Development and Validation of a Prognostic Model for Patients with Advanced Lung Cancer Treated with the Immune Checkpoint Inhibitor Atezolizumab

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ABSTRACT

Purpose: Immune checkpoint inhibitors (ICI) are a significant advance to the treatment of advanced non–small cell lung cancer (NSCLC); however, their initiation is associated with heterogeneity in outcomes. This study aimed to develop and validate a prognostic tool of survival in patients with advanced NSCLC treated with ICIs.

Experimental Design: A pretreatment prognostic model was developed and validated using clinicopathologic data. Development data consisted of patients with advanced NSCLC treated with atezolizumab from the randomised trials OAK and POPLAR ($n = 751$). Data from the single-arm atezolizumab trials BIRCH and FIR ($n = 797$) were used for external validation. Prognostic scores were categorized into low, intermediate-low, intermediate, intermediate-high, and high-risk prognostic groups. The primary outcome was overall survival (OS), with progression-free survival (PFS) secondary.

Results: Pretreatment C-reactive protein (CRP) was the most predictive variable for OS. The prognostic tool was optimally defined by CRP, lactate dehydrogenase, derived neutrophil-to-lymphocyte ratio, albumin, PD-L1 expression, performance status, time since metastatic diagnosis, and metastatic site count. Prognostic groups had significantly different OS (c-statistic = 0.72), with median OS ranging from >24 to 3 months for the low- to high-risk groups. Performance was maintained on validation ($c = 0.76$). These findings were similar for PFS, with median PFS ranging from 5 months to 1 month for the low- to high-risk groups. Benefit of atezolizumab (vs. docetaxel) was greatest in the low-risk group (>3 months median OS improvement), with little benefit apparent for the highest risk group.

Conclusions: A prognostic tool was developed and validated to identify patient groups with distinctly different survival following atezolizumab initiation for advanced NSCLC.

Introduction

Immune checkpoint inhibitors (ICI) are a significant advance to the treatment arsenal for advanced melanoma, non–small cell lung cancer (NSCLC), and renal cell carcinoma; however, their initiation is still associated with significant heterogeneity in survival outcomes. For example, while there is a significant increase in the likelihood of achieving long-term survival, the proportion of responders is similar to that achieved with conventional chemotherapies (1, 2).

Clinical prediction models integrate clinicopathologic data from many patients to identify subgroups with varying prognosis (3). Thereby, clinical prediction models may facilitate improved decision making by providing patients with personalized realistic expectations of treatment outcomes (4, 5). Prediction models may also be used to define patient groups with predicted good or poor prognosis, and subsequently allow a targeted analysis of genetic markers resulting in unexpectedly bad or good outcomes.

While much research has been conducted to assess pretreatment biomarkers associated with varying prognosis following the initiation of ICIs (6, 7), there has been minimal research on clinical prediction models to provide personalized risk predictions. One prominent recent example utilized the derived neutrophil to lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) to define a lung immune prognostic index (LIPI; ref. 8). While LIPI incorporates two robust prognostic inflammatory variables (8), its development did not extensively evaluate the multitude of routinely collected prognostic information to define an optimized prediction model. The aim of this study was to develop and validate a pretreatment prognostic tool for survival outcomes in patients with advanced NSCLC treated with ICIs, via the utilization of routinely collected clinicopathologic data.

Materials and Methods

Population

This study was a pooled *post hoc* analysis of individual-participant data (IPD) from the clinical trials BIRCH (NCT02031458; May 28, 2015 data cutoff; January 22, 2014 to December 4, 2014 participant enrollment period), FIR (NCT01846416; January 7, 2015 data cutoff; May 14, 2013 to June 27, 2014 participant enrollment period), OAK (NCT02008227; July 7, 2016 data cutoff; March 11, 2014 to April 29, 2015 participant enrollment period), and POPLAR (NCT01903993; May 8, 2015 data cutoff; August 5, 2013 to March 31, 2014 participant enrollment period; refs. 2, 9–11). Model development IPD was from patients with advanced NSCLC who received atezolizumab treatment within OAK and POPLAR. OAK and POPLAR were randomized trials of atezolizumab 1,200 mg i.v. every 3 weeks versus docetaxel 75 mg/m^2

