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# Literature meta-analysis about the efficacy of anti-programmed death protein 1 and anti-programmed death ligand 1 re-challenge in cancer patients

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*Méta-analyse de la littérature sur l'efficacité des inhibiteurs du checkpoint immunitaire PD-1/PD-L1 chez les patients cancéreux*

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## Abstract

**Introduction:** Immune checkpoint inhibitor (ICPi) re-challenge could be an attractive therapeutic option considering its good safety profile. However, little data is available regarding anti-PD-1/anti-PD-L1 retreatment. We conducted a meta-analysis focusing on outcomes of solid cancer patients performing this strategy. **Methods:** Fourteen full papers involving 74 patients were included. Individual data about best response or progression-free survival (PFS) upon the first and second course of anti-PD-1/ anti-PD-L1 were collected. **Results:** Non-small-cell lung cancer (53%) and melanoma (34%) were the most represented cancers. Higher objective response (46% versus 24%,  $p = 4.10^{-4}$ ) and disease control rates (73% versus 52%,  $p = 7.10^{-3}$ ) were obtained upon the first ICPi course compared to re-challenge. No association between responses obtained with the two ICPi courses was found ( $p = 3.10^{-1}$ ). The PFS upon the first ICPi (PFS1) was longer than that after re-challenge (PFSR) (6.6 versus 2.8 months, hazard ratio (HR) 0.57,  $p = 2.10^{-3}$ ). A longer PFSR was obtained in patients with a longer PFS1 ( $p = 6.10^{-3}$ ), in those who discontinued the first ICPi due to toxicity or per protocol (8.8 versus 2.1 months if disease progression occurs,  $p = 2.10^{-3}$ ), and in those not receiving intercalated treatment between the two ICPis (6.6 versus 2.1 months for the treated ones,  $p = 1.10^{-3}$ ). **Discussion:** Anti-PD-1/anti-PD-L1 re-challenge showed interesting clinical activity in selected patients, mainly in those achieving a long-term response upon the first ICPi course, that do not discontinue therapy because of disease progression, or that are able to keep a treatment-free period.

**Keywords:** Anti-programmed death protein 1; Anti-programmed death ligand 1; Immune checkpoint inhibitor; Re-challenge; Solid cancer; Meta-analysis

## Résumé

**Introduction:** La reprise des anti-PD1/PDL1 (ICPi) pourrait être une option intéressante mais peu de données sont disponibles concernant cette stratégie. Nous avons réalisé une méta-analyse à ce sujet portant sur des patients atteints de cancer. **Méthodes :** Quatorze articles concernant 74 patients ont été inclus. Les données individuelles sur la meilleure réponse et la survie sans progression (SSP) lors du premier et du deuxième ICPis ont été recueillies. **Résultats :** Cancer du poumon non à petites cellules (53%) et mélanome (34%) étaient les cancers les plus représentés. Une réponse objective (46% contre 24 %,  $p = 4.10^{-4}$ ) et des taux de contrôle de la maladie plus élevés (73% contre 52%,  $p = 7.10^{-3}$ ) ont été obtenus lors du premier ICPi par rapport à la reprise. La SSP lors du première ICPi (SSP1) était plus longue que à la reprise (SSPR) (6.6 contre 2.8 mois, HR= 0.57,  $p = 2.10^{-3}$ ). Une SSPR prolongé a été obtenu chez les patients ayant un SSP1 plus long ( $p = 6.10^{-3}$ ), qui ont interrompu la première ICPi pour une cause autre que la progression (8.8 contre 2.1 mois,  $p = 2.10^{-3}$ ), et qui n'ont pas reçu de la chimiothérapie entre les deux ICPis (6.6 contre 2.1 mois,  $p = 1.10^{-3}$ ). **Discussion:** La reprise des ICPis montre une efficacité intéressante chez des patients sélectionnés qui obtiennent une réponse à long terme lors du premier ICPi, qui interrompent le traitement pour une raison autre que la progression, ou qui peuvent faire une pause thérapeutique.

**Mots-clés** : Anti-programmed death protein 1 ; Anti-programmed death ligand 1 ; Immune checkpoint inhibitor ; Re-challenge ; Solid cancer ; Meta-analyse

## Introduction

Immune checkpoint inhibitors (ICPis) have completely changed the treatment algorithm of several cancer types because of the impressive results obtained in this field. Some patients achieve a long-term clinical benefit from this type of drugs. However, patients eventually discontinue ICPi due to disease progression or toxicities, as well as due to trial designs imposing discontinuation after a given treatment period. Primarily for those patients who achieve a long-term response without clinically-meaningful toxicities, ICPi re-challenge could represent an attractive therapeutic option, as the only possible alternative to chemotherapy. This strategy has already entered clinical practice in advanced melanoma patients who are permitted to being re-challenged with an anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4), as well as to being shifted across anti-programmed cell death 1 (anti-PD-1)/anti-programmed cell death ligand 1 (anti-PD-L1) and anti-CTLA-4. This strategy has been supported by several studies that specifically addressed this issue in melanoma patients, reporting promising results concerning ICPi re-challenge efficacy, along with a low toxicity profile [1–8] However, most of these trials included selected patients exhibiting significant clinical benefits, without severe undesirable events upon the first ICPi course. Consequently, in spite of no widely-recognized recommendations being available concerning this strategy, the National Comprehensive Cancer Network (NCCN) guidelines allow for considering ICPi re-induction in progressing patients with an initial response or disease stabilization lasting  $\geq 3$  months [9]. Much less is known about the efficacy and safety of re-challenge with anti-PD-1/anti-PD-L1 agents. The CheckMate-153 trial explored the clinical benefits of a fixed-duration nivolumab in second-line versus continuous treatment in advanced non-small-cell lung cancer (NSCLC) patients. In this

