

6 Risk Prognostication After Hypomethylating Agents Combined With Venetoclax in AML: The PRISM Risk Model

Curtis A. Lachowicz, MD¹ ; Joshua F. Zeidner, MD² ; Jad Othman, MBBS^{3,4,5} ; Andy Kaempf, MS¹ ; Seongseok Yun, MD, PhD⁶; Maël Heiblig, MD, PhD⁷ ; Michael Heuser, MD^{8,9} ; Rabia Shahswar, MD^{8,10}; Rafael Madero Marroquin, MD¹¹ ; Joseph M. Cannova, MD, PhD¹¹ ; Andrius Žučanka, MD, PhD¹² ; Jennifer Marvin-Peek, MD¹³ ; Jayastu Senapati, MBBS¹³ ; Yasmin Abaza, MD¹⁴ ; Alok Swaroop, MD, PhD¹⁴ ; Irene Zacheo, MD¹⁵ ; Federica Monaco, MD¹⁶; Amine Belhabri, MD¹⁷ ; Urbain Tauveron-Jalenques, MD¹⁸; Emmanuelle Tavernier, MD, PhD¹⁹ ; Martin Carré, MD²⁰; Gaspar Aspas Requena, MD²¹ ; Rachel J. Cook, MD, MS¹; Elie Traer, MD, PhD¹ ; Jennifer N. Saultz, DO¹ ; Jenny O'Nions, BM, BCh²²; Faisal Basheer, MBBS, FRCPath²³; John Laurie, MB, ChB²⁴ ; Shivani Handa, MD²⁵ ; Eytan M. Stein, MD²⁶ ; Maria R. Baer, MD²⁷; Rebecca Olin, MD, MSCE²⁸ ; William Blum, MD²⁹; Gary Schiller, MD³⁰ ; Tara Lin, MD³¹; Emily Curran, MD³² ; Ashley Yocum, PhD³³ ; Ellen Madarang, PharmD, BCOP³⁴; Naval Daver, MD¹³ ; Tapan M. Kadia, MD¹³ ; Giovanni Marconi, MD³⁵ ; Yazan Madanat, MD, PhD³⁶ ; Richard Dillon, MBBS, PhD³⁷ ; Courtney D. DiNardo, MD, MSCE¹³ ; Ronan Swords, MD, PhD, FRCPI, FRCPath¹; Juan E. Arango Ossa, MEng³⁸ ; Justin Watts, MD³⁴; Sanam Loghavi, MD³⁹ ; Daniel A. Pollyea, MD⁴⁰ ; and Elsa Bernard, PhD⁴¹ ; for the PRISM-AML Investigators

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ABSTRACT

PURPOSE As risk stratification for patients with AML treated with lower-intensity venetoclax-based therapy remains suboptimal, we developed and validated a prognostic model integrating clinical, cytogenetic, and molecular features.

METHODS We assembled a multinational data set comprising 2,092 adults with newly diagnosed AML treated with hypomethylating agents plus venetoclax (HMA + VEN). One thousand nine hundred eighteen patients with complete data were randomly divided into training (70%) and internal validation (30%) cohorts. Two independent external validation cohorts were assembled (n = 500 and n = 222). Modeling overall survival (OS), Elastic Net regression was applied in 1,000 bootstrap samples from the training cohort to select variables for a Ridge regression, which generated a continuous Prognostic Risk Integration for Survival Modeling (PRISM) score and risk categories based on tertiles (PRISM-3: low, moderate, high). These PRISM indices were then computed for the validation cohorts and compared with the 4-gene classifier (based on mutations in *FLT3*-ITD, *N/KRAS*, and *TP53*).

RESULTS PRISM integrated 17 clinical and genomic variables and demonstrated a linear association with OS. PRISM-3 stratified survival consistently across all cohorts (median OS: 25.1–28.8 months for low risk, 12.5–14.7 months for moderate risk, and 5.8–6.7 months for high risk; $P < .001$). Compared with the 4-gene classifier, PRISM-3 reassigned approximately 40% of patients (and >50% of those with favorable risk) and demonstrated significantly better discrimination in validation cohorts (C-index 0.63–0.65 v 0.59–0.61; $P < .05$).

CONCLUSION PRISM is a validated prognostic model for patients with AML receiving HMA + VEN that improves survival risk stratification beyond current standard tools and supports individualized, risk-adapted clinical decision making. The model, the PRISM-AML Risk Calculator, is publicly available.

ACCOMPANYING CONTENT

 Appendix
 Data Supplement

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INTRODUCTION

AML is an aggressive hematologic malignancy characterized by clinical and molecular heterogeneity, with patients often harboring multiple somatic genetic mutations at diagnosis.¹ Genomic profiling at presentation is central to disease classification and prognostication, and is incorporated in the current European LeukemiaNet (ELN)

and National Comprehensive Cancer Network (NCCN) guidelines.^{2–4}

Venetoclax (VEN) combined with a hypomethylating agent (HMA; azacitidine or decitabine) or low-dose cytarabine (LDAC) is the standard initial therapy for older or unfit patients with AML. However, risk stratification in this setting remains incompletely defined.⁵ Prognostic models

CONTEXT

Key Objective

Can we better predict outcomes for patients with AML treated with venetoclax-based therapy by using a risk prediction model that combines clinical, cytogenetic, and genomic information?

Knowledge Generated

The Prognostic Risk Integration for Survival Modeling (PRISM) model identified risk groups with consistent survival stratification across multiple patient cohorts. Substantial patient risk reclassification and improved prognostic discrimination were observed in independent validation data sets compared with existing risk models.

Relevance (C. Craddock)

The PRISM model provides important prognostic information to inform the management of adults with newly diagnosed AML treated with venetoclax-based therapy, including the timing of stem-cell transplantation. These innovative data have the potential to inform the design of future trials in fit and unfit adults with newly diagnosed AML receiving venetoclax-containing induction regimens.*

*Relevance section written by JCO Associate Editor Charles Craddock, MD.

derived from younger, intensively treated AML populations inadequately discriminate outcomes for venetoclax-treated patients, underscoring the need for therapy-specific approaches.⁶

The 4-gene classifier for patients treated with HMA + VEN, based on mutations in *NRAS*, *KRAS*, and *TP53*, and the presence of *FLT3*-ITD, represents a major advance in addressing prognosis and has been incorporated into the ELN-2024 recommendations.^{2,6} Despite this, its discrimination is modest and it does not incorporate clinical or cytogenetic variables that retain prognostic relevance.⁷⁻⁹ Moreover, other models from Beat AML, Mayo Clinic, and a refined ELN model were developed in relatively small cohorts, limiting generalizability.⁷⁻⁹

As lower-intensity venetoclax-based therapy is increasingly used across diverse patient populations, improved risk prediction is needed to guide individualized prognostication, therapeutic escalation or de-escalation, and clinical trial design. To address this ongoing need, we leveraged a large, diverse, multinational data set of patients with AML treated with HMA + VEN to develop and externally validate a therapy-specific prognostic model integrating clinical, cytogenetic, and genetic features.

METHODS

Inclusion Criteria and Patient Cohorts

We first assembled a multinational dataset of 2,092 adult patients (age ≥ 18 years) with treatment-naïve AML who received HMA + VEN at 78 participating academic medical centers. Clinical and molecular data ascertainable at the time of venetoclax initiation were abstracted, along with

treatment characteristics for cycles 1 and 2, response, and overall survival (OS). Patients with missing mutation characterization were excluded, resulting in 1,918 cases within the full initial data set that were randomly divided into training (70%; $n = 1,347$) and internal validation cohorts (IVC; 30%; $n = 571$) when stratifying on survival disposition, *TP53* mutation status, and receipt of HCT.

External validation was performed on patients derived from two cohorts: external validation cohort 1 (EVC1; $n = 500$) patients were treated on the Beat AML trial (ClinicalTrials.gov identifier: [NCT03013998](https://clinicaltrials.gov/ct2/show/study/NCT03013998)) or at seven academic medical centers. External validation cohort 2 (EVC2; $n = 222$) patients were treated at The University of Texas MD Anderson Cancer Center (Data Supplement, Table S1, online only). Participating centers and patient variables are listed in the Data Supplement (Tables S1 and S2). All patients provided informed consent in accordance with the Declaration of Helsinki.

Response and Survival

Complete remission (CR) and complete remission with incomplete hematologic recovery (CRi) were defined by ELN-2022 criteria.³ OS was calculated from HMA + VEN initiation until death from any cause or last follow-up and estimated using the Kaplan-Meier method. The exception to this was OS measured from (landmarked at) 45 and 75 days after therapy initiation for analyses of VEN dose and duration during cycles 1 and 2, respectively. Survival comparisons across groups were performed using the log-rank test and Cox proportional hazards regression, producing hazard ratios (HRs) and Wald test *P* values.

Hematopoietic cell transplantation (HCT) was coded as a time-dependent covariate. To specifically assess the impact

of risk group on the incidence of HCT, we performed competing risk analyses with HCT as the event of interest and death without HCT as the competing event on the full initial data set and EVC1 with available detailed HCT data. Gray's test was used to compare cumulative incidence functions, and Fine-Gray regressions were fit to estimate subdistribution hazard ratios (SHRs) and Wald test *P* values.

