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Hyper-progressive Disease in Patients With Non–Small Cell Lung Cancer Treated With Checkpoint Inhibitors: The Role of 18F-FDG PET/CT

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Abstract

Introduction: A new pattern of response, so-called hyper-progressive disease (HPD), is emerging during treatment with immune checkpoint inhibitors (ICI). Our aim was to investigate the prevalence of such phenomenon and to assess its association with clinical variables and metabolic parameters by 18F-fludeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT).

Methods: Data from 50 patients (34 male, 16 female, median age 73) with non-small cell lung carcinoma (NSCLC) and treated with ICI were prospectively collected. All patients underwent contrast-enhanced CT, 18F-FDG PET/CT, and complete peripheral blood sample at baseline before ICI. HPD was defined according to clinical and radiologic criteria. Because of the rapid disease progression or worsening of clinic conditions, radiologic response assessment was available for 46 patients. OS were analyzed using the Kaplan–Meier method and the log-rank test. A Cox proportional hazards regression analysis was used to evaluate factors independently associated with OS. Median follow-up was 12.4 months (9.7-15.2 months).

Results: We identified the following response categories: 10 cases as complete/partial response (CR/PR), 17 cases with stable disease (SD), 5 patients with progressive disease (PD), and 14 with HPD. Among metabolic parameters we observed a statistically significant association between HPD status and tumor burden, expressed by both MTV (756.1ml for HPD vs 475.6ml for non-HPD, p=0.011) and TLG (287.3 for HPD vs 62.1 for non-HPD, p=0.042). Among clinical variables, 12/14 patients (85.7%) within the HPD group compared with 8/32 patients (25%) in the non-HDP group had more than two metastatic sites (p<0.001). In addition, the derived neutrophil-to-lymphocyte ratio (dNLR) and platelet counts was significantly associated with HPD status (p=0.038, p=0.025, respectively). Survival analysis showed a median OS of 4 months for HPD group compared with 15 months within non-HPD patients (p=0.003). Likewise, median OS was significantly different when we considered all the response categories: CR/PR, SD, PD, and HPD (p=0.001). Finally, Multivariate analysis identified MTV and dNLR as independent predictors for OS.

Conclusion: Our results suggest that the use of ICI might represent a concern in patients with high metabolic tumor burden and inflammatory indexes at baseline. However Additional studies are needed.

The trial was registered at www.clinicaltrials.gov (NCT03563482)

Keywords: Non-small cell lung cancer; checkpoint inhibitors; 18F-FDG PET/CT; hyper-progressive disease

INTRODUCTION

Cancer therapy has been positively revolutionized with the introduction of immune checkpoint inhibitors (ICI) (*1*). By targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its ligand programmed cell death ligand 1 (PD-L1), ICI restore antitumor T-cell activity and prolong survival in several advanced malignancies, such as melanoma (*2,3*), non-small cell lung carcinoma (NSCLC) (*4*), head and neck squamous cell carcinoma (*5*), renal cell carcinoma (*6,7*), and Hodgkin lymphomas (*8*).

Beside survival advantage, there is growing evidence that treatment with ICI might have detrimental effect in a subset of patients, characterized by a rapid increase of tumor extension with worse clinical outcome, termed as hyper-progressive disease (HPD) (*9*). Despite such phenomenon has been described transversally in different cancer histotypes under immunotherapy, there is no worldwide accepted and clear definition and the exact underlying pathophysiology remains still unknown . As a result, the prevalence of HPD ranges from 4% to 29% according to the various criteria adopted in published studies (*10-14*). To date, weak potential predictive factors of HPD have been identified, all different across studies. Therefore, it is of critical importance to identify patients with HPD in order to early promote suspension of immunotherapy and switch to another anticancer treatment.

The role of 18F-fludeoxyglucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) for assessing early tumor response in NSCLC patients treated with ICI is in continuous evolution, as most of published studies have evaluated advanced melanoma patients. However, Lopci et al (*15*), reporting a correlation among metabolic parameters and immune markers (e.g. PD-1/PD-L1, CD8, and CD68), suggesting 18F-FDG PET/CT as a valid tool to explore changes within tumor microenvironment during ICI. In addition, Kaira et al (*16*) demonstrated that metabolic response by 18F-FDG could be effective for predicting efficacy and progressive-free survival (PFS) at 1 month after nivolumab treatment.

