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Are we ready to describe response or progression to immunotherapy in lung cancer?

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ABSTRACT

Immune checkpoint inhibitors have changed history and management of different tumor types, including non-small cell lung cancer (NSCLC). Response patterns may be more heterogeneous than those seen with cytotoxic chemotherapy. Besides atypical response patterns, new types of outcome should be taken into account such as pseudo-progression (PP) and hyper-progressive disease (HPD). PP is described as initial tumor increase or appearance of new lesions followed by their shrinkage during immunotherapy treatment while HPD is a rapid and severe pattern of progression with a not yet univocal definition. Physiopathology and underlying mechanism of these phenomena are not completely understood and in absence of reliable clinical and biological markers of response to immunotherapy, radiological evaluation remains a key point in clinicians' decision-making process but further efforts would be useful to identify a unique system of evaluation.In this review we summarize the main radiological criteria available in the evaluation of response to checkpoint inhibitors and we describe peculiar response patterns such PP and HPD with a focus on lung cancer.

1. Introduction

Anti-PD-1 and anti-PD-L1 immune checkpoint inhibitors have changed history and management of various tumor types including non-small cell lung cancer (NSCLC) (Gettinger et al., 2015; Rizvi et al., 2015; Borghaei et al., 2015; Brahmer et al., 2015; Rittmeyer et al., 2017; Garon et al., 2015; Herbst et al., 2016; Reck et al., 2016). After large use in advanced disease, recently positive data are emerging also in early NSCLC and both in neoadjuvant and adjuvant setting m (Antonia et al., 2018; Forde et al., 2018; Provencio-Pulla et al., 2018).

In advanced disease the use of combination therapy upfront is increasingly appealing: the combination of immunotherapy and chemotherapy is the new standard of care in first line treatment, and combinations of different immune checkpoints inhibithors or other strategies (e.g. anti-ICOS, anti-LAG3, anti-TGFβ, anti-IL-2, anti-adenosine pathways) will be offered to patients in the near future to prevent (or overcome) primary and secondary resistance to therapy (Paz-Ares et al., 2018; Gandhi et al., 2018; Socinski et al., 2018; Papadimitrakopoulou et al., 2018; Cappuzzo et al., 2018; Hellmann et al., 2018).

Besides considerable efficacy, immunotherapy also results in response patterns different from those of cytotoxic chemotherapy. In addition to atypical response patterns, new types of outcomes should be taken into account: in particular, Chiou and colleagues demonstrated the existence of 'pseudo-progression' (Chiou and Burotto, 2015) and recently, other authors described a rapid, severe pattern of progression called hyperprogression that nothing or very little has in common with 'usual' progression (Champiat et al., 2017; Saâda-Bouzid et al., 2017; Kato et al., 2017a).

In the absence of reliable clinical and biological markers of response to immunotherapy, radiological evaluation remains a key point in physicians' decision making process (Nishino et al., 2014). RECIST criteria accurately define progression for chemotherapy and target therapy, but with immunotherapy the situation may be different. (Figs. 1 and 2)

In this review we describe the main radiological criteria available and their use in the evaluation of response to immunotherapy. Moreover, we focus in particular on lung cancer and on two peculiar response patterns: pseudo-progression (PP) and hyper-progressive disease (HPD).

