Review Article on Immunotherapy in Other Thoracic Malignancies and Uncommon Populations

Novel patterns of progression upon immunotherapy in other thoracic malignancies and uncommon populations

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Abstract: In the immunotherapy era, considering the prolonged survival benefit and responses observed with immunecheckpoint inhibitors (ICI) in many cancer types, the identification of patients with rapid progression (PD) and deaths upon ICI has found some skepticism and resistance among the scientific community. Nevertheless, an acceleration of tumour during ICI, defined as hyperprogressive disease (HPD), has been recognized across different cancer types and evidence regarding rapid PDs and deaths are emerging in patients with malignant pleural mesothelioma (MPM), small cell lung cancer (SCLC) and thymic malignancies and in uncommon non-small cell lung cancer (NSCLC) populations. Of note, PD and early deaths (ED) rates upon single agent ICI were up to 60% and 30% in MPM and 70% and 38% in SCLC patients, respectively. Similarly, rapid PDs and deaths were observed in clinical trials and retrospective studies including patients with poor performance status (PS), HIV infection and rare NSCLC histologies. Atypical patterns of response, such as pseudoprogression (PsPD) may also occur in other thoracic malignancies (MPM) and in some uncommon populations (i.e., HIV patients), however probably at lower rate compared to HPD. The characterizations of HPD and PsPD mechanisms and the identification of common definition criteria are the next future challenges in this area of cancer research.

Keywords: Hyperprogressive disease (HPD); early deaths (ED); pseudoprogression (PsPD); other thoracic malignancies; uncommon populations

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Introduction

Immunecheckpoint inhibitors (ICI) have radically changed the treatment scenario of many cancer types (1). Despite its unquestionable benefits, the advent of immunotherapy has also brought new challenges for medical oncologists regarding use of ICI combinations (2), role of predictive biomarkers (3) and of novel study methodologies (4). In particular, the assessment of ICI efficacy in special subpopulations (5) and the characterization of atypical responses upon ICI (6) are clinical unmet needs. Although unconventional patterns of response [i.e., pseudoprogression (PsPD)] (7) or progression (PD) (i.e., hyperprogression) (8) have been described in ICI treatment advanced non-small cell lung cancer (NSCLC) patients, the mechanisms beyond them and the criteria to define these

patterns have not been fully elucidated. Furthermore, few data are available for these novel patterns in patients with other thoracic malignancies and special subpopulations. The aim of this review is to discuss the current knowledge about hyperprogressive disease (HPD), PsPD occurring during ICI in patients with thoracic malignancies other than NSCLC and in uncommon populations such as elderly, patients with poor ECOG performance status (PS), autoimmune diseases, HIV infection or rare NSCLC histology subtypes. We will also provide an insight on the potential biological mechanisms associated with HPD and PsPD, focusing on some unsolved problems and areas of future research.

Methods

We performed a literature review regarding the association between the use of ICI and the occurrence of HPD or PsPD in patients with thoracic malignancies other than NSCLC and in uncommon populations. We searched digital databases including PubMed, the Cochrane Library and EMBASE. The survey was carried out using keywords such as "immunotherapy", "immune checkpoint inhibitors", "malignant pleural mesothelioma", "thymic carcinoma", "thymoma", "small-cell lung cancer", "anti-PD-L1 antibody", "anti-PD-1 antibody", "anti-CTLA4 antibodies", "uncommon populations", "poor performance status", "HIV", "autoimmune diseases", "sarcomatoid lung cancer", "rare histology", "enteric lung adenocarcinoma", "hyperprogressive disease" "pseudoprogression", variously associated together. No language or period restrictions have been used. The great part of the studies was excluded according to the title or the abstract content. We have analyzed the full versions only for the most relevant papers. The reference lists of the most important studies were also evaluated.

PD, HPD and early deaths (ED) in other thoracic malignancies and uncommon populations

HPD, defined as a rapid disease growth during immunotherapy, has been reported in 3.8% (9) to 29.4% (10) of tumours and in 13.8% (11) to 37% (12) of advanced NSCLC patients treated with PD-1/PD-L1 inhibitors. In most of the studies including NSCLC patients, the median overall survival (OS) for patients with HPD ranged between 1.6–4.7 months (12,13) and was lower compared to the median OS (6.2–7.8 months) (11,14) of conventional disease PD according to RECIST v1.1. No validated clinical or molecular predictors of HPD have been identified due to the heterogeneity and retrospective nature of the studies. Furthermore, there is no consensus on HPD definition and distinct criteria (i.e., one-dimensional, volumetric or clinical) have been proposed (15-17).

