

Research Article

Hyperprogression after Immunotherapy in Advanced Urothelial Cancer: Prevalence and Clinical Correlations

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Abstract

Aim: Immune Checkpoint Inhibitors (ICIs) are widely used in Advanced Urothelial Cancer (aUC). However, predicting durable responses to ICIs remains challenging and conventional response criteria may not capture the complexities of immunotherapy-induced responses. Specifically, the occurrence of hyperprogression, characterized by rapid disease progression following ICI initiation, has not been adequately studied in aUC. We aimed to investigate the prevalence, clinical characteristics, and prognostic significance of hyperprogression in patients with aUC treated with ICIs.

Methods: In this retrospective study, we included 54 patients with aUC treated with ICI monotherapy. Hyperprogression was defined using two established criteria: hyperprogressive disease (HPD: ≥ 2 -fold increase in tumor growth rate before and after ICI initiation) and/or fast progression (FP: $\geq 50\%$ increase in disease burden within 12 weeks from ICI initiation). Measurements were based on radiology reports. Central radiology review was also performed when possible.

Results: All patients were assessed for FP and 43 for HPD. Central radiology review was performed in 23 cases. HPD was found in 7 cases (16.3%) and FP in 22 (40.7%). There was no association of the development of hyperprogression with baseline characteristics of patients. Median OS for patients with HPD was 11.8 (95% confidence interval [CI]: 3.8-19.6) vs. 17.6 (95% CI: 12.1-42) months for those without ($p=0.076$). The respective median OS for patients with FP was 10.8 (95% CI: 5.7-17.5) vs. 23.8 (95% CI: 15-52) ($p=0.005$). Similar results were found after central radiology review. Long-term survival and response to subsequent therapies was observed among patients with hyperprogression on ICIs.

Conclusion: Hyperprogression occurs in patients with aUC treated with ICIs. In the absence of predictive tools and specific therapeutic guidance, the occurrence of hyperprogression does not have a defined role in decision making.

INTRODUCTION

Treatment with Immune Checkpoint Inhibitors (ICIs), specifically of PD-1/PD-L1 interaction, represents a valid option in 1st and 2nd-line therapy of advanced urothelial cancer (aUC) [1-3]. Despite their undisputed efficacy, only around 25% of patients will enjoy durable responses [4]. Predicting these durable responses remains elusive. Furthermore, defining response to immunotherapy has been a challenge. There is evidence that RECIST criteria used to estimate the response to chemotherapy

may not be ideal for immunotherapy [5]. Furthermore, these new immunotherapies also result in novel tumor response patterns such as delayed tumor responses or pseudoprogessions [6,7]. In addition, rapid disease progression, called hyperprogression, has also been reported in various tumor types [7-10]. It is defined as a rapid increase in Tumor Growth Rate (TGR) compared to the expected growth rate. Although infrequent, this phenomenon could suggest that immune checkpoint blockade may have a deleterious effect by accelerating the disease in a subset of patients. In this context, it would be

important to develop reliable tools to identify this situation to promptly discontinue therapy.

The most accurate radiological definition of hyperprogression is by calculating the Tumor Growth Rate (TGR) before and after initiation of ICI therapy. TGR calculation is based on measuring tumor lesion sizes on two successive Computed Tomography (CT) scans before (baseline TGR) and after (on-treatment TGR) anti-PD(L)1 therapy [11]. However, pre-baseline CT scans can be difficult to collect and may be lacking in the context of the first-line therapy. Thus, fast progression (FP) has also been proposed as a surrogate definition of hyperprogression, with a 50% increase in the sum of long diameters of target lesions within 6 weeks of initiating treatment or death due to PD within 12 weeks [11,12]. Regardless of the method used to detect hyperprogression, this feature has been shown to be a strong adverse prognostic factor in Non-Small-Cell Lung Cancer (NSCLC) [13].