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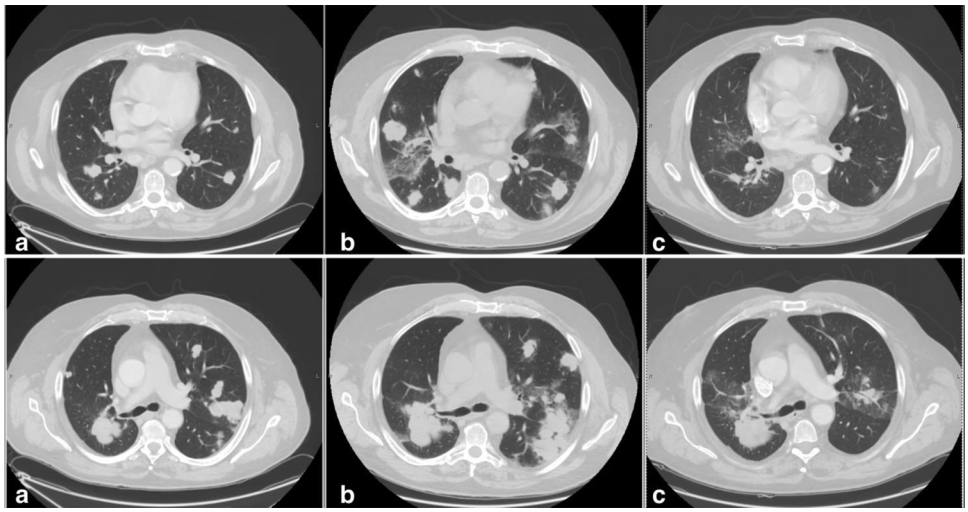

Fig. 1. CT scans of PP from our casuistry. A Caucasian 65-years old man diagnosed with stage IV NSCLC treated with four different chemotherapy lines from September 2013 to September 2015, the last with 7 cycles of Vinorelbine with SD (a: December 2015 CT). In February 2016 he started treatment with Nivolumab in the expanded access program; after ten days he was hospitalized due to respiratory failure with nodal and pulmonary lesions increase with ground glass area (b). Microbiological investigations were negative and steroid therapy was started (methylprednisolone 1 mg/kg) with clinical and radiological improvement. Nivolumab therapy was resumed and CT evaluation after eight cycles (June 2016, c) showed a good PR.

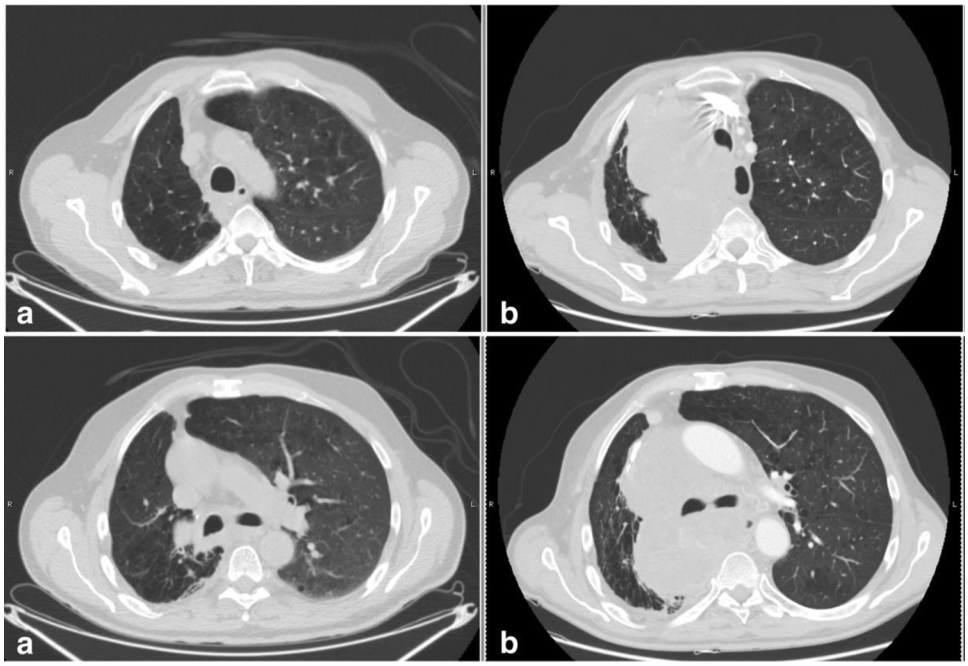

Fig. 2. CT scans of HPD from our casuistry. A Caucasian 57-years old man diagnosed with locally-advanced NSCLC treated with neoadjuvant chemotherapy (cisplatin/pemetrexed, four cycles from March to May 2016) and then subjected to right inferior bilobectomy with ilo mediastinal lymphadectomy in July 2016.
A PET/CT in October 2017 documented pulmonary and nodal relapse of the disease (a). Molecular analysis showed PD-L1 positivity with Tumor Proportion Score (TPS) 60%, therefore in November 2017 treatment with Pembrolizumab flat dose was started. CT scans of February 2018 (b) revealed a severe thoracic progression of disease, with massive nodal increase with vascular, esophageal and cardiac involvement.

