Clinical Models to Define Response and Survival With Anti-PD-1 Antibodies Alone or Combined With Ipilimumab in Metastatic Melanoma

DOI: 10.1200/JCO.21.01701

Document Version
Final published version

Link to publication record in Manchester Research Explorer

Citation for published version (APA):

Published in:
Journal of clinical oncology : official journal of the American Society of Clinical Oncology

Citing this paper
Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights
Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy
If you believe that this document breaches copyright please refer to the University of Manchester’s Takedown Procedures [http://man.ac.uk/04Y6Bo] or contact umr.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.
Clinical Models to Define Response and Survival With Anti–PD-1 Antibodies Alone or Combined With Ipilimumab in Metastatic Melanoma

Inês Pires da Silva, MD, PhD1,2,3; Tasnia Ahmed, MSc1; Jennifer L. McGuade, MD, PhD4; Caroline A. Nebhan, MD5; John J. Park, MD6; Judith M. Versluis, MD2; Patricio Serra-Bellver, MD6; Yasir Khan, MD6; Tim Slattery, MD4; Honey K. Obenrai, MD10; Selma Ugurel, MD11; Lauren E. Haydu, MD, PhD5; Rudolf Herbst, MD12; Jochen Utikal, MD13,14; Claudia Pföhler, MD13; Patrick Terheyden, MD14; Michael Weichenthal, MD15; Ralf Gutzmer, MD15; Peter Mohr, MD15; Rajat Rai, MD1; Jessica L. Smith, MD1; Richard A. Scolyer, MD1,2,21; Ana M. Arance, MD, PhD22; Lisa Pickering, MD, PhD4; James Larkin, MD, PhD9; Paul Lorigan, MD8,22; Christian U. Blank, MD, PhD7; Dirk Schadendorf, MD, PhD11; Michael A. Davies, MD, PhD4; Matteo S. Carlino, MD, PhD1,3; Douglas B. Johnson, MD5; Georgina V. Long, MD, PhD1,2,23; Serigne N. Lo, PhD1; and Alexander M. Menzies, MD, PhD1,23

PURPOSE Currently, there are no robust biomarkers that predict immunotherapy outcomes in metastatic melanoma. We sought to build multivariable predictive models for response and survival to anti-programmed cell death protein 1 (anti–PD-1) monotherapy or in combination with anticytotoxic T-cell lymphocyte-4 (ipilimumab [IPI]; anti–PD-1 ± IPI) by including routine clinical data available at the point of treatment initiation.

METHODS One thousand six hundred forty-four patients with metastatic melanoma treated with anti–PD-1 ± IPI at 16 centers from Australia, the United States, and Europe were included. Demographics, disease characteristics, and baseline blood parameters were analyzed. The end points of this study were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The final predictive models for ORR, PFS, and OS were determined through penalized regression methodology (least absolute shrinkage and selection operator method) to select the most significant predictors for all three outcomes (discovery cohort, N = 633). Each model was validated internally and externally in two independent cohorts (validation-1 [N = 419] and validation-2 [N = 592]) and nomograms were created.

RESULTS The final model for predicting ORR (area under the curve [AUC] = 0.71) in immunotherapy-treated patients included the following clinical parameters: Eastern Cooperative Oncology Group Performance Status, presence/absence of liver and lung metastases, serum lactate dehydrogenase, blood neutrophil-lymphocyte ratio, therapy (monotherapy/combination), and line of treatment. The final predictive models for PFS (AUC = 0.68) and OS (AUC = 0.77) included the same variables as those in the ORR model (except for presence/absence of lung metastases), and included presence/absence of brain metastases and blood hemoglobin. Nomogram calculators were developed from the clinical models to predict outcomes for patients with metastatic melanoma treated with anti–PD-1 ± IPI.

CONCLUSION Newly developed combinations of routinely collected baseline clinical factors predict the response and survival outcomes of patients with metastatic melanoma treated with immunotherapy and may serve as valuable tools for clinical decision making.

J Clin Oncol 40:1068-1080. © 2022 by American Society of Clinical Oncology

INTRODUCTION Treatment with immune checkpoint inhibitors improves survival, with long-term durable control of melanoma in a large subset of patients with metastatic disease. However, the highest 5-year overall survival (OS) is currently 52% with the combination of ipilimumab (IPI) and nivolumab; thus, half still die of this disease. To improve the clinical outcomes of patients further, there is a tremendous need to accurately identify patients who are likely to benefit from anti-programmed cell death protein 1 monotherapy (anti–PD-1; pembrolizumab or nivolumab) or in combination with anticytotoxic T-cell lymphocyte-4 (IPI; anti–PD-1 + IPI) as first or subsequent line of treatment, as well as those who are unlikely to respond for whom it may be best to offer targeted therapy or clinical trials instead.

Several factors have been identified as potential biomarkers of response to immune checkpoint inhibitors in metastatic melanoma. These include tumor-related factors (eg, tumor mutational burden, programmed
CONTEXT

Key Objective
Immune checkpoint inhibitors, anti-programmed cell death protein 1 (anti–PD-1) alone or in combination with anticytotoxic T-cell lymphocyte-4 (ipilimumab [IPI]; anti–PD-1 + IPI), have revolutionized the treatment of advanced melanoma; however, the majority of patients will eventually progress, and half still die of melanoma. Biomarkers of response and survival to immune checkpoint inhibitors in advanced melanoma are needed.

