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Original Article

Predominance of hyperprogression in mucosal melanoma during anti-PD-1 monotherapy treatment

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Abstract

Background: A minority subset of immunotherapy patients manifests hyperprogressive disease (HPD), with the disparity in melanoma subtypes yet to be reported. This study aimed to delineate the proportion and prognosis of HPD in patients receiving anti-PD-1 monotherapy and to identify patient with HPD clinical characteristics across melanoma subtypes to inform clinical decision making.

Methods: Utilizing 4 established HPD definitions, the incidence of HPD in patients with advanced melanoma on anti-PD-1 monotherapy was determined. The incidence rates and prognostic abilities of various HPD definitions were compared to elect the most effective one. This facilitated a comparative analysis of subtypes and clinical features between patients with HPD and traditional progression.

Results: A total of 262 patients with advanced melanoma treated with anti-PD-1 monotherapy from 5 prospectively registered clinical trials were included in the study. The objective response rate (ORR) and disease control rate (DCR) was 21% and 58%, respectively, with 42% showcasing progression disease. The HPD incidences by 4 definitions were 13.2%, 16.8%, 10.8%, and 28.2%. All definitions effectively segregated HPD patients, with significantly poorer outcome than other progressive patients. The Delta TGR > 100 definition was the most indicative of a reduced overall survival, corroborated by the highest hazard ratio and statistical significance. The number of metastatic organs over 2 is a risk factor for HPD (OR = 4.18, $P = .0103$). Mucosal melanoma was the HPD prevalent subtype (OR = 3.13, $P = .0489$) in multivariable analysis, which is also indicated by RECIST criteria ($P = .005$).

Conclusion: A delta TGR exceeding 100 best identified HPD patients in the advanced melanoma population treated with anti-PD-1 monotherapy. Hyperprogression was notably prevalent in mucosal melanoma patients with multiple metastatic organs. Caution against HPD is warranted when applying anti-PD-1 monotherapy in mucosal subtype.

Key words: melanoma; immunotherapy; hyperprogression.

Implications for practice

This study included 262 patients with advanced melanoma treated with anti-PD-1 monotherapy. The incidence of hyperprogression (HPD) defined by 4 different methods was 13.2%, 16.8%, 10.8%, and 28.2%, respectively. The delt TGR > 100 definition performed best, identifying patients with HPD with poorer survival, with a median overall survival (OS) of only 6.3 months compared to 10.1 months in the non-HPD progressive group. The study shows that mucosal melanoma patients had the highest incidence of HPD. Caution against HPD is warranted when applying anti-PD-1 monotherapy in mucosal melanoma patients. Combination therapy may reduce the incidence of HPD.

Introduction

The therapeutic panorama for metastatic melanoma has been revolutionized with the advent of novel agents. Immunotherapy, in particular, has substantially improved response rates and outcomes compared to conventional therapies. For unresectable or distantly metastatic disease, the recommended first-line immunotherapy treatments include anti-PD-1 monotherapy, a nivolumab/ipilimumab or nivolumab/relatlimab combination.[1-3] While combination therapy may improve progression-free survival (PFS), it also carries a heightened risk of immune-mediated adverse events and economic impacts. A significant number of patients in a

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metastatic setting opt for anti-PD-1 monotherapy for various reasons.

Immunotherapy response patterns diverge from those of conventional therapies, including phenomena such as pseudoprogression and hyperprogression.[4] Hyperprogression denotes a paradoxical rapid progression after initiation of immunotherapy, severely impairing patient survival.[5] Patients with hyperprogression have significantly worse prognosis than those with conventional progression.[6] In some clinical trials, early mortality rates among patients on immunotherapy surpassed those on chemotherapy, hypothesized to be linked to early hyperprogression post immunotherapy initiation.[7,8] Studies have reported the incidence of hyperprogression in various tumor types, ranging from 9% (melanoma)[9] to 29% (head and neck squamous cell carcinoma).[10] A consensus on HPD definition remains elusive, with most metrics involving tumor growth rate (TGR)[9] or tumor growth kinetics (TGK).[11] Calculating tumor growth rates needs at least 3 consecutive imaging assessments: pre-baseline, baseline, and first post-treatment evaluation, which often presents practical challenges in clinical application, particularly in cases without pre-baseline scans. To address this, some researchers have proposed for the adoption of an adapted RECIST criteria to define hyperprogression, which has demonstrated commendable predictive efficacy in some cohorts.[12]

Anti-PD-1 monotherapy's efficacy appears less favorable in Chinese melanoma patients compared to Caucasians. Acral and mucosal melanoma, which are predominant in China, respond inadequately to immunotherapy (ORR 0%-13%).[13,14] Moreover, due to ethnic and genetic profile variations, immunotherapy yields lower response rates in Chinese cutaneous melanoma patients than in Caucasians (20% vs 54%, $P < .001$).[15] This discrepancy underscores an urgent need to examine the proportion of Chinese melanoma patients experiencing hyperprogression, particularly across different subtypes.