On the basis of these findings, the aim of our prospective study was to investigate the prevalence of HPD in patients with NSCLC treated with ICI and to seek, among clinical and metabolic parameters, potential biomarkers of HPD.

MATERIALS and METHODS

Patients

This study was conducted in patients affected by metastatic or relapsed NSCLC who were referred to our hospital, Humanitas Clinical and Research Center, from December 2015 to May 2019 for treatment with ICI. The medical records of all consecutive patients (n=50) were analyzed. Prospective data were collected from patients (n=42) adhering to the same diagnostic trial, registered at https://clinicaltrials.gov/ (NCT03563482), and from other clinical trials for ICI (n=8). Before the administration of ICI, all patients underwent 18F-FDG-PET/CT scan, brain imaging and thoracic enhanced multi-detector CT scan. Likewise, baseline white blood cell counts, including absolute neutrophil counts, absolute lymphocyte counts, and platelet counts were collected. Nivolumab was administered intravenously at a dose of 3mg/kg every two weeks, pembrolizumab at a dose of 200mg every 3 weeks.

The current study has been conducted following the approval of the local institutional review board and in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained in all cases.

Imaging Protocol

18F-FDG PET/CT

After a fasting time of approximately 6 hours, PET/CT images was acquired 60 min after the injection of 250-500 MBq of FDG. PET/CT scans were performed using two scanners, accredited by EANM Research Ltd (EARL) program [19]: a) Siemens Biograph LSO 6 scanner (Siemens Erlangen; Munich, Germany), with an integrated 6-slice CT, and b) GE Discovery PET/CT 690 (General Electric Healthcare; Waukesha, WI), with an integrated 64-slice CT. Attenuation-correction images were obtained with a low-dose CT (120 kV, 30mA). A GE ADW4.6 workstation (GE Healthcare, Waukesha, WI, USA) was used to display images, which were interpreted by two experienced nuclear medicine physicians. For the semi-quantitative analysis, the threshold of the volumes of interest (VOIs) was set at 0.5 by PETVCAR (GE Healthcare, Waukesha, WI, USA). The maximum SUV

(SUVmax) was defined SUVmax was defined as the value of the highest pixel and average SUV (SUVmean) as the mean SUV related to the tumor burden. Volumetric parameters of each lesions, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG= MTV x SUVmean) were calculated by using a SUV threshold of 42%.

Definition of HPD

Radiologic evaluation was performed at treatment initiation and every 8 weeks thereafter. Tumor response was determined according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 and immunotherapy-related criteria (iRECIST) (*17,18*).

Among various criteria to define HPD available in the literature (*9*), we have chosen those described by Lo Russo et al (13), which involved NSCLC patients treated with ICI. In particular, we considered the following parameters: 1) time-to-treatment failure (TTF) < 2 months (TTF is defined as the time from the start of treatment with ICI to ICI discontinuation); 2) increase of ≥50% in the sum of target lesions major diameters between baseline and first radiologic evaluation; 3) appearance of at least two new lesions in an organ already involved between baseline and first radiologic evaluation; 4) spread of the disease to a new organ between baseline and first radiologic evaluation; 5) clinical deterioration with decrease in Eastern Cooperative Oncology Group (ECOG) performance status ≥2 during the first 2 months of treatment. Thus, patients who had at least three of the abovementioned criteria were considered experiencing HPD.

Statistical Analysis

Associations between HPD and categorical or continuous variables were evaluated using Fisher's exact test and Mann-Whitney test, respectively.

Overall survival (OS) was calculated as the duration between the date of initiation of immunotherapy and the date of death. OS were analyzed using the Kaplan–Meier method and the log-rank test. A Cox proportional hazards regression analysis was used to evaluate factors independently associated with OS. All

statistical analyses were carried out using the Statistical Package for Social Sciences, version 23.0, for Windows (SPSS, Chicago, IL), and p values < 0.05 were considered to be statistically significant.

RESULTS

Overall, we analyzed 50 patients (34 male, 16 female, median age 73) with advanced NSCLC and treated with ICI at our hospital. Forty-six patients were evaluable for response, as 4 (8%) patients early stopped ICI due to rapid clinical deterioration before the first imaging evaluation at 8 weeks.