Knowledge Generated
We have generated validated multivariable models of response, progression-free survival and overall survival to anti–PD-1 monotherapy and combination anti–PD-1 + IPI, and their respective nomograms, on the basis of an integrative analysis of a wide array of baseline pretreatment clinicopathologic factors. These routine clinicopathologic parameters are readily available in the clinic at the time of treatment initiation.

Relevance
These nomograms accurately forecast clinical outcome from checkpoint inhibitor immunotherapy in metastatic melanoma and can be used to lead discussions with patients about prognosis, and possibly guide treatment selection between anti–PD-1 monotherapy or anti–PD-1 combined with IPI.

METHODS

Study Design and Participants
We conducted a multicenter retrospective cohort study including consecutive patients with metastatic melanoma treated with anti–PD-1 or combination IPI + anti–PD-1 at 16 major melanoma centers in Australia, the United States, and Europe between December 2009 and April 2020 (Data Supplement, online only).

Procedures
Demographics, disease characteristics, and baseline blood parameters were analyzed (Data Supplement). Tumor response to anti–PD-1 monotherapy and IPI + anti–PD-1 therapy was assessed with regular scans as per standard of care and according to each institution’s protocols (in general, 3-monthly computed tomography or computed tomography–positron emission tomography imaging), and was determined on the basis of RECIST v1.19 by the site investigator, which was consistent across all sites. No confirmatory scan of response or progression was required.

Outcomes
The end points of this study were ORR, defined as the proportion of patients who have a RECIST partial or complete response to treatment; PFS, defined as time from starting anti–PD-1 ± IPI to RECIST progression or death from any cause or last follow-up if no progression and still alive, and PFS rate at 1 and 2 years; and OS, defined as time from starting anti–PD-1 ± IPI to death or last follow-up if still alive, and OS rate at 1 and 2 years.

Statistical Analysis

Clinical predictive models. The associations of each factor with OS and PFS were assessed from univariable Cox proportional hazards models, whereas for ORR, univariable Logistic regression model was used (Data Supplement). Factors for which the hazard ratios and odds ratio were statistically significant at the level of significance 0.2 (on the basis of Akaike information criterion \( \approx 0.157 \)) were then included in a multivariable Cox proportional hazard model and multivariable logistic regression model, respectively. The final predictive models were determined through penalized least absolute shrinkage and selection operator method using variables from multivariable model to select the most significant predictors for all three outcomes.

Subgroups of predicted outcomes. Three subgroups of predicted outcomes were predefined for each outcome.
ORR, PFS, and OS) before the generation of the model on the basis of the model linear predictive index risk score: predicted good outcome, predicted intermediate outcome, and predicted poor outcome.

The study followed the Transparent Reporting of a multi-variable prediction model for Individual Prognosis or Diagnosis guideline on reporting predictive models. All the statistical analyses were carried out in SAS 9.4 (SAS Institute Inc, Cary, NC) and R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

**Discovery, Validation-1, and Validation-2 Cohorts' Characteristics**

One thousand six hundred forty-four patients were studied. Patients were included in three cohorts: discovery cohort (N = 633); validation-1 cohort (N = 419); and validation-2 cohort (N = 592).

Baseline patient and tumor characteristics of the discovery and validation-1 cohorts (Table 1 and the Data

### TABLE 1. Baseline Patient and Tumor Characteristics of the Discovery, Validation-1, and Validation-2 Cohorts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Discovery (N = 633)</th>
<th>Validation-1 (N = 419)</th>
<th>P</th>
<th>Validation-2 (N = 592)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), years</td>
<td>62 (50-70)</td>
<td>60 (51-69)</td>
<td>.1839&lt;sup&gt;a&lt;/sup&gt;</td>
<td>59 (49-70)</td>
<td>.0918&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>207 (32.7)</td>
<td>141 (33.7)</td>
<td>.7997&lt;sup&gt;b&lt;/sup&gt;</td>
<td>237 (40.0)</td>
<td>.0091&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male</td>
<td>426 (67.3)</td>
<td>278 (66.3)</td>
<td></td>
<td>355 (60.0)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS, No. (%)</td>
<td></td>
<td></td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>323 (51.4)</td>
<td>292 (69.9)</td>
<td></td>
<td>354 (64.7)</td>
<td></td>
</tr>
<tr>
<td>≥ 1</td>
<td>306 (48.6)</td>
<td>126 (30.1)</td>
<td></td>
<td>193 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Missing values</td>
<td>4</td>
<td>1</td>
<td></td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Mutation status, No. (%)</td>
<td></td>
<td></td>
<td>.2325&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>&lt;.0001&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>BRAF-mutant</td>
<td>239 (38.4)</td>
<td>150 (36.4)</td>
<td></td>
<td>294 (50.2)</td>
<td></td>
</tr>
<tr>
<td>NRAS-mutant</td>
<td>155 (24.9)</td>
<td>90 (21.8)</td>
<td></td>
<td>171 (29.2)</td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>228 (36.7)</td>
<td>172 (41.8)</td>
<td></td>
<td>121 (20.6)</td>
<td></td>
</tr>
<tr>
<td>Missing values</td>
<td>11</td>
<td>7</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>AJCC staging v8, No. (%)</td>
<td></td>
<td></td>
<td>.1393&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>.0292&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>II/III/IV</td>
<td>204 (32.2)</td>
<td>154 (36.8)</td>
<td></td>
<td>227 (38.3)</td>
<td></td>
</tr>
<tr>
<td>M1C/M1D</td>
<td>429 (67.8)</td>
<td>264 (63.2)</td>
<td></td>
<td>365 (61.7)</td>
<td></td>
</tr>
<tr>
<td>Missing values</td>
<td>0</td>
<td>1</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. of organs involved, No. (%)</td>
<td></td>
<td></td>
<td>.3365&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>.0003&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt; 3</td>
<td>315 (49.8)</td>
<td>195 (46.5)</td>
<td></td>
<td>356 (60.1)</td>
<td></td>
</tr>
<tr>
<td>≥ 3</td>
<td>318 (50.2)</td>
<td>224 (53.5)</td>
<td></td>
<td>236 (39.9)</td>
<td></td>
</tr>
<tr>
<td>LDH, No. (%), U/L</td>
<td></td>
<td></td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Normal</td>
<td>379 (60.4)</td>
<td>289 (69.5)</td>
<td></td>
<td>313 (58.2)</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>248 (39.6)</td>
<td>127 (30.5)</td>
<td></td>
<td>225 (41.8)</td>
<td></td>
</tr>
<tr>
<td>Missing values</td>
<td>6</td>
<td>3</td>
<td></td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Treatment, No. (%)</td>
<td></td>
<td></td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>.3678&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>261 (41.2)</td>
<td>226 (53.9)</td>
<td></td>
<td>181 (30.6)</td>
<td></td>
</tr>
<tr>
<td>IPI + anti-PD-1</td>
<td>372 (58.8)</td>
<td>193 (46.1)</td>
<td></td>
<td>411 (69.4)</td>
<td></td>
</tr>
<tr>
<td>First line, No. (%)</td>
<td></td>
<td></td>
<td>&lt;.0001&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>.3678&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>No</td>
<td>252 (39.8)</td>
<td>259 (61.8)</td>
<td></td>
<td>207 (37.1)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>381 (60.2)</td>
<td>160 (38.2)</td>
<td></td>
<td>351 (62.9)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Statistically significant differences (P < .05) are shown in bold.

