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A prediction model for response to immune checkpoint inhibition in advanced melanoma

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Abstract

Predicting who will benefit from treatment with immune checkpoint inhibition (ICI) in patients with advanced melanoma is challenging. We developed a multivariable prediction model for response to ICI, using routinely available clinical data including primary melanoma characteristics. We used a population-based cohort of 3525 patients with advanced cutaneous melanoma treated with anti-PD-1-based therapy. Our prediction model for predicting response within 6 months after ICI initiation was internally validated with bootstrap resampling. Performance evaluation included calibration, discrimination and internal–external cross-validation. Included patients received anti-PD-1 monotherapy (n = 2366) or ipilimumab plus nivolumab (n = 1159) in any treatment line. The model included serum lactate dehydrogenase, World Health Organization performance score, type and line of ICI, disease stage and time to first distant recurrence—all at start of ICI—, and location and type of primary melanoma, the presence of satellites and/or in-transit metastases at primary diagnosis and sex. The over-optimism adjusted area under the receiver operating characteristic was 0.66 (95% CI: 0.64–0.66). The range of predicted response probabilities was 7%–81%. Based on these probabilities, patients were categorized into quartiles. Compared to the lowest response quartile, patients in the highest quartile had a significantly longer median progression-free survival (20.0 vs 2.8 months; $P < .001$) and median overall survival (62.0 vs 8.0 months; $P < .001$). Our prediction model, based on routinely available clinical variables and primary melanoma characteristics, predicts response to ICI in patients with advanced melanoma and discriminates well between treated patients with a very good and very poor prognosis.

KEYWORDS
immune checkpoint inhibition, immunotherapy, melanoma, prediction model, response prediction

What's new?

Only about half of patients with advanced melanoma respond to immune checkpoint inhibitor (ICI) therapy, but it is still difficult to predict which patients will benefit. Here, the authors present a prediction model for response to anti-PD-1-based therapy in patients with advanced melanoma. They based the model on characteristics of the primary melanoma and clinical variables from the metastatic setting that are readily available from routine clinical care. The model predicts response to ICI in patients with advanced melanoma and distinguishes well between patients with a very good and very poor prognosis.

1 | INTRODUCTION

Immune checkpoint inhibition (ICI) has tremendously improved the prognosis for patients with advanced melanoma in the last decade. For anti-PD-1 based treatment regimens, 5-year overall survival rates as high as >40% for monotherapy and >50% for combination with anti-CTLA-4 have been reported.[1]

Despite the overall improvements in survival, nearly half of advanced melanoma patients do not respond to ICI therapy.[2] However, they can still experience the potentially severe side effects.[3] Severe immune-related adverse events (irAEs) of anti-PD-1 therapy as a single agent occur in ~15% of patients, while more than half of patients treated with combination therapy with anti-CTLA-4 experience severe irAEs.[4] To add to that, ICI treatment costs are high, approaching 100,000 USD per quality-adjusted life year gained. This adds a substantial burden to the health care system.[5] Therefore, the search for potential biomarkers for response prediction has been extensive. Numerous clinical prognostic factors have been examined. For example, sex, World Health Organisation (WHO) performance score, serum lactate dehydrogenase and stage of disease have been shown to be associated with response.[6–8] Furthermore, the presence of symptomatic brain metastases is associated with a low response

rate.[9,10] Unfortunately, no single biomarker is currently available that can be confidently relied upon to predict ICI outcome for the majority of advanced melanoma patients.

Recent studies focused on developing prediction models with multiple clinical variables to predict outcome in melanoma patients receiving ICI.[11,12] To use readily available clinical factors could enhance implementation in clinical practice, since there are no extra costs in obtaining these variables. To add to that, previous literature has shown a correlation between primary melanoma characteristics, such as melanoma location and type, and response and survival in ICI treated patients with advanced disease.[13–15] These primary melanoma characteristics, which are also routinely evaluated as a part of standard medical care, can be effortlessly incorporated into a clinical prediction model along with clinical variables. To our knowledge, there has been no previous attempt to integrate all these available variables into a prediction model for evaluating the response to immunotherapy.

In this work, we aimed to develop and internally validate a prediction model for response to ICI in advanced melanoma patients. Candidate predictor variables were both routinely available clinical variables at initiation of ICI treatment and primary melanoma characteristics. This may aid in better identification of patients who have a low or a high chance of response.

2 | METHODS

2.1 | Patient cohort

In this cohort study, clinical data from the Dutch Melanoma Treatment Registry (DMTR) were used. The DMTR is a nationwide database in which data from all systemically treated advanced melanoma patients referred to designated melanoma centres in the Netherlands have been prospectively collected since 2012.[16] The DMTR encompasses clinical variables as well as primary melanoma characteristics are registered. The study was reported according to the TRIPOD guidelines.[17]

Patients who started treatment with anti-PD-1 therapy (either as monotherapy or in combination with anti-CTLA-4) from 2012 until March 31, 2022 were eligible. Inclusion criteria were unresectable stage III or stage IV cutaneous melanoma. Patients with mucosal melanoma and uveal melanoma were excluded because of their inherently different prognosis. Patients with an unknown primary tumour were also excluded because primary melanoma characteristics had our specific interest. For this study, the dataset cut-off date was September 1, 2022.

