

Lesion-Level Response Dynamics to Programmed Cell Death Protein (PD-1) Blockade

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abstract

PURPOSE Response to programmed cell death protein 1 (PD-1) blockade is often conceptualized as resulting from reinvigoration of tumor-infiltrating lymphocytes. However, recruited antitumor immunity from the periphery may also be an important contributor to response. A detailed assessment of the response dynamics of individual metastasis could provide insight to the systemic and local features that mediate response and resistance to immunotherapy.

MATERIALS AND METHODS Patients with metastatic non–small-cell lung cancer (NSCLC) or mismatch repair deficiency (MMRD) carcinoma treated with PD-1 monotherapy were evaluated independently. Absolute and percent change of each target lesion were quantified at each computed tomography scan using RECIST. Patterns of progression were predefined as systemic or mixed and were correlated with clinical outcomes.

RESULTS A total of 761 individual lesions from 214 patients with NSCLC and 290 lesions from 78 patients with MMRD carcinoma were examined. Individual target lesion responses aligned with best overall response of each patient (85% NSCLC and 93% MMRD lesions responded in patients with partial response/complete response). In responding patients, timing of response was uniform (73% NSCLC and 76% MMRD lesions responded synchronously), and deeper responses were associated with prolonged progression-free survival and overall survival. By contrast, at progression, mixed progression was common (45% of NSCLC and 53% of MMRD) and associated with improved survival compared with those who experienced systemic progression (NSCLC hazard ratio [HR], 0.58; $P = .001$; MMRD HR, 0.40; $P = .07$). Organ sites had differential responses, with lymph node and liver metastasis among the most and least responsive, respectively.

CONCLUSION Temporal-spatial patterns of response across individual metastases tend to be uniform, favoring the role of peripheral, clonally directed antitumor immunity as a key mediator of response to PD-1 blockade. In contrast, progression is more heterogeneous, potentially revealing the clinical importance of local features and intertumoral heterogeneity.

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INTRODUCTION

Monoclonal antibodies that inhibit the programmed cell death protein 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1), have revolutionized cancer therapeutics.¹⁻³ Inhibition of the PD-1/PD-L1 signaling pathway stimulates T-cell–mediated immunity, leading to potent antitumor activity and durable responses in a variety of cancers.⁴

Clinically meaningful antitumor immune response appears to be dependent on a complex interplay between peripheral immunity and the local tumor microenvironment. Although the mechanism of action of PD-1 blockade is often conceptualized as reinvigoration of T cells from within the tumor microenvironment,

recent studies demonstrating terminal dysfunction of tumor-infiltrating lymphocytes (TILs)⁵⁻⁷ highlight the possibility that immigration of peripheral T cells is also necessary. Still, the impact of tumor inflammation,^{8,9} metastatic organ microenvironment,^{10,11} and tumor clonal heterogeneity^{12,13} on response to T cell checkpoint blockade all emphasize that local, tumor-specific features contribute to effectiveness of immune responses. In short, the interplay between the peripheral and tumoral immune compartments to define the nature of response and progression to PD-1 blockade is not well understood.

We hypothesized that an examination of the patterns of response to PD-1 blockade at the level of individual

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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metastases—in contrast to the more typical summation within a given patient—could provide insight to the impact of systemic and local features on the antitumor immune response. To do so, we systematically assessed, at both individual metastatic site-specific and patient-specific levels, the dynamics of response and patterns of progression to PD-1 blockade in two independent cohorts of patients with metastatic cancers.

MATERIALS AND METHODS

Patients

After institutional review board approval, two cohorts of patients were examined: patients with metastatic non-small-cell lung cancer (NSCLC) treated with anti-PD-1 monotherapy (n = 214) and patients with metastatic carcinoma with mismatch repair deficiency (MMRD) treated with pembrolizumab (n = 78).¹⁴ All patients received at least one dose of PD-1 blockade and were evaluable for response.

Radiologic Assessments and Predefined Patterns of Response and Resistance

Computed tomography (CT) scans of individual patients during PD-1 treatment were reviewed by trained radiologists, and response was determined by RECIST v1.1. The absolute size and percent change of overall tumor burden and within individual metastases were quantified using unidimensional measurements (millimeters) of target lesions. Nontarget lesions were captured and followed qualitatively. The appearance of new lesions was captured at the time of onset.

In all patients, irrespective of their best overall response by RECIST, the pattern of progression was determined using predefined characteristics at the time that any target and/or nontarget lesion met the criteria for progression of disease (PD) and/or when a new lesion was present, whichever occurred first (Table 1). The patterns of progression were defined as:

1. Systemic progression: PD in two or more lesions (including target, nontarget, or new lesion) in patients with three or fewer target lesions or PD in three or more lesions (including target, nontarget, or new lesion) in patients with four or more target lesions.
2. Mixed progression: PD in only one lesion (including target, nontarget, new lesion) in patients with three or fewer target lesions; or PD in two or fewer lesions

(including target, nontarget, new lesion) in patients with four or more target lesions.

Timing of radiologic assessments was not prespecified in the NSCLC cohort; the median time of the first and second CT scans were 1.9 and 4.0 months, respectively, after starting treatment. Timing of CT scans in the MMRD cohort were prespecified as described.³

Statistical Approach

Longitudinal changes in tumor size were quantified and captured as percent change. Progression-free survival (PFS; defined as start of PD-1 therapy until RECIST-defined progression or death, or, if no progression, were censored at the data lock) and overall survival (OS; defined as start of PD-1 therapy until death, or, if no death, were censored at the data lock) among groups were depicted using the Kaplan-Meier method and compared using log-rank (Mantel-Cox) test. Two-way comparisons of continuous variables were performed using the Mann-Whitney test, and three-way comparisons were performed using the Kruskal-Wallis test. Two-way comparisons of categorical variables were performed using Fisher's exact test. Correlation analyses were performed using Spearman correlation test. All statistical tests were two sided, and $P < .05$ was set as the level of significance.

