in any target lesion (pattern 1), PD in any nontarget lesion (2), PD in at least 1 target lesion and at least 1 nontarget lesion (3), appearance of any new lesion without PD in either target or nontarget lesions (4), appearance of any new lesion with PD in any target lesion without PD in any nontarget lesion (5), appearance of a new lesion and PD in any nontarget lesion without PD in any target lesion (6), and appearance of a new lesion with PD in any target lesion and PD in any nontarget lesion (7). For the modified PD classification, patterns 1 to 3 (ie, PD in any existing lesion without new lesions) were defined as low risk, pattern 4 (ie, appearance of a new lesion without growth in any existing lesion) was defined as intermediate risk, and patterns 5 to 7 (ie, appearance of a new lesion with growth in any existing lesion) were defined as high risk.

Statistical analyses were conducted using RStudio Desktop (version 2023.06.0) with R, version 4.2.2 (R Foundation) using the packages "survival" (version 3.4-0), "survminer" (version 0.4.9), "ggplot2" (version 3.5.1), "gtsummary" (version 1.6.2) and "dplyr" (version 1.1.2) within the vivli.org secure research environment as a windows remote desktop tool. Univariate Kaplan-Meier estimation and log-rank tests, as well as univariate and multivariate Cox regression, were used to evaluate outcomes. A significance threshold of $P < .05$ was used for all statistical tests. The authors do not own copies of patient records because patient-level data were not able to be extracted from the environment according to vivli guidelines.

Results

A total of 1377 patients were analyzed across the 5 trials. In the atezolizumab + bevacizumab arm of the IMmotion151 trial, 253 of 453 patients (55.8%) experienced PD on trial according to investigator-assessed imaging (RECIST version 1.1). These patients were classified by 7 distinct patterns of PD that considered the progression of target and nontarget lesions, as well as new lesions, as follows: (1) PD of target lesion, (2) nontarget lesion, or (3) both; (4) non-PD of existing lesions but new lesion(s); (5) combination of target-lesion PD with new lesions; (6) nontarget lesion PD with a new lesion; or (7) PD of target + nontarget lesions and a new lesion. Most patients exhibited target-lesion PD or developed new lesions (**Figure 1**A). The patterns of PD were significantly associated with PPOS. Six-month PPOS ranged from 26% (95% CI, 8%-85%) for patients with progression in target and nontarget lesions as well as new lesions to 90% (95% CI, 84%-97%) for patients with progression in either target or nontarget lesions alone (Figure 1B), which highlights the prognostic effect of considering a PD pattern.

