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ORIGINAL ARTICLE

Major pathologic response on biopsy (MPR_{bx}) in patients with advanced melanoma treated with anti-PD-1: evidence for an early, on-therapy biomarker of response

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Background: With increasing anti-PD-1 therapy use in patients with melanoma and other tumor types, there is interest in developing early on-treatment biomarkers that correlate with long-term patient outcome. An understanding of the pathologic features of immune-mediated tumor regression is key in this endeavor.

Materials and methods: Histologic features of immune-related pathologic response (irPR) following anti-PD-1 therapy were identified on hematoxylin and eosin (H&E)-stained slides in a discovery cohort of pre- and on-treatment specimens from $n = 16$ patients with advanced melanoma. These features were used to generate an irPR score [from 0 = no irPR features to 3 = major pathologic response on biopsy (MPR_{bx}, ≤10% residual viable tumor)]. This scoring system was then tested for an association with objective response by RECIST1.1 and overall survival in a prospectively collected validation cohort of pre- and on-treatment biopsies ($n = 51$ on-treatment at 4-week timepoint) from melanoma patients enrolled on the nivolumab monotherapy arm of CA209-038 (NCT01621490).

Results: Specimens from responders in the discovery cohort had features of immune-activation (moderate–high TIL densities, plasma cells) and wound-healing/tissue repair (neovascularization, proliferative fibrosis) compared to nonresponders, ($P \leq 0.021$, for each feature). In the validation cohort, increasing irPR score associated with objective response ($P = 0.009$) and MPR_{bx} associated with increased overall survival ($n = 51$; HR 0.13; 95%CI, 0.054–0.31, $P = 0.015$). Neither tumoral necrosis nor pretreatment histologic features were associated with response. Eight of 16 (50%) of patients with stable disease showed irPR features, two of which were MPR_{bx}, indicating a disconnect between pathologic and radiographic features at the 4-week on-therapy timepoint for some patients.

Conclusions: Features of immune-mediated tumor regression on routine H&E-stained biopsy slides from patients with advanced melanoma correlate with objective response to anti-PD-1 and overall survival. An on-therapy biopsy may be particularly clinically useful for informing treatment decisions in patients with radiographic stable disease. This approach is inexpensive, straightforward, and widely available.

Key words: PD-1, melanoma, pathology, pathologic response, MPR, MPRbx

Introduction

Early on-treatment biomarkers of anti-PD-1 therapeutic efficacy are highly sought after. Predictors of response can affirm treatment choice or potentially indicate the need for a change in treatment regimen. The clinical appreciation of therapeutic response/resistance is not always reliable due to the confounding radiographic appearance of immune infiltration of tumors, i.e. pseudopregression, or the fact that the regression bed (where the tumor used to be prior to immune-mediated clearance) may appear radiographically identical to residual viable tumor (RVT) [1]. This uncertainty can delay a change to a potentially more effective therapeutic strategy by months.

Neoadjuvant studies are an opportune setting for the identification of early on-treatment biomarkers, as they provide for study a meaningful number of large, definitive resection specimens from tumors exposed to anti-PD-1 for only a few weeks. The first clinical trials for neoadjuvant anti-PD-1 for patients with non-small cell lung carcinoma (NSCLC) and melanoma have recently been resulted [2, 3]. In conjunction with the NSCLC study, Cottrell et al. [1] reported a detailed description of the histologic features assessed on routine hematoxylin and eosin (H&E)-stained slides of anti-PD-1-mediated immune regression and proposed associated immune-related pathologic response (irPR) criteria. Anecdotal histologic descriptions from the melanoma patients that responded to neoadjuvant anti-PD-1 highlighted similar morphologic characteristics [4].