trial, 39 patients in the fixed-duration arm progressed during the surveillance period and were retreated with the same anti-PD-1. The median time between progression and nivolumab reinduction was 0.6 months, and the median duration of retreatment 3.8 months [10]. Moreover, the Keynote-010 trial selected PD-L1-positive ( $\geq 1\%$ ), pretreated, advanced NSCLC patients to receive two different schedules of pembrolizumab or docetaxel. In this trial, 14 patients received a second course of pembrolizumab, with the majority of them (78%) showing either partial response or stable disease[11,12]. Recently, the UNIVOC study retrospectively analyzed more than 1500 NSCLC patients that received an ICPI retreatment after a discontinuation period from nivolumab of at least 6 weeks. The median overall survival (OS) from re-challenge was 15 months for patients receiving a second course of PD-1 inhibitor after a treatment-free interval and 18.4 months for those who performed an intercalated chemotherapy. Interestingly, median OS was significantly longer in patients with an initial nivolumab treatment duration longer than 3 months[13]. However, no information was reported about the nivolumab discontinuation reason, patients' clinical features such as the ECOG Performance Status (PS) and the retreatment tolerance. Consequently, it was not possible to know how selecting patients to these strategies according to clinical characteristics. Finally, two retrospective studies investigating the safety of resuming anti-PD1 agents in cancer patients showing that only 50 to 55% of patients experienced an irAEs of any grade at anti-PD1 resumption [14,15]. Recently, a large retrospective study on the World Health Organization database VigiBase, reported 452 cases of serious irAEs during re-challenge with the same ICPI [16]. Among them 28.8% experienced a recurrence of the initial irAEs and the recurrence rates of colitis, hepatitis and pneumonitis were higher compared with other irAEs, whereas the recurrence rate of adrenal irAE was lower. Despite these encouraging data, the usefulness of anti-PD-1 and anti-PD-L1 re-challenge is still being debated because of the lack of prospective studies that specifically address this topic. While attempting to further investigate this

issue, we have reviewed the literature and selected case reports and cases series that reported outcomes of adult solid cancer patients re-challenged with an anti-PD-1 or anti-PD-L1 agent during their disease history. Individual patient data were meta-analyzed regarding efficacy outcomes to possibly identify potential clinical features associated with greater clinical benefit.

## **Methods**

PubMed and Google Scholar were searched for clinical trials, case series, and case reports containing data on solid cancer patients who were retreated with an anti-PD-1/anti-PD-L1. Key words used included “rechallenge”, “reintroduction”, “retreatment”, “immune checkpoint inhibitors”, “immune checkpoint blockades”, and “immunotherapy”. We considered only English-written articles reporting information on best response or progression-free survival (PFS) achieved upon either a first or second ICPI course. We did not find any prospective trial published on this issue and we identified 14 full papers (five case reports and nine case series) reporting the outcomes of 74 patients treated according to this strategy (Fig. 1, Table 1)[17–30]. Data search ended the 25th January 2020. We then meta-analyzed the individual data of these patients.

## **Statistical analysis**

The following information were collected: cancer histology, patients’ age and gender, number of treatments before the first ICPI, best response during the first ICPI and at re-challenge, progression-free survival (PFS) during the first ICPI and at re-challenge, first ICPI discontinuation reason and intercalated treatments.

Descriptive analysis, including the mean, median, and range for continuous variables or frequencies and the percentage for categorical variables, was performed. Qualitative

variable association and correlation were performed using the Chi-squared test and Pearson test, respectively. The overall response rate (ORR) was defined as the percentage of complete responses and partial responses obtained as best response, while the disease control rate (DCR) included the ORR and percentage of stable disease results achieved. Reported PFS values were simply collected; in the case of values not clearly indicated, PFS data were calculated from the ICPI start date (month and year) to the progression of disease or death (month and year). The median PFS in regard to the first anti-PD-1/anti-PD-L1 agent was termed PFS1, while PFSR defined the PFS reached upon re-challenge. The Kaplan-Meier method and a Cox model were used to calculate and compare the median PFS [31,32]. Statistical analysis was performed using XLStat (2018 Version).

## **Results**

### Patient's general features

The patients' clinical characteristics are described in Table 2. The mean age was 63 years [23–87], and most of the patients were male ( $n=45$ , 61%). NSCLC and melanoma were the most common tumors ( $n=39$ , 53% and  $n=25$ , 34%, respectively), while 10 patients (13%) had other cancer types. Notably, three patients exhibited clear cell renal cell carcinomas, two urothelial carcinomas, two colorectal cancers, one breast cancer, one Merkel carcinoma, and one head and neck carcinoma. Patients received a median of two systemic treatments before the first ICPI, which was discontinued in most of cases because of either disease progression ( $n=56$ , 76%), toxicity ( $n=9$ , 12%), or per protocol for patients included in clinical trials ( $n=9$ , 12%). Approximately 72% of patients received at least 1 systemic agent with or without a local treatment, such as radiotherapy or surgery, between the two ICPIs courses (Table S1).