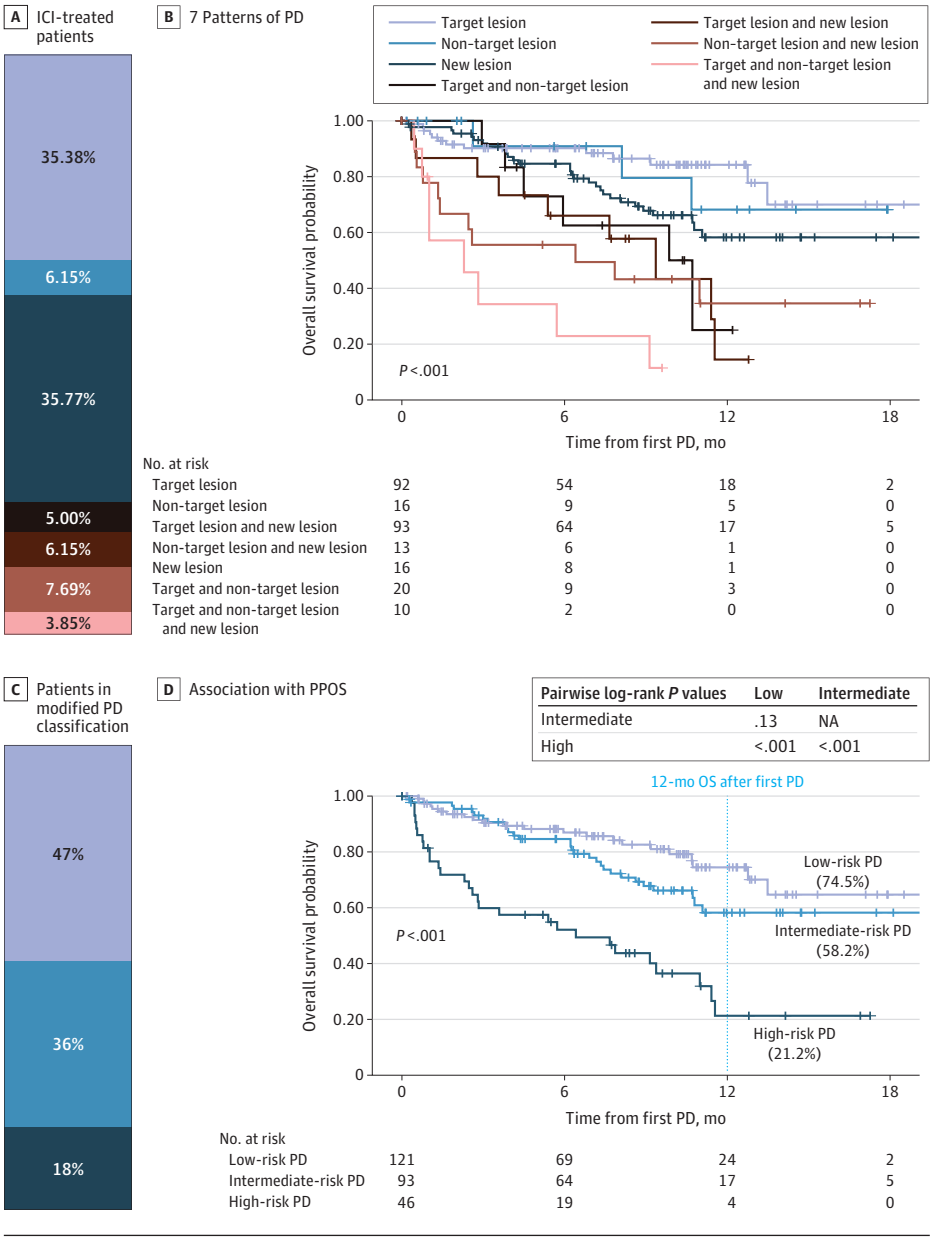
In clinical practice, the distinction between target and nontarget lesions as required by RECIST is time-consuming and resource intensive; therefore, use of RECIST is usually limited to clinical trials. To simplify the previously mentioned PD patterns for easier and straightforward clinical applicability, we defined 3 intuitive risk groups: low-risk PD, with progression of only existing lesion(s); intermediate-risk PD, with appearance of new lesion(s) without PD of existing lesion(s); and high-risk PD, including patients with PD in existing and new lesions (**Figure 2**). Almost half of the patients were classified as having low-risk PD in the IMmotion151 immunotherapy cohort (Figure 1C). Our modified PD classification predicted PPOS with 12-month PPOS ranging from 22% (95% CI, 10%-47%) for high-risk PD to 74% (95% CI, 65%-86%) for low-risk PD (Figure 1D). The hazard ratio (HR) for death was 0.23 (95% CI, 0.13-0.41; $P < .001$) for low-risk PD and 0.39 (95% CI, 0.23-0.66; $P < .001$) for intermediate-risk PD compared with high-risk PD (**Table**).

Next, we aimed to validate the modified PD classification in different cancers commonly treated with immunotherapy. We analyzed patients treated within 4 phase 3 randomized clinical trials that encompassed different entities, including UC (IMvigor211 trial),[11] NSCLC (OAK trial),[12] SCLC (Impower133 trial),[13] and melanoma (IMspire150 trial)[14] (**Figure 3**). The modified PD classification was associated with PPOS across all entities in the ICI and comparator arms, highlighting its prognostic value in a tumor-agnostic manner for ICI, tyrosine kinase inhibition (TKI) (comparator arm of IMmotion151 [sunitinib] and IMspire150 [placebo, vemurafenib, and cobimetinib]), and chemotherapy (comparator of IMvigor211 and OAK) (Figure 3; Table). The modified PD classification was able to predict PPOS in the entire trial population across trials (eFigure 2 in Supplement 1).

To assess whether the observed prognostic value is due to potential confounding factors, we analyzed the distribution of available baseline variables in each trial. However, we found a heterogenous picture across trials that patients experiencing high-risk PD were younger (significant for RCC and NSCLC), had higher-risk disease at baseline (higher IMDC [International Metastatic Renal Cell Carcinoma Database Consortium] risk score for RCC, higher Bellmunt risk score for UC), and more metastases (significantly more metastases to the bone in UC, NSCLC, and SCLC; to the liver in UC and NSCLC; and more visceral metastases in UC and more metastatic sites in melanoma; eTable 2 in Supplement 1). We performed a multivariable Cox regression analysis for each trial that included all baseline variables with significantly different distribution among PD risk groups. The modified PD classification was independently associated with PPOS across trials (with the exception of intermediate-risk PD showing a strong trend without reaching statistical significance in SCLC and melanoma; eTable 3 in Supplement 1).