Hyperprogression has been reported in patients with aUC treated with ICIs [8-15]. Nevertheless, studies focusing specifically on this cancer are lacking. We investigated the prevalence, the natural history, the predictive factors and the prognostic significance of hyperprogression in a retrospective series of patients with aUC, treated with anti PD-1/PD-L1 agents.

METHODS

Patients

Patients with histologically or cytologically proven aUC (cTNM stages IIIB-IVB) were selected from the institutional databases of two Greek referral centers for urogenital cancer. Selection criteria were: A. Treatment with ICI monotherapy for advanced/metastatic disease; b. Available reports of at least two successive disease evaluations with CT scans within 12 weeks after the initiation of ICI; c. complete set of clinical data in reference to the treatment of ICI and its outcome. Patients were excluded if ICI therapy had been given only within the following settings: a. Maintenance treatment; b. Chemotherapy/ICI combination; c. Adjuvant ICI.

Research was conducted according to Helsinki Declaration of Good Clinical Practice. All patients gave their written informed consent (approved by institutional IRBs) for analysis of their medical data.

Assessment of hyperprogression

Dimensions of target lesions were based on radiology reports. When CDs were available, hyperprogression was also assessed by an independent radiologist, blinded to the results of the CT scans reports.

FP was defined as a >50% increase in the sum of long diameters of target lesions within 12 weeks from initiating treatment with ICI. When pre-baseline scans were available, hyperprogressive disease (HPD) was defined as a > 2-fold increase of TGR-on treatment compared to TGR-baseline. TGRs were calculated by dividing the total change of target lesions with the time (in months) between the two scans. Since pre-baseline CDs were not available in most cases, changes were based on CT scan reports.

Statistical analysis

This was a retrospective study. Categorical variables were presented with absolute and relative frequencies (%). Continuous variables not normally distributed were described as medians with Interquartile Range (IQR). Normality of continuous variables was evaluated using Shapiro-Wilk test and graphical methods. The association of the baseline characteristics with FP/HPD was evaluated using parametric or non-parametric statistical tests (chi-squared test, Fisher's exact test, T-test, Mann-Whitney two-sample statistic). Survival was calculated from the day of initiation of immunotherapy until death from any cause or last follow up. Alive patients were censored at the date of last contact. Plots of the Kaplan-Meier estimators are presented. The log-rank test and stratified log-rank test were used to compare the survival distributions of subgroups. The factors chosen for prognostic significance were: FP (yes vs no) HPD (yes vs no), Eastern Cooperative Oncology Group (ECOG) PS (2+3 vs. 1+2), Non-LN metastases (yes vs no), white blood cell (WBC) count at the time of initiation of immunotherapy ($\geq$ median vs. < median) and radiology review (yes vs no). Associations [hazard ratio (HR) and 95% CI] of each of these factors with OS were evaluated using Cox proportional hazards models univariately and multi variately. To assess if the magnitude of the changes of survival due to each of the above factors depend on the other factors, we included interaction terms in the Cox model. To assess the concordance between FP and HPD we used the percent of agreement and kappa-statistic with 95% CI. The kappa-statistic was interpreted according to Landis and Koch [16]. A p-value less than 0.05 was considered statistically significant. All analyses were carried out in statistical software STATA 18.0 SE (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC.)

RESULTS

Demographics

Fifty-four patients with a median age of 68.8 years (IQR 61-72.1) were included in this analysis (Table 1). Most patients were male (85.2%), had transitional-cell histology (with or without variant) (94.4%), were located

Table 1: Baseline characteristics of patients included in the analyses according to hyperprogression. HPD was assessed in 43 patients and FP was assessed in 54.

