Titolo rivista/libro: Anti-cancer drugs (Online)

Titolo articolo/sezione: Hyperprogressive disease in advanced cancer patients treated with nivolumab: a case series study

Autore/i: Petrioli R , Mazzei MA , Giorgi S , Cesqui E , Gentili F , Francini G , Volterrani L , Francini E

ISSN: 1473-5741

DOI: 10.1097/CAD.0000000000000864

Anno: 2020

Volume: 31

Fascicolo: 2

Editore:

Pag. iniziale: 190

Pag. finale: 195

Hyperprogressive disease in advanced cancer patients treated with nivolumab: a case series study

Roberto Petrioli[a], Maria Antonietta Mazzei[b], Silvano Giorgi[c], Eleonora Cesqui[c], Francesco Gentili[b], Guido Francini[a], Luca Volterrani[b] and Edoardo Francini[d,e]

The aim of this retrospective study was to detail the main clinicopathological characteristics of advanced cancer patients exhibiting hyperprogressive disease (HPD) during immune checkpoint inhibitor (ICI) nivolumab as second- or third-line treatment. A cohort of patients starting second or third-line nivolumab for advanced cancer from 2016 to 2018 was identified from our institution IRB approved and prospectively collected registry. HPD was defined as at least two-fold increase in the tumor growth rate (TGR) during immunotherapy compared to TGR during the preimmunotherapy period. Overall, 47 patients were eligible for this analysis. HPD was observed in three patients (6%) with metastatic lung adenocarcinoma, metastatic urothelial transitional carcinoma, and metastatic hepatocellular carcinoma, respectively. These three patients showed a rapid clinical deterioration and survived less than 3.5 months from immunotherapy onset. Their chief preimmunotherapy characteristics were: age < 75 years, ≥2 metastatic sites, programmed death-ligand 1 < 50%, neutrophil-to-lymphocyte ratio > 3, and elevated lactate dehydrogenase. The results of the current study seem to reinforce the hypothesis that in some cases immunotherapy promotes a dramatic increase of TGR and may suggest possible clinical predictors of HPD during nivolumab. *Anti-Cancer Drugs* **31:190–195**

Anti-Cancer Drugs 2020, **31**:190–195

Keywords: hepatocellular carcinoma, hyperprogression, immunotherapy, nivolumab, nonsmall lung cancer

[a]Medical Oncology Unit, Department of Medicine, Surgery and Neurosciences, [b]Department of Medical, Surgical and Neuro Sciences, Diagnostic Imaging, [c]Oncological and Clinical Pharmacy, Azienda Ospedaliera Universitaria Senese, Siena, [d]Department of Oncology, La Sapienza University, Rome and [e]Department of Oncology, Medical Oncology Unit, Misericordia Hospital, Grosseto, Italy

Correspondence to Roberto Petrioli, Medical Oncology, University of Siena, Viale Bracci, 53100 Siena, Italy
Tel: +390577586139; fax: +390577586231;
e-mail: r.petrioli@ao-siena.toscana.it

Received 9 July 2019 **Revised form accepted** 21 October 2019

Introduction

Several immunotherapeutic agents that block immune checkpoints, such as programmed cell death 1 receptor (PD-1) and programmed death-ligand 1 (PD-L1), have been investigated and clinically used for various types of cancer [1,2]. In particular, nivolumab is an immune checkpoint inhibitor (ICI) targeting PD-1 which demonstrated a manageable safety profile and favorable clinical activity in pretreated patients with recurrent or metastatic nonsmall lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma, urothelial transitional cancer (UTC), and hepatocellular carcinoma (HCC) [3–5].