2. The evolution of radiological evaluation criteria

The first efforts to systematically develop response assessment criteria were made by the World Health Organization (WHO) in the first 1980 (WHO Handbook for Reporting Results of Cancer Treatment, 1979).

Up to now, literature proposes three types of response-criteria to cancer therapy: the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al., 2009) that have revised the RECIST version 1.0 (Therasse et al., 2000), the immune-related Response Criteria (irRC) (Wolchok et al., 2009) and its simplification the immune-related RECIST (irRECIST) (Bohnsack and Hoos, 2014) (Table 1). irRC were developed to standardize the assessment of response to immunotherapeutic agents (Wolchok et al., 2009); they consider the bi-dimensional measurement of lesions and the inclusion of new lesions measurement to evaluate tumor burden. Probably the more relevant difference between these criteria is the definition of progressive disease (PD) (Tazdait et al., 2018). To define PD according to irRECIST, in addition to an increase of more than 20% of the sum of the longest diameters (or of the total measured tumor burden) compared with nadir or progression of non-target lesions or new lesions, the two immune-response criteria need the confirmation of progression minimum 4 weeks after the first progression report (Seymour et al., 2017). Moreover, new lesions in immune-response criteria do not correspond to a formal progression. In irRECIST the longest diameter of the new lesions is added to the total measured tumor burden of all target lesions at baseline: an increase in tumor burden < 20% is not consider as PD (Bohnsack and Hoos, 2014).

A retrospective study comparing irRC with RECIST 1.1 for advance malignant melanoma treated with pembrolizumab has shown atypical response patterns by RECIST 1.1 in 15% of patients (Hodi et al., 2016). Atypical response rates seem to be lower in NSCLC: a small retrospective study on patients with metastatic or recurrent NSCLC treated with checkpoint inhibitors reported a 4.9% rate of delayed PP (2 of 41 patients), with similar overall response rate (ORR) comparing RECIST 1.1 to irRC (Kim et al., 2017). Another retrospective study on 56 patients treated with nivolumab monotherapy has found concordance in response rate (RR) evaluation between irRECIST 1.1 and RECIST 1.1, but longer time to progression (TTP) by irRECIST 1.1 than by RECIST 1.1 (Nishino et al., 2016).

Table 1
Comparison between different radiological evaluation criteria.

	WHO (Socinski et al., 2018)	RECIST 1.0 (Cappuzzo et al., 2018)	RECIST 1.1 (Papadimitrakopoulou et al., 2018)	irRC (Hellmann et al., 2018)	irRECIST (Chiou and Burotto, 2015)	iRECIST (Saâda-Bouzid et al., 2017)
CR[a]	- Disappearance of all lesions - (with confirmation after 4 weeks)	- Disappearance of all lesions - No new lesions (with confirmation after 4 weeks)	- Disappearance of all lesions (target and non-target[g]) - Nodal short axis < 10 mm - No new lesions	- Disappearance of all lesions (with confirmation after 4 weeks)	The same as RECIST 1.1	The same as RECIST 1.1
PR[b]	- ≥50% decrease in SPD[e] vs baseline (with confirmation after 4 weeks) - No PD in non-target lesions - No new lesions	- Decrease of ≥30% TM[f] vs baseline (with confirmation after 4 weeks) - No PD in non-target lesions - No new lesions	- Decrease of ≥30% TM vs baseline - No PD in non-target lesion - No new lesions	- ≥50% decrease in TM[h] vs baseline (with confirmation after 4 weeks)	The same as RECIST 1.1	The same as RECIST 1.1
SD[c]	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD	Neither PR nor PD
PD[d]	- At least 25% increase in SPD[e] vs nadir and/or unequivocal PD in non-index lesions and/or new lesions	- Increase of 20% TM[f] vs nadir - New lesions	- Increase of ≥20% TM vs nadir (minimum 5 mm) - PD of non-target lesions - New lesions	- At least 25% increase in TM[h] vs nadir (with confirmation after 4 weeks)	- Increase of ≥20% TM vs nadir (minimum 5 mm) - PD of non-target lesions - New lesions (confirmation recommended minimum 4 weeks after)	The same as irRECIST
Confirmed PD[d]	Not required	Not required	Not required	- At least 25% increase in TM[h] vs nadir	- New unequivocal PD - Worsened PD - Appearance of another new lesion	- Increased size of target or non-target lesions Increase in the sum of new target lesions > 5 mm - PD of new non-target lesions - Appearance of another new lesion