In the context of thoracic malignancies, most of the studies have described HPD in a dedicated NSCLC population and few data are available for patients with other thoracic malignancies. In fact, the existence of HPD was demonstrated only in retrospective studies because the definition criteria included the assessment of pre-ICI imaging (11-13) or the evaluation of metastatic spread upon ICI (14,18) and both these data were not collected in clinical trials. Large retrospective real-world studies useful to assess HPD in thoracic malignancies other than NSCLC are currently missing because ICI are not standard treatments in these settings. However, rapid PDs and ED in the first 3 months of treatments have been reported in clinical trials testing ICI in patients with malignant pleural mesothelioma (MPM), small cell lung cancer (SCLC) or thymic malignancies, suggesting the existence of HPD across different thoracic cancers.

Similarly, HPD may occur in uncommon populations. In fact, HPD has been associated with aging (8) or with worsening of PS (14), in addition a remarkable increase in tumour burden has been reported in HIV^+ patients receiving PD-1/PD-L1 inhibitors in clinical trials (19).

Although we reported that ED is not a surrogate of HPD in NSCLC patients, 55% of ED NSCLC patients experienced HPD according to tumour growth rate (TGR) variation (20). Therefore, in the absence of a proper evaluation of HPD in patients with MPM, SCLC and thymic malignancies enrolled in clinical trials, PD and ED rates may provide a rough estimate of HPD occurrence in these settings. A limitation to the use of ED would be the inclusion in this rate of toxic deaths from ICI, however considering that grade 5 events upon ICI are relatively rare, most of deaths labelled as ED can be considered due to radiological or clinical PD. In *Table 1* we reported rates of PD, HPD, ED and PsPD in patients with thoracic malignanices other than NSCLC and in uncommon populations.

PD, HPD and ED in MPM

In pretreated MPM, tremelimumab, an anti-CTLA-4 monoclonal antibody, has been compared to placebo in

Table 1 PD, HPD, ED and PsPD rates in other thoracic malignancies or uncommon populations

Author	Study	Tumour type or uncommon population	ICI treatment	PD, % (n/N)	ED, % (n/N)	HPD, % (n/N)	PsPD, % (n/N)
Maio *et al.* (DETERMINE)	Phase 3	MPM	Tremelimumab	46% (175/382)	21% (82/382)[#]	NA	NA
Okada *et al.* (MERIT)	Phase 2	MPM	Nivolumab	26% (9/34)	18% (6/34)[$]	NA	3%* (1/34)
Quispel-Janssen *et al.*	Phase 2	MPM	Nivolumab	50% (17/34)	9% (3/34)[#]	NA	9% (3/34)
Alley *et al.* (Keynote-028)	Phase 1b	MPM	Pembrolizumab	16% (4/25)	16% (4/25)[#]	NA	4%* (1/25)
Desai *et al.*	Phase 2	MPM	Pembrolizumab	37% (24/64)	NA	NA	3% (2/64)
Popat *et al.* (ETOP 9-15 PROIMISE)	Phase 3	MPM	Pembrolizumab	45% (33/73)	24% (18/73)[$]	NA	NA
Hassan *et al.* (JAVELIN)	Phase 1b	MPM	Avelumab	34% (18/53)	24% (13/73)[#]	NA	2% (1/53)
Nowak *et al.* (DREAM)	Phase 2	MPM	Pembrolizumab (maintenance)	15% (8/54)	7% (4/54)[#]	NA	4% (2/54)
Calabrò *et al.* (NIBIT-MESO)	Phase 2	MPM	Durvalumab + tremelimumab	35% (14/40)	10% (4/40)[‡]	NA	NA
Disselhorst *et al.*	Phase 2	MPM	Nivolumab + ipilimumab	32% (11/34)	6% (2/34)[#]	NA	NA
Scherpereel *et al.*	Phase 2	MPM	Nivolumab	60% (38/63)	30% (19/63)[&]	11% (7/63)[†]	NA
			Nivolumab + ipilimumab	48% (30/62)	21% (13/62)[&]	6% (4/62)[†]	NA
Baas *et al.* (Checkmate 743)	Phase 3	MPM	Nivolumab + ipilimumab	NA	10% (30/303)[#]	NA	NA
Reck *et al.* (Checkmate 331)	Phase 3	SCLC	Nivolumab	NA	26% (75/284)[#]	NA	NA
Chung *et al.* (Keynote-028 and Keynote-158)	Phase1b and Phase 2	SCLC	Pembrolizumab	54% (45/83)	23% (19/83)[#]	NA	NA
Pujol *et al.* (IFCT-1603)	Phase 2	SCLC	Atezolizumab	70% (30/43)	NA	NA	NA
Ready *et al.* (Checkmate 032)	Phase 1/2	SCLC	Nivolumab	59% (87/147)	38% (56/147)[#]	NA	NA
			Nivolumab + ipilimumab	43% (41/96)	37% (36/96)[#]	NA	NA
Owonikoko *et al.* (Checkmate 451)	Phase 3	SCLC	Nivolumab	46% (120/261)	13% (38/280)[#]	NA	NA
			Nivolumab + ipilimumab	46% (121/265)	17% (49/279)[#]	NA	NA
Reck *et al.*	Phase 3	SCLC	Chemotherapy + ipilimumab	6% (29/478)	6% (28/478)[$]	NA	NA

