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Duin, I.A.J. van; Elias, S.G.; Eertwegh, A.J.M. van den; Groot, J.W.B. de; Blokx, W.A.M.; Diest, P.J. van; ... ; Suijkerbuijk, K.P.M.

Received: 2 January 2023 | Accepted: 26 January 2023

DOI: 10.1002/ijc.34479

CANCER EPIDEMIOLOGY

IJC INTERNATIONAL JOURNAL of CANCER

Time interval from primary melanoma to first distant recurrence in relation to patient outcomes in advanced melanoma

Isabella A. J. van Duin[1] | Sjoerd G. Elias[2] | Alfonsus J. M. van den Eertwegh[3] | Jan Willem B. de Groot[4] | Willeke A. M. Blokx[5] | Paul J. van Diest[5] | Tim Leiner[6,7] | Joost J. C. Verhoeff[8] | Rik J. Verheijden[1] | Olivier J. van Not[1,9] | Maureen J. B. Aarts[10] | Franchette W. P. J. van den Berkmortel[11] | Christian U. Blank[12,13] | John B. A. G. Haanen[12] | Geke A. P. Hospers[14] | Anna M. Kamphuis[1] | Djura Piersma[15] | Rozemarijn S. van Rijn[16] | Astrid A. M. van der Veldt[17] | Gerard Vreugdenhil[18] | Michel W. J. M. Wouters[9,19,20] | Marion A. M. Stevense-den Boer[21] | Marye J. Boers-Sonderen[22] | Ellen Kapiteijn[23] | Karijn P. M. Suijkerbuijk[1]

[1]Department of Medical Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands

[2]Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[3]Department of Medical Oncology, Amsterdam UMC, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, The Netherlands

[4]Isala Oncology Center, Zwolle, The Netherlands

[5]Department of Pathology, University Medical Center Utrecht, Utrecht, The Netherlands

[6]Department of Radiology, Mayo Clinic, Rochester, Minnesota, USA

[7]Department of Radiology, University Medical Center Utrecht, Utrecht, The Netherlands

[8]Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands

[9]Scientific Bureau, Dutch Institute for Clinical Auditing, Leiden, The Netherlands

[10]Department of Medical Oncology, GROW-School for Oncology and Reproduction, Maastricht University Medical Centre+, Maastricht, The Netherlands

[11]Department of Medical Oncology, Zuyderland Medical Centre Sittard, Sittard-Geleen, The Netherlands

[12]Department of Molecular Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[13]Department of Medical Oncology & Immunology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[14]Department of Medical Oncology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[15]Department of Internal Medicine, Medisch Spectrum Twente, Enschede, The Netherlands

[16]Department of Internal Medicine, Medical Centre Leeuwarden, Leeuwarden, The Netherlands

[17]Department of Medical Oncology and Radiology & Nuclear Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

[18]Department of Internal Medicine, Maxima Medical Centre, Eindhoven, The Netherlands

[19]Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, The Netherlands

[20]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[21]Department of Internal Medicine, Amphia Hospital, Breda, The Netherlands

Abbreviations: AJCC, American Joint Committee on Cancer; BOR, best overall response; DMTR, Dutch Melanoma Treatment Registry; HR, hazard ratio; ICI, immune checkpoint inhibition; IQR, interquartile range; LDH, lactate dehydrogenase; ORR, overall response rate; OS, overall survival; PFS, progression free survival; TFDR, time to first distant recurrence; ULN, upper limit of normal.; WHO, World Health Organisation.

[22]Department of Medical Oncology, Radboud University Medical Centre, Nijmegen, The Netherlands

[23]Department of Medical Oncology, Leiden University Medical Centre, Leiden, The Netherlands

Correspondence
Isabella A. J. van Duin, Department of Medical Oncology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands.
Email: i.a.j.vanduin-3@umcutrecht.nl

Abstract

Since the introduction of BRAF(/MEK) inhibition and immune checkpoint inhibition (ICI), the prognosis of advanced melanoma has greatly improved. Melanoma is known for its remarkably long time to first distant recurrence (TFDR), which can be decades in some patients and is partly attributed to immune-surveillance. We investigated the relationship between TFDR and patient outcomes after systemic treatment for advanced melanoma. We selected patients undergoing first-line systemic therapy for advanced melanoma from the nationwide Dutch Melanoma Treatment Registry. The association between TFDR and progression-free survival (PFS) and overall survival (OS) was assessed by Cox proportional hazard regression models. The TFDR was modeled categorically, linearly, and flexibly using restricted cubic splines. Patients received anti-PD-1-based treatment (n = 1844) or BRAF(/MEK) inhibition (n = 1618). For ICI-treated patients with a TFDR <2 years, median OS was 25.0 months, compared to 37.3 months for a TFDR >5 years ($P = .014$). Patients treated with BRAF(/MEK) inhibition with a longer TFDR also had a significantly longer median OS (8.6 months for TFDR <2 years compared to 11.1 months for >5 years, $P = .004$). The hazard of dying rapidly decreased with increasing TFDR until approximately 5 years (HR 0.87), after which the hazard of dying further decreased with increasing TFDR, but less strongly (HR 0.82 for a TFDR of 10 years and HR 0.79 for a TFDR of 15 years). Results were similar when stratifying for type of treatment. Advanced melanoma patients with longer TFDR have a prolonged PFS and OS, irrespective of being treated with first-line ICI or targeted therapy.