Notes:
[a]Complete Response. bPartial Response. cStable Disease. dProgressive Disease.
[e]Sum of the Products of Diameters represents the tumor size and it is a measure of the 'tumor area'. It results by multiplication of the largest diameter of the tumor by the greatest perpendicular diameter and, when multiple lesions are present, by the sum of the products of the perpendicular diameters. Index lesions: 5 lesions per organ, up to 10 visceral lesions and 5 cutaneous.
[f]TM (tumor burden) in RECIST 1.0 is the sum of diameters of target lesions: max 10 lesions, 5 per organ.
gtarget lesions in RECIST 1.1 are a maximum of 5 lesions (2 per organ), other lesions are non-target. Tumor burden (TM) is calculated with the sum of the longest diameters (SLD) of target lesions. There are considerate measurable lesions those ≥10 mm or ≥15 mm for nodal lesions.
[h]TM (tumor burden) in irRC result from the sum of $SPD_{index\ lesions} + SPD_{new,\ measurable\ lesions}$.

Table 2
trials, response criteria and timing for evaluation used in advanced NSCLC treated with immunotherapy.

Trial	Setting	Primary end point	Lines of therapy	Criteria	Timing
Topalian et al. (Topalian et al. (2012))	Nivolumab for solid tumors; Phase I	Safety, activity, PK	II or more	modified RECIST 1.0[a]	after each 8-week treatment cycle
Gettinger et al. (Gettinger et al. (2015))	Nivolumab for NSCLC; Phase I	Safety and OS	II or more	modified RECIST 1.0	after each 8-week treatment cycle
Rizvi et al. (Rizvi et al. (2015)) (CheckMate 063)	Nivolumab for SQ NSCLC; Phase II	confirmed objective response	III or more	RECIST 1.1	8 weeks after the start of treatment, and every 6 weeks thereafter
Brahmer et al. (Brahmer et al. (2015)) (CheckMate 017)	Nivolumab vs docetaxel for SQ NSCLC; Phase III	OS	II	RECIST 1.1	at week 9 and every 6 weeks thereafter
Borghaei et al (Borghaei et al. (2015)) (CheckMate 057)	Nivolumab vs docetaxel for non SQ NSCLC; Phase III	OS	II	RECIST 1.1	at week 9 and every 6 weeks thereafter
Rittmeyer et al (Rittmeyer et al. (2017)) (OAK trial)	Atezolizumab vs docetaxel for NSCLC; Phase III	OS	II and III	RECIST 1.1	every 6 weeks until week 36 and every 9 weeks thereafter
Garon et al. (Garon et al. (2015)) (Keynote-001)	Pembrolizumab in NSCLC; Phase I	Safety and activity	I	RECIST 1.1 (firstly), irRC (secondary)	every 9 weeks
Reck et al.(Reck et al. (2016)) (Keynote-024)	Pembrolizumab vs CT in NSCLC PD-L1 > 50% Phase III	PFS	I	RECIST 1.1	every 9 weeks
Herbst et al.(Herbst et al. (2016)) (Keynote-010)	Pembrolizumab vs docetaxel in NSCLC PD-L1 > 1% Phase II-III	OS and PFS	II or more	RECIST 1.1[b]	every 9 weeks

Notes:
[a]In clinically stable patients, study treatment could be continued beyond apparent initial disease progression until progression was confirmed, as outlined by proposed immune-response criteria.
[b]Patients who progressed according to investigator assessed immune-related response criteria (irRC) could remain on treatment until a confirmatory scan done 4–6 weeks later.