Table 1 (*continued*)

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Author	Study	Tumour type or uncommon population	ICI treatment	PD, % (n/N)	ED, % (n/N)	HPD, % (n/N)	PsPD, % (n/N)
Rudin *et al.* (Keynote 604)	Phase 3	SCLC	Chemotherapy + pembrolizumab	NA	12% (27/223)[#]	NA	NA
Horn *et al.* (Impower 133)	Phase 3	SCLC	Chemotherapy + atezolizumab	11% (21/201)	9% (19/201)[#]	NA	NA
Paz-Ares *et al.* (CASPIAN)	Phase 3	SCLC	Chemotherapy + durvalumab	12% (32/268)	9% (24/268)[#]	NA	NA
			Chemotherapy + durvalumab + tremelimumab	NA	11% (30/268)[#]	NA	NA
Besse *et al.* (REACTION)	Phase 2	SCLC	Chemotherapy+ pembrolizumab (after two cycles of chemotherapy)	NA	7% (4/58)	NA	NA
Cho *et al.*	Phase 2	Thymoma	Pembrolizumab	0 % (0/0)	14% (1/7)[‡]	NA	3% (1/33)*
		Thymic carcinoma		27% (7/26)	23% (6/26)[‡]		
Giaccone *et al.*	Phase 2	Thymic carcinoma	Pembrolizumab	25% (10/40)	7.5% (3/40)[#]	NA	NA
Felip *et al.* (Checkmate 171)	Phase2	≥70 years	Nivolumab	18% (40/151)	25% (69/276)[#]	NA	NA
		ECOG PS 2		16% (10/39)	44% (45/103)[#]	NA	NA
Facchinetti *et al.*	Retrospective	ECOG PS 2	Pembrolizumab	63% (96/153)	63% (97/153)[&]	NA	NA
Gonzalez-Cao *et al.* (DURVAST)	Phase 2	HIV$^+$ lung cancer	Durvalumab	44% (4/9)	NA	NA	NA
Uldrick *et al.*	Phase 1	HIV$^+$ all cancer	Pembrolizumab	27% (8/30)	NA	NA	NA
Cook *et al.*	Metanalysis	HIV$^+$ NSCLC	Anti-PD-1/ PD-L1 or anti-CTLA-4 agents	35% (8/23)	NA	NA	NA
Signorelli *et al.*	Retrospective	Rare histotypes	Anti-PD1/PD-L1 agents	65% (20/31)	NA	NA	NA
Domblides *et al.*	Retrospective	Sarcomatoid NSCLC	Nivolumab/ pembrolizumab/ atezolizumab	43% (16/37)^	NA	NA	NA

*, still on treatment beyond PD (not known the response beyond PD); [#], in the first 3 months from treatment initiation; [$], in the first 4 months from treatment initiation; [&], in the first 5 months from treatment initiation; [‡], in the first 6 months from treatment initiation; [†], according to TGK ratio ≥2; ^, 32% of patients had a rapid PD. PD, progression; HPD, hyperprogressive disease; ED, early deaths; PsPD, pseudoprogression; NA, not available; MPM, malignant pleural mesothelioma; SCLC, small cell lung cancer; PS, performance status; NSCLC, non-small cell lung cancer; TGK, tumour growth kinetics.

the phase III DETERMINE trial. In this study the PD rate according to RECIST v1.1 was slightly lower in the tremelimumab arm (46%) *vs.* placebo arm (59%). Furthermore, OS curves overlapped for the first 3 months from randomization and the ED rate in this timeframe was similar between treatment arms: 21% (82/382) for tremelimumab and 22% (42/189) for placebo (21).

Nivolumab, an anti-PD1 monoclonal antibody, was tested in pretreated MPM patients enrolled in a single arm phase II Japanese trial (MERIT) (22) and in a Dutch prospective single arm phase II study (23). The PD rates according to RECIST modified for MPM (24) or a combination of RECIST modified for MPM and RECIST modified for ICI (25) were 26% and 50%, respectively. The ED rates within the first 3 or 4 months of treatment were 18% (6/34) and 9% (3/34) in the Japanese (22) and Dutch (23) trials, respectively. No HPD was reported in both studies, however in the MERIT trial 1 (11%) out of 9 patients experiencing PD, had an increase of 60% in the RECIST tumour burden compared to baseline (22).