Radiological patterns of response to ICI treatment include complete remission (CR), partial remission (PR), stable disease, progressive disease (PD), and pseudoprogression, defined as a response albeit in the presence of tumor growth or new lesions due to immune cell infiltration [6]. Recent radiological data suggested that a new pattern of progression termed hyperprogressive disease (HPD) may be observed in a small portion of patients receiving immunotherapy. HPD was defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as a two-fold or greater increase in the tumor growth rate (TGR) at the first radiological evaluation compared with that of ICI onset. This phenomenon was first described in a French study in which HPD occurred in 9% of 131 advanced cancer patients receiving ICI treatment [7]. HPD is typically associated with a rapid deterioration of the performance status which prevents continuation of the immunotherapy or start of any other anticancer treatment and prognosis is poor. In this regard, the remarkable death rates observed during the first 3 months of nivolumab in a few phase III trials was partly attributed to a rapid acceleration of the tumor growth including HPD [8,9]. Although a growing number of studies have recently focused on the causes and recognition of HPD during ICI therapy, the mechanisms underpinning the development of this phenomenon are yet to be fully unveiled. In addition, identifying clinical and biological factors able to predict a hyperprogressive response would allow for avoiding ICI in patients potentially at the risk of developing HPD. Therefore, in this retrospective study, we sought to detail the clinicopathological features of advanced cancer patients who exhibited HPD during treatment with nivolumab.

0959-4973 DOI: 10.1097/CAD.0000000000000864

Patients and methods

Eligibility criteria

This single-institution retrospective study received institutional review board approval prior to commencing. Consented patients with histologically proven and radiologically measurable locally advanced or metastatic solid tumors starting nivolumab as second- or third-line treatment between January 2016 and December 2018 were consecutively identified from our prospectively collected hospital registry. Patients who had prior immunotherapy were excluded. Other exclusion criteria included age less than 18 years, Eastern Cooperative Oncology Group (ECOG) performance status > 2, and a life expectancy < 3 months. The following data were registered: gender, age and ECOG performance status at baseline, stage at diagnosis per TNM staging system, type of primary tumor, type and number of metastatic sites at baseline, best response to first-line chemotherapy, and a life expectancy of at least 3 months.

Radiologic evaluation

Eligibility criteria included a computed tomography (CT) scan performed within 3 weeks prior to and one at least 3 weeks after initiating nivolumab. HPD was defined as at least two-fold increase in the TGR during immunotherapy compared with the reference (prior to treatment onset) period [10].

Patient evaluation

The PD-L1 expression was evaluated by immunohistochemistry on the biopsy tumor specimen and the cutoff for positivity was 1%. Patients were seen at the beginning of every nivolumab cycle for a physical examination, monitoring of symptoms and toxic effects, and a complete blood count. Then, disease was reassessed every six cycles of immunotherapy or before if clinically indicated. Nivolumab 3 mg/kg (or 240 mg fixed dose since April 2018) every 2 weeks was given intravenously until disease progression, unacceptable toxicity, or patient refusal.

Statistical considerations

The primary endpoint of this study was to detail the clinicopathological characteristics of patients with HPD during nivolumab treatment. The secondary endpoints were progression-free survival (PFS), as the time elapsed from immunotherapy start to progression or death from any cause, overall survival (OS), defined as the time from nivolumab onset to death from any cause or last follow-up visit, and objective response rate (ORR), defined as the rate of patients achieving CR or PR. RECIST criteria 1.1 and immune-related response criteria (irRC) were used to evaluate ORR and PFS [6]. Per irRC, radiological PD was defined by two consecutive positive CT scans performed within >4 weeks interval. The Kaplan–Meier method was used to assess the distributions of PFS and OS, including median time-to-event and its 95% confidence interval (CI). Statistical analyses were conducted by MEDcalc software.

Results

Patient characteristics

Overall, 51 patients were retrospectively selected and 47 patients resulted eligible for this analysis. Of the four excluded patients, two were removed due to nonmeasurable disease on baseline imaging, and two were lost to follow-up after one nivolumab administration. Baseline demographic, clinical, and pathologic characteristics of patients are presented in Table 1. Most subjects were men (72%, 34 of 47) less than 75 years old (median age, 68 years; range, 44–82 years) with ECOG performance status of 0-1 (91%, 43 of 47). The majority (77%, 36 of 47) had locally advanced or metastatic NSCLC and at least two metastatic sites (83%, 39 of 47).

