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Original Research

# Response to checkpoint inhibition and targeted therapy in melanoma patients with concurrent haematological malignancies

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**KEYWORDS**
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Survival

**Abstract** ***Background:*** Patients diagnosed with haematologic malignancies (HMs) have a higher risk of developing subsequent solid tumours, such as melanoma. Patients with HM were mostly excluded from clinical trials but potentially derive less benefit from immune checkpoint inhibitors (ICIs) due to disease- or treatment-related T- or B-cell dysfunction.
***Methods:*** All advanced melanoma patients treated with anti-PD-1-based treatment or targeted therapy between 2015 and 2021 were included from the prospective nationwide Dutch Melanoma Treatment Registry. Progression-free survival (PFS) and melanoma-specific survival (MSS) were analysed for patients with HM (HM+) and without HM (HM−). A cox model was used to account for confounders associated with PFS and MSS.
***Results:*** In total, 4638 advanced melanoma patients received first-line anti-PD-1 monotherapy (n = 1763), ipilimumab-nivolumab (n = 800), or BRAF(/MEK) inhibitors (n = 2075). Concurrent HMs were present for 46 anti-PD1-treated patients, 11 ipilimumab-nivolumab-treated patients and 43 BRAF(/MEK)-inhibitor-treated patients. In anti-PD-1-treated patients, the median PFS was 2.8 months for HM+ and 9.9 months for HM− (p = 0.01). MSS was 41.2 months for HM+ and 58.1 months for HM− (p = 0.00086). In multivariable analysis, the presence of an HM was significantly associated with higher risk of melanoma progression ($HR_{adj}$ 1.62; 95% confidence interval [95% CI] 1.15–2.29; p = 0.006) and melanoma-related death ($HR_{adj}$ 1.74; 95% CI 1.09–2.78; p = 0.020). Median PFS and MSS for first-line BRAF(/MEK-) inhibitor-treated HM+ and HM− patients were not significantly different.
***Conclusions:*** Patients with HM and advanced melanoma show significantly worse melanoma-related outcomes when treated with ICI, but not targeted therapy, compared to patients without HM. Clinicians should be aware of potentially altered effectiveness of ICI in patients with active HM.


## 1. Introduction

Patients diagnosed with haematologic malignancies (HMs) have a higher risk of developing certain types of second cancers, such as malignant melanoma [1,2]. Both B-cells and T-cells appear to play a role in obtaining a response to immune checkpoint inhibitors (ICIs) [3]. B-cells can present tumour-associated antigens to T-cells or produce antibodies benefitting anti-tumour response [4]. $CD4^+$ T-cells mediate anti-tumour immunity through direct cytotoxicity and immunologic help for cytotoxic $CD8^+$ T-cells and antibody responses [5,6]. Besides the induction of dysfunctional T-cell states by tumour antigen exposure, HMs, such as leukaemia and lymphoma, can contribute to impaired immune surveillance in several ways, including the promotion of a tolerogenic immune state [7]. B-cell lymphoma and chronic lymphocytic leukaemia (CLL) have also been found to be accompanied by a decrease in T-helper cells and an increase in regulatory T-cell activity, which has been associated with a poor prognosis to cancer immunotherapy [8–10]. Newly developed immunotherapies such as checkpoint inhibitors are currently being evaluated in several HM such as classical Hodgkin lymphoma, B-cell lymphoma, and CLL [11,12]. In advanced melanoma, these immunotherapies have already led to an increase in survival [13]. The prognosis of patients with HM has also improved over the last years [14]. This increase in survival gives patients with HM more time to develop other types of cancer, and this patient group has already proven to be more prone to developing skin malignancies [1,2,15,16]. So far, little is known about the influence of HM on the response to anti-PD-1 treatment for solid tumours such as advanced melanoma. This nationwide study aimed to investigate the influence of HM on the objective response rate (ORR), progression-free survival

(PFS), overall survival (OS), and melanoma-specific survival (MSS) in advanced stage III and IV melanoma patients treated with anti-PD-1. We hypothesised that patients with both an HM and advanced melanoma have a worse anti-tumour response to ICI than melanoma patients without HM.

## 2. Materials and methods

Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR). Since 2012, data from all systemically treated stage III and IV melanoma patients in the Netherlands has been registered in the DMTR [17]. We analysed all patients with advanced (i.e. unresectable) cutaneous melanoma who were treated with first-line checkpoint inhibitors (anti-PD-1 antibody monotherapy and ipilimumab-nivolumab combination therapy) or first-line BRAF(/MEK) inhibition registered in the DMTR between 2015 and 2021. Since ipilimumab monotherapy is no longer used as a first-line treatment, we did not include this treatment group. We compared patients with HM (HM+) and patients without HM (HM−). Since the status of the HM can be influential on the response to checkpoint inhibitors, additional data regarding the date of diagnosis, the disease status, and the treatment of the HM were retrieved from the electronic patient files of HM+ patients treated with first-line anti-PD-1. Baseline characteristics, ORR, and survival outcomes were compared between the two groups. The medical ethical committee approved research using DMTR data and concluded that it was not deemed subject to the Medical Research Involving Human Subjects Act in compliance with Dutch regulations. For this study, the dataset cut-off date was 7th December 2021.