RESULTS

Patients

In the NSCLC cohort, 214 patients with stage IV NSCLC were included, with a total of 761 baseline lesions (501 target, 260 nontarget) identified on imaging. The MMRD cohort consisted of 78 patients with metastatic MMRD carcinoma, with a total of 290 baseline lesions identified on imaging (187 target and 103 nontarget; Table 2; Data Supplement [online only]). The overall response rates were 21.5% in the NSCLC cohort and 59.1% in the MMRD cohort.

Temporal-Spatial Patterns of Response

We first evaluated the change in size of each target lesion over time in patients with NSCLC. We found that individual target lesion responses aligned with the RECIST-defined best overall response (BOR) of each patient (Figs 1A-1C). In NSCLC, among patients who achieved complete response or partial response (CR/PR; n = 46), 91 of 107 (85%) of individual target lesions also had objective response (> 30% reduction; Data Supplement). Patients with stable disease (SD) or PD as BOR also aligned in their individual target lesion response, although to a lesser extent. Among patients with SD (n = 74), 118 of 159 (74%) individual target lesions had SD, and among patients with PD (n = 94), 130 of 235 (55%) individual target lesions had PD (> 20% growth; Data Supplement). A similar alignment of individual target lesion responses relative to BOR was seen in patients with metastatic MMRD carcinoma (Figs 1D-1F; Data Supplement).

TABLE 1. Definition of Patterns of Progression

Pattern of Progression	Patients With ≤ 3 Target Lesions	Patients With ≥ 4 Target Lesions
Systemic	PD in ≥ 2 lesions	PD in ≥ 3 lesions
Mixed	PD in only 1 lesion	PD in ≤ 2 lesions
No progression	No PD in any lesion	No PD in any lesion

NOTE. Includes progression of any new target or nontarget lesion and appearance of a new lesion.

Abbreviation: PD, progression of disease.

TABLE 2. Clinical Characteristics of Patients Treated With PD-1 Blockade

Characteristic	NSCLC (n = 214)	MMRD (n = 78)
Sex		
Female	107 (50.0)	39 (50)
Male	107 (50.0)	39 (50)
Age, years, median (range)	65.1 (32-93)	57 (24-92)
Smoking status		
Current	54 (25.3)	Not recorded
Former	128 (59.8)	Not recorded
Never	32 (14.9)	Not recorded
Pathology	ADC 178 (83.2)	Colorectal 37 (47.4)
	Non-ADC 36 (16.8)	Endometrial 14 (18)
		Others 27 (34.6)
PD-L1 expression, %		
< 50	68 (31.8)	14 (18)
≥ 50	29 (13.6)	0 (0)
Not available	117 (54.6)	64 (82)
Lines of prior therapy		
0	29 (13.6)	1 (1.3)
1	161 (75.2)	14 (18)
2	10 (4.6)	25 (32)
≥ 3	14 (6.6)	38 (48.7)
Best overall response (RECIST)		
CR	2 (0.9)	18 (23.1)
PR	44 (20.6)	28 (36)
SD	74 (34.6)	20 (25.6)
PD	94 (43.9)	12 (15.3)

NOTE. Data presented as No. (%) unless otherwise noted.

Abbreviations: ADC, adenocarcinoma; CR, complete response; MMRD, mismatch repair deficiency; NSCLC, non-small-cell lung cancer; PD, progression of disease; PR, partial response; SD, stable disease.

Of note, pseudoprogression, defined as tumor growth of $\geq 20\%$ followed by partial or complete response by RECIST, occurred in only one patient in the NSCLC cohort (Data Supplement). Two additional patients with NSCLC had isolated pseudoprogression in individual target lesions (Data Supplement). In the MMRD cohort, no pseudoprogression was observed, either in terms of overall response or in individual lesions.

We analyzed the synchrony of response in the lesions from patients who achieved CR or PR by RECIST (107 lesions in the NSCLC cohort and 101 lesions in the MMRD carcinoma cohort). We found that 82 of the 107 lesions (76%) in the NSCLC cohort achieved initial response ($\geq 30\%$) synchronously with other target lesions at the same CT scan, within a given patient (Fig 1G). In addition, 90% and 95% of lesions responded by 3 and 6 months, respectively, from the first responding lesion in a given patient. In responders with MMRD carcinoma, 74 of 101 responding lesions

(73%) achieved initial partial response at the same CT scan within a given patient; 81% and 93% lesions responded within 3 or 6 months, respectively, of the first responding lesion (Fig 1H).

We also evaluated whether PD-L1 expression, which may be a proxy for the degree of intratumoral cytotoxic immune infiltration,^{15,16} influenced the patterns of response in the NSCLC cohort (available in 28 out of 46 responders). There were no differences in the patterns of response, synchrony, timing, or clinical outcomes (PFS and OS) between patients with high ($\geq 50\%$ PD-L1, $n = 15$) and low ($< 50\%$ PD-L1, $n = 13$) expression of PD-L1 (Data Supplement). In the MMRD cohort, direct quantification of CD8⁺ TILs was available in a subset of patients ($n = 14$). There were no differences in outcomes between patients with low (< 200 tumor CD8⁺ cells/mm², $n = 7$) and high (> 200 tumor CD8⁺ cells/mm², $n = 7$) TILs (Data Supplement). Similarly, the patterns and synchrony of responses were unchanged regardless of TIL status (Data Supplement).