Abbreviations: AJCC staging v8, American Joint Committee on Cancer staging version 8; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; IQR, interquartile range; LDH, lactate dehydrogenase; anti-PD-1, anti-programmed cell death protein 1.

<sup>a</sup>Wilcoxon rank sum test for continues variables.

<sup>b</sup>Pearson's chi-square test with Yates correction was used for categorical variables.

<sup>c</sup>Pearson's chi-squared test.
FIG 1. Objective response. Risk calculator for objective response in patients treated with anti–PD-1 ± IPI. (A) Nomogram calculators for objective response (event = response [good outcome]). (B) Bar plot showing the ORR in the three predefined subgroups of predicted outcomes: predicted good (blue), intermediate (orange), and poor (red) response, from the discovery, the validation-1, and the validation-2 cohorts. On the basis of the predefined subgroups of predicted outcomes, the ORR was 76% (discovery; n = 123), 76% (validation-1; n = 68), and 69% (validation-2; n = 100) for patients with predicted good response (score: > 208 points); 47% (discovery; n = 367), 53% (validation-1; n = 253), and 48% (validation-2; n = 240) for patients with predicted intermediate response (score: 123-208 points); and (continued on following page)
FIG 1. (Continued). 21% (discovery; n = 123), 31% (validation-1; n = 93), and 33% (validation-2; n = 80) for patients with predicted poor response (score: 0–122 points). Patients with missing data on at least one of the factors included in the nomogram were excluded from these subgroups of predicted outcomes: discovery cohort—20 patients; validation-1 cohort—5 patients; and validation-2 cohort—172 patients. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; LDH, lactate dehydrogenase; Neutro-Lympho Ratio, neutrophil-lymphocyte ratio; ORR, objective response rate; anti–PD-1, anti-programmed cell death protein 1.

Models for Objective Response, PFS, and OS

With a total of 633 patients, 293 objective responses, 358 disease progression/death, and 229 deaths, the discovery cohort met the required criteria to derive a robust predictive model for each outcome (Data Supplement). To build a predictive model for objective response, we first performed univariable analysis of the discovery cohort to study the association between clinical factors (patient demographics, disease characteristics, and blood parameters) and response. From the variables associated with response in the univariate analysis, the final predictive model was built and included ECOG PS, presence/absence of lung and liver metastases, LDH, neutrophil-lymphocyte ratio (NLR), and type and line of treatment (Data Supplement), with an area under the curve (AUC) = 0.71 (Data Supplement). A nomogram was developed (Fig 1A) and tested comparing the ORR in the discovery and validation cohorts, for the three predefined subgroups of predicted response: good, intermediate, and poor (Fig 1B and the Data Supplement). Internal (C-statistics = 0.69) and external validation (C-statistics = 0.67 for validation-1 and C-statistics = 0.67 for validation-2) confirmed the consistency of the model (Data Supplement).

The same method was used to develop the final predictive model for PFS and OS. The final predictive model for PFS included presence/absence of brain metastases and hemoglobin, in addition to the same factors included in the ORR model (except for lung metastases): ECOG PS, liver metastases, LDH, NLR, and type and line of treatment (Data Supplement), with an AUC = 0.68 (Data Supplement). A nomogram was generated (Fig 2A) and patients were categorized into predicted good PFS, predicted intermediate PFS, and predicted poor PFS according to the nomogram score in the discovery cohort, and tested in the validation-1 and validation-2 cohorts (Fig 2B and the Data Supplement). Internal (C-statistics = 0.67), and external validation (C-statistics = 0.67 for validation-1 and C-statistics = 0.66 for validation-2) of this model (Data Supplement) were also performed.