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Translational Relevance

This study identified pretreatment C-reactive protein (CRP) as the single most prognostic variable for OS in advanced NSCLC patients treated with the immune checkpoint inhibitor (ICI) atezolizumab. Furthermore, a prognostic tool was developed and validated that discriminates patient groups with clinically significant differences in survival outcomes; the tool is the first to incorporate CRP and PD-L1 expression, along with lactate dehydrogenase, derived neutrophil-to-lymphocyte ratio, albumin, performance status, time since metastatic diagnosis, and metastatic sites count. The prognostic tool had substantially improved performance compared to other previously proposed options. For patients considering the initiation of ICIs for the treatment of advanced NSCLC, the prognostic tool presented may enable the provision of more personalized expectations of survival outcomes.

i.v. every 3 weeks for patients with advanced NSCLC whose disease progressed on platinum-containing therapy (2, 11). IPD from patients with advanced NSCLC who received atezolizumab treatment within BIRCH and FIR were used as an external validation dataset. BIRCH and FIR were single-arm studies of atezolizumab 1,200 mg i.v. every 3 weeks in programmed death-ligand 1 (PD-L1)-positive advanced NSCLC (9, 10). Exploratory analysis of prognostic models was conducted in patients with advanced NSCLC who received docetaxel treatment within OAK and POPLAR.

All trials were done in full accordance with the guidelines for Good Clinical Practice and the Declaration of Helsinki and approval was obtained from an independent ethics committee for each trial site (2, 9–11). All patients gave written informed consent (2, 9–11). Secondary analysis of anonymized clinical trial data was deemed negligible risk research by the Southern Adelaide Local Health Network, Office for Research and Ethics and was exempt from review. Data were accessed according to Roche's policy and process for clinical study data sharing (12).

Predictors and outcomes

The primary outcome predicted was overall survival (OS), with progression-free survival (PFS) assessed as a secondary outcome. Primary study definitions of PFS were utilized; PFS was investigator-assessed as per Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) in POPLAR and OAK (2, 11); an independent review facility–assessed PFS per RECIST (version 1.1) in BIRCH (10), and PFS was investigator-assessed per modified RECIST in FIR (9). Median follow-up was calculated using Kaplan–Meier analysis for the censored times.

Analyzed pretreatment patient and tumor characteristics were prespecified based upon availability, prior evidence (6–8), and biological plausibility. Utilized pretreatment clinicopathologic data were the values closest to, but prior to, the start of treatment. Analyzed clinicopathologic data included sex, age, race, body mass index (BMI), smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), histology (nonsquamous vs. squamous), stage, time since metastatic diagnosis (months), number of prior treatments, PD-L1 expression, metastatic sites count (i.e., number of organs with metastases), neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio [dNLR; calculated as neutrophil count/(white blood cell count – neutrophil count)], lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and eosinophils, lactate dehydrogenase (LDH), C-reactive protein (CRP), alkaline phosphatase (ALP), calcium, hemoglobin, and albumin levels.

PD-L1 expression was categorized according to previously published scoring criteria (2, 9–11). Briefly, PD-L1 expression (0 vs. 1 vs. 2 vs. 3) was defined as the maximum score according to tumor cell scoring (TC0/1/2/3) or tumor-infiltrating immune cell scoring (IC0/1/2/3; refs. 2, 9–11). TC0 corresponds to a percentage of PD-L1–expressing tumor cells <1%, TC1 is ≥1% and <5%, TC2 is ≥5% and <50%, and TC3 is ≥50%. IC0 corresponds to a percentage of PD-L1–expressing tumor-infiltrating immune cells <1%, IC1 is ≥1% and <5%, IC2 is ≥5% and <10%, and IC3 is ≥10% (2, 9–11).

Univariate analysis

Cox proportional hazard models were used to assess the association between clinicopathologic data and survival outcomes within a pooled analysis of OAK and POPLAR. The associations were reported as HR with 95% confidence intervals (95% CI), and *P* values (likelihood ratio test). Continuous variables were explored for observed nonlinear effects using restricted cubic splines, and skewed data was log transformed. Analyses were conducted with a focus on facilitating clinical use and interpretability. Continuous variables were then categorized based upon model fit [assessed via the Akaike information criterion (AIC)], observed nonlinear effects, and standard/interpretable reference cut-off points. All analyses were stratified by study, allowing separate baseline hazard functions for each study. All *P* values less than 0.05 were considered statistically significant. As minimal data was missing (<10%) for the assessed variables, complete case analyses were conducted. Discrimination performance of models were assessed via the concordance statistic (*c*-statistic).

