REGULAR ARTICLE

blood advances

Global outcomes and prognosis for relapsed/refractory mature T-cell and NK-cell lymphomas: results from the PETAL consortium

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Submitted 29 August 2024; accepted 17 October 2024; prepublished online on *Blood Advances* First Edition 31 October 2024. https://doi.org/10.1182/bloodadvances.2024014674.

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The preliminary results from this study were presented at the 64th American Society of Hematology annual meeting, New Orleans, LA, 12 December 2022, and at the 65th American Society of Hematology annual meeting, San Diego, CA, 9 December 2023.

Original data are available on request from the corresponding author, Salvia Jain (salvia.jain@mgh.harvard.edu).

The full-text version of this article contains a data supplement.

Key Points

- Prognostic index for R/R TCL is a novel prognostic model for R/R MTCL and MNKCL that defined risk groups with differing outcomes.
- Small-molecule inhibitors offer survival advantage relative to chemotherapy in AITL, warranting continued investigation in clinical trials.

Variances in global access to drugs and treatment practices make it challenging to understand the benefit of contemporary therapies in patients with relapsed and refractory (R/R) mature T-cell and natural killer–cell lymphomas (MTCL and MNKCL). We conducted an international retrospective cohort study of 925 patients with R/R MTCL and MNKCL. In peripheral T-cell lymphoma–not otherwise specified and anaplastic lymphoma kinase–negative anaplastic large cell lymphoma (ALK$^-$ ALCL), patients with relapsed lymphoma demonstrated a superior median overall survival (OS) relative to refractory from the time of second-line treatment. We identified several independent predictors of OS for R/R lymphoma including age >60 years, primary refractory disease, histological subtype other than angioimmunoblastic T-cell lymphoma (AITL), extranodal sites >1, Ki67 ≥40%, and absolute lymphocyte count less than the lower limit of normal. A multivariable model incorporating these formed the basis for a prognostic index for R/R TCL, in which patients are stratified into low-risk (0-1 risk factor), intermediate-risk (2-3 risk factors), or high-risk (≥4 risk factors) groups, which were associated with 3-year OS of 57.14%, 23.3%, and 7%, respectively. Patients received either a "novel" single agent (SA; 35%) or cytotoxic chemotherapy (CC; 60%) for their second-line treatment. Higher progression-free survival was observed with SA over CC for the entire cohort with a higher 3-year OS in AITL and ALK$^-$ ALCL. Among the SA, small-molecule inhibitors demonstrated OS advantage relative to CC in AITL. Our results highlight continued efficacy of novel drugs globally and the potential of a new prediction model in informing heterogeneous prognosis within the R/R population of MTCL and MNKCL.

Introduction

For common subtypes of mature T-cell lymphoma (MTCL) and mature natural killer–cell lymphomas (MNKCL), the identification of risk factors and subgroups within the relapsed and refractory (R/R) population that lead to heterogeneous outcomes to therapies remains unclear.[1-3] Histological subtype-specific prognostic scores for newly diagnosed patients with extranodal natural killer/T-cell lymphoma (ENKTCL), angioimmunoblastic T-cell lymphoma (AITL), and adult T-cell leukemia/lymphoma (ATLL) exist but not for the R/R group. Although anthracycline-based regimens are commonly used in the frontline setting for the common nodal subtypes of MTCL, the optimal strategy for the R/R patients remains ill defined. Historically, for this group, when clinical trial enrollment is not feasible, treatment with a platinum-, ifosfamide-, and gemcitabine-based cytotoxic chemotherapy (CC) is selected for the "fit" patient. In contrast, single agents (SAs) including histone deacetylase inhibitors (HDACis), antifolates (AFs) such as pralatrexate, and antibody-drug conjugates (ADCs) such as brentuximab vedotin (BV) are favored for the "unfit" patient. There is a paucity of randomized clinical data around the use of SA, and their comparative efficacy with CC outside of a clinical trial has not been well defined.[4-6] We first identified several independent predictors of overall survival (OS) for patients with R/R MTCL and MNKCL, a highly selected poor-prognosis group to begin with. Next, these pretreatment clinical and laboratory characteristics were integrated into a multivariable model for our cohort to estimate outcomes. The performance of the final multivariable model was compared with other risk scores with respect to their ability to predict, discriminate, and calibrate outcomes based on the measure of concordance index (C-index). We validated the prognostic model's survival predictive power in test and independent study cohorts and developed a web-based calculator available for use by health care professionals. Next, we sought to contrast OS, progression-free survival (PFS), and the ability to bridge to hematopoietic stem cell transplantation (HSCT) with either SA or CC in the second-line treatment for patients with R/R MTCL and MNKCL. Finally, among patients with R/R MTCL and MNKCL, we juxtaposed the outcomes of various SA to gain more knowledge on distinct populations benefiting from specific classes of drugs.