Talking about difficulties in tumors' response evaluation brain metastases deserve a special mention. In 1990 MacDonald and colleagues proposed specific criteria for brain tumors (Macdonald et al., 1990). These criteria, however, failed to address some particular response such as PP. In subsequent years the RANO group proposed specific response criteria for glioma (Wen et al., 2010). In 2015 Lin et al. proposed the RANO-BM criteria. They considered not only target and non-target lesions into the brain, but also corticosteroids use and clinical status. In clinical practice and trials these criteria might be more feasible to use than other brain metastases response criteria (Lin et al., 2015).

Last but not least, an unsolved question in tumor response evaluation is the timing of response evaluation as it may differ among clinical trials and between trials and clinical practice (Table 2). The new criteria propose some specific timing indication, but 'common practice' evaluation remains undefined and sometime difficult.

3. Pseudo-progression

PP can be described as an initial tumor increase in tumor size or appearance of new lesions followed by their shrinkage during immunotherapy treatment. This peculiar pattern of response was first described in melanoma patients treated with ipilimumab (Wolchok et al., 2009; Saenger and Wolchok, 2008) and then has been described in many other malignancies in the last years (Chae et al., 2017; Sweis et al., 2018) including a small proportion of patients with advanced NSCLC experiencing progressive disease according to RECIST criteria at first assessment and then a clinical response at the following evaluations (Borghaei et al., 2015; Brahmer et al., 2015). In literature many cases of PP of NSCLC are reported, especially during nivolumab therapy (Curioni-Fontecedro et al., 2017; Kato et al., 2017b; Kolla and Patel, 2016; Sarfaty et al., 2017), both in primary tumor or in secondary lesions, including CNS metastasis (Curioni-Fontecedro et al., 2017; Kato et al., 2017b; Sarfaty et al., 2017; Doherty et al., 2015).

A 4.6% rate of PP has been reported in patients with NSCLC treated with nivolumab (Gettinger et al., 2015); an even lower rate (0.6%) was reported by Nishino in the evaluation of response on patients treated with nivolumab and pembrolizumab (Nishino et al., 2017). Consistent with these evidence, Ferrara and colleagues recently reported 4.7% rate (Ferrara et al., 2018) indicating that the real PP incidence in this setting is not well established, but it seems to be a rare phenomenon (Nishino et al., 2016).

PP may be related with favorable long-term outcomes after immunotherapy treatment (Kurra et al., 2016; Solinas et al., 2017) but further evaluations are needed.

The physiopathology of this phenomenon could be explained as tumor growing until a sufficient immune response occurs (Hodi et al., 2016) or a transient immune-cell infiltration in tumor tissue associated with edema and necrosis (Chiou and Burotto, 2015; Sarfaty et al., 2017; Kazandjian et al., 2017). Similarly the development of new lesions may be related to T-cells infiltration into lesions radiologically undetectable or not measurable at baseline evaluation (Wolchok et al., 2009).

There are concerns about the best imaging techniques to evaluate PP: maybe hybrid imaging could be more helpful than classical imaging in the discrimination between PP and true progression (Solinas et al., 2017). With commonly available techniques a suspicious PP requests adequate vigilance: on one hand continuation of immunotherapy can lead to late responses, on the other overtreatment might be detrimental and could lead to miss potential useful treatments.

Discernment may be also obtained with histological evaluation (Tanizaki et al., 2016) because enlarging lesions due to PP could present dense immune-cell infiltration, however the right time to perform a biopsy is not established and it could be not feasible or diriment: considering these aspects, it should be considered only for very critical cases.

Apart from imaging and pathology, to discern PP from a true progression other features should be taken into account, such as patient

Table 3
comparison between studies reporting HPD.

