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Radiological dynamics and SITC-defined resistance types of advanced melanoma during anti-PD-1 monotherapy: an independent single-blind observational study on an international cohort

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ABSTRACT

Background Although the Society for Immunotherapy of Cancer (SITC) Immunotherapy Resistance Taskforce recently defined primary and secondary resistance to anti-programmed cell death protein 1 (anti-PD-1) therapy, there is lack of real-world data regarding differences in these resistance subtypes with respect to radiological dynamics and clinical manifestations.

Methods We performed single-blind re-evaluations of radiological images by independent radiologists on a retrospectively assembled cohort of patients with advanced melanoma (n=254, median follow-up 31 months) receiving anti-PD-1 monotherapy at Massachusetts General Hospital and Peking University Cancer Hospital. Radiological characteristics and timing at multiple crucial time points were analyzed and correlated with each other and with survival. Primary and secondary resistance was defined as per the SITC Immunotherapy Resistance Taskforce definitions.

Results The most significant target lesion measurement change took place within the first 3 months after anti-PD-1 initiation. Patients with stable disease with versus without tumor shrinkage at the initial evaluation exhibited distinct disease trajectory, as the rate of further upgrade to a partial or complete remission (CR/PR) was 44% and 0%, respectively. Eleven per cent of PR patients ultimately achieved a CR. In multivariate analyses, deeper response depth was independently associated with a more limited progression pattern, fewer involved organs, lower tumor burden, slower growth rate at disease progression (PD) (all p≤0.001), and longer post-progression survival (PPS) (bivariate analysis, p=0.005). Compared with primary resistance, secondary resistance was associated with less widespread PD pattern, lower tumor burden and slower tumor growth (all p≤0.001). Patients with secondary resistance were less likely to receive further systemic therapy (28% vs 57%, p<0.001) yet had significantly better PPS (HR 0.503, 95% CI 0.288 to 0.879, p=0.02).

Conclusions Radiological dynamics were variable, yet significantly correlated with survival outcomes. SITC-defined primary and secondary resistance are distinct clinical manifestations in patients with melanoma, suggesting the possibility of resistance-type-based therapeutic decision-making and clinical trial design, once further validated by future prospective studies.

INTRODUCTION

Anti-programmed cell death protein 1 (PD-1) monotherapy has greatly reshaped the systemic treatment landscape for advanced melanoma.[1 2] Emerging data demonstrate that radiological data taken at different static time points, for example, baseline, maximal response and disease progression (PD) were associated with survival outcomes of patients with melanoma under anti-PD-1 monotherapy.[3–7] Specifically, patients who achieved complete remission (CR) had the most durable survival benefit.[4 8 9] Therefore, in the absence of other biomarkers,[10] radiological response measurement is the most reliable and available data guiding therapeutic decision-making.

During routine clinical practice, clinicians seldom make decisions solely relying on instantaneous information but rather taking disease tempo into consideration.[11] At every imaging time point, the physician and patient try to determine, given the tumor response and kinetics information at hand, if the patient will benefit from ongoing anti-PD-1 therapy, and if so to what degree. Currently, there is no literature addressing the

radiographic evolution of patients who achieve a partial remission (PR) or stable disease (SD). Also lacking is a description of the kinetics of growth/regression across different crucial time points aside from previous reports specifically focusing on early-on-treatment tumor growth rate,[7] particularly in a small subgroup of patients, that is, hyperprogression.[12 13] Although consensus has been reached for clinical definitions of types of resistance to anti-PD-1 therapy largely based on accumulating translational research data, with the hope to facilitate future clinical trial design in the post anti-PD-1 scenario,[14] clinical data are limited in describing the difference between primary and secondary resistance from tumor characteristics at progression and evolving trajectory thereafter.

We hypothesize that a deep examination of radiological response dynamics, PD patterns and detailed clinical characterization of primary versus secondary resistance may provide further insight to address this clinically relevant issue and to facilitate therapeutic decision-making. To do so, we assembled a melanoma cohort from two independent melanoma centers in the USA and China and performed independent radiological re-evaluation by radiologists in a single-blind manner.

METHODS

Patients

All patients with advanced melanoma treated with anti-PD-1 monotherapy both within and outside a clinical trial setting with longitudinal radiological data available were identified at Massachusetts General Hospital (MGH) (n=164, anti-PD-1 monotherapy initiated between September 2009 and August 2018) and Peking University Cancer Hospital (PUCH) (n=90, between Mar 2016 and May 2018) with medical notes/clinical trial data extracted and reviewed. Radiological images were retrieved and re-evaluated in a single-blind manner using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST V.1.1) criteria by radiologists from MGH Tumor Imaging Metrics Core (TIMC) and PUCH Radiological Department, respectively. This study has been conducted in compliance with local Institutional Review Board policies.