Factor	Total	FP	p	Total	HPD	p
Age [median (IQR)]	68.8 (61-72.1)	67.1 (57.2-71.1)	.085	69.2 (64.3-73.4)	71.3 (68.5-76)	.26
Bmi [median (IQR)]	26 (23.2-29.3)	25.6 (23.2-28.1)	.34	26.5 (23.2-29.3)	26.6 (23.4-30.8)	.93
Gender						
Male	46 (85.2)	17 (77.3)	.25	35 (83.3)	4 (57.2)	.077
Female	8 (14.8)	5 (22.7)		7 (16.7)	3 (42.9)	
Primary site						
Bladder	45 (83.3)	18 (81.8)	.94	35 (83.3)	5 (71.4)	.33
Pelvis	5 (9.3)	2 (9.2)		5 (11.9)	1 (14.3)	
Ureter	2 (3.7)	1 (4.5)		1 (2.4)	0 (0)	
Bladder & Ureter	2 (3.7)	1 (4.5)		1 (2.4)	1 (14.3)	
Histology						
TCC	51 (94.4)	20 (90.9)	.51	41 (97.6)	7 (100)	>.99
Squamous	2 (3.7)	1 (4.6)		1 (2.4)	0 (0)	
Neuroendocrine	1 (1.9)	1 (4.6)		0 (0)	0 (0)	
Perioperative chemotherapy						
Yes	17 (31.5)	9 (40.9)	.11	14 (33.3)	3 (42.9)	.87
Neoadjuvant	8 (14.8)	6 (27.3)		6 (14.3)	1 (14.3)	
Adjuvant	9 (16.7)	3 (13.6)		8 (19.1)	2 (28.6)	
No	37 (68.5)	13 (59.1)		28 (66.7)	4 (57.1)	
Non-lymph node metastases						
Yes	37 (68.5)	14 (63.6)	.52	28 (66.7)	4 (57.1)	.67
No	17 (31.5)	8 (36.4)		14 (33.3)	3 (42.9)	
Metastatic sites						
Lymph nodes	38 (70.4)	15 (68.2)	.77	29 (69.1)	5 (71.4)	>.99
Bone	15 (27.8)	5 (22.7)	.49	10 (23.8)	0 (0)	.17
Lung	15 (27.8)	5 (22.7)	.49	13 (31)	1 (14.3)	.41
Liver	13 (24.1)	5 (22.7)	.85	9 (21.4)	0 (0)	.31
Soft tissue	10 (18.5)	6 (27.3)	.29	7 (16.7)	3 (42.9)	.077
Local	2 (3.7)	1 (4.6)	>.99	1 (2.4)	0 (0)	>.99
Peritoneum	1 (1.9)	0 (0)	>.99	1 (2.4)	0 (0)	>.99
WBC [mean (SD)] (n=46)	8.3 (4.3)	9 (4.6)	.2	8.3 (4.3)	10 (3.8)	.36
ECOG PS						
0	16 (29.6)	4 (18.2)	.33	13 (31)	2 (28.6)	.84
1	24 (44.4)	10 (45.5)		19 (45.2)	4 (57.1)	
2	8 (14.8)	4 (18.2)		5 (11.9)	0 (0)	
3	1 (1.9)	1 (4.5)		0 (0)	0 (0)	
missing	5 (9.3)	3 (13.6)		5 (11.9)	1 (14.3)	
Line of therapy						
1 st	28 (51.9)	10 (45.6)	.52	24 (57.1)	2 (28.6)	.23
2 nd	22 (40.7)	11 (50)		14 (33.3)	4 (57.1)	
3 rd	4 (7.4)	1 (4.6)		4 (9.5)	1 (14.3)	
Therapy						
Atezolizumab	28 (51.9)	16 (72.7)	.011	20 (47.6)	7 (100)	.003
Pembrolizumab	5 (9.3)	2 (9.1)	>.99	5 (11.9)	0 (0)	.57
Durvalumab	7 (13)	1 (4.6)	.22	6 (14.3)	0 (0)	.57
Durvalumab/Tremelimumab	4 (7.4)	1 (4.6)	.64	4 (13)	0 (0)	>.99
Nivolumab (+Ipilimumab)	10 (18.5)	2 (9.1)	.17	7 (16.7)	0 (0)	.33