Recognizing the limited efficacy of immunotherapy in Chinese melanoma patients, our study seeks to assess the incidence and clinical outcomes of hyperprogression, to mitigate potential detriments to patient survival from immunotherapy monotherapy. We also aim to validate various hyperprogression definitions from the literature and evaluate their predictive values and associations with clinical subtypes and characteristics.

Methods

This study included patients with melanoma undergoing anti-PD-1 monotherapy at Peking University Cancer Hospital between April 2016 and September 2017, sourced from 5 clinical trials: KEYNOTE-151[14] (pembrolizumab), 2 toripalimab trials (CT1 and CT4[13,16]), tisleilizumab,[17] and camrelizumab.[18] We prospectively collected patient data, including clinical features, imaging, and outcomes. This study was approved by the Ethics Committee of Peking University and written informed consent was obtained from each patient.

Patients were subject to tumor assessments based on clinical trials protocols, which stipulated chest/abdomen/pelvis CT scans within 4 weeks prior to anti-PD-1 therapy and every 8-9 weeks post-treatment commencement. Exclusion criteria applied to patients missing these scheduled assessments. Tumor responses were evaluated per RECIST 1.1 criteria, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The protocols permitted continued immunotherapy beyond initial PD if deemed potentially beneficial by the investigators. Two radiologists independently reviewed the imaging assessments for HPD definitions, and any discrepancies were resolved through consensus.

Hyperprogressive metrics used included tumor growth rate (TGR) or tumor growth kinetics (TGK), defined as the percentage increase in tumor volume within 1 month. TGR was calculated via TGR = 100 × [exp (TG) – 1], with TG as 3× log (S_t/S_0), and S representing the sum of largest tumor diameters.[19] TGK was the monthly change in S, calculated as $(S_t - S_0)/(t - t_0)$.[11] Central to HPD identification is its prognostic distinction from non-HPD.

Four HPD definitions were scrutinized, denoted for ease of reference as A, B, C, and D in this context. Definition A, proposed by Champiat et al,[9] identified HPD by a doubling of the monthly tumor volume increase post-immunotherapy relative to pre-treatment levels (TGRratio > 2). Definition B assesses HPD through a TGKratio exceeding 2, coupled with a time to treatment failure (TTF) of less than 2 months and an increase in the tumor burden exceeding 50% as per RECIST criteria.[11] Definition C characterizes HPD as an increase in the absolute value of TGR by 100 (Delta TGR > 100).[20] The computation of TGR and TGK necessitates a series of 3 consecutive imaging assessments: pre-baseline (conducted within 3 weeks prior to initiating immunotherapy), baseline (immediately before starting immunotherapy), and the first evaluation post-treatment. Since some first-line patients lack pre-baseline scans, an adapted RECIST criteria (definition D) were adopted to include such cases, identifying HPD by a RECIST progression over 40% or over 20% with new lesions in over 2 different organs.[12] For comprehensive HPD assessment, all new lesions were included in the total tumor burden analysis.[21]

Statistical evaluations involved Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for non-normal distributions. A multivariate logistic regression model was constructed to assess the association between baseline characteristics and the likelihood of HPD. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for each predictor. Wald tests were used to determine the statistical significance of each predictor, with P-values <.05 considered significant. Overall survival predictions used Kaplan-Meier estimates, with comparative analyses via the log-rank test. A 2-tailed P-value <.05 denoted statistical significance. Analyses were conducted using GraphPad Prism (version 9, GraphPad Software, USA) or R studio (version 4.3.2).

Results

From the 273 metastatic melanoma patients received anti-PD-1 monotherapy at Peking University Cancer Hospital in clinical trials between 2016 and 2017, 262 were eligible for analysis post-exclusion of those without requisite tumor assessments (Figure 1). Each participant underwent scheduled imaging evaluations aligned with RECIST criteria.

Forty-seven percent of the patients had acral primaries, 37% had cutaneous or unknown primaries, and 17% had mucosal melanoma. The mutation rates for BRAF, NRAS, and CKIT were 14%, 9%, and 5%, respectively. 24% of the patients were treatment-naïve, while the remainder had prior chemotherapy or targeted therapy but no prior immunotherapy.

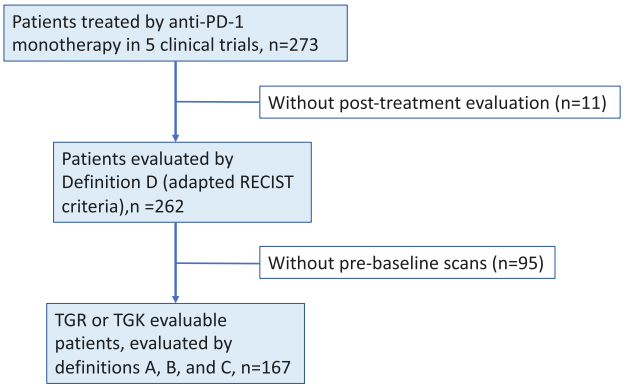

Figure 1. Flowchart of study selection process.