Thirty-one patients (62%) received nivolumab, sixteen (32%) pembrolizumab, two patients (4%) with a combination of nivolumab and ipilimumab, and only 1 (2%) patient with atezolizumab. The median number of immunotherapy cycles was 6 (range, 1–47). Two patients performed only 1 cycle of ICI and four patients 2 cycles because of the rapid disease progression or worsening of clinic conditions.

Median follow-up was 12.4 months (9.7-15.2 months). According to iRECIST, we identified the following response categories: complete and partial response (CR/PR, 10 patients, 21.7%), stable disease (SD, 17 patients, 37%), and progressive disease (PD, 19 patients, 41.3%). Among this latter group, 14 patients (30.4%) fulfilled criteria for HPD.

Association between HPD and clinical-metabolic variables

Among metabolic parameters by 18F-FDG PET/CT, we observed a statistically significant association between HPD status and metabolic tumor burden at baseline, expressed by both MTV and TLG. In fact, patients with HPD had higher values of both MTV and TLG than patients without HDP (756.1 vs 475.6, p=0.011; 287.3 vs 62.1, p=0.042, respectively) (Table 1). Furthermore, HPD was significantly associated with more than 2 (median) metastatic sites at baseline: 12 out of 14 patients (85.7%) within the HPD group compared with 8 out of 32 patients (25%) in the non-HDP group (p<0.001).

In our cohort, we also analyzed the presence of significant differences between HPD and non-HPD according to inflammatory indexes at baseline before ICI. In particular, the derived neutrophil-to-lymphocyte ratio (dNLR) was significantly associated with HPD status (3.5 in HPD vs 2.2 in non-HPD patients, respectively, p=0.038). Likewise, we found that platelet counts were higher in patients with HPD (305 vs 211, p=0.025). Among the other clinical variables, no significant differences were observed according to age, gender, smoking

history, as well as HPD status was independent from histology. In addition, we examined the influence of previous treatments. Again, we did not observe any association between HPD status and the number of previous therapies. Finally, we were able to assess PD-L1 tumor expression only for 27 patients (54%) due to insufficient quality or quantity from biopsied material.

insufficient quality or quantity, but we did not observe any difference between HPD and other patients, as well as no association was found between nivolumab or pembrolizumab and HPD status (Table 2).

Association between HPD and survival

Overall, the median OS was 4.1 months 12.4 months (95% CI, 9.7-15.2 months). To evaluate the association between HPD status and prognosis, we performed survival analysis by Kaplan-Meier considering the following categories: CR/PR, SD, non-HPD, and HPD. There was a significant association with worse outcome for patients with HPD (median OS, 4.0 months; 95% CI, 1-10.6) compared with the patients with non-HPD (median OS, 15.2 months; 95% CI, 9.4-21.1, p=0.003) (Fig. 1). Moreover, log-rank test for OS was highly significant among response groups (p=0.001) (Fig. 2).

Finally, in a multivariate Cox model analysis, we observed that both MTV and dNLR at baseline were strongly associated with OS: MTV (HR, 1.003; 95% CI, 1.001-1.005; p=0.008); NLR (HR, 1.191; 95% CI, 1.043-1.359; p=0.01) (Table 3).

In Fig. 3 we suggest a potential algorithm to consider prior to start treatment with ICI.

DISCUSSION

Although the advent of ICI in clinical oncology has positively revolutionized the standard of care of patients with NSCLC, some challenges have to be faced by the oncologists. Indeed, on one hand these new drugs have shown an extraordinary antitumor potential, but on the other hand may also induce a dramatic tumor surge in a fraction of patients, the so-called hyper-progression.

In our cohort 30.4% of evaluable patients (n = 14 of 46) with NSCLC experienced HPD during therapy with anti-PD-1/PD-L1. Moreover, we did not consider 4 patients because of clinical deterioration before imaging evaluation, thus it is likely that HPD frequency here reported might be underestimated. The occurrence of HPD also correlated with shorter OS. Previous studies on the HPD reported prevalence rates quite large, ranging from 9% to 29% throughout tumor types, including NSCLC (*10-12,14*). In all these articles, tumor growth rate before and during ICI treatment was adopted for HPD definition, even though with cutoff values slightly different. Nevertheless, such parameter presupposes radiological imaging before, at the start, and during ICI, which are often unavailable in clinical practice. Likewise, treatment with ICI is frequently started as first-line therapy, as also evident in our series with 24% of patients (12 of 50), thus tumor growth rate cannot be computed. Furthermore, being a pure radiologic index, it does not take in count of clinical conditions (e.g. decrease of performance status), leading a possible underestimation of HPD. Therefore, we adopted stringent criteria, the same used by Lo Russo et al (*13*) in a cohort of NSCLC patients treated with ICI, which combined both radiologic and clinical parameters. As a matter of fact, our HPD frequency was consistent with the abovementioned paper from Italian group, although further prospective clinical trials are warranted to specifically validate the criteria for HPD diagnosis.