2.2 | Candidate predictor variables

Candidate predictors for the model were variables used in previous prediction models[11,12] and primary melanoma characteristics. Based on earlier research, we also added the presence of symptomatic brain metastases as a candidate predictor and incorporated this variable in stage of disease as a separate category.[9,10] The clinical predictor variables at start of ICI were age at start of ICI treatment, sex, intended type of therapy, having received previous systemic treatment, WHO performance status, presence of BRAF V600 mutation, lactate dehydrogenase (LDH) levels, stage of disease (based on the 8th edition of the AJCC melanoma staging system[18]), presence of symptomatic brain metastases, number of organs affected and time to first distant recurrence (TFDR). We incorporated the variable 'presence of symptomatic brain metastases' in the variable 'stage of disease': M1D stage was subcategorized either as 'M1D-non-symptomatic' or 'M1D-symptomatic'. The TFDR was defined as the time from diagnosis of the primary tumour to first detection of metastatic disease.[19] For primary melanoma characteristics, the following variables were included as candidate predictor variables: location, histological subtype, presence of ulceration, presence of satellites and/or intransit metastases (at time of primary diagnosis) and Breslow thickness.

2.3 | Patient outcomes

For the outcome assessment, real world evaluations of best response were used. Response evaluation was determined by the treating physician based on radiology reports, in line with the Response Evaluation Criteria in Solid Tumours, version 1.1.[20] Responses were defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD, including melanoma-related death before first response assessment). The primary endpoint of this study was overall response rate (ORR) at 6 months, defined as CR or PR as Best Overall Response (BOR) reached within 6 months of initiating therapy. Secondary endpoints were progression-free survival (PFS) and overall survival (OS). PFS was defined as time from start of ICI to progressive disease or death. OS was defined as the time from start of ICI to death from any cause. For patients who did not have a response registered, the outcome was labelled as missing. Patients were censored on the last date they were known to be alive without progression (for PFS) or alive (for OS).

2.4 | Statistical analysis

We used descriptive statistics to describe the study population. This included medians and interquartile intervals (IQI) for continuous variables, and percentages and frequencies for categorical variables. Follow-up data and patient outcomes were described using (reverse) Kaplan–Meier approaches.

Based on published recommendations,[21] we had sufficient data to model 27 candidate predictor parameters. Some variables are represented by more than one candidate predictor parameters, for example WHO performance status, which has three levels, thus accounting for two candidate predictor parameters. Continuous variables were modelled flexibly using restricted cubic splines to allow for non-linearity. Regarding the candidate predictor variables, 51% of patients had at least one missing candidate predictor variable. The total percentage of missing data among the entire dataset was 7%. We used multiple imputation using Substantive Model Compatible Fully Conditional Specification for every candidate predictor variable with missing data and for missing outcome data. The primary prediction model was