Pembrolizumab, another anti-PD1 monoclonal antibody, was tested in pretreated MPM patients included in two non-randomized studies, a phase 1b (Keynote-028) (26) and a phase II study (27). In both trials, responses were assessed according to RECIST v1.1 and RECIST modified for MPM, respectively and the PD rates were 16% (26) and 37% (27). Of note in the phase II trial, 2 (8%) out of 24 patients with PD experienced an increase of 100% in the RECIST tumour burden compared to baseline (27). In the phase 1b trial, an ED rate in the first 3 months of 16% (4/25) was reported (26).

Pembrolizumab was the only ICI compared to single agent chemotherapy (gemcitabine or vinorelbine) in a randomized phase 3 trial (ETOP 9-15 PROMISE) (28). Although the overall response rate (ORR) was significantly higher with pembrolizumab compared to chemotherapy (22% *vs.* 6%), survival did not differ between treatment arms and the PD rates according to RECIST v1.1 also were similar (45% with pembrolizumab *vs.* 49% with single agent chemotherapy). Two patients (one in pembrolizumab arm and one in chemotherapy arm) had an increase of 60% in the RECIST tumour burden compared to baseline. Of note, in the first 4 months of treatment single agent chemotherapy performed better than pembrolizumab and the ED rate in this timeframe was 24% in the pembrolizumab arm *vs.* 18% in the chemotherapy arm (28).

Avelumab, an anti-PD-L1 monoclonal antibody, was administered in advanced pretreated MPM enrolled in a phase 1b trial (JAVELIN). The PD rate according to RECIST v1.1 and the ED rate in the first 3 months of treatment were 34% and 24% (13/53). Interestingly, 1 (5.5%) out of 18 patients with PD, had a 90% increase in the RECIST tumour burden compared to baseline (29).

Durvalumab, an anti-PD-L1 monoclonal antibody, has been tested as maintenance treatment after six cycles of chemotherapy in treatment naïve MPM (30). In this single arm phase II study (DREAM trial), PD rates were 15% and 13% according to RECIST modified for MPM and RECIST modified for ICI. 2 (28%) out of 7 patients with PD upon durvalumab had an increase higher than 130% in the RECIST tumour burden compared to baseline (30). ED rate in the first 3 months of treatment was 7% (4/54).

Four trials have tested PD-1/PD-L1 inhibitors in combination with anti-CTLA-4 agents in advanced MPM. The first study was a single arm phase II trial (NIBIT-MESO) in MPM patients (30% treatment naïve) receiving tremelimumab and durvalumab. The PD rates were of 35% and 38% according to immunorelated modified RECIST (31) or RECIST modified for MPM (24), respectively. The ED rate in the first 6 months was 10% (4/40) (32). INITIATE was a single arm phase II study of nivolumab and ipilimumab, an anti-CTLA-4 monoclonal antibody in pretreated MPM. The PD rate according to RECIST modified for MPM (24) was 32% and 6% (2/34) of patients died in the first 3 months of treatment (33).

MAPS-2 study was a double arm non-comparative trial testing nivolumab or nivolumab plus ipilimumab in pretreated advanced MPM. ED rates in the first 5 months after randomization were 30% (19/63) and 21% (13/62) in nivolumab and nivolumab plus ipilimumab, respectively. The PD rates according to RECIST modified for MPM (24) were high for both nivolumab (60%) and nivolumab plus ipilimumab (48%) (34). Interestingly 1 patient upon nivolumab and 1 upon nivolumab plus ipilimumab experienced striking PDs with an increase higher than 160% in the RECIST tumour burden compared to baseline (34). MAPS-2 was the only study were pre-ICI radiological evaluation were collected and used to assess HPD. According to the volumetric criteria previously used in NSCLC, HPD defined as RECIST PD and >50% increase in the tumour growth rate (TGR) during ICI compared to TGR before ICI (11) was found in 6 (5%) out of 125 patients (4 patients in the nivolumab arm and 2 patients in the nivolumab and ipilimumab arm) and median OS did not differ between HPD and conventional RECIST PD both in nivolumab and in nivolumab plus ipilimumab

arms. Considering that in the TGR computation, tumour is considered as a sphere (35) and that mesothelioma rarely harbours spherical features, the TGR definition is difficult to be applied. Tumour growth kinetics (TGK) definition was previously used to assess HPD in head and neck tumours and HPD was defined as a doubling in the RECIST sum of longest diameter (SLD) of target lesions upon ICI compared to pretreatment period (10). According to TGK definition, HPD was reported in 11 (9%) out of 125 MPM patients in the MAPS-2 trial (7 patients in the nivolumab arm and 4 patients in the nivolumab plus ipilimumab arm). Of note, HPD was significantly associated with negative PD-L1 expression (<1%) on tumour cells (8 out of 11 HPD patients had negative PD-L1 expression). In addition, patients with conventional disease PD had a better median OS compared to HPD patients according to TGK definition in the whole population [5.5 (95% CI: 2.6–8.9) *vs.* 2.6 (95% CI: 0.8–7.7) months, HR: 0.37 (95% CI: 0.19–0.75), P=0.006] (36).