64% had metastases in multiple organs, 52% presented with an ECOG performance score above 0, and 30% exhibited elevated LDH levels (Table 1).

The study observed an ORR of 21% and a DCR of 58% for all patients, detailed as 4 CR, 51 PR, 98 SD, and 109 PD cases. Hyperprogression rates as per definitions A, B, and C were 13.2%, 16.8%, and 10.8%, respectively, for 167 patients with pre-baseline scans. Definition D, inclusive of the remaining 95 patients without such scans, yielded an HPD rate of 28.2%.

All definitions discernibly segregated HPD from non-HPD patients in terms of overall survival, with HPD cases exhibiting significantly inferior outcomes. The median OS was 8.5 versus 9.5 months by definition A (P = .0195), 7.4 versus 10.7 months by definition B (P = .0008), 6.3 versus 10.1 months by definition C (P < .0001), and 8.4 versus 13.8 months by definition D (P = .0001; Table 2; Figure 2). PFS curves overlap was noted at the first assessment for HPD and non-HPD progressors.

The concordance between A, B, and C definitions was 56% for A and B, 54% for A and C, and 59% for B and C. The concordance between these 3 and RECIST definitions was 26% for A and RECIST criteria, 38% for B and RECIST criteria, and 24% for C and RECIST criteria (Supplementary Table S1). Hazard ratio analyses confirmed definition C as the most prognostically significant (HR = 3.27, 95% CI 1.47-7.26), followed by B (HR = 2.21, 95% CI 1.27-3.85), and A (HR 1.76, 95% CI 0.99-3.14). The broad application of RECIST criteria resulted in a wider identification of HPD, or "rapid progression," with notably shorter OS (HR = 2.11, 95% CI 1.44-3.08; Figure 3).

Given definition C's superior predictive efficacy, we compared baseline characteristics, blood markers, and genomic variants between C-defined HPD and non-HPD progressive patients. Univariate analysis showed no associations between HPD and age, gender, gene mutations, treatment line, ECOG performance score, LDH, or NLR. The number of metastatic organs over 2 is a risk factor for HPD (P = .015). Mucosal melanoma patients had the highest incidence of HPD (21.9%) with a statistical trend (P = .078; Table 3). The multivariate logistic regression analysis revealed that the variables mucosal subtype (OR = 3.13, 95% CI = 0.97-9.68, P = .0489) and multiple organs involved (OR = 4.18, 95% CI = 1.38-12.63, P = .0103) were significantly associated with an increased likelihood of HPD. Other variables such as age, ECOG, LDH, and NLR did not show statistically significant associations with HPD (Supplementary Figure S1). These results indicate that specific primary sites and organ involvement are key factors in the occurrence of HPD. RECIST criteria for the entire cohort also indicated mucosal melanoma as the HPD prevalent subtype, with incidences of 45.5% in mucosal melanoma, 29.5% in acral melanoma, and 18.8% in cutaneous or unknown primaries (P = .005; Table 4).

Table 1. Patient characteristics.

Characteristics (n = 262)	No. of patients
Age, median (range), years	55 (22-68)
Sex	
Male	117(45%)
Female	145 (55%)
Subtype	
Cutaneous or unknown	96 (37%)
Acral	122 (47%)
Mucosal	44 (17%)
Stage	
IIIc	39 (15%)
IV	223 (85%)
Mutation	
BRAF	36 (14%)
NRAS	24 (9%)
CKIT	14 (5%)
Prior lines of therapy	
0	62 (24%)
≥ 1	200 (76%)
No. of involved organs	
1	94 (36%)
2	117 (45%)
≥ 3	51 (19%)
ECOG performance status	
0	127 (48%)
1	135 (52%)
LDH level	
Normal	183 (70%)
Elevated	79 (30%)
NLR	
≤3	187 (71.4%)
>3	75 (28.6%)

Discussion

This seminal study presents the first comprehensive analysis of the incidence and clinical features of hyperprogressive disease in various melanoma subtypes treated with anti-PD-1 monotherapy. Through a comparative evaluation of 4 HPD definitions, definition C emerged as the most effective in identifying patients with HPD within this cohort. Apart from subtype and number of metastatic organs, we found no significant correlation between HPD and other clinicopathologic features and laboratory markers.

A recent study proposed that hyperprogressive disease rarely occurs during checkpoint inhibitor treatment for advanced melanoma, which observed only one case of hyperprogression

Table 2. Incidence and overall survival of hyperprogression across various definitions.