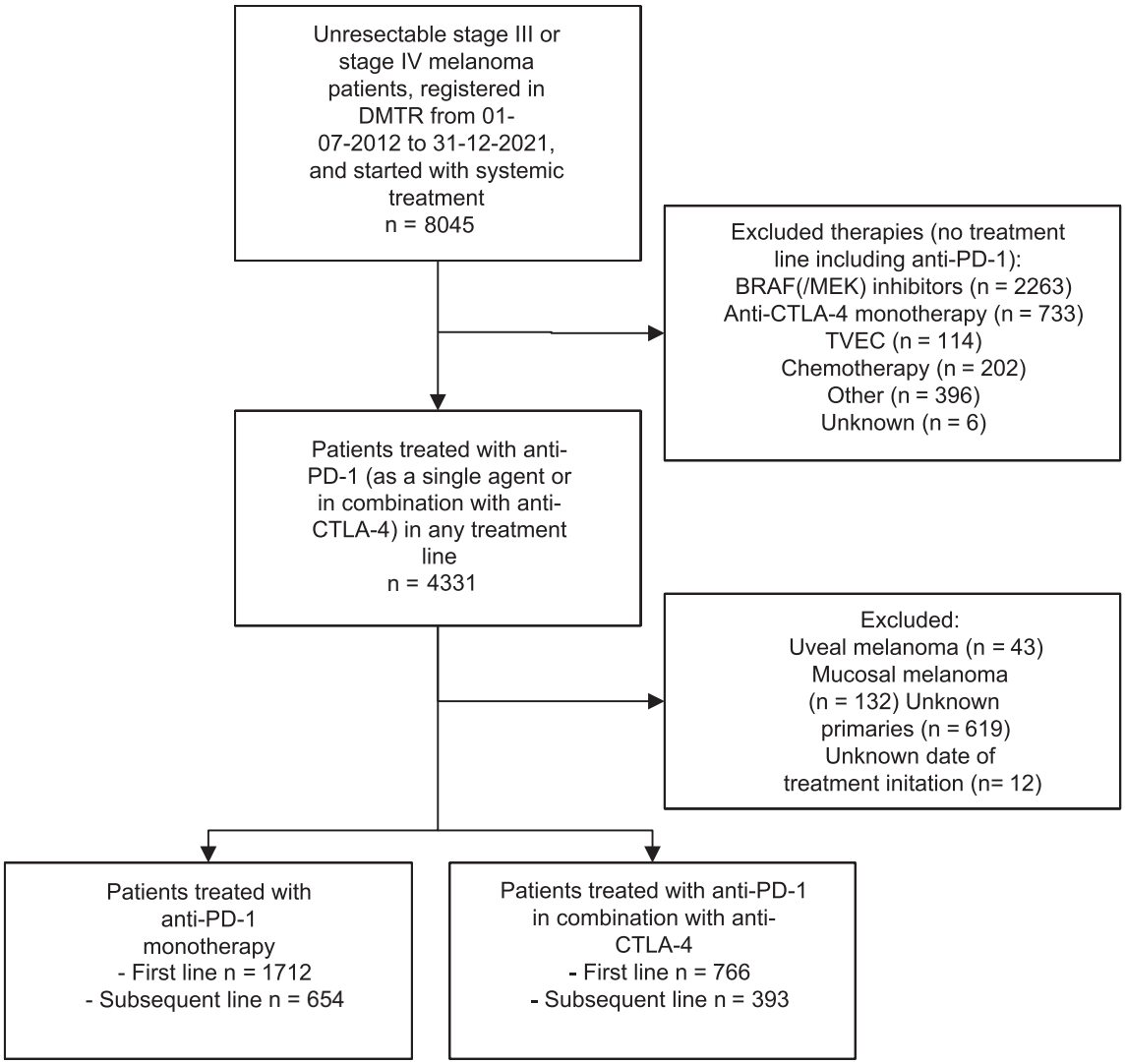

FIGURE 1 Flowchart of the study population. Anti-PD-1 + anti-CTLA4 was Ipilimumab + Nivolumab for all patients in this study.

developed in the whole cohort, using a logistic regression model with Akaike Information Criterion (AIC)-based backward selection in each imputed dataset leading to a model only including predictors selected in ≥50% of imputed datasets. We focused solely on the main effects of the variables of interest and did not consider any potential interactions. The model performance was assessed using a calibration plot, discrimination (area under the receiver operating characteristic [AUROC]) and a receiver operating characteristic (ROC) curve. To prevent over-optimism, we used internal validation by 500-fold bootstrap resampling, repeating all model development steps in each bootstrap sample, to obtain an overoptimism-corrected model and AUROC. In an additional analysis, patients were divided into three geographic regions (North, Middle and South of the Netherlands) based on the location of their melanoma treatment centre. We then used internal–external cross-validation including all modelling steps to evaluate the generalizability of model performance based on these regions.[22]

To further assess the model's potential prognostic relevance, we used Kaplan–Meier plots for PFS and OS, categorizing patients based on quartiles of the predicted probabilities for 6-months response. Logrank tests were used to assess differences in PFS and OS between these groups. To show how the model predicts the probability of the outcome in different clinical situations, we used the final model to calculate the probabilities of 6-months response for three different, hypothetical patients.

A more detailed explanation of the used methods is described in Data S1. Analyses were performed using R version 4.2.2 with the following libraries: rms (V6.3.0), survival (V3.5.0), smcfcs (V1.7.1) and mice (V3.15.0).

3 | RESULTS

3.1 | Patient characteristics

A total of 3525 patients were included in this study. Exactly 2366 patients were treated with anti-PD-1 monotherapy, and 1159 with

TABLE 1 Patient characteristics of 3525 Dutch advanced melanoma patients treated with ICI between 2012 and 2022, divided in three geographic regions of the Netherlands: North (n = 657), Middle (n = 2014) and South (n = 854).

	North (N = 657)	Middle (N = 2014)	South (N = 854)	Total (N = 3525)
Age[a] (years)				
Median [IQI]	66.0 [55.5, 74.4]	64.9 [54.9, 73.9]	65.4 [54.7, 73.5]	65.1 [54.9, 73.9]
Sex				
Male	388 (59.1%)	1200 (59.6%)	527 (61.8%)	2115 (60.0%)
Female	269 (40.9%)	814 (40.4%)	326 (38.2%)	1409 (40.0%)
Missing	0	0	1	1
WHO performance status[a]				
WHO 0	374 (60.9%)	1067 (56.9%)	371 (45.7%)	1812 (54.9%)
WHO 1	190 (30.9%)	672 (35.8%)	400 (49.3%)	1262 (38.2%)
WHO 2–4	50 (8.1%)	137 (7.3%)	41 (5.0%)	228 (6.9%)
Missing	43	138	42	223
LDH levels[a]				
Not elevated	430 (67.3%)	1379 (69.5%)	565 (67.5%)	2374 (68.6%)
1–2× ULN	160 (25.0%)	463 (23.3%)	207 (24.7%)	830 (24.0%)
>2× ULN	49 (7.7%)	142 (7.2%)	65 (7.8%)	256 (7.4%)
Missing	18	30	17	65
BRAF V600 mutation[a]				
Wildtype	302 (50.3%)	917 (53.2%)	430 (57.0%)	1649 (53.6%)
Mutant	298 (49.7%)	806 (46.8%)	325 (43.0%)	1429 (46.4%)
Missing	57	291	99	447
Stage of disease[a]				
IIIC	62 (9.7%)	244 (12.5%)	74 (9.3%)	380 (11.2%)
M1a	52 (8.2%)	134 (6.9%)	58 (7.3%)	244 (7.2%)
M1b	64 (10.0%)	245 (12.6%)	111 (13.9%)	420 (12.4%)
M1c	249 (39.0%)	774 (39.8%)	365 (45.7%)	1388 (41.0%)
M1d—non-symptomatic	124 (19.4%)	344 (17.7%)	119 (14.9%)	587 (17.4%)
M1d—symptomatic	87 (13.6%)	206 (10.6%)	71 (8.9%)	364 (10.8%)
Missing	19	67	56	142
Time to first distant recurrence (years)[a]				
Median [IQI]	2.75 [0.95, 6.34]	3.01 [1.09, 6.31]	2.71 [1.04, 6.02]	2.87 [1.05, 6.23]
Missing	1	4	4	9
Type of systemic therapy[a]				
Anti-PD-1	447 (68.0%)	1340 (66.5%)	579 (67.8%)	2366 (67.1%)
Ipilimumab + Nivolumab	210 (32.0%)	674 (33.5%)	275 (32.2%)	1159 (32.9%)
Number of organs affected[a]				
Median [IQI]	2 [1, 4]	2 [1, 3]	2 [1, 4]	2 [1, 4]
Missing	47	166	80	293
Line of first systemic ICI therapy for advanced melanoma[a]				
First-line	435 (66.2%)	1459 (72.4%)	584 (68.4%)	2478 (70.3%)
Not first-line	222 (33.8%)	555 (27.6%)	270 (31.6%)	1047 (29.7%)
Location of primary melanoma				
Head and neck	91 (14.0%)	354 (17.8%)	129 (15.2%)	574 (16.5%)
Trunk	318 (48.8%)	909 (45.8%)	418 (49.2%)	1645 (47.2%)
Extremities	219 (33.6%)	653 (32.9%)	262 (30.8%)	1134 (32.5%)