Finally, at World Lung Cancer Conference 2020, Checkmate 743 phase 3 trial showed promising survival results in favour of nivolumab and ipilimumab combination compared to cisplatin and pemetrexed, in particular in the sarcomatoid subtype. In the overall population and in patients with epithelioid or sarcomatoid histology ED rates were 10% (30/303), 10% (22/229) and 11% (8/74) respectively in the immunotherapy arm *vs.* 11% (34/302), 10% (23/227) and 15% (11/75) in the chemotherapy arm (37).

If data regarding HPD in MPM from clinical trials are few, even less evidence is available from retrospective cohorts. In the first study of HPD in patients with different tumour types treated with anti-PD-1/PD-L1 agents in phase I trials, only 1 out of 131 patients included had MPM and did not experience HPD according to TGR criteria (8). In another recent study, where HPD was assessed by both TGR and RECIST criteria in a large cohort of cancer patients, 67 out of 270 patients were classified as having other histology, however it was not reported whether MPM were included in that subgroup (18).

Overall, PD (from 15% up to 60%) and ED (from 9% up to 30%) rates reported in clinical trials and specific analyses from MAPS-2 study suggest the occurrence of HPD also in pretreated MPM, both upon PD-1/PD-L1 inhibitors as single agents or in combination with CTLA-4 inhibitors.

The characterization of HPD mechanisms in MPM is an unmet need. In NSCLC patients and patients derived xenografts, an involvement of immune suppressive M2 ($CD163^+CD33^+PD\text{-}L1^+$) tumour associated macrophages via the Fc portion of anti-PD-1 monoclonal antibody was reported (14). Considering that the immune microenvironment of MPM is dominated by macrophages (38) and that a high M2 to $CD8^+$ T cells ratio has been associated with poor prognosis in MPM (39), a reprogramming of intratumoral macrophages to M2 upon ICI may occur and be responsible for HPD and ED in MPM.

PD, HPD and ED in SCLC

In pretreated SCLC patients, nivolumab was compared to topotecan in Checkmate 331 trial (40). Although PD rates were not available, the ED rates in the first 3 months were similar: 26% (75/284) in the nivolumab arm and 22% (64/285) in the topotecan arm. A pooled analysis from pretreated SCLC cohorts receiving single agent pembrolizumab in the phase 1b KEYNOTE 028 and in the phase II KEYNOTE 158 studies showed a PD rate of 54% and an ED rate in the first 3 months of treatment of 23% (19/83). Of note 1 (2%) of 45 patients with PD experienced an increase of 100% in the RECIST tumour burden compared to baseline (41).

Atezolizumab, an anti-PD-L1 monoclonal antibody, was tested in a randomized non-comparative phase II trial (IFCT-1603) versus topotecan or reinduction of initial chemotherapy. PD rates were higher compared to any other trial with 70% of PD as best response in the atezolizumab arm compared to 30% in the chemotherapy arm (42).

In pretreated SCLC patients, PD-1/PD-L1 inhibitors were tested also in combination with anti-CTLA-4 agents. In Checkmate 032 phase1-2 trial, SCLC patients were randomized to nivolumab or nivolumab and ipilimumab after a failure of at least one line of platinum-based chemotherapy. PD rates were 10% and 18% with nivolumab and nivolumab plus ipilimumab respectively. ED rates in the first 3 months were also similar 38% (56/147) and 37% (36/96) (43).

Nivolumab and nivolumab plus ipilimumab were also compared to placebo as maintenance treatments after platinum-based chemotherapy in extensive stage SCLC (Checkmate 451 trial). PD rates were similar in nivolumab (46%) and nivolumab plus ipilimumab arm (46%) while were slightly higher in the placebo arm (57%). ED rates in the first 3 months from randomization were 13% (38/280), 17% (49/279) and 14% (38/275) in nivolumab, nivolumab plus ipilimumab and placebo groups (44).

Six studies tested combination of ICI and platinum-based chemotherapy in treatment naïve SCLC. Ipilimumab was

tested in combination with platinum-based chemotherapy showing a PD rate of 6% in the combination arm and 9% in the chemotherapy arm. The ED rates in the first 4 months from randomization were 6% (28/478) and 5% (22/476) in the ipilimumab plus chemotherapy and chemotherapy alone, respectively (45). In the KEYNOTE 604 phase 3 trial, pembrolizumab in combination with platinum-etoposide was compared to chemotherapy alone. Although a significant survival benefit was observed in the pembrolizumab arm, ED rate in the first 3 months was double in the immunotherapy arm compared to chemotherapy [12% (27/223) *vs.* 5% (12/223)] (46). Similar shapes of survival curves with likely similar ED rates were observed in the ECOG-ACRIN EA5161 phase 2 study comparing platinum-etoposide with nivolumab or placebo in untreated extensive stage SCLC (47).