KEYWORDS
BRAF(/MEK) inhibition, immune checkpoint inhibition, immunotherapy, melanoma, prognosis

What's new?

Time to first distant recurrence (TFDR) in melanoma can be long, probably due to effective immune surveillance. Patients with long TFDR potentially survive longer upon presentation with metastases, though evidence supporting this association is currently scant. Here, the association between TFDR and survival was examined among Dutch patients with advanced melanoma. Survival was found to be prolonged in patients with longer TFDR. This association was observed in patients treated with immune checkpoint inhibitors and in patients treated with BRAF(/MEK) inhibitors. The study identifies TFDR as a novel factor for consideration in prognostic assessment of advanced melanoma.

1 | INTRODUCTION

Cutaneous melanoma accounts for almost 2% of global cancer diagnoses, with an approximate number of 325.000 cases per year. In 2020, approximately 57.000 people died from the disease worldwide.[1] It is estimated that melanoma will become the second most common cancer in 2040.[2] Survival in unresectable stage III and stage IV melanoma has historically been poor, but since the introduction of new therapeutic agents, the 5-year overall survival rates have increased significantly[3] to over 50% in recent trials.[4]

In patients with melanoma, it is not uncommon for distant metastases to occur long after the primary tumor diagnosis.[5] Historically, it has been suggested that patients with a longer time

between their primary melanoma diagnosis and detection of advanced disease have better survival once metastasized,[6-8] although not all evidence supports this.[9] A long time to first distant recurrence (TFDR) is often ascribed to metastatic dormancy, where disseminated tumor cells are thought to persist in a relatively non-proliferative state.[10] This could suggest effective innate and adaptive immune surveillance. One might hypothesize that a more pronounced effect of TFDR could be observed in patients treated with immune checkpoint inhibition (ICI), which reinforces immune surveillance. However, other mechanisms dictating metastatic dormancy have also been suggested. For example, disseminated tumor cells activate self-imposed dormancy programs that allow them to adapt to the new tumor microenvironment.[10] This would argue for the association between TFDR and survival to be independent of type of systemic treatment.

The prognostic relevance of TFDR has not yet been analyzed in large cohorts in this setting. The aim of our study was to investigate the correlation between the TFDR and progression-free survival (PFS) and overall survival (OS) in advanced melanoma patients treated with first-line ICI or BRAF(/MEK) inhibition, and to investigate whether this effect is treatment dependent.

2 | METHODS

2.1 | Study design and patients

For this retrospective observational study, we used data from the Dutch Melanoma Treatment Registry (DMTR). The DMTR is a database in which clinical data from all advanced melanoma patients in The Netherlands have been prospectively collected since 2012.[11]

Patients were eligible for the current analysis if they had unresectable stage III or stage IV cutaneous melanoma (according to the AJCC v8 Cancer Staging Manual), were treated with first-line anti-PD-1 based treatment (single agent or in combination with anti-CTLA-4) or BRAF(/MEK) inhibitors, and initiated therapy between 2012 and 2020. We excluded patients with mucosal melanoma and uveal melanoma because of their inherently different prognosis. Patients with an unknown primary tumor were also excluded (Figure 1). Data cutoff for follow-up was September 20, 2021.

Response evaluation was done according to RECIST v1.1. Best overall response (BOR) was evaluated for all patients. Responses were determined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), including melanoma-related death before first response assessment. The overall response rate (ORR) was defined as the proportion of patients who had a partial or complete response to therapy as BOR.

TFDR was defined as the time from the pathological diagnosis of the primary melanoma to the clinical diagnosis of advanced disease. If metastatic disease was found before the primary tumor, the time interval was set to zero. The TFDR for every patient was known at the start of systemic therapy, which was the baseline in our analyses. Progression-free survival (PFS) was defined as time from start of first-line systemic treatment to progressive disease or death. Overall survival (OS) was defined as the time from start of first-line systemic treatment to death from any cause. Patients were censored on the last date they were known to be alive without progression (for PFS) or alive (for OS).

2.2 | Statistical analysis

When analyzing TFDR as a categorical variable, we used three TFDR groups (<2, 2-5 and > 5 years). Synchronously metastasized patients were included in the TFDR <2 years group. The cutoff points for these groups were based on tertiles, so that each group represented a roughly equal number of patients. In a sensitivity analysis, we analyzed metachronous patients only (with synchronous metastases as metastases detected within 3 months after diagnosis of the primary melanoma). Baseline characteristics between the groups were compared using standard descriptive statistics.

