Management of heterogeneous tumor response patterns to immunotherapy in patients with metastatic melanoma

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Immunotherapy has revolutionized the treatment of metastatic melanoma. Response to therapy can be complex to evaluate, as Response Evaluation Criteria in Solid Tumor (RECIST) does not capture heterogeneous responses. In this retrospective single-institution analysis, we describe the management, clinicopathological characteristics, RECIST and disease course of metastatic melanoma patients with a heterogeneous response to first-line anti-CLTA-4 and/or anti-PD-1 between September 2011 and September 2020. In 196 patients, 37 had a heterogeneous response to immunotherapy (19%). Distinct identified responses included a mixed response (MR) (15%), pseudoprogressive disease (PP) (3%), and a sarcoid-like reaction (2%). Patients with a MR and possibly no response to therapy (MR-NR) had a higher median lactic acid dehydrogenase (LDH) ($P = 0.01$), were more often male ($P = 0.04$), had more involved disease sites ($P = 0.01$), and had brain metastasis more frequently ($P = 0.02$). MR patients with later response to therapy (MR-R) and PP patients had a longer overall survival of 1.7 [95% confidence interval (CI), 1.1–2.7] and 1.6 years (95% CI, 1.3–2.0) versus MR-NR 1.2 (0.7–1.7) ($P < 0.01$). In this cohort study, we identified prognostic clinical characteristics that can contribute to clinical decision-making for patients with a MR. Additionally, patients with pseudoprogression had benefited from therapy continuation, suggesting the importance of not halting therapy early in case of suspected PP. The male sex, more involved disease sites, brain metastasis and had a higher median LDH were associated with a poor survival for patients with a MR, suggesting that these clinical variables could be used to predict whether a mixed responder will possibly respond to therapy. *Melanoma Res* **32: 45–54**

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Introduction

The emergence of immunotherapy has transformed the treatment landscape of metastatic melanoma. Approval and implementation of systemic immunotherapy, anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab/pembrolizumab) have significantly improved overall survival in metastatic melanoma patients [1,2]. Concurrently, the combination of anti-PD-1/anti-CTLA-4 has resulted in even higher response rates and prolonged overall survival [3]. To optimize these current treatment strategies in individual patients, careful and meticulous monitoring of tumor response is a prerequisite. Accurate determination of clinical response to therapy can be complex, as heterogeneous responses may occur [4,5]. Responding tumor sites may initially increase in size, due to edema and immunological infiltration, prior to shrinkage, so-called pseudoprogression (PP) [6]. Adequate and precise radiological imaging and clinical assessment are needed in suspected PP, in order to differentiate immunotherapy-induced inflammation from disease progression, so that optimal therapeutic options can be applied in these patients. Furthermore, a mixed response (MR) can occur, in which some tumor lesions simultaneously decrease and increase in size [7,8]. Accurate radiological and clinicopathological assessment in patients with a MR can potentially be of aid in determining subsequent response or progression of disease and is urgently needed to optimize therapeutic management in these patients. In addition, a sarcoid-like reaction (SR) in lymph nodes or in the lungs during immunotherapy can appear and can be challenging in assessing whether the patient is responding to therapy [9]. Moreover, the progression of solely one tumor lesion during a long-lasting tumor response is termed oligoprogression [10]. Radiological evaluation of these distinct patterns can be difficult, since the traditionally used Response Evaluation Criteria in Solid Tumor (RECIST) v1.1. does not adequately capture these heterogeneous responses [11,12]. Partially to overcome this problem, immune-related response criteria have been introduced, with iRECIST in 2017 being the most recent version [13]. However, these criteria have not yet been validated. In clinical practice, the interpretation of heterogeneous

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response patterns remains a clinical decision-based issue, especially because of the shortcomings of RECIST v.1.1 for these distinct responses.

The intertumor heterogenic mechanisms are still being studied to identify potential novel routes for treatment options [14]. Conversely, therapeutic outcomes of these heterogeneous response patterns have not been studied in detail. Only one study on mixed responders has been published, describing the management, but without exact RECIST information, details on tumor measurements and tumor site information [7]. While the incidence of PP has been explored, therapeutic management has not been elaborated upon yet [15]. Correct clinicoradiological interpretation is warranted for these patients, since continuation or change of treatment is dependent on radiological and clinical information. In this retrospective, single-center study, we analyzed metastatic melanoma patients who developed a heterogeneous response during first-line anti-CTLA-4 and or anti-PD-1 treatment. The incidence, management, clinicopathological characteristics, (1) RECIST evaluations and survival outcomes were assessed per heterogeneous response type.

Methods

Data source and study design

In this retrospective single-center study, patients with unresectable metastatic melanoma treated with checkpoint inhibitor therapy between September 2011 and November 2020 at the Leiden University Medical Center were analyzed. This study was performed in accordance with and approved by the medical ethical committee.

Patients

Selected patients were 18 years of age or older, had histologically confirmed unresectable metastatic cutaneous melanoma, were classified as stage IV according to the eighth edition of the American Joint Committee on Cancer (AJCC) classification [including metastases to skin (M1a), lung (M1b), other visceral sites (M1c), and brain (M1d)] and had a WHO performance score of 0 or 1 [16,17]. All patients were treated with first-line systemic immunotherapy (anti-CTLA-4, ipilimumab and/or anti-PD-1, nivolumab/pembrolizumab) or BRAF/MEKi initiation therapy followed by systemic immunotherapy, and received standard therapeutic doses and cycles. In addition, Exclusion criteria consisted of ocular melanoma and missing or incomplete medical records. Follow-up included standard of care radiologic response evaluation every twelve weeks and clinical examination every 3 to 6 weeks in which physical exam and laboratory values were evaluated.