### Response under Re-challenge

Best response achieved upon either the first or second ICPI course was available for 73 patients (Fig. 2). In the overall population, a higher ORR (46% versus 24%,  $p = 4.10^{-3}$ ) and higher DCR (73% versus 52%,  $p = 7.10^{-3}$ ) were obtained upon the first course of anti-PD-1 or anti-PD-L1 as compared to re-challenge. Focusing on NSCLC, a higher ORR (41% versus 15%,  $p = 1.10^{-2}$ ) and higher DCR (64% versus 38%,  $p = 1.10^{-2}$ ) were confirmed upon the first ICPI. In melanoma patients, neither the ORR (44% versus 32%,  $p = 3.10^{-1}$ ) nor the DCR (76% versus 64%,  $p = 3.10^{-1}$ ) were statistically different between the two ICPIs courses. However, no association was found between the best response achieved during the first ICPI exposition and that obtained at re-challenge in the whole population ( $p = 3.10^{-1}$ ).

#### Progression-free survival under re-challenge

Paired PFS1 and PFSR were evaluable in 61 patients. As expected, the PFS1 was longer than the PFSR (6.6 [95% CI: 4.9–8.4] versus 2.8 months [95% CI: 2.0–4.0], HR 0.57 [95% CI: 0.00–0.87],  $p = 2.10^{-3}$ ) (Fig. 3). The median PFS1 was 5.6 months [95% CI: 2.8–8.9] in NSCLC patients, 6 months [95% CI 3.9–8.4] in melanoma patients, and 15.8 months [95% CI: 8–22.9] in other cancer types. Interestingly, the median PFSR was quite similar among the NSCLC and melanoma patients at 2.1 months [95% CI: 1.6–3.3] and 2.7 months [95% CI: 1.8–7.0], respectively, while it reached 6 months [95% CI: 4.1 – 12.9] in the case of other histology. Note that a longer PFS1 can predict a longer PFSR, these values being positively correlated (Pearson correlation coefficient 0.347,  $p = 6.10^{-3}$ ) (Fig. 4). Patients with a PFS1  $\geq 12$  months were shown to display a longer PFSR compared to those presenting a PFS1 <12 months (5.1 [95% CI: 2.0–11.1] versus 2.4 months [95% CI: 1.7–3.4],  $p = 4.10^{-2}$ ) (Fig. 4). Shorter cut-offs were also tested (3, 6, and 9 months), whereas no statistically significant differences were obtained. As expected, a longer PFSR was achieved in patients who discontinued the first anti-PD-1/anti-PD-L1 agent due to toxicity or per protocol as compared to those who experienced disease progression (8.8 [95% CI



5.1–15] versus 2.1 months [95% CI: 1.8–3.1],  $p = 2.10^{-3}$ ), as well as in patients who did not receive another treatment between the two ICPis courses compared to those who did (6.6 months [95% CI: 2.3 – 14.8] versus 2.1 months [95% CI: 1.6 – 3.3],  $p = 1.10^{-3}$ ) (Fig. 4). Similar results were obtained, without considering the eight patients receiving ipilimumab (anti-CTLA-4) between the two ICPis (data not shown).

### Re-challenge safety profile

Concerning toxicities, a higher percentage of all grade adverse events occurred during the first anti-PD-1/anti-PD-L1 course, as compared to re-challenge ( $n = 58$ , 78% versus  $n = 43$ , 63%,  $p = 8.10^{-3}$ ) (Table 3). Rash and diarrhea were the most commonly reported adverse events.

## **Discussion**

Solid cancers can gain durable clinical benefit from ICPi therapy due to the effector memory T-cells' differentiation resulting in a long-term immunological response that is able to respond to tumor antigen re-exposition [33–35]. Thus, ICPi re-challenge may constitute a useful therapeutic approach, as it has already been successfully applied in advanced melanoma patients. However, while the anti-CTLA-4 re-challenge and sequential administration of anti-CTLA-4 and anti-PD-1/PD-L1 agents have previously been explored in several clinical trials [1,2,5–8], little data is available on the efficacy and safety of anti-PD-1/anti-PD-L1 retreatment. Our meta-analysis of published case reports and case series has certainly improved our understanding of the clinical benefits associated with this strategy, possibly facilitating patient selection. As expected, patients achieved better outcomes over the first exposure to the anti-PD-1/anti-PD-L1 as compared to the re-challenge; however, the clinical benefits obtained with retreatment were quite interesting. Most patients (60%) achieved disease control, and 28% of cases even presented disease shrinking, consistent with the literature data reported about the re-challenging strategy with