Efficacy

In the overall population, the ORR was 27.6%: three patients achieved CR, 10 achieved PR, 15 patients had stable disease, and 19 had PD (Table 2). One responding NSCLC patient was initially defined as PD, but

Table 1 Patient characteristics

Variable	All patients (n=47)
Age, years	
Median	68
Range	44–82
Sex	
Male	34
Female	13
ECOG performance status	
0	29
1	14
2	4
Primary tumor	
Lung	36
Head and neck	4
Kidney	3
Bladder	2
HCC	2
Metastatic sites	
Lung	31
Lymph node	29
Liver	8
Bone	13
Adrenal gland	3
Brain	4
Pleura	2
Peritoneum	1
Best response to first-line therapy	
PR	21
Stable disease	19
PD	7
>1 metastatic site	39
PD-L1 status	
Positive	14
Negative	4
Unknown	29
EGFR mutation	0
ALK rearrangement	0
Unknown	34
Lactate dehydrogenase level (U/ml)	
>Upper limit of normal	19
Neutrophil-to-lymphocyte ratio	
<3	33
≥3	14

Data are expressed as numbers (%) except where otherwise noted.
ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial remission.

deterioration in performance status or increase of clinical symptomatology was not observed and the CT scan performed 2 months after the initial documentation of PD revealed a dramatic decrease in target lesions. This patient was reported having a pseudoprogression. After a median follow-up of 11.8 months, 31 patients were died and 16 were still alive. Median PFS was 6.2 months (95% CI, 4.5–7.8 months) and median OS was 12.3 months (95% CI, 10.2–22.4 months). In the consistent subgroup of 36 NSCLC, the ORR was 25%, median PFS was 6.6 months (95% CI, 4.8–12.1), and median OS was 12.8 months (95% CI, 9.8–26.7) (Fig. 1).

Hyperprogressive disease case series

HPD was observed in three of 47 patients (6%) (Table 3). All three cases were less than 75 years old, had a good ECOG performance status (0-1), and bone and liver metastases. Two of three were females.

Table 2 Secondary endpoints

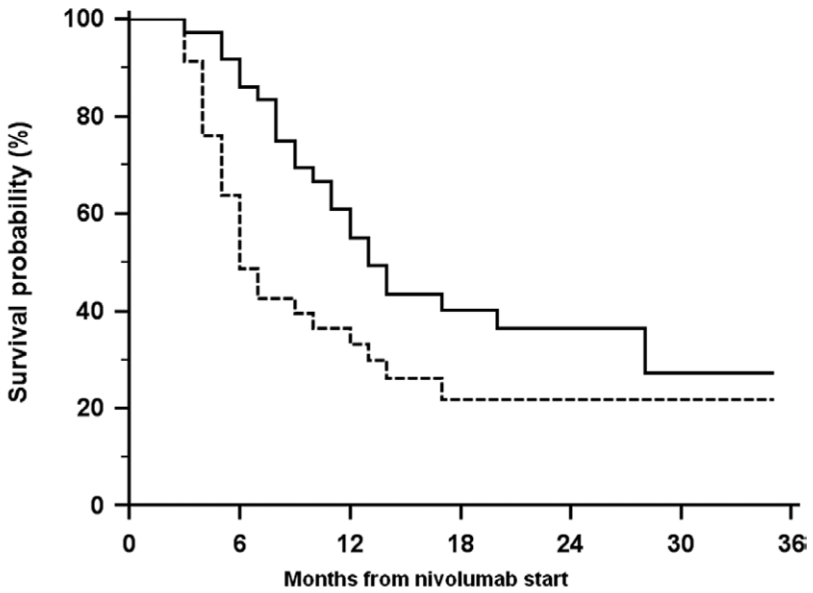
Variable	
Nivolumab cycles, *n* median (range)	9 (2–88)
Objective response rate, *n* (%)	13 (27.6)
Complete remission	3 (6.3)
Partial remission	10 (21.2)
Stable disease	15 (31.9)
Progressive disease	19 (40.4)
Median progression free survival, months (95% CI)	6.2 (4.5–7.8)
Median overall survival, months (95% CI)	12.3 (10.2–22.4)
Median follow-up, months (range)	11.8

CI, confidence interval.