Those factors were measured at baseline, while the modified PD classification was applied at the time of PD. Patients who experienced progression early while receiving treatment may have a different, more aggressive disease biology than those who experience progression later. Therefore, we analyzed whether time to first PD was associated with PPOS. High-risk PD was more common in patients who experienced progression within the first 6 months after treatment initiation (eTable 4 in Supplement 1). However, in multivariate analysis with time to progression as a covariate, the modified PD classification was independently associated with PPOS (with the exception of intermediate-risk PD), showing a strong trend without reaching statistical significance in SCLC and melanoma (eTable 5 in Supplement 1).

Figure 1. Development of a Modified Progressive Disease (PD) Classification



A, Subgrouping of patients with renal cell carcinoma treated with immune checkpoint inhibitors (ICIs) from the IMmotion151 trial by pattern of PD; most patients experienced progression either in target lesions only or developed new lesions only. B, The 7 patterns of PD are associated with postprogression overall survival (PPOS). C, Subgrouping of patients into the modified PD classification: low-risk PD, defined as progression in existing lesion(s) only; intermediate-risk PD, defined as appearance of new lesion(s) without PD of existing lesion(s); and high-risk PD, defined as PD in existing and new lesions. D, The modified PD classification is associated with PPOS. NA indicates not applicable; OS, overall survival.

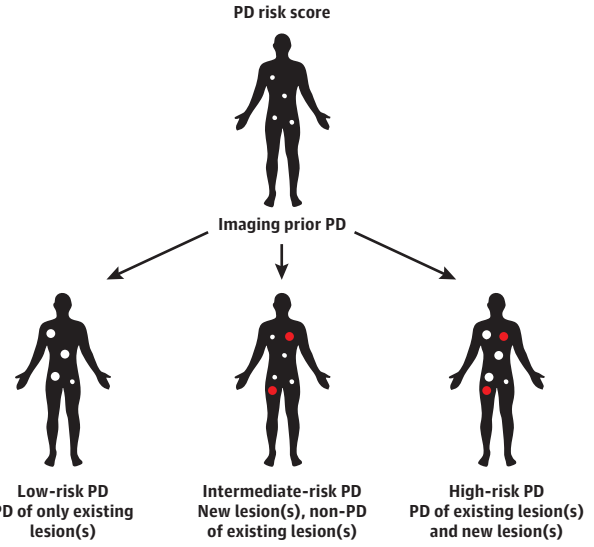
A special case of intermediate-risk PD is the appearance of new lesions in a patient with responding target lesions. This PD pattern was termed *mixed PD* and was characterized by a response in target lesions (ie, all target lesions combined met criteria for partial response/complete response) with the concurrent appearance of new lesions. It was associated with favorable PPOS across trials, with the notable exception of SCLC, for which patients with mixed PD had outcomes comparable with intermediate-risk PD (eFigure 3 in Supplement 1).

Discussion

In this study, we developed an intuitive and easy-to-implement modified PD classification that considered the primary patterns of PD, which are the emergence of growing or new lesions. The study findings reveal a significant association between the modified PD classification and PPOS across various solid tumor types treated with immunotherapy, TKI, or chemotherapy. This approach potentially holds promise for enhancing prognostication and guiding clinical decision-making in oncology settings.

PD is the most critical finding in imaging, as it typically is followed by a change of treatment. For patients, fear of progression is associated with anxiety and mental stress.[15] We highlighted that, within 5 phase 3 clinical trials, here was substantial heterogeneity in outcomes among patients experiencing PD. We developed a simple scoring approach for the PD patterns (our modified PD classification) that can be integrated into clinical practice to provide information on PPOS for bet-

Figure 2. Definition of 3 Risk Groups in Modified Progressive Disease (PD) Classification



Patients are classified as having low-risk PD if existing lesions are growing without the appearance of new lesions. Intermediate risk was defined as new lesions without growth of existing lesions and high risk as new and growing lesions.

ter patient counselling and prognostication. When patients present with PD, difficult decisions arise: should treatment be continued, or should there be a change to a different regimen or discontinuation of therapy? A better understanding of an individual patient's prognosis may help patients and clinicians in shared decision-making. Prognostic models like the modified PD classification may be integrated in clinical trials and guidelines and support clinical decision-making.