Finally, the final predictive model for OS included the same factors as for PFS: ECOG PS, liver and brain metastases, hemoglobin, LDH, NLR, and type and line of treatment (Data Supplement), with AUC = 0.77 (Data Supplement). After generation of the nomogram (Fig 3A), patients were classified into predicted good OS, predicted intermediate OS, and predicted poor OS according to the nomogram score in the discovery cohort, and tested in the validation-1 and validation-2 cohorts (Fig 3B and the Data Supplement show the calibration of the nomogram). Internal (C-statistics = 0.76) and external validation (C-statistics = 0.72 for validation-1 and C-statistics = 0.74 for validation-2) were performed (Data Supplement).

The performance of these three models was similar when applied to patients treated in the first-line setting only (same variables, excluding line of treatment; data not shown).

Tool for Treatment Selection: Anti–PD-1 Monotherapy Versus IPI + Anti–PD-1

To help select the most appropriate treatment (anti–PD-1 monotherapy v IPI + anti–PD-1) for patients with advanced
FIG 2. Progression-free survival. Risk calculator for PFS in patients treated with anti–PD-1 ± IPI. (A) Nomogram calculator for PFS (event = progression [poor outcome]). (B) Calibration plots (as Kaplan-Meier curves) for PFS of patients in the three predefined subgroups of (continued on following page)
melanoma, we then built a predictive model for response to anti–PD-1 monotherapy and for IPI + anti–PD-1, separately. The final predictive model for anti–PD-1 monotherapy included melanoma primary site, mutation status, LDH, and NLR (Data Supplement), with an AUC of 0.73 (Data Supplement). Differently, the final predictive model for IPI + anti–PD-1 included ECOG PS, presence/absence of lung and liver metastases, LDH, NLR, and line of treatment (Data Supplement), with an AUC of 0.74 (Data Supplement).

Using these two models, we calculated the predicted response for each treatment separately (anti–PD-1 monotherapy and IPI + anti–PD-1) for each patient and compared the predicted response with the real response, confirming the consistency of our model for both treatments (Data Supplement). We then compared the expected response rate for anti–PD-1 monotherapy and IPI + anti–PD-1 for each patient (Fig 4). For those patients with predicted response to IPI + anti–PD-1 significantly higher (>25%) than that for anti–PD-1 monotherapy (26% of the entire cohort of this study), combination IPI + anti–PD-1 should be favored. For the remaining patients, treatment selection should be discussed case by case, taking into account the predicted response for anti–PD-1 monotherapy and the benefit with IPI + anti–PD-1, toxicity profile of both treatment strategies, and comorbidities of the patient.

**DISCUSSION**

To our knowledge, this is the first study to develop clinically useful nomograms that will accurately forecast clinical outcome from checkpoint inhibitor immunotherapy in metastatic melanoma, on the basis of an integrative analysis of a wide array of baseline pretreatment clinicopathologic factors. Moreover, these tools might also help guiding treatment selection between anti–PD-1 monotherapy and combination IPI + anti–PD-1. In a large international data set of 1,644 patients with metastatic melanoma, we generated validated multivariable models of response, PFS, and OS to anti–PD-1 monotherapy and combination anti–PD-1 + IPI. Unlike many proposed molecular markers in development, these routine clinical parameters are readily available in the clinic at the time of treatment initiation, and should serve as useful tools when discussing first or further lines of treatment with patients, and should also constitute the basis for future molecular biomarker studies in this setting. Furthermore, novel biomarkers, such as primary melanoma site, anatomical sites of metastases (ie, liver, lung, and brain metastases) and hemoglobin, may offer insights into tumor biology that will spur further translational research.

A common characteristic of the available predictive models to immunotherapy is the high sensitivity, but low specificity, as it has been easier to identify good responders, but very difficult to predict nonresponders. This may be a consequence of clinical and molecular heterogeneity within the nonresponders to immunotherapy. Therefore, this study sets the bar for further molecular biomarker studies to improve prediction in this setting. Moreover, these models should help and supplement, but not replace, best clinical judgment and honest discussion with patients about risk and benefits of each immunotherapy approach, anti–PD-1 monotherapy or in combination with IPI. It will also assist clinicians to identify those unlikely to respond, who need novel clinical trial options from the outset (ie, first-line).

Several clinical (eg, ECOG PS and presence/absence of liver and brain metastases) and hematologic factors (eg, LDH and NLR) have been described to be associated with response or resistance to immune checkpoint inhibitors, however, in the majority of the cases, these factors have been studied in small cohorts and not included in multivariable models. It remains largely unknown which factors are simply prognostic, reflecting natural history, which predict drug benefit, or which may be both. Moreover, many studies have only looked at OS, without considering response or PFS, and may reflect natural history rather than a treatment effect.