HPD case 1 was a 61-year-old man with NSCLC with mediastinal lymph nodes, liver, and bone metastases. PD-L1 was <1% and epidermal growth factor receptor (EGFR) mutational status was negative. He received cisplatin + pemetrexed as first-line chemotherapy and achieved PR on primary tumor and metastatic sites. During pemetrexed maintenance, after 13 months from the start of chemotherapy, PD (mainly on liver metastases) was reported and the patient started nivolumab as second-line treatment. The increase in tumor burden before starting immunotherapy was about 36%. During immunotherapy, the patient developed rapid worsening of fatigue, dyspnea, and abdominal and bone pain. A CT scan performed 2.3 months after starting nivolumab revealed more than 50% increase in liver metastases and lymph nodes volume, pericardial effusion and carcinomatous lymphangitis, as well as new liver lesions, compared with prenivolumab imaging. The patient died 2.8 months after starting immunotherapy.

HPD case 2 was a 59-year-old woman with local relapse, liver, bone, and pelvic lymph node metastases from UTC surgically removed 3 years before. This patient received cisplatin and gemcitabine as first-line treatment and achieved PR during chemotherapy. PD-L1 was positive. After 8 months from the start of first-line therapy, a CT scan revealed PD on bone and liver metastases, with TGR about 60% increase in tumor burden. During the following nivolumab treatment the patient presented rapid worsening of right hypochondriac region and bone pain, and quick clinical deterioration which prompted the physician to interrupt immunotherapy and obtain a CT scan. The imaging was performed 2.1 months after

Fig. 1



Kaplan–Meier estimates of PFS (----) and OS (–) from nivolumab start. PFS, progression-free survival; OS, overall survival.

Table 3 Characteristics of patients with hyperprogressive disease

	HPD case 1	HPD case 2	HPD case 3
Age, years	61	59	73
Gender	Male	Female	Female
ECOG performance status	0	0	1
Primary tumor	Lung adenocarcinoma	UTC	HCC
Site of metastases	Liver, bone, lymph nodes	Bone, liver, lymph nodes	Liver, bone
Best response to first-line therapy	Partial remission	Partial remission	Progressive disease
Nivolumab cycles	5	4	5
Time from baseline CT-scan and start of Nivolumab, days	9	12	14
PD-L1	Negative	Positive	Positive
EGFR mutation	No	No	No
LDH (U/ml)	285	364	422
Neutrophil-to-lymphocyte ratio	3.6	5.1	4.2

Data are expressed as numbers (%) except where otherwise noted.
CT, computed tomography; EGFR, ; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HPD, hyperprogressive disease; LDH, lactate dehydrogenase; PD-L1, programmed death-ligand 1; UTC, urothelial transitional cancer.

nivolumab onset and showed remarkable progression locally and distantly at the liver, presence of ascites, and bilateral pleural effusion. The patient died 27 days later (OS = 3 months).

HPD case 3 was a 73-year-old woman with HCC and bone metastases. After 4 months of first-line treatment with sorafenib, a CT scan documented PD on liver metastases, with about 44% increase in tumor burden, and the patient started nivolumab. PD-L1 was positive. A rapid worsening of bone pain and fatigue grade 4 was reported 1.8 months after nivolumab start and immunotherapy was interrupted. A CT scan revealed progression of the liver metastases with massive parenchymal disruption as well as several new hepatic lesions, bilateral lung metastases, and impressive increase in the osteolytic bone lesions. The patient died 3.4 months after the start of immunotherapy.

Figure 2a–c shows CT scan images at 2–3 months before the start of immunotherapy (pre), immediately before the start of immunotherapy (baseline), and at the first evaluation after immunotherapy (post) in the three HPD patients.