In our series, HPD was significantly associated with a high metabolic tumor burden, expressed by MTV and TLG. To our knowledge, this study is the first to define metabolic PET-based parameter as predictors for HPD in course of ICI therapy. In our preliminary analysis on 27 NSCLC patients, we found almost all cases with worse outcome having a SUVmax ≤ 17.1 or a SUVmean ≤ 8.3 (*20*). The reason of these seemly contrasting results may rely on different criteria adopted. In fact, in the preliminary work we identified patients as "*fast*

progressors or responders" mostly on oncologists-based opinion, instead of the rigorous criteria used in the present work. Furthermore, in our cohort HPD was significantly associated with a high number of metastatic sites before ICI therapy started, which reflects the impact of whole tumor burden on HPD pathophysiology. This finding is in line with previous publication by Ferrara et al (*11*), indicating that HPD was more frequent among NSCLC patients who had more than two metastatic sites.

Among clinical variables, dNLR and platelet count were found to be associated with HPF status. These findings are consistent with previous studies, where dNLR greater than 3 was demonstrated to negatively influence the survival outcome in NSCLC patients treated with ICI (*21*), as well as thrombocytosis (defined as a platelet count of >450,000 per cubic millimeter) is common in solid tumors and fuels tumor growth, neoangiogenesis and metastasization (*22*). Contrary to what was observed by Lo Russo et al (*13*), no significant association between HPD and PD-L1 tumor expression was found in our study, although PD-L1 status was not available in 23 patients (46%). However, our recent paper demonstrated an independent expression between circulating and tissue PD-L1 levels, suggesting potential prognostic role also for soluble PD-L1 (*23*). Yet, as reported here, we did not observe any difference in the rate of HPD across the different clinical variables such as age, gender, tumor type, and performance status. However, Champiat et al (*10*) and Kanjanapan et al (*24*) were the only studies where HPD was associated with age (e.g.> 66) and gender (e.g. female), respectively, and need further studies to be confirmed. In addition, in our study we did not observe any effect related to the number of previous therapies, therefore minimizing the risk that the HPD was related to previous "conventional" treatments.

Despite hyper-progression is an atypical, but not rare, pattern of response during ICI therapy, the underlying biological mechanisms are not still completely elucidated. Main hypothesis seems to consider HPD as a real immunological phenomenon that involves both innate and adaptive immune system, enhancing growth and cancer development. For instance, Lo Russo et al (*13*) suggested that the interaction between ICI and Fc receptor on intra-tumoral macrophages could affect alternative signaling networks of these cells toward a cancer-promoting function. Likewise, PD-1 blockade increased tumor-infiltrating regulatory T cells that

suppress antitumor T-cell responses (*25*). Furthermore, through the production of free radicals that damage the DNA or by the secretion of growth factors that favorite angiogenesis and tissue remodeling promotion, immune system play a fundamental role in the cancer development.

Our study has some limitations. First the lack of a control arm: it would have been interesting to perform a similar analysis in a cohort of patients treated with different agents from ICI. As a consequence, the immuno-related hypothesis causing hyper-progression cannot be accepted completely. However, Kaplan-Meier curves from the main clinical trials (e.g. CheckMate-026, CheckMate-056, CheckMate-227, and Keynote-042) showed a better OS and PFS in the chemotherapy arm compared with immunotherapy arm in the first three months of treatment, suggesting a disease progression or death in the immunotherapy arm earlier than expected (*4, 26-28*). Second, tumor mutational burden analysis was not available at the time of the current study and should be addressed in our future studies. Third, the relative small number of patients weakens the consistency of our results.