We assessed PFS and OS using the Kaplan-Meier method. We evaluated differences in ORR between TFDR groups with chi-square tests and used Cox proportional hazard regression for the associations between TFDR and survival, yielding hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was evaluated using visual inspection of Schoenfeld residuals and was not found to be violated. We used Cox models with restricted cubic splines with three knots to flexibly model the continuous effects of TFDR on PFS and OS, resulting in hazard ratio curves to depict the shape of the estimated hazard ratio of progressive disease or dying for each value of TFDR together with 95% confidence bands relative to a TFDR of 0 (synchronously metastasized patients). We compared linear and restricted cubic splines models using the likelihood ratio test to assess statistical evidence of nonlinearity. In Cox regression we adjusted for type of systemic therapy and age at start of systemic treatment. We adjusted for age besides type of systemic therapy since older advanced melanoma patients implicitly have shorter to live regardless of their disease, and therefore large TFDR intervals can only occur in older patients, possibly resulting in a bias toward an overestimation of the risk of long TFDR intervals if not accounted for. The results of these Cox regression models can be interpreted as the relative change in hazard of PFS or OS given a certain change in TFDR, conditional on keeping age at start and type of systemic therapy constant. We explicitly refrained from adjusting for other clinicopathological variables to yield estimates of the prognostic relevance associated with TFDR including any possible overlapping information with these other variables.

In all analyses, patients treated with BRAF inhibitors and BRAF/MEK inhibitors were analyzed together. Due to the small amount of

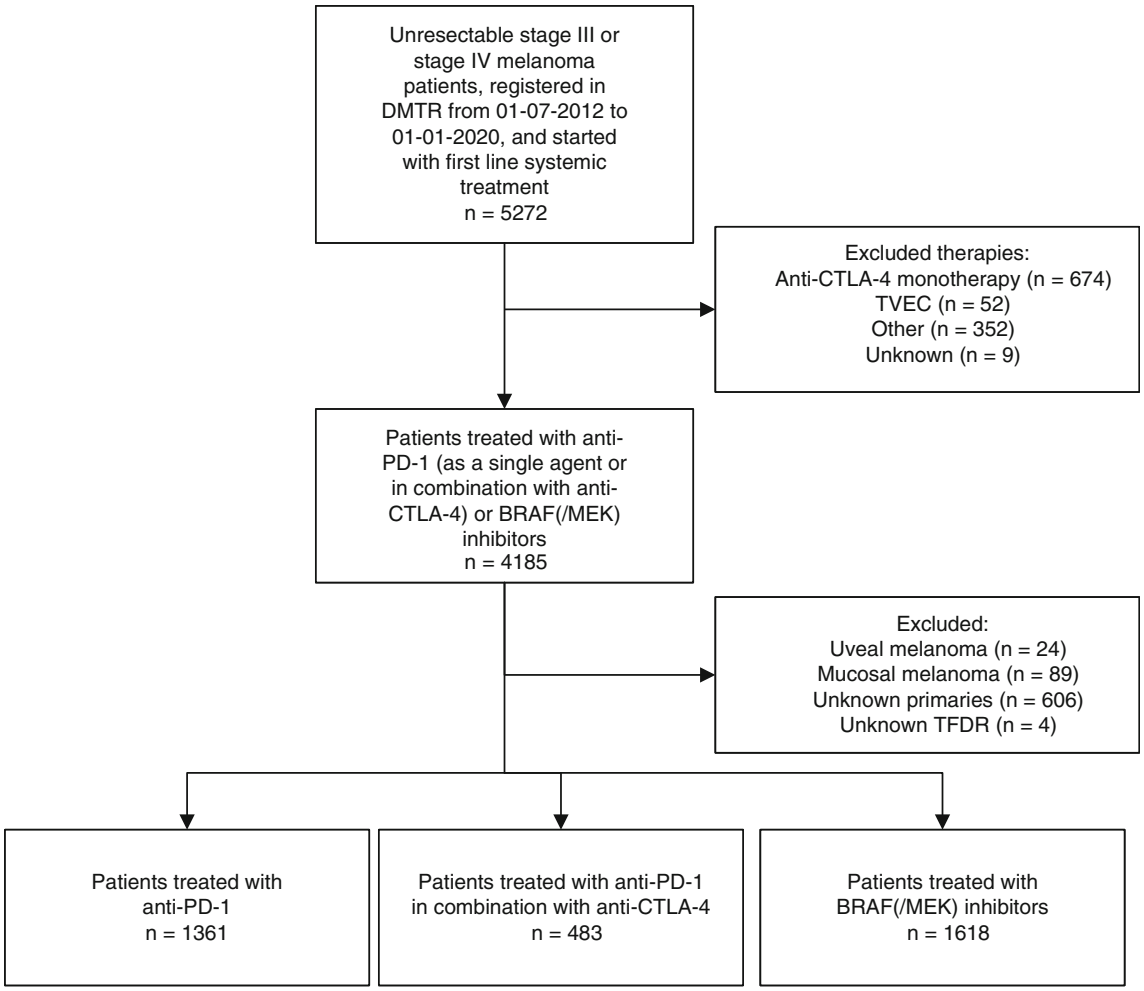

FIGURE 1 Flowchart of the study population.

missing data (0.16%) in TFDR, missing data were handled by complete-case analysis.

All statistical analyses were performed using R version 4.1.2 (packages ggplot2 3.3.5, survival 3.2-13, survminer 0.4.9 and rms 6.2-0).[12-16] A two-sided *P*-value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patients

A total of 3462 patients were available for analysis, of whom 1361 were treated with first-line anti-PD-1, 483 with a combination of anti-PD1 and anti-CTLA4 (ipilimumab + nivolumab), and 1618 with first-line BRAF(/MEK) inhibitors. Baseline characteristics are listed in Table 1, stratified by TFDR (<2 years, 2-5 years and >5 years).