Patients with no RVT following neoadjuvant therapy are considered complete pathologic responders (CPR), while those with $\leq$10% RVT are termed major pathologic responders (MPR). For NSCLC patients treated with neoadjuvant chemotherapy, MPR at the time of definitive resection is indicative of treatment effect and has been shown to strongly associate with survival [5]. Recognition of the histologic features of irPR to immunotherapy is essential for an accurate calculation of percent RVT (%RVT = RVT surface area/total tumor bed surface area). Importantly, the tumor bed includes both RVT and areas where viable tumor *used* to be. irPR features are the histologic key to determining the latter parameter in immunotherapy-treated patients. It is also this explicit measurement of the regression bed that differentiates irPR criteria from chemotherapy scoring approaches [1, 6]. However, unlike for chemotherapy, immune-related neoadjuvant CPR and MPR have yet to be associated with long-term patient outcomes, as survival data are not available.

The purpose of this study was to determine if the histologic features of anti-PD-1-mediated tumor regression characterized in the neoadjuvant setting could be identified in biopsies from patients receiving anti-PD-1 for advanced disease and used as an early on-treatment biomarker of long-term outcomes. To determine this, individual histologic features of immune-mediated tumor regression similar to those originally described for NSCLC were assessed in a discovery cohort of melanoma specimens and a composite irPR score was generated. The irPR scoring was then tested in a separate prospectively collected validation cohort of early on-treatment biopsies from patients with advanced melanoma with 5 years of clinical follow up. Increasing irPR score was associated with objective response, and MPR on biopsy (MPR_{bx}) was associated with improved overall survival (OS).

Methods

This project was approved by the Johns Hopkins Institutional Review Board and adheres to the REMARK criteria for biomarker discovery. The participant flow diagram for specimens in the discovery and validation cohorts is shown in supplementary Figure S1, available at *Annals of Oncology* online.

Discovery cohort

Sixteen patients with advanced melanoma treated with anti-PD-1 monotherapy ($n=7$ nivolumab and $n=9$ pembrolizumab) who had on-treatment or post-treatment tumor specimens available for study were identified. Of these, 14 also had pre-treatment tumor specimens available. Response status to anti-PD-1 therapy was assessed using RECIST v1.1, with first assessment conducted after approximately 8 weeks on therapy. H&E-stained slides from formalin-fixed and paraffin-embedded (FFPE) tissues were reviewed by two board-certified pathologists (AS, JMT), who were blinded to patient outcome, to assess for immune and nonimmune histologic features associated with therapeutic response [1, 2, 5–7], Figure 1. Individual histologic features were compared between responders and nonresponders and a composite irPR score was developed (see Results).

Validation cohort

One hundred and ninety-five samples (127 pretreatment biopsies and 68 on-treatment biopsies) were obtained from the nivolumab monotherapy arm of CA209-038 (NCT01621490), a multi-institutional, multiarm prospective trial investigating the pharmacodynamics of nivolumab in patients with unresectable or metastatic melanoma. Pretreatment biopsies were obtained a median of 4 days prior to therapy start (90% within 1 year). On-treatment biopsies were taken at days 22–36 on therapy. Additional demographic and clinicopathologic details for both cohorts are provided in supplementary Table S1 and Supplementary Methods, available at *Annals of Oncology* online, and the REMARK profile for the validation cohort is provided in supplementary Table S2, available at *Annals of Oncology* online.

H&E-stained slides were scored by two pathologists (AS, JMT) using the semiquantiative irPR scale developed in the discovery cohort. The pathologists were blinded to patient outcome and whether the specimen was a pretreatment versus on-treatment biopsy.

Statistical analyses

In the discovery cohort, Fisher's exact test was used to assess for differences in histopathologic features and irPR score between responders and nonresponders. McNemar's test was used to compare individual histologic features between paired pre- and on-treatment specimens. For the validation cohort, Fisher's exact test was used to assess for differences between responders versus nonresponders and between patients who had previously progressed on ipilimumab versus those who were ipilimumab naïve. Wilcoxon signed-rank test was used to compare irPR scores between paired pre- and on-treatment specimens. The Kaplan–Meier estimator was used to perform survival analysis, using the log-rank test to determine statistical significance. All tests were two-sided, and P values of <0.05 were considered significant. Analyses were performed in GraphPad and R.