CONCLUSION

To summarize, our results show that it might represent a concern for the use of ICI in patients with high metabolic tumor burden, expressed by either MTV, TLG, or more than 2 metastatic sites, as well as in those with high pro-inflammatory indexes (e.g. elevated platelets and dNLR). Despite many potential biomarkers have been tested, none of them have reached enough strength due to different tumor types, small sample studies, and lack of standard definition of HPD. Therefore, additional studies are warranted to better understand the molecular basis of HDP in order to identify patients at baseline who are at high risk of developing such atypical response and allow in advance to initiate alternative therapies.

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Conflict of interest statement

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Key-points

- HPD seems a new phenomenon induced by ICI therapy, which accelerates tumor growth
- MTV, dNLR, and platelet counts are associated with HPD status
- MTV is a prognostic factor for OS
- Clinicians should be aware of HPD in order to carefully monitor disease evolution and, in case, to switch to another treatment.

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FIGURE LEGENDS:

Figure 1. OS between HPD and non-HPD patients.

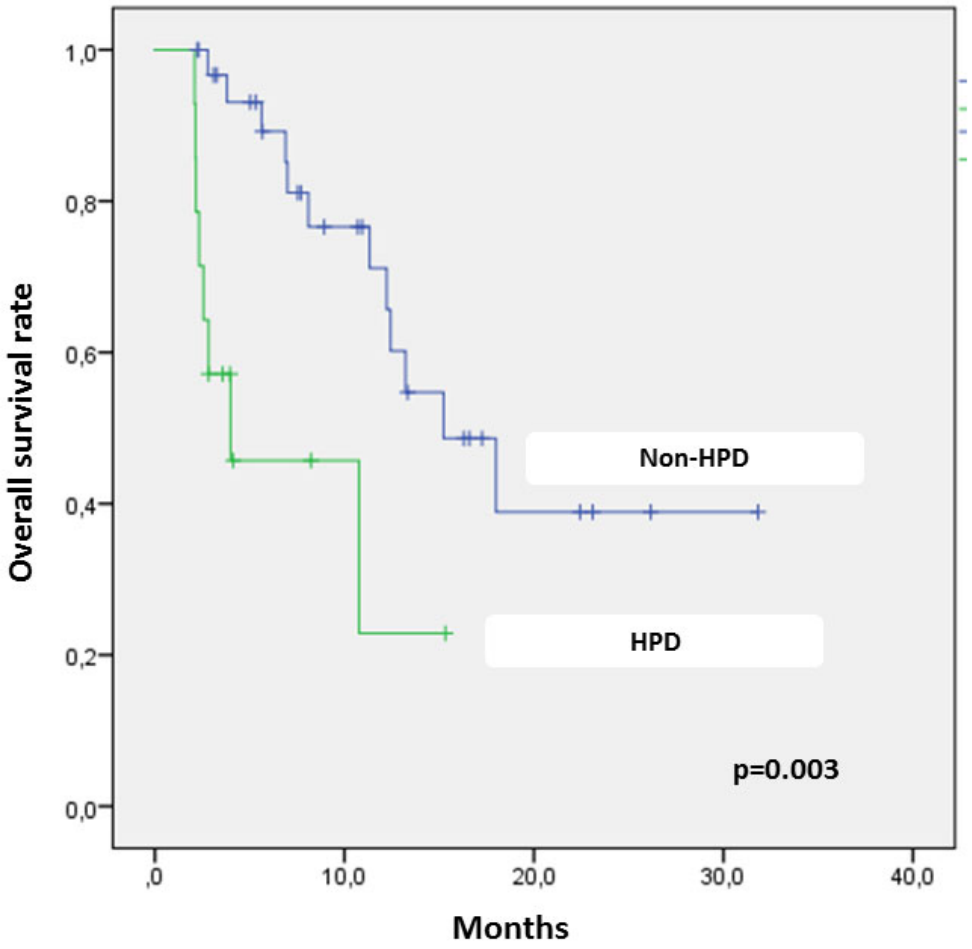

Figure 2. OS among response categories according to iRECIST criteria.