The median TFDR for all patients was 36.3 months (interquartile range, 14.2-75.5). In patients with a BRAF V600 mutation, the TFDR was significantly longer (median 40.7 months) compared to patients without a BRAF V600 mutation (median 29.7 months). Nodular melanoma was more common in the TFDR >5 years group, while superficial spreading melanoma was less common. In the TFDR <2 years group, patients were more often male, and less frequently had symptomatic brain metastases compared to the other two groups. Patients who received combination ICI therapy or BRAF(/MEK) inhibitors were younger and had worse prognostic features (higher stage of disease and LDH levels, and more often liver metastases and symptomatic brain metastases) compared to anti-PD-1 treated patients (Table S1).

3.2 | TFDR and response to therapy

The ORR for anti-PD-1 treated and ipilimumab-nivolumab treated patients were 52% and 53%, respectively. For BRAF(/MEK) inhibitor treated patients, the ORR was 48%. Table 2 describes the ORR for the three different TFDR groups. The ORR was not significantly different in patients with TFDR <2, 2-5 and >5 years. This observation also held in the three treatment groups separately. The best overall response for the three treatment groups can be found in the online-only supplements (Table S2).

TABLE 1 Baseline characteristics of 3462 advanced melanoma patients treated with first-line ICI or BRAF(/MEK) inhibitors between 2012 and 2020, based on TFDR categories <2 years, 2-5 years and > 5 years.

	<2 years (n = 1310)	2-5 years (n = 1018)	>5 years (n = 1134)	Total (n = 3462)
Age[a] (years)				
Median [IQR]	65.0 [54.0, 73.0]	62.0 [52.0, 71.0]	62.0 [53.0, 72.0]	63.0 [53.0, 72.0]
Missing	1	0	0	1
Sex				
Male	842 (64.3%)	617 (60.6%)	588 (51.9%)	2047 (59.1%)
Female	468 (35.7%)	401 (39.4%)	546 (48.1%)	1415 (40.9%)
Primary melanoma subtype				
Superficial spreading	576 (52.5%)	547 (64.5%)	599 (72.9%)	1722 (62.2%)
Nodular	409 (37.2%)	220 (25.9%)	146 (17.8%)	775 (28.0%)
Acral lentiginous	36 (3.3%)	18 (2.1%)	14 (1.7%)	68 (2.5%)
Lentigo maligna	22 (2.0%)	24 (2.8%)	15 (1.8%)	61 (2.2%)
Desmoplastic	13 (1.2%)	3 (0.4%)	2 (0.2%)	18 (0.7%)
Other	42 (3.8%)	36 (4.2%)	46 (5.6%)	124 (4.5%)
Missing	212	170	312	694
WHO performance status[a]				
WHO 0	643 (52.4%)	466 (50.0%)	484 (45.7%)	1593 (49.5%)
WHO 1	425 (34.7%)	344 (36.9%)	404 (38.2%)	1173 (36.5%)
WHO 2-4	158 (12.9%)	122 (13.1%)	170 (16.1%)	450 (14.0%)
Missing	84	86	76	246
Brain metastases[a]				
No	949 (74.6%)	626 (63.3%)	751 (68.5%)	2326 (69.3%)
Yes, not symptomatic	179 (14.1%)	159 (16.1%)	137 (12.5%)	475 (14.1%)
Yes, symptomatic	144 (11.3%)	204 (20.6%)	208 (19.0%)	556 (16.6%)
Missing	38	29	38	105
Liver metastases[a]				
No	826 (65.5%)	640 (64.6%)	762 (69.9%)	2228 (66.7%)
Yes	435 (34.5%)	350 (35.4%)	328 (30.1%)	1113 (33.3%)
Missing	49	28	44	121
BRAF V600 mutation[a]				
No	521 (40.8%)	349 (35.5%)	318 (28.9%)	1188 (35.4%)
Yes	756 (59.2%)	634 (64.5%)	782 (71.1%)	2172 (64.6%)
Missing	33	35	34	102
Stage of disease[a]				
IIIC	104 (8.0%)	35 (3.5%)	59 (5.2%)	198 (5.8%)
M1a	107 (8.3%)	59 (5.8%)	85 (7.5%)	251 (7.3%)
M1b	162 (12.5%)	101 (10.0%)	116 (10.3%)	379 (11.0%)
M1c	596 (46.1%)	455 (44.9%)	524 (46.4%)	1575 (45.9%)
M1d	323 (25.0%)	363 (35.8%)	345 (30.6%)	1031 (30.0%)
Missing	18	5	5	28
LDH levels[a]				
Not elevated	770 (60.0%)	578 (58.0%)	683 (60.9%)	2031 (59.7%)
1-2× ULN	335 (26.1%)	247 (24.8%)	282 (25.2%)	864 (25.4%)
>2× ULN	178 (13.9%)	172 (17.3%)	156 (13.9%)	506 (14.9%)
Missing	27	21	13	61

(Continues)

TABLE 1 (Continued)

