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ORIGINAL RESEARCH ARTICLE

Dissociated Responses in Patients with Metastatic Solid Tumors Treated with Immunotherapy

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Abstract

Background Immune checkpoint inhibitors have been demonstrated to improve overall survival. Atypical patterns of response have been reported, including dissociated response (DR). We evaluated the prevalence of DR.

Patients and methods Patients had to have a baseline computed tomography (CT) scan and at least one follow-up CT scan and two target lesions (TLs). Three types of DR were evaluated using RECIST1.1: DR1, defined as at least one progressive and one responding TL; DR2, defined as at least one progressive and one stable TL; and DR3, defined as at least one stable and one responding TL.

Results A total of 1244 measurements of 272 TLs were performed in 100 patients. Forty-nine out of the 272 TLs (18%) had received old or recent radiotherapy, and 42 (15%) had been biopsied. An objective response was observed in 22 patients (22%) and on 52 TLs (19%). DR1 were observed in 8% of patients. At the tumor measurement level, the response rate was lower in the case of prior radiotherapy (29% vs 34%, $p = 0.01$) and higher in the case of prior biopsy (40% vs 32%, $p = 0.02$).

Conclusions A DR was observed in 8% of patients. Response rate was lower in the case of prior radiotherapy and higher in the case of prior biopsy.

1 Introduction

Tumor cells escape the immune system by turning away the immune system control pathways with the cell surface overexpression of programmed cell death ligand 1 (PD-L1) ligands that interact with the program death 1 (PD-1) receptor expressed on immune cells to prevent lymphocyte activation. Immune checkpoint inhibitors (ICIs) that target the PD-1/PD-L1 axis might therefore restore lymphocyte anergy. ICIs have been shown to improve survival in multiple tumor types.

Immune checkpoint inhibitors (ICIs) are being evaluated in combination with radiotherapy, which has an immunogenic effect via several mechanisms, including immunogenic cell death with release of new antigens, release of immunostimulatory cytokines, and increased systemic

Key Points

Dissociated responses among patients receiving immunotherapy are common, with 8% of patients having at least one responding and one progressive target lesion.

Lung metastases and metastatic lymph nodes were more sensitive to immunotherapy than liver metastases.

Lesions that received prior radiotherapy were less sensitive to immunotherapy, whereas biopsied lesions were more sensitive to immunotherapy.

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anti-tumor immunity [1]. On the opposite hand, radiotherapy might also display an immunosuppressive effect via iatrogenic lymphopenia [2], by changing the tumor microenvironment by increasing PD-L1 expression because of hypoxia [3], and by the appearance of fibrosis related to inflammation [4].

New patterns of response have been reported with ICIs, including pseudoprogression, hyperprogression, and durable responses [5]. Dissociated responses (DRs) with new lesions over time while others decrease were also reported in different histological types like melanoma (4%) and non-small cell lung cancer (NSCLC) (8%) [6, 7].

We aimed in this study to evaluate the prevalence of DRs in patients with metastatic solid tumors treated with an ICI and to identify predictive factors of DR.

2 Patients and Methods

2.1 Patient Selection

We retrospectively retrieved all patients treated at the Curie Institute in a clinical trial with an ICI alone or in combination with another ICI in the recurrent and/or metastatic setting. Patients had to have a baseline computed tomography (CT) scan and at least one follow-up CT scan, as well as at least two target lesions (TLs) using RECIST1.1 [8]. There was no selection on tumor type. Informed consent was obtained from all patients. The study has received approval from the Institutional Review Committee of Curie Institute.

2.2 Procedures

The following clinical data were collected: gender, age, primary tumor location and histology, number of prior lines of treatment in the recurrent and/or metastatic setting, prior radiotherapy on each TL and timeframe before initiation ICI, and prior biopsy on each TL. The following radiological data were collected: number and sites of metastases, number and dates of radiological tumor evaluations, number and locations of TLs, and measurements of all TLs over time by two independent reviewers (PV and VS).