Development of a pretreatment prognostic tool

Pretreatment multivariable Cox proportional hazards models were developed via a stepwise forward inclusion of variables with a $P < 0.05$ and the greatest increase in the *c*-statistic; this was followed by a stepwise backwards elimination of univariables with $P > 0.05$ and those that did not increase the *c*-statistic by 0.05. To facilitate clinical use, model coefficients were scaled from 0 to 10 to allow calculation of prognostic scores (i.e., calculation of linear predictor score). Prognostic scores were categorized into low, intermediate-low, intermediate, intermediate-high, and high-risk prognostic groups (categorized according to the lower 15th, 15th–35th, 35th–65th, 65th–85th, and upper 15th risk percentiles). All analyses were stratified by study. Kaplan–Meier analysis was used for plotting and estimating probabilities of the prognostic groups. Five-fold cross validation (averaged over 20 repetitions) of a stepwise approach involving forward inclusion and backward elimination based on AIC was applied to estimate internal validity.

Exploratory analyses were conducted to assess the discrimination performance of a defined decision tree, random forest, and least absolute shrinkage and selection operator (LASSO) regression model. A decision tree was defined by means of recursive partitioning analysis (13), with a stop criterion set at a multiplicity-adjusted univariate *P* value of less than 0.05, with no subgroup size below 100. Random forest analysis, a machine learning regression approach, was conducted using the Breiman-Cutler permutation method for survival analysis, with imputation using a parallel out-of-bag error estimate method (14, 15). A LASSO regression model was evaluated using the *glmnet* package (16). For comparison, the performance of established immune-related prognostic scores were assessed, including the LIPI (8), Sen and colleagues (17) prognostic model,

Gustave Roussy Immune Score (GRIm-Score; ref. 18), and Systemic Immune-Inflammation Index (SII; $\leq 6 \times 10^{11}$ vs. > 6 and $\leq 15 \times 10^{11}$ vs. $> 15 \times 10^{11}$; refs. 19, 20).

All data analysis was conducted using R version 3.4.3.

Data sharing statement

Individual-participant data utilized was accessed according to Roche's policy and process for clinical study data sharing (12).

Results

Patient population

Model development data consisted of 751 patients who received atezolizumab for advanced NSCLC within OAK and POPLAR. Median follow-up was 20 months (95% CI, 19–20) within the cohort. Validation data from BIRCH and FIR consisted of 797 patients. Supplementary Table S1 provides a summary of the patient characteristics from the four trials.

Univariate analysis

Univariable Cox proportional hazard analysis identified CRP, NLR, dNLR, hemoglobin, albumin, PLR, metastatic sites count, LMR, ECOG PS, LDH, months since metastatic diagnosis, ALP, histology, PD-L1 expression, race, and eosinophils as pretreatment prognostic markers of OS in patients who received atezolizumab for advanced NSCLC ($P < 0.05$; Supplementary Table S2). CRP (<3 vs. 3–9.9 vs. 10–49.9 vs. ≥ 50 mg/L) was the most predictive univariable for OS ($c = 0.64$). **Figure 1** presents Kaplan–Meier estimate of OS for CRP within the development data. Discrimination performance of the derived CRP groups was maintained on validation ($c = 0.71$; Supplementary Fig. S1). In the validation dataset CRP ($c = 0.71$), NLR ($c = 0.69$), LMR ($c = 0.66$), dNLR ($c = 0.65$), and PLR ($c = 0.65$) were the five most prognostic variables of OS in patients who received atezolizumab for advanced NSCLC ($P < 0.001$).

Univariable Cox proportional hazard analysis identified metastatic sites count, hemoglobin, NLR, CRP, dNLR, LMR, PLR, albumin, ECOG PS, LDH, PD-L1 expression, months since metastatic diagnosis, ALP, smoking history, and eosinophils as pretreatment prognostic markers of PFS in patients who received atezolizumab for advanced NSCLC ($P < 0.05$; Supplementary Table S3).

Prognostic tool for OS prediction

The optimal OS multivariable Cox proportional hazard model was defined by CRP, LDH, dNLR, albumin, PD-L1 expression, ECOG PS, time since metastatic diagnosis, and metastatic sites count ($P < 0.05$; Supplementary Table S4). Model coefficients were scaled to an integer between 0 and 10 based on Cox model coefficients (Supplementary Table S5). **Table 1** presents the points allocated to each predictor to calculate a prognostic score.