other ICPI [1,2,5–8,11,12]. However, when considering different histology types separately, these results were confirmed in NSCLC patients only, whereas no differences were found in melanomas or other cancer patients. While this can be partially explained by the small number of patients included in these latter groups, it probably suggests a different pattern of antitumor immune response according to histology. More interestingly, patients reported a PFSR of 2.8 months upon re-challenge, which is very similar to what is expected when using anti-PD-1 or anti-PD-L1 agents in pretreated cancer patients. In fact, the median PFS obtained in pretreated patients receiving nivolumab or pembrolizumab within Phases II and III clinical trials ranged from 2.3 to 4.0 months in NSCLC patients and from 4.1 to 5.5 months in melanoma patients, representing the histology primarily included in the current analysis [11,12,36–38]. Unfortunately, the UNIVOC study did not provide information on PFS but only on TTF. On the contrary, in the present meta-analysis we have no information on the patients' survival. Consequently, a cross-studies comparison is not feasible. Anyway, these results suggest that anti-PD-1 and anti-PD-L1 efficacy in pretreated patients is not affected by previous ICPI treatment, thereby representing an attractive and certainly less toxic alternative to chemotherapy. In our analysis, no increased toxicities were registered upon the ICPI re-challenge, in line with previous studies [1,5–8,39]. Nevertheless, no information pertaining to AE grades was available in most papers considered for this study.

The other primary issue we wished to investigate was as follows: which patients should be candidates for this strategy. Melanoma patients who achieve an objective response lasting  $\geq 3$  months with ICPI without experiencing Grade III or IV AEs can be considered for re-challenge with anti-CTLA-4 or a sequential treatment with another ICPI. Here, we consistently found a better PFS upon re-challenge for patients who achieved a longer PFS during the first ICPI course, especially if  $\geq 12$  months. Moreover, patients who did not receive any treatment between the two ICPIs courses and those who discontinued the first

course without experiencing disease progression seem to be the best candidates.

Conversely, the best response obtained regarding the first ICPi was unable to predict the response upon re-challenge. These results are not surprising, given that patients with these characteristics are likely to have a more favorable prognosis with a more indolent disease. In addition, we cannot exclude the possibility that re-challenge did not specifically change their disease history, which would have been favorable even with another type of treatment. Nevertheless, the re-challenge strategy resulted in interesting clinical benefits in these selected patients.

Clinical cases/series considered in this retrospective analysis, included up to 14 patients maximum representing single center experiences about the re-challenge strategy.

Consequently, clinical characteristics of patients, their history of disease and treatments received as well as the re-challenge setting are heterogeneous. Moreover, no information pertaining to patients' performance status, grade of AEs, and survival was available, limiting the analysis of the clinical benefits provided by anti-PD-1/anti-PD-L1 re-challenge. However, our population currently represents the largest multi-disease cohort of patients treated with this strategy, providing detailed data on patient outcomes and possibly allowing for patient selection criteria to be considered. Several Phase II clinical trials (NCT03526887, NCT03847649, NCT02743819, NCT03262779, NCT03041181, NCT03847649, NCT03334617, and NCT03469960), either already ongoing or scheduled to start patient recruitment soon, have been designed to investigate the safety and efficacy of anti-PD-1/anti-PD-L1 re-challenge among different tumor types. These trials will certainly help better define both the clinical benefits and criteria for improved patient selection, as regards this promising strategy. Moreover, the biological and immune characteristics of patients who benefit most from this strategy have not yet been identified. The analysis of the mechanisms of resistance to the first course of immunotherapy and the biological

profile of patients responding to the re-challenge is therefore indispensable and should be the subject of dedicated ancillary studies.

## **Conclusion**

Anti-PD-1/anti-PD-L1 re-challenge has been shown to display interesting clinical activity in selected cancer patients. Patients who achieve a long-term response upon the first ICPI course, do not discontinue therapy because of disease progression, or are able to keep a treatment-free period may be good candidates for this therapeutic strategy.

## **Abbreviations**

NSCLC: Non-small-cell Lung Cancer

CCRCC: Clear Cell Renal Cell Carcinoma

CRC: Colon-Rectal-Cancer

ICPi: Immune checkpoint inhibitors

Anti-CTLA-4: anti-cytotoxic T-lymphocyte antigen 4

Anti-PD-1: anti-programmed cell death 1

Anti-PD-L1: anti-programmed cell death ligand 1

PFS: Progression free survival

PFS1: median PFS in regard to the first anti-PD-1/anti-PD-L1 agent

PFSR: median PFS at re-challenge

OS: Overall survival

ORR: Overall response rate

DCR: Disease control rate

AE: adverse event

irAE: immune-related adverse event

NCCN: National Comprehensive Cancer Network

ECOG PS: Eastern Cooperative Oncology Group Performance Status

## **Declarations**

Ethics approval and consent to participate : Not applicable

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Figure captions

### Fig. 1. Consort diagram.

anti-PD-1, anti-programmed cell death 1; anti-PD-L1, anti-programmed cell death ligand 1.

### Fig. 2. Best responses upon first course of anti-PD1 or anti-PDL1 and re-challenge.

NSCLC, non-small-cell lung cancer; anti-PD-1, anti-programmed cell death 1; anti-PD-L1, anti-programmed cell death ligand 1; SD, stable disease; PR, partial response; CR, complete response; PD, progression disease.