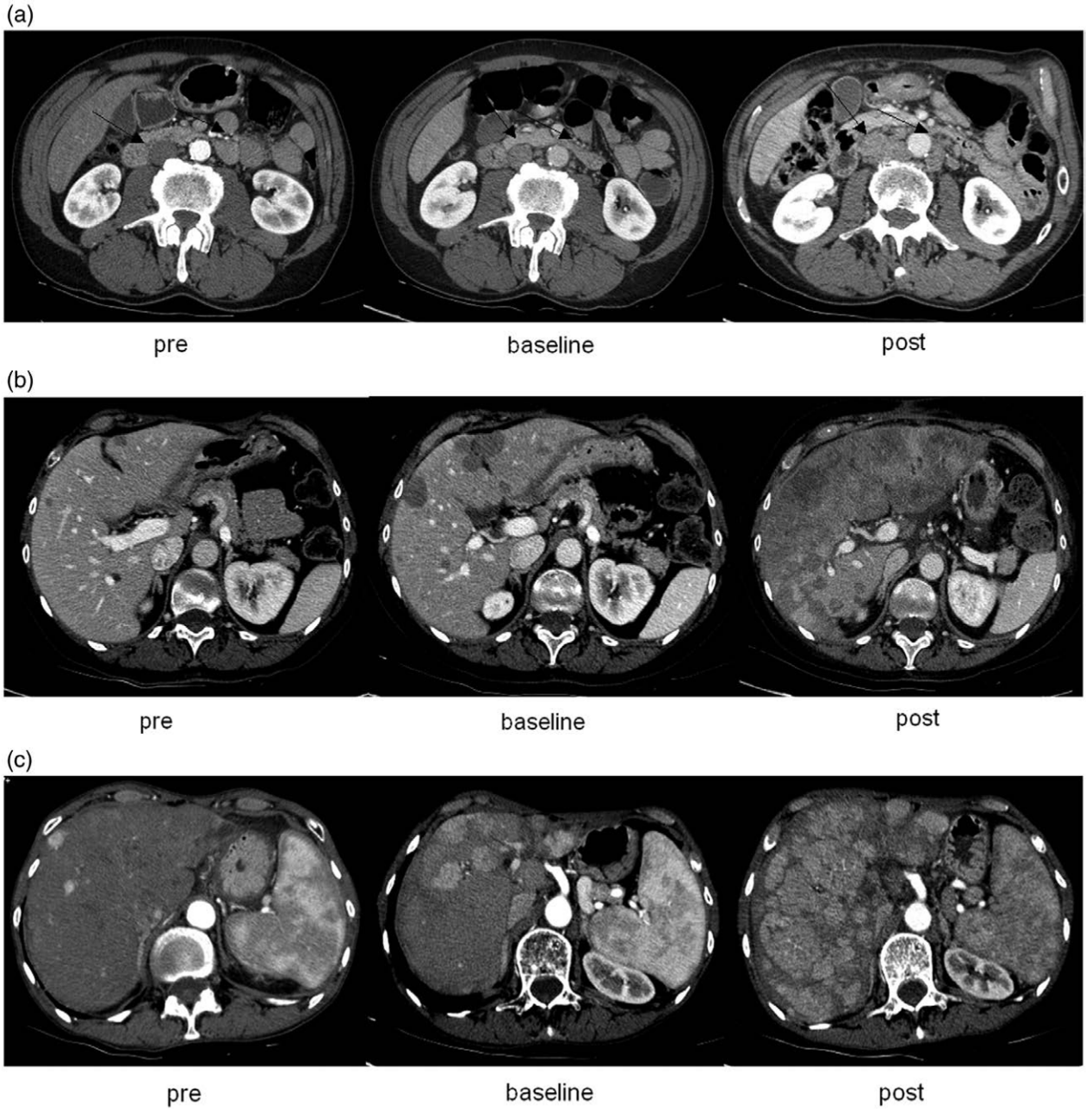
Discussion

In this retrospective analysis of 47 patients with advanced solid tumors treated with the ICI nivolumab as second- or third-line treatment, HPD was observed in 6% of subjects. This HPD rate was similar to that reported in a recent study of 182 patients with different tumor types treated in phase I trials with ICI therapy (7%) [11]. However, the observed HPD incidence varies largely in the literature ranging from a 29% rate reported in a series of 34 patients with recurrent or metastatic HNSCC treated with ICI and a 4% shown in a study that investigated genomic alterations associated with accelerated TGR [12,13]. Particularly, HPD was recently documented in 25% of 187 patients with NSCLC treated with ICI [14]. In this regard, although the subgroup of 36 NSCLC patients of the present study showed ORR (25%), median PFS (6.6 months), and median OS (12.8 months) comparable to those observed in other larger studies [3,8], HPD was reported in only one subject (3%). The different rates observed across these various clinical experiences could be partly attributed to the lack of a common definition of HPD. Furthermore, there are still doubts over HPD being a real phenomenon associated with ICI treatment rather than simply a fast progression that existed also with chemotherapy in the pre-ICI era [15]. The clinicopathological characteristics and evolution of the three HPD cases reported during ICI nivolumab in the present analysis seem to exclude the possibility of those being regular PD. In fact, these three patients showed an impressive radiological worsening of their disease and a rapid deterioration of their clinical conditions. The OS observed for these three subjects (2.8, 3.0, and 3.4 months) was poorer than expected with best supportive care which further reinforces the association between occurrence of HPD and ICI use.