### 2.1. Patient characteristics

The following baseline patient and tumour characteristics were analysed for all patients: age at diagnosis, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), lactate dehydrogenase (LDH) levels, primary melanoma location, type of melanoma, Breslow thickness, ulceration, liver metastasis, brain metastasis, number of organ sites with metastases, stage according to American Joint Committee on Cancer 8th edition [18], and mutation status. Type of HM, diagnosis sequence (HM or primary melanoma), treatment for HM, and response to HM treatment are described for the HM+ group.

### 2.2. Statistical analysis

Descriptive statistics were used to analyse baseline characteristics. Pearson's chi-squared test was used to compare categorical variables, and the t-test or Mann-Whitney U test for continuous variables depending on their distribution. The reversed Kaplan-Meier method was used to estimate median follow-up [19]. We calculated the ORR for the first treatment line for advanced melanoma. The treating physician determined the response evaluation according to the Response Evaluation Criteria in Solid Tumors version 1.1 [20]. The ORR was defined as the proportion of evaluable patients who achieved a complete response (CR) or partial response. Patients who did not have a response evaluation registered in the DMTR or who died from non-melanoma-related causes before their first response evaluation were excluded from the analysis of ORR. The Kaplan-Meier method was used to calculate median PFS, OS, and MSS. PFS was defined as start of systemic therapy for advanced melanoma to first progression of the melanoma or death. OS was defined as start of systemic therapy to death by any cause. MSS was defined as start of systemic therapy to melanoma-related death. Patients not reaching the end-point were right-censored at the date of the last contact. Cox proportional hazards models were used to estimate the association between HM and PFS/OS/MSS in a multivariable analysis. The variables for this analysis were selected based on earlier literature [21–23]. Factors used in multivariable analysis were age, gender, ECOG PS, LDH levels, liver metastasis, brain metastasis, number of organ sites with metastasis, and *BRAF* mutation status. Comparisons were considered statistically significant for two-sided p-values $< 0.05$. Statistical software used was R studio version 4.0.2 [24]: packages tableone [25], survival [26], and survminer [27].

## 3. Results

In total, 4638 advanced melanoma patients were included that were treated with first-line anti-PD-1 monotherapy (n = 1763), ipilimumab-nivolumab (n = 800), or BRAF(/MEK) inhibitors (n = 2075). Concurrent haematological malignancies were present at start of systemic treatment for 46 anti-PD1 treated patients, 11 ipilimumab-nivolumab treated patients and 43 BRAF(/MEK)-inhibitor-treated patients (Fig. 1). Median follow-up time was 34.2 months.

### 3.1. Patient characteristics

At baseline, patients with HM were significantly older and had worse ECOG PS than patients without HM. The distribution of the melanoma location was significantly different ($p = 0.003$), and *BRAF* mutations were less frequent in the HM group (54.0% versus 65.7%; $p = 0.020$). No other significant differences existed at baseline (Table 1). Patient characteristics per treatment type can be found in Supplementary Tables 1–3. In the HM+ group treated with anti-PD-1, the most frequent type of HM was non-Hodgkin's lymphoma (NHL) (n = 13; 29%), followed by CLL (n = 11;