In the Impower 133 trial, SCLC patients were randomized to first-line platinum-etoposide with atezolizumab or placebo. PD rates and ED rates in the first 3 months were 11% *vs.* 9% and 9% (19/201) *vs.* 8% (16/202) respectively in the atezolizumab arm compared to placebo (48). Finally, durvalumab was tested in combination with platinum-etoposide in the CASPIAN trial. PD rates were 12% for both arms, ED rates in the first 3 months after randomization were 9% (24/268) in the durvalumab arm *vs.* 10% (27/269) in the placebo arm (49). The same trial included also an arm of durvalumab plus tremelimumab in combination to platinum-etoposide which showed no median OS improvement compared to platinum-etoposide. In the first 3 months, ED rate was 11% (30/268), similar to the ED rates in the chemotherapy or durvalumab plus chemotherapy arms (50). Finally, combination of platinum-etoposide and pembrolizumab was tested as maintenance therapy after induction with two cycles of platinum-etoposide in one EORTC phase 2 study (REACTION), showing improvement in OS with similar ED rate (7%) in the immunotherapy and in the placebo arm (51).

So far, HPD has not been reported in SCLC, however, in some retrospective series assessing HPD upon ICI it was not specified the histology subtype of lung cancer patients and it's possible that SCLC were included. In Champiat *et al.* (8) and in Kanjanapan *et al.* (52), 13 of 131 and 28 of 182 patients respectively had lung cancer with no specified histology subtype. Furthermore, in Champiat *et al.* no lung cancer patient experienced HPD, in Kanjanapan *et al.* the rate of HPD in lung cancer subgroup was not reported. Singavi *et al.* (53) identified 5 patients with HPD according to TGR variation and 1 of them had lung neuroendocrine tumour harbouring FGF3, FGF4 amplification.

Overall, considering the PD (from 6% to 70%) and ED (from 6% up to 38%) rates reported in clinical trials, it is not possible to exclude the occurrence of HPD in SCLC patients particularly upon single agent ICI administered in second or further line.

PD, HPD and ED in thymic malignancies

Pembrolizumab was tested in a single arm phase II Korean trial including patients with thymoma or thymic carcinoma. PD rates were 0% and 7% in thymoma and thymic carcinoma. ED rates in the first 6 months of treatment were 14% (1/7) of thymoma and 23% (6/26) for thymic carcinoma. All patients experiencing PD upon pembrolizumab had a change of RECIST tumour burden from baseline <40% (54).

Pembrolizumab was also tested in a single arm phase 2 trial including only thymic carcinoma due to the 71% grade 3–4 adverse events observed in thymoma patients from the Korean study. PD rate and ED rate in the first 3 months (100 days) were 25% and 7.5% (3/40). Of note, one of 10 patients experiencing PD had an increase in the RECIST tumour burden from baseline of 140% (55). Altogether these data suggest that although rare, striking or rapid PDs with deaths may occur in thymic malignancies upon single agent ICI.

PD, HPD and ED in uncommon populations

The efficacy of ICI in special populations, such as elderly, patients with HIV infection, poor ECOG PS, autoimmune disorders (AID) and uncommon histology is controversial because these categories of patients were excluded or less represented in clinical trials and most of available evidence comes from retrospective or real-world studies.

Regarding elderly NSCLC population, although the age cut-offs used in clinical trials were different, one metanalysis (56) and some studies including patients older than 75 years (57-59) suggested an absence of a significant survival benefit of ICI in this subgroup. On the other hand, a pooled analysis of three trials comparing pembrolizumab to chemotherapy in NSCLC patients (60), a phase II study of nivolumab including 34% of patients older than 70 years (61) and real-world data (62-65) showed a survival improvement with single agent ICI in the elderly population with no safety concerns. In pretreated NSCLC patients, PD rates upon single agent nivolumab were

50% for both patients younger than 65 years and between 65–75 years (64) and ranged between 13% (61) and 54% (64) for NSCLC patients older than 75 years in a phase II trial and in a retrospective study. ED rates in the first 3 months from nivolumab initiation in a phase II trial were 25% (69/276).

Only one retrospective study assessing HPD in patients treated with single agent PD-1/PD-L1 inhibitors in phase I trials found a statistically significant correlation between HPD and age. In this study, HPD was defined by volumetric criteria as doubling of TGR and HPD rate was 19% among patients older than 65 years and 5% among younger patients (8). It's likely that immunological age rather than chronological age impairs ICI efficacy. Specifically, the expansion of low replicative, proinflammatory and oligoclonal senescent T-cells occurring upon persistent antigenic stimulation may negatively affect ICI outcomes (66). To this regard, we recently reported a significant correlation between circulating T-cell immunosenescence and HPD upon ICI in advanced NSCLC patients and all HPD patients had very high rate of circulating senescent ($CD28^-$ $CD57^+$ $KLRG1^+$) $CD8^+$ T-cells (67). Of note, immunosenescence was not associated with age, further suggesting the absence of overlap between chronological and immunological age.