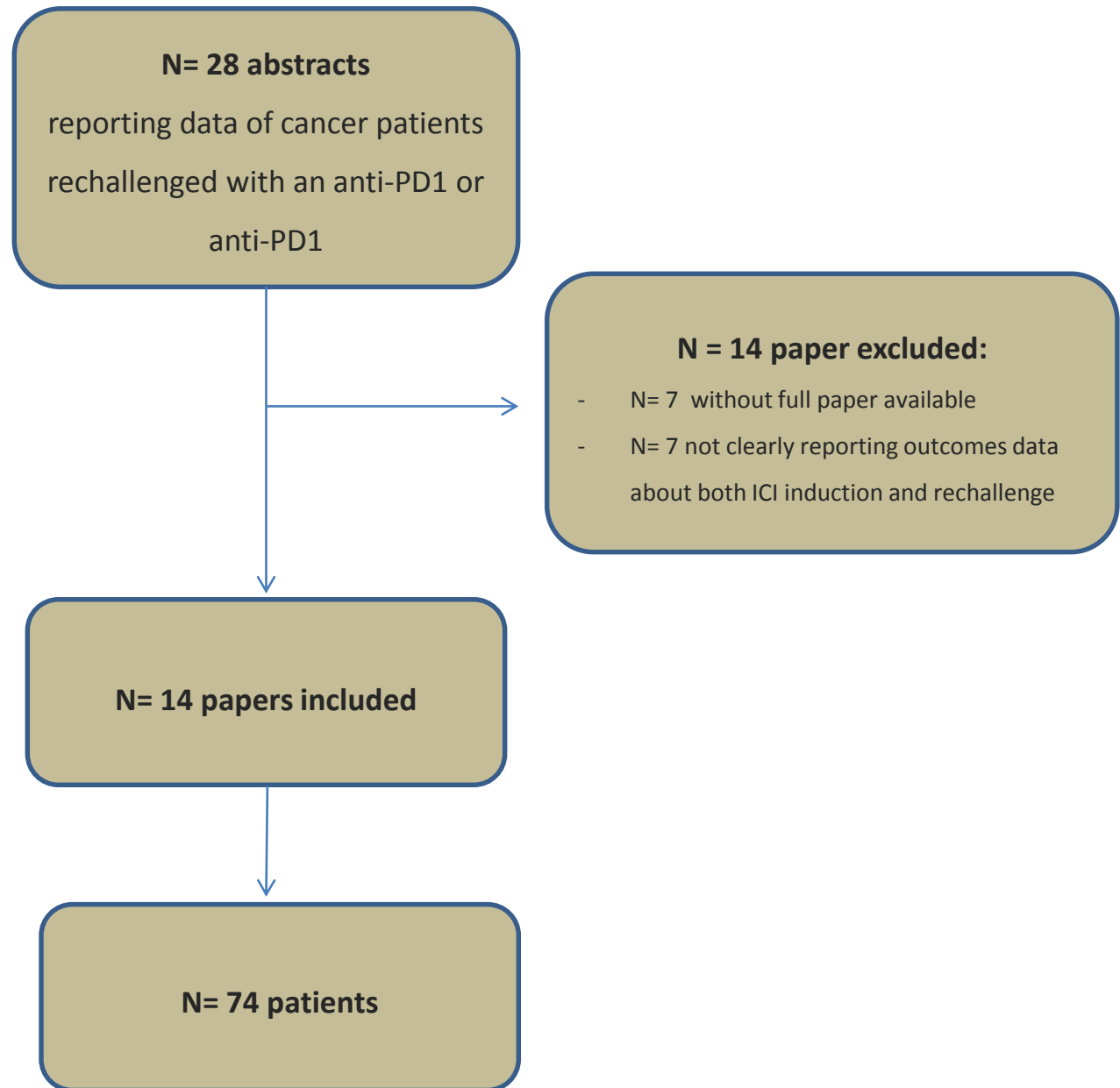
### Fig. 3. PFS1 and PFR comparison in the overall population and across histology.

PFS, progression-free survival; PFR, progression-free recurrence; HR, hazard ratio; NSCLC, non-small –cell lung cancer.

