

LETTER / *Cancer imaging*

## Hyperprogressive disease of non-small-cell lung adenocarcinoma under immune-checkpoint inhibitors: A new response pattern to be recognized by the radiologist



**Keywords** Lung cancer; Immunotherapy; Hyperprogression; Tumor response evaluation

Dear Editor,

Immunotherapy using immune-checkpoint inhibitors (ICI) is now a major treatment for advanced stage non-small-cell lung cancer (NSCLC). ICI boosts the immune response toward cancer cells and is associated with new response patterns. Some of these patterns are not captured by RECIST 1.1 response criteria. Recently, hyperprogressive disease (HPD) has been brought to the forefront [1]. HPD is characterized by rapid and severe progression of tumor load, along with severe alteration of patient's performance status and dramatic reduced survival with a median overall survival of 3 months. We herein illustrate HPD in a patient with stage IV NSCLC receiving immune-checkpoint inhibitors.

A 69-year-old man with a stage IV (cT2N2M1b) NSCLC diagnosed by mediastinoscopy received 4 cycles of platinum-pemetrexed and bevacizumab chemotherapy before progression, then a second line chemotherapy with 6 cycles of docetaxel before progression. The patient had metastatic mediastinal lymph nodes and bone metastasis to the left 10th rib. Immunohistochemical analysis revealed presence of PD-L1+ in 80% of tumor cells and negativity for *KRAS* mutation. The patient was included in a clinical trial testing the combination of two immunotherapies. Computed tomography (CT) was performed at 4 weeks (Fig. 1a) and then 2 weeks (Fig. 1b) before the start of treatment. The patient was hospitalized 3 weeks after the first administration of ICI because of severe worsening of performance status. An early CT examination showed a major increase in tumor size and newly developed right pleural effusion (Fig. 1c). The patient died one week later. Table 1 shows changes in size of right lower lobe tumor, increasing from 47 mm to 57 mm before the ICI starting to 106 mm one month after starting the treatment. The tumor growth rate (TGR) calculation [2] revealed a TGR factor > 2 after the introduction of immunotherapy (43% before ICI and 124% after ICI).

HPD is defined as an increase in TGR by a factor  $\geq 2$  after ICI initiation [2]. HPD occurs in 8 to 16% of patients

with NSCLC and is not limited to any tumor type. Ferrara et al. reported HPD in 16% of patients with NSCLC, with no significant difference in terms of tumor burden at baseline, clinical, molecular or pathological characteristics, PDL1 expression, or response rate to treatment before the introduction of immunotherapy [3]. Repeat biopsy of tumor progression may thus be warranted to confirm HPD. Identification of HPD within 8 weeks after introduction of ICI is therefore a new challenge for radiologists because RECIST 1.1. criteria do not allow differentiating between HPD, pseudo progression and true progression. Champiat et al. have suggested that an early CT examination should be performed 6 weeks after introduction of ICI to identify patients with HPD [2]. Pre-treatment imaging may be thus used to calculate the TGR before and after introduction of immunotherapy. Such a new paradigm will introduce a new task for the radiologist such as the integration of pre-treatment imaging and TGR calculation before starting ICI and early control with CT at 6 weeks after starting ICI and in case of progression, calculation of the TGR under ICI. The main differential diagnostic of HPD is pseudo-progression, which is characterized by an increase in tumor dimensions due to tumor infiltration by T-lymphocytes, followed by a decrease under ICI that meets criteria for partial or complete response [4,5]. Pseudo progression is uncommon but challenging as it is not possible at the time of tumor enlargement to differentiate true progression from pseudo-progression. Therefore, iRECIST, an evaluation system dedicated to patients receiving ICI, recommends an early follow-up CT at 4–8 week after the first progression in order to confirm or exclude true progression. Pseudo-progression can be suspected if there is a discrepancy between tumor progression on imaging and improvement of general status. Immunotherapy has changed the prognostic of patients with a variety of cancers but also the radiologic patterns of tumor response. Radiologists should be aware of this new pattern of tumor response under ICI.