FP: Fast Progression; HPD: Hyperprogressive Disease; IQR: Interquartile Range; TCC: Transitional-Cell Carcinoma; ECOG: Eastern Cooperative Oncology Group; SD: Standard Deviation; WBC: White Blood Cells; PS: Performance Status.

in the bladder (83.3%), had non-LN metastases (68.5%) and ECOG PS 0 or 1 (74%). Patients were assessed for hyperprogression after receiving immunotherapy in 1st-line (51.9%), 2nd-line (40.7%) or 3rd-line (4.7%) for aUC. ICIs used included: atezolizumab (51.9%), pembrolizumab (9.3%), durvalumab (13%), durvalumab/tremelimumab (7.4%), nivolumab or nivolumab/ipilimumab (18.5%). Pre-baseline scans were available in 43 cases (23 were reviewed blindly by radiologist).

Frequency of hyperprogression

Our analysis revealed different rates of hyperprogression

based on the criterion employed. Applying the definition of HPD based on TGR we found 7 cases among the 43 cases studied (16.3%, 95% CI: 7-31.4%). We also found 22 cases of FP among the 54 studied (40.7%, 95% CI: 27.6-55%). Among the 35 cases without HPD, 29 were found not to fulfill the definition of FP, and among the 7 cases with HPD, 6 fulfilled the definition of FP. This resulted in a 83.3% (95% CI: 66.4-99.9) agreement between the two methods. The kappa statistic measure for concordance was moderate (0.533, 95% CI 0.325-0.742).

We investigated the correlation between hyperprogression and other clinical factors, such as age,

tumour location, metastatic status, Eastern Cooperative Oncology Group Performance Status (ECOG PS), WBC and treatment line. We found no significant associations between hyperprogression and any of the factors studied, regardless of the definition of hyperprogression used (Table 1). Atezolizumab was associated with more frequent occurrence of HPD as well as FP (Table 1).

Hyperprogression and survival

Survival data were available for 53 of 54 patients (42 with pre-baseline tumor assessment). Median overall (OS) survival for the whole population was 16.3 months (95% CI: 11.7-23.8). During follow up 35 patients (64.8%) died. Causes of death was disease progression in 33 cases and comorbidity/other in 2 cases. Patients with hyperprogression had significantly shorter median OS. Median OS for patients with HPD was 11.8 months (95% CI: 3.8-19.6) vs. 17.6 (95% CI: 12.1-42) for those without ($p=0.076$). The respective median OS for FP were 10.8 months (95% CI: 5.7-17.5) vs. 23.8 (95% CI: 15-52) ($p=0.005$). (Fig. 1A, 1B). When log rank test was stratified by line of therapy, the significance of hyperprogression was retained for either definition ($p<0.001$ and $p=0.002$, respectively) (**Supplementary Figures 1A,B**).

Multivariate analysis including the presence of non-LN metastases, ECOG PS and showed that hyperprogression retained its prognostic significance regardless of the definition used (Table 2).

Results after central radiology review

In 23 cases central blind radiology review was possible. HPD was studied in 21 cases with pre-baseline imaging available. There were no differences in baseline characteristics between the cases reviewed by the radiologist and those who did not (**Supplementary Table 1**) with the exception of agents used: durvalumab and tremelimumab were more frequent in the radiologist group, while pembrolizumab was not used in any of the cases reviewed by radiologist.

We found 3 cases of HPD (14.3% 95% CI: 3-36.3%) and 7 cases of FP (30.4%, 95% CI: 13.2-52.9%) (**Supplementary Table 1**). This resulted in a 76.2% (95% CI: 53.9 -98.5) agreement between the two methods. The kappa statistic measure for concordance was fair (0.314, 95% CI -0.056-0.683, $p=0.126$) There was no association between hyperprogression and age, tumour location, metastatic status, ECOG PS and treatment line (**Supplementary Table 1**). When survival analyses were restricted to cases with radiology review we found no significant association of