(Continues)

TABLE 1 (Continued)

	North (N = 657)	Middle (N = 2014)	South (N = 854)	Total (N = 3525)
Acral	24 (3.7%)	70 (3.5%)	41 (4.8%)	135 (3.9%)
Missing	5	28	4	37
Type of primary melanoma				
Superficial spreading	341 (65.8%)	937 (58.5%)	428 (62.1%)	1706 (60.7%)
Nodular	142 (27.4%)	479 (29.9%)	187 (27.1%)	808 (28.8%)
Acral lentiginous	10 (1.9%)	52 (3.2%)	23 (3.3%)	85 (3.0%)
Lentigo maligna	10 (1.9%)	47 (2.9%)	17 (2.5%)	74 (2.6%)
Desmoplastic	4 (0.8%)	14 (0.9%)	5 (0.7%)	23 (0.8%)
Other	11 (2.1%)	74 (4.6%)	29 (4.2%)	114 (4.1%)
Missing	139	411	165	715
Ulceration of primary melanoma				
No	292 (57.1%)	983 (60.9%)	386 (58.8%)	1661 (59.7%)
Yes	219 (42.9%)	632 (39.1%)	270 (41.2%)	1121 (40.3%)
Missing	146	399	198	743
Satellites/in transit metastases				
No	461 (87.6%)	1554 (90.0%)	589 (88.4%)	2604 (89.2%)
Yes	65 (12.4%)	172 (10.0%)	77 (11.6%)	314 (10.8%)
Missing	131	288	188	607
Breslow thickness (mm)				
Median [Q1, Q3]	2.50 [1.50, 4.30]	2.40 [1.40, 4.10]	2.40 [1.30, 4.20]	2.40 [1.40, 4.20]
Missing	75	261	91	427

Note: Stage of disease: M1a = distant metastasis to skin, soft tissue and/or nonregional lymph node, M1b = Distant metastasis to lung with or without M1a sites, M1c = Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites, M1d = distant metastasis to CNS with or without M1a, M1b or M1c sites.

Abbreviations: IQI, interquartile interval; LDH, lactate dehydrogenase; mm, millimetre; ULN, upper limit of normal; WHO, World Health Organisation.

[a]Variables at start of systemic treatment.

combination therapy (Ipilimumab and Nivolumab). A flowchart of the study population is shown in Figure 1. An overview of the number of patients included from the individual years based upon type of therapy and BRAF mutant status is shown in Table S1. Patient characteristics divided by geographical region in the Netherlands are depicted in Table 1, and the distribution of patient characteristics after imputation is shown in Table S2. Overall, the median age was 65 years and 40.0% were females. Most patients had normal LDH levels (68.6%), did not have brain metastases (71.8%) and were treated in first line (70.3%). The most common location of the primary melanoma was the trunk (47.2%), and superficial spreading was the most common histological subtype of primary melanoma (60.7%). Most patients did not have satellites and/or in-transit metastases at diagnosis of their primary tumour (89.2%). Tables S3 and S4 show that patients had generally unfavourable patient characteristics in the Ipilimumab–Nivolumab treated group (compared to anti-PD-1 monotherapy), and if they had received ICI in a subsequent line (compared to first-line), reflected in higher stage of disease, higher levels of LDH and higher WHO performance status.

3.2 | Patient outcomes

The primary endpoint was available for 3414 patients. For 111 patients, no follow-up data was available. In 1562 patients a CR or PR was observed within 6 months after start of treatment, resulting in an observed 46% overall response rate at 6 months in the overall cohort. The overall observed response rate at 6 months was 47% in the anti-PD-1 monotherapy group, and 43% in the combination treatment group. The median follow-up was 36 months. The median PFS was 6.4 months, and the median OS was 24.9 months.

3.3 | Model for overall response rate at 6 months

After AIC-informed backward selection, the final model included 10 out of 15 candidate predictor variables: sex, LDH level, WHO performance status, type of systemic therapy, first-line systemic therapy, stage of disease (including presence of symptomatic brain metastases), location of primary melanoma, type of primary melanoma, satellites and/or in-transit metastases, and time to first distant recurrence. The

TABLE 2 Specifications of the multivariable prediction model for overall response at 6 months.