	Definition of HPD	N. patients	Incidence	PFS	OS	Association with HPD	No association with HPD
Champiat et al. (Champiat et al. (2017))	- RECIST PD at 1 st evaluation - ≥ 2-fold increase of the TGR[a] between REF and EXP periods	131 (13 lung, 6 head and neck)	9% (24% of pt with PD)[b]	–	4.6 vs 7.6 mo (p = 0.19)	Higher age; worse outcome (p = 0.19); inverse correlation between TGR REF and response	Tumor burden at baseline; N. of M sites; RMH prognostic score; Previous lines: histology; Blood characteristics
Saada-Bouzid et al. (Saâda-Bouzid et al., 2017)	TGK_R[c] ≥ 2	34 head and neck SCC	29%	2.5 vs 3.4 mo (p = 0.003)	6.1 vs 8.1 mo (p = 0.77)	Regional recurrence; Shorter PFS (RECIST and irRECIST); Shorter OS but not statistical significance	Tumor size at baseline; T and M stage; Tumor burden at baseline; Local recurrence
Kato et al. (Kato et al. (2017a))	- TTF[d] < 2 mo - > 50% increase in tumor burden compare to pre-immunotherapy. - > 2-fold increase in progression pace	155 (38 NSCLC, 11 head and neck)	31,6% TTF < 2 m; nd for HPD in tot pts. but 2 EGFR alteration (1,3% of tot) and 4 MDM2/4 amplification (2,6% of tot)	–	–	EGFR alteration (7 of 8 had TTF < 2.2 HPD); MDM2/4 amplification (6 of 6 had TTF < 2.4 HPD); DNMT3A alterations (3 of 4 had TTF < 2, but not statistical significance)	–
Matos et al. (Matos et al. (2018))	TTF < 2 mo and minimum increase in measurable lesion of 10 mm plus: - Increase of ≥40% in target tumor burden compared to baseline or - Increase of ≥20% plus appearance of multiple new lesions	214 (22% melanoma, 14% lung, 10% breast, 6% colon, 48% others)	15% (40% of pts with PD)	–	4.8 vs 8.7 mo (p = 0.03)		
Ferrara et al (Ferrara et al. (2018))	- RECIST 1.1 PD at 1st evaluation - Δ TGR > 50%	406 NSCLC	13.8%	–	3.4 vs 6.2 mo (in PD non HPD) (p = 0.003)	More than 2 metastatic sites before PD1/PD-L1 inhibitors: lower os	No significant differences according to baseline tumor burden, no previous line, age, ECOG and other variables
Zuazo-Ibarra et al. (Zuazo-Ibarra et al., 2018)	TGK_R[c] ≥ 5	34 NSCLC	20.6%	6 wks vs 8.9 wks (p = 0.002)	–	A negative T_{HD} baseline profile significantly correlates with HPD	
Lo Russo et al.(Lo Russo et al. (2018))	- TTF[d] < 2 mo - increase ≥50% in the sum of target lesions major diameters - at least 2 new lesions in an organ already involved - spread to a new organ - clinical deterioration with ECOG ≥ 2 during 2 mo	152 NSCLC	25.7%		4.4 vs 17.7 mo (in non HPD pts) (p not reported)	MPO + myeloid cells within the tumor directly correlated with HPD and PD-L1 expression was inversely related with HPD. A trend was shown for M2 macrophage/ MDSC marker Argl on peritumoral immune cells.	Not found any significant difference in frequency of MDM2/4 amplification. Role of EGFR cannot be discussed due to low number of pts. No significant differences respect the subsets of TILS.

Notes: [a]Tumor Growth Rate percent of increase in tumor volume during 1 months → TGR = 100 (exp(TG)-1) where TG is the growth rate calculated with TG = 3(Log(Dt/D0)/t), having Dt = diameter at time t, D = 2R (radius), tumor volume $V = 4\pi R^3/3$. TGR was calculate at relevant time: TGR REF: assessed during the wash-out therapy before experimental drug and TGR EXP: assessed during the first cycle of treatment. To notice that TGR was computed on the target lesions only, new lesions were not included in the RECIST sum.
[b]But 8% not be evaluated because of clinical PD before evaluation and TGR was computed on the target lesions only → patients who exhibit a fast growing rate in new lesions only were not considered as HPD.
[c]Tumor Growth Kinetics: $TGK_{PRE} = (S_0 - S_{PRE})/(T_0 - T_{PRE})$, difference of the sum of the largest diameters of the target lesions according to RECIST per unit of time between pre-baseline (S_{PRE}) and baseline imaging (S_0). $TGK_{POST} = (S_{POST} - S_0)/(T_{POST} - T_0)$, difference of the sum of the largest diameters of the target lesions according to RECIST per unit of time between post-baseline (S_{POST}) and baseline imaging (S_0). TGK_R = ratio of TGK_{POST} to TGK_{PRE}. $TGK_R > 1$: indicated tumor growth acceleration, $0 < TGK_R < 1$: tumor deceleration, $TGK_R < 0$: tumor shrinkage. [see: Le Tourneau C et al. br J Cancer 2012].
[d]TTF (Time to treatment failure is defined as the time from the start of treatment with ICI to ICI discontinuation for any reason).