	Definition A	Definition B	Definition C	Definition D (RECIST)
	TGRratio > 2	TGKratio > 2, time to treatment failure (TTF) < 2 months and RECIST > 50%	Delta TGR > 100	RECIST > 40% or > 20% with new lesions in ≥ 2 different organs
HPD incidence (%)	22/167 (13.2)	28/167 (16.8)	18/167 (10.8)	74/262 (28.2)
mOS (95% CI), months				
HPD	8.5 (7.1-9.3)	7.4 (5.6-9.2)	6.3 (5.0-8.6)	8.4 (7.5-9.3)
Non-HPD PD	9.5 (8.0-12.6)	10.7 (8.6-14.6)	10.1 (8.7-12.6)	13.8 (11.3-20.7)
P value	.0195	.0005	<.0001	.0001

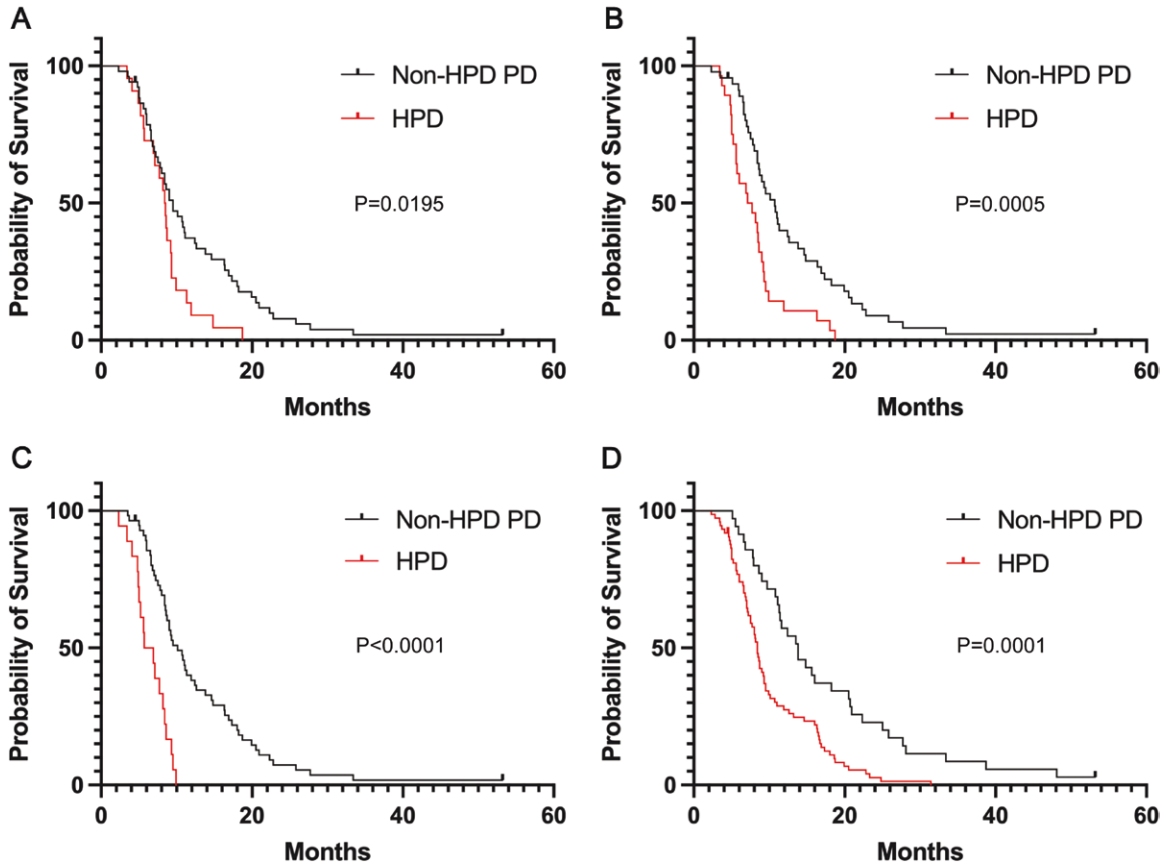

Figure 2. Kaplan-Meier overall survival curves delineating hyperprogression (HPD) and non-HPD progression across various definitions. Definition A: TGRratio > 2; definition B: TGKratio > 2, time to treatment failure (TTF) < 2 months and RECIST > 50%; definition C: Delta TGR > 100; definition D: RECIST > 40% or > 20% with new lesions in ≥ 2 different organs.

and one possible case among 168 patients.[22] Previous studies reported a 9% hyperprogression rate in melanoma treated by anti-PD-1/PD-L,[19] similar to the HPD rate in cutaneous and acral melanomas in our study. Reports of HPD have also been observed in advanced melanoma patients treated with ipilimumab.[23,24] Our study focuses on a specific melanoma that may have a different hyperprogression profile. In our cohort, acral and mucosal melanomas, constituting 47% and 17% of cases, respectively, corroborate previous findings,[25] demonstrating suboptimal responses to immunotherapy. Additionally, 39% of patients presented with cutaneous or unknown primaries, which similarly exhibited poorer outcomes in comparison to Western cohorts. The low prevalence of BRAF and NRAS mutations in the Chinese population,[26] along with low tumor mutational burden and a high incidence of structural and copy number variations,[27-29] may contribute to the attenuated efficacy of immunotherapy. Consequently, this study investigates the potential for increased HPD incidence among Chinese melanoma subtypes.