In this study, we validated some of these factors as prognostic (associated with survival; ECOG PS, presence/absence of liver and brain metastases, LDH, and NLR), and although we lack a control group of untreated patients in our study, our data suggest that these factors may also be predictive (associated with response). ECOG PS, which in our study was associated with ORR, PFS, and OS, is a well-known prognostic factor, shown to be associated with shorter OS in various cancers, but it may also be predictive, as patients with a poorer performance status have a lower response rate to immune checkpoint inhibitors. Importantly, the presence of brain metastases associated with shorter PFS and OS, but it did not associate with poorer response in this study and therefore suggesting being mainly prognostic. Clinical trial data suggest this, with intracranial and extracranial response rates to combined immunotherapy in asymptomatic patients being similar to...
FIG 3. Overall survival. Risk calculator for OS in patients treated with anti–PD-1 ± IPI. (A) Nomogram calculator for OS (event = death [poor outcome]). (B) Calibration plots (as Kaplan-Meier curves) for OS of patients in the three predefined subgroups of predicted outcomes: predicted good (blue), intermediate (orange), and poor (red) OS, from the discovery (continuous line), the validation-1(continued on following page)
extracranial response rates in patients without brain metastases.\textsuperscript{28,29} Moreover, although brain metastases were not a key variable to predictive response to anti–PD-1 ± IPI or anti–PD-1/IPI monotherapy, ABC clinical trial\textsuperscript{28} showed a clear benefit of IPI + anti–PD-1 over anti–PD-1 monotherapy in this subgroup of patients. Recent studies have shown that within AJCC stage M1C, the presence of liver metastases is predictive of poorer response and it is associated with shorter PFS in patients with melanoma and NSCLC treated with immunotherapy.\textsuperscript{16,30,31} In this study, the presence of liver metastases was associated with lower ORR, shorter PFS, and shorter OS in patients treated with immunotherapy, suggesting this is both a predictive and prognostic factor. The liver is a known site of immune tolerance because of the constant interaction with gut bacteria and food-derived antigens.\textsuperscript{32,33} This creates a distinct microenvironment, which induces T-cell tolerance through multiple mechanisms. These include the interaction of naïve CD4 and CD8 T cells with liver sinusoidal endothelial cells, causing a switch to regulatory T cells and partially activated CD8 T cells that undergo apoptosis.\textsuperscript{34,35} Compared with other sites of metastases, such as lymph nodes and lung metastases, liver metastases’ microenvironment has a lower intratumoral T-cell density,\textsuperscript{36} and further research is ongoing to determine specific mechanisms of resistance in patients with liver and brain metastases.

In this study, we identified blood parameters associated with clinical outcome, including LDH, NLR, and hemoglobin. LDH is included in the melanoma AJCC staging\textsuperscript{37} and is a prognostic factor across other cancer types.\textsuperscript{38} In addition, LDH has also been shown to be a predictive marker, and elevated LDH is associated with lower ORR and shorter PFS with immunotherapy.\textsuperscript{39,40} Similarly, in this study, LDH was a key variable in the models for all three outcomes, indicating true predictive and prognostic value. Similar to other studies where high NLR was associated with worse PFS and OS regardless of treatment and across various cancer types,\textsuperscript{18,19,41} in our data set, NLR was essentially a prognostic factor in patients treated with immunotherapy. Interestingly, in our study, higher hemoglobin is associated with longer PFS with immunotherapy, which

![Figure 3](image-url)  
**Figure 3.** (Continued). (dashed line), and the validation-2 (dotted line) cohorts. On the basis of the predefined subgroups of predicted outcomes, the 1-year OS was 99% (discovery; \(n = 123\)), 95% (validation-1; \(n = 68\)), and 92% (validation-2; \(n = 72\)) for patients with predicted good OS (score: 0-84 points); 75% (discovery; \(n = 366\)), 82% (validation-1; \(n = 272\)), and 72% (validation-2; \(n = 177\)) for patients with predicted intermediate response (score: 85-210 points); and 30% (discovery; \(n = 123\)), 45% (validation-1; \(n = 74\)), and 39% (validation-2; \(n = 61\)) for patients with predicted poor response (score: \(> 210\) points). Patients with missing data on at least one of the factors included in the nomogram were excluded from these risk groups: discovery cohort—21 patients; validation-1 cohort—5 patients; and validation-2 cohort—282 patients. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, ipilimumab; LDH, lactate dehydrogenase; Neutro-Lympho Ratio, neutrophil-lymphocyte ratio; OS, overall survival; anti-PD-1, anti-programmed cell death protein 1.

![Figure 4](image-url)  
**Figure 4.** Treatment selection tool. Scatter plot showing the predicted response to anti–PD-1 monotherapy (x-axis) versus IPI + anti–PD-1 (y-axis) for each patient (from the entire cohort of this study [discovery + validation-1 + validation-2 cohorts]). Above the oblique line defines the group of patients (\(n = 335\); 26%) with predicted response to IPI + anti–PD-1 > predicted response to anti–PD-1 monotherapy, with \(> 25\)% difference between both treatments. Patients with missing data on at least one of the factors included in the nomogram were excluded from these groups. IPI, ipilimumab; anti–PD-1, anti-programmed cell death protein 1.
was previously reported for patients with NSCLC; however, the biology behind this finding is yet to be defined.

Combination IPI + anti–PD-1 and immunotherapy as first-line treatment were both predictors of higher response rate and longer PFS and OS in our models. The CheckMate-067 trial has shown a numerical advantage of the combination treatment over anti–PD-1 monotherapy in response, PFS, and OS. Although the trial was not powered to detect this difference, and this benefit is small, this has been consistent in subsequent analysis, including the most recent 5-year PFS (36% v 29%) and OS (52% v 44%). In our study, although type of treatment was not significantly associated with any of the outcomes, it was included in the final predictive model for ORR, PFS, and OS, and combination IPI + anti–PD-1 was associated with better clinical outcomes. As expected, first-line treatment was associated with better response and longer survival. Immunotherapy loses efficacy when given as second line of treatment or later (e.g., after BRAF/MEK inhibitors), likely because of a larger volume of disease, poorer condition of patient as well as possible changes in biology as a result of previous treatments. This was shown in previous studies, which we have validated in our study. Moreover, these models showed similar accuracy for patients treated in the first-line setting.