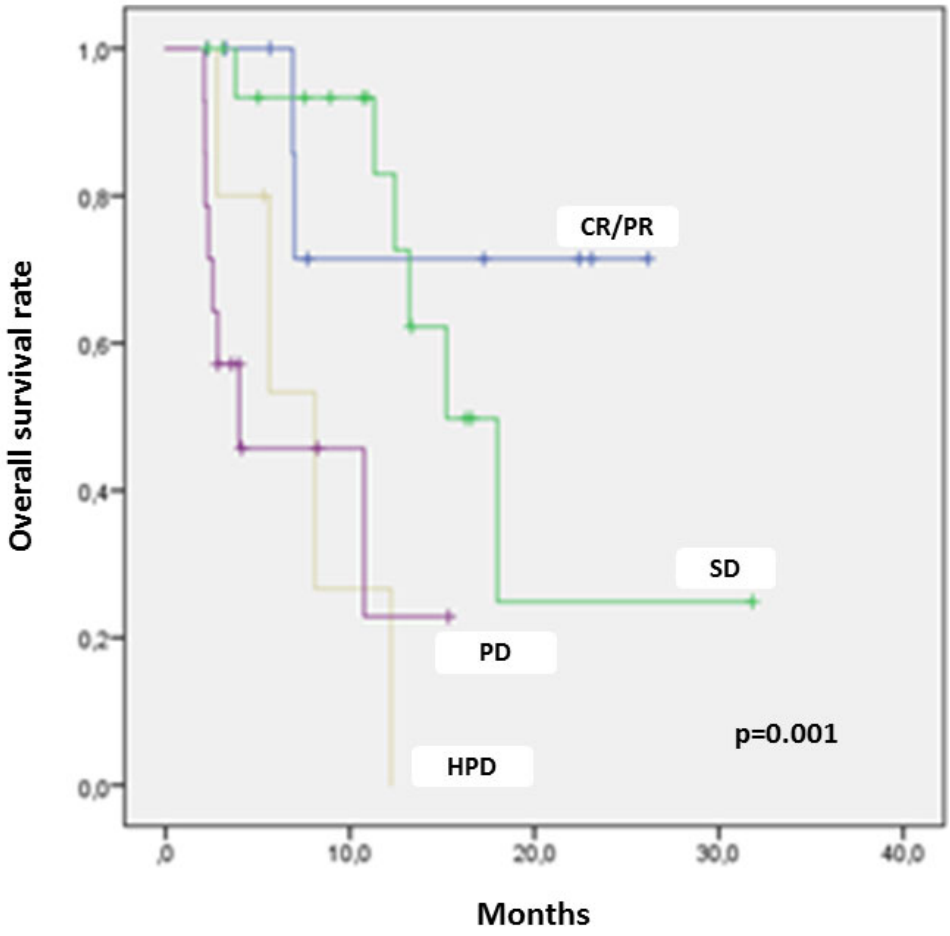

Figure 3. Potential algorithm for hyper-progression. A) Patient with elevated metabolic tumor burden (MTV=148 ml) and dNLR (3.19) at baseline showed hyper-progression after 4 cycles of nivolumab and died approximately after 3 months since ICI therapy started. B) Patient with low MTV (66 ml) and inflammatory index (dNLR=2.46) experienced partial metabolic response at first restaging and he was still alive after approximately 12 months.