Statistical analysis

Longitudinal dynamic changes in target lesion measurement were quantified as percent change from baseline. The date of anti-PD-1 monotherapy initiation was used as the index date for both progression-free survival (PFS) and overall survival (OS). Post-progression survival (PPS) was defined as the length of time from PD by RECIST V.1.1 to survival events. Nadir was defined as the time point when the minimum target lesion measurement was reached. Best response was defined according to RECIST V.1.1, taking both target and non-target lesions into account. Among patients who experienced PD, those who had PD or SD for <6 months as their best response were categorized into primary resistance; otherwise, PD was designated secondary.[14]

Categorical variables were summarized and described by frequency and percentage, while continuous variables by median and range. Correlation analysis was analyzed using Spearman correlation test. The two-way comparison of continuous variables was performed via Wilcoxon rank sum test (p values of multiple comparison adjusted using Bonferroni correction), multiple-way comparison via Kruskal-Willis test.

Survival data were analyzed using multivariate Cox proportional hazard regression model adjusting for different covariates in a context-dependent way. Dichotomous and continuous outcomes were analyzed using multivariate logistic and linear regression models, respectively, adjusting for different covariates in a context-dependent way.

All statistical tests were two-sided and p<0.05 was defined as of statistical significance. All analyses were performed using R V.3.6.0 (R packages *tidyverse*, *survival*, *survminer* and *ggplot2*).

Results

In total, 254 patients were identified with the median follow-up of 31 months. The median PFS and OS was 4 (95% CI 3 to 6) and 30 (95% CI 24 to 54) months, respectively. The dominant melanoma subtype of this cohort was cutaneous (n=150, 59%), followed by acral (n=37, 15%), melanoma of unknown primary (n=30, 12%), mucosal (n=25, 10%) and ocular melanomas (n=12, 5%). Ninety-six (38%) patients were stage M1c, and 41 (16%) stage M1d. Ninety-nine (39%) patients had prior systemic immunotherapy (including interleukin-2 and ipilimumab), 30 (12%) received prior targeted therapy (MAPK inhibitors). Detailed baseline demographic and clinical characteristics of the patients are listed in the online supplemental table 1.

Response dynamics

To explore the radiological response dynamics, we limited analysis to patients who had both baseline (with measurable target lesion(s)) and at least one radiological evaluation after anti-PD-1 monotherapy initiation (n=215) (figure 1), among whom 109 (51%) had two imaging time points available (including 96 (45%) who experienced disease progression at the initial 3-month evaluation), 106 (49%) had more than two scans to track further disease evolving trajectory.

Drastic tumor size change early during treatment

The greatest change in tumor size occurred within the first 3 months after anti-PD-1 monotherapy initiation (ie, at 3-month evaluation), and the discrepancy of tumor percent change from baseline was already significant between patients with CR (median −70%, range −100% to −23%), PR (median −37%, range −76% to −2%), and SD (median −1%, range −30% to 18%) as their best response (p<0.001) (figure 2A,B). By comparing the tumor percent change at 3 months with the maximal response depth (tumor % change at 3 months/maximal % regression)