Patients were selected for analysis if a heterogeneous response during immunotherapy in the first or second treatment cycle was noted in the original report. A central revision of all performed imaging modalities was performed by a specialized radiologist with ample experience in the assessing tumor response using the RECIST version 1.1 [12]. Patients were excluded if a heterogeneous response to therapy was due to other causes than metastatic melanoma disease.

Clinical variables

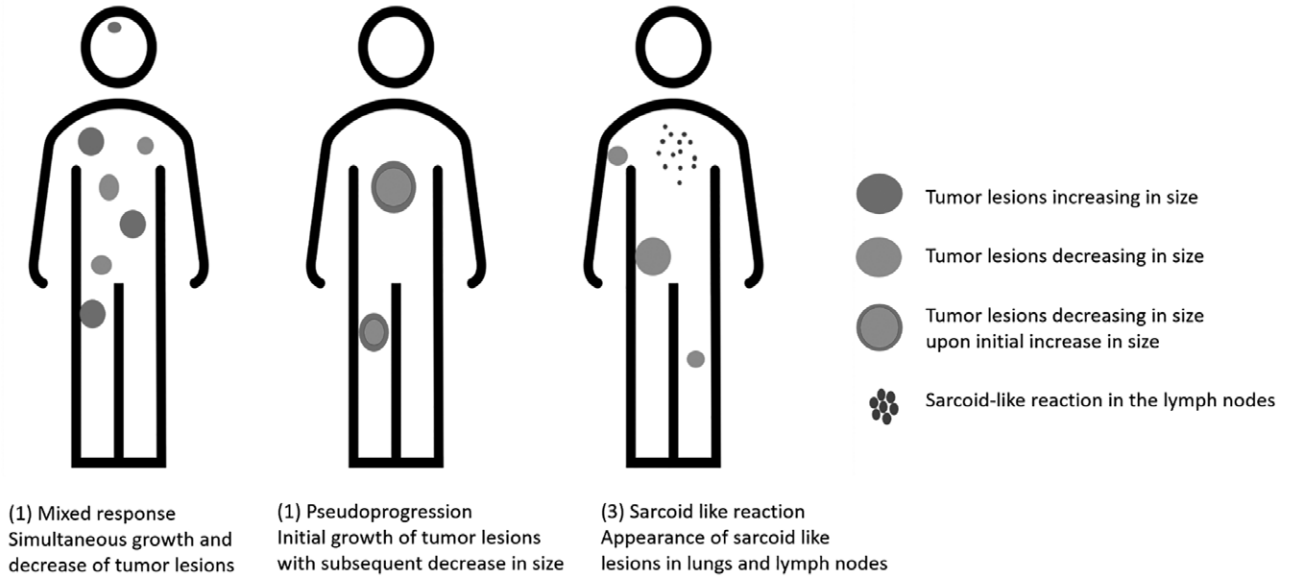
Demographic variables (age, sex and WHO performance status) were obtained from the electronic medical record (EMR). Tumor characteristics (histology, Breslow thickness, ulceration, location of primary tumor and mutational status) were extracted from the dermatopathological report. Lactic acid dehydrogenase (LDH) values were obtained from laboratory results. Detailed information of immunotherapy (duration time, type, cycles), timing of radiotherapy and type/date of surgery were collected from the EMR.

Assessment

Response to immunotherapy was assessed with computed tomography (CT-scan), MRI and/or FDG-PET–CT. Patients in whom a heterogeneous response during immunotherapy in the first or second follow-up CT-scan was reported were analyzed in more detail by a radiologist experienced in using RECIST version 1.1 [12].

Additional response assessment using iRECIST was performed in case PD, according to RECIST v1.1., was present. The location of a heterogeneous response to therapy included a single (target or non-target) lesion; multiple lesions within one organ or between organs, and to the occurrence of new tumor lesions in combination with non-progressive existing target or non-target lesions. Radiated tumor lesions were assessed according to RECIST v1.1. criteria, and patients with increasing tumor lesions and shrinkage of tumor lesions due to radiation therapy, were not regarded as a heterogeneous response, a heterogeneous response was based on true tumoral response to immunotherapy only. Furthermore, we classified a heterogeneous response into three groups: MR, PP and SR (Fig. 1). We defined a MR as simultaneous growth of some and shrinkage of other existing tumor lesions, presence of stable lesions and increasing tumor lesions or responding lesions with simultaneously appearance of new lesions. PP was defined as an increase in tumor size or the occurrence of new tumor lesions, subsequently followed by a decrease in tumor size on a later scan. The occurrence of PP was confirmed retrospectively by a certified radiologist, in order to separate patients with a PP from the MR group. In addition, PP was differentiated from patients with progression and subsequent response based on radiological findings. A SR was noted, the moment a scan was performed, in case of responding lesions with simultaneously appearance of lymph nodes and or lung nodules with a sarcoid-like pattern. The details of RECIST evaluation [involved organs, size of target lesions and response of individual target lesions and non-target lesions per

Fig. 1



Visual display of different types of heterogeneous response. (1) Mixed response: simultaneous growth of some tumor lesions and shrinkage of others; stable tumor lesions and growing lesions; stable or responding tumor lesions and the appearance of new tumor lesions. (2) Pseudoprogression: initially growth of tumor lesions with subsequent decrease in tumor lesion size. (3) Sarcoid-like reaction: simultaneously appearance of lymph nodes and/or lung nodules with a sarcoid-like pattern.

location, and the location of new lesions (if present)] were analyzed. The course of disease of the heterogeneous responses was divided into clinical responders and clinical non-responders, based on physical, radiological and clinical evaluation. Patients with a MR were divided into two groups: MR and later response (MR-R) and patients with a MR and later no response (MR-NR). Subsequent comparative analysis was performed for the MR-R and MR-NR groups. An overall survival analysis was conducted for the PP, SR and MR group, and overall survival was defined as the time between metastatic disease detection up to the last follow-up date or death.