2.3 Outcomes

We evaluated the overall response rate (ORR) to ICIs of the whole cohort according to RECIST1.1, as well as the best response of each TL taken individually. Overall survival (OS) and progression-free survival (PFS) were also evaluated. Three types of DR were evaluated using RECIST1.1: DR1, defined as at least one progressive TL and one responding TL; DR2, defined as at least one progressive TL and one stable TL; and DR3, defined as at least one stable TL and one responding TL (Fig. 1). If several DRs occurred in the same patient at different time points, we decided that DR1 would prevail over DR2 and DR2 would prevail over DR3 given their respective clinical meaningfulness. The prevalence of DRs was assessed per patient and per radiological evaluation.

The predictive value of the location of TLs (particularly in the lymph nodes given the mechanism of action of ICIs), prior radiotherapy on TLs, and prior biopsy of TLs on the occurrence of a DR was also assessed.

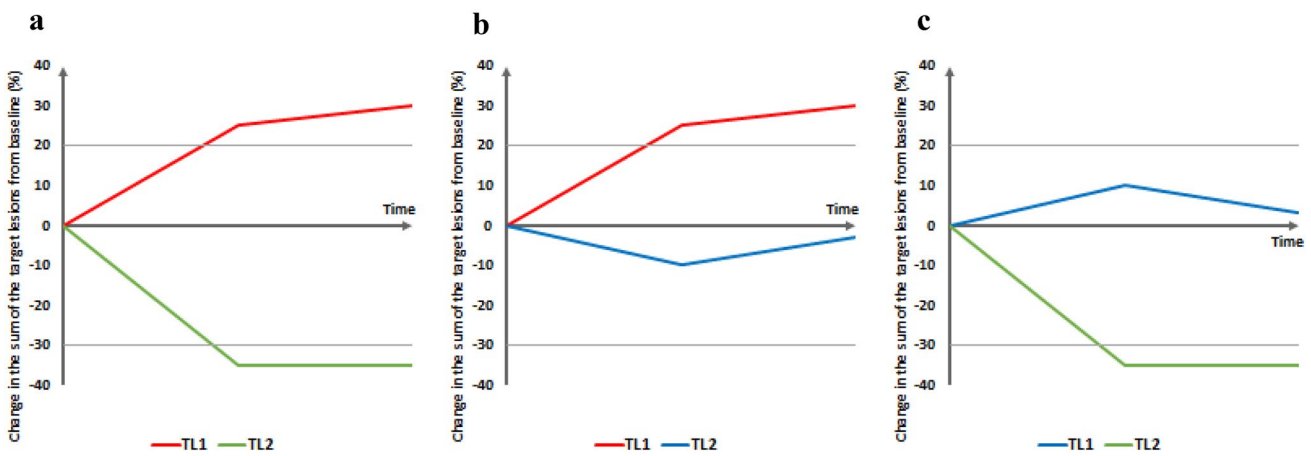

Fig. 1. Types of dissociated response (DR). **a** DR1 was defined as at least one progressive target lesion and one responding tumor lesion according to RECIST1.1. **b** DR2 was defined as at least one progressive target lesion and one stable target lesion according to RECIST 1.1. **c** DR3 was defined as at least one stable target lesion and one responding target lesion according to RECIST1.1. *TL1* target lesion 1, *TL2* target lesion 2

2.4 Statistical Analysis

OS was calculated from the date of inclusion in the clinical trial to the date of death due to any cause. PFS was calculated according to RECIST1.1 from the date of inclusion to the date of first disease progression or death, whatever occurred first. OS and PFS curves were estimated using the Kaplan–Meier method. The description of DRs was tabulated.

The evaluation of associations between patient parameters required us to take into account multiple measurements within the same tumor evaluation and multiple measurements of the same TL in several tumor evaluations of the same patient. For categorical or binary variables, a logistic model for repeated data was implemented to carry out a multivariate analysis. A hierarchical model was implemented with an "evaluation" effect nested in the "patient" effect, knowing that for a given tumor evaluation, all measurements were made on the same date. The variance matrix of covariance was estimated without constraint, either in the case of interchangeability or by an autoregressive process. This latter model was preferred in the case of convergence difficulty of the "unconstrained" model.

3 Results

3.1 General Results

Among 269 patients identified in 19 clinical trials, 169 patients were ineligible because of screening failure (n = 104), concomitant chemotherapy (n = 33), only one single TL (n = 16), no follow-up CT scan (n = 15), and concomitant targeted therapy (n = 1) (Fig. 2). Ninety-seven patients out of the 100 eligible patients (97%) were treated with an anti-PD1/PD-L1 agent as a single agent, while three patients (3%) were treated with a combination of two ICIs.