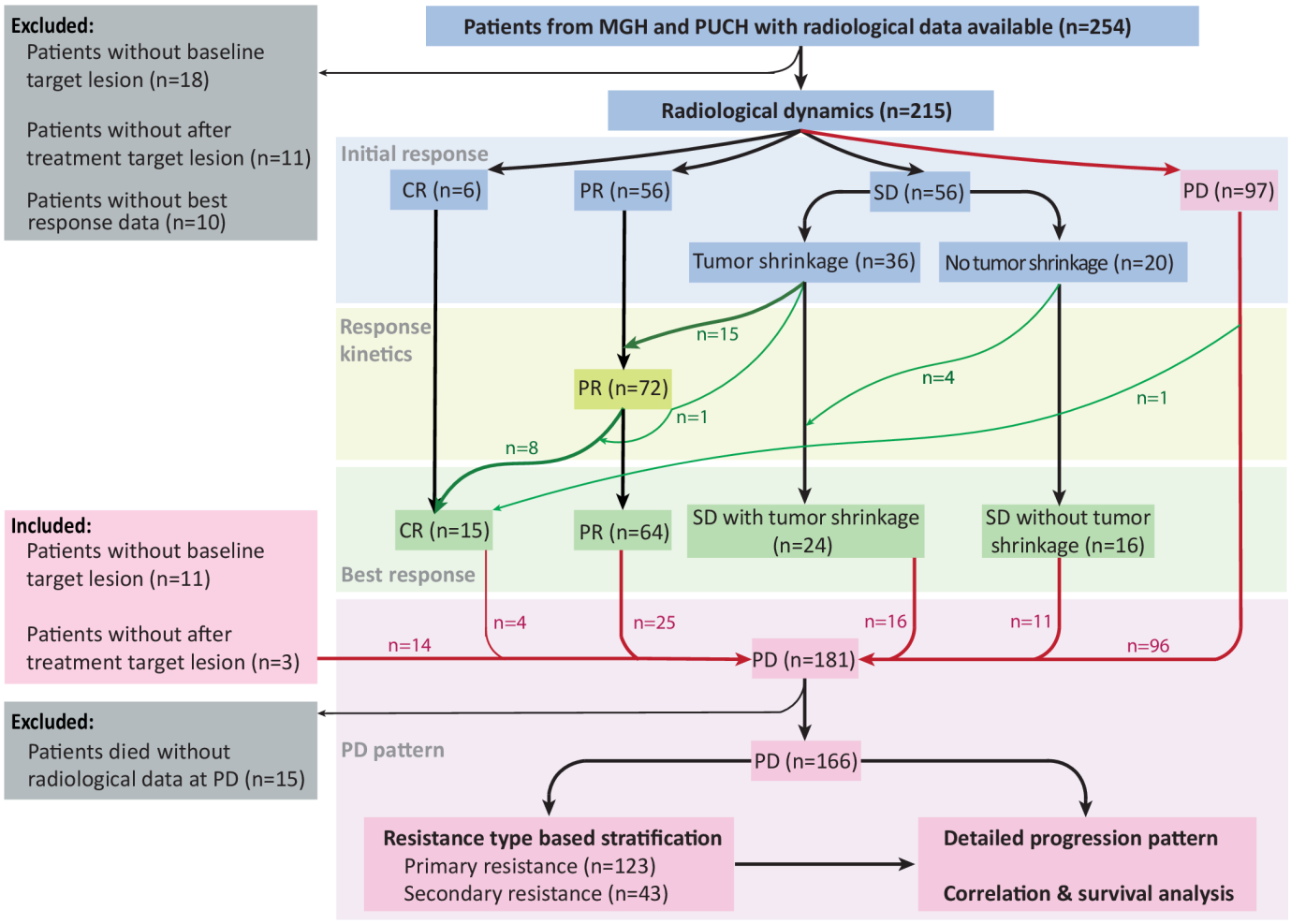

Figure 1 Patient populations included and general research schema of this study. CR, complete remission; PD, disease progression; PR, partial remission; SD, stable disease.

for CR and PR patients, median proportion was 70% and 71%, respectively.

Clinical outcomes once patients reached CR/PR/SD

For CR patients (n=15, figure 1), median duration of CR was 21 months (95% CI 20 to not reached). Once patients achieved PR (n=72, yellow box in figure 1), median duration of response was 46 months (95% CI 24 to not reached); 8 (11%) experienced further tumor regression and achieved CR (median time from initial PR to CR was 6 months (range 3 to 21); median duration of the eventual CR in this subset of patients was not reached (95% CI 21 to not reached)).

For patients who initially achieved SD (n=56), median duration of disease control from the time of first response assessment scan was 6 months (95% CI 4 to 24). One (2%) patient experienced further tumor shrinkage and upgraded into CR 22 months later, 15 (27%) upgraded into PR after the median time of 4 months (range 2 to 34). All patients who upgraded into CR/PR had initial tumor shrinkage (median tumor percent change −20%, range −30% to −2%) when graded as SD. Whereas in SD patients who had tumor growth (n=17) or no change in target lesion size (n=3) when first graded SD, the median duration of response was 4 months (95% CI 2 to not reached) and 3 months (95% CI 2 to not reached), respectively; and only 3 out of 17 (18%) and 1 out of 3 (33%) had further tumor shrinkage (compared with baseline), respectively; none reached PR/CR by the date of last follow-up (3/4 already experienced PD). The 6-month PFS rate was 64% (95% CI 52% to 79%) for the entire SD subgroup, 72% (95% CI 58% to 89%) for patients with tumor shrinkage, and 42% (95% CI 23% to 76%) for patients without.

For patients who reached PR or SD at the initial 3-month radiological evaluation (n=112), 32 (29%) had tumor shrinkage greater than 40%, 50 (45%) between 10% and 40%, and 30 (27%) no greater than 10%, with the median PFS of 49 (95% CI 25 to not reached), 38 (95% CI 17 to not reached), and 7 months (95% CI 6 to 21), respectively (p<0.001).