Statistical analysis

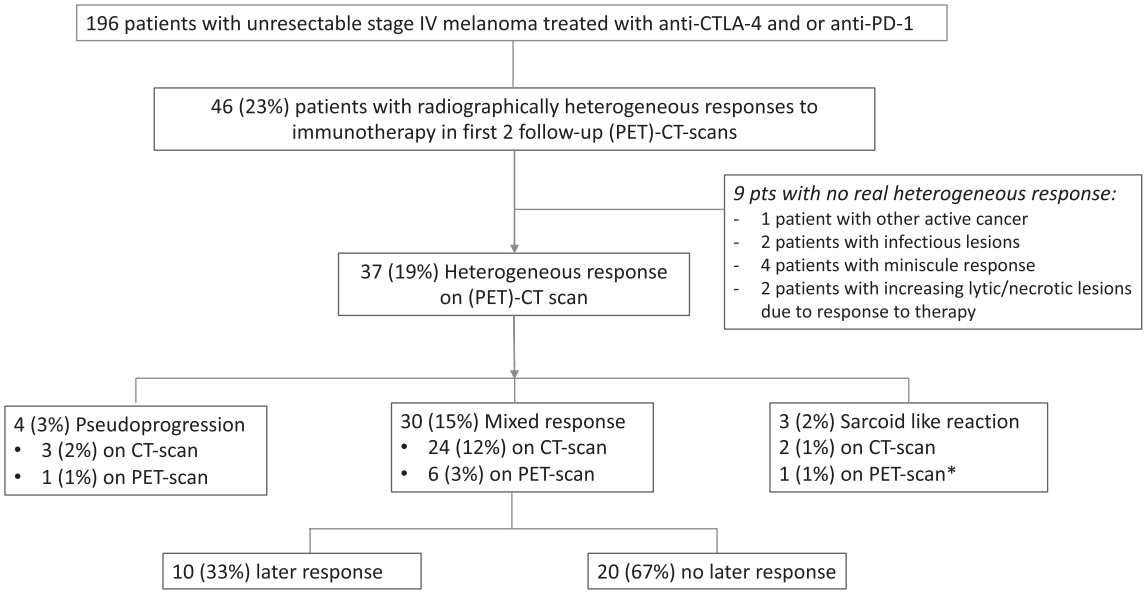
A descriptive analysis was performed to assess frequencies of demographic-, clinicopathological variables, therapy information and tumor response according to RECIST v1.1 and iRECIST (if applicable). The incidence of variables was compared between the three different heterogeneous response groups (MR, PP and SR) and a separate comparative analysis was undertaken between the MR-R and MR-NR groups, using a Chi-square test, Fisher's exact test and or Wilcoxon Rank test when suitable. Survival analysis was performed with the Kaplan–Meier procedure and survival rates were compared using the Log Rank test for each individual response group. P-values were two-sided and a *P*-value greater than 0.05 was considered to be statistically significant. All statistical analyses were conducted using IBM SPSS Statistics version 24 (Armonk, New York, USA).

Results

Heterogeneous response

Between September 2011 and September 2020, a total of 196 WHO 0-1 performance score patients with unresectable stage IV melanoma were treated with first-line systemic immune checkpoint inhibitors and were included in this study. During treatment, a total of 46 (23%) patients had a heterogeneous tumor response to immunotherapy on the first or second follow-up scan (after 3 or 6 months) according to the original radiologic report. Clinicoradiological examination revealed that 37 patients (19%) had a heterogeneous response pattern on either CT-scan or PET-scan, and nine patients were excluded for analysis, as they had no objectifiable heterogeneous melanoma tumor response, but had a second active cancer, infectious disease, minimal changes in measurements within the range of normal variation in measurements (1 mm) or delayed lytic response (increasing lytic lesions due to response to therapy) (Fig. 2). Out of 37 patients with a heterogeneous response, 30 patients (15%) were classified as mixed responders, four (3%) as pseudoprogressive disease and three patients (2%) with a SR. Each individual distinct response group will be addressed in separate text subdivisions. For the included patients with a heterogeneous response, the median age was 64 [interquartile range (IQR) 53–73], 23 were male (62%), 17 patients had brain metastases (46%), and 21 patients had increased LDH value upon treatment initiation (57%) (Table 1). Detailed RECIST v1.1. assessment could be performed in 29 patients (78%), and

Fig. 2



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Scheme displaying type of responses 196 WHO 0–1 patients with metastatic melanoma treated with immunotherapy were analyzed. A total of 37 patients had a true heterogeneous response, and nine patients were excluded. A heterogeneous response pattern was subdivided into mixed responders, pseudoprogression and sarcoid-like reaction. Additionally, the figure shows the type of radiological scan that has been used to capture the distinct response. Lastly, the mixed response group was further divided into mixed response with a later response, and mixed response with no later response.

eight patients (22%) received clinicoradiological assessment as they underwent baseline and/or follow-up with PET-CT scans and RECIST v1.1 criteria could not be applied in these patients. Of the patients who received a CT-scan, a heterogenous response was observed on the first response time point scan in 18 cases (62%), and the moment of heterogeneous response occurrences was classified as PD in 22 patients (76%) and measured as PR and SR in five patients (17%) and two patients (7%), respectively. Additional radiologic analysis revealed that a heterogeneous response occurred most frequently within specific disease sites, including lymph nodes in seven patients (24%), lungs in five patients (17%) and brain in six patients (21%). Other heterogeneous response locations included multiple disease sites/organs, for example, progressive lesions in the brain with concurrent responding lesions in the lymph nodes. As for individual lesions, brain progression (38%), lung response (41%) and lymph node response (59%) occurred most frequently (Table 2).