Depth of Response and Baseline Tumor Burden

We examined if there was a correlation between overall depth of response and survival. Among responders in both the NSCLC and MMRD cohorts, patients with depth of response equal or greater than the median response in each cohort (-51% in NSCLC, -72% in MMRD) had improved PFS compared with those responders with depth of response lower than the median response (NSCLC cohort: PFS hazard ratio [HR], 0.39; 95% CI, 0.13 to 1.15; $P = .03$; MMRD cohort: PFS HR, 0.08; 95% CI, 0.01 to 0.5; $P = .008$; Figs 2A and 2B). NSCLC responders with depth of response equal or greater than the median response also had a significantly prolonged OS when compared with those responders with depth of response lower than the median response (OS HR, 0.22; 95% CI, 0.05 to 0.93; $P = .01$; Fig 2C). In MMRD, all responders were alive at time of follow-up, and therefore there were no differences between groups (Fig 2D).

The impact of baseline tumor burden on response was also assessed. There was no difference in the baseline tumor burden among RECIST-defined responders (CR/PR) versus nonresponders (SD or PD) among patients with NSCLC or MMRD ($P = .83$ and $P = .09$, respectively, Kruskal-Wallis test; Data Supplement). In the NSCLC cohort, there was also no correlation between tumor burden and percent best response (Spearman rho, 0.0003; $P = .9$). In the MMRD cohort, there was a weak positive correlation between responders (CR/PR) and tumor burden (Spearman rho, 0.37; $P = .008$). Furthermore, the patterns, timing, synchrony, and overall survival in responders in both cohorts were unaffected by high versus low tumor burden (Data Supplement).

Patterns of Progression

We next analyzed the patterns of progression in all patients (irrespective of their initial BOR) and the association with clinical outcomes. Patterns of progression were predefined to assess heterogeneity in the pattern of progression