In the treatment-specific predictive models of response, in anti–PD-1–treated patients, BRAF-mutant melanomas were associated with worse response when compared with WT- or NRAS-mutant melanomas, but this was not seen in the combination therapy cohort. Data from the CheckMate-067 trial confirm this, showing lower 5-year PFS with nivolumab in patients with (largely V600E) BRAF-mutant melanoma than those with BRAF WT (22% v 32%) but a similar PFS with combination therapy (38% v 35%). In our study, mutation status was insufficiently predictive to be included in our models, probably because of the fact that these models were built and validated in a cohort combining anti–PD-1 monotherapy– and IPI + anti–PD-1–treated patients.

The site of primary melanoma was another factor associated with response in anti–PD-1 monotherapy–treated patients (but not in patients treated with the combination) in this study, whereby patients with metastases from head and neck primaries had better outcomes compared with patients with primaries from other sites. Head and neck primary melanomas have a higher degree of chronic sun damage and tumor mutation burden compared with other sites, and we have previously shown that metastatic melanomas with the BRAF V600K mutation, typically associated with head and neck melanoma primaries, respond better to immunotherapy compared with BRAF V600E melanomas. Efficacy of combination immunotherapy may be less reliant on tumor mutation burden and consequent immune activation; for example, efficacy is not as strongly associated with programmed death-ligand 1 expression as anti–PD-1 monotherapy, and thus, the site of primary melanoma may not be as important with combination therapy. Mucosal melanomas were included as a small category within melanoma subtype associated with shorter PFS and OS in anti–PD-1 ± IPI–treated patients, however, data on melanoma subtype were missing in more than 10% of the cohort, and this variable was not included in the multivariable and modeling analysis. These models were based on large retrospective cohorts, with patient selection bias for each treatment, lacking a control group of untreated patients to accurately assess the interaction between treatment options and predictive factors, which is a limitation of this study. Despite these biases, these validated multivariable predictive models were built with clinical variables available for free at the time of treatment initiation, and on the basis of a large international cohort of more than 1,500 patients from several centers from Australia, Europe, and the United States, and can be used by any medical oncologist around the world. In summary, this is the first study to generate predictive clinical models and clinically useful nomograms using routinely collected clinical factors available at consultation to lead discussions with patients about prognosis and possibly guide treatment selection between anti–PD-1 monotherapy or anti–PD-1 combined with IPI. An online version of each nomogram is publicly available.

### AFFILIATIONS

1. Melanoma Institute Australia, The University of Sydney, Sydney, Australia
2. Charles Perkins Centre, The University of Sydney, Sydney, Australia
3. Westmead and Blacktown Hospitals, Sydney, Australia
4. The University of Texas MD Anderson Cancer Center, Houston, TX
5. Vanderbilt University Medical Center, Nashville, TN
6. Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia
7. Netherlands Cancer Institute, Amsterdam, the Netherlands
8. The Christie NHS Foundation Trust, Manchester, United Kingdom
9. The Royal Marsden NHS Foundation Trust, London, United Kingdom
10. Hospital Clinic, Barcelona & IDIBAPS, Barcelona, Spain
11. University Hospital Essen, University of Duisburg-Essen, German Cancer Consortium, Partner Site Essen, Essen, Germany
12. Helios Klinikum Erfurt, Erfurt, Germany
13. Skin Cancer Unit, German Cancer Research Center (DKFZ), Heidelberg, Germany
14. Department of Dermatology, Venereology and Allergology, University Medical Center Mannheim, Ruprecht-Karl University of Heidelberg, Mannheim, Germany
15. Saarland University Medical Center, Homburg/Saar, Germany
16. Department of Dermatology, University of Lübeck, Lübeck, Germany
17. University Skin Cancer Center Kiel, University Hospital of Schleswig-Holstein, Kiel, Germany
18. Skin Cancer Center, Department of Dermatology, Mühlenkreiskliniken, Ruhr University Bochum Campus Minden, Minden, Germany
19. Elbe-Klinikum Buxtehude, Buxtehude, Germany
20. Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital and NSW Health Pathology, Sydney, Australia
21. Faculty of Medicine and Health, The University of Sydney, Sydney, Australia
Author Contributions

Conception and design: Inês Pires da Silva, Tasnia Ahmed, Georgina V. Long, Serigne N. Lo, Alexander M. Menzies

Administrative support: Richard A. Scolyer


Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Acknowledgment

The authors wish to thank the patients and families involved in this study, as well as all staff at Melanoma Institute Australia, Vanderbilt University Medical Center, MD Anderson Cancer Center, The Netherlands Cancer Institute, The Christie NHS Foundation Trust, The Royal Marsden NHS Foundation Trust, Hospital Clinic de Barcelona, University Hospital Essen, Hannover Medical School, Saarland University Medical Center, Helios Klinikum Erfurt, University Hospital Kiel, University Medical Center Mannheim, University Hospital Lübeck, Elbe-Klinikum Buxtehude, and associated institutions.
Inês Pires da Silva  
Consulting or Advisory Role: MSD  
Speakers’ Bureau: Roche, Novartis, Bristol Myers Squibb  
Travel, Accommodations, Expenses: Roche, Bristol Myers Squibb  

Jennifer L. McQuade  
Honoria: Merck, Bristol Myers Squibb, Roche  
Consulting or Advisory Role: Bristol Myers Squibb, Roche Pharma AG  
Travel, Accommodations, Expenses: Merck  