Results

Identification of irPR features using the discovery cohort

Responders were found to have features of immune-activation [moderate-high tumor infiltrating lymphocytes (TIL) densities, plasma cells] compared to nonresponders ($P=0.005$ and $P=0.021$,

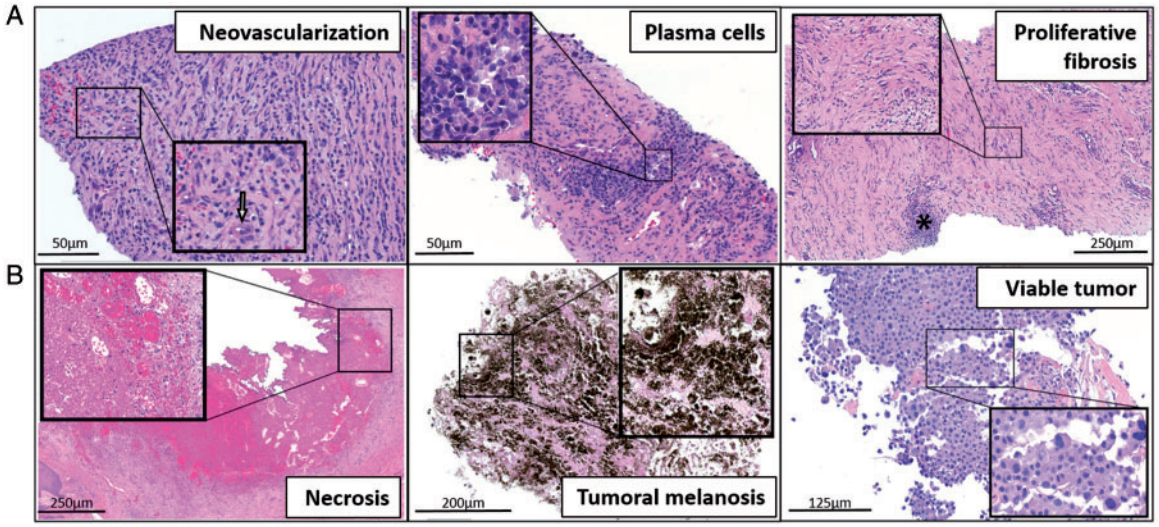

Figure 1. Representative photomicrographs showing histologic features in on-treatment specimens from melanoma patients receiving anti-PD-1. (A) On-treatment specimens from responders showed features of neovascularization (left; arrow on inset points to a small vessel), plasma cell infiltration (middle), and proliferative fibrosis (right; inset shows high fibroblast: collagen ratio). An asterisk labels a lymphoid aggregate. (B) Features that were not associated with response to anti-PD-1 included necrosis (left), tumoral melanosis (middle), and residual viable tumor (right). All panels, hematoxylin and eosin staining.

respectively), Figure 1A. Interestingly, features of wound healing/tissue repair (neovascularization and proliferative fibrosis) were consistently seen in areas of immune-mediated regression ($P = 0.0006$ for both, responders versus nonresponders). These major features were in keeping with those described for patients with NSCLC who responded to neoadjuvant anti-PD-1 [1]. Lymphoid aggregates showed a borderline association with response ($P = 0.07$), while the presence of necrosis, tumoral melanosis, hyalinized fibrosis, granulomas, cholesterol clefts, foamy macrophages, giant cells, and neutrophils were not associated, Figures 1B and 2. In fact, necrosis was more prevalent in nonresponding lesions. There were no differences in features identified in either pre- or on-treatment specimens in patients who had received prior systemic therapy (each individual feature, $P > 0.05$). None of the studied pathologic features in pretreatment specimens were predictive of response, supplementary Figure S3, available at *Annals of Oncology* online.