Mixed responders

Of the total 30 patients with a MR, the median age was 64 years (IQR 53–73), 20 were male (67%) and had a median LDH of 212 (IQR 176–338). A total of 20 patients (66%) with MR had three or more involved organs with metastatic disease involvement. Anti-PD-1 monotherapy was administered to 21 patients (70%) with a MR, and the median received treatment duration prior to MR development was 11 weeks (IQR 8.9–11) (Table 3). In addition, detailed RECIST information was available in 24 MR patients (80%) who received CT-scan surveillance. The moment of MR observation was classified as PD in 18 patients (75%) and as PR/CR in five (21%) cases (Table 4). The course of disease with accessory RECIST findings are displayed in Fig. 3a and b, respectively. A total of 20 patients with a MR had later no response to therapy (67%), and 10 patients were later objectified as responders to therapy (MR-R) (33%). The majority of patients with a later response to therapy continued immunotherapy and three patients discontinued therapy early due to immunotherapy-related adverse events. MR-NR patients received immunotherapy for a shorter period, and 13 patients went on to receive targeted therapy (BRAF/MEKi), and survival analysis demonstrated a mean survival time of 5.7 months (range 3.9–8.1), calculated from the moment of therapy change, up to the last moment alive.

A comparative analysis between the MR-R and MR-NR groups showed similar demographic variables such as age and WHO performance score (Table 5). In contrast, a univariate analysis demonstrated clinicopathological differences between the MR-NR and MR-R group and demonstrated that MR-NR patients were mostly male, 15 patients (75%) versus five patients (50%) (P = 0.04), had

Table 1 Baseline characteristics of the heterogeneous response group

	Total patients ($n = 37$)
Median age (range) (years)	64 (53–73)
ECOG, no.(%)	
0	19 (51)
1	18 (49)
Sex, no. (%)	
Female	14 (38)
Male	23 (62)
Location primary, no. (%)	
Trunk	11 (30)
Lower extremity	6 (16)
Upper extremity	3 (8)
Head/neck	6 (16)
Anogentinal	1 (3)
Unknown	10 (27)
Tumor histology, no. (%)	
SSM	12 (32)
Nodular	6 (16)
LM	1 (3)
Unknown	18 (49)
Ulceration, no. (%)	
Absent	16 (43)
Present	6 (16)
Unknown	15 (41)
Median Breslow (range) in mm	2.8 (1.1–4.2)
Metastasis stage, no. (%)	
M1a, M1b, M1c	20 (54)
M1d	17 (46)
Mutational status, no. (%)	
Wildtype	9 (24)
BRAFV600E/K	14 (38)
NRAS	11 (30)
KIT	1 (3)
CDKN2a	2 (5)
LDH moment of metastatic disease, no. (%)	
≤2× ULN	16 (43)
>2× ULN	21 (57)
Total disease sites ≥3, no. (%)	
No	16 (43)
Yes	21 (57)

Demographic characteristics showed that patients were mostly male, had a median age of 64 (IQR 53–73), had mainly an elevated LDH value (57%) and metastatic disease was present in 57% of the patients with three or more disease sites.
ECOG, Eastern Cooperative Oncology Group score; IQR, interquartile range.

Table 2 Disease site response at the moment of heterogeneous response

Disease sites	Progressive lesion(s), no. (%)	Responding lesion(s), no. (%)
Lung	8 (28)	12 (41)
Lymph node	10 (34)	17 (59)
Subcutaneous	4 (14)	4 (14)
Liver	7 (24)	10 (35)
Brain	13 (45)	6 (21)
Adrenal	3 (10)	NA
Spleen	3 (10)	1 (3)
Renal	1 (3)	NA

Patients with a heterogeneous response had most frequently disease progression in the brain (38%) and lymph nodes (34%), while a disease response was seen in the lymph nodes (59%), lung(s) (41%) and the liver in most cases.

brain metastases more often 11 (55%) versus two (20%) ($P = 0.02$), had a higher median LDH at the moment of MR, had three or more organ sites involved with metastases 15 (75%) versus five (50%) ($P = 0.01$), had cerebral disease progression more often 12 patients (71%) versus one patient (10%), while patients with MR-R had cutaneous disease progression more frequently on the moment of MR confirmation, compared to MR-NR patients, five (50%) versus three (14%) ($P = 0.04$). One-year landmark survival analysis demonstrated an intermediate median survival of 3.4 years [95% confidence interval (CI), not reached –1.4]. Interestingly, survival analysis revealed an prolonged mean overall survival of 1.7 years (95% CI, 1.1–2.7) (median overall survival and 1-year land mark analysis not reached) for the MR-R group compared to a median overall survival of 1.0 years (95% CI, 0.5–1.4) (1-year land mark analysis not reached)of the MR-NR group (log rank-test $P < 0.01$) (Fig. 4).