3.2 Patient Characteristics

Patient characteristics are presented in Table 1. A median delay of 12 months (range 1–119) elapsed between the diagnosis of the recurrent and/or metastatic disease and the initiation of an ICI.

A total of 272 TLs were followed in 463 tumor evaluations (100 at baseline and 363 post-baseline), corresponding to 1244 TL measurements, including 972 post-baseline measurements. The median number of tumor evaluations per patient was three (range 2–17). The median number of TLs per patient was three (range 2–5). Ninety-four TLs (35%) were lung metastases, 63 (23%) lymph node TLs, 45 (17%) liver metastases, 25 (9%) recurrence in the neck, 11 (4%) adrenal metastases, and 34 (13%) other metastatic sites.

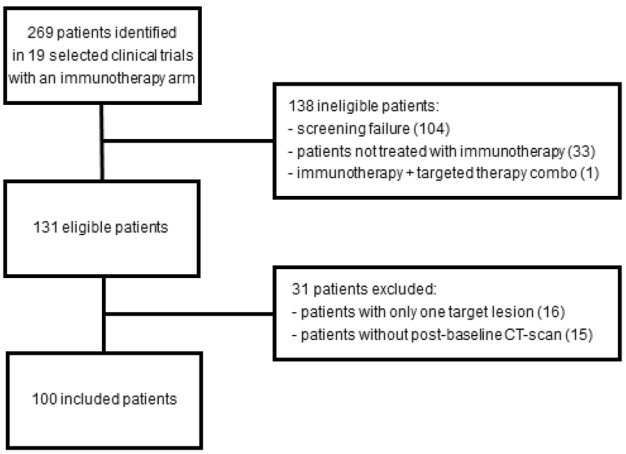

Fig. 2. Patient selection flow chart. *CT* computed tomography

Forty-nine out of the 272 TLs (18%) had received prior radiotherapy, including 11 (4%) within 6 months before starting ICI and 38 (14%) at least 6 months before starting ICI. Among the 49 irradiated TLs, 18 (37%) were in the neck, 15 (31%) were lymph node TLs, and seven (14%) were lung metastases. Forty-two TLs (15%) had been biopsied before starting ICI, including 13 lung metastases (31%), nine in the neck (21%), eight liver metastases (19%), four lymph node TLs (10%), and eight in other metastatic sites (19%).

3.3 Response to Treatment

The median duration of ICI treatment was 6 months (range 1–36). Twenty-two patients (22%) experienced an objective response according to RECIST1.1 (Table 2). Objective responses lasting more than 2 years occurred in eight patients (8%). Fourteen patients (14%) had a treatment duration of less than 2 months. Fourteen patients (14%) continued treatment post-progression; none of them eventually responded. Median PFS was 3.8 months, and median OS was 13.4 months (Supplementary Figure S1, see the electronic supplementary material).

Taking each TL individually, an objective response was observed in 52 out of the 272 TLs (19%), and in 324 out of the 972 post-baseline TL measurements (33%) (Table 2). TLs in the liver had the lowest response rate (2%), whereas lung TLs and lymph node TLs had higher response rates (25% and 17%, respectively) (Fig. 3).

DRs were observed in 62 patients (62%), including eight patients (8%) with DR1, 44 patients (44%) with DR2, and ten patients (10%) with DR3. A DR was reported in 169 out of the 363 post-baseline radiological evaluations (47%). None of the patients experiencing a DR1 response had a biopsy of the progressive lesion.