A semiquantitative scale of irPR was generated based on these features. Specifically, 0 = no features of irPR; 1 = <3 colocalized features of irPR (e.g. TIL and/or fibrosis), or if more features are present, they are not colocalized; 2 = at least 3 colocalized features of irPR are present and there is >10% RVT; and 3 = MPR_{bx}; at least three features of irPR present and ≤10% RVT). irPR score was associated with objective response and durable clinical benefit [DCB; responders plus stable disease (SD)] ($P < 0.0006$, for both).

Patients with SD showed some histopathologic features of response, and by definition, no radiographic evidence of response, Figure 2. Notably, despite radiographic SD, Patient #9's specimen had no RVT, Figure 3.

irPR features associate with patient outcome in the validation cohort

The irPR scores developed in the discovery cohort were then tested in the validation cohort for an association with objective response and OS. Responders had higher irPR scores than did nonresponders (excluding patients with SD, $P = 0.009$; including patients with SD, $P = 0.02$, Figure 4A). Patients with an irPR score of 3 in their on-treatment specimens had significantly improved OS as compared to patients with scores 0–2 ($n = 51$, HR 0.13, $P = 0.015$), Figure 4B. irPR scores in pretreatment specimens were not associated with improved OS ($P = 0.61$), supplementary Figure S4, available at *Annals of Oncology* online.

Previous scoring systems grading treatment response to chemotherapy, etc. have included necrosis when quantifying treatment effect [6, 8]. In this cohort, however, there were no significant associations between necrosis scores and objective response or DCB, Figure 4A, which corroborates a previous report that examined the association of necrosis with response in anti-PD-1-treated patients [9]. There was also no significant association between prior ipilimumab therapy and increasing irPR scores in either pre-treatment or on-treatment specimens ($P = 0.15$ and $P = 0.94$, respectively).

irPR scores increase in paired pre- versus on-treatment biopsies

On-treatment specimens showed significantly higher irPR scores than pretreatment specimens, $P = 0.014$, supporting the concept that irPR features in on-treatment biopsies are a function of anti-PD-1 therapy administration. In contrast, there was not a difference in the presence or degree of necrosis between pre- and on-treatment PD-1 specimens ($P = 0.47$).

Features of irPR in patients with SD

The full constellation of features of irPR, i.e. score 2 or 3, was seen in 8 of 16 (50%) of patients with SD in the validation cohort. This indicates that pathologic features in this group are heterogeneous and also highlights the lack of correlation between pathologic and radiographic features at the 4-week on-therapy timepoint.