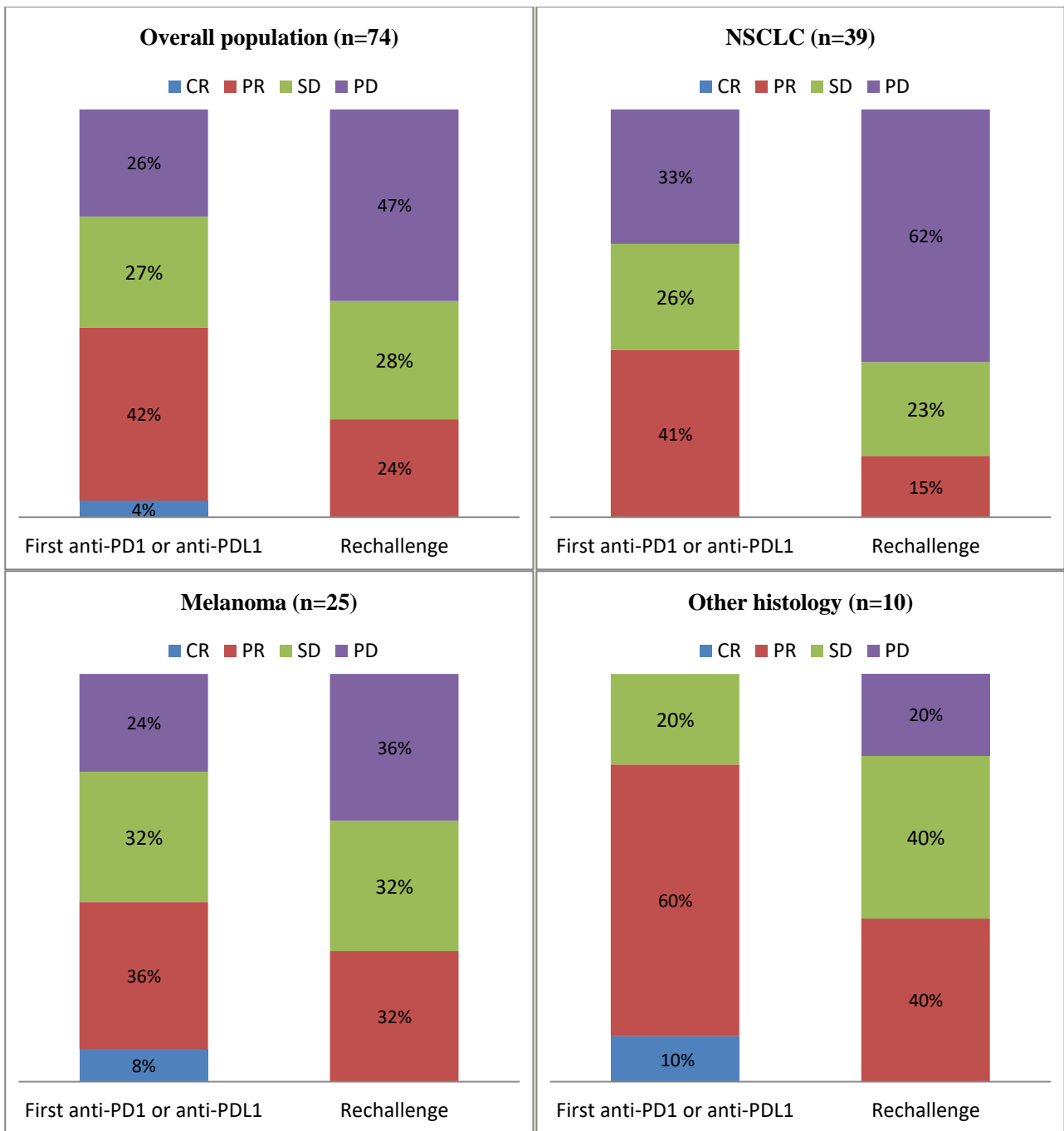
### Fig. 4. PFSR according to PFS1, discontinuation reason and treatment received between the two anti-PD1/PDL1 courses.

<sup>a</sup>PD, progression disease; PFS1, progression-free survival; Other, toxicity or per protocol; <sup>b</sup>No, no treatment received between the two immune checkpoint inhibitor courses; Yes, systemic therapy with or without local treatment (surgery or radiotherapy) between the two immune checkpoint inhibitor courses.