performance status: PP should not be accompanied by clinical deterioration because this may reflect a real progressive disease (Seymour et al., 2017).

4. Hyper-progressive disease

HPD is a recently described phenomenon and its definition is not yet univocal (Champiat et al., 2017; Saâda-Bouzid et al., 2017; Kato et al., 2017a; Matos et al., 2018). The first complete description was made by Champiat in 2016 on a population of 131 patients enrolled in phase I trials with anti-PD1/PD-L1 monotherapy for different malignancies, including 13 patients with lung cancer (Champiat et al., 2017). HPD was defined as a progression of the disease at first evaluation according to RECIST 1.1 and an increase of more than two-fold of the tumor growth rate (TGR, refers to a percent increase in tumor volume in a defined period of time) from baseline with an incidence rate of this phenomenon of 9% (Champiat et al., 2017). Researchers also found a correlation between HPD status and age, with HPD patients older than patients who did not experienced HPD (66 vs 55 years; P = 0.007) (Champiat et al., 2017). Interestingly, there was no association between HPD and tumor burden at baseline (P = 0.64) and patients with HPD had a lower rate of new lesions than patients with non-HPD progression (33% vs 84%; P = 0.0019) (Champiat et al., 2017). A different definition was recently provided by Vall d'Hebron Institute Oncology (VHIO): HPD was defined as TTF < 2 months and minimum increase in measurable lesion of 10 mm plus increase of ≥40% in target tumor burden at baseline or increase of ≥20% with the appearance of multiple new lesions (Matos et al., 2018). No concordance has been found between these criteria and Istitute Gustave Roussy one as reported in a retrospective study presented at ESMO 2018, but authors underline that VHIO criteria are strongly prognostic and easy to use in clinical practice (Matos Garcia et al., 2018).

Saada-Bouzid et al, evaluating patients with metastatic head and neck squamous cell carcinoma treated with anti-PD1/PD-L1 therapy, defined the same phenomenon like an increase of more than two times of the tumor growth kinetics rate (TGK_R) (Saâda-Bouzid et al., 2017). TGK_R refers to the ratio between kinetics of tumor growth pre and post baseline (pre and post starting immunotherapy); a kinetics ratio more than one indicated an acceleration in tumor growth, between 0 and one a deceleration of growth and less than 0 a tumor shrinkage (Saâda-Bouzid et al., 2017).

Kato and collaborators defined HPD like an increase of more than two-fold in progression pace, a time-to-treatment-failure (TTF) less than two months and an increase of more than 50% in tumor burden compared to pre-immunotherapy imaging (Kato et al., 2017a). Authors made also a retrospective genomic assessment of patients with diverse cancers who received immunotherapy and found a 67% hyperprogression rates in patients with MDM2/MDM4 amplification, and 20% in patients with EGFR mutation (Kato et al., 2017a). These alterations were associated with a TTF inferior than two months (Kato et al., 2017a). The underlying mechanisms are not exactly elucidated, but these evidences suggest that in the future genomic analysis may guide physicians in the selection of patients more likely to benefit from immunotherapy.

All these works refer to the same phenomenon emerged with the more extensive use of immunotherapy, but the absence of a not unique definition could bring some confusion.