Table 1 Patient characteristics

	n (%)	Median [range]
Age at inclusion		59 [21–90]
Sex		
Male	59 (59%)	
Female	41 (41%)	
Tumor location		
Head and neck	43 (43%)	
Lung	16 (16%)	
Adrenocortical	9 (9%)	
Breast	8 (8%)	
Cervical	6 (6%)	
Urothelial	5 (5%)	
Endometrial	3 (3%)	
Neuroendocrine	2 (2%)	
Ovarian	2 (2%)	
Pancreas	1 (1%)	
Stomach	1 (1%)	
Renal	1 (1%)	
Penile	1 (1%)	
Neuroblastoma	1 (1%)	
Myoepithelial tumor of the maxillary gland	1 (1%)	
Number of metastases		
< 5 lesions	18 (18%)	
≥ 5 lesions	82 (82%)	
Location of metastases		
Lung	60 (60%)	
Lymph node	54 (54%)	
Liver	31 (31%)	
Head and neck	27 (27%)	
Bone	22 (22%)	
Pleural	13 (13%)	
Peritoneum	8 (8%)	
Skin	7 (7%)	
Adrenal	7 (7%)	
Brain	3 (3%)	
Breast	1 (1%)	
Stomach	1 (1%)	
Ovarian	1 (1%)	
Pancreas	1 (1%)	
Psoas	1 (1%)	
Bladder	1 (1%)	
Number of lines of treatment before starting immunotherapy in the recurrent and/or metastatic setting		
0	15 (15%)	
1	47 (47%)	
2	20 (20%)	
≥ 3	18 (18%)	
Prior radiotherapy		
No prior radiotherapy	38 (38%)	
Prior radiotherapy	62 (62%)	
Radiotherapy of the primary tumor	44 (44%)	
Radiotherapy of a distant metastasis	18 (18%)	

Table 1 (continued)

	n (%)	Median [range]
Radiotherapy within 6 months before starting immunotherapy	17 (17%)	
Radiotherapy of the primary tumor within 6 months before starting immunotherapy	7 (7%)	
Radiotherapy of a distant metastasis within 6 months before starting immunotherapy	10 (10%)	

Table 2. Best overall response according to RECIST1.1 and best response per target lesion and per target lesion measurement

	Per patient ($n = 100$)	Per TL ($n = 272$)	Per TL measurement ($n = 972$)
CR	2 (2%)	10 (4%)	41 (4%)
PR	20 (20%)	42 (15%)	283 (29%)
(O)RR	22 (22%)	52 (19%)	324 (33%)
SD	33 (33%)	142 (52%)	399 (41%)
PD	45 (45%)	78 (29%)	249 (26%)

CR complete response, *(O)RR* (overall) response rate, *PD* progressive disease, *PR* partial response, *TL* target lesion, *SD* stable disease

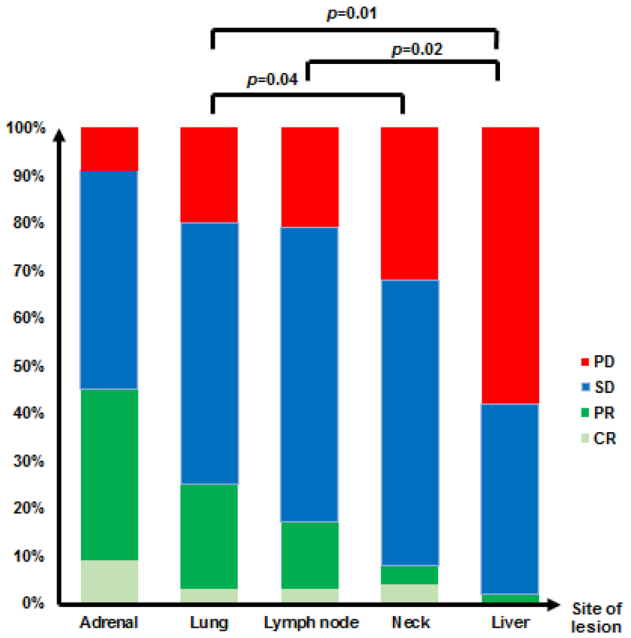

Fig. 3. Best response of target lesions according to the sites of metastases. *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

3.4 Predictors of Response to Treatment

We evaluated the response rate according to the sites of metastases, prior radiotherapy on TLs, and prior biopsy of TLs.

The response rate was similar in the lymph nodes and in other sites of metastases at the TL level (20% vs 18%, $p = 0.8$) and at the tumor measurement level (29% vs 35%, $p = 0.8$).

At the TL level, the response rate did not differ according to prior radiotherapy (20% vs 19%, $p = 0.5$). At the tumor measurement level, the response rate was lower in the case of prior irradiation (29% vs 34%, $p = 0.01$). This difference was larger when considering TLs that were irradiated at least 6 months before receiving an ICI (26% vs 34%, $p = 0.36$). Conversely, TLs irradiated within 6 months before starting ICI tended to have a higher response rate than TLs that were never irradiated, although this did not reach statistical significance (38% vs 34%, $p = 0.6$).