		Selected model		
Variable	**Level**	**OR (95% CI)**	***P*-value**	**Shrunk OR**
Sex	Male	REF	.086	
	Female	1.14 [0.98–1.33]		1.13
LDH level	Not elevated	REF	<.005	
	Elevated (1–2× ULN)	0.88 [0.74–1.04]		0.89
	Elevated (≥2× ULN)	0.49 [0.36–0.67]		0.52
WHO performance score	WHO 0	REF	<.005	
	WHO 1	0.73 [0.62–0.85]		0.75
	WHO 2–4	0.47 [0.34–0.65]		0.50
Type of systemic therapy	Anti-PD-1-based	REF	.054	
	Ipilimumab/nivolumab	1.18 [1.00–1.40]		1.16
First-line systemic therapy	Yes	REF		
	No	0.53 [0.45–0.63]		0.56
Stage of disease	Irresectable IIIC	REF	<.005	
	M1a	0.74 [0.53–1.04]		0.76
	M1b	0.67 [0.50–0.90]		0.70
	M1c	0.45 [0.35–0.58]		0.48
	M1d—not symptomatic	0.41 [0.31–0.56]		0.45
	M1d—symptomatic	0.33 [0.24–0.46]		0.36
Location of primary melanoma	Trunk	REF	.007	
	Head and neck	1.28 [1.04–1.59]		1.25
	Extremities	1.03 [0.87–1.21]		1.02
	Acral	0.47 [0.25–0.89]		0.51
Type of primary melanoma	Superficial spreading	REF	.275	
	Nodular	1.17 [0.98–1.40]		1.16
	Acral lentiginous	0.92 [0.39–2.20]		0.93
	Lentigo maligna	1.62 [0.97–2.71]		1.55
	Desmoplastic	0.92 [0.39–2.20]		0.93
	Other	0.86 [0.56–1.34]		0.87
Satellites and/or intransit-metastases	No	REF	.127	
	Yes	0.82 [0.63–1.06]		0.83
Time to first distant recurrence		Non-linear [>1]	.025	Non-linear

Note: Specifications of the pooled selected model. For the pooled model, the model odds ratios and the overfitting-adjusted odds ratio's (shrunk) are shown. The apparent model odds ratio's and the overfitting-adjusted odds ratio's (shrunken) are shown ($\beta_{\text{adjusted}} = \beta_{\text{unadjusted}} \times$ shrinkage factor obtained via bootstrapping during internal validation). Multivariable Wald D1 *P*-values are shown. TFDR, as a continuous variable, was modelled non-linearly using restricted cubic splines, for which the odds ratios are shown in Figure S1. A general direction of the effect for this variable is shown in brackets.
Abbreviations: LDH, lactate dehydrogenase; TFDR, time to first distant recurrence; WHO, World Health Organization.

OR's of the model are shown in Table 2 (the non-linear plot for TFDR, the only included continuous variable, is shown in Figure S1).

3.4 | Performance and validation of model

The performance of the prediction model was assessed by calibration and discrimination. The estimated and observed probabilities for response at 6 months were well-calibrated (Figure 2A). For discrimination, the AUROC was 0.670 (95% CI: 0.651–0.688). The shrinkage factor obtained through internal validation was 0.91. The shrunken ORs shown in Table S5. The estimated optimism-adjusted AUROC was 0.657 (95% CI: 0.639–0.675). This resulted in a ROC curve as depicted in Figure 2B. Following shrinkage, the model generated predictions of the probability of achieving response at 6 months. The range of these probabilities was 7%–81% (interquartile interval [IQI] 36%–55%).

The predictive performance of the model was comparable in subgroups of patients treated with monotherapy and combination