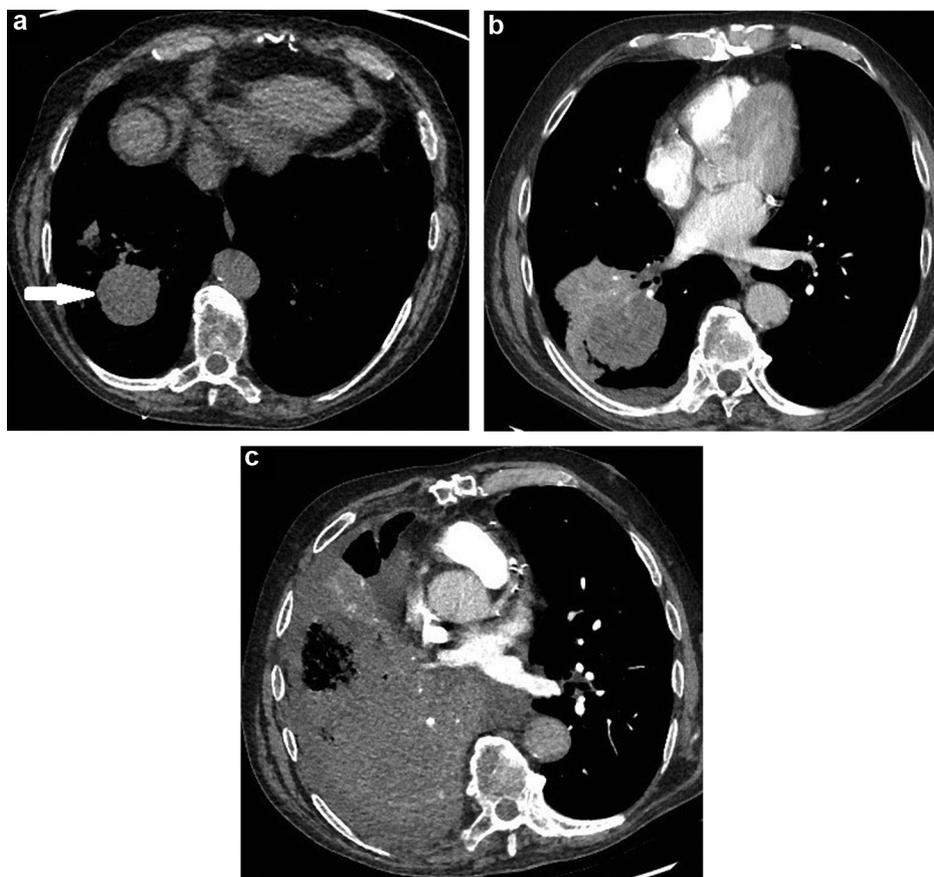
### Disclosure of interest

G.R. Ferretti reports personal fees from Roche, Boehringer Ingelheim, Bristol-Myers Squibb.

D. Moro Sibilot declares to participate to Advisory Board: Pfizer, Novartis, Lilly, Boehringer Ingelheim, Astra Zeneca, Amgen, Bristol-Myers Squibb, MSD, Roche, Abbvie, Takeda.

A. Jankowski declares that he has no competing interest.

M. Gaj Levra declares to participate to advisory boards: Roche, Bristol-Myers Squibb, Novartis, Amgen; declares personal fees from Bristol-Myers Squibb, Astra Zeneca, Roche.



**Figure 1.** Hyperprogression observed after initiation of immune-checkpoint inhibitors (ICI) treatment in a 69-year-old man with stage IV non-small-cell lung adenocarcinoma: a: computed tomography (CT) image in the transverse plane at 4 weeks before the start of ICI treatment, shows right lower lobe mass (arrow) with a diameter of 47 mm; b: CT image in the transverse plane 2 weeks before the start of treatment, shows that the diameter of right lower lobe has increased, measuring 57 mm. CT image in the transverse plane after 3 weeks shows a major increase of lesion size that reaches 106 mm and a newly developed right pleural effusion.

**Table 1** Tumor growth rate before and after immune-checkpoint inhibitor therapy in a patient with non-small-cell lung adenocarcinoma.

Date	Pre ICI	Pre ICI	First cycle ICI	Post ICI	Death
Delay before/after treatment (days)	−34	−13	0	18	23
Longest diameter of tumor (mm)	47	57		106	
Tumor growth rate		43%		124%	

ICI indicates immune-checkpoint inhibitor. TGR indicates tumor growth rate. Tumor growth rate was calculated according to Champiat et al. [2]. Tumor size (D) is defined as the sum of the longest diameters of the target lesions as per RECIST 1.1 criteria.  $t$  is the time at tumor evaluation (in months). Assuming the tumor growth (TG) follows an exponential law,  $V_t$ , the tumor volume at time  $t$ , is equal to  $V_t = V_0 \exp(TG \cdot t)$ , where  $V_0$  is the volume at baseline and TG is the growth rate. We approximated the tumor volume (V) by  $V = 4 \pi R^3/3$ , where R, the radius of the sphere is equal to  $D/2$ . Consecutively, TG is equal to  $TG = 3 \text{ Log}(Dt/D_0)/t$ . To report the TGR results in a clinically meaningful way, we expressed TGR as a percentage of increase in tumor volume during 1 month using the following transformation:  $TGR = 100 [\exp(TG) - 1]$ . ICI indicates immune-checkpoint inhibitor.

A.C. Toffart reports grants, personal fees and non-financial support from Roche, personal fees from Lilly, BMS, Novartis, MSD, Astra Zeneca, Pfizer, Boehringer Ingelheim.

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<https://doi.org/10.1016/j.diii.2018.12.004>

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