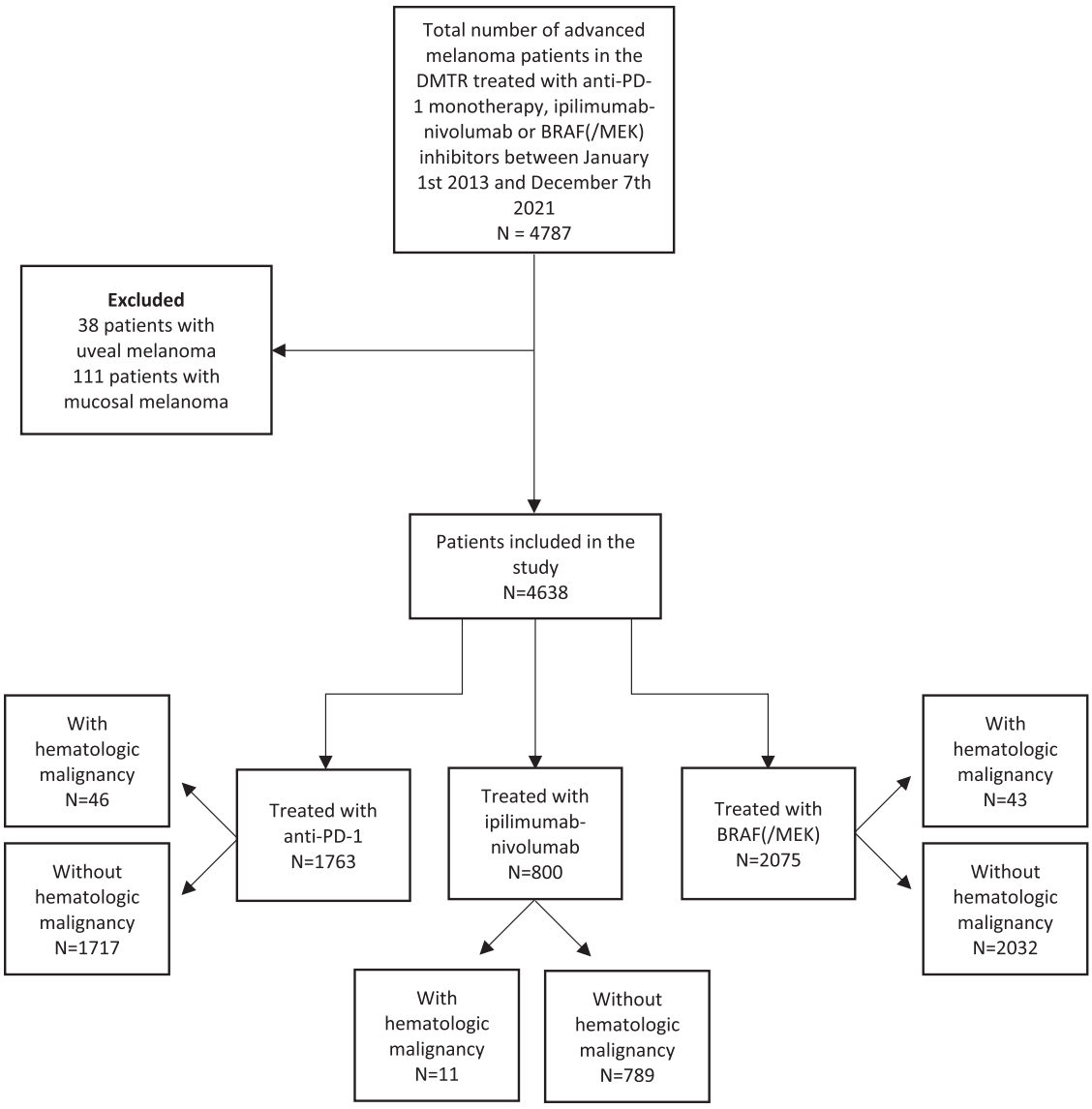


Fig. 1. Flowchart of included patients.

24%). Information regarding the type of HM and the treatment of HM can be found in Supplementary Table 4. Eighteen patients (39%) had a CR to HM treatment at the start of anti-PD-1 treatment for their advanced melanoma. Detailed information regarding the response to treatment at the time of anti-PD-1 treatment of the advanced melanoma can be found in Supplementary Table 5.

### 3.2. Anti-PD-1

In the anti-PD-1 cohort, ORR to first-line treatment was 41% in the HM+ group and 55% in patients without HM (Table 2). The median PFS was 2.8 months (95% confidence interval [95% CI] 2.6–7.3) for patients with HM and 9.9 months (95% CI 8.6–11.8) for patients without HM (p = 0.01) (Fig. 2). In multivariable analysis, being diagnosed with an HM was significantly associated with an increased risk of progression or death ($HR_{adj}$ 1.62; 95% CI 1.15–2.29; p = 0.006) (Fig. 3). MSS was significantly longer for patients without HM. Median MSS was 41.2 (95% CI 12.8–NR) for HM + patients and 58.1 months (95% CI 47.5–NR) for HM− patients (p = 0.00086) (Fig. 4). Adjusting for potential confounders showed a significant association between the presence of an HM and melanoma-related death ($HR_{adj}$ 1.74; 95% CI 1.09–2.78; p = 0.020) (Fig. 5). Median OS was 12.8 months (95% CI 6.2–NR) for HM +. For HM−, median OS was significantly longer (32.3 months; 95% CI 29.1–35.8) (p = 0.00033)

Table 1
Patient characteristics comparison of patient and disease characteristics of anti-PD-1, ipilimumab-nivolumab and BRAF(/MEK) inhibitors treated advanced melanoma patients with and without haematologic malignancy.