	<2 years (n = 1310)	2-5 years (n = 1018)	>5 years (n = 1134)	Total (n = 3462)
Type of systemic therapy				
BRAF inhibitor	258 (19.7%)	215 (21.1%)	273 (24.1%)	746 (21.5%)
BRAF/MEK inhibitor	292 (22.3%)	268 (26.3%)	312 (27.5%)	872 (25.2%)
Anti-PD-1	576 (44.0%)	394 (38.7%)	391 (34.5%)	1361 (39.3%)
Ipilimumab + nivolumab	184 (14.0%)	141 (13.9%)	158 (13.9%)	483 (14.0%)
Time to first distant recurrence (years)				
Median [IQR]	0.8 [0.4, 1.4]	3.3 [2.6, 4.1]	8.8 [6.4, 13.3]	3.0 [1.2, 6.3]

Note: Stage of disease based on the eighth edition of the AJCC melanoma staging system.
Abbreviations: IQR, interquartile range; LDH, lactate dehydrogenase; ULN, upper limit of normal; WHO, World Health Organisation.
[a]Variables at start of systemic treatment.

TABLE 2 Objective response rate (defined as best overall response CR or PR) in % with 95% CI's for the three time to first distant recurrence (TFDR) groups, for the three treatment groups and all patients combined.

	ORR in % (95% CI) TFDR			
	<2 years	2-5 years	>5 years	*P*-value
BRAF/MEK inhibitor	48 (44-52)	44 (39-48)	51 (47-55)	.067
Anti-PD-1 antibody	51 (47-55)	53 (48-58)	54 (49-59)	.785
Ipilimumab + nivolumab	46 (39-53)	57 (49-65)	56 (48-64)	.072

3.3 | TFDR and survival

For first-line ICI-treated patients, the median PFS was 8.6 months (9.6 months for anti-PD-1; 6.0 months for ipilimumab-nivolumab treated patients). The median PFS for BRAF(/MEK) treated patients was 6.2 months. The median OS for ICI-treated patients was 29.2 months (anti-PD-1 group 29.5 months, ipilimumab-nivolumab group 24.3 months), with a 1-year survival probability of 69% (anti-PD-1 group 71%, ipilimumab-nivolumab group 62%). For the first-line BRAF (/MEK) treated patients, the median OS was 9.3 months with a 1-year survival probability of 41%.

Whereas we observed no significant difference in PFS between TFDR groups in the ICI-treated patients (Figure 2A, $P = .412$), we found a significant difference in median OS. In the group with a TFDR <2 years the median OS was 25.0 months, compared to 29.2 months for 2-5 years and 37.3 months for >5 years (Figure 2B, $P = .014$). In the BRAF(/MEK) treated patients, median PFS was significantly longer in the TFDR >5 years group (5.7 months, 5.8 months, and 7.3 months for TFDR <2, 2-5 and >5 years, respectively; Figure 2C, $P = .006$). Patients in this group also had a longer OS (8.6 months for TFDR<2 year, 8.1 months for 2-5 years, and 11.1 months for >5 years; Figure 2D, $P = .004$).

When analyzing TFDR as a categorical variable (<2, 2-5 or >5 years) for all systemically treated patients with adjusting for age and type of treatment, patients with a TFDR >5 year had a better PFS than patients with a TFDR <2 years (HR 0.89, 95% CI 0.81-0.98). The same association was found between TFDR and OS (HR 0.83, 95% CI 0.75-0.92).

When analyzing TFDR linearly as a continuous variable corrected for age and type of treatment in the overall cohort, a significant association with both PFS and OS was observed. Patients with a longer TFDR had a longer OS, with an HR of 0.93 with every TFDR increase of 5 years (95% CI 0.90-0.97). A similar, although less strong, association was observed between TFDR and PFS (HR of 0.96 with every TFDR increase of 5 years, 95% CI 0.93-0.99).

To further evaluate the exact nature of the relationship between TFDR and survival, we used restricted cubic spline models to assess the presence of a possible nonlinear association. Figure 3 shows the results of this analysis for PFS and OS. Compared to synchronous disease (a TFDR of zero, the reference), the hazard of dying rapidly decreased with increasing TFDR until approximately 5 years (HR 0.87), after which the hazard of dying further decreased with increasing TFDR, but less strongly (HR 0.82 for a TFDR of 10 years and HR 0.79 for a TFDR of 15 years). The hazard for progression or dying showed the same trend, with a HR of 0.96 at a TFDR of 5 years, decreasing to 0.89 at a TFDR of 10 years and 0.87 at a TFDR of 15 years. The shape of the association between TFDR and survival was similar for each treatment subgroup (Figure S1). Although we did not find statistical evidence that the models with restricted cubic splines were superior to linear models ($P = .423$ for PFS and $P = .181$ for OS), they do provide insight in the flattening association with increasing TFDR and survival.

In a sensitivity analysis, we analyzed patients with metachronous metastatic disease only, excluding patients who developed metastases within 3 months of their primary melanoma. In the metachronous metastasized group, the TFDR remained significantly associated with both PFS and OS (data not shown).