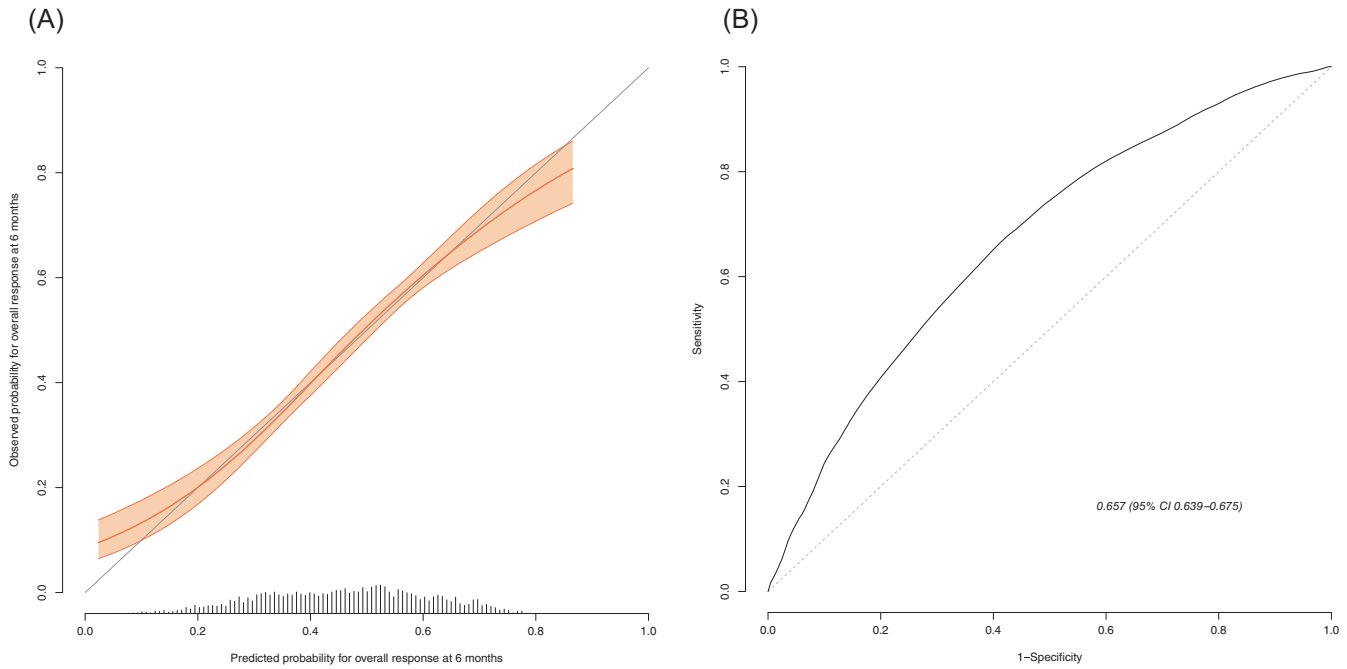

FIGURE 2 (A) Calibration plot for the predicted overall response at 6 months apparent probabilities versus the observed probability for overall response at 6 months are shown, with the 95% confidence interval band. The apparent performance is shown, before internal validation. The histogram shows the distribution of the predicted probabilities. (B) Receiver operating characteristic (ROC) curve with AUROC (and 95% CI) for predicting overall response at 6 months.

therapy, in subgroups of patients who were treated with targeted therapy in a previous line and who had not received targeted therapy, and in subgroups of patients who had received ICI in the neoadjuvant or adjuvant setting and who were naive to ICI-treatment. The AUROC's and corresponding ROC curves for these subgroups are shown in Figure S2.

Based on quartiles, patients were categorized in predicted very low response (probability <36%), predicted low response (probability 36%–45%), predicted intermediate response (probability 46%–54%) and predicted good response (probability >54%). The median predicted response probability was 30% (IQR 25%–33%) for the lowest quartile and 62% (IQR 58%–66%) for the highest quartile.

Based on these defined subgroups of response, the model was able to discriminate well for PFS (logrank test between groups $P < .0001$) and OS (logrank test between groups $P < .0001$) (Figure 3). After stratifying for line of treatment, the model demonstrated consistent capability in discriminating for PFS and overall survival OS (Figure S3).

The model was further validated for generalizability by internal–external cross-validation based on three geographical regions. The models developed with data from the other regions had adequate performance in each left-out region (AUROCs with 95% CIs and calibration plots are shown in Table S6 and Figure S4). To add to that, based on subgroups of response, the models were able to discriminate for PFS (logrank test between groups $P < .0001$) and OS (logrank test between groups $P < .0001$) in all the left-out regions (Figures S5–S7).

In Appendix S1, the full model specifications and the model's formula can be found, to calculate the predicted response for individual patients. In Box 1, clinical utility of the model is shown by giving three patient examples.

4 | DISCUSSION

In this study, we developed a clinical prediction model for response to ICI using readily available clinical variables, including primary melanoma characteristics. We chose 6 months OR as the primary outcome, since response has been shown to be strongly related to long term survival.[23] Response can be meaningfully predicted with our model by leveraging readily available predictors that are routinely obtained through clinical care. The range of predicted response probabilities was 7%–81% (IQI 36%–55%). The expected generalizability of the model is good. Our response prediction model can discriminate clinically relevant differences in response probabilities, reflected in significant different PFS and OS.

Previous studies demonstrated that response to ICI in advanced melanoma patients can be predicted with clinical variables. Nosrati et al developed a model in which LDH, age, sex, previous therapy and presence of liver metastases were included.[12] This model reached an AUROC of 0.70 after internal validation. However, when this prediction model was externally validated using data from our registry as an independent cohort, the predictive value could not be confirmed (with an AUROC of 0.55).[24] Pires da Silva et al presented a clinical model which predicted ORR, PFS and OS.[11] Their prediction model for ORR included, amongst others, WHO performance status, LDH, presence of liver and lung metastases, treatment type and line of treatment. The model had a good performance in their external validation cohort with an AUROC of 0.67. After adjustment for over-optimism, the performance of our model was comparable. However, because of up to 47% of missings per variable in their data, primary melanoma