| | HM+ 100 | HM− 4538 | p-Value |
|---|---|---|---|
| Median age [IQR][a] | 70.5 [62.8, 77.0] | 64.0 [54.0, 73.0] | < 0.001 |
| Sex (%) | | | 0.090 |
| Male | 69 (69.0) | 2727 (60.1) | |
| Female | 31 (31.0) | 1811 (39.9) | |
| ECOG PS[a] (%) | | | 0.012 |
| 0 | 39 (39.0) | 1999 (44.1) | |
| 1 | 27 (27.0) | 1584 (34.9) | |
| ≥2 | 25 (25.0) | 641 (14.1) | |
| Unknown | 9 (9.0) | 314 (6.9) | |
| Melanoma location[b] (%) | | | 0.003 |
| Primary unknown | 6 (6.0) | 703 (15.5) | |
| Head-Neck | 24 (24.0) | 593 (13.1) | |
| Trunk | 40 (40.0) | 1876 (41.3) | |
| Extremities | 26 (26.0) | 1237 (27.3) | |
| Acral | 4 (4.0) | 85 (1.9) | |
| Unknown | 0 (0.0) | 44 (1.0) | |
| Melanoma type[b] (%) | | | 0.605 |
| Superficial spreading | 46 (46.0) | 1899 (41.8) | |
| Nodular | 18 (18.0) | 866 (19.1) | |
| Acral lentiginous | 3 (3.0) | 68 (1.5) | |
| Lentigo maligna | 3 (3.0) | 74 (1.6) | |
| Desmoplastic | 1 (1.0) | 18 (0.4) | |
| Other | 3 (3.0) | 114 (2.5) | |
| Unknown | 26 (26.0) | 1499 (33.0) | |
| Median Breslow thickness [IQR][b] | 2.5 [1.6, 4.0] | 2.3 [1.3, 4.0] | 0.557 |
| Ulceration[b] (%) | | | 0.034 |
| No | 48 (48.0) | 1821 (40.1) | |
| Yes | 27 (27.0) | 1182 (26.0) | |
| Unknown | 25 (25.0) | 1535 (33.8) | |
| LDH levels[a] (%) | | | 0.388 |
| Not determined | 2 (2.0) | 99 (2.2) | |
| Normal | 50 (50.0) | 2632 (58.0) | |
| 250–500 | 28 (28.0) | 1136 (25.0) | |
| > 500 | 20 (20.0) | 671 (14.8) | |
| AJCC stage (8th edition)[a] (%) | | | 0.236 |
| IIIc unresectable | 6 (6.0) | 306 (6.7) | |
| IV-M1a | 4 (4.0) | 321 (7.1) | |
| IV-M1b | 14 (14.0) | 481 (10.6) | |
| IV-M1c | 53 (53.0) | 1997 (44.0) | |
| IV-M1d | 23 (23.0) | 1412 (31.1) | |
| Unknown | 0 (0.0) | 21 (0.5) | |
| Liver metastases[a] (%) | | | 0.164 |
| No | 59 (59.0) | 3081 (67.9) | |
| Yes | 39 (39.0) | 1397 (30.8) | |
| Unknown | 2 (2.0) | 60 (1.3) | |
| Brain metastases[a] (%) | | | 0.280 |
| No | 77 (77.0) | 3105 (68.4) | |
| Yes, asymptomatic | 9 (9.0) | 636 (14.0) | |
| Yes, symptomatic | 14 (14.0) | 776 (17.1) | |
| Unknown | 0 (0.0) | 21 (0.5) | |
| Organ sites[a] (%) | | | 0.154 |
| < 3 | 42 (42.0) | 2166 (47.7) | |
| ≥3 | 56 (56.0) | 2343 (51.6) | |
| Unknown | 2 (2.0) | 29 (0.6) | |
| Melanoma mutation status (%) | | | 0.020 |
| *BRAF* | 54 (54.0) | 2981 (65.7) | |
| *NRAS* | 23 (23.0) | 769 (16.9) | 0.145 |
| *KIT* | 0 (0.0) | 45 (1.0) | 0.628 |
| Systemic treatment | | | 0.057 |
| Anti-PD-1 | 46 (46.0) | 1717 (37.8) | |
| Ipilimumab-nivolumab | 11 (11.0) | 789 (17.4) | |
| BRAF(/MEK) inhibitors | 43 (43.0) | 2032 (44.7) | |

IQR: interquartile range;
ECOG PS: Eastern Cooperative Oncology Group Performance Status;
LDH: lactate dehydrogenase;
AJCC: American Joint Committee on Cancer.
[a] Determined at time of advanced melanoma.
[b] Determined at time of primary melanoma.

(Supplementary Figs. 1 and 2). Four (8.7%) HM+ and 329 (19.2%) HM− patients received BRAF(/MEK) inhibitors in a later line. Grade ≥3 anti-PD1 toxicity occurred in 17.4% of HM+ and 13.7% of HM− patients.

### 3.3. Ipilimumab-nivolumab

In first-line ipilimumab-nivolumab-treated patients, ORR was 36% for HM+ versus 52% for HM−. Although limited by small numbers, the same survival trends as in anti-PD-1-treated patients were seen in ipilimumab-nivolumab-treated patients. Median PFS was 2.3 months (95% CI 2.0–NR) for HM+ patients versus 6.8 (95% CI 5.5–9.2) for HM− patients. Median OS for HM+ patients was 4.6 months (95% CI 2.4–NR) and 31.7 months (95% CI 22.1–39.0) for HM− patients. Median MSS was 4.6 months (95% CI 2.4–NR) for HM + patients and 46 months (95% CI 33.4–NR) for HM− patients. Grade ≥3 toxicity occurred in 36.4% of HM + and 49.9% of HM− patients.

### 3.4. BRAF(/MEK) inhibitors

In patients treated with BRAF(/MEK) inhibitors, ORR was 50% in HM+ versus 48% in HM−. HM+ patients receiving targeted therapy had a median PFS of 4.7 months (95% CI 3.6–8.0), whereas HM− patients had a median PFS of 6.3 months (95% CI 6.0–6.6)(p = 0.078). For HM+ patients, median OS was 8.1 months (95% CI 6.0–15.3) and 9.4 months (95% CI 8.9–10.1) for HM− patients (p = 0.4). Median MSS in HM+ patients with a *BRAF* mutation and first-line treatment with BRAF (/MEK) inhibitors was 12.6 months (95% CI 8.1–44.2) and 11.8 months for HM− patients (95% CI 10.9–12.8) (p = 0.96) (Supplementary Figs. 3 and 4). Eighteen (41.9%) HM+ patients received checkpoint inhibitors in a later treatment line and 937 (46.1%) HM− patients. Grade ≥3 toxicity occurred more frequently in HM− than HM+ patients treated with BRAF(/MEK)