**Figure 1: Consort diagram**

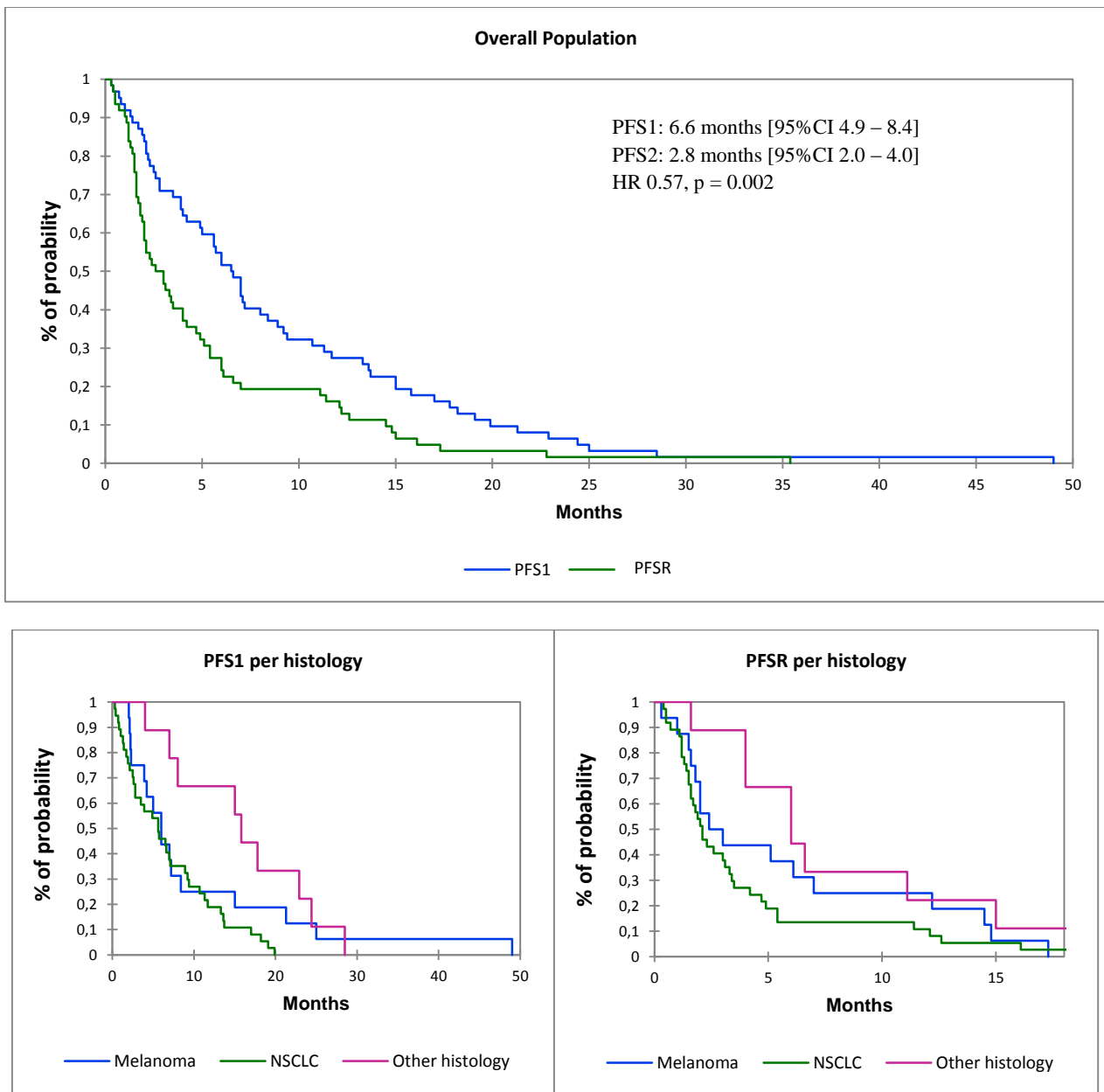


**Figure 2: Best responses upon first course of anti-PD1 or anti-PDL1 and rechallenge**

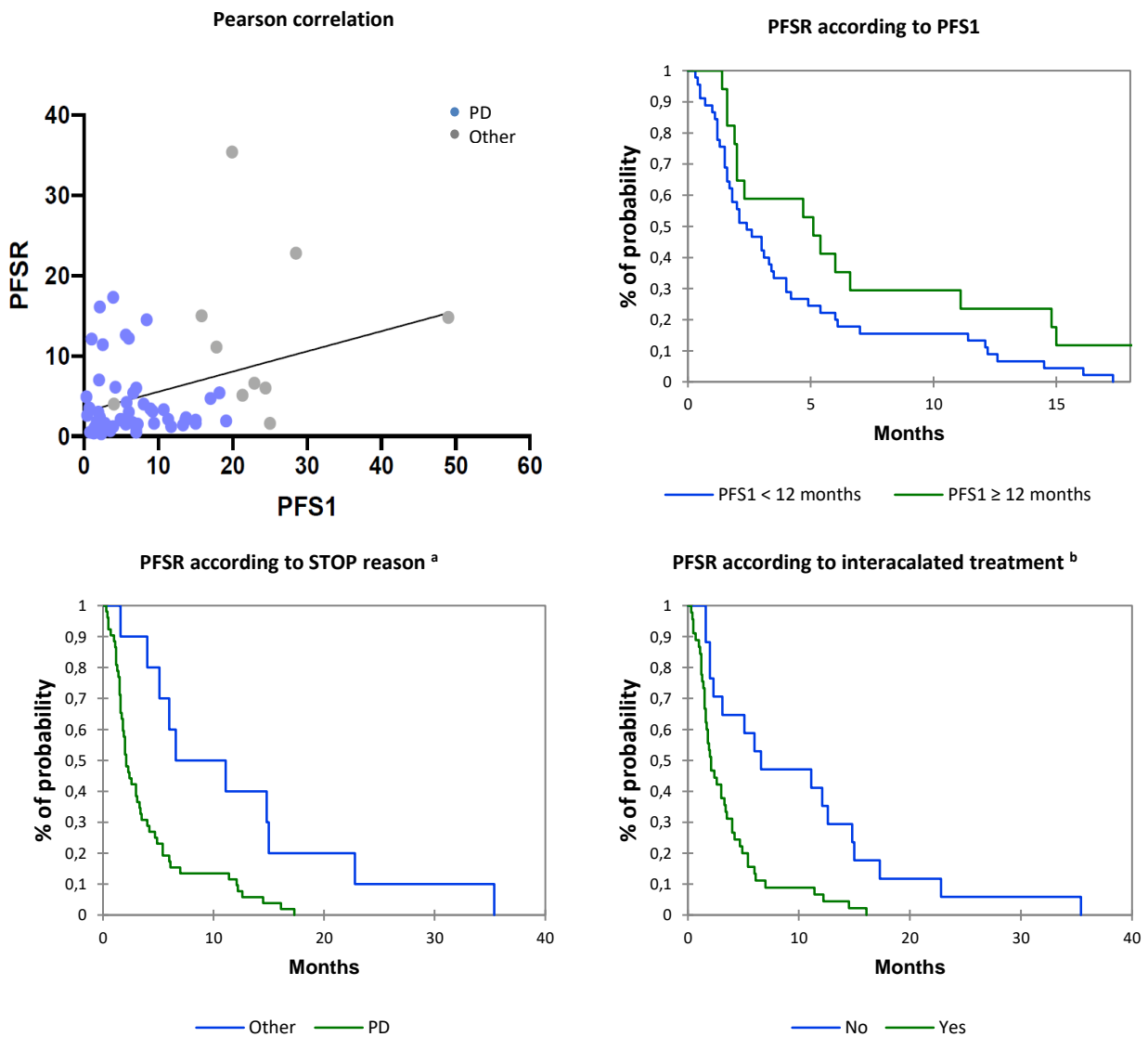


SD: stable disease, PR: partial response, CR: complete response, PD: progression disease

**Figure 3: PFS1 and PFS2 comparison in the overall population and across the histology**



**Figure 4: PFSR/PFS1 correlation according to the first-ICPi discontinuation reason, discontinuation reason and treatment received between the two anti-PD1 or anti-PDL1 courses.**



a. PD: progression disease, Other: toxicity or per protocol; b. No: no treatment received between the two ICI courses, Yes: systemic therapy with or without local treatment (surgery or radiotherapy) between the two ICI courses

**Table 1: Case reports and case series reported outcomes of cancer patients receiving an anti-PD1/PDL1 re-challenge**

Reference	Year	N° of patients	Histology	First ICPI	Re-challenge
Lipson E.J. et al.[17]	2012	1	Melanoma	anti-PD1	anti-PD1
Nomura M. et al.[18]	2017	8	Melanoma	nivolumab	nivolumab
Spain L. et al.[19]	2017	3	Melanoma	ipilimumab + nivolumab	ipilimumab + nivolumab
Martini D. et al.[20]	2017	3	CCRCC	anti-PDL1 or pembrolizumab	nivolumab
Blasig H. et al.[21]	2017	8	Melanoma	nivolumab or pembrolizumab	pembrolizumab
Delyon J. et al.[22]	2018	2	Merkel Cell Carcinoma and Melanoma	avelumab or ipilimumab + nivolumab	avelumab or pembrolizumab
Niki M. et al.[23]	2018	11	NSCLC	nivolumab	nivolumab or pembrolizumab
Dizman N. et al.[24]	2018	1	CRC	anti-PD1	nivolumab
Fujita K. et al.[25]	2018	12	NSCLC	nivolumab	Pembrolizumab
Bernard-Tessier A. et al.[26]	2018	8	NSCLC, Urothelial carcinoma, Melanoma, Breast cancer, CRC	anti-PD1 or anti-PDL1	anti-PD1 or anti-PDL1