Pseudoprogression

Out of four patients with PP, three patients (25%) had three or more involved disease sites. The median LDH was 189 (IQR 163–255) at PP observation. Of the four patients, two patients had brain metastases (50%) (Table 3). All PP patients were treated with anti-CTLA-4/anti-PD-1 combination therapy and received therapy during a period of 12 weeks (IQR 11–20) prior to the onset of PP. Detailed CT-scanning was performed in three patients, demonstrating that PP detection was classified as PD in all cases according to RECIST v1.1 (Table 4). Conducted iRECIST evaluations demonstrated that patients with PD were obviously all classified as iUPD (unconfirmed progressive disease) on that time point, and second-time point evaluation revealed iPR (partial response) in 67% of the cases and iCPD in 33% (confirmed progressive disease). Regarding treatment, these patients went on to receive immunotherapy, despite observed PD and, all patients had later clinical response to therapy (Fig. 2). Survival analysis demonstrated a mean overall survival of 1.6 years (95% CI, 1.3–2.0), (median overall survival and landmark time point of 1-year survival was not reached) (Fig. 5).

Sarcoid like reaction

Of the three patients with a SR, median age was 54 years (IQR 42–54), two were female (67%) were staged most frequently M1a (67%) and had less than three organ sites with disease involvement in the majority of the cases (67%) (Table 3). Two patients received anti-PD-1 monotherapy (67%) and one patient (33%) received anti-ctla4/anti-PD-1 combination therapy (33%). Two out of three patients underwent follow-up with CT scans, which demonstrated that the moment of sarcoid-like response observation was classified either as PD (50%) or SD (50%) (Table 4). Two of the three patients had later response to therapy, while one patient had no later response. Regarding survival, a conducted survival analysis demonstrated an intermediate mean survival of 1.4 years (0.5–3.2) (median overall survival and landmark time point of 1-year survival was not reached) (Fig. 5).

Discussion

In this retrospective single-institution study, we analyzed heterogeneous responses to immunotherapy on the first and/or second follow-up scan combined with clinical assessment in patients with metastatic melanoma. Between 2011 and 2020, a total of 196 patients with unresectable metastatic melanoma were treated with first-line systemic immunotherapy. A heterogeneous response was not uncommon and occurred in 19% of the patients and was seen on the first response evaluation scan in most of the patients (62%). Baseline radiologic assessment demonstrated that the majority of patients had a high burden of disease, with three or more disease sites with metastatic lesions (57%) and an increased median LDH value (57%). With regard to the high burden of disease, previously published studies have demonstrated the association of multiple number of tumor clones that can potentially harbor various mutations which contribute to a high level of tumor heterogeneity [14,18]. A recently published study demonstrated that highly heterogeneous melanoma tumors are associated with a decreased survival, implying the importance and need for detailed disease assessment of patients with a heterogeneous response, next to genomic analysis [19].

As for the exact location of a disease progression, this was observed in the brain in most of the cases and responding lesions were seen more frequently in the lymph nodes, suggesting that the location of disease does matter. In

Table 3 Clinical characteristics per response group

	Mixed response	Pseudoprogression	Sarcoid like reaction
Age	64 (53–73)	64 (55–70)	54 (42–54)
Sex, no. (%)			
Female	10 (33)	2 (50)	2 (67)
Male	20 (67)	2 (50)	1 (33)
M stage, no. (%)			
M1a	2 (7)	1 (25)	2 (67)
M1b	6 (20)	1 (25)	NA
M1c	9 (30)	NA	NA
M1d	13 (43)	2 (50)	1 (33)
Total disease sites ≥3, no. (%)			
No	10 (34)	1 (25)	2 (67)
Yes	19 (66)	3 (75)	1 (33)
Type immunotherapy, no. (%)			
Anti-PD-1	21 (70)	NA	2 (67)
Anti-CLTA-4	4 (13)	NA	NA
Anti-PD-1/Anti-CTLA-4	5 (17)	4 (100)	1 (33)
Total treatment weeks to response (range)	11 (8.9–11)	12 (11–20)	12 (6.0–23)
LDH at moment of response, no. (%)	212 (176–338)	189 (163–255)	179 (177–179)