Data from a larger study focused on 406 NSCLC reported 13,8% rate of HPD and an association with worse survival (Ferrara et al., 2018). HPD was significantly associated with more than two metastatic sites at baseline, while other clinical features had not significant correlation with HPD. Prognosis in HPD patients was worse and OS significantly lower compared with other patients with progressive disease (3.4 vs 6.2 months) (Ferrara et al., 2018).

An Italian retrospective experience analyzed 187 patients with advanced NSCLC treated with immunotherapy, finding a 25,7% rate of HPD in the 152 patients evaluable for response (Lo Russo et al., 2018). Correlation was described between MPO + myeloid cells within the tumor with HPD and an inverse correlation between PD-L1 expression and HPD. A trend was shown for M2 macrophages/myeloid derived suppressor cells (MDSC) marker ArgI on peritumoral immune cells. A significant difference in frequency of MDM2/4 amplification and respect the subsets of TILs was found while the role of EGFR was not discussed due to the low number of patients (Lo Russo et al., 2018).

Zuazo-Ibarra and colleagues studied 34 patients with NSCLC focusing their attention to the impact of highly differentiated T (T_{HD}) cells over clinical responses to immunotherapy (Zuazo-Ibarra et al., 2018). They found 20,6% rate of HPD (defined like TGK rate ≥ 5) and 17,6% rate of suspected HPD by clinical parameters, but no radiological confirmed for death. Median PFS in patients with HPD was 6 weeks. Patients with HPD were correlated with a negative T_{HD} baseline profile and presented a burst of peripheral senescent CD4 T cells (Zuazo-Ibarra et al., 2018).

Further studies are needed to obtain more precise information on incidence and characteristic of this phenomenon.

Incidence of HPD changes between these studies (see Table 3 for comparison) and its correlation too. One constant, however, may be cited: its association with a worse outcome even if statistically significant data are missing (Champiat et al., 2017).

Finally Lahmar compared the accuracy of TGR and RECIST to assess the benefit of immunotherapy in 58 advance NSCLC patients: TGR during immunotherapy inferior to TGR pre immunotherapy was significantly associated with better survival (p = 0.02)l (Lahmar et al., 2016). This evidence is consistent with a retrospective study that has reported that patients experiencing tumor burden growth < 20% have longer median overall survival (OS) than those experiencing higher tumor growth (P < 0.001) (Nishino et al., 2017). These studies underline the importance of tumor growth kinetics for prognosis estimation.

5. Conclusions

To date, after the introduction of immunotherapy, oncologists and radiologists are facing with patterns of response different from those previously seen with cytotoxic or target therapies and many questions are still unanswered.

In the last decade different radiological evaluation criteria have been proposed to evaluate response to immunotherapy, and maybe further efforts would be useful to identify a unique system of evaluation, uniform both in clinical trials and clinical practice. Additionally, the identification of other biomarkers may be useful to integrate radiology in the assessment of response.

Radiologists' expertise will probably improve even in the evaluation of PP, that is still a phenomenon with non-univocal definition, especially in lung cancer where reported rates are quite low. Moreover, the better radiological techniques for its evaluation are yet not well defined and neither its possible prognostic significance.

The pattern of HPD has been described with more accuracy in different malignancies including lung cancer and we can say that with immunotherapy treatment it is necessary to consider this phenomenon. Further studies are needed to give a better definition of HPD and above all to find if there are clinical and molecular predisposing factors for HPD in order to identify patients for whom immunotherapy may have a detrimental effect. We still know very little about these phenomena and perhaps the introduction of combination strategies in clinical practice will open up new scenarios and provide additional prognostic or predictive elements. For the time being, suspicion of HPD should be guided by a careful and frequent clinical and bio humoral surveillance to recognize signs of progression and even to distinguish them from more common adverse events. Besides clinical patterns, radiological evaluations remain fundamental and for sure we have to pay attention to patients in which tumor growth kinetic starts to accelerate during

treatment. Probably there is no need to increase the frequency of radiological assessments to detect HPD: the suspicion is guided by clinical evidences. HPD is usually associated with clinical deterioration and its early detection may be useful to evaluate different therapeutic options as long as the patient is fit enough.

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