The efficacy of ICI in patients with poor ECOG PS is a debated topic. In fact, baseline ECOG PS ≥2 is associated with worse outcome both in first line setting and in previously treated NSCLC. Interestingly, PD rates were 16% in 39 pretreated patients included in a phase II trial of nivolumab (Checkmate 171) (61) but raised up to 63% in 153 treatment naïve PD-L1 ≥50% NSCLC with ECOG PS 2, with half of them recorded as clinical PD as patients died before any radiological evaluation (68). In this study ED rate in the first 5 months from pembrolizumab initiation was 63% (97/153). Furthermore, patients with ECOG PS 2 determined by comorbidities had significantly better outcome compared to disease-burden induced PS 2.

In a post-hoc analysis of the OAK trial comparing atezolizumab to docetaxel in pretreated NSCLC patients (69), in a Japanese retrospective study including NSCLC treated with nivolumab (70) and in a Food and Drug Administration (FDA) analysis of different anti-PD-1/PD-L1 agents in NSCLC patients (71) ED rates upon single agent ICI were 5.6%, 18.9% and 9.7% respectively. Interestingly, in all the three studies ED significantly correlated with worse baseline ECOG PS. Considering that the concept of HPD implies a treatment induced acceleration of the disease during ICI compared to pre-treatment period, it is likely that baseline PS is more a prognostic factor able to predict ED and PD rather than HPD. However, dynamic PS worsening during ICI is a different concept from baseline PS and it was included as a criterium to define HPD in one retrospective study (14). Mechanisms beyond the impairment of immunotherapy efficacy induced by poor ECOG PS remain unclear but may be related to the negative effects of protein catabolism (including rapid clearance of monoclonal antibodies) or to the use of concomitant medications, such as steroids (72,73) or antibiotics (65,74) in poor PS patients.

ICI are being increasingly used in patients with HIV infection and cancer. In a systematic review and metanalysis treatment with ICI was effective and safe, however PD rate was 35% in NSCLC patients (75). In a phase II trial in HIV patients (DURVAST study), durvalumab was safe and showed a 25% ORR across different cancer types. PD rate was 44% and 1 patient had a striking PD with increase in the RECIST tumour burden from baseline of 100%. Among 9 patients with lung cancer (8 NSCLC and 1 SCLC), 4 (44%) had PD as best response to durvalumab (76). In a phase 1 study of pembrolizumab in HIV^+ cancer patients, PD rate was 27% and one patient with solid tumour experienced an increase in the RECIST tumour burden from baseline greater than 300% (19).

Nivolumab and ipilimumab have been administered in HIV^+ NSCLC patients with ECOG PS 2, or renal/hepatic impairment or untreated brain metastases included in a non-randomized phase 3 trial (Checkmate-871) (77). ORR was 24% in these special populations, however data on PD and ED rates for single patients' categories were not presented.

In retrospective series including patients with baseline AID treated with ICI (78-80), no correlation was observed between AID and ORR, a no ED or HPD was reported so far.

Finally, the efficacy of ICI in rare NSCLC histotypes is controversial and in a retrospective series including patients with sarcomatoid, enteric, adenosquamous or large cell neuroendocrine tumours a trend towards an higher PD rate (65% *vs.* 47%) and a decreased OS was reported in rare NSCLC histologies (4.6 months; 95% CI: 0.03–12.0) compared to common NSCLC (9.2 months; 95% CI: 7.4–10.9) (81).

In another retrospective study, including only pretreated NSCLC patients with sarcomatoid histology, although ORR was higher (40.5%) compared to historical 15–20% ORR observed for single agent ICI in further lines. However, PD

rate was 43% (16/37), 32% (12/37) of patients had a rapid PD and half of them (5/37) died without a radiological evaluation. Of note three of these rapid PDs had PD-L1 expression on tumour cells of 50%, 90% and 100% suggesting that PD-L1 in the context of rare histology may lose some of its predictive power (82) in contrast to what observed in other case series (83). The characterization of mechanism of PD and ED in patients with rare histotypes is an unmet need. Considering that some molecular alterations such as LKB1 mutation have been associated with HPD in NSCLC patients (13), it is possible that they can be enriched in patients with rare NSCLC histotypes. In this regard, it was recently reported that enteric lung carcinoma showed higher incidence of LKB1 mutations compared to conventional lung adenocarcinoma (84).

PsPD in other thoracic malignancies and uncommon populations

PsPD has been described as tumour PD followed by radiological response and initially reported in 4.6–9.7% of melanoma (85,86) and in up to 7% of renal cell carcinoma (87) treated with ICI.