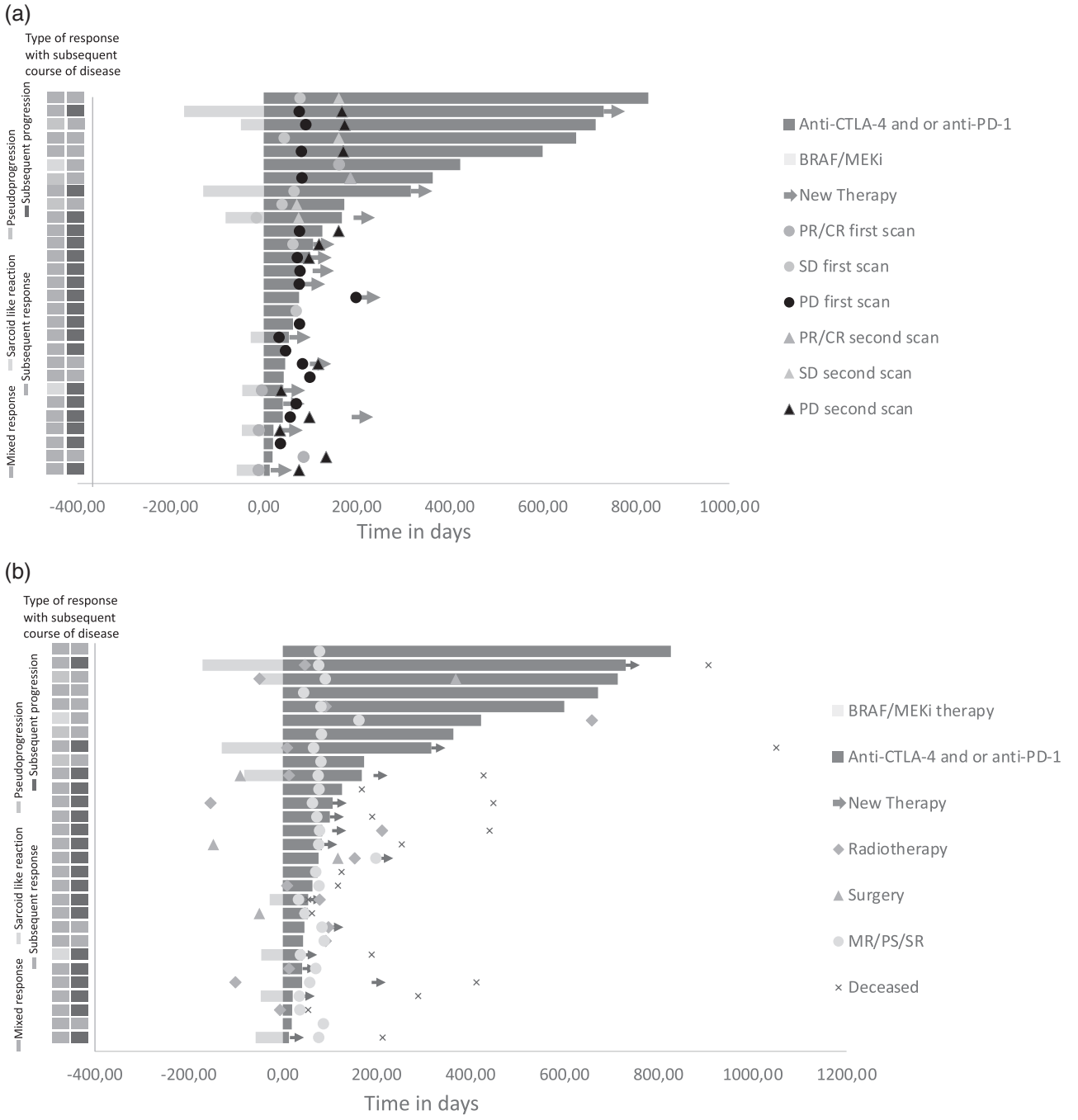
Mixed responders were more often male (67%), had three or more organ sites with metastatic disease, had a median LDH of 212 (IQR 176–338), and were treated most often with anti-PD-1. Patients with pseudoprogressive disease had fewer involved organ sites with metastatic disease (75%) and were all treated with anti-PD1/anti-CTLA-4 combination therapy. Patients who had a sarcoid-like reaction received anti-PD-1 only, were more often female and were most frequently staged with M1a disease and had a median LDH of 270 (IQR 197–743).
IQR, interquartile range.

Table 4 Radiographical disease assessment

	Mixed response	Pseudoprogression	Sarcoid like reaction
Sum lesions	84 (47–118)	74 (44–74)	77 (38–77)
Median total lesions	5 (4.0–7.0)	6 (3.0–7.0)	5 (4.0–5.0)
Disease site			
Subcutaneous	9 (38)	NA	NA
Lymph nodes	18 (75)	2 (50)	2 (100)
Lung	14 (58)	1 (25)	1 (50)
Liver	13 (44)	1 (25)	1 (50)
Brain	10 (42)	1 (25)	NA
Visceral[a]	8 (33)[a]	NA	1 (50)[b]
RECIST at MR/PR/SR			
PR/CR	5 (21)	NA	NA
SD	1 (4)	NA	1 (50)
PD	18 (75)	3 (100)	1 (50)
Clinical response upon MR/PR/SR			
Response	6 (25)	3 (100)	1 (50)
No response	18 (75)	NA	1 (50)

Baseline disease assessment according to RECIST version 1.1 showed no clear differences in the total sum of tumor lesions and size. Patients with pseudoprogressive and sarcoid-like reaction had no subcutaneous disease sites involved, in contrast to patients with mixed response (38%). Patients with mixed response and pseudoprogressive disease were classified as PD most frequently in 75 and 100% of the cases, respectively.
MR, mixed response; RECIST, Response Evaluation Criteria in Solid Tumor.
[a]Visceral metastases in mixed response group contained 3 adrenal, 3 spleen, 1 renal and 1 peritoneal lesion.
[b]Visceral metastases in the Sarcoid like reaction group contained 1 spleen lesion.