Best response

Median tumor size percent change at the time of maximal tumor reduction was −5% (range −100% to 241%), and 116 (54%) patients had tumor regression to some degree. CR rate was 7% (95% CI 4% to 11%), objective response

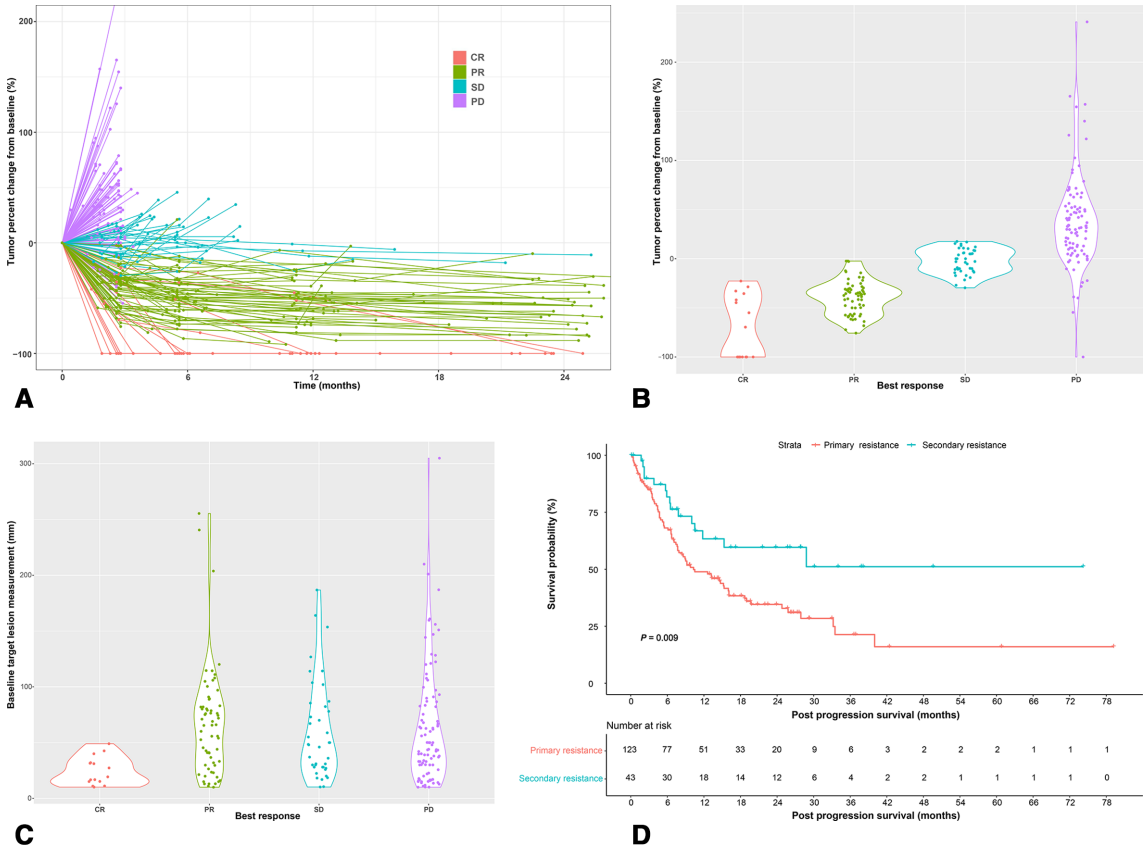

Figure 2 Radiological dynamics and progression patterns. (A) Spider plot for the whole cohort (n=215). Within the entire cohort, 15 (7.0%) patients achieved complete remission (CR); 64 (29.8%) and 40 (18.6%) patients had partial remission (PR) and stable disease (SD) as their best response, respectively; 96 (55.7%) patients experienced disease progression (PD) without clinical benefit. The most drastic change in tumor size occurred within the first 3 months after anti-programmed cell death protein 1 (anti-PD-1) monotherapy initiation. (B) Tumor percent change at 3 months after anti-PD-1 monotherapy initiation (n=215). The median tumor percent change at 3-month evaluation from baseline was −69.6% (range −100% to −22.7%) in patients with CR as their best response, −36.6% (range −75.7% to −2.4%) in patients with PR as the best response, and −1.4% (range −29.6% to 17.6%) in SD patients. (C) Baseline tumor measurement distribution between different best response groups (n=215). The median baseline target lesion size of patients who had CR/PR/SD/PD as their best response was 19.3 mm (range 10.1 to 49.0 mm), 65.5 mm (range 10.0 to 255.4 mm), 48.2 mm (range 10.2 to 186.8 mm) and 46.0 mm (range 10.0 to 305.0 mm), respectively. (D) Resistance type and post-progression survival (PPS) (n=166). PPS of patients with primary resistance was significantly shorter than those developed secondary resistance (p=0.009), with median PPS of 10.3 months (95% CI 7.7 to 16.1) and not reached (95% CI 11.8 to not reached), respectively.

rate (ORR) 37% (95% CI 30% to 44%), and disease control rate (DCR) 43% (95% CI 37% to 50%).