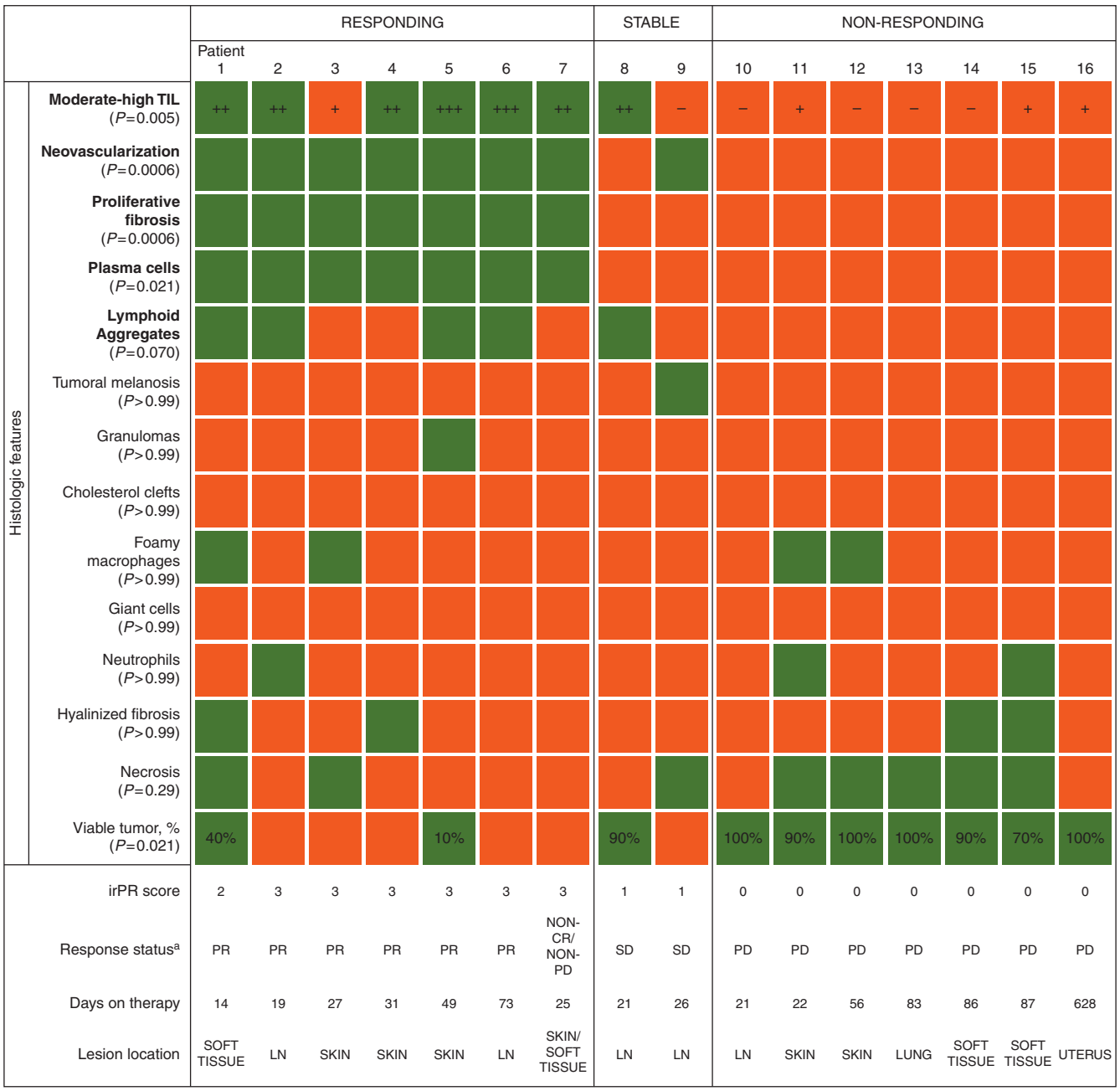

Figure 2. Heat maps of individual histologic features in a discovery cohort of on-treatment melanoma specimens by response status. Green indicates feature is present. Red indicates feature is absent. Responding lesions show features (in bold) of dense TIL infiltration (including some lymphoid aggregates), neovascularization, proliferative fibrosis, and plasma cells. These features were used to generate an irPR score. The earliest on-treatment specimen from a responder (Patient #1) was taken 14 days after only one dose of anti-PD-1 therapy. The full constellation of pathologic findings associated with response was already evident at this time point. [a]Assessed on closest scan to biopsy. PR, partial response; CR, complete response; PD, progressive disease; SD, stable disease; (–) no TIL; (+) grade 1 TIL, mild; (++) grade 2 TIL, moderate; (+++) grade 3 TIL, high.

Discussion

Comparison between responding and nonresponding lesions and pre- and on-treatment biopsies from patients with advanced melanoma revealed that anti-PD-1-mediated tumor regression is characterized by the colocalization of neovascularization, proliferative fibrosis, dense TIL, and plasma cells. The pathologic features identified in the discovery cohort were then tested in a uniform, prospectively collected validation cohort of patients who had biopsies performed approximately 4 weeks after initiation of anti-PD-1 (nivolumab). Increasing irPR score was associated with objective response, and MPR_{bx} (irPR score = 3) was found to correlate with OS, suggesting that MPR_{bx} may serve as an early, on-treatment biomarker.