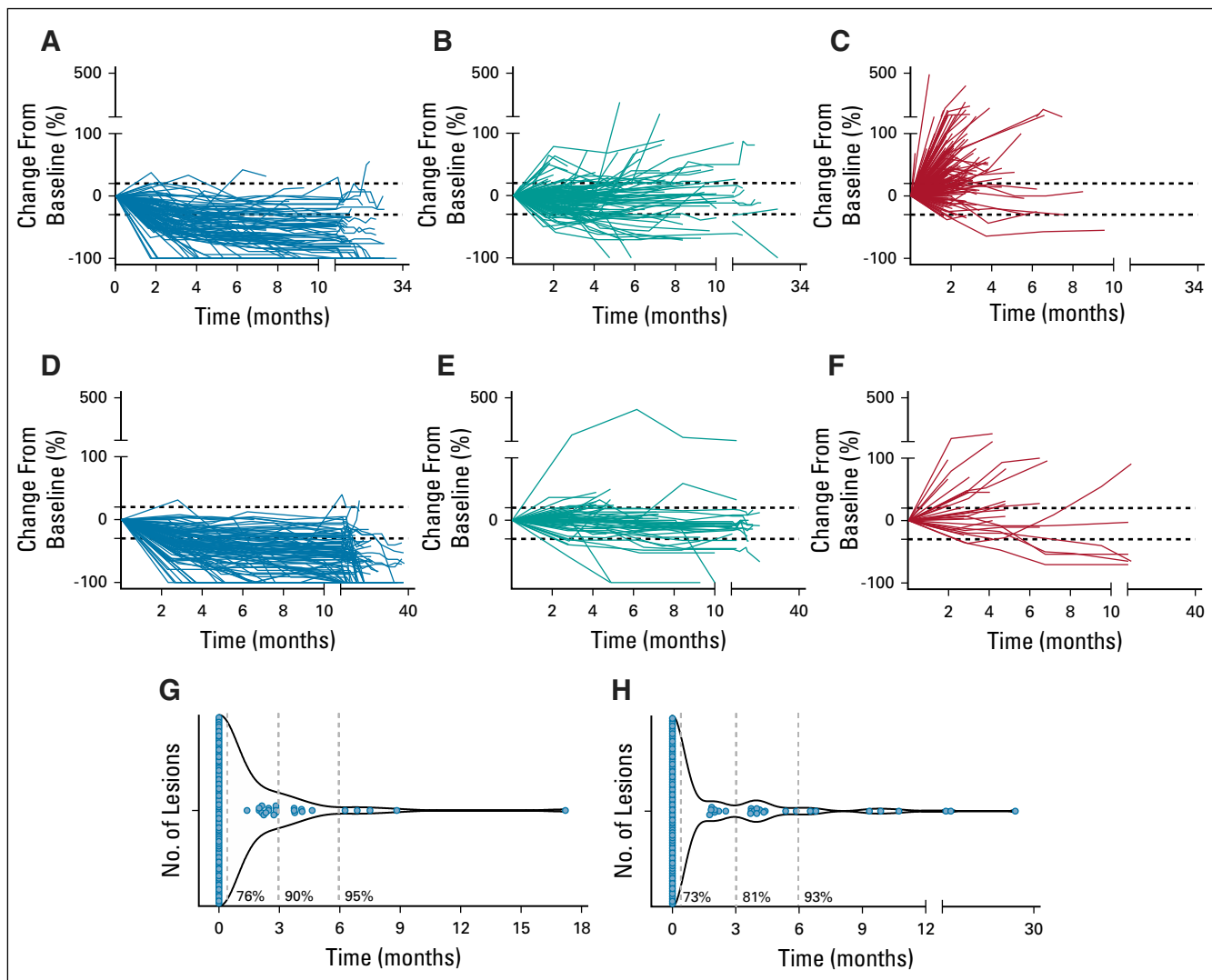


FIG 1. Patterns of response in patients treated with programmed cell death protein 1 (PD-1) blockade. (A-F) Spider plot of tumor burden changes of target lesions during the course of treatment with PD-1 blockade. Tumor burden was considered 0 at baseline, and longitudinal follow-up (x-axis) was captured in percentage of change (y-axis). (A) Target lesions (n = 107) from patients with non-small-cell lung cancer (NSCLC) who achieved complete response (CR) or partial response (PR) as their best overall response (BOR) per RECIST (n = 46). (B) Target lesions (n = 159) from patients with NSCLC and stable disease (SD; n = 74). (C) Target lesions (n = 235) from patients with NSCLC and progression of the disease (PD; n = 94). (D) Target lesions (n = 101) from patients with mismatch repair deficiency (MMRD) carcinoma with CR/PR (n = 46). (E) Target lesions (n = 57) from patients with MMRD carcinoma and SD (n = 20). (F) Target lesions (n = 29) from patients with MMRD carcinoma and PD (n = 12). (G-H) Violin plots of the timing of response of individual target lesions in patients that achieve CR or PR per RECIST. The first time at least one target lesion responded (> 30% response) was considered 0; then other target lesions were assessed for relative timing of initial response on the same or subsequent scans. (G) Time to achieve response in target lesions from patients who achieved CR or PR with NSCLC (n = 107). (H) Time to achieve response in target lesions from patients who achieved CR or PR with MMRD carcinomas (n = 101).

(Table 1). In patients with NSCLC, mixed pattern of progression was common (78 of 214 [36.4% of all patients treated, 45% of those who progressed at some point during treatment]); systemic progression pattern occurred in 94 patients (43.9% and 55%, respectively), and 42 (19.6%) did not experience progression (Fig 3A). Patients with mixed progression had improved PFS (per RECIST) and OS when compared with patients with systemic progression (PFS HR, 0.45; 95% CI, 0.32 to 0.61; $P < .0001$; OS HR, 0.58; 95% CI, 0.41 to 0.82; $P = .001$; Figs 3B and 3C).

In patients with MMRD carcinoma, most patients did not experience progression (61.5%), but among those who did experience progression, mixed progression pattern was again common (20.5% of all patients treated, 53% of those who experience progression), whereas systemic progression occurred in 17.9% and 47%, respectively (Fig 3D). Similar to the NSCLC cohort, patients with MMRD with mixed progression had improved PFS and OS when compared with patients who experienced systemic progression (PFS HR, 0.28; 95% CI, 0.11 to 0.72; $P = .0009$;