Table 2
Objective response rate comparison of first-line objective response rate (ORR) of anti-PD-1, ipilimumab-nivolumab, and BRAF(/MEK) inhibitors treated advanced melanoma patients with and without haematologic malignancy.

| Objective response rate (ORR) | | | | | | |
|---|---|---|---|---|---|---|
| | Anti-PD-1 | | Ipilimumab-nivolumab | | BRAF (/MEK) inhibitors | |
| | HM+ | HM− | HM+ | HM− | HM+ | HM− |
| CR | 7 (17%) | 360 (22%) | 0 (0%) | 97 (13%) | 0 (0%) | 93 (5%) |
| PR | 9 (21%) | 539 (32%) | 4 (36%) | 284 (39%) | 20 (50%) | 848 (43%) |
| SD | 7 (17%) | 300 (18%) | 1 (9%) | 88 (12%) | 10 (25%) | 566 (29%) |
| PD or melanoma-related death | 19 (45%) | 460 (28%) | 6 (55%) | 262 (36%) | 10 (25%) | 456 (23%) |
| ORR | 16 (38%) | 899 (54%) | 4 (36%) | 381 (52%) | 20 (50%) | 941 (48%) |
| Total (n) | 42 | 1659 | 11 | 731 | 40 | 1963 |

CR: complete response;
PR: partial response;
SD: stable disease;
PD: progressive disease;
ORR: objective response rate (=CR + PR).

inhibitors (20.1% versus 7.0%), with skin toxicity being most frequent in the HM− group (n = 123; 6.1%) and pyrexis the most frequent in the HM+ group (n = 2; 4.7%).

### 3.5. Other survival outcomes

Furthermore, we investigated PFS and MSS in patients who had a CR to HM therapy at the time of anti-PD-1 initiation versus patients who did not have a CR. Although not significant, we did notice a trend towards better survival outcomes in patients who reached a CR (Supplementary Figs. 5 and 6).

## 4. Discussion

To our knowledge, this is the largest cohort study of first-line ICI or targeted therapy-treated patients with both an HM and advanced melanoma and the first to directly compare advanced melanoma patients treated with first-line ICIs or targeted therapy with and without HM. Patients with HM showed worse outcomes than patients without HM after ICI treatment, even after correcting for potential confounders. The results of our study confirm our hypothesis that patients with HM have worse melanoma-related outcomes upon ICI treatment than patients without HM. Interestingly, we

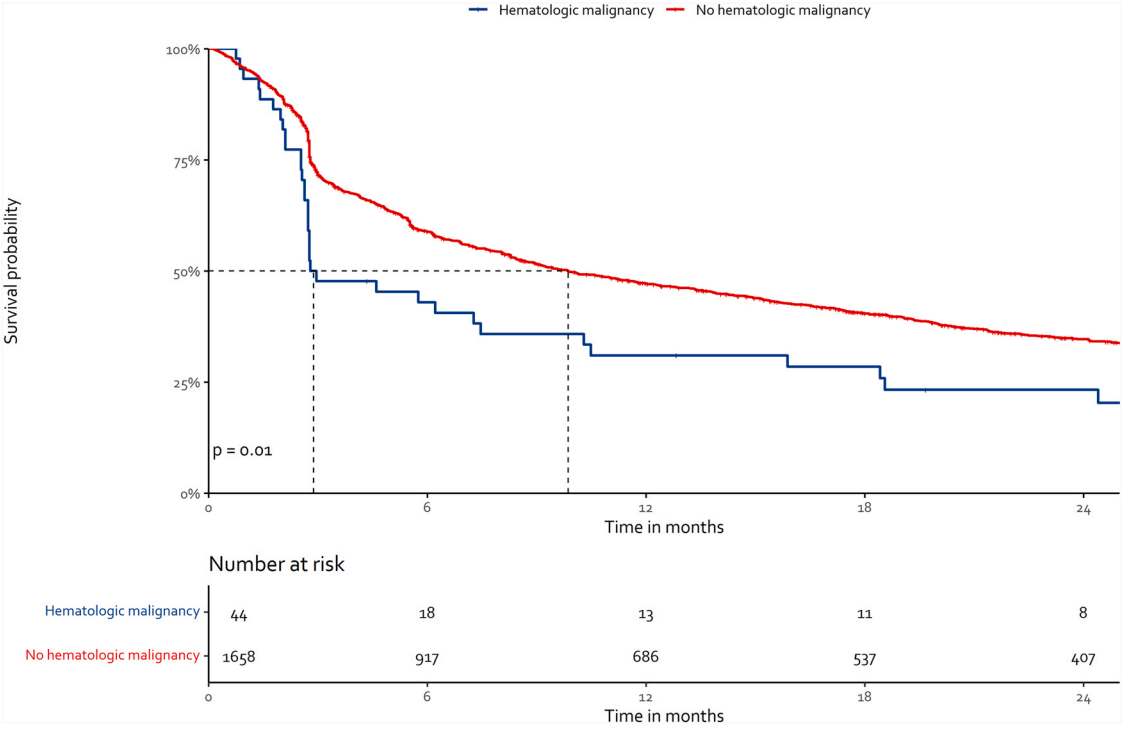


Fig. 2. Kaplan-Meier estimate of progression-free survival in anti-PD-1-treated advanced melanoma patients with and without haematologic malignancy.