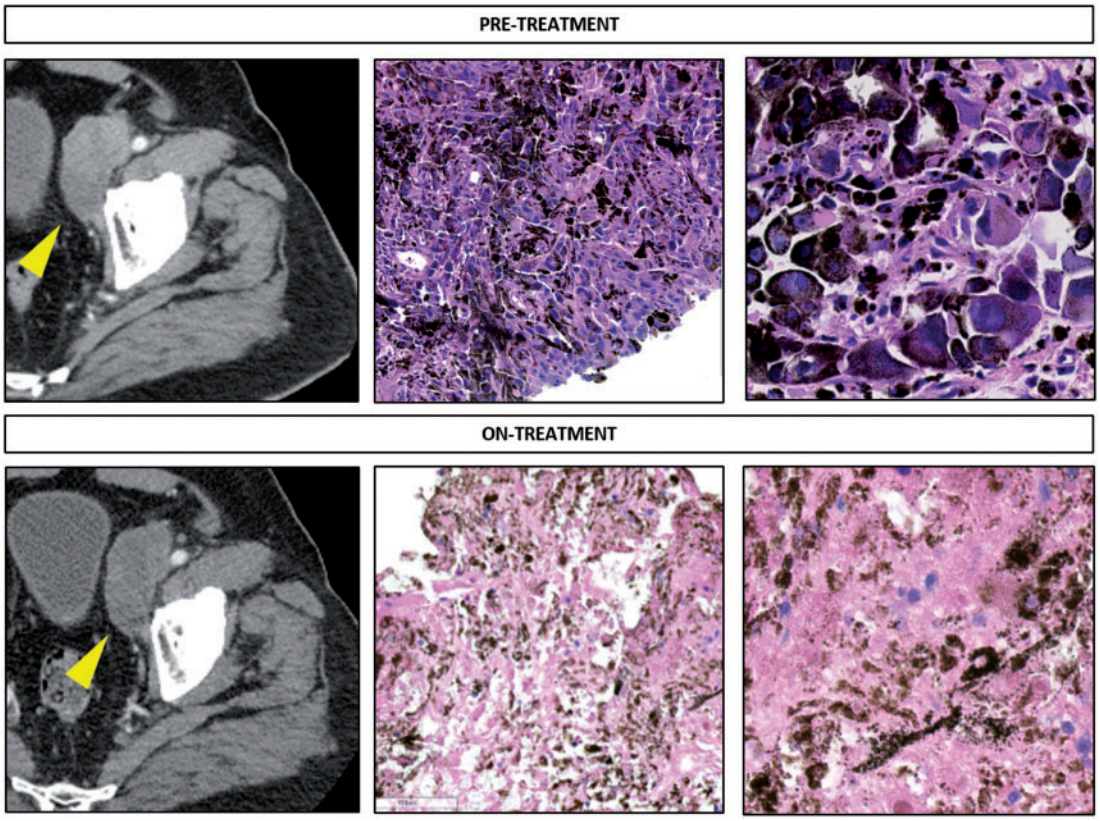

Figure 3. Discordant radiographic and pathologic findings in Patient #9 with SD. Top: Pre-treatment CT scan (left) indicating lesion of interest (yellow arrowhead), pre-treatment biopsy shown at low-power (middle; 100×) and high-power (right; 100×) showing viable melanoma. Bottom: On-treatment CT scan (left) showing stable radiographic size of lesion of interest (yellow arrowhead). On-treatment biopsy shown at low-power (middle; 100×) and at high-power (right; 400×) show features of immune-mediated regression with no remaining residual viable tumor apparent in the specimen despite no change in size by radiography.

A few early on-treatment tissue-based biomarker approaches for assessing response to anti-PD-1 have been proposed. These approaches include digital quantitation of immunohistochemically stained slides highlighting select immune cell subsets, gene expression profiling, and flow-cytometric studies of lysates from on-treatment biopsies [9–11]. The majority of these candidate assays were not tested for their association with OS. Further, these methodologies require the use of special technologies and specimen workflow. As a result, most are expensive and not widely available. In contrast, the H&E-based assessment of MPR_{bx} described here can be determined by surgical pathologists as a part of routine practice.