PsPD is even more uncommon in NSCLC patients, where it occurs in less than 5% of ICI treated NSCLC patients (88,89). However, no standard definition of PsPD is available so far. In some studies, not only patients with partial or complete response after initial RECIST PD but also patients experiencing prolonged disease stabilization were labelled as pseudoprogressors and the PsPD rate raised at 8–19.5% (90,91) of ICI treated patients.

In thoracic malignancies other than NSCLC, few data regarding PsPD upon ICI are available.

Three (9%) of 34 MPM patients treated with single agent nivolumab in the Dutch trial experienced PsPD defined as partial response after initial RECIST PD (23). Although in the MERIT trial with nivolumab in Japanese MPM patients no PsPD was formally reported, one (3%) of 34 patients received nivolumab beyond RECIST PD and was still on treatment at 18 months (22).

Two (3%) of 64 pretreated MPM who received single agent pembrolizumab in a phase II trial showed partial response after initial RECIST PD (27). In the phase 1b Keynote-028 trial, no PsPDs were reported, however 1 (4%) out of 25 patients was treated beyond PD and was still on treatment at 22 months (26). Similarly, in the JAVELIN trial, 1 (2%) out of 53 pretreated MPM, received avelumab beyond RECIST PD and experienced subsequent stable disease (29). Two (4%) of 54 MPM receiving single agent durvalumab maintenance in the DREAM trial were pseudoprogressors, having a PD followed by partial response (30). No PsPD were formally reported in trials testing anti-CTLA agents alone or in combination with PD-1/PD-L1 inhibitors (32-34). Interestingly, PsPD in MPM was associated with worsening of clinical condition (23). This finding is peculiar for MPM and was not observed in other tumour types where PsPD is usually characterized by radiological PD and stable clinical PS. It's likely that the immune cell infiltration within the pleura observed during PsPD may affect disease related symptoms much more in MPM compared to other tumour types due to the occurrence of pleural effusions, causing dyspnoea, and the sensitive innervation of the parietal pleura, causing chest pain. The fact that clinical evaluation is not helpful in discriminating between PsPD and true PD, together with the rarity of PsPD (2–9%) upon ICI make challenging the use of ICI beyond PD in MPM patients.

Regarding thymic malignancies, although no cases of PsPD have formally been reported, in the Korean study, 1 (3%) out of 33 patients was treated beyond PD occurred at 30 weeks and was still on pembrolizumab at 66 weeks (54). As far as we are concerned, no PsPD was reported in SCLC patients upon ICI.

Of note, PsPD was not reported for elderly patients, for patients with poor ECOG PS or with rare NSCLC histology. Similarly, in patients with AID no PsPD has been reported, although it's likely that in presence of a more reactive immune system, immune cell infiltration of tumour lesions and subsequent PsPD may more easily occur.

In the phase I trial of pembrolizumab in HIV^+ cancer patient, one patient experienced an atypical PD with a rapid increase in the tumour burden from baseline followed by a subsequent tumour reduction. This cannot be formerly defined as PsPD, however it suggests that PsPD upon ICI may occur also in the setting of HIV infection (19).

The characterization of mechanisms of PsPD remains an unmet need. Up to now, one study has explored the role of circulating tumour (ct) DNA in melanoma ICI treated patients showing that all 9 patients with PsPD had a favourable ctDNA (undetectable ctDNA or decreased ctDNA by at least 10-fold during treatment) (92). Another potential biomarker of PsPD is decrease in the levels of circulating IL-8. In fact, in two NSCLC patients and one patient with bladder cancer experiencing PsPD upon single agent anti-PD1 treatment, serum IL-8 levels decreased and remained lower compared to baseline (93). Considering

that IL-8 favours neutrophil infiltration in the tumour microenvironment and the formation of neutrophil extracellular traps (94), it's likely that granulocytic inflammation remains low in patients experiencing PsPD and the initial PD is mainly due to intratumorally infiltration by lymphocytes rather than myeloid cells. Future studies able to characterize mechanisms of PsPD also in other rarer malignancies such as MPM and thymic carcinoma are needed.

Conclusions

In the immunotherapy era, the identification of patients with rapid PD and deaths upon ICI has found some skepticism and resistance among the scientific community. Nevertheless, HPD upon ICI has been recognized as a phenomenon occurring across different cancer types and evidence regarding rapid PDs and ED is emerging also for other thoracic malignancies such as MPM, SCLC and thymic carcinoma and for elderly patients or patients with HIV infection, poor PS and rare NSCLC histotype. Similarly, PsPD may also occur in other thoracic malignancies (MPM) and in some uncommon populations (i.e., HIV patients), however probably at lower rate compared to HPD. The characterizations of HPD and PsPD mechanisms and the identification of common definition criteria are the next future challenges in this area of cancer research.

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