Selma Ugurel  
Honoria: Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Merck Serono  
Consulting or Advisory Role: Bristol Myers Squibb, Roche, Merck Serono  
Research Funding: Bristol Myers Squibb (Inst), Merck Serono (Inst)  
Travel, Accommodations, Expenses: Bristol Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Pierre Fabre  

Rudolf Herbst  
Employment: Helios Kliniken  

Jochen Uitital  
Stock and Other Ownership Interests: BioNTech, Moderna Therapeutics, Pfizer, Merck, Sanofi  
Honoria: Bristol Myers Squibb, Novartis, MSD Oncology, Roche, Pierre Fabre, Sanofi  
Consulting or Advisory Role: Bristol Myers Squibb, Roche, MSD Oncology, Novartis, Pierre Fabre, Amgen, Sanofi  
Research Funding: Apogenix (Inst), Noxoon Pharma (Inst), Elsaliys Biotech (Inst), TILT Biotherapeutics (Inst)  
Travel, Accommodations, Expenses: MSD Oncology, Roche, Novartis, Pierre Fabre, Bristol Myers Squibb, Amgen, Sanofi  

Claudia Pföhler  
Honoria: Bristol Myers Squibb, Novartis, Roche, MSD, Merck Serono, Sun Pharma, Amgen, AbbVie  
Consulting or Advisory Role: Bristol Myers Squibb Foundation, Novartis, MSD, Roche, Sanofi, Allergy Therapeutics, Merck Serono  
Travel, Accommodations, Expenses: Bristol Myers Squibb, Novartis, Roche, Pierre Fabre, Colgenie, AbbVie, Merck Serono  

Patrick Terheyden  
Honoria: Bristol Myers Squibb, Novartis, Roche, CureVac, Merck Serono, MSD Oncology  
Consulting or Advisory Role: Bristol Myers Squibb, Novartis, Pierre Fabre, Roche, Sanofi, Merck KGaA, 4SC, Almirall  
Travel, Accommodations, Expenses: Bristol Myers Squibb, Pierre Fabre  

Michael Weichenthal  
Honoria: Merck Sharp & Dohme, Roche, Novartis, Bristol Myers Squibb, Sanofi  
Consulting or Advisory Role: Merck Sharp & Dohme, Roche, Novartis, Bristol Myers Squibb, Sun Pharma, Sanofi, Pierre Fabre  
Research Funding: Merck Sharp & Dohme (Inst), Millennium (Inst), Bristol Myers Squibb (Inst), Johnson & Johnson (Inst), Novartis (Inst)  

Ralf Gutzmer  
Honoria: Bristol Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, Novartis, Merck Serono, Almirall Hermal GmbH, Amgen, Sun Pharma, Pierre Fabre, Sanofi/Regeneron, Immunocore  
Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, Novartis, Almirall Hermal GmbH, 4SC, Amgen, Pierre Fabre, Merck Serono, Sun Pharma, Sanofi, Immunocore  
Research Funding: Pfizer (Inst), Novartis (Inst), Johnson & Johnson (Inst), Amgen (Inst), Merck Serono (Inst), Sun Pharma (Inst), Sanofi (Inst)  
Travel, Accommodations, Expenses: Bristol Myers Squibb, Roche, Merck Serono, Pierre Fabre, Sun Pharma

Peter Mohr  
Honoria: Bristol Myers Squibb, Merck Sharp & Dohme, Roche/Genentech, Novartis, Amgen, Pierre Fabre, Merck, Sanofi  
Consulting or Advisory Role: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen, Roche, Pierre Fabre, Sanofi  
Speakers’ Bureau: Novartis, Roche, Bristol Myers Squibb, Merck Sharp & Dohme, Amgen, Sanofi  
Research Funding: Merck Sharp & Dohme (Inst), Bristol Myers Squibb (Inst), Novartis (Inst)  
Travel, Accommodations, Expenses: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Amgen, Roche, Sun Pharma, Sanofi  

Jessica L. Smith  
Honoria: Pierre Fabre  
Travel, Accommodations, Expenses: MSD Oncology  

Richard A. Scolyer  
Employment: Royal Prince Alfred Hospital  
Honoria: GlaxoSmithKline, Harvard Medical School, Wake Forest School of Medicine  
Consulting or Advisory Role: Bristol Myers Squibb (Switzerland), GlaxoSmithKline, Merck Sharp & Dohme, NeraCare GmbH, Novartis Australia, Amgen, Myriad Genetics, MSD Sharp & Dohme (Australia) Pty Limited, Novartis, QBiomics, Proventus Biopharmaceuticals Australia, Evaxion BioTech A/S, Novartis Pharmaceuticals Australia Pty Limited, Roche  
Research Funding: The Ainsworth Foundation (Inst), National Health and Medical Research Council, Melanoma Research Alliance (MRA) Grant  
Travel, Accommodations, Expenses: Bristol Myers Squibb, Novartis Australia  
Uncompensated Relationships: Melanoma Institute Australia  

Ana M. Arance  
Consulting or Advisory Role: BMS, Roche, Novartis, Pierre Fabre, MSD, Merck, Sanofi  
Speakers’ Bureau: Novartis, BMS, Roche, Merck, Sanofi  
Research Funding: Pierre Fabre, Novartis, Roche, BMS, MSD, Merck, Sanofi, Amgen  
Travel, Accommodations, Expenses: BMS, MSD, Novartis, Pierre Fabre, Roche, Merck, Sanofi  