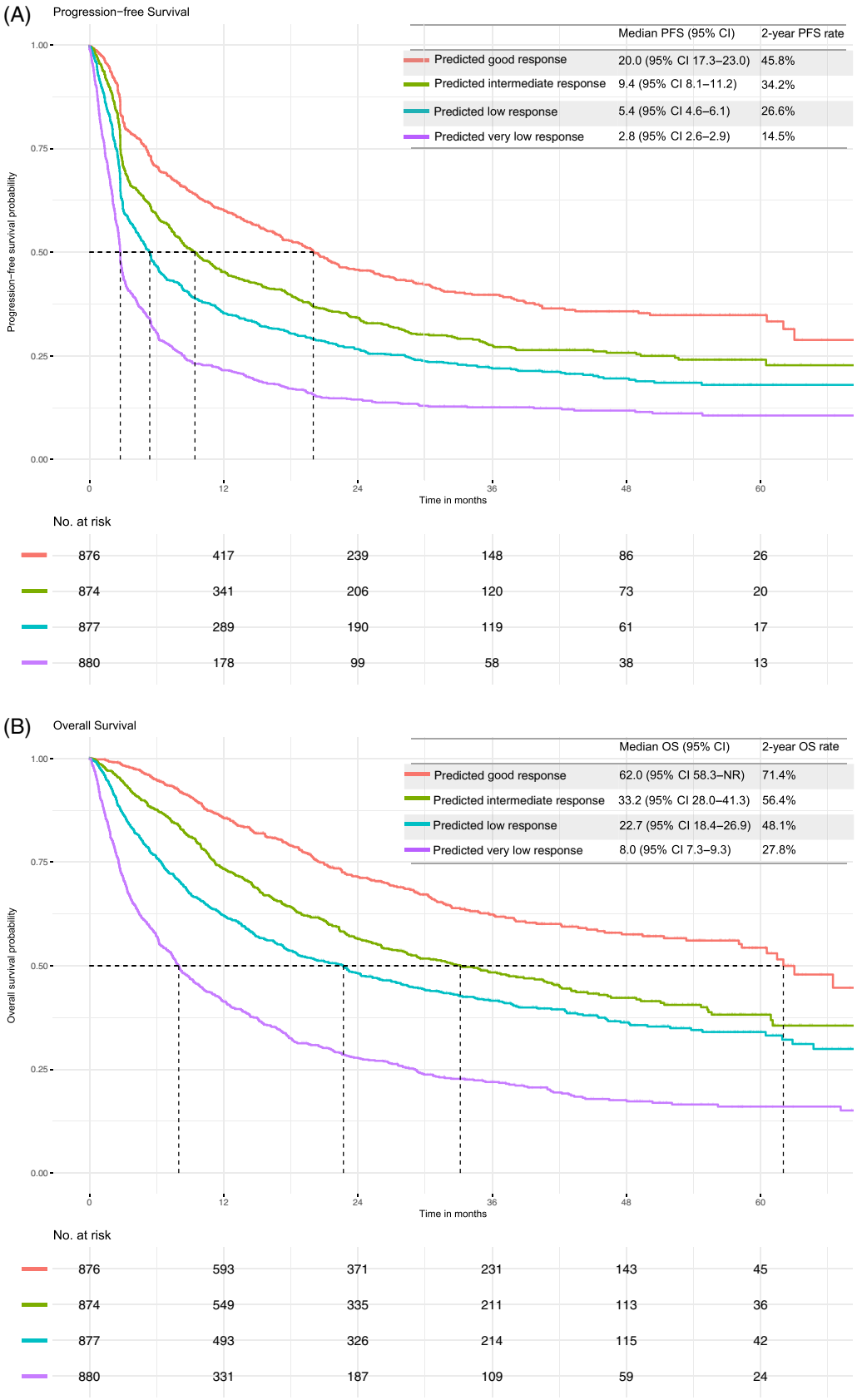

FIGURE 3 (A,B) Kaplan–Meier plots for progression-free survival (A) and overall survival (B) according to quartiles of predicted response groups (very low, low, intermediate and good). Logrank test between groups $P < .0001$ (PFS) and $P < .0001$ (OS). Exactly 18 patients were not included in this analysis because of missing survival time. Median PFS time, median OS time and 2-year PFS rate and OS are shown. CI, confidence interval; NR, not reached.

BOX 1 Clinical utility of the model: Three patient examples

Below, we describe three patients. With these examples, we show how the model predicts the probability of response to ICI at 6 months after treatment initiation in different clinical situations. The calculations for each patient can be found in Appendix S1.

Patient A, an 83-year-old woman, is referred to the outpatient clinic with a hepatic mass, shown to be metastatic melanoma by tissue biopsy. Her history reveals a superficial spreading melanoma on the trunk which was surgically removed 15 years ago. She has a WHO performance status of 1, and her serum LDH is 345 U/L. The brain MRI scan shows no brain metastases. Her physician suggests first-line treatment with anti-PD-1 monotherapy. The model predicts a probability for response to treatment of 44%.

Patient B, a 54-year-old man, has a history of an acral lentiginous melanoma on his left palm 2 years ago, with an in-transit metastasis which was surgically removed. Now, he presents to the ER with seizures and a mild left hemiparesis. He used to swim three times a week, but recently he has been feeling unwell, and spends most of his time in bed, so his WHO performance status is 2. His computed tomography (CT) scan shows bulky lymph node metastases, and the MRI reveals multiple brain metastases. His LDH is 761 U/L. His treating physicians suggests to start combination treatment with Ipilimumab and Nivolumab. For this patient, the predicted chance of responding to therapy is 8%.

Patient C, a 48-year-old woman, has had a dry cough for several months without other complaints. She is referred to the outpatient clinic after an x-ray of the chest, which showed pulmonary abnormalities. Eight years ago, a dermatologist removed a nodular melanoma located on her neck. A CT scan of the lungs reveals several lung lesions, a biopsy showing melanoma metastases. She has a WHO performance status of 0. Laboratory results show a normal serum LDH. Her oncologist discusses Ipilimumab plus Nivolumab with her. The predicted probability of response for this patient is 75%.

characteristics were not included in their model. As primary melanoma characteristics are available in routine care for cutaneous melanoma patients, we incorporated them in our model. The performances of our model and the model from Pires da Silva et al are comparable in terms of AUROC, probably because they included Hb and neutrophil–lymphocyte ratio in their model. In our cohort these data were not available, which might (especially for neutrophil–lymphocyte ratio) be the case for more patients in standard clinical practice. Both models display similar abilities to predict a subset of patients with a lower response to immune checkpoint inhibitors (ICI). In our model, the subgroup predicted to have a very low response had a median response rate of 30%. In Pires da Silva's model, the group predicted to have a poor response had an ORR of 31%–33% in their validation cohorts.