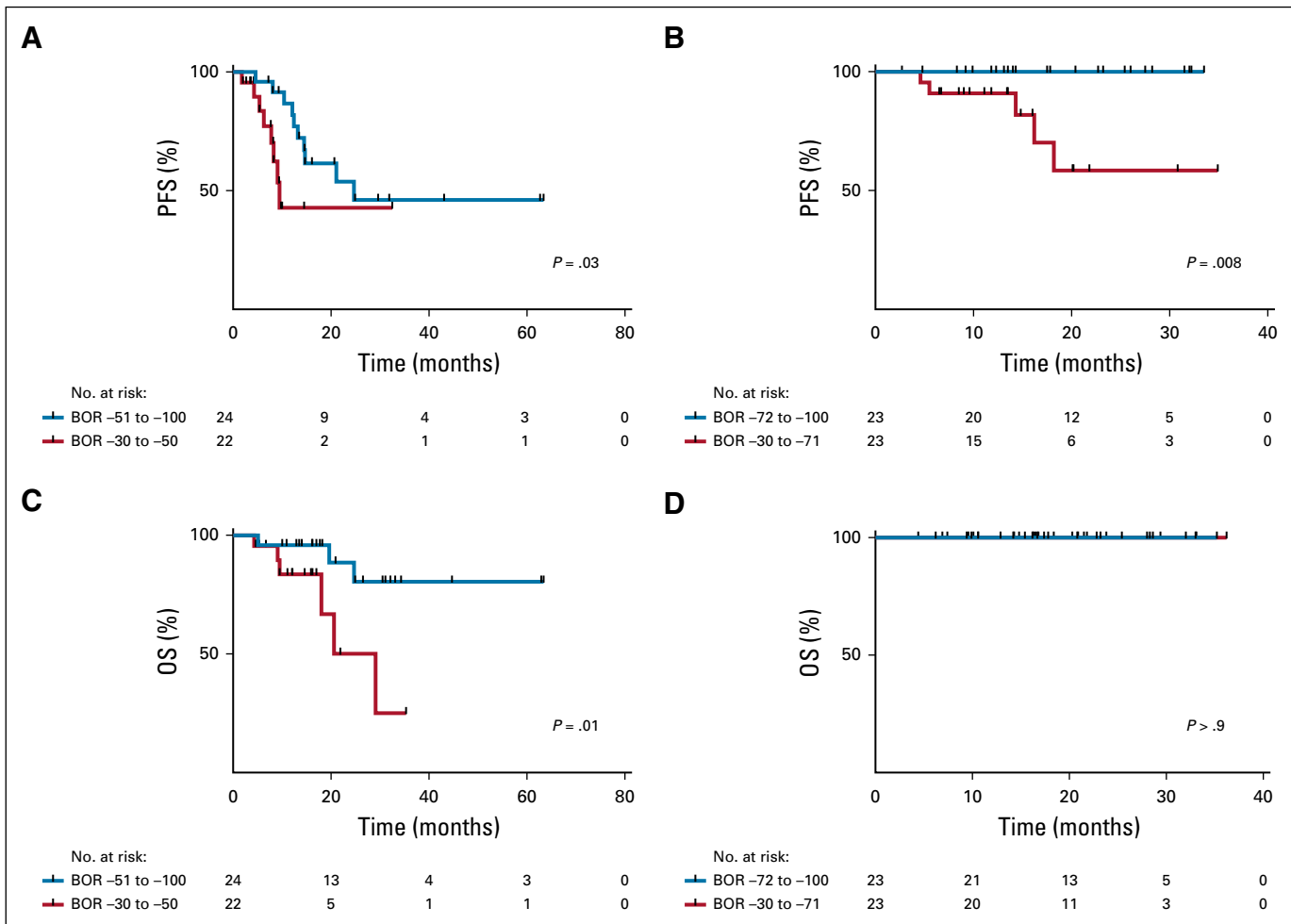


FIG 2. Depth of response and association with clinical outcomes. (A-D) Patients with complete response (CR) or partial response (PR) by RECIST in the non-small-cell lung cancer (NSCLC) cohort ($n = 46$) and the mismatch repair deficiency (MMRD) cohort ($n = 46$) were divided into two groups on the basis of the median best overall response (BOR; NSCLC cohort, $\leq v \geq -51\%$; and MMRD cohort, $\leq v \geq -72\%$, respectively). (A) Progression-free survival (PFS) in the NSCLC cohort, and (B) MMRD cohort comparing these two groups. (C) Overall survival (OS) in the NSCLC, and (D) MMRD cohort comparing these two groups.

OS HR, 0.40; 95% CI, 0.13 to 1.21; $P = .07$; Figs 3E and 3F).

Impact of Site of Metastasis on Response and Resistance

Last, we examined whether organ site of the metastasis was associated with response to PD-1 blockade. In the NSCLC cohort, individual metastases in lymph nodes tended to have the best responses; lung, adrenal, and pleura had intermediate responses, and bone and liver had the least responses (Fig 4A). Lymph node lesions had significantly better responses when compared with lung, pleural, and liver lesions ($P = .011$, $P = .002$, and $P = .003$, respectively). In the MMRD cohort, most lesions responded regardless of site of disease, and there were no significant differences among metastatic sites; numerically, lymph nodes and GI tract lesions were more responsive to PD-1 blockade, whereas responses were less substantial in liver metastases (Fig 4B). When considering the appearance of new lesions ($n = 125$ in NSCLC; $n = 37$ in MMRD), the liver, lung, and lymph nodes were the most

common sites of new metastases in both cohorts (Data Supplement).

DISCUSSION

We investigated whether an assessment of individual metastases dynamics in two independent cohorts could contribute to a better understanding of how response and progression to PD-1 blockade occurs. We found in patients with NSCLC and MMRD cancers, individual target lesion responses closely aligned with the best overall response of each patient. In particular, when response occurred, it tended to be uniform across metastases and occur synchronously. By contrast, progression tended to occur more heterogeneously across metastases, with differential survival seen in patients with mixed versus systemic progression.

We infer that the largely uniform dynamics of response within a given patient suggest that response to PD-1 blockade is a result of systemic, clonally directed antitumor