The ability for pathologists to readily identify features of irPR that are associated with improved patient outcome will be especially important as anti-PD-1 moves into the neoadjuvant setting. There are currently over 60 planned or ongoing clinical trials that include neoadjuvant checkpoint blockade, including several for patients with melanoma. Similar to clinical trials for neoadjuvant chemotherapy [5, 6], many will include pathologic response as an end point, as this allows for a surrogate 'readout' on H&E slides by pathologists of projected patient outcome within weeks of therapy administration, rather than waiting for years for survival data. Here, we analyze the irPR features previously seen in neoadjuvant therapy-treated resection specimens (from approximately 4 weeks and 6–8 weeks on-therapy in patients with NSCLC and melanoma, respectively) and for the first time associate them with OS—in this instance on biopsies from patients with advanced melanoma at a compatible on-treatment timepoint (22–36 days on-therapy). These findings lend support to the idea that identification of the regression bed using irPR features and subsequent determination of MPR in specimens from neoadjuvantly treated patients may indeed project long-term patient outcomes, though MPR and OS still need to be explicitly correlated in that clinical setting.

The observed increase in intratumoral TIL density following anti-PD-1 was anticipated. However, the presence of prominent plasma cells has not previously been described for patients with melanoma treated with anti-PD-1. It remains to be determined whether these plasma cell infiltrates are, in fact, indicative of an antibody-mediated anti-tumor effect [12]. The identification of features of tissue repair in this setting for both melanoma and NSCLC is also noteworthy, as it contradicts previous reports suggesting that features of wound healing are detrimental to anti-PD-1 response [13, 14]. It may be that in those studies, pre-treatment rather than on-treatment specimens were tested. It may also be that expression of proteins associated with wound healing in the tumor itself, i.e. acquiring a de-differentiated fibroblastic phenotype, may be associated with shorter OS. Here, a benign, fibroblastic proliferation with neovascularization is only observed where the tumor used to be. This seeming disparity highlights the need for a careful histopathologic understanding of the tumor microenvironment compartment and timepoint being studied.

A

	Responders (CR+PR) *n* (%)	Non-Responders (PD) *n* (%)	*P* value[a]	Clinical Benefit (CR+PR+SD) *n* (%)	No Clinical Benefit (PD) *n* (%)	*P* value[a]
irPR Score						
0	4 (12)	12 (36)	0.009	12 (25)	12 (25)	0.02
1	1 (3)	3 (9)		1 (2)	3 (6)	
2	3 (9)	4 (12)		9 (18)	4 (8)	
3	6 (18)	0 (0)		8 (16)	0 (0)	
Necrosis Score						
0	8 (24)	12 (36)	0.87	21 (43)	12 (25)	0.90
1	1 (3)	2 (6)		3 (6)	2 (4)	
2	5 (15)	5 (15)		6 (12)	5 (10)	

[a]Evaluated using Fisher's exact test.

B

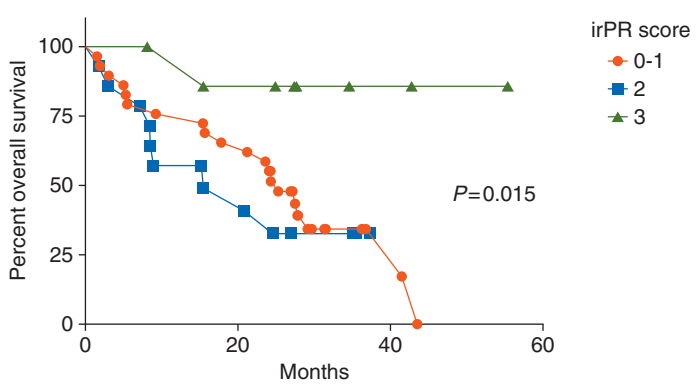

Figure 4. irPR scores associate with objective response and long-term survival. (A) Scores of irPR, but not necrosis, associate with objective response and clinical benefit in a validation cohort. (B) Long-term overall survival (OS) associates with MPR_{bx} (irPR score = 3). In the validation cohort ($n = 51$ on-treatment specimens), OS was markedly increased in patients with irPR scores of 3, as compared to scores 0–2 ($P = 0.015$, log-rank test).