Methods

A total of 1240 patients with R/R MTCL and MNKCL from 13 institutions participating in the Global Peripheral T-cell lymphoma (PETAL) consortium based in 10 countries (Australia, Brazil, Chile, United States, Japan, South Korea, South Africa, Saudi Arabia, Italy, and India) with lymphoma diagnosis between 1 January 2010 and 30 September 2021 were screened for eligibility. A total of 312 patients were excluded due to not receiving second-line therapy. This includes patients from Chile, who were screened but could not be included in the final analysis because they did not have details on second-line treatment. The number of patients enrolled at each site across various countries is summarized in supplemental Table 1. Further details of the methods section are included in the supplemental Data.

Results

Baseline demographic and clinical characteristics

Of the 1240 patients screened, 925 were eligible for this study and subsequently included in the final analysis (Figure 1). Table 1 summarizes the baseline demographic and clinical characteristics of these 925 study patients with R/R MTCL and MNKCL receiving SA or CC for their second-line treatment. Most patients in the cohort were diagnosed and treated in the United States, Brazil, South Korea, and India. The median age at diagnosis was 58 years, with patients in Japan (median age, 69 years) being older. Most patients were males (578/925 [62%]), with higher proportions in Saudi Arabia (10/13 [77%]), India (56/75 [75%]), and South Africa (14/19 [74%]). Of patients whose race was known, 54% were White (453/843), 6% were Black (53/843), and 32% were Asian (273/843). Expectedly, the overall dominant lymphoma subtypes included peripheral T-cell lymphoma–not otherwise specified (PTCL-NOS; 385/925 [42%]), AITL (213/925 [23%]), anaplastic lymphoma kinase–negative anaplastic large cell lymphoma (ALK^- ALCL; 88/925 [10%]), ENKTCL (88/925 [10%]), anaplastic lymphoma kinase–positive anaplastic large cell lymphoma (ALK^+ ALCL; 38/925 [4%]), ATLL (38/925 [4%]), enteropathy-associated T-cell lymphoma (21/925 [2%]), hepatosplenic TCL (21/925 [2%]), T-cell prolymphocytic leukemia (19/925 [2%]), and other PTCL subtypes (14/925 [2%]). Exceptions included ALCL as the dominant subtype in Saudi Arabia (7/13 [53%]) and ENKTCL and ATLL as the second most common subtype in South Korea (40/123 [33%]) and Brazil (27/138 [20%]), respectively. Most patients had Ann Arbor stage III to IV disease (723/925 [81%]), intermediate-risk (IR) to high-risk (HR) international prognostic index (IPI) from 3 to 5 (307/585 [53%]), and prognostic index for T-cell lymphoma (PIT) scores from 2 to 4 (331/636 [52%]). The median follow-up was 1.92 years (interquartile range, 0.94-3.94). At the time of data collection, of the 925 patients, 303 (33%) were alive, 515 (56%) had died, and 107 (12%) were lost to follow-up.

Treatment characteristics

Table 2 summarizes the treatment characteristics of the 925 cohort patients with R/R MTCL and MNKCL receiving SA or CC for their second-line treatment. Of the 925 patients, 452 (49%) were refractory to frontline therapy with and without HSCT consolidation, and 468 (51%) had relapsed, with a higher proportion of refractory cases in Saudi Arabia (10/13 [83%]). Anthracycline-based initial chemotherapy, including CHOP (cyclophosphamide + hydroxydaunorubicin + vincristine + prednisone), CHOEP (cyclophosphamide + hydroxydaunorubicin + vincristine + etoposide + prednisone), or EPOCH (infusional etoposide phosphate + prednisone + vincristine + cyclophosphamide + hydroxydaunorubicin), remained the dominant upfront regimen globally, accounting for 69% (637/925) of all the first-line treatments. A higher number of other regimens were administered in Japan (30/38 [79%]) and India (47/75 [63%]). A table outlining the distribution of these "other" therapies is included in supplemental Table 5. Only 21% of patients (186/875) underwent autologous-HSCT (auto-HSCT) consolidation in first remission, with higher rates in Saudi Arabia (5/10 [50%]), United States (122/409 [30%]), and South Korea (32/122 [26%]) and lower rates in India (1/66 [2%]) and Japan (0/38 [0%]). Approximately 14% (121/855) of patients received radiation as part of first-line treatment. All survival