Maximal response depth

Although there was no correlation between baseline tumor burden and response depth (Spearman rho 0.02, p=0.79), a significant difference was observed between baseline target lesion size and best response categories (p=0.002), specifically between patients who had CR (median 19 mm, range 10–49 mm) and all others. No between-group difference was observed between PR (median 66 mm, range 10–255 mm), SD (median 48 mm, range 10–187 mm) and PD groups (median 46 mm, range 10–305 mm) (online supplemental table 2, figure 2C). The largest diameter of a single lesion that achieved a CR was 43 mm (lymph node). Notably, high baseline tumor burden (>50 mm) precluded the possibility of CR in this cohort, but not PR, and low disease burden did not guarantee tumor response (online supplemental figure 1).

The time to the maximal tumor reduction varied greatly, with median of 3 months (range 0.4–37 months). The median time to reach CR and PR was 6 months (range 2–25) and 2.7 months (range 2–37), respectively.

Both tumor percent change from baseline and time to nadir as continuous variables were significantly correlated with both PFS (HR 1.014 and 0.830; 95% CI 1.011 to 1.017 and 0.788 to 0.874; both p<0.001; respectively) and OS (HR 1.009 and 0.897; 95% CI 1.004 to 1.013 and 0.851 to 0.946; both p<0.001, respectively) in multivariate analysis adjusted for known prognostic factors (online supplemental table 3). Greater response depth did not necessarily preclude PD (online supplemental figure 2).

Table 1 Progression pattern overview (n=166)

Progression pattern	
Categorical metrics	**Number (%)**
Resistance type	
Primary resistance	123 (74)
Secondary resistance	43 (26)
Number of involved organ(s)	
1	80 (48)
2	50 (30)
>=3	36 (22)
General progression pattern	
Enlargement only	41 (25)
New lesion(s) only	42 (25)
Both	83 (50)
LDH at PD	
Normal	72 (43)
Elevated	79 (48)
NA	15 (9)
Continuous metrics	Median (range)
Target lesion size at PD (mm)*	49.0 (0 to 415.0)
Tumor enlargement dynamics†	
Percent change from last evaluation (%)	26.2 (–100.0 to 241.0)
Percent change from last evaluation (%) per month	10.0 (–28.6 to 109.1)
LDH elevation dynamics‡	
Percent change from last evaluation (%)	6.2 (–33.7 to 354.6)
Percent change from last evaluation (%) per month	7.9 (–49.7 to 409.2)

*Thirteen patients with no available target lesion size data at PD.
†Eighteen patients with no available tumor enlargement dynamics data.
‡Twenty-four patients without LDH dynamics data at PD.
LDH, lactate dehydrogenase; NA, not available; PD, disease progression.

Progression pattern

In total, 181 patients experienced PD, among whom 15 died without radiological data and thus were excluded from the PD pattern analysis (figure 1). Time of PD from anti-PD-1 initiation varied widely (median 3 months, range 0.3–49). In general, 86 (52%) patients had PD in more than one organ/system with enlarging or newly emerging lesions, 83 (50%) had widespread PD pattern (defined as with both enlargement of existing lesions and emergence of new lesions), and 79 (48%) had elevated LDH at PD. Median target lesion size was 49 mm, median target lesion size enlargement and LDH increase per month from the last pre-PD evaluation was 10% and 8%, respectively (table 1).

We further explored correlates of the PD patterns (online supplemental tables 4–9). Multivariate analyses incorporating all covariates with definitive or marginal statistical significance in bivariate analyses (adjusted for baseline target lesion size), after controlling for baseline target lesion size, demonstrated that response depth was the strongest correlate with significant less widespread PD pattern, fewer involved organs, smaller target lesion size, as well as slower target lesion enlargement (online supplemental tables 5 and 7–9).

Primary versus secondary resistance

One hundred and twenty-three patients (74%) developed primary and 43 (26%) secondary resistance (table 1). Compared with secondary resistance, primary resistance was associated with higher proportion of broad progression (57% vs 30%, p<0.001), more involved organs (28% vs 2% with >=3 organs involved, p<0.001), more frequent LDH elevation (54% vs 28%, p=0.005), as well as more rapid tumor growth and LDH elevation (table 2). However, no baseline characteristics were significantly correlated with the resistance type (online supplemental table 10).