Model Development

To avoid low counts that could impair precision of statistical estimates, only genetic and clinical features observed in >4% of the initial full data set were considered for OS modeling (Data Supplement, Fig S1). In addition, *DDX41*, mutated in 3.8% of patients tested with a next-generation sequencing panel containing this gene (74%, *n* = 1,413/1,918), was included. This decision to include *DDX41* was driven by (1) its inclusion in ELN-2024 risk stratification guidelines and (2) its expanding coverage on targeted myeloid hotspot sequencing platforms (Data Supplement, Fig S2).^{2,10,11}

Variable categorizations were explored on training cohort patients, with consolidation of smaller-sized groups exhibiting similar associations with OS (Data Supplement, Figs S3 and S4). Karyotype was coded as a 4-level categorical variable (diploid [reference], favorable/intermediate, adverse, and missing) after consolidating favorable- and intermediate-risk cytogenetics defined by ELN-2022. The missing karyotype category accounted for the 7% of patients with culture failure or missing cytogenetics in the initial data set.

Multivariable Cox regression for OS with Elastic Net regularization (mixing parameter $\alpha = .5$) was applied to 1,000 bootstrap samples from the training cohort. Retained features for postselection modeling were those with unidirectional selection (ie, nonzero β coefficients of the same sign) in $\geq 75\%$ of bootstrap iterations. These features were subsequently fit using Cox regression with Ridge regularization to address multicollinearity. Coefficient estimates from this Ridge model of OS were multiplied by the corresponding variable values and summed to generate the linear predictor, termed the Prognostic Risk Integration for Survival Modeling (PRISM) score. Penalized spline modeling was applied to assess linearity in the log-hazard of death for continuous predictors of OS. For clinical interpretability, the PRISM score was divided into tertiles using training cohort patients to produce PRISM-3 risk groups: low, moderate, and high. The training set-derived β coefficients for calculating PRISM and the cut points for producing PRISM-3 were directly applied to score and risk-stratify all validation cohort patients.

After constructing PRISM, exploratory analyses were performed on the full initial data set to evaluate the OS effects of VEN duration during cycles 1 and 2 (Data Supplement, Figs S5 and S6), VEN dosing in the presence of a strong CYP3A4 inhibitor (Data Supplement, Fig S7), and model performance

in patients attaining CR/CRi and/or receiving extended venetoclax cycles. Exploratory subgroup analyses were performed in younger (age <65 years) and older (age ≥ 65 years) patients using all four cohorts.

Cohort and Model Comparison

Between-cohort differences were evaluated using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Discriminatory performance of Cox OS models was quantified by Harrell's concordance index (C-index) with comparisons between models based on 5,000 bootstraps.

RESULTS

Patient Demographics

Characteristics of the training and IVC (*n* = 1,918) are summarized in Table 1. Median age at diagnosis was 74 years (range, 19–93; Data Supplement, Fig S8A). According to the 4-gene classifier, 56% of patients were favorable-, 21% intermediate-, and 23% adverse-risk, with similar distribution across age quartiles (Data Supplement, Fig S8B).

Overall, 57% of patients had de novo AML (*n* = 1,099), while 43% had sAML (*n* = 819), including sAML-AHD (*n* = 638) and therapy-related AML (defined as receipt of prior cytotoxic chemotherapy or radiotherapy; *n* = 181). Among patients with available dosing information (76%, *n* = 1,459), 75% received >14 days of venetoclax during cycle 1. Median number of treatment cycles received was three (range, 0–71); 12% (*n* = 225) of patients underwent allogeneic HCT.

Diploid (33%) and ELN-2022 adverse-risk karyotypes (34%) were most common (Data Supplement, Fig S8C). Patients had a median of three mutations at diagnosis (Data Supplement, Fig S8D). The most frequently detected mutations were *TP53* (23%), *ASXL1* (22%), *TET2* (21%), *RUNX1* (21%), *SRSF2* (20%), *DNMT3A* (19%), *NPM1* (14%), *IDH2* (14%), and *NRAS* (11%; Data Supplement, Fig S8E).

Distinct patterns of mutational enrichment were observed across AML subtypes (Data Supplement, Figs S8E and S9). sAML was enriched for mutations in *ASXL1*, *TET2*, *SRSF2*, *JAK2*, *SF3B1*, and *KRAS*, which frequently co-occurred (Data Supplement, Fig S8F). As expected, *TP53* mutations were more prevalent in therapy-related (33%) as opposed to de novo AML (20%), whereas *NPM1* mutations were more common in de novo (19%) versus sAML-AHD (6%) or therapy-related AML (12%). There were no clinically meaningful differences in baseline characteristics between the training and IVC (Table 1).

PRISM Risk Score Generation and PRISM-3 Risk Groups

Seventeen clinical and genomic variables were selected for the final PRISM model (Data Supplement, Fig S10).

TABLE 1. Cohort Comparisons

Characteristic	Overall (N = 1,918)	Training (n = 1,347)	Validation (n = 571)	P
Age at diagnosis, years, median (range)	74 (19-93)	73 (19-93)	74 (20-91)	.98
4-gene classifier risk, No. (%)				.97
Favorable	1,072 (56)	754 (56)	318 (56)	
Intermediate	410 (21)	286 (21)	124 (22)	
Adverse	436 (23)	307 (23)	129 (23)	
Karyotype group, No. (%)				.90
Diploid karyotype	627 (33)	443 (33)	184 (32)	
ELN 2022 favorable/intermediate karyotype (excluding diploid)	489 (25)	344 (26)	145 (25)	
ELN22 adverse karyotype	660 (34)	456 (34)	204 (36)	
Missing karyotype	142 (7.4)	104 (7.7)	38 (6.7)	
AML type, No. (%)				.32
De novo AML	1,099 (57)	762 (57)	337 (59)	
Secondary AML	819 (43)	585 (43)	234 (41)	
Prior CMML	58 (3.0)	39 (2.9)	19 (3.3)	
Prior MDS	440 (23)	313 (23)	127 (22)	
Prior MPN	127 (6.6)	85 (6.3)	42 (7.4)	
Prior AHD-NOS	13 (0.7)	8 (0.6)	5 (0.9)	
Therapy-related	181 (9.4)	140 (10)	41 (7.2)	
HMA backbone, No. (%)				
Azacitidine	1,691 (88)	1,189 (88)	502 (88)	.83
Decitabine	227 (12)	158 (12)	69 (12)	.83
Treatment cycles, median (range)	3.0 (0.0-71.0)	3.0 (0.0-66.0)	3.0 (1.0-71.0)	.22
Cycle 1 venetoclax dose, median (range)	100 (20-800)	100 (20-800)	100 (50-400)	.57
Cycle 1 strong CYP3A4 use, No. (%)	958 (68)	670 (67)	288 (70)	.16
Cycle 1 VEN duration, weeks, No. (%)				.19
1-7 days	102 (6.6)	68 (6.2)	34 (7.5)	
8-14 days	283 (18)	202 (18)	81 (18)	
15-21 days	293 (19)	221 (20)	72 (16)	
22-28 days	826 (53)	571 (52)	255 (57)	
>28 days	41 (2.7)	32 (2.9)	9 (2.0)	
Cycle 1 VEN duration, days, median (range)	28 (0-42)	28 (0-42)	28 (0-42)	.69
Cycle 2 VEN dose, median (range)	100 (50-800)	100 (50-800)	100 (50-400)	.77
Cycle 2 strong CYP3A4 use, No. (%)	422 (77)	302 (77)	120 (77)	.96
Cycle 2 VEN duration, weeks, No. (%)				.25
1-7 days	18 (3.0)	14 (3.3)	4 (2.4)	
8-14 days	123 (21)	94 (22)	29 (17)	
15-21 days	164 (28)	111 (26)	53 (31)	
22-28 days	274 (46)	198 (47)	76 (45)	
>28 days	15 (2.5)	8 (1.9)	7 (4.1)	
Cycle 2 VEN duration, days, median (range)	21.0 (0-51)	21.0 (0-41)	21.0 (0-51)	.43
OS, months, median (95% CI)	12.6 (11.4 to 13.8)	12.4 (11.2 to 14.2)	12.9 (10.7 to 14.4)	.71
Follow-up, months, median (95% CI)	22.3 (20.3 to 24.1)	21.8 (19.8 to 24.1)	22.6 (20.3 to 29.5)	.29
Allogeneic HCT, No. (%)	225 (12)	160 (12)	65 (11)	.76

Abbreviations: AHD-NOS, antecedent hematologic disorder- not otherwise specified; CMML, chronic myelomonocytic leukemia; ELN, European LeukemiaNet; HCT, hematopoietic cell transplantation; MDS, myelodysplastic neoplasm; MPN, myeloproliferative neoplasm; OS, overall survival; PRISM, Prognostic Risk Integration for Survival Modeling; VEN, venetoclax.

Adverse-risk features included mutations in *KRAS*, *TP53*, *JAK2*, and *ASXL1*; *FLT3*-ITD; nondiploid cytogenetics (ie, ELN-2022 adverse-risk cytogenetics; ELN-2022 favorable and nondiploid intermediate); sAML; male sex; and older age. Favorable-risk features included mutations in *BCOR*, *IDH1*, *STAG2*, *RUNX1*, *IDH2*, *CEBPA*, *NPM1*, and *DDX41*. Feature

weights derived from the postselection Ridge regression model are shown in [Figure 1A](#). Missing karyotype (included to accommodate patients without cytogenetic data) had a small prognostically favorable coefficient, consistent with a near-null effect.

The continuous PRISM score demonstrated a linear association with OS and was discretized into three risk groups (PRISM-3 low, moderate, and high) for clinical interpretation. Distinct enrichment patterns were observed across PRISM-3 groups in the training cohort ([Fig 1B](#)). Low-risk patients were enriched for *IDH2* (31%), *RUNX1* (29%), and *NPM1* (28%) mutations, with a higher frequency of *DDX41* (8%). Moderate-risk patients exhibited higher frequencies of male sex (70%), *ASXL1* mutations (28%), and *SAML* (50%). High-risk patients had a predominance of *TP53* mutations (63%) and ELN-2022 adverse-risk cytogenetics (76%). *NRAS* mutations, not selected for the final PRISM model, were not associated with OS in the training cohort (HR, 0.90 [95% CI, 0.72 to 1.13]; $P = .37$).