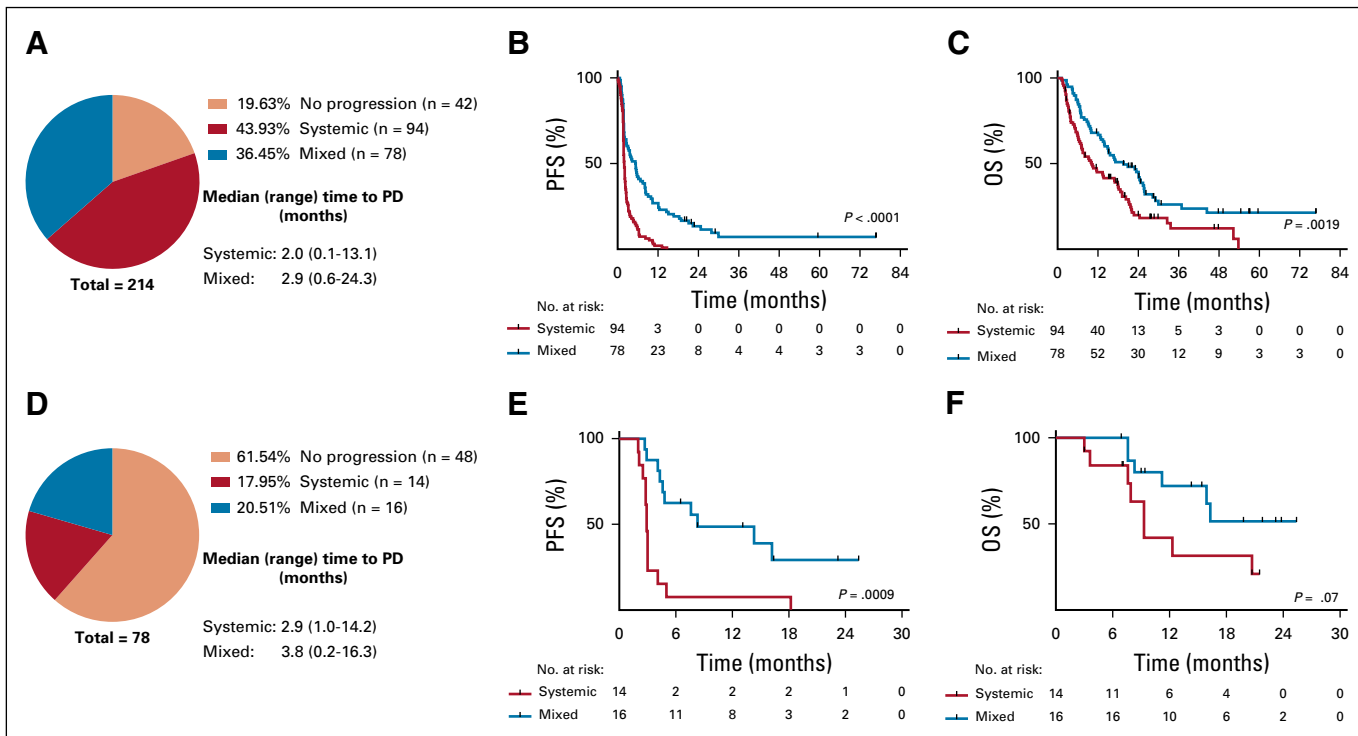


FIG 3. Patterns of progression of disease (PD) during programmed cell death protein 1 (PD-1) blockade. (A-C) Patterns of progression in patients with non-small-cell lung cancer (NSCLC) on the basis of prespecified criteria. (A) Proportion of patients who experienced systemic or mixed progression. Median time (months) and range of progression are described. (B) Kaplan-Meier plots of progression-free survival (PFS), and (C) overall survival (OS) in patients with systemic (n = 94) or mixed progression patterns (n = 78) in the NSCLC cohort. (D-F) Patterns of progression in patients with mismatch repair deficiency (MMRD) carcinoma on the basis of prespecified criteria. (D) Proportion of patients who experienced systemic or mixed progression. (E) Kaplan-Meier plots of PFS, and (F) OS in patients with systemic (n = 14) or mixed progression patterns (n = 16) in the MMRD cohort.

immunity that is recruited from the periphery to invade tumors (Fig 5). It seems more challenging to achieve such temporal-spatial uniformity solely through coordinated reinvigoration of local infiltrating lymphocytes. In addition, differential PD-L1 expression or TIL quantity among responders did not influence the patterns of response, which may have been expected if reinvigorated TILs were the dominant effector of response. This proposed model emphasizing the importance of recruited rather than reinvigorated immune responses aligns with emerging preclinical¹⁷ and clinical data.^{18,19} For example, a recent analysis using single-cell RNA sequencing of paired biopsies of several patients with melanoma treated with immune checkpoint blockade found that a cluster of T cells characterized by increased memory, early activation, and survival were enriched in responders and found distinctly in on-treatment, rather than pretreatment, samples.²⁰ In addition, another study using paired single-cell RNA and T-cell receptor sequencing to track individual T-cell clones in response to PD-1 blockade found that on-treatment expanded intratumoral T-cell clones were new rather than preexisting in pretreatment tissue.²¹ Overall, these single-cell data favor that T-cell clones involved in response to immune checkpoint blockade are largely recruited from outside of the tumor microenvironment. Other studies

have also incorporated analysis of peripheral immune cell populations²²⁻²⁴ as potential predictors of response to PD-1 blockade. We believe our report similarly encourages further pursuit of biomarkers of immunotherapy response by profiling the circulating immune landscape.

Of course, even if not the dominant source, intratumoral T cells still undoubtedly contribute to the process of response to PD-1 blockade. Tumor PD-L1 expression and gene expression signatures of intratumoral cytotoxic lymphocytes unequivocally associate with whether response occurs.^{16,25,26} In addition, data are emerging to refine the biology of responsive infiltrating T-cell populations. A recent study, for example, demonstrated that intratumoral exhausted CD8⁺ T cells are heterogeneous, and a subtype, termed progenitor exhausted CD8⁺ T cells, distinctly retain responsiveness to immune checkpoint blockade in a murine model of melanoma.²⁷ Future mechanistic studies are critical to dissect the contributions and interactions of tumor-specific T cells derived from both the peripheral and intratumoral compartments. Ultimately, these findings will have important therapeutic implications for rationally guiding synergistic combinations and guiding diagnostic and biomarker discovery efforts.