PFS, which is the most common primary end point in randomized clinical trials in oncology,[16] is based on response evaluation using RECIST. However, the accuracy of RECIST and PFS has been scrutinized in the context of immunotherapy.[17,18] The large variability in postprogression survival highlights the shortcomings of using PFS as a surrogate for therapeutic benefit and OS[17] and underscores the need for complementary biomarkers and scoring approaches, such as our modified PD classification, for prognostication.

There is growing evidence that PD in the context of immunotherapy is heterogenous. Topp et al[5] demonstrated that there is significant heterogeneity on the lesion level at the time of PD, with only a subset of lesions progressing with ongoing tumor control in other lesions. This hints toward biological heterogeneity between lesions and their respective tumor microenvironment. Attempts have been made to incorporate lesion-level data into decision-making using quantitative systems pharmacology.[5] However, due to the complexity and limited resources in many clinical settings, RECIST is often not used in clinical practice outside of clinical trials, and there is substantial discordance between clinician-documented imaging results and RECIST.[19] Lesion-level dynamics are even more complex and therefore difficult to integrate into clinical practice, especially in low-resource settings. The classification proposed in this article that defines 3 intuitive risk groups based on the 2 main PD patterns, growth of either existing lesion(s) or emergence of new lesion(s), is much simpler and does not require the preselection of target lesions, which is subject to selection bias.[20] Thus, we are convinced that our modified PD classification represents an advancement for clinical practice; furthermore, the high across-entities relevance of the modified PD classification underlines the heterogeneity of RECIST-based PD and reinforces the need for refinement of RECIST.

To date, there have been multiple attempts to improve RECIST for immunotherapy, including immune response criteria[21] and iRECIST.[22] However, uptake of those immunotherapy-specific response criteria has been slow, and most trials investigating immunotherapy agents use standard RECIST, version 1.1.[23] Thus, there is still a lack of clear evidence of the optimal use of imaging in the era of immunotherapy.

Resistance mechanisms to immunotherapy are diverse.[24] Acquired resistance in only some lesions driven by clonal evolution[25] can lead to focal progression (ie, single lesions progress while others are well controlled). Mixed progression occurs frequently in ICI-treated patients and has been described to be associated with improved OS.[7]

The appearance of new lesions defines PD according to RECIST, version 1.1.[1] Metastases are known to be substantially different from their primary tumors.[26] Therefore, the appearance of new metastases is not necessarily accompanied by a loss of treatment response at existing lesions. This is most probably reflected in the intermediate-risk PD group, which demonstrates tumor control in existing lesion(s), and is even more pronounced in mixed PD. New lesions indicate immune escape of micrometastases during tumor evolution; however, continued control of previous lesions is the proof of an ongoing antitumor immune response, which is considered within the framework of oligoprogressive disease, for which trials that include MDT (eg, radiotherapy) are ongoing.[27] Risk stratification of patients at the time of PD may help select patients who may benefit from treatment with MDT. In high-risk PD, which is associated with the worst prognosis across entities, progression in existing lesions with the emergence of new lesions indicates rapid tumor dynamics and loss of tumor control. Therefore, this patient group may not derive clinical benefit of ongoing treatment with ICI, which could have implications for patient selection for treatment beyond progression.

An important clinical scenario is the development of new lesions during target-lesion response (mixed PD). We found this PD pattern to be associated with favorable PPOS across trials. This was consistent with the hypothesis that ongoing tumor control in target lesions is associated with benefit from immunotherapy. Therefore, these patients could be particularly well suited for MDT that targets the new lesions. However, as the mixed PD definition requires the definition of target lesions and adds complications to the clinical applicability, we did not include it in our modified PD classification. The prognostic effect of the modified PD classification was particularly marked in patients with clear-cell RCC, which could be

Table. Prognostic Value of the Modified Progressive Disease (PD) Classification Across Trials in the Immune Checkpoint Inhibitor (ICI) and Comparator Arms