At the tumor measurement level, the response rate was higher in the case of prior biopsy (40% vs 32%, $p = 0.02$). Analyses could not be performed at the TL level because the sample size was too small.

3.5 Predictors of Dissociated Response

No association was identified between the occurrence of a DR and the presence of lymph node TLs, at the patient level (59% vs 65%, $p = 0.5$) and the tumor measurement level (46% vs 48%, $p = 0.9$). Similarly, no association was identified between the occurrence of a DR and prior radiotherapy of a TL, at the patient level (67% vs 59%, $p = 0.6$) and the tumor measurement level (53% vs 43%, $p = 0.5$). Finally, no association existed between the occurrence of a DR and prior biopsy of a TL, at the patient level (34% vs 47%, $p = 0.7$) and the tumor measurement level (38% vs 60%, $p = 0.2$).

4 Discussion

DRs with at least one responding TL and one progressive TL according to RECIST1.1 were observed in 8% of patients receiving an ICI. At the TL level, a higher response rate was observed in lung metastases and lymph nodes as compared to liver metastases. Response rate was lower in the case of prior radiotherapy and higher in the case of prior biopsy. The occurrence of a DR was not associated with the site of metastases, prior biopsy, and prior radiotherapy of a TL.

The outcome of patients treated in our study was favorable, with an ORR of 22%, a PFS of 3.8 months, and an OS of 13.4 months. All patients included in our study were patients included in clinical trials. In addition, patients without any follow-up CT scan were excluded, the main reason being most likely rapid disease progression. The PFS curve in our study plateaus at 20%, corresponding to the proportion of long-responder patients, which is in line with a recent meta-analysis of 19 randomized clinical trials involving ICIs [9].

We found that 62% of patients had a DR rate in our study, including 8% of patients with at least one responding TL and one progressive TL (DR1). The 8% rate of DR1 is in line with the literature. DR were also reported in melanoma (4%) and NSCLC patients (8%) [6, 7]. In these studies, a DR was defined differently as a persistent reduction in the sum of the TLs in the presence of new lesions but not by the analysis of the different TLs.

Our study showed a different response rate depending on the site of TLs. A significantly higher response rate was observed in lymph node and lung metastases than in liver metastases. Similar results were reported in the literature [10, 11]. These differences in response may be due to stromal and immune heterogeneity of the tumor microenvironment causing a variability of sensitivity to immunotherapy. The hepatic microenvironment is therefore intrinsically immunosuppressive with an initial state of active tolerance to overcome autoimmune mechanisms due to the constant flow of antigens through the hepatic circulation [12]. The higher response rate observed in lymph nodes and lung metastases might be explained by the lymphoid nature of these organs promoting the ICI-stimulated anti-tumor response [13]. Other immunological factors may explain the heterogeneity of response such as the density and variability of TLs, and the higher expression of PD-L1 and other potential biomarkers of efficacy of ICIs such as tumor mutational burden [14].

Our study showed that prior radiotherapy at least 6 months before starting ICI was associated with a lower response rate, while radiotherapy within 6 months before starting ICI was associated with a higher response rate. The lower response rate in TLs that received radiotherapy at least 6 months before starting ICI might be explained by the immunosuppressive effect of radiotherapy [3, 15]. In contrast, numerous studies support the rationale for combining radiotherapy with ICI [16]. The PACIFIC trial was the first randomized trial demonstrating the efficacy of an ICI following chemoradiation in NSCLC patients [17]. Interestingly, the outcome of patients who started durvalumab in that study within 2 weeks after the end of radiotherapy had a better outcome than those who started between 2 and 6 weeks after the end of radiotherapy [17].

A higher response rate was observed in biopsied TLs in our study. The biopsy itself might induce inflammation, trigger a danger signal with increased cytokine concentration, and release tumor antigens that stimulate adaptive anti-tumor immunity [18–20]. Such an immune stimulation might therefore induce a priming of the anti-tumor immunity locally or even generate systemic effects thanks to the circulation of anti-tumor immune cells [21]. However, these results need to be interpreted with caution since biopsied TLs were mostly lung metastases (31%) and lymph node TLs (10%), which were associated with a higher response rate, and less frequently liver metastases (19%), which were associated with a low response rate. A larger sample size would be needed in order to integrate the sites of metastases into the multivariate analysis.