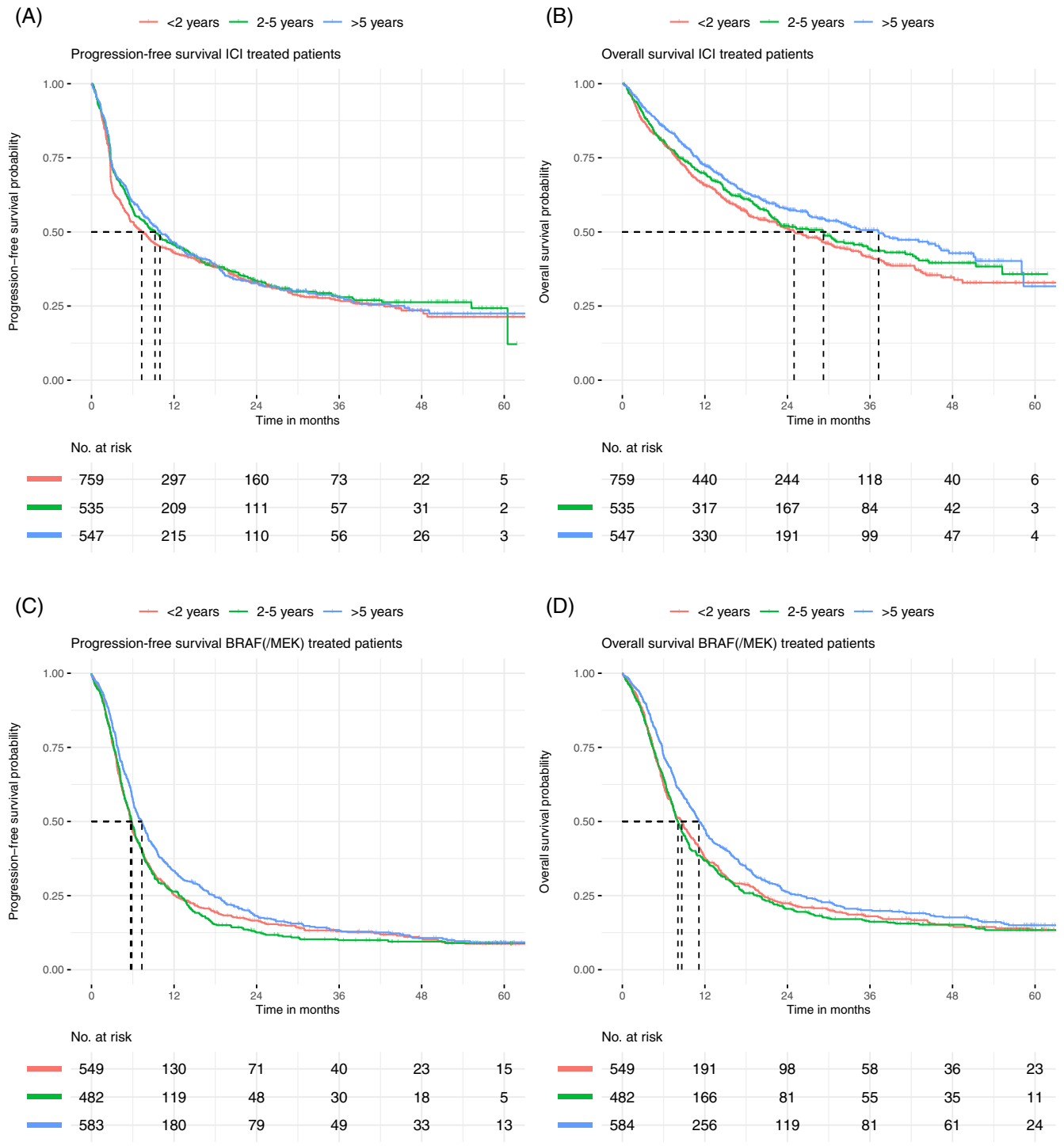

FIGURE 2 Kaplan-Meier curves for progression-free survival (A) and overall survival (B) in ICI treated patients, and progression-free survival (C) and overall survival (D) in BRAF(/MEK) treated patients, categorized by TFDR. (A) Logrank test between groups $P = .412$. Three patients were not included in this analysis because of missing PFS time. (B) Logrank test between groups $P = .014$. Three patients were not included in this analysis because of missing OS time. (C) Logrank test between groups $P = .006$. Four patients were not included in this analysis because of missing PFS time. (D) Logrank test between groups $P = .004$. Three patients were not included in this analysis because of missing PFS time. [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

In our study, we evaluated the association between TFDR and patient outcome in advanced melanoma patients. We found that a longer TFDR is significantly associated with better PFS and OS. With increasing TFDR, the prognosis improved as well. The hazard of progression and dying quickly decreased with increasing TFDR until a TFDR of approximately 5 years. After that, this hazard decreased further with increasing TFDR, but less strongly.