Table 2: Uni and multivariate analyses

Factor		n	HR	95% CI		p-value
Univariate						
FP	yes no	21 32	2.67	1.32	5.39	0.006
HPD	yes no	7 35	2.28	0.89	5.84	0.085
Non-LN metastases	yes no	36 17	1.31	0.62	2.76	0.475
ecog ps	2+3 0+1	9 39	1.2	0.49	2.94	0.7
WBC	≥ median < median	23 23	2.79	1.29	6.04	0.009
Multivariate for HPD						
ecog ps	2+3 0+1	5 32	0.66	0.15	2.95	0.604
Non-LN metastases	yes no	25 12	1.63	0.63	4.23	0.317
HPD	yes no	6 31	3.04	1.002	9.21	0.049
WBC	≥ median < median	17 18	3.20	1.07	9.54	0.037
Multivariate for FP						
ecog ps	2+3 0+1	9 39	0.98	0.39	2.43	0.96
Non-LN metastases	yes no	33 15	1.08	0.49	2.4	0.85
FP	yes no	18 30	3.67	1.66	8.11	0.001

HR: Hazard Ratio; CI: Confidence Interval; HPD: Hyperprogressive Disease; FP: Fast Progression; LN: Lymph Node; ECOG: Eastern Cooperative Oncology Group; PS: Performance Status; WBC: White Blood Cells

HPD or FP with OS. When radiology review was added to the multivariate analysis, hyperprogression retained its independent prognostic significance regardless of the definition used (**Supplementary Table 2**).

Non-HPD/FP progressive disease and association with response to chemotherapy

In order to study the potential biological impact of hyperporgression, we compared outcomes between patients with this feature and patients who progressed on immunotherapy without fulfilling the criteria of hyperprogression.

Thirty patients experienced PD at the first disease assessment on immunotherapy. Fifteen fulfilled the criteria of HPD/FP. Median OS for these patients was 11.8 months (95% CIs: 3.8-17.5) vs. 15 months (595% CIs: 8-NR) for those without HPD/FP (Figure 1C). The respective 1-year survival rates were: 44% (95% CIs: 18.5-67.1) vs. 65.5% (95% CIs: 35.7-84).

In order to study the association of response to chemotherapy with the development of hyperprogression, we performed exploratory analysis in the group of 24 patients who received chemotherapy only in 1st-line. We found no association between response to

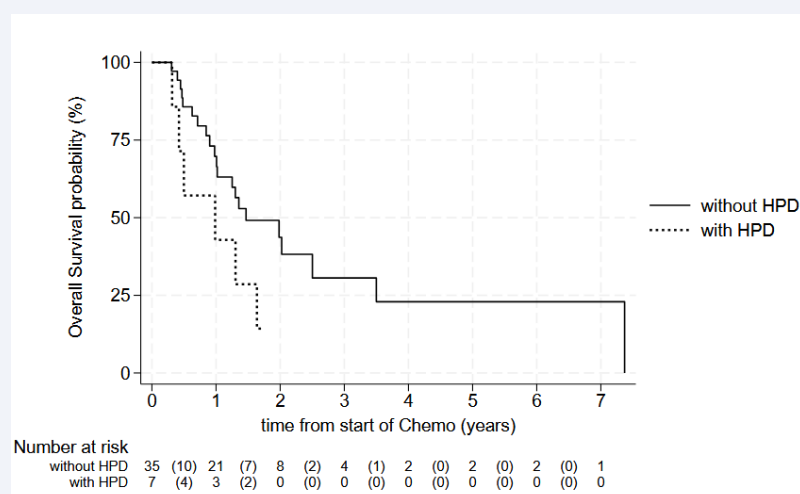


Figure 1 Overall survival curves of patients with advanced/metastatic urothelial cancer showing hyperprogression after treatment with immune checkpoint inhibitors according to hyperprogressive disease (A, n=42) or fast progression (B, n=53).

chemotherapy and subsequent development of HPD/FP (**Supplementary Table 3**). Nevertheless, this result should be viewed with caution due to the small number of patients in each group.