Fig. 3



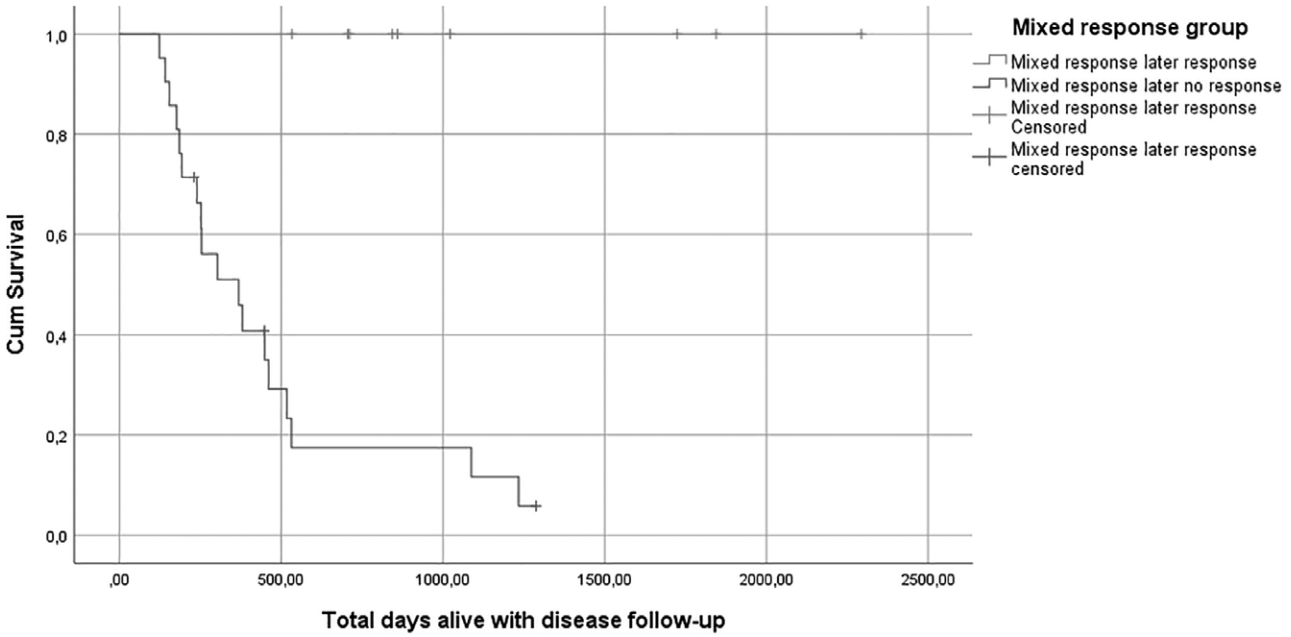
Swimmerplots displaying the type of heterogeneous response (mixed response, sarcoid-like reaction and pseudoprogression) and subsequent response to therapy on the Y axis. The duration of immunotherapy is displayed on the x axis, together with the moment of new therapy initiation. (a) Swimmerplot displaying the RECIST v1.1 timepoint measurements. The majority of patients had a fixed, that is, similar RECIST value on the first and second scan, 79% versus 21%. Patients with a subsequent response to therapy were assessed as PD on the first follow-up scan in the majority of cases (50%). Patients with no later response to therapy were classified mainly as PD, 84% of the cases. (b) Swimmerplot showing the management for systemic therapy, radiotherapy, surgery and, if the case, time to decease. Notably, all three patients with pseudoprogressive disease (yellow bar), continued to receive immunotherapy. Sixteen patients with a mixed response and no later response, discontinued immunotherapy and were treated with targeted therapy most frequently, while three patients with a later clinical response after initial mixed response continued therapy. RECIST, Response Evaluation Criteria in Solid Tumor.

Table 5 Demographic and clinicoradiological characteristics for the mixed response later no response and mixed response later response groups

	MR later R	MR later NR	*P*-value
Median age (range) (years)	65 (52–73)	64 (53–73)	0.9
Sex, no. (%)			0.04
Female	5 (50)	5 (25)	
Male	5 (50)	15 (75)	
Metastasis stage, no. (%)			0.02
M1a	2 (20)	NA	
M1b	3 (30)	3 (15)	
M1c	3 (30)	6 (30)	
M1d	2 (20)	11 (55)	
Total disease sites ≥3, no. (%)			0.01
No	5 (50)	5 (25)	
Yes	5 (50)	15 (75)	
Median LDH at MR moment, no. (%)	178 (162–209)	281 (188–387)	**0.01**
RECIST at MR confirmation, no. (%)			0.12
PR/CR	2 (20)	3 (20)	
SD	1 (10)	NA	
PD	3 (30)	15 (75)	
Progression site at MR, no. (%)			
Subcutaneous progression	5 (50)	3 (14)	**0.04**
Lymph node progression	4 (40)	5 (22)	0.43
Lung progression	2 (20)	6 (27)	0.68
Liver progression	2 (20)	4 (18)	0.35
Brain progression	1 (10)	12 (71)	**0.02**

MR-NR patients were staged m1d more frequently, had a higher median LDH at the moment of MR confirmation, were staged as PD more frequently and had cerebral disease progression in most of the cases.
Significant values are highlighted in bold.
MR, mixed response; MR-NR, mixed response later no response; MR-R, mixed response later response group; RECIST, Response Evaluation Criteria in Solid Tumor.