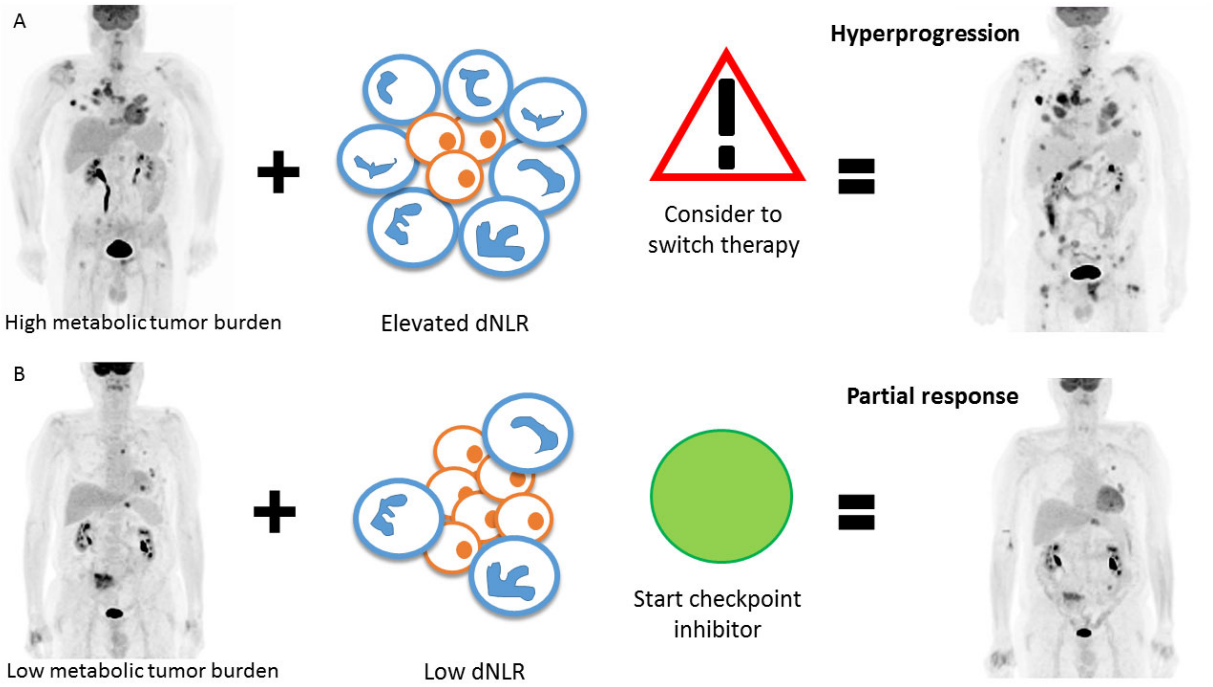

Table 1. Patient characteristics and association between HPD and continue variables.

Variable	All patients (n=46)	non-HPD (n=32)	HPD (n=14)	*p*
SUVmax	15.1 (4.9-35.7)	13.8 (4.9-25.7)	17.5 (5.3-35.7)	.232
SUVmean	6 (3.2-10.3)	6.1 (3.2-10.3)	5.8 (3.3-9)	.527
MTV	143.2 (2.7-1772)	62.1 (2.7-256.5)	287.3 (11.3-1772)	**.011**
TLG	576.6 (12.3-2504)	475.6 (12.3-2504.1)	756.1 (41.8-2424.5)	**.042**
White Blood Count	9 (3.8-24.5)	8.3 (4-21.3)	10.2 (3.8-24-5)	.443
Neutrophils	6.4 (1.9-6.9)	5.6 (1.9-14.5)	7.8 (2-20.9)	.272
dNLR	2.7 (0.7-12.9)	2.2 (0.7-5.5)	3.5 (0.9-12.9)	**.038**
Platelets	265.9 (118-517)	211 (123-449)	305 (118-517)	**.025**

HPD, hyper-progressive disease; MTV, metabolic tumor volume; TLG, total lesion glycolysis; dNLR, derived-neutrophil-to-lymphocyte ratio.

Table 2. Patient characteristics and association between HPD and categorial variables.

	All patients n=46 (%)	non-HPD n=32 (%)	HPD n=14 (%)	*p*
Age				
<73	22 (47.8)	15 (46.9)	7 (50)	>.99
≥73	24 (52.2)	17 (53.1)	7 (50)	
Gender				
male	32 (69.6)	24 (75)	8 (57.1)	.30
female	14 (30.4)	8 (25)	6 (42.9)	
Smoking status				
Current/former	41 (89.1)	28 (87.5)	13 (92.9)	>.99
None	5 (10.9)	4 (12.5)	1 (7.1)	
No of previous lines of treatment				
0	12 (26.1)	8 (75.0)	4 (57.1)	.71
≥1	34 (73.9)	24 (31.3)	10 (28.6)	
Metastatic sites (median)				
≤2	26 (69.6)	24 (75)	2 (14.3)	**<0.001**
>2	20 (30.4)	8 (25)	12 (85.7)	
Histology				
Non-squamous	34 (73.9)	24 (75)	10 (71.4)	>.99
Squamous	12 (26.1)	8 (25)	4 (28.6)	
Tumor PD-L1 status				
negative	9 (19.6)	5 (15.6)	4 (28.6)	.67
positive	16 (34.8)	11 (34.4)	5 (35.7)	
missing	21 (45.6)	16	5	

Table 3. Multivariate analysis of progression-free survival and overall survival.

Parameters	Overall Survival		
	Hazard ratio	95% IC	p value
MTV	1.003	1.001-1.005	**0.008**
dNLR	1.191	1.043-1.359	**0.01**

MTV, metabolic tumor volume; dNLR, derived neutrophil-to-lymphocyte ratio