The absence of a consensus for HPD definition often results in ambiguity. We compared the consistency and predictive power of 4 HPD definitions, noting approximately 50% concordance between conventional definitions based on tumor growth metrics. Definitions A and B leveraged TGR and TGK ratios to delineate HPD. Previous research recommended a delta TGR of 100 as the demarcation

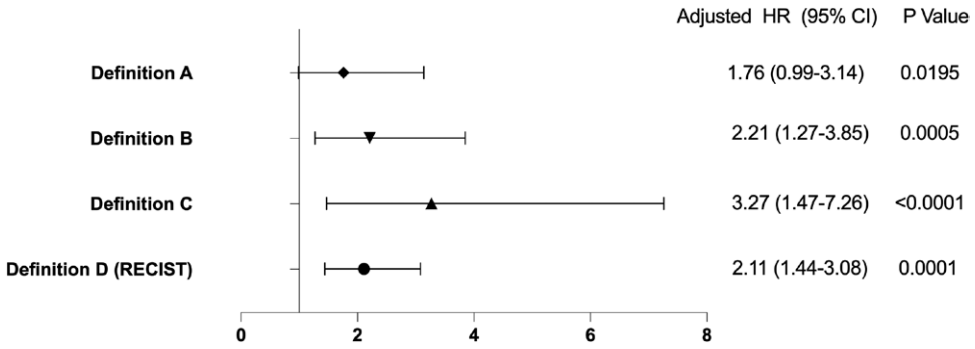

Figure 3. Forrest plot of hazard ratios for hyperprogression across different definitions.

Table 3. Comparative clinical characteristics of hyperprogression (HPD) versus non HPD as defined by definition C in patients with pre-baseline imaging.

Characteristics (n = 167)	Non HPD (n = 149)	HPD (n = 18)	P
Age, median (range), years	54 (22-68)	60 (32-57)	.251
Sex			.883
Male	67 (91.8%)	6 (8.2%)	
Female	82 (87.2%)	12 (12.8%)	
Subtype			**.078**
Cutaneous or unknown	53 (91.4%)	5 (8.6%)	
Acral	71 (92.2%)	6 (7.8%)	
Mucosal	25 (78.1%)	7 (21.9%)	
Mutation			
BRAF	24 (16.1%)	1 (5.6%)	.316
NRAS	15 (10.1%)	2 (11.1%)	>.999
CKIT	8 (5.4%)	0 (0)	.601
Prior lines of therapy			.223
0	18 (100%)	0 (0)	
≥ 1	131 (87.9%)	18 (12.1%)	
No. of involved organs			**.015**
1	55 (94.8%)	3 (5.2%)	
2	69 (90.8%)	7 (9.2%)	
≥ 3	25 (75.8%)	8 (24.2%)	
ECOG performance status			.620
0	71 (87.7%)	10 (12.3%)	
1	78 (90.7%)	8 (9.3%)	
LDH level			.787
Normal	103 (92.0%)	9 (8.0%)	
Elevated	46 (83.6%)	9 (16.4%)	
NLR			.999
≤3	105 (89.7%)	12 (10.3%)	
>3	44 (88.0%)	6 (12.0%)	

Bold values indicate statistically significant differences or those approaching statistical significance.

between HPD and non-HPD progression, a threshold that proved to be prognostically significant in non-small cell lung cancer.[20] Our study corroborates this threshold's predictive accuracy in the context of Chinese melanoma, with definition C accurately identifying HPD patients with a shorter overall survival. Under this definition, HPD was identified in 10.8% of patients, correlating with a median overall survival of merely 6.3 months. These metrics, reliant on pre-baseline scans, may not be applicable in all clinical scenarios. The adapted RECIST criteria identified the largest HPD subset, potentially overestimating true hyperprogressors in cases with intrinsically rapid aggressive disease. Nonetheless, patients categorized as HPD by RECIST exhibited significantly poorer outcomes than

Table 4. Predominance of hyperprogression in mucosal melanoma according to RECIST criteria across the entire cohort.

	CR/PR/SD	Non-HPD PD	HPD	Total ($n = 262$)	P
Cut/UP	64 (66.7%)	14 (14.6%)	18 (18.8%)	96	
Acral	65 (53.3%)	21 (17.2%)	36 (29.5%)	122	.005
Mucosal	24 (54.5%)	0 (0)	**20 (45.5%)**	44	

Bold values indicate statistically significant differences and the corresponding number.

other progressors, warranting caution when contemplating the continuation of immunotherapeutic interventions.

Previous studies reported associations between HPD and factors such as older age, number of metastatic organs, regional recurrence, and MDM2 mutations.[6,9-11] Based on definition C, our comparison of clinical and laboratory features between HPD and non-HPD progressors found number of metastatic organs as a risk factor. A previous study using clinical criteria feasible in daily practice also identified more than 3 metastatic sites as risk factor for HPD.[30] Other factors, including age, gender, gene mutations, lines of treatment, ECOG performance score, LDH levels, and NLR, did not demonstrate a significant association with HPD, posing a challenge for its prediction based on clinical features alone.