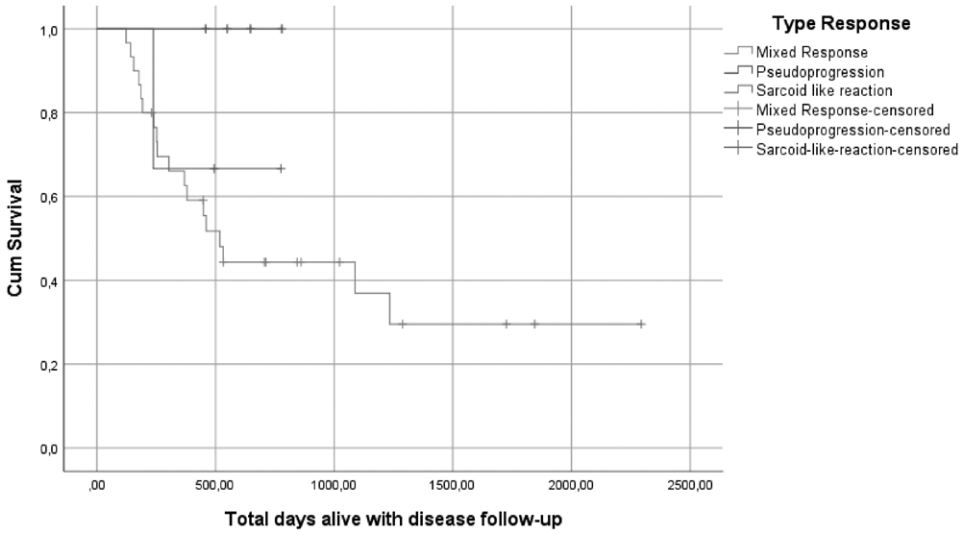
Fig. 4



Kaplan–Meier curve showing the overall survival of patients with Mixed response and later response (MR-R) and survival for mixed response patients with subsequent no response (MR-NR). Patients with a mixed response and subsequent response had a prolonged overall survival compared to patients who went on to have progressive disease after an initial mixed response ($P < 0.01$).

fact, the progression of brain metastases could presumably be caused by the inequal distribution of the immunotherapy agents in the blood, due to semi-permeable blood-brain barrier and distinct brain tumor microenvironment [20,21]. Frequent disease response evaluation in the brain is necessary and important in these patients, since early detected brain metastases can potentially be managed surgically or with radiation therapy, according to previously published case reports describing the management of mixed cerebral responses [22].

Fig. 5



Overall survival per response group. Survival per heterogeneous response group showed that patients with pseudoprogressive disease had an improved overall survival of 1.6 years (95% CI, 1.3–2.0) and patients with a sarcoid-like reaction had an intermediate mean survival of 1.4 years (95% CI 0.5–3.2). CI, confidence interval.

Considering radiological response evaluation in patients with a heterogeneous response, 76% of the patients were classified as PD according to RECIST v1.1., despite that 40% of the patients later had a response to therapy, hence unfolding the rationale for not halting therapy the moment PD is observed in patients with no clear progression or response to therapy. The indistinct response should be followed up in addition to clinical assessment, up to the next RECIST timepoint measurement in order to determine the 'true' response to therapy. Additionally, a shorter scan interval next to the application of iRECIST should be considered with a low threshold in these complex cases. Furthermore, performed PET-CT scans should be analyzed in more detail to assess the avidity of individual tumor lesions to predict potential response or progression.

To provide potentially prognostic indicators, we analyzed three distinct response groups (MR, PP and sarcoid-like reaction). A MR was not uncommon and was noted in 15% of the cases, which is in line with previously conducted studies [8,23,24]. This relatively high incidence should raise the awareness of the existence of this clinicoradiological phenomenon, and suspected patients with a MR should be evaluated in more detail so that most optimal clinical-based decision can be made. A MR to therapy was a dynamic disease state, as patients possibly had response (MR-R) or no response to therapy (MR-NR), and no patients remained their MR status. Identified clinical characteristics associated with later no response included male sex, brain metastases, higher median LDH on the moment of MR confirmation and cerebral disease progression. These identified clinical characteristics associated with later no response, have been established as prognostic factors in metastatic melanoma, in previously published studies [25–27]. Our results suggest, that these clinical characteristics are also applicable as a prognostic tool in this patient group and have been suggested as a prognostic tool in a previously conducted study [7].

Considering PP, this specific response occurred less frequently, in 4 (3%) out of 196 patients treated with immunotherapy, which is in accordance with incidence rates of this phenomenon in other published studies [6,15]. The moment of PP detection was insufficiently captured by RECIST; with PD in 100% of the cases. Despite evaluation of PD according to RECIST, clinical-based decision making and additionally used iRECIST criteria resulted in continuation of immunotherapy in these patients. Patients with PP had a prolonged overall survival of 1.6 years, which is in line with previously published survival rates of patients with PP [6,14]. The management and results of our cohort justify the continuation of immunotherapy in presumed PP in patients with metastatic melanoma. It is important to emphasize this finding since not all clinical trials and compassionate care situations are designed to re-consenting patients for treatment beyond progression after removing them from experimental regimen(s) at the first sign of disease progression. Meticulous clinicoradiological measurements should be performed in order to rule out PP before halting therapy too early and withholding a beneficial effect of the therapy.

Considering a SR, this was less common, as only three (2%) patients in our series had a SR. Since the number of patients with SR was little and heterogeneous, additional research is needed to identify potential prognostic

clinical characteristics and therapeutic management for these patients.

Limitations and strengths

Our study was limited by the retrospective single-institution nature of the analysis. Despite this, we performed in depth RECIST analysis and iRECIST by an experienced radiologist in addition to already available radiological data. To our knowledge, this is the first study, describing real-world outcomes in management and detailed radiographically description of MR, PP and sarcoid-like reaction during treatment with immunotherapy. In addition, our results are in line with previously published less detailed studies investigating PP and MR. Lastly, by showing the occurrence of this clinicoradiological phenomenon, hopefully, national databases will notify and or register these unique responses in the future, so that the further requested research can be performed.

Conclusion

A heterogeneous response in our cohort was not uncommon, and consisted mainly of a MR, while PP and sarcoid-like reaction were observed less frequently. A MR represented a dynamic disease state, as patients possibly had response or no response to therapy during follow up. Identified clinical characteristics associated with later no response to therapy upon initial MR included the male sex, increased LDH, brain metastasis, cerebral progression, and more involved disease sites the moment a MR was noted. These clinical characteristics can contribute to clinical decision-making in MR cases. Important is that patients with PP had benefited from therapy continuation, demonstrating the importance of not halting therapy too early in case of suspected pseudoprogressive disease.

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Conflicts of interest

There are no conflicts of interest.

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