| Variable | | N | Hazard ratio | p |
|---|---|---|---|---|
| **Hematologic malignancy** | No | 1532 | Reference | |
| | Yes | 41 | 1.62 (1.15, 2.29) | 0.006 |
| **Age** | 0-69 | 824 | Reference | |
| | >70 | 749 | 1.13 (0.99, 1.28) | 0.069 |
| **Gender** | Male | 982 | Reference | |
| | Female | 591 | 1.01 (0.89, 1.15) | 0.880 |
| **ECOG** | 0-1 | 1465 | Reference | |
| | 2-4 | 108 | 1.43 (1.13, 1.80) | 0.003 |
| **LDH** | Normal | 1202 | Reference | |
| | 250-500 U/l | 317 | 1.22 (1.05, 1.42) | 0.009 |
| | >500 U/l | 54 | 2.16 (1.59, 2.93) | <0.001 |
| **Liver metastasis** | No | 1253 | Reference | |
| | Yes | 320 | 1.23 (1.05, 1.43) | 0.010 |
| **Brain metastasis** | No | 1339 | Reference | |
| | Yes, asymptomatic | 141 | 1.09 (0.88, 1.34) | 0.444 |
| | Yes, symptomatic | 93 | 1.32 (1.03, 1.68) | 0.028 |
| **Organsites** | <3 | 1001 | Reference | |
| | >2 | 572 | 1.25 (1.09, 1.44) | 0.001 |
| **BRAF mutation** | No | 939 | Reference | |
| | Yes | 634 | 1.08 (0.95, 1.23) | 0.237 |

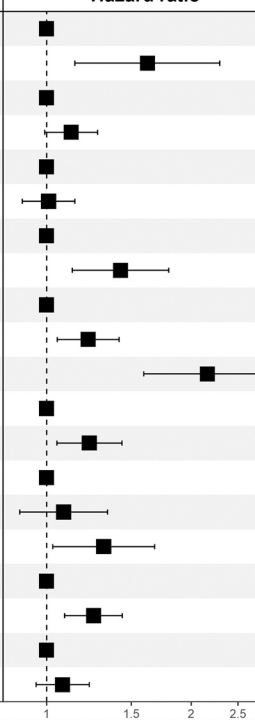


Fig. 3. Cox proportional hazard model of progression-free survival in anti-PD-1-treated advanced melanoma patients with and without haematologic malignancy.

did not find significant differences in PFS and MSS between HM+ and HM− patients treated with BRAF (/MEK) inhibitors. Some of the HM+ patients in our cohort received chimeric antigen receptor-modified (CAR) T-cell therapy or rituximab as a treatment for their HM. CAR T-cell therapy (which involves conditioning chemotherapy) can lead to cytopenias, such as lymphopenia [28,29], that may persist for several

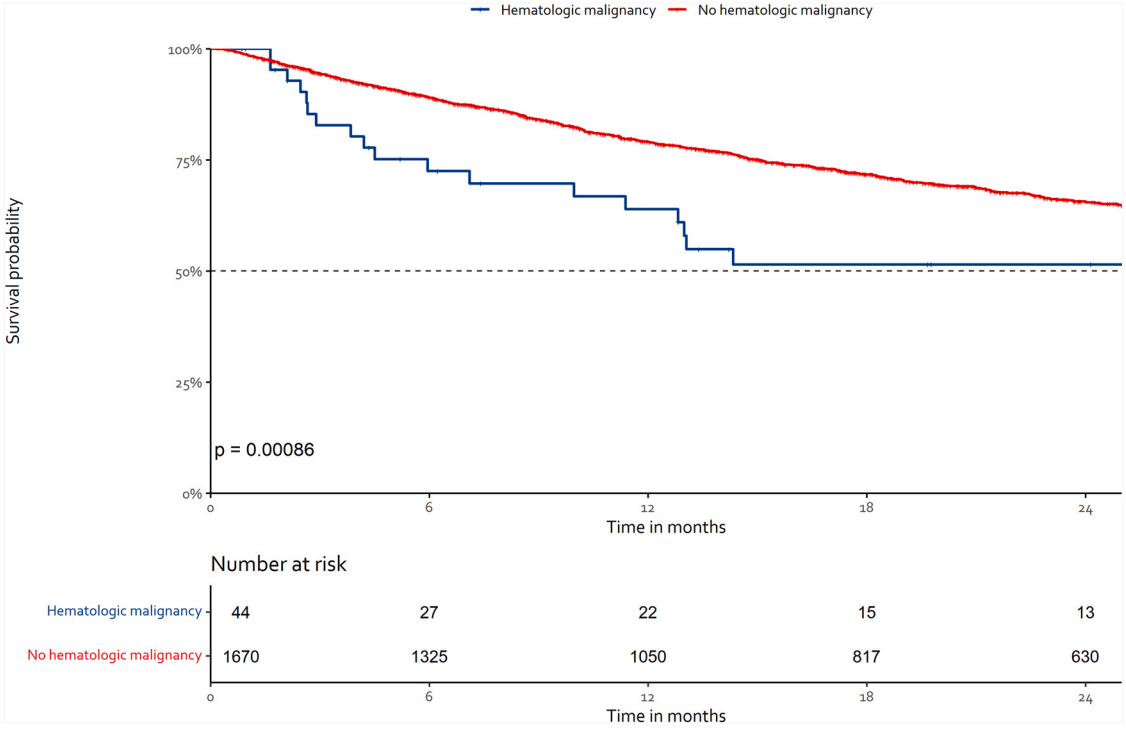


Fig. 4. Kaplan-Meier estimate of melanoma-specific survival in anti-PD-1-treated advanced melanoma patients with and without haematologic malignancy.