Figure 1 presents Kaplan–Meier estimates of OS within the development data for defined pretreatment prognostic groups. The discrimination performance of the prognostic groups in the development and validation data were 0.72 and 0.76, respectively. **Table 2** presents OS estimates for the prognostic groups in the development data, where median OS ranged from greater than 24 to 3 months for the low- to high-risk prognostic groups. Supplementary Table S6 and Supplementary Fig. S1 present Kaplan–Meier estimates of OS for the prognostic groups in the validation data. Supplementary Fig. S2 presents calibration plots of OS for prognostic groups in the development and validation data. The discrimination performance of the stepwise 5-fold cross validation model was 0.70 in the development data, which is similar to the presented prognostic tool and an internal test that overfitting has not occurred.

Exploratory analyses were undertaken to assess a simpler (decision tree) and a more complex (random forest) modeling approach. With respect to prediction performance on the validation dataset, the decision-tree model (Supplementary Fig. S3) had discrimination (*c*-statistic) of 0.69 and the random forest model had discrimination

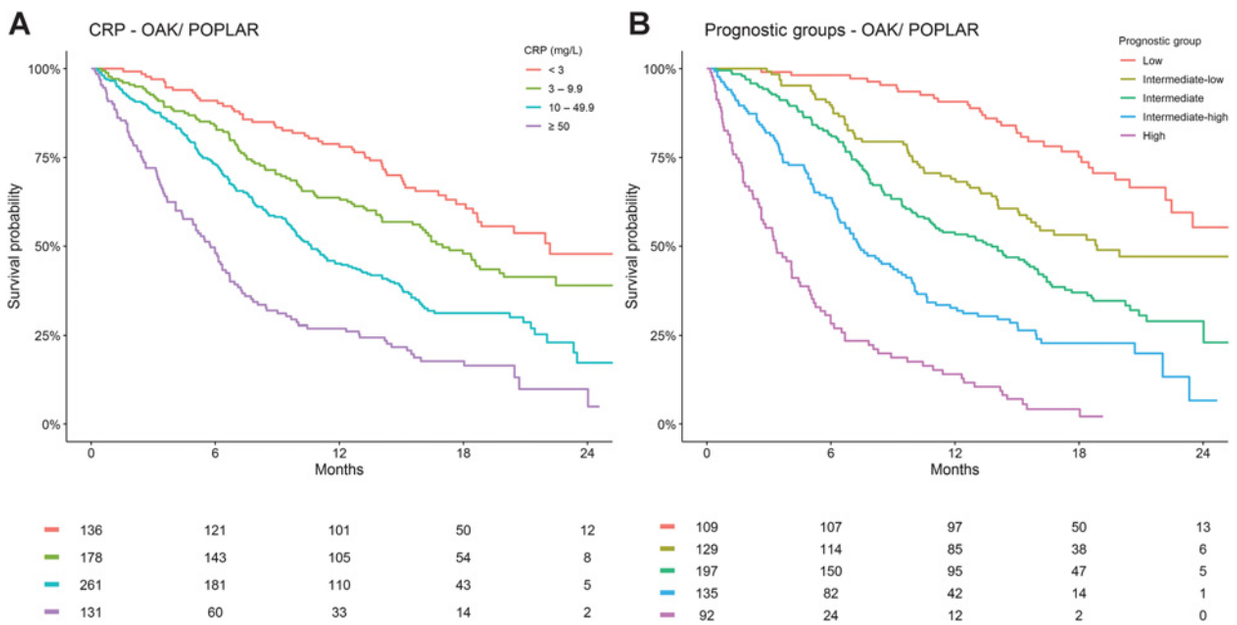

Figure 1.
Kaplan–Meier estimates of OS by pretreatment CRP (**A**) and prognostic group (**B**) for advanced NSCLC patients who received atezolizumab within OAK/POPLAR.

Table 1. Points allocated to each pretreatment factor to calculate an OS and PFS prognostic score.