Despite melanoma's historical characterization as immunogenic, this does not extend to acral and mucosal melanoma. Tumor behaviors of HPD in advanced acral melanoma have been have described in our previous research.[31] Our findings recommend prudence in administering immunotherapy monotherapy for these subtypes, particularly given the high incidence of HPD in advanced mucosal melanoma, a novel discovery from our study. The multivariate logistic regression analysis revealed a significant association between mucosal subtype and the likelihood of HPD ($P = .0489$). However, the 95% CI (0.97-9.68) includes 1, indicating a potential inconsistency. This discrepancy might be due to sample size limitations. Further investigation and validation with a larger dataset are recommended to confirm this finding. To better manage and mitigate the risks associated with hyperprogression in mucosal melanoma, we can consider combination therapies that include anti-PD-1 with other treatments such as targeted therapy, other immunotherapies, or anti-angiogenic agents, which are under active investigation.[32-34] Early biomarker testing including genetic, proteomic, and immune profiling may facilitate to identify patients at high risk of hyperprogression. This emphasized the necessity for additional research into their clinical and biological behavior and associated molecular mechanisms.

The molecular underpinnings of HPD are remain largely enigmatic. Our research supports the notion that hyperprogression is a real biological entity. It not only occurs in patients undergoing immunotherapy but has also been reported in those receiving chemotherapy,[6,30] where treatment has led to accelerated tumor progression. In immunotherapy, HPD represents primary resistance, which can be caused by various intrinsic and extrinsic factors that impair the immune response. Intrinsic factors include loss of tumor antigen expression, defective antigen presentation, persistent PD-L1 expression, and IFNγ pathway alterations. Extrinsic factors include upregulation of other immune checkpoint molecules like LAG3 and TIM3, infiltration of immunosuppressive cells like Tregs, M2 macrophages, and MDSCs, increased expression of immunosuppressive enzymes such as IDO, and release of inhibitory cytokines like IL-10, TGFβ, or metabolites such as ATP/ADP/adenosine in the tumor microenvironment.[35-37] Although HPD is characterized by a paradoxical stimulation of tumor growth, distinct from traditional drug resistance, foundational research in this area is sparse. Notably, recent studies have highlighted the role of PD-1 + effector Treg cells[38] and CD8 + T-cell-derived IFNγ in promoting HPD through alterations in cancer metabolism.[39] Another study finds tumor-intrinsic NLRP3-HSP70-TLR4 signaling axis drives the development of a premetastatic niche and hyperprogression by promoting PMN-MDSCs accumulation,[40] suggesting new avenues for research into HPD's intrinsic mechanisms.

Our study is subject to certain limitations. The retrospective nature of this analysis may introduce certain biases, although the data were collected prospectively in clinical trials. Some patients lacked pre-baseline scans for conventional HPD definition evaluations, reducing sample sizes after exclusion. As mentioned before, using RECIST criteria to identify HPD may result in an overestimation in patients with intrinsically rapid progressive disease. Eleven patients were excluded from the study for not undergoing efficacy evaluations, often due to rapid progression preventing scans, potentially underestimating the hyperprogression rate. The majority of patients in our study had received prior chemotherapy. However, all patients were immunotherapy-naïve, allowing us to focus on the impact of first-line immunotherapy in this population. Prior chemotherapy may have resulted in high tumor burden and reshaped the immune microenvironment. The conclusions of this study are specific to the Chinese population due to these factors and the particular race and ethnicity involved. Considering the distinct responses to immune checkpoint inhibitors in the Chinese population, whether these findings apply to other regions remains to be confirmed. The generalizability of our findings across different tumor types with unique biological behaviors also remains to be validated.

Conclusion

A delta TGR exceeding 100 best identified HPD patients in the advanced melanoma population treated with anti-PD-1 monotherapy. Hyperprogression was notably prevalent in mucosal melanoma patients with multiple metastatic organs. Caution against HPD is warranted when applying anti-PD-1 monotherapy in mucosal subtype.

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Author contributions

Conception and design: Li Zhou, Lu Si, Jun Guo, Ying-shi Sun; Development of methodology: Min Cao, Haibin Zhu, Acquisition of data: Zhihong Chi, Chuanliang Cui, Xinan Sheng, Lili Mao, Bin Lian, Bixia Tang, Xieqiao Yan, Xue Bai, Xuan Wang, Siming Li. Analysis and interpretation of data (eg, statistical analysis, biostatistics, and computational analysis): Li Zhou, Min Cao, Haibin Zhu. Writing, review, and/or revision of the manuscript: all authors.

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Conflicts of Interest

Li Zhou receives a merit award supported by ASCO. Jun Guo serves as a consultant for or is on advisory boards for MSD, Roche, Pfizer, Bayer, Novartis, Simcere Pharmaceutical Group, Shanghai Junshi Biosciences and Oriengene. Lu Si has received speakers' honoraria from MSD, Roche, Novartis, Shanghai Junshi Biosciences and Oriengene. All of the remaining authors have no conflicts of interest to declare.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking University and written informed consent was obtained from each patient.