Risk Reclassification Relative to the 4-Gene Classifier

Within the training cohort ($n = 1,347$), PRISM-3 reclassified 43% of patients relative to the 4-gene classifier. Reclassification was most pronounced among patients categorized by the 4-gene classifier as favorable-risk, of whom 52% were reassigned to PRISM-3 moderate-risk (40%) or high-risk groups (12%; [Fig 1C](#)). Similarly, in the IVC ($N = 571$), 42% of all patients were reclassified, with 52% of 4-gene favorable-risk patients reassigned to moderate-risk (41%) or high-risk (11%) PRISM categories.

Clinical Outcomes Across PRISM-3 Groups

Rates of CR/CRi differed significantly across PRISM-3 groups in the training (low: 78% v moderate: 61% v high: 42%; [Fig 2A](#)) and IVC (76% v 49% v 40%; [Fig 2B](#)).

After a median follow-up of 22 and 23 months, 59% of patients in both training and IVC were deceased. Median OS differed markedly across PRISM-3 low-, moderate-, and high-risk groups in the training cohort (25.1 v 14.6 v 6.7 months; $P < .001$) and the IVC (25.6 v 14.7 v 6.0 months; $P < .001$; [Figs 2C](#) and [2D](#)). OS HRs comparing PRISM-3 groups were consistent across cohorts, supporting model reproducibility ([Fig 2E](#)). Adjustment for HCT did not alter these associations (Data Supplement, Table S3).

PRISM-3 had superior discrimination for OS compared with the 4-gene classifier (C-index 0.63 v 0.60; $P = .030$) in the IVC, on which PRISM was not built ([Fig 2F](#)).

External Validation of the PRISM Model

Patient features in the training, IVC, EVC1, and EVC2 were broadly comparable ([Table 2](#)), although EVC1 included fewer male and *SAML* patients, while EVC2 had higher-risk

patients per the 4-gene classifier and PRISM-3 risk categories ([Figs 3A](#) and [3B](#); Data Supplement, Fig S11A).

In EVC1, PRISM-3 risk assignment (available in 93% [$n = 467/500$] of patients) reclassified 42% of patients relative to the 4-gene predictive signature, including 52% of favorable-risk patients (Data Supplement, Fig S11B). In EVC2, PRISM-3 reclassified 41% of patients relative to the 4-gene classifier, including 57% of favorable-risk patients (Data Supplement, Fig S11B).

Within the combined EVCs, PRISM-3 stratified OS with significantly inferior outcomes for moderate-risk (HR, 2.05 [95% CI, 1.60 to 2.63]; $P < .001$) and high-risk patients (HR, 3.96 [95% CI, 3.11 to 5.03]; $P < .001$) versus low-risk patients. Compared with the 4-gene classifier, PRISM-3 improved survival discrimination (C-index 0.65 v 0.61; $P < .001$; [Figs 3C](#) and [3D](#)).

In pooled analyses using patients with available PRISM scores across all cohorts ($N = 2,607$), the prognostic effect of PRISM-3 was consistent across 4-gene risk strata ([3E](#), [3F](#), and [3G](#)). OS based on 4-gene versus PRISM-3 for all cohorts is displayed in the Data Supplement (Figs S12 and S13).

Within all validation cohort patients ($n = 1,260$), PRISM-3 (C-index 0.65) significantly improved survival prognostication compared with the 4-gene classifier (0.61, $P < .001$), Beat AML (0.62, $P < .001$), and Mayo Clinic (0.62, $P < .001$) risk models, and trended toward improvement versus the refined ELN-2024 risk model (0.63, $P = .071$; Data Supplement, Fig S14).

Impact of Allogeneic Hematopoietic Cell Transplantation

Across training, IVC, and EVC1 cohorts, 12% of patients underwent HCT ($n = 286/2,407$) after a median of 4.6 months. There was significant OS improvement with HCT across PRISM-3 favorable-risk (24-month OS: 74% v 55%), moderate-risk (79% v 34%), and high-risk groups (35% v 15%; $P < .001$; [Figs 4A–4C](#)).

In competing risk analyses, patients with moderate-risk PRISM-3 were less likely to undergo HCT (SHR, 0.67 [95% CI, 0.52 to 0.87]; $P = .003$) and more likely to die without HCT (SHR, 1.71 [95% CI, 1.49 to 1.96]; $P < .001$) compared with PRISM-3 low-risk patients. These effects were even more pronounced when comparing high- versus low-risk PRISM-3 groups (SHR, 0.37 [95% CI, 0.27 to 0.52]; $P < .001$ for HCT and SHR, 3.39 [95% CI, 2.95 to 3.90]; $P < .001$ for death without HCT; [Fig 4D](#)).

PRISM-3 Stratification in Exploratory Subgroups

PRISM-3 stratified survival across age strata (<65 v ≥ 65 years; Data Supplement, Figs S15A–S15D). Within validation cohort patients, PRISM-3 improved prognostic performance

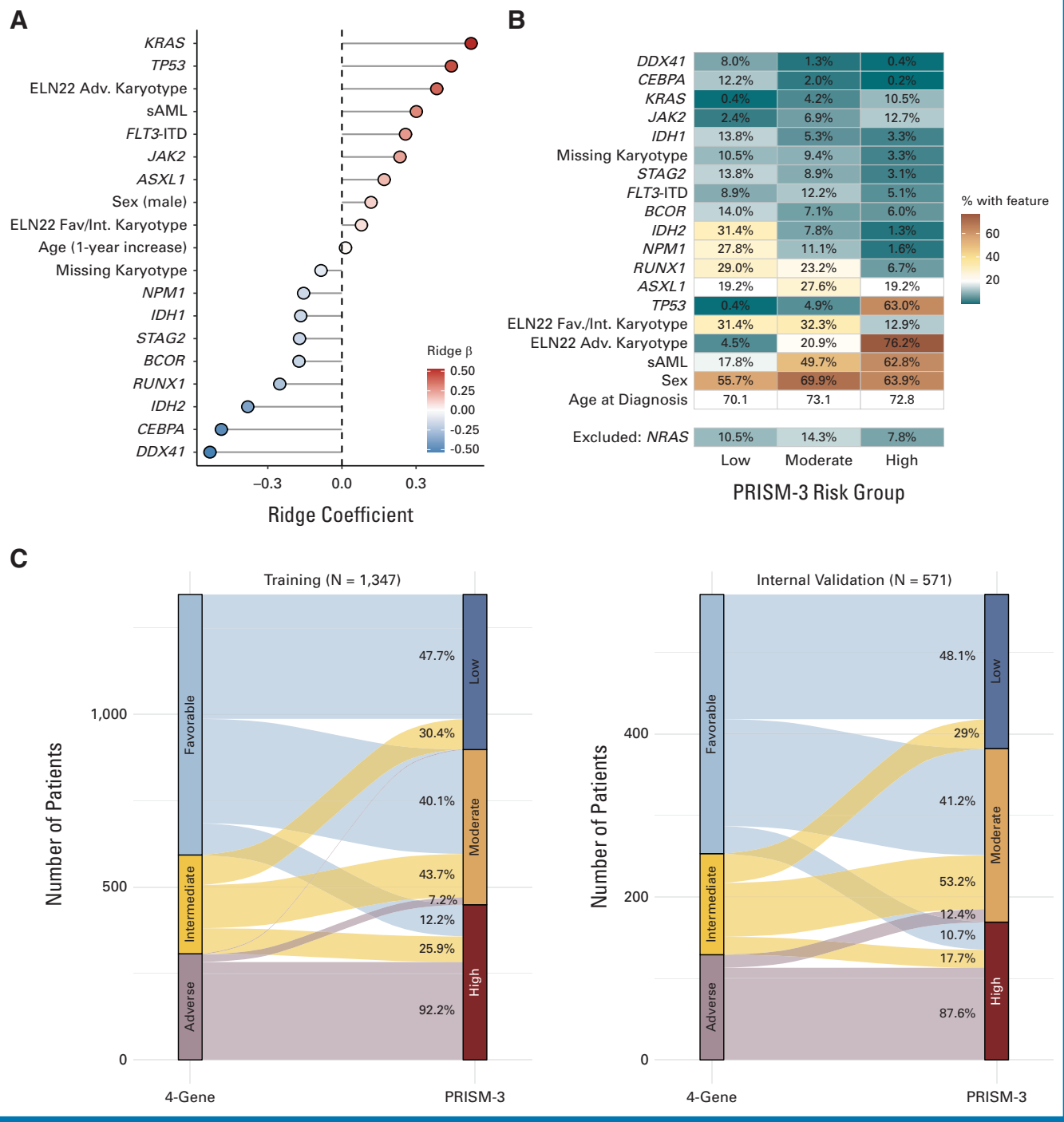


FIG 1. Construction of the PRISM prognostic model and comparison with the 4-gene classifier. (A) Ridge regression β coefficients for clinical, cytogenetic, and molecular features selected for the final PRISM model, with positive coefficients indicating adverse prognostic impact and negative coefficients indicating favorable impact. Karyotype groups are compared with diploid karyotype as the reference group. Intermediate-risk karyotypes are those classified as favorable or intermediate risk, excluding diploid karyotype, according to ELN 2022 criteria. (B) Enrichment of key clinical and genomic features across PRISM-3 risk groups (low, moderate, and high) in the training cohort, expressed as percentage of patients with each feature. (C) Alluvial plots demonstrating patient reclassification from 4-gene risk categories to PRISM-3 risk groups in the training cohort (left) and IVC (right), highlighting substantial redistribution within the 4-gene favorable-risk group. ELN, European LeukemiaNet; IVC, internal validation cohort; PRISM, Prognostic Risk Integration for Survival Modeling.

versus the 4-gene classifier in younger ($n = 163$; C-index 0.65 v 0.61 , $P = .076$) and older patients ($n = 1,097$; C-index: 0.64 v 0.61 , $P < .001$).