| Variable | | N | Hazard ratio | p |
|---|---|---|---|---|
| **Hematologic malignancy** | No | 1541 | Reference | |
| | Yes | 41 | 1.74 (1.09, 2.78) | 0.020 |
| **Age** | 0-69 | 827 | Reference | |
| | >70 | 755 | 1.21 (1.01, 1.45) | 0.035 |
| **Gender** | Male | 988 | Reference | |
| | Female | 594 | 0.96 (0.80, 1.15) | 0.647 |
| **ECOG** | 0-1 | 1473 | Reference | |
| | 2-4 | 109 | 1.60 (1.17, 2.19) | 0.003 |
| **LDH** | Normal | 1210 | Reference | |
| | 250-500 U/l | 318 | 1.32 (1.08, 1.62) | 0.007 |
| | >500 U/l | 54 | 3.02 (2.09, 4.37) | <0.001 |
| **Liver metastasis** | No | 1259 | Reference | |
| | Yes | 323 | 1.57 (1.28, 1.93) | <0.001 |
| **Brain metastasis** | No | 1346 | Reference | |
| | Yes, asymptomatic | 141 | 1.39 (1.07, 1.82) | 0.015 |
| | Yes, symptomatic | 95 | 1.97 (1.47, 2.65) | <0.001 |
| **Organsites** | <3 | 1007 | Reference | |
| | >2 | 575 | 1.33 (1.10, 1.61) | 0.003 |
| **BRAF mutation** | No | 945 | Reference | |
| | Yes | 637 | 0.76 (0.63, 0.91) | 0.003 |

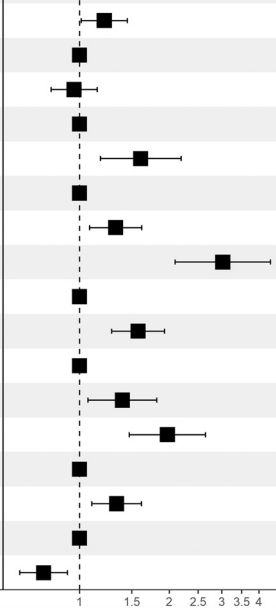


Fig. 5. Cox proportional hazard model of melanoma-specific survival in anti-PD-1-treated advanced melanoma patients with and without haematologic malignancy.

months [28]. Treatment with rituximab, even after discontinuation, can result in prolonged B-cell depletion [30]. These therapy-induced cytopenias and consequently immunocompromised state may play a role in the poor outcomes of ICIs in HM+ patients. However, it is difficult to assess the clinical implications of these factors. A large, observational study including 151,949 patients showed a significantly elevated risk of developing primary cutaneous melanoma in patients with a history of large B-cell lymphoma (standardised incidence ratio of 1.22; 95% CI 1.02–1.45) or a history of Hodgkin lymphoma (standardised incidence ratio of 1.75; 95% CI 1.33–2.26). Survivors of most lymphoid neoplasm subtypes had a higher risk of death by any cause after a diagnosis of melanoma. Among survivors of melanoma, the diagnosis of a lymphoid neoplasm also increased the risk of death by any cause [31]. The cause of the poor outcomes in patients with HM remains to be fully elucidated, but dysregulation of the immune system in various manners, not limited to classically induced exhaustion as observed in solid tumours, seems to be an important factor [7,32]. Studies have focused on T-helper cells and regulatory T-cells as the cause of this immune dysregulation [8,9]. More recently, several studies have highlighted the importance of tertiary lymphoid structures and B-cells for response to checkpoint inhibition [33,34]. In our HM+ cohort, patients achieving a CR to HM therapy seem to perform better than patients who did not achieve a CR. Potentially this is due to the fact that these patients experience less treatment- or disease-related B- and T-cell dysfunction than patients with an active HM. Brewer et al. [35] investigated the influence of having a history of CLL or NHL on the survival of malignant melanoma patients. In line with our findings, they reported a significantly worse OS and MSS for patients with both malignant melanoma and CLL or NHL. The same effect was described by Famenini et al. [36], who found melanoma patients with a history of CLL or NHL to have a higher risk of death than melanoma patients without CLL or NHL. However, both studies did not report the melanoma disease stage or the given treatment, which complicates comparison to our findings. Clinical studies investigating the response to checkpoint inhibitors in patients with both advanced melanoma and HM are rare, and patients suffering from HM were excluded from trials. Leiter et al. [37] conducted a retrospective multicentre study including 52 ICI-treated melanoma patients with concurrent HM, of whom 44 had unresectable melanoma, and eight received adjuvant ICI treatment for melanoma. In this unresectable group, ORR was 28.6%, median PFS was 8.4 months, and median OS was not reached. These patients were treated with either anti-PD-1 monotherapy (n = 32), anti-CTLA-4 monotherapy (n = 5), or a combination (n = 7). Six of these patients had received prior systemic melanoma therapy, making comparisons difficult since we only included patients treated first-line ICIs. An earlier study investigated whether developing CLL before or after malignant melanoma influenced mortality