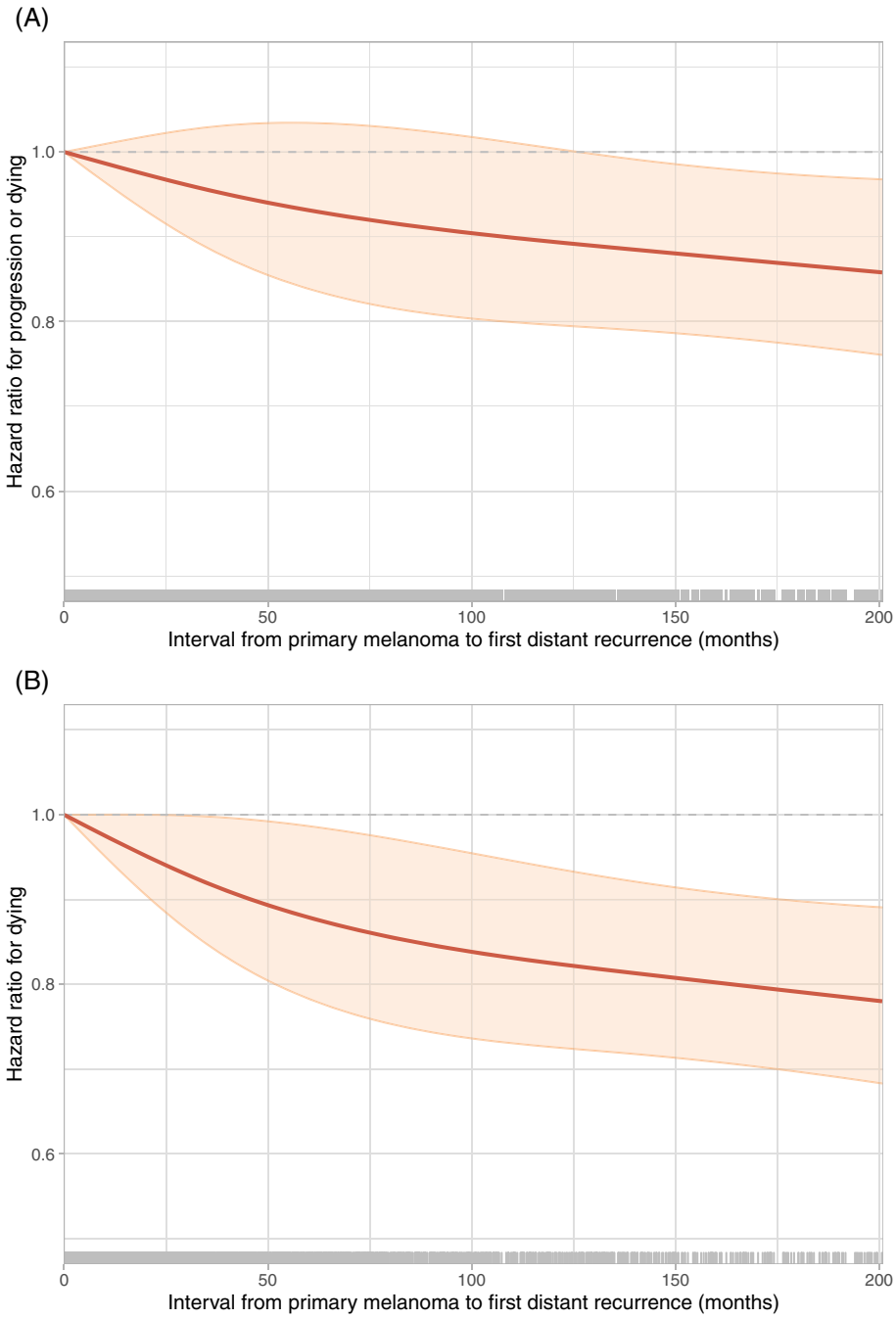

FIGURE 3 Restricted cubic spline model of TFDR (in months, adjusted for age and type of treatment) on PFS (A) and OS (B), reflecting hazard ratios with their 95% confidence intervals. TFDR of 0 months was taken as the reference. Below on the X-axis, the individual TFDR-data points are shown. [Color figure can be viewed at wileyonlinelibrary.com]

We showed that the association between TFDR and survival was similar in subgroup analysis when stratifying for treatment and is therefore unlikely to be treatment dependent. We also showed that the association is independent of the timing of metastatic disease: in a sensitivity analysis when excluding patients with synchronous metastases, the effect of TFDR on survival was still significant. Our study is the first study to show these effects in a large group of ICI and targeted therapy-treated melanoma patients.

Vallet et al previously analyzed the association between TFDR and outcomes in systemically treated advanced melanoma patients, including 274 ICI and 180 targeted therapy treated patients, and found a similar trend for PFS and OS. While analyzing all patients together, they found a nonsignificant trend for increased PFS (HR 0.62; 95% CI 0.47-1.01) and OS (HR 0.61; 95% CI 0.54-1.03).[17] Likewise, in a randomized trial of metastasectomy with or without vaccine therapy in 496 patients with stage IV melanoma, Faries et al found that patients with a longer time from primary diagnosis to randomization showed a trend toward longer survival (HR 0.36, 95% CI 0.10-1.30).[18] In our study, we were able to demonstrate this association was statistically significant, probably because of a larger sample size. Even when assessing ICI and targeted therapy patients separately, the relationship was still apparent.

A long TFDR reflects long metastatic dormancy which could be caused by effective immune surveillance.[10,19] Interestingly, in our analyses, we did not see a relevant difference between the ICI and targeted therapy cohorts' with respect to the association between ORR,

PFS and OS and TFDR. Furthermore, studies before the ICI and targeted therapy era did show an association with survival and a longer TFDR.[6-8] This underlines the assumption that the influence of TFDR on survival is independent of systemic treatment.