Supplementary material

Supplementary material is available at *The Oncologist* online.

References

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381(16):1535-1546. https://doi.org/10.1056/NEJMoa1910836
2. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med*. 2015;372(4):320-330. https://doi.org/10.1056/NEJMoa1412082
3. Tawbi HA, Schadendorf D, Lipson EJ, et al; RELATIVITY-047 Investigators. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022;386(1):24-34. https://doi.org/10.1056/NEJMoa2109970
4. Frelaut M, du Rusquec P, de Moura A, Le Tourneau C, Borcoman E. Pseudoprogression and hyperprogression as new forms of response to immunotherapy. *BioDrugs* 2020;34(4):463-476. https://doi.org/10.1007/s40259-020-00425-y
5. Borcoman E, Kanjanapan Y, Champiat S, et al. Novel patterns of response under immunotherapy. *Ann Oncol*. 2019;30(3):385-396. https://doi.org/10.1093/annonc/mdz003
6. Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive disease in patients with advanced non-small cell lung cancer treated with PD-1/PD-L1 inhibitors or with single-agent chemotherapy. *JAMA Oncol*. 2018;4(11):1543-1552. https://doi.org/10.1001/jamaoncol.2018.3676
7. Bellmunt J, de Wit R, Vaughn DJ, et al; KEYNOTE-045 Investigators. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med*. 2017;376(11):1015-1026. https://doi.org/10.1056/NEJMoa1613683
8. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627-1639. https://doi.org/10.1056/NEJMoa1507643
9. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. *Clin Cancer Res*. 2017;23(8):1920-1928. https://doi.org/10.1158/1078-0432.CCR-16-1741
10. Saada-Bouzid E, Defaucheux C, Karabajakian A, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. *Ann Oncol*. 2017;28(7):1605-1611. https://doi.org/10.1093/annonc/mdx178
11. Kato S, Goodman A, Walavalkar V, et al. Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. *Clin Cancer Res*. 2017;23(15):4242-4250. https://doi.org/10.1158/1078-0432.CCR-16-3133
12. Matos I, Martin-Liberal J, Garcia-Ruiz A, et al. Capturing hyperprogressive disease with immune-checkpoint inhibitors using RECIST 1.1 criteria. *Clin Cancer Res*. 2020;26(8):1846-1855. https://doi.org/10.1158/1078-0432.CCR-19-2226
13. Tang B, Chi Z, Chen Y, et al. Safety, efficacy, and biomarker analysis of toripalimab in previously treated advanced melanoma: results of the POLARIS-01 Multicenter Phase II Trial. *Clin Cancer Res*. 2020;26(16):4250-4259. https://doi.org/10.1158/1078-0432.CCR-19-3922
14. Si L, Zhang X, Shu Y, et al. A phase Ib study of pembrolizumab as second-line therapy for Chinese patients with advanced or metastatic melanoma (KEYNOTE-151). *Transl Oncol*. 2019;12(6):828-835. https://doi.org/10.1016/j.tranon.2019.02.007
15. Bai X, Shoushtari AN, Betof Warner A, et al. Benefit and toxicity of programmed death-1 blockade vary by ethnicity in patients with advanced melanoma: an international multicentre observational study. *Br J Dermatol*. 2022;187(3):401-410. https://doi.org/10.1111/bjd.21241
16. Tang B, Yan X, Sheng X, et al. Safety and clinical activity with an anti-PD-1 antibody JS001 in advanced melanoma or urologic cancer patients. *J Hematol Oncol*. 2019;12(1):7. https://doi.org/10.1186/s13045-018-0693-2
17. Shen L, Guo J, Zhang Q, et al. Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. *J ImmunoTher Cancer*. 2020;8(1):e000437. https://doi.org/10.1136/jitc-2019-000437
18. Zhou L, Wu X, Chi Z, et al. Safety, activity, and pharmacokinetics of camrelizumab in advanced Asian melanoma patients: a phase I study. *BMC Cancer* 2022;22(1):565. https://doi.org/10.1186/s12885-022-09663-5
19. Ferte C, Fernandez M, Hollebecque A, et al. Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. *Clin Cancer Res*. 2014;20(1):246-252. https://doi.org/10.1158/1078-0432.CCR-13-2098
20. Kas B, Talbot H, Ferrara R, et al. Clarification of definitions of hyperprogressive disease during immunotherapy for non-small cell lung cancer. *JAMA Oncol*. 2020;6(7):1039-1046. https://doi.org/10.1001/jamaoncol.2020.1634
21. Wang Z, Liu C, Bai Y, et al. Redefine hyperprogressive disease during treatment with immune-checkpoint inhibitors in patients with gastrointestinal cancer. *Front Oncol*. 2021;11:761110. https://doi.org/10.3389/fonc.2021.761110
22. Schuiveling M, Tonk EHJ, Verheijden RJ, Suijkerbuijk KPM. Hyperprogressive disease rarely occurs during checkpoint