Post-progression survival (PPS) and its correlates

Ninety-two patients (55%) were deceased at the time of this analysis. Median PPS was 15 months (95% CI 9 to 20). In total, 58 patients with PD received regional treatment (either radiotherapy or surgery), 82 switched to other systemic treatments, including 19 with ipilimumab±nivolumab, 20 BRAFi/MEKi combo, 25 chemotherapy±anti-angiogenesis agent(s), and 18 others (online supplemental table 11). BRAF V600 mutant patients treated with MAPKi (including some who had received it prior to anti-PD-1 therapy) had a median PFS of 5 months (95% CI 4 to 12) and an ORR of 50% (95% CI 26% to 74%), patients treated with anti-CTLA-4 monotherapy had a median PFS of 3 months (95% CI 2 to 13) and an ORR of 21% (95% CI 5% to 51%), whereas those treated with conventional chemotherapy typically had abysmal clinical outcomes with no responses noted and a median PFS of 1 month (95% CI 1 to 4) (online supplemental table 12).

All response parameters, PD patterns, and resistance type demonstrated strong associations with PPS (table 3). For response pattern, tumor percent change and longer PFS were significantly associated with longer PPS (HR 1.005 and 0.959, 95% CI 1.002 to 1.009 and 0.921 to 0.998, p=0.005 and 0.04, respectively). Patients with widespread PD pattern, more involved organs, larger total target lesion measurement, more rapid tumor growth, LDH elevation, and more rapid LDH increase at PD were all significantly associated with shorter PPS. Compared with primary resistance, patients with secondary resistance had borderline higher likelihood to receive local/regional treatment after anti-PD-1 failure (47% vs 31%, p=0.08), significantly lower likelihood to switch to other systemic treatments (28% vs 57%, p<0.001) (online supplemental

Table 2 Correlation between primary versus secondary resistance and progression pattern (n=166)

Progression pattern	Resistance type		
	Primary resistance (n=123)	Secondary resistance (n=43)	P value
General progression pattern			<0.001
Enlargement only	34 (28)	7 (16)	
New lesion(s) only	19 (15)	23 (54)	
Both	70 (57)	13 (30)	
No of involved organ(s)			<0.001
1	49 (40)	31 (72)	
2	39 (32)	11 (26)	
>=3	35 (28)	1 (2)	
LDH at PD			0.005
Normal	48 (39)	24 (56)	
Elevated	67 (54)	12 (28)	
NA	8 (7)	7 (16)	
Target lesion size at PD (mm)*	64.0 (0 to 415.0)	29.2 (0 to 229.0)	<0.001
Tumor enlargement dynamics†			
Percent change from last evaluation (%)	31.3 (–100.0 to 241.0)	3.3 (–71.4 to 120.0)	0.001
Percent change from last evaluation (%) per month	13.2 (–28.6 to 82.2)	0.8 (–14.6 to 109.1)	0.001
LDH elevation dynamics‡			
Percent change from last evaluation (%)	12.3 (–33.7 to 354.6)	2.1 (–25.4 to 42.6)	0.003
Percent change from last evaluation (%) per month	13.3 (–49.7 to 409.2)	2.4 (–36.3 to 41.7)	0.003

*Thirteen patients with no available target lesion size data at PD.
†18Eighteen patients with no available tumor enlargement dynamics data.
‡Twenty-four patients without LDH dynamics data at PD.
LDH, lactate dehydrogenase; NA, not available; PD, disease progression.

table 11), and had significantly longer PPS (figure 2D) (HR 0.503, 95% CI 0.288 to 0.879, p=0.02, table 3).

However, no significant correlation was found between baseline characteristics and PPS (online supplemental table 13), although BRAF mutation seemed to be a protective factor with marginal significance towards longer PPS (HR 0.630, 95% CI 0.368 to 1.080, p=0.09) with targeted therapy as a second-line regimen after PD from anti-PD-1 monotherapy for these subgroup of patients.

DISCUSSION

Frontline anti-PD-1 monotherapy is a standard therapy associated with significant clinical benefit. Imaging data at different time points have demonstrated constant correlations with survival outcomes.[3–6] However, as part of routine clinical practice, clinicians typically consider disease kinetics (fast vs slow growth/regression) to be one essential piece of information during therapeutic decision-making. At present, there are limited available data addressing the issue of tumor kinetics based on pretreatment and on-treatment radiographic imaging, change in tumor volume, and outcome for melanoma patients treated with anti-PD-1 monotherapy. Additionally, the PD pattern has not been well described, particularly in the setting of primary/refractory versus secondary/acquired resistance, and based on maximal tumor regression.[14] This report represents the first international effort incorporating melanoma patients with detailed longitudinal radiological data, specifically focusing on disease kinetics at crucial time points during anti-PD-1 monotherapy, and demonstrates for the first time that time course and disease kinetics are associated with survival outcomes.