There are limitations to using observational data from a nationwide population-based registry. Some biases are inevitable, such as indication bias. This is, for example, reflected in the response rates in our study. Compared to clinical trials, ORR in anti-PD-1 treated patients in our study was better, which is probably explained by selection of patients with favorable characteristics. Contrarily, ORR in targeted therapy treated patients was worse than in the registration studies, which could be explained by the fact that in the real world targeted therapy is prescribed to patients with worse prognostic features.

5 | CONCLUSIONS

We found that advanced melanoma patients with longer TFDR have a prolonged PFS and OS, regardless of being treated with ICI or targeted therapy. TFDR may therefore be taken into consideration when estimating prognosis of advanced melanoma patients in clinical practice.

AUTHOR CONTRIBUTIONS

Conceptualization: Karijn Suijkerbuijk, Isabella van Duin. *Data curation*: Isabella van Duin. *Formal analysis*: Isabella van Duin, Sjoerd Elias, Rik Verheijden. *Methodology*: Isabella van Duin, Sjoerd Elias, Karijn Suijkerbuijk. *Writing—original draft*: Isabella van Duin. *Writing—review & editing*: Karijn Suijkerbuijk, Sjoerd Elias, Rik Verheijden, Alfonsus van den Eertwegh, Jan Willem de Groot, Willeke Blokx, Paul van Diest, Tim Leiner, Joost J.C. Verhoeff, Olivier van Not, Maureen Aarts, Franchette van den Berkmortel, Christian Blank, John Haanen, Geke Hospers, Anne Marleen Kamphuis, Djura Piersma, Rozemarijn S. van Rijn, Astrid A.M. van der Veldt, Gerard Vreugdenhil, Michel Wouters, Marion Stevense-den Boer, Marye J. Boers-Sonderen, Ellen Kapiteijn. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

FUNDING INFORMATION

For this work, no funding was granted. For the Dutch Melanoma Treatment Registry (DMTR), the Dutch Institute for Clinical Auditing foundation received a start-up grant from governmental organization The Netherlands Organization for Health Research and Development (ZonMW, project number 836002002). The DMTR is structurally funded by Bristol Myers Squibb, Merck Sharpe & Dohme, Novartis, and Roche Pharma. Roche Pharma stopped funding in 2019, and Pierre Fabre started funding the DMTR in 2019.

CONFLICT OF INTEREST STATEMENT

Dr Van den Eertwegh has advisory board relationships with Bristol Meyers Squibb, MSD Oncology, Amgen, Novartis, Sanofi, Pfizer, Ipsen, Merck, Pierre Fabre and has received research study grants from Sanofi, Roche, Bristol Myers Squibb, Idera and TEVA and has received travel expenses from MSD Oncology, Ipsen and Sanofi and has received speaker honoraria from Bristol Meyers Squibb and Novartis. Dr De Groot has advisory board relationships with BMS. Dr Aarts has advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, Bayer and received research grants from Merck-Pfizer and all were paid to the institution and not related to current work. Dr Leiner has received funding from Netherlands Organization for Health Research and Development. Dr Blank has received commercial research grants from Novartis, Bristol Myers Squibb, and NanoString; is a paid advisory board member for Bristol Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, GenMab, and Pierre Fabre; and holds ownership interest in Uniti Cars, Neon Therapeutics, and Forty Seven. Dr Haanen has advisory relationships with Achilles Therapeutics, BioNTech, BMS, CureVac, GSK, Imcyse, Immunocore, Instil Bio, Iovance Bio, MSD, Merck, Molecular Partners, Neogene Therapeutics, Novartis Pfizer, PokeAcell, Sanofi, Scenic T-knife, Third Rock Ventures and has received research grant support from Asher Bio, BioNTech, BMS, Amgen, MSD, Novartis. Dr Hospers has consultancy/advisory relationships with Amgen, Bristol Myers Squibb, Roche, MSD, Pfizer, Novartis, Sanofi and Pierre Fabre and has received research grants from Bristol Myers Squibb and Seerave and all were paid to the institution. Dr Piersma has received advisory board honoraria from BMS and Pierre Fabre, and the institution received advisory board honoraria from Novartis, BMS and Pierre Fabre. Dr Van der Veldt has consultancy relationships paid to institute with Bristol Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai, and Merck. Dr Suijkerbuijk has consulting/advisory relationships with Bristol Myers Squibb, Merck Sharp and Dome, Abbvie, Pierre Fabre Novartis, Sairopa, received honoraria from Novartis, Roche, Merck Sharp and Dome and received research funding from TigaTx, Bristol Myers Squibb and Philips and all were paid to institution and not related to the study. The remaining authors of this manuscript have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT

In compliance with Dutch regulations, the research using DMTR data was evaluated by the medical research ethics committee and was not considered subject to the Medical Research Involving Human Subjects Act. Patients were offered an opt-out option.

ORCID

Isabella A. J. van Duin https://orcid.org/0000-0002-9583-7115
Paul J. van Diest https://orcid.org/0000-0003-0658-2745

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: van Duin IAJ, Elias SG, van den Eertwegh AJM, et al. Time interval from primary melanoma to first distant recurrence in relation to patient outcomes in advanced melanoma. *Int J Cancer*. 2023;152(12):2493-2502. doi:10.1002/ijc.34479