	ICI			Comparator		
Characteristic	No.	HR (95% CI)	*P* value	No.	HR (95% CI)	*P* value
RCC (IMmotion151)						
High-risk PD	45	1 ([Reference]	NA	71	1 [Reference]	NA
Intermediate-risk PD	87	0.39 (0.23-0.66)	<.001	98	0.58 (0.36-0.95)	.03
Low-risk PD	121	0.23 (0.13-0.41)	<.001	118	0.45 (0.28-0.75)	.002
UC (IMvigor211)						
High-risk PD	126	1 [Reference]	NA	104	1 [Reference]	NA
Intermediate-risk PD	88	0.55 (0.41-0.74)	<.001	88	0.59 (0.44-0.80)	<.001
Low-risk PD	135	0.51 (0.40-0.66)	<.001	131	0.49 (0.37-0.64)	<.001
NSCLC (OAK)						
High-risk PD	136	1 [Reference]	NA	100	1 [Reference]	NA
Intermediate-risk PD	117	0.65 (0.49-0.87)	.003	119	0.82 (0.60-1.11)	.20
Low-risk PD	231	0.62 (0.49-0.79)	<.001	211	0.73 (0.56-0.96)	.03
SCLC (IMpower133)						
High-risk PD	42	1 [Reference]	NA	57	1 [Reference]	NA
Intermediate-risk PD	44	0.73 (0.46-1.19)	.20	42	0.72 (0.46-1.13)	.20
Low-risk PD	74	0.51 (0.33-0.78)	.002	74	0.69 (0.47-1.00)	.05
Melanoma (IMspire150)						
High-risk PD	23	1 [Reference)]	NA	34	1 [Reference]	NA
Intermediate-risk PD	80	0.55 (0.32-0.95)	.03	97	0.89 (0.55-1.43)	.60
Low-risk PD	28	0.43 (0.21-0.87)	.02	36	0.50 (0.27-0.93)	.03

Abbreviations: HR, hazard ratio; NA, not applicable; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; UC, urothelial carcinoma.

due to its specific biology, as clear-cell RCC is the prototype of a heterogenous tumor[26] and a subgroup of patients achieves long-term ICI response.[28]

In this aggregation of studies, most patients treated with immunotherapy across trials experienced progression during the trial (IMmotion151: 55%; IMvigor211: 75%; OAK: 79%; IMspire150: 51%; Impower133: 80%). This excludes patients who died or left the trial before PD was documented on imaging. This was consistent with the clinical experience that most patients with advanced tumors will be faced with disease progression at some point during their disease course.