Current radiographic approaches do not reliably indicate changes in RVT following anti-PD-1 therapy [1, 2]. That is exemplified by one of the two patients with stable disease by radiographic studies in the discovery cohort, who showed no evidence of RVT on pathology. Furthermore, 2 of 16 patients with SD in the validation cohort demonstrated MPR_{bx}. This is in keeping with findings recently reported in NSCLC, whereby 44% of patients showed SD by radiographic studies but demonstrated MPR on the definitive resection specimen [1, 2]. Taken together, these two studies provide an initial estimate of the prevalence of this phenomenon at somewhere around 25%–30% of cases. The radiographic-pathologic disconnect lends support for a DCB metric (rather than just PR and CR) when response is being assessed radiographically. It also suggests that a biopsy could be of clinical utility in assessing treatment efficacy in patients with SD. Lastly, it highlights the need for more sophisticated imaging approaches that could potentially resolve the difference between viable tumor and immune-mediated tumor regression. It is possible that by identifying specific pathologic features of the regression bed, such as the neovascularization highlighted here, innovative imaging approaches that capitalize on this signature could be considered [15].

The main limitation of the approach used in this study is the need for an on-treatment biopsy. This necessitates a procedure for the patient, which may not be feasible in some instances. Peripheral blood-based biomarkers such as circulating tumor DNA (ctDNA) [16, 17] are an attractive alternative for that reason. However, ctDNA approaches typically require genomic sequencing of the tumor, and may not work in patients with a low tumor burden or those with tumors lacking genetic hotspot mutations. Analyzing tumor tissue samples is advantageous in that they can be queried to potentially identify a mechanism of immune-resistance in nonresponders, such as identification of immune exclusion [18], loss of HLA expression or acquisition of IFN-γ pathway mutations [19], or immune checkpoint expression beyond PD-1/PD-L1 that could potentially be cotargeted [20].

Other limitations to this study include that we were not able to perform subgroup analyses to potentially associate the different irPR histologic scores in SD patients with clinical outcomes. Riaz et al. conducted genomic analysis of samples derived from the same clinical trial as the validation cohort described here, and found that patients with SD represented an "intermediate molecular phenotype" of mutational contraction, with genomic variant loss at a level in between that of CR/PR and PD [21]. It is unclear whether patients with SD truly represent a discrete patient population with an intermediate response phenotype, or whether they are a heterogeneous population that could be resolved into responders or nonresponders with additional characterization of a larger number of patients. Additionally, patients underwent biopsy at 4 weeks on therapy, while their first CT scan for response evaluation occurred at 8 weeks on therapy. Given that the pathologic-radiographic disconnect was present at 8 weeks, it is likely that this disconnect would be even greater if a CT scan was taken at the time of biopsy at 4 weeks. However, future studies investigating this discordance could benefit from including a scan at the time of biopsy to allow for more direct comparison of pathologic and radiographic response.

Conclusion

Provisional scoring approaches for pathologic response to immune checkpoint blockade in patients with melanoma should not only include assessment of TIL and associated macrophages, but also the identification of a potential regression bed characterized by proliferative fibrosis, neovascularization, and plasma cells. MPR_{bx} may be assessed using routine microscopy and correlates with objective response as well as OS, and as such, represents a widely available, early on-treatment biomarker of response to anti-PD-1. Larger studies using this scoring system will be necessary to further substantiate our findings. Future studies will also be necessary to assess whether this approach is generalizable to other solid tumor types.

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