An important consideration for treatment selection prior to the initiation of frontline therapy is the kinetics of response of any potential therapy. We demonstrate here that most tumor volume change takes place within the first 3 months after initiation of anti-PD-1 monotherapy, comprising around 70% of total tumor reduction in PR/CR patients. This is in agreement with a study showing that tumor size change at month 3 is distinctively predictive of survival.[7] Another important issue is how well the timing and degree of tumor regression are associated with long-term benefit. Here we show for the first time the clinical outcomes of patients based on when they achieve CR/PR/SD. Interestingly, CR patients who

Table 3 Response and PD patterns and their correlations with PPS (bivariate analysis, n=166)

	PPS (months)*	
Bivariate analysis	**HR (95% CI)**	**P value**
Response pattern		
Tumor percent change (%)†	1.005 (1.002 to 1.009)	0.005
Time to nadir (months)†	0.959 (0.904 to 1.018)	0.17
PFS (months)†	0.959 (0.921 to 0.998)	0.04
PD pattern		
General PD pattern‡	2.261 (1.469 to 3.480)	<0.001
Number of involved organ†	1.427 (1.187 to 1.715)	<0.001
Target lesion measurement†	1.010 (1.004 to 1.016)	<0.001
Enlargement dynamics†	1.017 (1.005 to 1.029)	0.006
LDH elevation at PD§	2.735 (1.695 to 4.413)	<0.001
LDH elevation dynamics¶	1.007 (1.004 to 1.009)	<0.001
Resistance type**	0.503 (0.288 to 0.879)	0.02

*Cox proportional hazards regression model, adjusted for baseline target lesion size.
†As continuous variables.
‡Dichotomous variable, defined as both new lesion(s) and enlargement vs either new lesion(s) or enlargement only, with the latter as the reference group.
§Dichotomous variable (normal vs elevated, normal as the reference).
¶Continuous variable, compared with last pre-PD LDH level, unit as percent change per month.
**Dichotomous variable, primary resistance as the reference group.
LDH, lactate dehydrogenase; PD, disease progression; PFS, progression-free survival; PPS, post-progression survival .

experienced PR first, compared with those who achieved CR at the first evaluation, seemed to have a numerically longer duration of response. Given the small number of patients, it is possible that this difference may be an artifact. However, there are data showing that CR patients treated for more than 6 months had a lower relapse risk compared with those treated for a shorter duration.[8] Presuming those treated for less than 6 months were more likely to have a CR on first evaluation, it is possible that these two sets of data are corroborating. Notably, our study demonstrated that the SD category is heterogeneous with distinct evolving patterns between patients with versus without tumor shrinkage at the initial radiological evaluation, for example, no patients without tumor shrinkage upgraded into CR/PR, whereas 44% of patients with tumor shrinkage did.

While tumor size variation has been well appreciated to be associated with outcomes when evaluated at baseline and nadir,[3 5] PD pattern has generally and arbitrarily categorized as oligo and systemic.[15 16] We depicted PD patterns with more granularity by viewing them as a continuous heterogeneous spectrum, characterized by different types of progression (enlargement vs new lesion vs both), numbers of involved organs, target lesion size, and tumor growth rate. By doing this, we revealed a high degree of heterogeneity. As opposed to a stochastic appearance of tumor size at different static time points, we observed that response depth, timing, PD pattern, and survival outcomes were highly correlated after adjustment for baseline tumor burden. In terms of target lesion size, the correlation between baseline measurement and response depth is complicated. Consistent with a previous finding,[16] we did not observe a simple linear correlation between baseline tumor measurements and response depth. However, significantly lower tumor burden was observed in patients with CR compared with all others. This may reflect the fact that smaller tumor burden at baseline simply requires less tumor size reduction to reach CR. Additionally, we speculate that some long-lasting partial responses may indeed be complete pathologically with residual scarring/fibrosis, a phenomenon that has been observed in the neoadjuvant setting,[17] but as these lesions are rarely biopsied, we are left, by convention, to calling these responses partial. However, while larger baseline tumor size precluded CR, smaller tumor size did not guarantee response. Additionally, no discrepancy is observed between PR, SD, and PD patients, consistent with an observation in ipilimumab/nivolumab-treated melanoma cohort.[18] Noticeably, in different multivariate analysis using different metrics of PD pattern, response depth stayed constantly the most significantly correlated factor among different covariates, in concert with the previous observation that PD after objective response was associated with excellent clinical outcomes.[15]