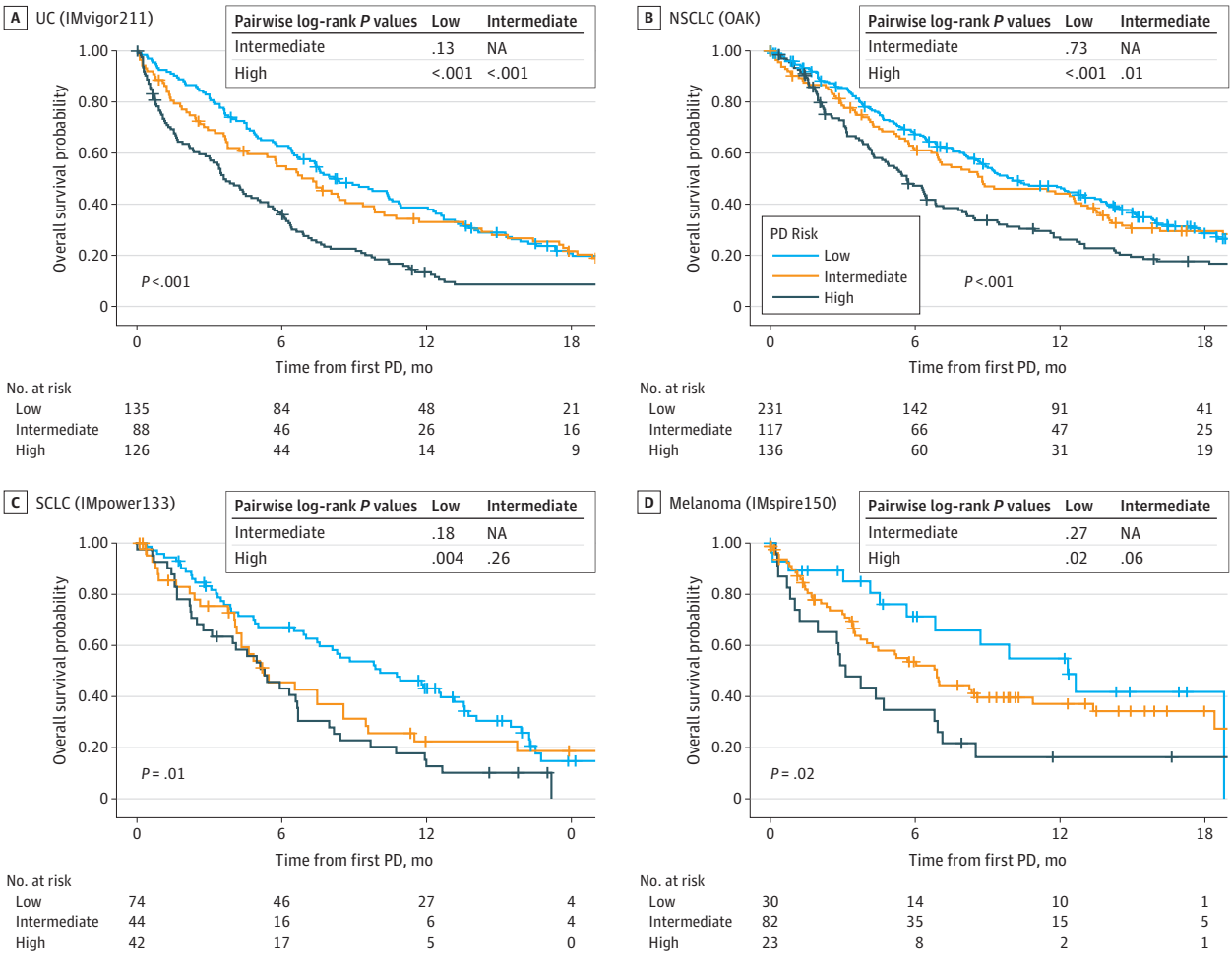
Limitations

This study had several limitations. Our research was based on a post hoc analysis of randomized clinical trials that was not prespecified, which adds potential for bias. All trials included the programmed cell death protein ligand 1 antibody atezolizumab, and validation of the modified PD classification in different trials using other ICI agents would be important to show generalizability. We found an association between high-risk PD and higher disease risk according to established risk scores. Although this may explain a part of its prognostic value, the modified PD classification was an independent prognostic factor in multivariable analysis. In addition, patients with more metastases at baseline were more likely to experience high-risk PD. This was to be expected, as those patients already had a cancer that tends to form new metastases and the higher number of existing lesions makes clonal immune escape more likely. In 2 trials, younger patients (<65 years) were more likely to have high-risk PD. Whether this is due to more aggressive disease dynamics in younger patients or immunological factors remains an open question.

The fact that PD appears at very different points for different patients complicates interpretation of the results. Patients who experience PD later while receiving treatment may have a different disease biology than patients who experience progression immediately after initiating treatment. Therefore, PPOS was chosen as the main outcome measure, as it resets the clock at the time of PD, which provides a clinically intuitive scenario and removes lead-time bias. Integration of more factors, like time to progression, could potentially improve prediction of PPOS; however, it would complicate its broad clinical application. The modified PD classification was prognostically independent of the time to first PD. Across trials, high-risk PD was most common in patients who experienced progression within the first 6 months, which was likely due to a number of patients experiencing primary progression, for which tumor control is never achieved.

Understanding the heterogeneous nature of PD will be critical to optimizing response assessment, particularly as PD is the most critical outcome in the RECIST framework and typically is followed by treatment cessation. Future clinical trials and cohorts should prospectively investigate our modified PD classification to further optimize response assessment criteria for clinical research, drug development, and everyday clinical practice.

Figure 3. Association of Classification With Postprogression Overall Survival (PPOS) With Modified Progressive Disease (PD) Classification Across Entities



The modified PD classification was associated with PPOS in the immune checkpoint inhibitor–treated arms of the IMvigor211 (A; urothelial carcinoma [UC]), OAK (B; non–small cell lung cancer [NSCLC]), Impower133 (C; small cell lung cancer [SCLC]), and IMspire150 (D; melanoma) trials. *P* values in the lower left corner are global score (log-rank) *P* values. Pairwise log-rank *P* values are depicted in the upper right corner. NA indicates not applicable.

Conclusions

In this study, we developed a pragmatic, intuitive, and easy-to-implement modified PD classification by considering the 2 main patterns of PD (growing or new lesions). Our modified PD classification was associated with PPOS across solid tumor entities treated with immunotherapy, TKI, or chemotherapy and thus may improve prognostication and clinical decision-making.

ARTICLE INFORMATION

Accepted for Publication: September 18, 2024.