Cabezas-Camarero S. et al.[27]	2018	1	Head and Neck cancer	anti-PDL1	Nivolumab
Hakozaki T. et al.[28]	2018	1	NSCLC	anti-PD1	nivolumab
Tedbirt B. et al.[29]	2019	1	Melanoma	pembrolizumab	Nivolumab
Watanabe H. et al.[30]	2019	14	NSCLC	anti-PD1 or anti-PDL1	anti-PD1

NSCLC : Non-Small-Cell Lung Cancer; CCRCC: Clear Cell Renal Cell Carcinoma; CRC: Colon-Rectal-Cancer

**Table 2: Patients' general features**

<b>Clinical feature</b>	<b>N = 74</b>
<b>Mean age [range]</b>	63 [23 – 87]
<b>Gender N (%) (MD = 5)</b>	
Male	45 (61)
Female	26 (35)
<b>Mean number of previous treatments (MD = 9)</b>	2
<b>Histology N(%)</b>	
Non-Small-Cell Lung cancer	39 (53)
Melanoma	25 (34)
Other histology	10 (13)
Clear Cell Renal Cell Carcinoma	3
Urothelial Carcinoma	2
Colon-rectal cancer	2
Breast cancer	1
Merkel carcinoma	1
Head and neck carcinoma	1
<b>Reason of first ICPI discontinuation N(%)</b>	
Disease progression	56 (76)
Toxicity	9 (12)
Per protocol	9 (12)
<b>Treatments between the two ICPIs N(%) (MD = 1)</b>	
None	21 (28)
Systemic therapy	37 (50)
Systemic therapy + local treatment <sup>a</sup>	16 (22)

MD= Missing data; a: radiotherapy or surgical resection

**Table 3: All grade toxicities<sup>a</sup> during first and second course of anti-PD1 or anti-PDL1**

Adverse event n(%)	First ICPI	Re-challenge
<b>Total</b>	<b>58(78)</b>	<b>43(63)</b>
Fever	7 (10)	4 (5)
Appetite loss	3 (4)	4 (5)
Hepatitis	4 (5)	5 (7)
Pneumonitis	5 (7)	1 (1)
Mucositis	3 (4)	1 (1)
Fatigue	6 (8)	4 (5)
Rash	8 (11)	7 (10)
Diarrhea	7 (10)	8 (11)
Nausea/vomiting	1 (1)	3 (4)

a: Toxicities occurring in  $\geq 5\%$  of the overall population either during the first or the second course of anti-PD1 or anti-PDL1 have been detailed