The occurrence of DRs raises the question of local treatments of oligoprogressive lesions. Catching DRs is key since local treatments of progressive lesions in the case of oligoprogressive disease might improve patients' outcome [22, 23]. The treatment of oligoprogressive lesions has been shown to be effective and improve survival in different cancer types with chemotherapy and some targeted therapies [23–25]. Local treatments included radiotherapy, surgery, and interventional radiology. As opposed to chemotherapy, whose hematotoxicity might hamper local therapies, ICIs can be continued during these treatments given their favorable toxicity profiles. In regard to local radiotherapy, ICIs have a synergistic effect when given sequentially or concomitantly. In a retrospective study of patients with advanced melanoma, a response rate of 45% was reported for oligoprogressive lesions under ICI with extracranial radiotherapy and/or intracranial stereotactic radiosurgery, with no increased toxicity [26]. The combination of local radiotherapy with an ICI might be able to produce an abscopal effect [27], which is rarely observed in the case of radiotherapy alone, but that might be more important with a multisite irradiation [28].

Before considering the local treatment of oligoprogressive disease, it is necessary to confirm that the increase in size is a real progression and not in relation to an inflammatory, immunological, or infectious reaction. Granulomatous pseudo-sarcoidosis reactions with the appearance of pulmonary micronodules or mediastinal or hilar lymph node involvement have indeed been reported with ICIs [29]. A biopsy of progressive disease might be needed. There is, however, no consensus on how many progressive lesions can/should be treated with local treatments [22]. It is also important to ensure that stable lesions are also shrinking and to take non-TLs into account. Finally, the clinical condition of the patient has to be good enough to consider these treatments.

Our study has several limitations. The patient population is limited and heterogeneous, with only 100 patients and more than 18 different histological subtypes. From a radiological point of view, the tumor evaluation criteria used were RECIST1.1, which might not be the most appropriate

criteria for the evaluation of patients receiving an ICI, but are those that were used in all clinical trials included. iRECIST are criteria that might be used for evaluating response to ICI [30]. iRECIST allows continuation of treatment beyond progression and therefore the continuation of an effective treatment in the case of pseudoprogression. iRECIST is also relevant for accounting for DRs. Finally, it would be interesting to compare the microenvironment and the proportion in tumor-infiltrating lymphocytes of TLs according to their response, although challenging.

5 Conclusions

In conclusion, DRs with at least a responding TL and a progressive TL according to RECIST1.1 were observed in 8% of patients with solid tumors in our study. The immunological and stromal heterogeneity of the tumor microenvironment as well as previous biopsy or radiotherapy seem to be associated with individual responses of TLs, but are not predictors of DRs. The therapeutic management of progressive lesions should be discussed in the case of oligoprogression. The feasibility and efficacy of a local ablative treatment for progressive lesions has to be confirmed in larger patient populations. Our results suggest that radiotherapy might be a technique of choice because of the synergistic effect with ICI. Finally, a consensual definition of DR is greatly needed, as well as guidelines that help handle the treatment of oligoprogressive disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40268-021-00362-3.

Declarations

Funding None declared.

Conflict of interest Christophe Le Tourneau has participated in advisory boards from MSD, BMS, Merck Serono, Astra Zeneca, Roche, Amgen, Nanobiotix, GSK, Celgene, and Rakuten. Delphine Loirat has participated in advisory boards from MSD, Roche, BMS, Astra Zeneca, Novartis, and Nanobiotix. The other authors have declared no conflicts of interest.

Ethics approval All patients included in the study were included in a clinical trial and treated at the Curie Institute. Our study pertaining to these patients received approval from the Institutional Review Committee of Curie Institute (OBS200216). The study was performed in accordance with the Declaration of Helsinki.

Consent to participate All patients signed an informed consent to be treated.

Consent for publication Not applicable.

Availability of data and material All data are available at the Curie Institute upon request of the corresponding author.

Code availability Not applicable.

Authors' contributions PV, CLT and XP designed the study. XP made the statistical analyses. PV and CLT wrote the manuscript. All authors reviewed the manuscript.

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