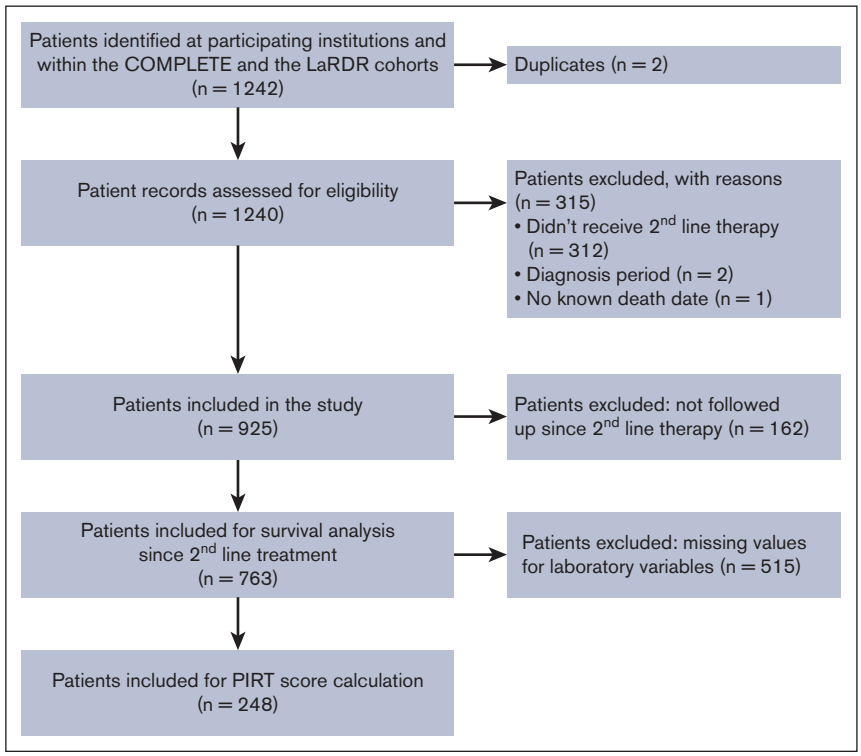

Figure 1. Study flowchart CONSORT diagram.

Table 1. Baseline demographic and clinical characteristics for the global cohort (training and test)

Characteristic	All (n = 925)	United States (n = 410)	Australia (n = 68)	Brazil (n = 138)	South Korea (n = 123)	South Africa (n = 19)	Saudi Arabia (n = 13)	Japan (n = 38)	Italy (n = 41)	India (n = 75)	*P* value*
Time period diagnosed, n (%)											<.001†
2010-2013	214 (23)	147 (36)	17 (25)	0	14 (11)	8 (42)	0	13 (34)	5 (12)	10 (13)	
2014-2017	404 (44)	156 (38)	23 (34)	72 (52)	79 (64)	7 (37)	4 (31)	15 (39)	10 (24)	38 (51)	
2018-2021	307 (33)	107 (26)	28 (41)	66 (48)	30 (24)	4 (21)	9 (69)	10 (26)	26 (63)	27 (36)	
Age at lymphoma diagnosis, median (IQR), y	58 (47-66)	60 (51-67)	63 (53-71)	51 (39-60)	57 (48-65)	45 (34-54)	45 (31-57)	69 (65-78)	57 (50-63)	53 (45-60)	<.001
Biological sex, n (%)											.3†
Male	578 (62)	255 (62)	44 (65)	81 (59)	70 (57)	14 (74)	10 (77)	24 (63)	24 (59)	56 (75)	
Race, n (%)											<.001†
White	453 (54)	319 (80)	24 (89)	66 (59)	0	3 (19)	0	0	41 (100)	0	
Black	53 (6)	37 (9)	1 (4)	11 (10)	1 (<1)	3 (19)	0	0	0	0	
Asian	273 (32)	25 (6)	2 (7)	2 (2)	122 (99)	0	9 (69)	38 (100)	0	75 (100)	
Other	64 (8)	18 (5)	0	32 (29)	0	10 (62)	4 (31)	0	0	0	
Unknown	82	11	41	27	0	3	0	0	0	0	
Lymphoma subtypes, n (%)											
AITL	213 (23)	131 (32)	13 (19)	13 (9)	20 (16)	4 (21)	0	12 (32)	6 (15)	14 (19)	<.001†
ALCL (ALK^-)	88 (10)	28 (7)	11 (16)	21 (15)	6 (5)	3 (16)	5 (38)	7 (18)	6 (15)	1 (1)	<.001†
ALCL (ALK^+)	38 (4)	18 (4)	3 (4)	7 (5)	3 (2)	2 (11)	2 (15)	1 (3)	2 (5)	0	.1†
ATLL	38 (4)	10 (2)	0	27 (20)	0	0	0	1 (3)	0	0	–
EATL	21 (2)	10 (2)	0	1 (1)	8 (7)	0	0	2 (5)	0	0	–
ENKTCL	88 (10)	22 (5)	3 (4)	12 (9)	40 (33)	0	2 (15)	0	1 (2)	8 (11)	<.001†
HSTCL	21 (2)	5 (1)	5 (7)	5 (4)	2 (2)	1 (5)	0	0	3 (7)	0	.01†
PTCL-NOS	385 (42)	160 (39)	33 (49)	51 (37)	44 (36)	9 (47)	3 (23)	15 (39)	18 (44)	52 (69)	<.001
T-PLL	19 (2)	18 (4)	0	0	0	0	0	0	1 (2)	0	–
Other	14 (2)	8 (2)	0	1 (1)	0	0	1 (8)	0	4 (10)	0	–
Ann Arbor stages at diagnosis, n (%)											
I	75 (8)	35 (9)	4 (7)	13 (9)	13 (11)	3 (16)	0	1 (3)	3 (7)	3 (4)	
II	92 (10)	31 (8)	3 (5)	16 (12)	21 (17)	3 (16)	3 (27)	2 (5)	1 (2)	12 (17)	.003†
III	224 (25)	112 (29)	7 (12)	24 (17)	26 (21)	1 (5)	3 (27)	11 (29)	16 (39)	24 (34)	
IV	499 (56)	212 (54)	46 (77)	85 (62)	63 (51)	12 (63)	5 (45)	24 (63)	21 (51)	31 (44)	
Not available	35	20	8	0	0	0	2	0	0	5	