PRISM-3 maintained its prognostic discrimination in patients attaining CR/CRi ($n = 1,063$; C-index 0.61 ; Data Supplement, Figs S16A and S16B), receiving ≥ 7 treatment

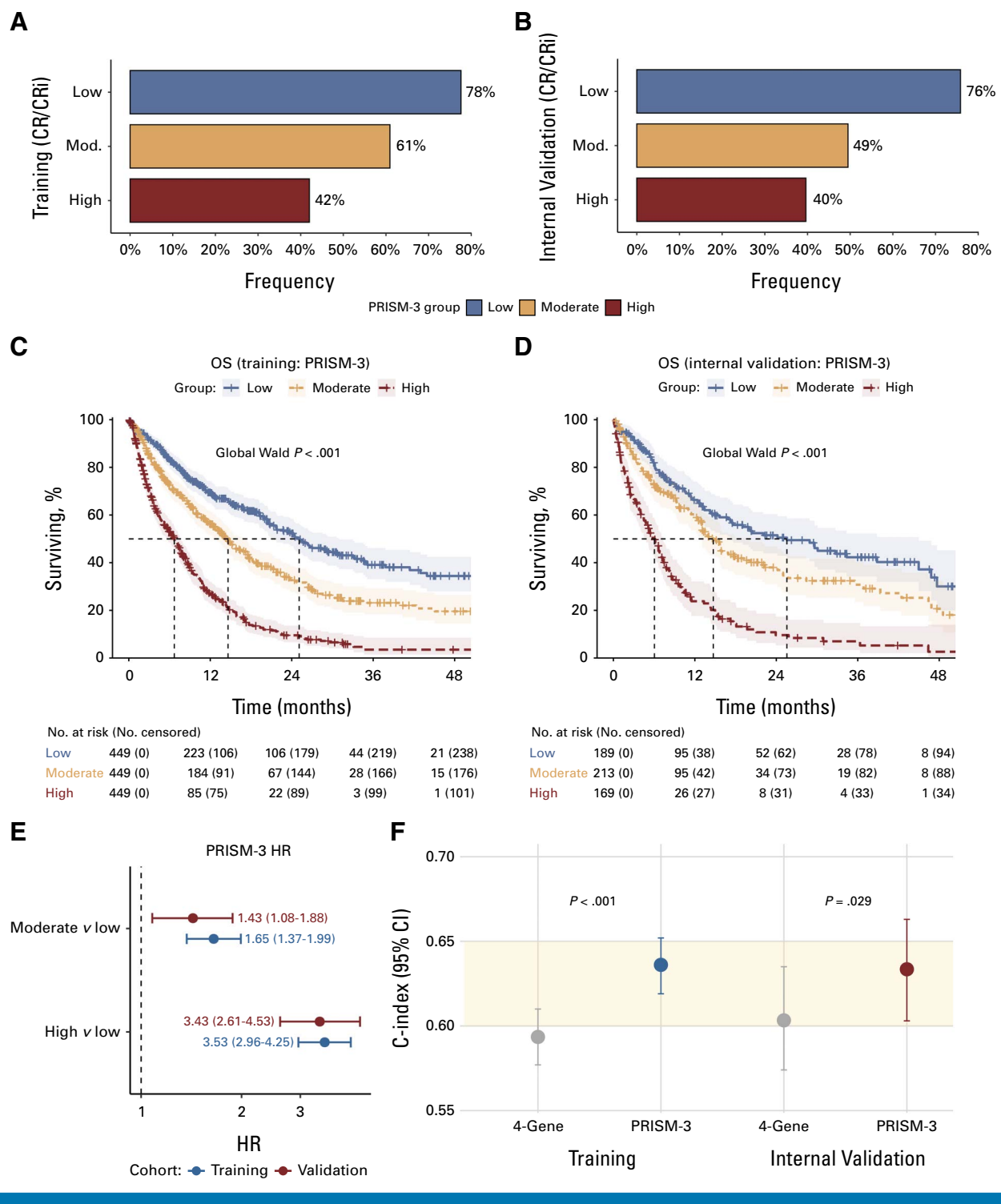


FIG 2. Treatment response and OS according to PRISM-3 risk stratification. (A, B) Rates of CR/CRI across PRISM-3 risk groups in the (A) training cohort and (B) IVC. (C, D) Kaplan-Meier estimates of OS by PRISM-3 risk group in the (C) training cohort and (D) IVC, demonstrating consistent and marked separation of survival curves. Cox regression global Wald test P values are displayed. (E) HRs for OS comparing PRISM-3 moderate-risk and high-risk groups to the low-risk group in the training cohort and IVC. (F) Comparison of prognostic discrimination between PRISM-3 and the 4-gene classifier using Harrell's concordance index (C-index), demonstrating superior performance of PRISM-3. CR/CRI, complete remission or complete remission with incomplete hematologic recovery; HR, hazard ratio; IVC, internal validation cohort; OS, overall survival; PRISM, Prognostic Risk Integration for Survival Modeling.

TABLE 2. PRISM Score Features Across Cohorts

Characteristic	Training (n = 1,347)	IVC (n = 571)	EVC1 (n = 467)	EVC2 (n = 222)
Age at diagnosis, years, median (range)	73 (19-93)	74 (20-91)	74 (46-92)	75 (26-92)
Sex (male), No. (%)	851 (63)	338 (59)	256 (55)	135 (61)
Secondary AML, No. (%)	585 (43)	234 (41)	149 (32)	91 (41)
4-gene risk, No. (%)				
Favorable	754 (56)	318 (56)	256 (55)	99 (45)
Intermediate	286 (21)	124 (22)	99 (21)	43 (19)
Adverse	307 (23)	129 (23)	112 (24)	80 (36)
PRISM score, median (range)	1.35 (−0.29 to 2.89)	1.32 (0.01-2.78)	1.34 (−0.05 to 2.59)	1.56 (0.32-2.74)
PRISM-3 group, No. (%)				
Low	449 (33)	189 (33)	153 (32.7)	61 (28)
Moderate	449 (33)	213 (37)	166 (36)	60 (27)
High	449 (33)	169 (30)	148 (32)	101 (45)
Genetic features (PRISM), No. (%)				
<i>DDX41</i>	44 (3.3)	17 (3.0)	6 (1.3)	6 (2.7)
<i>CEBPA</i>	65 (4.8)	30 (5.3)	32 (6.9)	8 (3.6)
<i>NPM1</i>	182 (14)	88 (15)	63 (13)	42 (19)
<i>IDH1</i>	101 (7.5)	47 (8.2)	38 (8.1)	15 (6.8)
<i>IDH2</i>	182 (14)	85 (15)	67 (14)	29 (13)
<i>FLT3</i> -ITD	118 (8.8)	54 (9.5)	40 (8.6)	11 (5.0)
<i>KRAS</i>	68 (5.0)	27 (4.7)	32 (6.9)	9 (4.1)
<i>JAK2</i>	99 (7.3)	32 (5.6)	44 (9.4)	6 (2.7)
<i>RUNX1</i>	264 (20)	132 (23)	112 (24)	32 (14)
<i>ASXL1</i>	296 (22)	131 (23)	109 (23)	36 (16)
<i>STAG2</i>	116 (8.6)	42 (7.4)	35 (7.5)	7 (3.2)
<i>BCOR</i>	122 (9.1)	61 (11)	56 (12)	5 (2.3)
<i>TP53</i>	307 (23)	129 (23)	112 (24)	80 (36)
Karyotype risk (PRISM), No. (%)				
Diploid	443 (33)	184 (32)	180 (39)	67 (30)
ELN 2022 adverse risk	456 (34)	204 (36)	163 (35)	114 (51)
ELN 2022 fav./int. risk	344 (26)	145 (25)	89 (19)	33 (15)
Missing karyotype	104 (7.7)	38 (6.7)	35 (6.9)	8 (3.6)
Allogeneic HCT, No. (%)	160 (12)	65 (11)	61 (13)	24 (11)
Time to HCT, months, median (range)	5.0 (0.1-25.3)	4.9 (1.5-33.8)	3.9 (0.1-9.4)	3.9 (2.3-16.2)
Follow-up time, months, median (range)	21.8 (19.8-24.1)	22.6 (20.3-29.5)	28.1 (23.2-37.1)	48.8 (44.7-59.7)
OS, months, median (range)	12.4 (11.2-14.2)	12.9 (10.7-14.4)	12.5 (10.8-14.3)	9.6 (7.9-12.1)

Abbreviations: ELN, European LeukemiaNet; EVC, external validation cohort; HCT, hematopoietic cell transplantation; IVC, internal validation cohort; OS, overall survival; PRISM, Prognostic Risk Integration for Survival Modeling.

cycles similar to VIALE-A patients (n = 376; C-index 0.65; Data Supplement, Figs S16C and S16D), and treated with ≥21 days of venetoclax in cycle 1 (n = 1,133; C-index 0.64; Data Supplement, Figs S6C and S6D).