Lisa Pickering  
Consulting or Advisory Role: Pfizer, Ipsen, BMS, Eisai, MSD Oncology, Novartis  
Speakers’ Bureau: Pfizer, BMS  
Research Funding: NIHR (Inst), Rosetrees Trust (Inst), Kidney and melanoma cancer fund of RMH charity (Inst)  

James Larkin  
Honoria: Bristol Myers Squibb, GlaxoSmithKline, Pfizer, Novartis, Roche/Genentech, Incyte, iOnctura, Merck Serono, Eisai, Dynavax Technologies, Cancer Research UK, touchIM, touchEXPERTS  
Consulting or Advisory Role: Bristol Myers Squibb, GlaxoSmithKline, Pfizer, Novartis, Boston Biomedical, Incyte, iOnctura,iovance Biotherapeutics, Immunocore, YKT Corporation, Apple Tree Partners  
Research Funding: Pfizer (Inst), Novartis (Inst), MSD (Inst), Bristol Myers Squibb (Inst), Achilles Therapeutics (Inst), Roche (Inst), Nektar (Inst), Covance (Inst), Immunocore (Inst), AVEO (Inst), Pharmacists (Inst)  
Travel, Accommodations, Expenses: Bristol Myers Squibb, Pfizer, Novartis, Roche/Genentech, AstraZeneca, Incyte, GlaxoSmithKline, Pierre Fabre, Merck Serono, iOnctura, British Uro-Oncology Group (BUG), ESMO, National Cancer Research Institute (N CGI), EUSA Pharma, Syneos Health, Kidney Cancer Association, Bioevents, MedConcept, RV Mais  

Paul Lorigan  
Honoria: Novartis, Pierre Fabre, Merck, BMS, MSD, NeraCare GmbH, Amgen, Roche, Oncology Education, Nektar  
Consulting or Advisory Role: Merck Sharp & Dohme, Bristol Myers Squibb, Amgen, Pierre Fabre, Novartis, Nektar  
Speakers’ Bureau: Merck Sharp & Dohme, Novartis, Bristol Myers Squibb, Pierre Fabre  
Research Funding: BMS, Pierre Fabre  
Travel, Accommodations, Expenses: Merck Sharp & Dohme, Bristol Myers Squibb

Clinical Models to Define Outcome From Immunotherapy in Melanoma  

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST  
Clinical Models to Define Response and Survival With Anti–PD-1 Antibodies Alone or Combined With Ipilimumab in Metastatic Melanoma  
The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript.  
For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/wcc or ascopubs.org/jco/authors/author-center.  
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).
Christian U. Blank
Stock and Other Ownership Interests: Uniti Cars, Immagene
Consulting or Advisory Role: Roche/Genentech (Inst), MSD Oncology (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), GlaxoSmithKline (Inst), Pfizer (Inst), AstraZeneca (Inst), Lilly (Inst), Pierre Fabre (Inst), GenMab (Inst), Third Rock Ventures
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst), NanoString Technologies (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb

Dirk Schadendorf
Honoraria: Roche/Genentech, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Immunocore, Merck Serono, Array BioPharma, Pfizer, Pierre Fabre, Philogen, Regeneron, 4SC, Sanofi/Regeneron, NeraCare GmbH, Sun Pharma, InflanGmbH, Ultimovacs, Sandoz
Consulting or Advisory Role: Roche/Genentech, Novartis, Bristol Myers Squibb, Merck Sharp & Dohme, Merck Serono, 4SC, Pierre Fabre, Sanofi/Regeneron, Nektar
Speakers’ Bureau: Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, Sanofi/Regeneron, Merck KGaA
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst), Roche (Inst), MSD Oncology (Inst), Array BioPharma/Pfizer (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, Bristol Myers Squibb, Merck Serono, Novartis, Merck Sharp & Dohme, Pierre Fabre, Sanofi/Regeneron

Michael A. Davies
Consulting or Advisory Role: Genentech/Roche, Novartis, Bristol Myers Squibb, NanoString Technologies, Array BioPharma, Apexigen, ABM Therapeutics, Pfizer, Eisai
Research Funding: GlaxoSmithKline (Inst), Genentech/Roche (Inst), AstraZeneca (Inst), Merck (Inst), Oncothyreon (Inst), Myriad Genetics (Inst), Sanofi (Inst), Pfizer (Inst)

Matteo S. Carlino
Honoraria: Bristol Myers Squibb, MSD, Novartis
Consulting or Advisory Role: Bristol Myers Squibb, MSD, Amgen, Novartis, Pierre Fabre, Roche, IDEAYA Biosciences, Sanofi, Merck Serono, Regeneron, QBiotics, Nektar, Eisai, OncoSec
Research Funding: Incyte, Bristol Myers Squibb
Patents, Royalties, Other Intellectual Property: Intellectual property and patents pending surrounding use of MHC-II and response to immune therapy

Georgina V. Long
Honoraria: BMS, Pierre Fabre
Consulting or Advisory Role: Aduro Biotech, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Hexal, Highlight Therapeutics, Merck Sharpe & Dohme, Novartis, OncoSec, Pierre Fabre, QBiotics, Regeneron, SkylineDx, Specialised Therapeutics, Array BioPharma, Evoxion Biotech AS, Evoxion Biotech AS, SkylineDX B.V

Alexander M. Menzies
Consulting or Advisory Role: MSD Oncology, Novartis, Pierre Fabre, Bristol Myers Squibb, Roche, QBiotics

No other potential conflicts of interest were reported.