Post hyperprogression treatment and outcomes

Among the 23 patients who developed HPD and/or FP, 14 did not receive any further treatment following the development of hyperprogression and they all died within 6 months. Two patients received only palliative radiotherapy and both died within 9 months. The remaining 7 patients received further systemic therapy, while one of them also received palliative radiotherapy (**Supplementary Table 4**). Their survival ranged from 8 months to 7 years. One patient achieved partial remission on chemotherapy following hyperprogression on atezolizumab, while 4 patients continued ICIs in spite of hyperprogression: one patient achieved partial remission of his disease, while the remaining 3 had stabilization of their disease. Two of these patients survived for 15 and 38 months after hyperprogression, while another one remained alive two years after the development of hyperprogression.

DISCUSSION

Hyperprogression has been a matter of concern since the wide application of ICIs in oncology. This concern was mainly due to the notion that inferior outcomes compared with standard chemotherapy of PD-1/PD-L1 blockade during the first months of treatment, observed in some phase III studies, has been attributed to hyperprogression. Early death and crossing survival curves in phase III trials

have been mainly observed in NSCLC, head and neck squamous cell carcinoma or urothelial cancers but the mechanism of instigation of hyperprogression is largely unknown. Expansion of tumor-infiltrating PD-1+ Treg cells during PD-1 blockade to overwhelm tumor-reactive PD-1+ effector T cells has been proposed as a possible mechanism [17]. In addition, since hyperprogression is a phenomenon happening at the onset of anti-PD(L)1 monotherapies, changes in routine practice, involving first tumor assessment as early as 3 weeks after the initiation of anti-PD(L)1 has been suggested [13] to prevent exposing patients to a potential ineffective or even deleterious therapy.

To our knowledge, this is the only study of hyperprogression focused exclusively on urothelial cancer and we believe that contributes useful real-world evidence in this poorly understood manifestation. We used both definitions of hyperprogression reported in the literature: HPD (based on TGR before and after initiation of immunotherapy) and FP (based on >50% increase in disease at first tumor assessment and certainly no later than 12 weeks after the initiation of immunotherapy). The definition of FP was not identical to that of previous studies [13,18], using 6 weeks as the cut off, since such early routine tumor assessment is not favored in everyday practice. A fraction of our cases were also blindly reviewed by a radiologist. With this methodology we attempted to establish whether the easiest to apply method in routine practice, i.e. FP could offer similar clinical information with the other two methods, which are associated with difficulties for everyday application, such as availability

of pre-baseline scans or dedicated radiologists. The rate of HPD (16.7%) concur with those previously reported for UC: Soria et al reported hyperprogression in 25% of patients treated with ICIs [14], while Hwang et al reported a 11.9% hyperprogression rate [15]. FP was found in 40.7% of our patients. Different hyperprogression rates according to the definition used has also been reported for NSCLC: Gandara et al. showed a 10% hyperprogression rate among patients with NSCLC treated with atezolizumab, which was raised to 48% when only 50% increase at 6 weeks was considered [13]; similarly, Kim et al. reported a 20.5% hyperprogression rate based on TGR and a 37.3% rate based on time to treatment failure < 2 months (similar to our criterion of 50% increase at first tumor assessment) [19]. Radiology review also did not result in meaningful differences in hyperprogression rates with either definition compared to the non-reviewed cases.