Published Online: December 26, 2024. doi:10.1001/jamaoncol.2024.5672

Author Affiliations: Medical Clinic III for Oncology, Hematology, Immune-Oncology and Rheumatology, University Hospital Bonn, Bonn, Germany (Saal, Brossart); Institute of Experimental Oncology, University Hospital Bonn, Bonn, Germany (Saal, Hölzel, Klümper); Center for Integrated Oncology Aachen/Bonn/Cologne/Düsseldorf, Germany (Saal, Ritter, Brossart, Ellinger, Hölzel, Klümper); Institute of Pathology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany (Eckstein); Comprehensive Cancer Center EMN, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany (Eckstein); Bavarian Center for Cancer Research, Erlangen, Germany (Eckstein); Department of Urology and Pediatric Urology, University Hospital Bonn, Bonn, Germany (Ritter, Ellinger, Klümper); Department of Diagnostic and Interventional Radiology, University Hospital Bonn, Bonn, Germany (Luetkens); Quantitative Imaging Lab Bonn, Bonn, Germany (Luetkens); Clinic for Internal Medicine (Tumor Research) and Clinic for Urology, Interdisciplinary Genitourinary Oncology at the West German Cancer Center, Essen University Hospital, Essen, Germany (Grünwald).

Author Contributions: Mr Saal and Dr Klümper had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Saal, Hölzel, Klümper.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Saal, Klümper.
Critical review of the manuscript for important intellectual content: Saal, Eckstein, Ritter, Brossart, Luetkens, Ellinger, Grünwald, Hölzel.
Statistical analysis: Saal.
Obtained funding: Klümper.

Administrative, technical, or material support: Eckstein, Ritter, Brossart, Ellinger, Hölzel. *Supervision:* Luetkens, Grünwald, Hölzel, Klümper.

Conflict of Interest Disclosures: Dr Luetkens reported personal fees from Novartis, Philips Healthcare, Siemens Healthineers, Bayer Healthcare, and GE Healthcare outside the submitted work. Dr Grünwald reported personal fees from AAA/Novartis, Amgen, Apogepha, Astellas, AstraZeneca, Bristol Myers Squibb, EISAI, Ipsen, Janssen-Cilag, Merck Serono, MSD Oncology, Ono Pharmaceutical, Pfizer, Cureteq, Debiopharm, Gilead Sciences, Oncorena, PCI Biotech, and Synthekine outside the submitted work. Dr Hölzel reported personal fees from BioTex Inc/OncoMagnetix and TME Pharma, grants from TME Pharma, and travel support from TME Pharma outside the submitted work. Dr Klümper reported personal fees from AstraZeneca, Merck, Astellas, Novartis, Eisai, MSD, and Bicycle Therapeutics outside the submitted work. No other disclosures were reported.

Funding/Support: Dr Saal is supported by the Deutsche Krebshilfe (German Cancer Aid) through a clinician scientist grant within the Mildred Scheel School of Oncology Aachen-Bonn-Cologne-Düsseldorf (project-ID: 70113307). Dr Klümper is supported by the Bundesministerium für Bildung und Forschung–funded Advanced Clinician Scientist Program Bonn (ACCENT) of the Medical Faculty of the University of Bonn (grant ID 01EO2107).

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

Additional Information: This publication was based on research using data from Roche that has been made available through Vivli Inc. Vivli has not contributed to or approved, and is not in any way responsible for, the contents of this publication.

REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

2. Luo J, Wu S, Rizvi H, et al. Deciphering radiological stable disease to immune checkpoint inhibitors. *Ann Oncol*. 2022;33(8):824-835. doi:10.1016/j.annonc.2022.04.450

3. Topp B, Snyder A, Wolchok J. RECISTv1.1 progression in oncology: Shades of gray. *Cancer Cell*. 2023;41(6):1003-1005. doi:10.1016/j.ccell.2023.04.012

4. Borcoman E, Kanjanapan Y, Champiat S, et al. Novel patterns of response under immunotherapy. *Ann Oncol*. 2019;30(3):385-396. doi:10.1093/annonc/mdz003

5. Topp BG, Thiagarajan K, De Alwis DP, Snyder A, Hellmann MD. Lesion-level heterogeneity of radiologic progression in patients treated with pembrolizumab. *Ann Oncol*. 2021;32(12):1618-1625. doi:10.1016/j.annonc.2021.09.006

6. Topp BG, Channavazzala M, Mayawala K, et al. Tumor dynamics in patients with solid tumors treated with pembrolizumab beyond disease progression. *Cancer Cell*. 2023;41(9):1680-1688.e2. doi:10.1016/j.ccell.2023.08.004