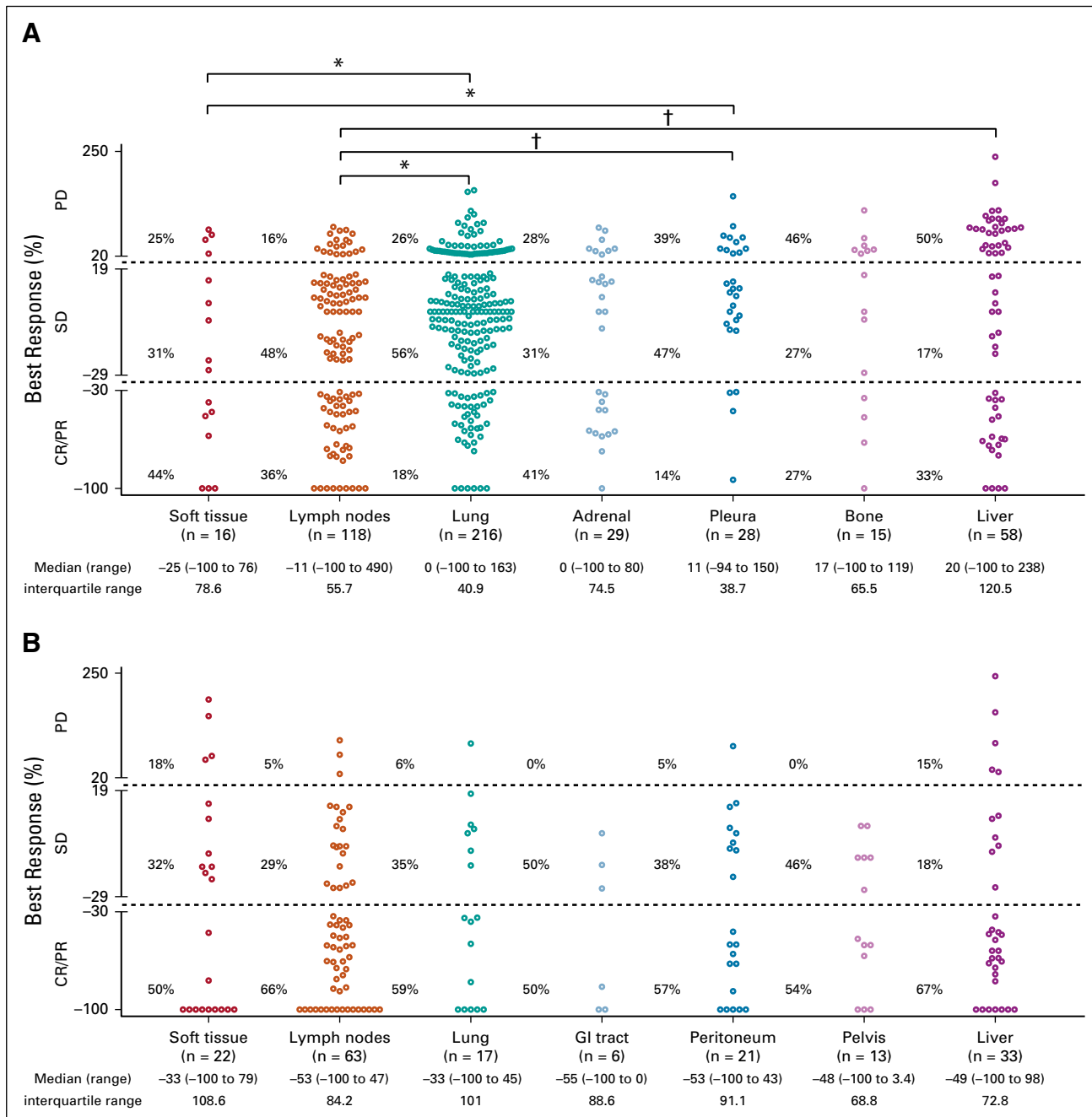


FIG 4. Site of disease and response to programmed cell death protein 1 (PD-1) blockade. Distribution of best response (%) of individual target lesions to PD-1 blockade grouped by organ of metastasis in patients with (A) non-small-cell lung cancer (NSCLC), and (B) mismatch repair deficiency (MMRD) carcinoma. Response by RECIST criteria, median and range of the percentage of response, and interquartile range of best responses are depicted. Comparisons among responses: * $P < .05$; † $P < .01$. CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease.

Beyond the originating site of effective antitumor immunity, the systemic pattern of clinical response also appears to align with the importance of clonal neoantigens as a primary target of response to PD-1 blockade.¹³ If response was achieved through targeting of subclonal antigens, we would have expected more substantial spatiotemporal heterogeneity of response. Potentially relatedly, we did not, in contrast to other studies,²⁸ identify a correlation

between tumor burden and response to PD-1 blockade. As intratumoral heterogeneity of neoantigens has been demonstrated to associate with response to PD-1 blockade,¹³ we conclude that tumor size is not proportional to heterogeneity. Therefore, tumor heterogeneity is not simply a byproduct of tumor growth but rather mediated by distinct characteristics of a tumor and selective immune pressure.