In line with experience from other solid tumors, patients with hyperprogression had worse prognosis than those without [8-19]. This is not, however, a specific feature of immunotherapy with ICIs. Subanalyses of randomized trials in NSCLC showed that patients developing hyperprogression after chemotherapy have also worse outcomes compared with those who did not [13]. Therefore, in relation to this phenomenon, clinically important questions for patients treated with ICIs would be: a. Is there a higher percentage of hyperprogressors among patients treated with ICIs than among those treated with chemotherapy? b. Can we predict hyperprogression in order to change practice in patients likely to develop it? c. Should we manage patients with hyperprogression differently than those developing progression at a later stage or after other forms of anti-cancer treatment? Data from NSCLC regarding the incidence of hyperprogression during immunotherapy and chemotherapy are contradicting: Ferrara reported 13.6% hyperprogressors on ICIs vs. 5.1% on chemotherapy using the TGR estimation to define hyperprogression [18]. When FP was used, no difference between atezolizumab and docetaxel was observed in another study [13]. In aUC, early crossing of survival curves in randomized trials has been attributed to higher frequency of hyperprogression among patients treated with ICIs [20-22]. Nevertheless, focused analysis on hyperprogression in populations from randomized trials has not been performed. Regional recurrence has been associated with hyperprogression in head & neck cancer treated with ICIs [9]. In NSCLC, number of metastatic sites and ECOG PS have been associated with hyperprogression [13,18], although other studies found no correlation with clinicopathological factors [8,19]. We also found no such correlation in our study.

Predicting the development of hyperprogression has been so far elusive. We found no correlation with previous response to chemotherapy or line of treatment with immunotherapy. Results from translational correlative studies have also been contradictory: EGFR alteration was found to be strong predictor in a case series including several cancers [10], but such correlation was not found in a study of NSCLC [13]. T-lymphocyte subpopulations have also been suggested as promising predictors of hyperprogression [17,19].

In our study, most patients succumbed to their disease short after hyperprogression without further treatment. Nevertheless, we could not find a significantly different outcome compared to patients who showed PD not fulfilling hyperprogression criteria in first tumor assessment. Furthermore, among 7 patients who received systemic therapy after hyperprogression, 3 of them (13% of hyperprogressors) surviving beyond 2 years. Importantly, in 4 cases (17% of hyperprogressors) at least stabilization of disease was achieved by continuing the same agent, suggesting pseudoprogession rather than hyperprogression.

Our study has several limitations. First, our study was retrospective without any control arm. It would have been interesting to perform a similar analysis in a cohort of patients treated in the same setting with other drugs than checkpoint inhibitors. Second, independent radiological review was not possible in many cases. It is, however, reassuring that results among patients whose imaging was reviewed did not differ from those who did not have available scans. A strength of our study is that we studied hyperprogression in patients receiving only ICIs without chemotherapy, which could confound our results. In addition, our study is representative of everyday practice, where decisions are frequently based on imaging reports without independent review and pre-baseline scans are not available for the measurement of TGR. The relatively small sample size also represents a limitation of the present study and may have restricted the statistical power to detect additional associations. Future prospective studies with larger patient cohorts and standardized imaging protocols are warranted to validate our findings.

In conclusion, in the first study focused in patients with aUC treated with ICIs, we report a 16.7% HPD, which is among the highest reported in cancer immunotherapy. When pre-baseline imaging is not available, FP can be used as an alternative to define hyperprogression. Although HPD is a clinically relevant phenomenon, its role in treatment decision-making remains undefined. Currently, there is no recommendation for earlier routine assessment

to exclude asymptomatic hyperprogression in patients treated with immunotherapy or different management than that of patients developing non-hyperprogressive PD, while clinical criteria are suggested to differentiate HPD from pseudoprogression. These limitations highlight the importance of further investigation into the biology of this phenomenon and focused drug development in this field.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Zakopoulou R, Fillipiadis J, Tzannis K, , Nikolaidou VK, Bamias A. Performed data acquisition, as well as provided administrative, technical, and material support: Zakopoulou R, Fillipiadis J, Kratiras Z, Koutsoukos K, Mamali A, Grigoriou F, Papatheodoridi AM, Lontos M, Kakogianni K, Chrisofos M, Dimopoulos MA, Bamias A.

Availability of data and materials
Not applicable.

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Conflicts of interest

RZ declared honoraria from Janssen

AB declared honoraria, advisor compensation and/or research support from Pfizer, AZ, BMS, MSD, Merck

Ethical approval and consent to participate

Research was conducted according to Helsinki Declaration of Good Clinical Practice. All patients gave their written informed consent (approved by institutional IRBs) for analysis of their medical data

Consent for publication: Not applicable.

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