	0	1	2	3	4	5	6	7	8	9	10
CRP (mg/L)	<3		3 to 9.9				10 to 49.9		≥50		
LDH (U/L)	<230		230 to 459					≥460			
dNLR	<2					2 to 3.49			≥3.5		
Albumin (g/L)	≥38		34 to 37.9				< 34				
PD-L1 expression level	3							2			0 or 1
ECOG PS	0				1+						
Months since metastatic diagnosis	≥18				<18						
Metastatic sites count	1 to 2					3 or 4		≥5			

Abbreviations: CRP, C-reactive protein; dNLR, derived neutrophil-to-lymphocyte ratio [dNLR = neutrophil count/(white blood cell count − neutrophil count)]; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

(*c*-statistic) of 0.77. The discrimination performance of a defined LASSO regression model was 0.75 on validation. The discrimination performance of LIPI (Supplementary Fig. S4), Sen and colleagues (17) prognostic model, GRIm-Score, and SII were 0.66, 0.67, 0.71, and 0.69, respectively, on validation data (Supplementary Table S7).

Prognostic tool for PFS prediction

The discrimination performance (*c*-statistic) of prognostic groups defined according to a scoring tool based upon multivariable Cox proportional hazards prediction of PFS (Supplementary Table S8) was 0.61 and 0.60 within the development and validation data, respectively. Comparatively, the PFS discrimination performance (*c*-statistic) of the OS prognostic scoring tool groups was 0.62 and 0.63, respectively. As the OS prognostic scoring tool groups performed superiorly, **Table 2** presents PFS estimates derived according to the OS prognostic scoring tool in the development data, where median PFS ranged from 5 months to 1 month for the low- to high-risk prognostic groups. Supplementary Figure S5 presents Kaplan–Meier estimates of PFS according to prognostic groups. Supplementary Figure S2 presents calibration plots of PFS for prognostic groups in the development and validation data.

The PFS discrimination performance of LIPI (Supplementary Fig. S5), Sen and colleagues (17) prognostic model, GRIm-Score, and SII were 0.59, 0.59, 0.60, and 0.58, respectively, on validation data (Supplementary Table S7).

CRP and prognostic tool in patients treated with docetaxel

CRP (<3 vs. 3–9.9 vs. 10–49.9 vs. ≥50 mg/L) was significantly associated with OS ($P < 0.001$, $c = 0.66$) in a pooled analysis of patients who received docetaxel within OAK/POPLAR (Supplementary Table S9). Supplementary Figure S6 presents Kaplan–Meier estimates of OS by CRP for patients who received docetaxel within OAK/POPLAR.

The prognostic scoring tool groups were significantly associated with OS ($P < 0.001$, $c = 0.67$) and PFS ($P < 0.001$, $c = 0.60$) for patients who received docetaxel within OAK/POPLAR. Supplementary Table S10 and Supplementary Fig. S7 provide a summary of OS/PFS estimates for patients who received docetaxel within OAK/POPLAR. Comparing the pooled randomized arms of OAK/POPLAR, the observed improvement in median OS for participants randomized to atezolizumab (versus docetaxel) within the low, intermediate-low, and intermediate prognostic groups was >3 (>24 vs. 21), 2 (19 vs. 17), and 4 (14 vs. 10) months, respectively. Little apparent benefit in median OS was observed for atezolizumab (vs. docetaxel) for the intermediate-high (7 vs. 8 months) and high-risk (3 vs. 4 months) prognostic groups (**Fig. 2**). No benefit in median PFS was observed for atezolizumab versus docetaxel for the low- to high-risk groups (Supplementary Fig. S8).

Discussion

Using large high-quality data, this study developed and validated a pretreatment prognostic tool able to clearly distinguish patient groups with distinct differences in OS and PFS when considering atezolizumab initiation for advanced NSCLC treatment. To the best of the authors' knowledge, this is the first published NSCLC-ICI–specific prognostic tool that accounts for pretreatment CRP which was demonstrated as the single most predictive variable for OS in advanced patients with NSCLC initiating atezolizumab. Because of this, it is

Table 2. OS and PFS estimates by pretreatment prognostic group for patients treated with atezolizumab within OAK/POPLAR.

		OS		PFS	
Prognostic group	Prognostic Score	Median [95% CI] T2E (months)	24 month [95% CI] OS probability (%)	Median [95% CI] T2E (months)	12 month [95% CI] PFS probability (%)
Low	<18	>24 [22–24]	55 [42–72]	5 [4–8]	25 [18–34]
Intermediate-low	18–23	19 [15–24]	47 [38–58]	4 [3–5]	23 [17–32]
Intermediate	24–31	14 [11–16]	29 [22–38]	3 [2–4]	17 [13–24]
Intermediate-high	32–38	7 [6–10]	7 [1–35]	2 [1–3]	10 [6–17]
High	≥39	3 [3–5]	0 [NA]	1 [1–1]	6 [2–13]

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; T2E, time to event.