In line with previous models, our model included, LDH, sex, type of therapy and previous therapy. The direction of the effects of these variables was the same. Also, having received previous therapy and level of LDH emerged as robust predictors in our model, aligning with findings from previous models. Furthermore, our model included stage of disease, while the two other models included location of metastasis, which are largely overlapping variables. In conclusion, these variables seem to be reproducibly contributing to predicting response to ICI in advanced melanoma patients.

A strength of our study is that our prediction model for response was developed in a cohort of patients from a nationwide population-based registry, encompassing all 14 academic and regional hospitals treating advanced melanoma patients in the country, and is thus representative for a general advanced melanoma population undergoing ICI treatment. Furthermore, we are the first to develop a predictive model incorporating primary melanoma characteristics as predictive factors for response to ICI. As expected, this addition led to substantial percentage of missing data (with a maximum of 21% missings per variable) which we handled by multiple imputation. In the final model, location of primary melanoma, primary melanoma type and presence of satellites and/or in-transit metastases were selected as predictor variables. Also, TFDR was included in the final model, a variable for which we recently demonstrated to be is associated with survival in ICI-treated advanced melanoma patients.[19]

Our study has several limitations. First, using observational data from a nationwide cohort leads inevitably to indication bias. This is, for example, reflected in the response rates in our study. Compared to clinical trials, the ORR in anti-PD-1 treated patients in our study was better, which is probably explained by selection of patients with favourable characteristics. Second, we did not have access to laboratory values other than LDH level. In the prediction model from Pires da Silva, neutrophil–lymphocyte ratio at start of treatment was one of the variables with strongest predictive value. Adding other laboratory values as candidate predictors could further enhance the performance of our model. Third, we were unable to externally validate our prediction model beyond the internal–external cross-validation. This was due to the absence of an entirely external cohort and the number of candidate predictors regarding sample size calculations. The fact that our dataset was limited in size was also why we solely focused on the main effects of the variables of interests. Although it is a nationwide study encompassing several years, the number of events was too small to add more candidate predictor parameters and interaction terms. We carefully selected the chosen predictors, however, it is possible that a model with interactions and other predictors could achieve a better performance.

The performance of our model could be further improved by including additional promising predictor variables, which may better identify patients who will respond to ICI. Examples include histopathological features such as tumour infiltrating lymphocytes or features from baseline radiological imaging. In the future, combining features from different modalities, including clinical variables and primary melanoma characteristics, may lead to better predictions for response to ICI. In the clinical setting, if a patient would have a high predicted probability of not responding to ICI, a different treatment option could be considered.

5 | CONCLUSION

We present a model based on both clinical variables and primary melanoma characteristics capable of predicting response to ICI in patients with advanced melanoma. Our model can discriminate between treated patients with a very good and very poor prognosis. After further external validation, the response prediction model might offer guidance in shared decision-making regarding ICI in patients with advanced melanoma.

AUTHOR CONTRIBUTIONS

Isabella A. J. van Duin: Conceptualization; data curation; formal analysis; methodology; writing – original draft. **Rik J. Verheijden:** Data curation; formal analysis; methodology; writing – review and editing. **Paul J. van Diest:** Writing – review and editing. **Willeke A. M. Blokx:** Writing – review and editing. **Mary-Ann El-Sharouni:** Writing – review and editing. **Joost J. C. Verhoeff:** Writing – review and editing. **Tim Leiner:** Writing – review and editing. **Alfonsus J. M. van den Eertwegh:** Writing – review and editing. **Jan Willem B. de Groot:** Writing – review and editing. **Olivier J. van Not:** Writing – review and editing. **Maureen J. B. Aarts:** Writing – review and editing. **Franchette W. P. J. van den Berkmortel:** Writing – review and editing. **Christian U. Blank:** Writing – review and editing. **John B. A. G. Haanen:** Writing – review and editing. **Geke A. P. Hospers:** Writing – review and editing. **Djura Piersma:** Writing – review and editing. **Rozemarijn S. van Rijn:** Writing – review and editing. **Astrid A. M. van der Veldt:** Writing – review and editing. **Gerard Vreugdenhil:** Writing – review and editing. **Michel W. J. M. Wouters:** Writing – review and editing. **Marion A. M. Stevense-den Boer:** Writing – review and editing. **Marye J. Boers-Sonderen:** Writing – review and editing. **Ellen Kapiteijn:** Writing – review and editing. **Karijn P. M. Suijkerbuijk:** Conceptualization; methodology; writing – review and editing. **Sjoerd G. Elias:** Conceptualization; formal analysis; methodology; writing – review and editing. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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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. Leiner has received funding from Netherlands Organization for Health Research and Development.

Dr. Blank has a potential financial conflict as follows: Bristol Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Eli Lilly, Genmab, Pierre Fabre, Third-Rock Ventures, Immagine BV, Signature Oncology, IDEAYA.

Dr. Haanen has advisory relationships with Astra Zeneca, BioNTech, Bristol Myers Squibb, CureVac, Eisai, MSD, Neogene Tx, Iovance Bio, Instil Bio, Novartis, Roche, Sanofi, T-knife, Sastra Cell Therapy.

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. Van der Veldt has consultancy relationships paid to institute with Bristol Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai.

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.

Dr. van Diest has consulting/advisory relationships paid to the institute with Sectra, Paige.AI and Visiopharm, and received research funding from Pfizer paid to the institution and not related to the study.

The remaining authors of this article have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this 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.

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SUPPORTING INFORMATION

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

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