DISCUSSION

In this large, multinational study of patients with newly diagnosed AML treated with HMA + VEN, we developed and externally validated PRISM, a therapy-specific risk model integrating clinical, cytogenetic, and molecular features to provide individualized risk estimation. PRISM-3 risk

groups outperformed current standard-of-care risk models in external validation set patients and demonstrated robust generalizability. To facilitate clinical translation, PRISM has been implemented as a publicly available web-based clinical decision support tool, the PRISM-AML Risk Calculator.²⁵

Multiple prognostic models exist for patients with AML treated with venetoclax; however, many were derived from smaller cohorts or include limited molecular features.⁶⁻⁹ The 4-gene classifier represents an important advancement, is widely validated, and is incorporated within the context of

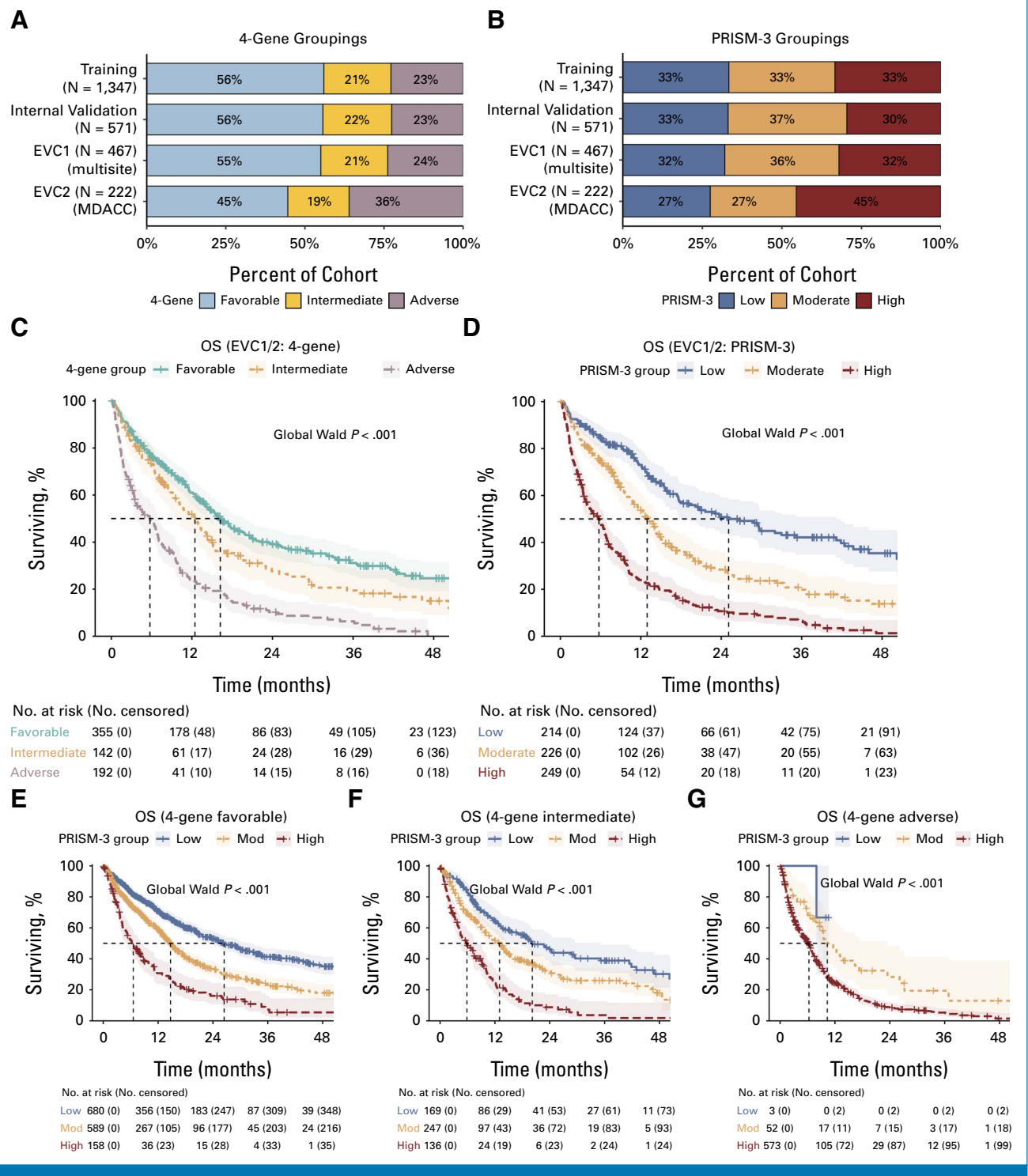


FIG 3. Validation of PRISM-3 across EVCs. (A) Distribution of patients by 4-gene risk category in the training, internal validation, and two EVCs (EVC1 and EVC2). (B) Distribution of patients by PRISM-3 risk group in these same cohorts. (C, D) Kaplan-Meier estimates of OS by 4-gene classifier and PRISM-3 risk group in patients comprising EVC1 and EVC2. (E-G) Kaplan-Meier estimated OS by PRISM-3 risk group within each 4-gene classifier category (favorable, intermediate, and adverse risk), illustrating that PRISM-3 furnishes prognostic discrimination even within established molecular risk strata for AML. EVC, external validation cohort; MDACC, MD Anderson Cancer Center; OS, overall survival; PRISM, Prognostic Risk Integration for Survival Modeling.

ELN-2024 risk stratification.^{2,6-9,12} However, its discriminatory capacity is modest, presumably reflecting the substantial proportion of patients deemed favorable-risk as well

as conflicting data regarding the prognostic value of certain mutations (ie, *NRAS*) at diagnosis.⁷ Additionally, clinical variables such as age, sex, AML ontogeny, and karyotype are

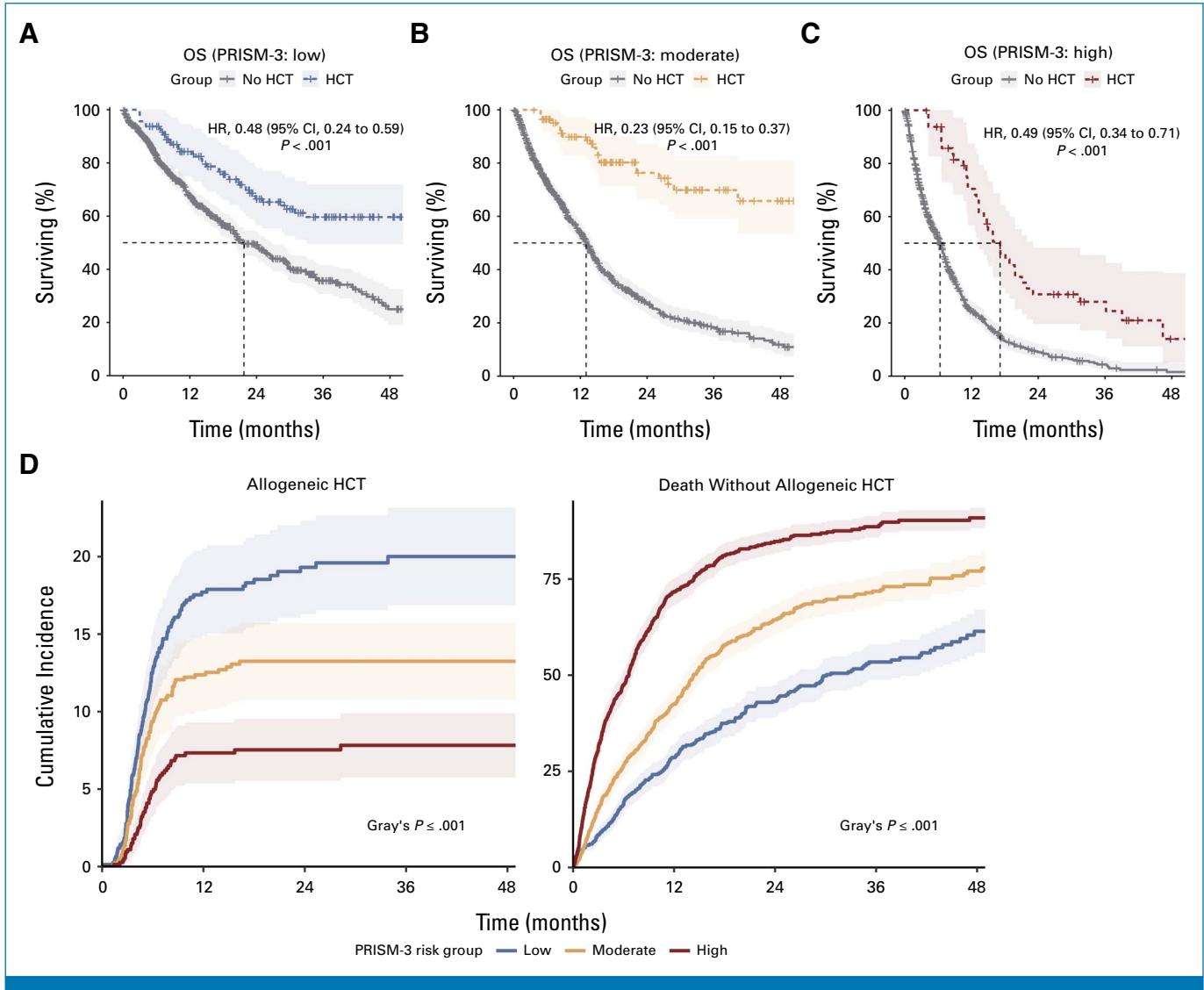


FIG 4. Impact of allogeneic HCT across PRISM-3 risk groups in the training, IVC and EVC1. Time of HCT was not collected for EVC2. (A-C) Extended Kaplan-Meier curves (Simon-Makuch plots) of OS by time-dependent HCT status within PRISM-3 low-, moderate-, and high-risk groups. P values are from Wald tests based on Cox regression models of OS with HCT coded as a time-dependent predictor. (D) PRISM-3 risk group CIF estimates for the competing events of HCT and death without HCT, measured from HMA + VEN initiation. P values are from 2 degree-of-freedom Gray's tests comparing CIF differences across PRISM-3 groups for each competing event. CIF, cumulative incidence function; EVC, external validation cohort; HCT, hematopoietic cell transplantation; IVC, internal validation cohort; OS, overall survival; PRISM, Prognostic Risk Integration for Survival Modeling; VEN, venetoclax.

not currently incorporated despite retaining prognostic significance.^{8,13,14} By integrating a broader, consistently selected feature set and validating performance across diverse patient populations, PRISM provides prognostic information that improves upon existing risk stratification frameworks.