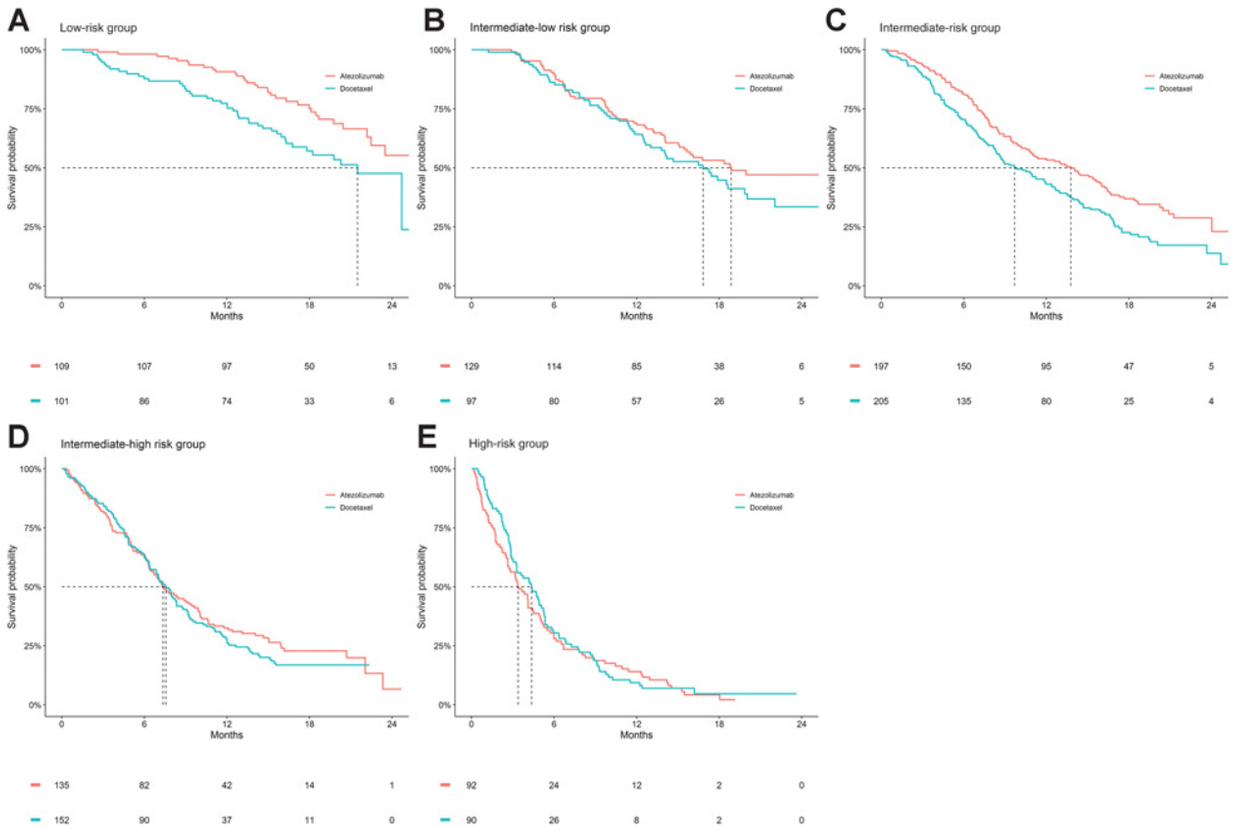

Figure 2.
A–E, Kaplan–Meier comparisons of OS by pretreatment prognostic groups for pooled randomised arms of OAK/POPLAR (atezolizumab versus docetaxel).

unsurprising that on external validation, the discrimination performance of the developed tool was substantially superior than other previously proposed options (8, 17–22). Importantly, the presented study includes data from trials including randomized treatment allocation, enabling valid assessment of treatment effect of atezolizumab compared to docetaxel by identified prognostic groups.