inhibitor treatment for advanced melanoma. *Cancer Immunol Immunother*. 2021;70(5):1491-1496. https://doi.org/10.1007/s00262-020-02716-3
23. Borcoman E, Nandikolla A, Long G, Goel S, Le Tourneau C. Patterns of Response and Progression to Immunotherapy. *Am Soc Clin Oncol Educ Book*. 2018;38(38):169-178. https://doi.org/10.1200/EDBK_200643
24. Barham W, Guo R, Park SS, et al. Case report: simultaneous hyperprogression and fulminant myocarditis in a patient with advanced melanoma following treatment with immune checkpoint inhibitor therapy. *Front Immunol*. 2021;11:561083. https://doi.org/10.3389/fimmu.2020.561083
25. Chi Z, Li S, Sheng X, et al. Clinical presentation, histology, and prognoses of malignant melanoma in ethnic Chinese: a study of 522 consecutive cases. *BMC Cancer* 2011;11:85. https://doi.org/10.1186/1471-2407-11-85
26. Bai X, Kong Y, Chi Z, et al. MAPK Pathway and TERT promoter gene mutation pattern and its prognostic value in melanoma patients: a retrospective study of 2,793 cases. *Clin Cancer Res*. 2017;23(20):6120-6127. https://doi.org/10.1158/1078-0432.CCR-17-0980
27. Kong Y, Si L, Li Y, et al. Analysis of mTOR gene aberrations in melanoma patients and evaluation of their sensitivity to PI3K-AKT-mTOR Pathway inhibitors. *Clin Cancer Res*. 2016;22(4):1018-1027. https://doi.org/10.1158/1078-0432.CCR-15-1110
28. Xu L, Cheng Z, Cui C, et al. Frequent genetic aberrations in the cell cycle related genes in mucosal melanoma indicate the potential for targeted therapy. *J Transl Med*. 2019;17(1):245. https://doi.org/10.1186/s12967-019-1987-z
29. Newell F, Kong Y, Wilmott JS, et al. Whole-genome landscape of mucosal melanoma reveals diverse drivers and therapeutic targets. *Nat Commun*. 2019;10(1):3163. https://doi.org/10.1038/s41467-019-11107-x
30. Fournier M, Mortier L, Dereure O, et al. Hyperprogression in advanced melanoma is not restricted to immunotherapy. *Eur J Cancer*. 2023;193:113289. https://doi.org/10.1016/j.ejca.2023.113289
31. Zhou L, Shao L, Gao S, et al. Impact of response patterns for patients with advanced acral melanoma treated with anti-programmed death-1 monotherapy. *Br J Dermatol*. 2023;188(1):112-121. https://doi.org/10.1093/bjd/ljac005
32. Mao L, Lian B, Li C, et al. Camrelizumab plus apatinib and temozolomide as first-line treatment in patients with advanced acral melanoma: the CAP 03 Phase 2 Nonrandomized Clinical Trial. *JAMA Oncol*. 2023;9(8):1099-1107. https://doi.org/10.1001/jamaoncol.2023.1363
33. Sheng X, Yan X, Chi Z, et al. Axitinib in combination with toripalimab, a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1, in patients with metastatic mucosal melanoma: an open-label phase IB Trial. *J Clin Oncol*. 2019;37(32):2987-2999. https://doi.org/10.1200/JCO.19.00210
34. Mao L, Fang M, Chen Y, et al. Atezolizumab plus bevacizumab in patients with unresectable or metastatic mucosal melanoma: a multicenter, open-label, single-arm Phase II Study. *Clin Cancer Res*. 2022;28(21):4642-4648. https://doi.org/10.1158/1078-0432.CCR-22-1528
35. Jenkins RW, Barbie DA, Flaherty KT. Mechanisms of resistance to immune checkpoint inhibitors. *Br J Cancer*. 2018;118(1):9-16. https://doi.org/10.1038/bjc.2017.434
36. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell*. 2017;168(4):707-723. https://doi.org/10.1016/j.cell.2017.01.017
37. Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune checkpoint targeting. *Lancet Oncol*. 2017;18(12):e731-e741. https://doi.org/10.1016/S1470-2045(17)30607-1
38. Kamada T, Togashi Y, Tay C, et al. PD-1(+) regulatory T cells amplified by PD-1 blockade promote hyperprogression of cancer. *Proc Natl Acad Sci USA*. 2019;116(20):9999-10008. https://doi.org/10.1073/pnas.1822001116
39. Li G, Choi JE, Kryczek I, et al. Intersection of immune and oncometabolic pathways drives cancer hyperprogression during immunotherapy. *Cancer Cell* 2023;41(2):304-322.e7. https://doi.org/10.1016/j.ccell.2022.12.008
40. Theivanthiran B, Yarla N, Haykal T, et al. Tumor-intrinsic NLRP3-HSP70-TLR4 axis drives premetastatic niche development and hyperprogression during anti-PD-1 immunotherapy. *Sci Transl Med*. 2022;14(672):eabq7019. https://doi.org/10.1126/scitranslmed.abq7019