Finally, we evaluated the resistance subtype (primary vs secondary) based on a previously reported resistance definition that emerged from the SITC Immunotherapy Resistance Taskforce.[14] Of note, patients included in this study are heterogeneous, 39% had prior immunotherapy, 12% had prior targeted therapy; 16% had brain metastasis;

and 29% were with acral, mucosal, or ocular melanomas which are known to be less responsive to immunotherapy. Therefore, the proportion of primary resistance observed in this cohort may be higher than in the general melanoma population with anti-PD-1 monotherapy as the first-line treatment. With those caveats, we demonstrate that primary resistance is correlated with more rapid progression tempo, that is, broader PD pattern, more involved organs, higher LDH level, and larger target lesion measurement at progression. Although patients with primary resistance were treated more intensely (exemplified by lower proportion of local/regional therapy and higher rate of systemic treatment), they had poorer PPS compared with those with secondary resistance. This may relate to the fact that patients who developed secondary resistance were more likely to have oligoprogression, thus making those patients more amenable to local/regional treatment. This suggests that anti-PD-1 therapy in these patients changed the trajectory of these patients' disease, which is obvious since these patients had a response or prolonged SD prior to progression, and that the biology of secondary resistance is distinct from primary resistance. As such, the distinct clinical manifestations of these two resistance types implicate that specific therapeutic strategies and trial enrollment recommendations should be applied accordingly.

The analysis of different systemic therapy in the post-PD-1 setting is instructive. Although no direct comparison between first line and post-PD-1 setting could be made for MAPKis and CTLA-4 monotherapy, they both demonstrated reasonable antitumor effect, similar to prior reports.[6 19–21] We also report that chemotherapy in the post-PD-1 scenario at these institutions was futile and is associated with similar lack of benefit as seen prior to the dawn of immunotherapy and targeted therapy.[22]

We acknowledge that the major limitation of this study resides in its retrospective nature. Although we performed independent radiological re-evaluations strictly following RECIST V.1.1 in a single-blind manner, potential selection and measurement biases cannot be entirely eliminated. Thus, further validation is required.

In summary, by describing response and progression dynamics in a large cohort of patients with advanced melanoma treated at two institutions, we provide a rationale for radiological parameter-based therapeutic decision-making by showing the drastic tumor volume change shortly after anti-PD-1 initiation and the strong correlation between response dynamics, progression patterns, and survival. We present for the first time the progression patterns of both primary and secondary resistance, which may provide data from which decisions regarding patient eligibility for clinical trials in the post-PD-1 scenario can be based.

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Competing interests Dr XB receives a merit award supported by BMS. Dr JC serves as a consultant for BMS and Sanofi-Genzyme. KR serves on advisory boards for Merck & BMS. Dr KF serves on the Board of Directors of Loxo Oncology, Clovis Oncology, Strata Oncology and Vivid Biosciences; on the Corporate Advisory Boards of X4 Pharmaceuticals and PIC Therapeutics; on the scientific advisory boards of Sanofi, Amgen, Asana, Adaptimmune, Fount, Aeglea, Array BioPharma, Shattuck Labs, Arch Oncology, Tolero, Apricity, Oncoceutics, Fog Pharma, Neon Therapeutics and Tvardi; and as a consultant to Novartis, Genentech, BMS, Merck, Takeda, Verastem, Checkmate, Boston Biomedical, Pierre Fabre, Cell Medica and Debiopharm. Dr RS serves as consultant for Amgen, Asana Biosciences, BMS, Merck, Novartis, Array BioPharma, Compugen, and Replimune; he receives research support from Amgen and Merck. Dr JG serves as consultant or is on advisory boards for MSD, Roche, Pfizer, Bayer, Novartis, Simcere Pharmaceutical Group, Shanghai Junshi Biosciences, and Oriengene. Dr GB has a sponsored research agreement with Takeda Oncology, Olink Proteomics, and Palleon Pharmaceuticals; serves as a consultant for NW Biotherapeutics, served as a speaker for Novartis and Takeda Oncology; and served on a scientific advisory board and steering committee for Nektar Therapeutics. All remaining authors have declared no conflicts of interest.

Patient consent for publication All authors have made a substantial contribution to the material submitted for publication, and have read and approved the manuscript.

Ethics approval This study has been conducted in compliance with local Institutional Review Board policies.

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