As described in previous reports [7], also in our study HPD seems to occur irrespective of the primary tumor histology because it was observed also in UTC and HCC. However, the current literature reports small data on the occurrence of HPD in patients with UTC or HCC treated with nivolumab. Particularly, a recent case report described a 58-year-old male with advanced UTC who developed HPD during ICI treatment upon progression on adjuvant chemotherapy with cisplatin and gemcitabine [16]. Interestingly, this patient presented with similar clinicopathologic characteristics to our HPD case 2: age < 75 years, PD-L1 positive, and at least two metastatic sites. To the best of our knowledge, only a recent retrospective study performed at the National Cancer Centre of Singapore reported a series of HPD in a group of HCC patients treated with immunotherapy [17].

Given the extremely poor prognosis associated with HPD occurrence, the research is also focusing on identifying possible predictive factors. In this regard, in a large retrospective study of patients with advanced NSCLC treated with ICIs or chemotherapy, HPD was documented in 13.8% of subjects and was associated with a

Fig. 2



(a) High increase in the size and number of abdominal metastatic lymph nodes after immunotherapy in a man with advanced lung adenocarcinoma. (b) Impressive progression of liver metastases after immunotherapy in a woman with advanced UTC. (c) Massive liver involvement after immunotherapy in a woman with advanced HCC. HCC, hepatocellular carcinoma; UTC, urothelial transitional cancer.

high metastatic burden at baseline; early death occurred mostly in the first 2–3 months of immunotherapy [18]. In a similar fashion, all three HPD cases of the present report had at least two metastatic sites at baseline and an OS ranging from 2 to 4 months. Data from previous clinical experiences seem to confirm the association between metastatic burden and risk of HPD during immunotherapy [7,12,19]. Other studies suggested a correlation between older age as well as previous radiotherapy with HPD occurrence [12]. Our findings seem contrast with this hypothesis because two of three HPD cases in the current report were <65 years old and none had previously received radiotherapy. However, most of our population was relatively young and only two of four patients with HNSCC and six of 36 with NSCLC had prior radiotherapy on target lesions. Furthermore, murine double

minute 2 (MDM2) amplifications and EGFR mutations were frequently reported associated with HPD, whereas no correlation between PD-L1 status and HPD has yet been observed [13,20]. Although the determination of MDM2 amplification was not available at our Institution, which of the EGFR mutational status was performed in all three HPD cases resulting wild type.

It is noteworthy that all our HPD patients presented with higher than normal lactate dehydrogenase (LDH) serum levels and >3 neutrophil-to-lymphocyte ratio (NLR) before starting nivolumab. Although the increase in these two parameters have been associated with a shorter OS in several trials of advanced tumors treated with ICI [21,22], it should be noted that LDH was high in five patients and NLR was >3 in nine patients who achieved a disease control rate (CR, PR, or stable disease).

In conclusion, the findings of this retrospective single-institution study contribute to reinforce the hypothesis that in some cases immunotherapy leads to a dramatic acceleration of TGR and add useful data to the research focusing on the identification of clinical predictors of HPD during ICI therapy. Finally, based on our data as well as previous studies, we recommend particular caution regarding the use of ICI therapy for pretreated advanced cancer patients who present with two or more metastatic sites.

Acknowledgement

Conflicts of interest

There are no conflicts of interest.

References

1 Giroux Leprieur E, Dumenil C, Julie C, Giraud V, Dumoulin J, Labrune S, Chinet T. Immunotherapy revolutionises non-small-cell lung cancer therapy: results, perspectives and new challenges. *Eur J Cancer* 2017; **78**:16–23.

2 Nishijima TF, Shachar SS, Nyrop KA, Muss HB. Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy in patients with advanced cancer: a meta-analysis. *Oncologist* 2017; **22**:470–479.