The identified optimal combination of predictors for OS included CRP, LDH, dNLR, albumin, PD-L1 expression, ECOG PS, months since metastatic diagnosis, and metastatic sites count. This study is the largest to evaluate the predictive performance of CRP within a cohort of advanced NSCLC patients initiating ICI therapy (6, 7, 23–26). Smaller prior studies have suggested that CRP may be an important prognostic factor in patients with advanced cancer initiating ICIs (23–26), and the prognostic significance of CRP in NSCLC is established (27, 28). Of the investigated univariables in this study, CRP was the strongest predictor of OS within the OAK and POPLAR cohort ($c = 0.64$; Supplementary Table S2), and performance was maintained on validation ($c = 0.71$). Exemplifying the need to appreciate the prognostic significance of CRP in patients with advanced NSCLC initiating ICI therapy, is that even with enforced easy to use cut-off points, its *c*-statistic was superior in the development (0.64 vs. 0.61) and validation (0.71 vs. 0.66) data as compared with LIPI, which incorporates only dNLR and LDH.

In addition to presenting the first NSCLC-ICI–specific prognostic tool that accounts for pretreatment CRP, the presented tool is also the first to incorporate the prognostic potential of PD-L1 expression. Thus, while the potential for PD-L1 expression to consistently and conclusively discriminate treatment benefit to ICIs remains under investigation (7, 9, 10, 29), this study demonstrates the clinical application of evaluating PD-L1 expression to provide patients with realistic prognostic information, which has not been accounted for in prior tools. Furthermore, exemplifying the need to evaluate beyond PD-L1 expression, CRP, dNLR, and LDH is that each of albumin, ECOG PS, months since metastatic diagnosis, and metastatic sites count substantially improved model performance (demonstrated by an increase in the c-statistic by at least 0.05). It is not surprising these variables provide important prognostic information given prior literature demonstrating their prognostic significance for advanced NSCLC- or ICI-treated patients (6, 7).

While this study had a focus on optimising prediction performance, equally there was a preference to develop a pretreatment prognostic tool that was practical for clinical use. This included using routinely available clinical data, a preference for a single model for OS and PFS, and avoiding complex numerical derivations. The developed prognostic tool has a similar structure to the widely utilized Hurria and colleagues (30) tool for predicting chemotherapy-related toxicity in older adults, and thus has significant potential for integration within clinical use (31, 32). In addition to evaluating the performance of a developed decision tree, the machine learning approach, random forest, was evaluated. Despite a series of simplifications, including enforcing simple cut-off points to continuous variables, minimizing the number of variables via backward deletion, using a single risk score for both OS and PFS, and scaling coefficients to integers between 0 to

10, the performance of the developed prognostic tool on validation was comparable to the black-box random forest approach.

While the numerical calculations required to utilize the prognostic tool developed herein are greater than LIPI (ref. 8; the most assessed tool to date; refs. 8, 21, 22), the discrimination performance (*c*-statistic) was markedly superior in the development (0.72 vs. 0.61) and validation (0.76 vs. 0.66) data. The developed prognostic tool was also superior to other previously proposed options (8, 17–22). Demonstrating the importance of this optimized discrimination performance from a patients perspective is that within the pooled OAK and POPLAR cohort, the observed difference in median OS and 24-month OS probability between the high- to low-risk groups was greater than 21 (3 vs. >24) months and 55% (0 vs. 55), respectively, for the tool herein. Comparatively, the difference in median OS and 24-month OS probability was 13 (5 vs. 18) months and 17% (14 vs. 31), respectively, between the LIPI defined poor to good prognostic groups, indicative of a significantly greater spread of risks for the tool developed herein.

The developed prognostic tool allows the simultaneous interpretation of personalized risks for OS and PFS in individuals commencing ICI therapy for advanced NSCLC. While the OS and PFS estimates presented in **Table 2** are only applicable to patients who corresponded to the inclusion criteria of OAK and POPLAR (i.e., patients with advanced NSCLC whose disease has progressed on platinum-containing therapy), the maintained discrimination performance within BIRCH and FIR indicates prognostic performance in external cohorts. For example, in contrast to OAK and POPLAR, BIRCH and FIR included only PD-L1–positive patients and was not limited to patients whose disease had progressed on prior platinum-containing therapy. Thus, the developed tool should be explored further as a mechanism to provide patients with realistic expectation of ICIs. The importance of this is highlighted by the difference in median OS and 24-month OS probability being greater than 21 (range = 3 to >24) months and 55% (0 vs. 55) between the high- to low-risk groups within OAK and POPLAR. Another potential utilization of the developed tool is to aid clinical trial randomization, whereby balancing prognostic scores between arms can aid valid treatment comparisons. Future directions of research include evaluation as a prognostic tool or treatment-effect predictor for other ICIs used for advanced NSCLC (durvalumab, nivolumab, pembrolizumab), for first-line use of ICIs, and ICIs used in combination therapies. Moreover, the prognostic tool may be considered as an aid to basic research design, whereby it may be used to select patients with predicted good or bad prognosis, and subsequently allow a targeted analysis of genetic profiles to determine markers resulting in patients with unexpectedly bad or good outcomes (i.e., a targeted utilization of model unpredictability).