Several features incorporated into PRISM underscore the therapy-specific nature of risk stratification in AML. Mutations in *RUNX1*, *STAG2*, and *BCOR*—mutations characteristic of AML with myelodysplasia-related changes (AML-MRC) and historically associated with adverse outcomes after intensive chemotherapy—were associated with

favorable outcomes, consistent with their enhanced sensitivity to venetoclax observed in clinical practice.¹⁴⁻¹⁷ *IDH1/2* mutations retained a favorable prognostic effect and were enriched within the PRISM-3 low-risk group despite not being incorporated into the 4-gene classifier. *CEBPA* mutations also had a favorable influence, independent of biallelic or bZIP domain status.^{18,19} In contrast, *NPM1* mutations contributed modestly to risk discrimination, suggesting that outcomes in this subgroup are more dependent on comutations.^{2,6,8,20,21}

Conversely, *TP53* mutations and ELN-2022 adverse-risk cytogenetics had a strong negative prognostic impact,

reaffirming the therapeutic resistance of this biologic subgroup. *NRAS* mutations, previously associated with venetoclax resistance, were not sufficiently prognostic to be included in PRISM, suggesting their effects are context-dependent and influenced by co-occurring mutations and clinical factors.^{20–22} These findings exemplify how PRISM captures treatment-relevant biology not reflected in existing molecular classifiers.

Beyond prognostic discrimination, PRISM provides clinically actionable risk reclassification. Approximately 40%–50% of patients were reassigned relative to the 4-gene classifier, including a substantial subset of patients initially labeled as favorable-risk. Notably, patients classified as favorable-risk by the 4-gene classifier but reassigned to higher-risk PRISM groups had markedly poor outcomes.

Higher PRISM-3 risk groups were associated with a reduced likelihood of undergoing HCT and an increased cumulative incidence of death without HCT, suggesting that excess mortality in higher-risk patients is not driven by inferior post-transplant outcomes. These findings have clinical implications, indicating that PRISM-3 identifies patients at high risk for mortality before reaching potentially curative transplantation and may support prioritization of early HCT evaluation and expedited referral pathways.

Although venetoclax-based regimens are approved in older or unfit patients, their use is expanding into younger, intensive chemotherapy-eligible populations with differing molecular drivers of AML and competing risk models based on therapy applied. In an exploratory analysis of patients younger than 65 years, PRISM-3 retained its ability to stratify survival. This suggests broader applicability of PRISM by identifying younger, fit patients who may benefit most from HMA + VEN (ie, patients classified as PRISM-3 low-risk and ELN 2022 intermediate-/adverse-risk) and patients who benefit most from alternative strategies, including intensified chemotherapy, triplet regimens incorporating targeted agents, and early transition to HCT, particularly among those classified as PRISM-3 moderate-risk or high-risk.

Beyond prognostication, PRISM-3 may inform the design of future clinical trials in both fit and unfit AML populations. In younger or fit patients, PRISM-3 could identify and allocate

higher-risk patients unlikely to benefit from HMA + VEN into trials incorporating intensified or novel combination strategies, including triplet regimens or transplant-directed approaches. In patients unfit for intensive therapy, PRISM may help identify candidates for novel triplet combinations to facilitate HCT candidacy. Alternatively, within an older, unfit patient population, PRISM low-risk patients may represent ideal candidates for dynamic, measurable residual disease-adapted treatment de-escalation or time-limited treatment strategies.^{21,23} Such applications position PRISM as a framework not only for prognostication but for treatment selection and clinical trial eligibility and design.

To support clinical implementation, we deployed PRISM as a publicly accessible web-based clinical support tool enabling point-of-care risk estimation using routinely available clinical and molecular data. The platform provides the continuous PRISM score, PRISM-3 risk, and 4-gene classifier risk to support shared decision making in routine clinical care. A paired exploratory survival page enables evaluation of outcomes in additional clinical, molecular, and cytogenetic subgroups not explicitly represented in PRISM. To our knowledge, as the largest genomically annotated data set of patients treated with HMA + VEN, PRISM provides a robust reference framework and a valuable benchmark for future studies evaluating venetoclax-based combinations or novel agents, especially within biologically defined subgroups.

Several limitations merit consideration. Despite leveraging a large data set with external validation, low-frequency mutations with the potential for prognostic significance were not included due to less reliable estimation for small counts. Furthermore, AML phenotype and dynamic variables such as measurable residual disease, which can influence survival after initiation of venetoclax-based therapy, were not routinely collected.^{21,23,24} These limitations aside, PRISM demonstrated robust performance across a global population of patients, thereby accounting for heterogeneity in treatment settings.

In conclusion, PRISM is a validated, therapy-specific risk model that improves survival stratification beyond current standards and provides a clinically actionable framework to guide treatment selection, transplant timing, and clinical trial design in patients with AML treated with venetoclax-based therapy.

AFFILIATIONS

¹Oregon Health and Science University, Portland, OR

²University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC

³Department of Medical and Molecular Genetics, King's College London, London, United Kingdom

⁴University of Sydney, Sydney, NSW, Australia

⁵Haematology Department, Royal North Shore Hospital, St. Leonards, NSW, Australia

⁶Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

⁷Hematology Department, Lyon-Sud Hospital, Hospices Civils de Lyon, Pierre Bénite, France

⁸Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany

⁹Department of Internal Medicine IV, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Halle, Germany

¹⁰Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, NY

¹¹Section of Hematology-Oncology, Department of Medicine, University of Chicago, Chicago, IL

¹²Hematology and Oncology Department, Faculty of Medicine, and Hematology, Oncology, and Transfusion Medicine Center, National Cancer Center, Vilnius University Hospital Santaros Klinikos, Vilnius University, Vilnius, Lithuania

¹³Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

¹⁴Leukemia Program, Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

¹⁵Hematology Unit, IRCSS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, FC, Italy

¹⁶U.O. Ematologia, Ospedale Infermi Rimini, AUSL ROMAGNA, Rimini, Italy

¹⁷Hematology Department and Centre de Recherche en Cancerologie de Lyon (CRCL) - UMR INSERM 1052 CNRS 5286, Leon Berard Cancer Center, Lyon, France

¹⁸Cellular Therapy and Clinical Haematology Department, Clermont-Ferrand University Hospital, Clermont-Ferrand, France

¹⁹University Hospital Saint Etienne, St-Priest-en-Jarez, France

²⁰Clinical Hematology Department, CHU Grenoble Alpes - Université Grenoble Alpes, Grenoble, France

²¹Clinical Hematology Department, Nîmes University Hospital, Gard Cancer Institute, Nîmes, France

²²University College London Hospitals NHS Foundation Trust, London, United Kingdom

²³Department of Haematology, Addenbrooke's Hospital, Cambridge, United Kingdom

²⁴University Hospitals Sussex NHS Foundation Trust, Worthing, United Kingdom

²⁵Division of Hematology, The Ohio State University Wexner Medical Center, Columbus, OH

²⁶Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

²⁷University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD

²⁸University of California San Francisco, San Francisco, CA

²⁹Winship Cancer Institute of Emory University, Atlanta, GA

³⁰David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA

³¹Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas, Kansas City, KS

³²University of Cincinnati, Cincinnati, OH

³³Blood Cancer United, Washington, DC

³⁴Division of Hematology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

³⁵University of Bologna, Hematology Unit, Ospedale S. Maria Delle Croci, Ravenna, RA, Italy

³⁶University of Texas Southwestern Medical Center, Dallas, TX

³⁷Department of Medical and Molecular Genetics, King's College, London, United Kingdom

³⁸Computational Oncology Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

³⁹Department of Hematopathology, MD Anderson Cancer Center, Houston, TX

⁴⁰Division of Hematology, University of Colorado School of Medicine, Aurora, CO

⁴¹Paris-Saclay University, Gustave Roussy, INSERM U1361, IHU PRISM National PRECISiOn Medicine Center in Oncology, Villejuif, France

CORRESPONDING AUTHOR

Curtis A. Lachowicz, MD; e-mail: lachowie@ohsu.edu.