7. Osorio JC, Arbour KC, Le DT, et al. Lesion-level response dynamics to programmed cell death protein (PD-1) blockade. *J Clin Oncol*. 2019;37(36):3546-3555. doi:10.1200/JCO.19.00709

8. Zhou J, Cipriani A, Liu Y, Fang G, Li Q, Cao Y. Mapping lesion-specific response and progression dynamics and inter-organ variability in metastatic colorectal cancer. *Nat Commun*. 2023;14(1):417. doi:10.1038/s41467-023-36121-y

9. Kumar R, Qi T, Cao Y, Topp B. Incorporating lesion-to-lesion heterogeneity into early oncology decision making. *Front Immunol*. 2023;14:1173546. doi:10.3389/fimmu.2023.1173546

10. Rini BI, Powles T, Atkins MB, et al; IMmotion151 Study Group. Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet*. 2019;393(10189):2404-2415. doi:10.1016/S0140-6736(19)30723-8

11. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2018;391(10122):748-757. doi:10.1016/S0140-6736(17)33297-X

12. Rittmeyer A, Barlesi F, Waterkamp D, et al; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255-265. doi:10.1016/S0140-6736(16)32517-X

13. Horn L, Mansfield AS, Szczęsna A, et al; IMpower133 Study Group. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med*. 2018;379(23):2220-2229. doi:10.1056/NEJMoa1809064

14. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced *BRAF*^{V600} mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;395(10240):1835-1844. doi:10.1016/S0140-6736(20)30934-X

15. Grassi L, Caruso R, Riba MB, et al; ESMO Guidelines Committee. Anxiety and depression in adult cancer patients: ESMO clinical practice guideline. *ESMO Open*. 2023;8(2):101155. doi:10.1016/j.esmoop.2023.101155

16. Booth CM, Eisenhauer EA, Gyawali B, Tannock IF. Progression-free survival should not be used as a primary end point for registration of anticancer drugs. *J Clin Oncol*. 2023;41(32):4968-4972. doi:10.1200/JCO.23.01423

17. Oxnard GR, Morris MJ, Hodi FS, et al. When progressive disease does not mean treatment failure: reconsidering the criteria for progression. *J Natl Cancer Inst*. 2012;104(20):1534-1541. doi:10.1093/jnci/djs353

18. Johal S, Santi I, Doan J, George S. Is RECIST-defined progression free-survival a meaningful endpoint in the era of immunotherapy? *J Clin Oncol*. 2017;35:488-488. doi:10.1200/JCO.2017.35.6_suppl.488

19. Ma X, Bellomo L, Hooley I, et al. Concordance of clinician-documented and imaging response in patients with stage IV non–small cell lung cancer treated with first-Line therapy. *JAMA Netw Open*. 2022;5(5):e229655. doi:10.1001/jamanetworkopen.2022.9655

20. Iannessi A, Beaumont H, Liu Y, Bertrand AS. RECIST 1.1 and lesion selection: how to deal with ambiguity at baseline? *Insights Imaging*. 2021;12(1):36. doi:10.1186/s13244-021-00976-w

21. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420. doi:10.1158/1078-0432.CCR-09-1624

22. Seymour L, Bogaerts J, Perrone A, et al; RECIST Working Group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143-e152. doi:10.1016/S1470-2045(17)30074-8

23. Ramon-Patino JL, Schmid S, Lau S, et al. iRECIST and atypical patterns of response to immuno-oncology drugs. *J Immunother Cancer*. 2022;10(6):e004849. doi:10.1136/jitc-2022-004849

24. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168(4):707-723. doi:10.1016/j.cell.2017.01.017

25. Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. *Lancet Oncol*. 2017;18(12):e731-e741. doi:10.1016/S1470-2045(17)30607-1

26. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med*. 2012;366(10):883-892. doi:10.1056/NEJMoa1113205

27. Cheung P, Patel S, North SA, et al. Stereotactic radiotherapy for oligoprogression in metastatic renal cell cancer patients receiving tyrosine kinase inhibitor therapy: a phase 2 prospective multicenter study. *Eur Urol*. 2021;80(6):693-700. doi:10.1016/j.eururo.2021.07.026

28. Díaz-Montero CM, Rini BI, Finke JH. The immunology of renal cell carcinoma. *Nat Rev Nephrol*. 2020;16(12):721-735. doi:10.1038/s41581-020-0316-3