The developed and validated prognostic groups had modestly superior discrimination performance in the atezolizumab-treated patients from OAK and POPLAR, albeit a similar prognostic association within docetaxel-treated patients highlights the prognostic groups are largely not specific to ICI treatment. Nonetheless, when comparing the pooled randomized arms of OAK/POPLAR, the benefit of atezolizumab treatment (vs. docetaxel) was greatest in the low-risk group (>3 months median OS improvement), with little benefit apparent for the highest-risk group. Future directions of research should include further evaluation of the prognostic groups as a marker of heterogeneity in ICI treatment effect (both relative and absolute; refs. 33–35) for randomized clinical trials across other ICIs used for advanced NSCLC (durvalumab, nivolumab, pembrolizumab), first-line use of ICIs, and combination use of ICIs.

Clinical trials are a pillar of evidenced-based medicine and the data collected within are high-quality and stringently regulated. Equally, the inclusion criteria of trials can limit generalizability to clinical practice (36). For example, ECOG PS is an important cancer prognostic marker; however, no participants within the OAK, POPLAR, BIRCH, or FIR trials had scores of three or four (2, 9–11). Furthermore, this study is a *post hoc* analysis, and assessed predictors were limited to available data. Nonetheless, data from OAK and POPLAR were pooled to increase study power and generalizability; the extent of commonly collected clinicopathologic data was vast and ultimately the full prediction model required reduction to facilitate clinical potential. The data also contained PFS which is often not collected in registry data, yet is an important outcome to patients (5).

The discrimination performance of the developed tool for OS prediction was consistent with a strong-performing model in both the development and external validation cohorts ($c > 0.72$; ref. 37). Ideally the discrimination performance for PFS would have a *c*-statistic greater than 0.7, albeit a significant association between prognostic groups and PFS was identified. Differences in inclusion criteria (e.g., prior treatments received), nuances of disease progression definitions between trials, and variable subsequent therapies between patients following study completion may have contributed to the poorer prediction of PFS. While this study was able to validate the developed tool within data external to the development data, future research will ideally validate and recalibrate, if necessary, using real-world population data to optimize generalizability and performance. Nonetheless, the study presents a model developed using data which underpins the use of atezolizumab within the advanced NSCLC population, and thus the developed tool may be used to better understand likely survival outcomes from therapy than is currently possible.

In conclusion, a pretreatment prognostic tool for OS and PFS in patients with advanced NSCLC initiating atezolizumab was developed and validated. Importantly the prognostic tool incorporates a multitude of factors to provide more nuanced survival predictions than previously presented options, and notably these factors include CRP and PD-L1 expression which are among the most prognostic factors in advanced NSCLC patients treated with ICIs. There is the potential for the developed prognostic tool to provide patients with advanced NSCLC with more realistic expectations of long-term disease control and survival when considering the initiation of ICIs.

Disclosure of Potential Conflicts of Interest

G. Kichenadasse is an advisory board member/unpaid consultant for Merck. C.S. Karapetis is an advisory board member/unpaid consultant for Roche, Bristol-Myers Squibb, Merck Serono, AstraZeneca, and Amgen. A. Rowland reports receiving commercial research grants from Pfizer. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.M. Hopkins, A. Rowland, M.J. Sorich
Development of methodology: A.M. Hopkins, M.J. Sorich
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.M. Hopkins, A. Rowland, M.J. Sorich
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.M. Hopkins, G. Kichenadasse, E. Garrett-Mayer, C.S. Karapetis, A. Rowland, M.J. Sorich
Writing, review, and/or revision of the manuscript: A.M. Hopkins, G. Kichenadasse, E. Garrett-Mayer, C.S. Karapetis, A. Rowland, M.J. Sorich
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Rowland, M.J. Sorich
Study supervision: A.M. Hopkins, A. Rowland, M.J. Sorich

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