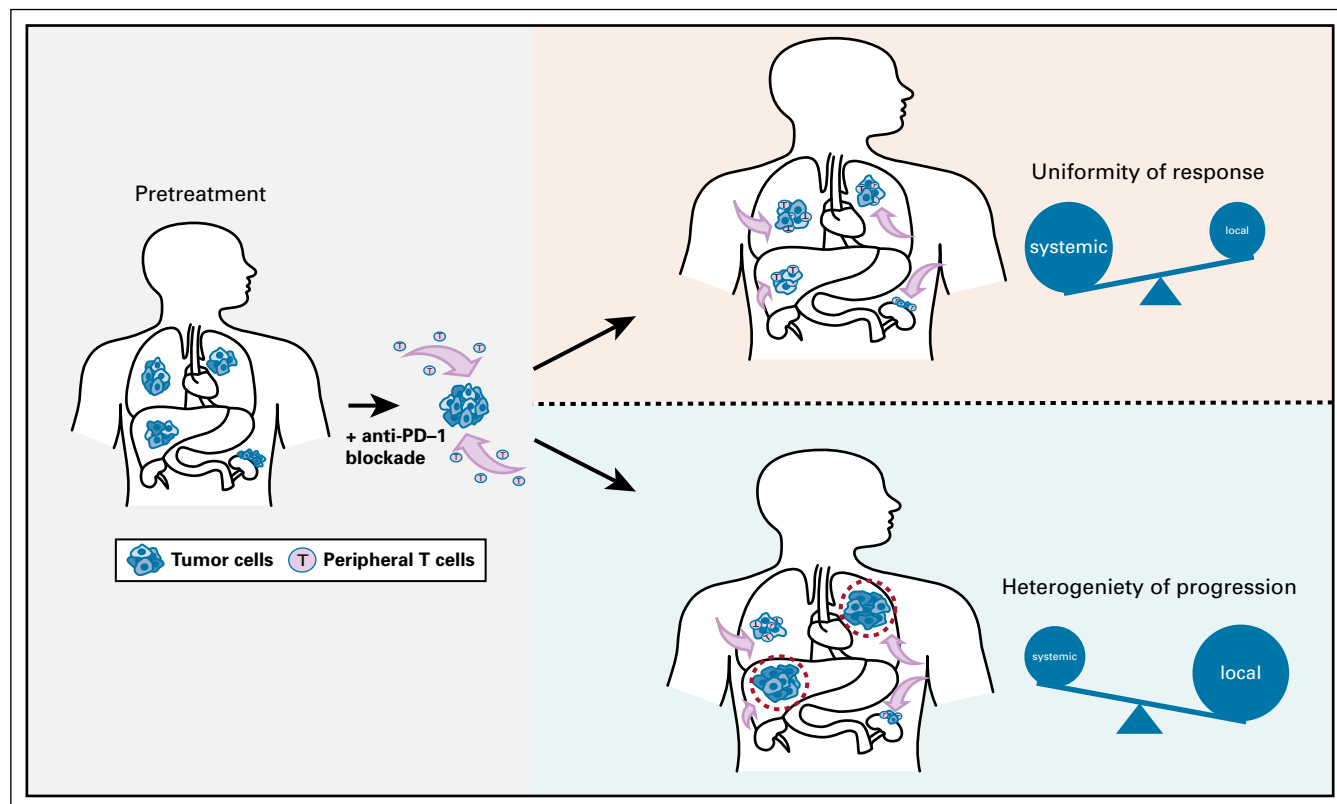


FIG 5. Hypothesized model of patterns of response and progression to programmed cell death protein 1 (PD-1) blockade. PD-1 blockade is proposed to achieve benefit largely from a systemic, clonal-directed antitumor immune response, which is recruited from the periphery to infiltrate tumors (lavender arrows), consistent with the uniform spatiotemporal pattern of response across metastases seen within a given patient (top right panel). In contrast, patterns of progression can be more mixed, which may reflect the heterogeneous and organ-specific properties of the local tumor microenvironment (red dashed circles) that can block or restrain the systemic immune response to PD-1 blockade, and produce mixed progression across metastases within a given patient (bottom right panel).

In contrast to the uniformity of response dynamics, progression is characterized by two different patterns—mixed and systemic—which are associated with distinct survival outcomes. We speculate that progression might be more affected by local intratumoral features and intertumor heterogeneity (Fig 5). The frequency of and survival difference in those patients with mixed progression suggest that selective immune pressure against individual metastasis can modulate the relative immunogenicity of a metastasis at a local level. Consistent with these results, other groups have demonstrated robust pharmacodynamic peripheral immune changes in response to PD-1 blockade even among nonresponding patients.^{23,29} Overall, our data suggest that progression may not be simply a lack of antitumor immunity but rather its own active process governed by a confluence of features that define the ultimate outcome.

Another local feature that may dictate the heterogeneous radiographic response is the site of metastasis. Lymph nodes were among the most responsive in both NSCLC and MMRD, which may be explained by the local populations of T cells and the role of tumor-draining lymph nodes in

priming and conditioning antigen-specific responses to PD-1 blockade.^{30,31} Similar to previous data,¹¹ liver metastases had among the poorest responses to PD-1 blockade and were the most common site of appearance of new lesions. The liver appears to have distinct immune tolerance affecting local^{32,33} and systemic³⁴⁻³⁶ immunity. These trends of differential response depending on the location of metastasis aligns conceptually with recent data demonstrating organ-specific “immunostats,” that is, varying thresholds for immune activation within each organ.³⁷ Additional work is needed to explain the mechanistic basis for how local organ sites affect the immunophenotype and immunogenicity of metastases.

Our study has important limitations. We performed a largely retrospective analysis using moderate-sized cohorts. Still, both independent cohorts demonstrated similar results in nearly each analysis, adding confidence to the conclusions. In addition, our predefined “systemic” and “mixed” progression criteria were applied for the first time in this study. Additional studies in larger cohorts are needed to corroborate and refine these concepts of patterns of progression. Interestingly, these categories differentiated phenotypes of

progression with significant differences in mortality, suggesting they have clinical relevance.

In conclusion, our study characterized the individual lesion-level dynamics of response and progression to PD-1 blockade in two independent tumor types. We found that individual metastases tend to be consistent and align with the overall response of each patient and, by contrast,

patterns of progression are more heterogeneous. Although our study lacks mechanistic evidence, it provides clinical evidence to support the inference of peripherally recruited, clonally directed tumor immunity as a key mechanism of action of immune checkpoint blockade and that progression may be more affected by intertumor heterogeneity and specific features of the local tumor microenvironment.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI <https://doi.org/10.1200/JCO.19.00709>.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Lesion-Level Response Dynamics to Programmed Cell Death Protein (PD-1) Blockade**

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