EQUAL CONTRIBUTION

D.A.P. and E.B. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Curtis A. Lachowicz, Jad Othman, Martin Carré, Eytan M. Stein, Ronan Swords, Daniel A. Pollyea, Elsa Bernard

Administrative support: Ashley Yocum

Provision of study materials or patients: Seongseok Yun, Maël Heiblig, Joseph M. Cannova, Jayastu Senapati, Yasmin Abaza, Federica Monaco, Amine Belhabri, Urbain Tauveron-Jalenques, Emmanuelle Tavernier, Gaspar Aspas Requena, Elie Traer, Rebecca Olin, William Blum, Gary Schiller, Tara Lin, Tapan M. Kadia, Courtney D. DiNardo, Justin Watts, Daniel A. Pollyea

Collection and assembly of data: Curtis A. Lachowicz, Joshua F. Zeidner, Jad Othman, Seongseok Yun, Maël Heiblig, Michael Heuser, Rabia Shahswar, Rafael Madero Marroquin, Joseph M. Cannova, Andrius Žučenka, Jennifer Marvin-Peek, Jayastu Senapati, Yasmin Abaza, Alok Swaroop, Irene Zacheo, Federica Monaco, Amine Belhabri, Urbain Tauveron-Jalenques, Emmanuelle Tavernier, Martin Carré, Gaspar Aspas Requena, Elie Traer, Jenny O'Nions, Faisal Basheer, John Laurie, Shivani Handa, Eytan M. Stein, Maria R. Baer, Rebecca Olin, Gary Schiller, Emily Curran, Ashley Yocum, Ellen Madarang, Tapan M. Kadia, Giovanni Marconi, Yazan Madanat, Richard Dillon, Juan E. Arango Ossa, Sanam Loghavi, Daniel A. Pollyea

Data analysis and interpretation: Curtis A. Lachowicz, Joshua F. Zeidner, Jad Othman, Andy Kaempf, Michael Heuser, Jayastu Senapati, Emmanuelle Tavernier, Rachel J. Cook, Jennifer N. Saultz, Eytan M. Stein, Maria R. Baer, Rebecca Olin, William Blum, Tara Lin, Emily Curran, Naval Daver, Tapan M. Kadia, Courtney D. DiNardo, Justin Watts, Sanam Loghavi, Daniel A. Pollyea, Elsa Bernard

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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The PRISM-AML Investigators are listed in the Appendix (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk Prognostication After Hypomethylating Agents Combined With Venetoclax in AML: The PRISM Risk Model

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Curtis A. Lachowicz

Consulting or Advisory Role: SERVIER, Rigel, AbbVie/Genentech, Cota Healthcare, Syndax, Astellas Pharma, Oryzon Genomics

Research Funding: AbbVie

Travel, Accommodations, Expenses: SERVIER, AbbVie

Joshua F. Zeidner

Consulting or Advisory Role: AbbVie, Shattuck Labs, SERVIER, Gilead Sciences, Foghorn Therapeutics, Syndax, Novartis, Sellas Life Sciences, Daiichi Sankyo/UCB Japan, AstraZeneca, Sumitomo Pharma Oncology, NeoGenomics Laboratories, Genmab, Astellas Pharma, Crossbow Therapeutics, Ipsen, Jazz Pharmaceuticals, Johnson and Johnson/Janssen, Relmada Therapeutics, Rigel, Kura Oncology, Genentech, Geron, Halia Therapeutics, Cullinan Oncology

Research Funding: Merck (Inst), Gilead Sciences (Inst), Arog (Inst), Astex Pharmaceuticals (Inst), Sumitomo Dainippon Pharma Oncology (Inst), AbbVie (Inst), Stemline Therapeutics (Inst), Shattuck Labs (Inst), Jazz Pharmaceuticals (Inst), Zentalis (Inst), Sellas Life Sciences (Inst), Newave Pharmaceutical (Inst), Loxo (Inst), AstraZeneca (Inst), Faron Pharmaceuticals (Inst), Akeso Biopharma (Inst), Novartis (Inst), Ascentage Pharma (Inst), Auron Therapeutics (Inst), Aptevio Therapeutics (Inst), Lin BioScience (Inst), Kura Oncology (Inst), Daiichi Sankyo/UCB Japan (Inst)

Jad Othman

Consulting or Advisory Role: SERVIER

Speakers' Bureau: Pfizer, Astellas Pharma

Michael Heuser

Honoraria: Pfizer, Daiichi Sankyo Europe GmbH, Astellas Pharma, Otsuka, SERVIER

Consulting or Advisory Role: AbbVie, Daiichi Sankyo Europe GmbH, Ascentage Pharma, Astellas Pharma, Janssen Oncology, Miltenyi Biotec, SERVIER

Research Funding: Bayer (Inst), AbbVie (Inst), Glycostem (Inst), Jazz Pharmaceuticals (Inst), PinotBio (Inst), SERVIER, Toray Industries

Andrius Žučenka

Consulting or Advisory Role: AbbVie, SERVIER, Molecular Partners, Astellas Pharma, Pfizer, Bristol Myers Squibb/Sanofi, Janssen, Takeda

Travel, Accommodations, Expenses: AbbVie, SERVIER

Jennifer Marvin-Peek

Consulting or Advisory Role: SERVIER, Rigel

Jayastu Senapati

Uncompensated Relationships: Omeros Pharma

Yasmin Abaza

Consulting or Advisory Role: SERVIER, Astellas Pharma, Rigel, Bristol Myers Squibb/Celgene, Geron, Daiichi Sankyo, Ascentage Pharma, Taiho Pharmaceutical, AbbVie, Biomea Fusion, Kura Oncology

Research Funding: ALX Oncology (Inst), Biosight (Inst), Curis (Inst), Novartis (Inst), Biomea Fusion (Inst), AbbVie (Inst), Bristol Myers Squibb/Celgene (Inst), Sumitomo Pharma Oncology (Inst)

Alok Swaroop

Stock and Other Ownership Interests: ICON Clinical Research, CVS, Agenus, Anika Therapeutics

Amine Belhabri

Consulting or Advisory Role: AbbVie

Emmanuelle Tavernier

Consulting or Advisory Role: Bristol Myers Squibb/Celgene, Amgen, AbbVie

Travel, Accommodations, Expenses: Pfizer, Grifols

Gaspar Aspas Requena

Honoraria: Novartis, AbbVie, Bristol Myers Squibb Foundation, Gilead Sciences, SERVIER

Speakers' Bureau: AbbVie, Novartis, Bristol Myers Squibb Foundation, SERVIER

Travel, Accommodations, Expenses: Novartis, AbbVie, SERVIER, Gilead Sciences, Bristol Myers Squibb Foundation

Elie Traer

Consulting or Advisory Role: Astellas Pharma, AbbVie, Daiichi Sankyo/UCB Japan, Rigel, SERVIER, Syndax, Incyte, Geron, Am Max

Research Funding: AstraZeneca, Prelude Therapeutics, Schrodinger, Incyte

Patents, Royalties, Other Intellectual Property: Patent for human marrow organoid model held by myself OHSU. Also on patent for ex vivo drug prediction assay with OHSU

Jennifer N. Saultz

Consulting or Advisory Role: Rigel, Arog

Jenny O'Nions

Consulting or Advisory Role: Daiichi Sankyo Europe GmbH

Speakers' Bureau: Daiichi Sankyo Europe GmbH, SERVIER, Astellas Pharma, Jazz Pharmaceuticals, AbbVie

Travel, Accommodations, Expenses: Daiichi Sankyo Europe GmbH, AbbVie, SERVIER

Faisal Basheer

Honoraria: Sanofi, Johnson and Johnson/Janssen, GlaxoSmithKline, Menarini

Consulting or Advisory Role: Daiichi Sankyo Europe GmbH, Bristol Myers Squibb, Johnson and Johnson/Janssen

Speakers' Bureau: Johnson and Johnson/Janssen, Sanofi, Pfizer, GlaxoSmithKline

Travel, Accommodations, Expenses: Sanofi, AbbVie

John Laurie

Honoraria: Bayer

Eytan M. Stein

Stock and Other Ownership Interests: Auron Therapeutics

Consulting or Advisory Role: Novartis, Janssen, Bristol Myers Squibb/Celgene, Agios, Menarini, Genentech, Genesis Pharma, AbbVie, Neoleukin Therapeutics, Gilead Sciences, Syndax, OnCusp Therapeutics, Immunogen, CTI BioPharma Corp, Foghorn Therapeutics, SERVIER, Calithera Biosciences, Daiichi Sankyo, Aptose Biosciences, Ono Pharmaceutical, Blueprint Medicines, GEMoAB, Jnana Therapeutics, Debiopharm Group

Research Funding: Eisai (Inst), Bristol Myers Squibb/Celgene (Inst), Bayer (Inst), agios (Inst), BioTheryX (Inst), Syros Pharmaceuticals (Inst), SERVIER (Inst), Foghorn Therapeutics (Inst), Syndax (Inst), Gilead Sciences (Inst), Cleave Biosciences (Inst), Prelude Therapeutics (Inst), Loxo/Lilly (Inst)

Maria R. Baer

Research Funding: AbbVie (Inst), FORMA Therapeutics (Inst), Kite, a Gilead company (Inst), Takeda (Inst), Kura Oncology (Inst), Ascentage Pharma (Inst), Sumitomo Pharma Oncology (Inst)

Rebecca Olin

Honoraria: Aptitude Health (I), Axiom Healthcare Strategies (I), Clarion Healthcare (I), Equinox Group (I)

Consulting or Advisory Role: SERVIER, Rigell, Janssen Oncology (I), Gilead Sciences (I), Bayer (I), Bristol Myers Squibb/Pfizer (I)

Research Funding: Novartis (Inst), Mirati Therapeutics (Inst), Roche (Inst), AstraZeneca (Inst), Spectrum Pharmaceuticals (Inst), Takeda (Inst), Cellectis (Inst), Puma Biotechnology (Inst), Pfizer (Inst), Verastem (Inst)

Gary Schiller

Stock and Other Ownership Interests: Bristol Myers Squibb, Amgen, Johnson and Johnson, Medtronic, Urogen pharma