rates. They found no differences in mortality rates between patients diagnosed with CLL before or after malignant melanoma [38]. Our study has some limitations. Firstly, population-based studies are generally more prone to missing data than clinical trials. However, data in the DMTR are registered by annually trained, independent data managers. The registered data are checked by treating physicians to further warrant the high quality. In addition, patients are registered in an online registry, which warns data managers when data are inconsistent or have missing values. The high quality and the low number of missing values of the DMTR have been demonstrated in an earlier study [17]. Secondly, observational studies are, by definition, prone to the introduction of bias, such as indication bias. Thirdly, despite adjusting for potential confounders in our multivariable analysis, residual confounding cannot be ruled out as a potential explanation for our findings. Fourthly, there is a broad spectrum of different HM and their therapies, ranging from chemotherapy to no treatment. This warrants caution when interpreting the outcomes of the HM+ group. Finally, the number of included patients is both a strength and a weakness in our study. Our cohort of patients with both HM and advanced melanoma is one of the largest described. Nonetheless, the number of included patients with HM remains small. Concluding, our results show that patients with both advanced melanoma and an HM have worse melanoma-related outcomes than advanced melanoma patients without an HM upon treatment with ICIs. Remarkably, this difference was not observed for targeted therapy-treated patients. Our findings stress the importance of studies analysing rare patient subgroups not represented in clinical trials, helping clinicians inform these patients of their chances of response and long-term survival.

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## CRediT authorship contribution statement

**Van Not**: Conceptualisation, Methodology, Formal analysis, Writing – Original Draft, Writing – Review & Editing. **Van den Eertwegh**: Writing – Review & Editing. **Haanen**: Writing – Review & Editing. **Van Rijn**: Writing – Review & Editing. **Aarts**: Writing – Review & Editing. **Van den Berkmortel**: Writing – Review & Editing. **Blank**: Writing – Review & Editing. **Boers-Sonderen**: Writing – Review & Editing. **Van Eijs**: Writing – Review & Editing. **De Groot**: Writing – Review & Editing. **Hospers**: Writing – Review & Editing. **Kapiteijn**: Writing – Review & Editing. **De Meza**: Conceptualisation, Writing – Review & Editing. **Piersma**: Writing – Review & Editing. **Stevense-den Boer**: Writing – Review & Editing. **Van der Veldt**: Writing – Review & Editing. **Vreugdenhil**: Writing – Review & Editing. **Wouters**: Conceptualisation, Writing – Review & Editing, Supervision. **Suijkerbuijk**: Conceptualisation, Writing – Review & Editing, Supervision. **Blokx**: Conceptualisation, Writing – Review & Editing, Supervision.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

A.vdE. has advisory relationships with Amgen, Bristol Myers Squibb, Roche, Novartis, MSD, Pierre Fabre, Sanofi, Pfizer, Ipsen, Merck and has received research study grants not related to this paper from Sanofi, Roche, Bristol Myers Squibb, Idera and TEVA and has received travel expenses from MSD Oncology, Roche, Pfizer and Sanofi and has received speaker honoraria from BMS and Novartis.

J.H. has advisory relationships with Achilles Therapeutics, AstraZeneca, Bristol Myers Squibb, BioNTech, Immunocore, Iovance Biotherapeutics, Instil Bio, Ipsen, MSD, Merck Serono, Molecular Partners, Novartis, Neogene Therapeutics, Pfizer, PokeAcel, Roche/Genentech, Sanofi, T-Knife and has received research grants not related to this paper from Asher Bio, Amgen, Bristol Myers Squibb, MSD, BioNTech, Neogene Therapeutics and Novartis. All grants were paid to the institutions.

C.B. has/had advisory role: BMS, MSD, Roche, Novartis, GSK, AZ, Pfizer, Lilly, GenMab, Pierre Fabre, Third Rock Ventures, received research funding: BMS, Novartis, NanoString, 4SC, stockownership: co-founder Immagene BV and Signature Oncology, patents (incl. submitted): WO 2021/177822 A1, N2027907, P091040NL2.

M.A. has advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, Bayer. Research grants Merck-Pfizer. Not related to current work and paid to institute.

J.dG. has consultancy/advisory relationships with Bristol Myers Squibb, Pierre Fabre, Servier, MSD, Novartis.

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E.K. has consultancy/advisory relationships with Bristol Myers Squibb, Novartis, Merck, Pierre Fabre, Lilly and Bayer, and received research grants not related to this paper from Bristol Myers Squibb and Pierre-Fabre. Not related to current work and paid to institute.

R.vR. has advisory board/consultancy honoraria from Pfizer and an expert meeting fee from Roche.

A.vdV. has consultancy relationships with Bristol Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai, Merck.

M.B.S. has consultancy/advisory relationships with Pierre Fabre, MSD and Novartis.

K.S. has advisory relationships with Bristol Myers Squibb, Novartis, MSD, Pierre Fabre, AbbVie, received honoraria from Novartis, MSD and Roche and received research funding from BMS, Philips and TigaTx.

All remaining authors have declared no conflicts of interest.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.03.009.

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