3 Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, *et al.* Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015; **373**:123–135.

4 El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, *et al.* Nivolumab in patients with advanced hepatocellular carcinoma (checkmate 040): an open-label, non-comparative, phase ½ dose escalation and expansion trial. *Lancet* 2017; **389**:2492–2502.

5 McDermott DF, Drake CG, Sznol M, Choueiri TK, Powderly JD, Smith DC, *et al.* Survival, durable response, and long-term safety in patients with previously treated advanced renal cell carcinoma receiving nivolumab. *J Clin Oncol* 2015; **33**:2013–2020.

6 Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, *et al.* Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; **15**: 7412–7420.

7 Champiat S, Dercle L, Ammari S, Massard C, Hollebecque A, Postel-Vinay 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**:1920–1928.

8 Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373**:1627–1639.

9 Inoue T, Tamiya M, Tamiya A, Nakahama K, Taniguchi Y, Shiroyama T, *et al.* Analysis of early death in japanese patients with advanced non-small-cell lung cancer treated with nivolumab. *Clin Lung Cancer* 2018; **19**:e171–e176.

10 Ferté C, Fernandez M, Hollebecque A, Koscielny S, Levy A, Massard C, *et al.* Tumor growth rate is an early indicator of antitumor drug activity in phase I clinical trials. *Clin Cancer Res* 2014; **20**:246–252.

11 Kanjanapan Y, Day D, Wang L, Hansen A, Razak A, Spreafico A, *et al.* Hyperprogressive disease (HPD) in early-phase immunotherapy (IO) trials. *J Clin Oncol* 2018; **36**:3063.

12 Saâda-Bouzid E, Defaucheux C, Karabajakian A, Coloma VP, Servois V, Paoletti X, *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**:1605–1611.

13 Kato S, Goodman A, Walavalkar V, Barkauskas DA, Sharabi A, Kurzrock R. Hyperprogressors after immunotherapy: analysis of genomic alterations associated with accelerated growth rate. *Clin Cancer Res* 2017; **23**:4242–4250.

14 Lo Russo G, Moro M, Sommariva M, Cancila V, Boeri M, Centonze G, *et al.* Antibody-fc/fcr interaction on macrophages as a mechanism for hyperprogressive disease in non-small cell lung cancer subsequent to PD-1/PD-L1 blockade. *Clin Cancer Res* 2019; **25**:989–999.

15 Popat S. Hyperprogression with immunotherapy: is it real? *Cancer* 2019; **125**:1218–1220.

16 Mao S, Zhang J, Guo Y, Zhang Z, Wu Y, Zhang W, *et al.* Hyperprogression after anti-programmed cell death ligand-1 therapy in a patient with recurrent metastatic urothelial bladder carcinoma following first-line cisplatin-based chemotherapy: a case report. *Drug Des Devel Ther* 2019; **13**:291–300.

17 Wong DJ, Lee J, Choo SP, Thng CH, Hennedige T. Hyperprogressive disease in hepatocellular carcinoma with immune checkpoint inhibitor use: a case series. *Immunotherapy* 2019; **11**:167–175.

18 Ferrara R, Mezquita L, Texier M, Lahmar J, Audigier-Valette C, Tessonnier L, *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**:1543–1552.

19 Tamiya M, Tamiya A, Inoue T, Kimura M, Kunimasa K, Nakahama K, *et al.* Metastatic site as a predictor of nivolumab efficacy in patients with advanced non-small cell lung cancer: a retrospective multicenter trial. *PLoS One* 2018; **13**:e0192227.

20 Chubachi S, Yasuda H, Irie H, Fukunaga K, Naoki K, Soejima K, Betsuyaku T. A case of non-small cell lung cancer with possible 'disease flare' on nivolumab treatment. *Case Rep Oncol Med* 2016; **2016**:1075641.

21 Zhang Z, Li Y, Yan X, Song Q, Wang G, Hu Y, *et al.* Pretreatment lactate dehydrogenase may predict outcome of advanced non small-cell lung cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Cancer Med* 2019; **8**:1467–1473.

22 Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, *et al.* Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer* 2017; **111**:176–181.