Honoraria: Rigell, Menarini Group, Bristol Myers Squibb

Consulting or Advisory Role: Agios, Celgene, Incyte, Novartis, AbbVie, Astellas Pharma, Autolus Therapeutics, Rigell, Bristol Myers Squibb/Celgene, AVM Biotechnology, GlaxoSmithKline

Speakers' Bureau: Astellas Pharma, Kite, a Gilead company, Jazz Pharmaceuticals, Stemline Therapeutics, Bristol Myers Squibb, Sanofi, Karyopharm Therapeutics, Incyte, AbbVie, Rigell, Blueprint Medicines, Agios, Seattle Genetics/Astellas, Amgen

Research Funding: AbbVie, Actinium Pharmaceuticals, Actuate Therapeutics, Arog, Astellas Pharma, Bristol Myers Squibb/Celgene, Celator, Constellation Pharmaceuticals, Daiichi Sankyo, Deciphera, Delta-Fly Pharma, FORMA Therapeutics, Fujifilm, Gamida Cell, Genentech/Roche, Geron, Incyte, Karyopharm Therapeutics, Kite, a Gilead company, Mateon Therapeutics, Onconova Therapeutics, Pfizer, PRECOG, REGIMMUNE, Samus Therapeutics, Sangamo Bioscience, Sellas Life Sciences, Stemline Therapeutics, Takeda, Tolero Pharmaceuticals, Trovogene, Agios, Amgen, Jazz Pharmaceuticals, ElevateBio, Ono Pharmaceutical, Novartis, Sanofi, AVM Biotechnology,

Syros Pharmaceuticals, Glycomimetics, Aptevo Therapeutics, Biomea Fusion, Bio-Path Holdings, Biosight, Cellectis, Celularity, Cogent Biosciences, Cullinan Oncology, Fate Therapeutics, Immune-Onc Therapeutics, Kronos Bio, Kura Oncology, Loxo, Marker Therapeutics, REGIMMUNE, Syros Pharmaceuticals, Oncovert, Kartos Therapeutics, Rigell, Electra, Priothera, Systimmune

Tara Lin

Consulting or Advisory Role: Jazz Pharmaceuticals, Daiichi Sankyo, Syndax, Johnson and Johnson/Janssen, Sumitomo Pharma Oncology

Research Funding: Bio-Path Holdings, Inc (Inst), Aptevo Therapeutics (Inst), Kura Oncology (Inst), Lin BioScience

Emily Curran

Honoraria: Pfizer, SERVIER, University of Chicago, Duke University, CE Synergy, Jazz Pharmaceuticals, Clinical Care Options

Consulting or Advisory Role: Kite/Gilead, Jazz Pharmaceuticals, Kite, a Gilead company, Incyte, Autolus Therapeutics

Speakers' Bureau: Clinical Care Options

Travel, Accommodations, Expenses: Dava Oncology, Creative Educational Concepts, Creative Educational Concepts, American Society of Hematology, Kite/Gilead, Society of Hematologic Oncology, Duke University, University of Chicago, CE Synergy

Ellen Madarang

Speakers' Bureau: Kura Oncology

Naval Daver

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Employment: MD Anderson Cancer Center

Consulting or Advisory Role: Celgene, Agios, Jazz Pharmaceuticals, Pfizer, AbbVie, Astellas Pharma, Daiichi Sankyo, Novartis, Bristol Myers Squibb, Amgen, Immunogen, Genentech, SERVIER, Syndax, Trillium Therapeutics, Gilead Sciences, Arog, Shattuck Labs, Kite, a Gilead company, Stemline/Menarini

Research Funding: Bristol Myers Squibb (Inst), Pfizer (Inst), Immunogen (Inst), Genentech (Inst), AbbVie (Inst), Astellas Pharma (Inst), Servier (Inst), Daiichi Sankyo (Inst), Gilead Sciences (Inst), Amgen (Inst), Trillium Therapeutics (Inst), Hanmi (Inst), Trovogene (Inst), FATE Therapeutics (Inst), Novimmune (Inst), Glycomimetics (Inst), Kite, a Gilead company (Inst)

Tapan M. Kadia

Honoraria: CURE

Consulting or Advisory Role: Novartis, Jazz Pharmaceuticals, Pfizer, AbbVie/Genentech, Agios, Daiichi Sankyo/UCB Japan, Liberum, Sanofi, SERVIER, Pinot Bio, Sellas Life Sciences, Bristol Myers Squibb/Celgene, Syndax, SOBI

Research Funding: Bristol Myers Squibb, Celgene, Amgen, BiolineRx, Incyte, Genentech/AbbVie, Pfizer, Jazz Pharmaceuticals, AstraZeneca, Astellas Pharma, Ascentage Pharma, Genfleet Therapeutics, Cyclacel, Pulmotec, Cellenkos, Glycomimetics, Astex Pharmaceuticals, Iterion Therapeutics, Delta-Fly Pharma, Regeneron (Inst), Sellas Life Sciences, Abcuro, DAAN Biotherapeutics

Giovanni Marconi

Consulting or Advisory Role: AbbVie, Astellas Pharma, Enable Lifescience, Flow Veiw Diagnostic, Immunogen, Jazz Pharmaceuticals, Menarini, Pfizer, Ryvu Therapeutics, SERVIER

Speakers' Bureau: AstraZeneca, Janssen, Takeda, uknequas

Research Funding: AbbVie (Inst), Pfizer (Inst), Syros Pharmaceuticals (Inst), Astellas Pharma (Inst), AstraZeneca (Inst), Daiichi Sankyo Europe GmbH (Inst)

Travel, Accommodations, Expenses: Jazz Pharmaceuticals, BeiGene

Yazan Madanat

Honoraria: Blueprint Medicines, OncLive/MJH Life Sciences, Stemline Therapeutics, Taiho Oncology, Bristol Myers Squibb, Kura Oncology, GERON, SOBI, Rigel, SERVIER, Curio Science, Cogent Biosciences, AbbVie, Aptitude Health, Takeda, Foundation Medicine

Consulting or Advisory Role: Geron, Kura Oncology

Travel, Accommodations, Expenses: Blueprint Medicines, MorphoSys

Richard Dillon

Honoraria: AbbVie, Pfizer, Novartis, Jazz Pharmaceuticals, Astellas Pharma

Consulting or Advisory Role: AbbVie, Novartis, Pfizer, Jazz Pharmaceuticals

Research Funding: Amgen (Inst), AbbVie (Inst)

Courtney D. DiNardo

Honoraria: AbbVie, GlaxoSmithKline, SERVIER, Genentech/AbbVie, Astellas Pharma, Bristol Myers Squibb Foundation, Schrodinger, Daiichi Sankyo/AstraZeneca, Ellipses Pharma

Consulting or Advisory Role: AbbVie, AstraZeneca, Genmab, Molecular Partners, SERVIER, Schrodinger, Rigel, Ryvu Therapeutics

Research Funding: AbbVie, Cleave Therapeutics, Foghorn Therapeutics, Immune-Onc Therapeutics, Jazz Pharmaceuticals, SERVIER, Loxo/Lilly, Astex Pharmaceuticals, Bristol Myers Squibb/Celgene, BeiGene, Remix Therapeutics

Juan E. Arango Ossa

Employment: Memorial Sloan-Kettering Cancer Center, Genentech

Justin Watts

Consulting or Advisory Role: Rigel, SERVIER, Bristol Myers Squibb/Celgene, Aptose Biosciences, Daiichi Sankyo/UCB Japan, Incyte, Opna Bio, Vyne Therapeutics, Attivare Therapeutics

Research Funding: Takeda, Rigel, Immune System Key

Sanam Loghavi

Employment: MD Anderson Cancer Center

Honoraria: Curio Science, Pathology learning center, MD Education, OncLive, Binaytara Foundation, NCCN, Mashup Media, NCTN, Medscape

Consulting or Advisory Role: Seagen, Gerson Lehrman Group, Guidepoint Global, Gerson Lehrman Group, Qualworld, AbbVie, Blueprint medicine, Daiichi Sankyo, Caris Diagnostics, Recordati, VJ Hemeo, Alpha sight, Arima, Qiagen, Gerson Lehrman Group, Kura Oncology, Syndax, SERVIER, Daiichi Sankyo/Lilly, Tempus, Bristol Myers Squibb/Sanofi, Arima Genomics, Recordati, Stemline Therapeutics

Research Funding: Amgen, Astellas

Travel, Accommodations, Expenses: Curio Science, MD Education, Pathology learning center, Binaytara Foundation, NCCN

Daniel A. Pollyea

Consulting or Advisory Role: AbbVie, Janssen, Genentech, Syndax, Bristol Myers Squibb, Kura Oncology, Ryvu Therapeutics, Daiichi Sankyo/Arqule, Rigel, Sanofi, BeiGene, SERVIER, Oncovertity, Taiho Oncology, Astellas Pharma, Geron

Research Funding: AbbVie (Inst), Karyopharm Therapeutics (Inst), Teva (Inst), Bristol Myers Squibb/Celgene (Inst)

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APPENDIX: PRISM-AML INVESTIGATORS

Anand A. Patel (Section of Hematology-Oncology, Department of Medicine, University of Chicago), Wendy Stock (Section of Hematology-Oncology, Department of Medicine, University of Chicago), Dimitrios Drekolias (Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL), Fatima Tuz Zahra (Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research

Institute, Tampa, FL), Nicola Long (Oregon Health and Science University, Portland, OR), Jessica Altman (Leukemia Program, Division of Hematology and Oncology, Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL), Ying Huang (Division of Hematology, The Ohio State University Wexner Medical Center), Rina Li Welkie (Division of Hematology, The Ohio State University Wexner Medical Center)