PIT score is determined based on the presence of the 4 variables: age (≤60 vs >60 years), performance status (ECOG ≤1 vs >2), LDH level (low vs high), and BM involvement (negative vs positive). Depending on the number of adverse prognostic factors (0, 1, 2, or ≥3), patients were classified into LR, low-IR, high-IR, or HR groups, respectively. IPI score is determined based on the presence of 5 dichotomous variables (age, stage, LDH, ECOG performance status, and number of involved extranodal sites). Depending on the number of adverse prognostic factors (0-1, 2, 3, or >3), patients were classified into LR, low-IR, high-IR, or HR groups, respectively.

β2M, beta-2 microglobulin; CRP, C-reactive protein; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HSTCL, hepatosplenic T-cell lymphoma; IQR, interquartile range; IgG, immunoglobulin G; Ki-67, proliferation index; LDH, lactate dehydrogenase; LLN, lower limit of normal; PIT, prognostic index for T-cell lymphoma; T-PLL, T-cell prolymphocytic leukemia; ULN, upper limit of normal.

**P* values for the comparison between patients in different national cohorts were calculated using Kruskal-Wallis and χ^2 tests for nonnormally distributed continuous variables and categorical variables, respectively.

†*P* values based on Fisher exact test due to some small cell counts; χ^2 test for the *P* value calculation of all other categorical variables.

Table 1 (continued)

Characteristic	All (n = 925)	United States (n = 410)	Australia (n = 68)	Brazil (n = 138)	South Korea (n = 123)	South Africa (n = 19)	Saudi Arabia (n = 13)	Japan (n = 38)	Italy (n = 41)	India (n = 75)	*P* value*
IPI scores at diagnosis, n (%)											
0	17 (3)	10 (4)	1 (3)	0	5 (4)	0	0	0	0	1 (2)	
1	83 (14)	33 (13)	2 (5)	14 (17)	22 (18)	0	2 (40)	1 (4)	3 (38)	6 (14)	<.001†
2	178 (30)	93 (37)	7 (18)	30 (36)	29 (24)	3 (38)	1 (20)	3 (12)	3 (38)	9 (21)	
3	204 (35)	80 (32)	20 (53)	33 (39)	44 (36)	3 (38)	1 (20)	3 (12)	2 (25)	18 (43)	
4	88 (15)	32 (13)	5 (13)	7 (8)	22 (18)	2 (25)	1 (20)	12 (48)	0	7 (17)	
5	15 (3)	4 (2)	3 (8)	0	1 (1)	0	0	6 (24)	0	1 (2)	
Not available	340	158	30	54	0	11	8	13	33	33	
PIT scores at diagnosis, n (%)											
0	79 (12)	36 (14)	2 (5)	10 (11)	16 (13)	2 (15)	0	3 (8)	4 (29)	6 (10)	
1	226 (36)	85 (33)	8 (21)	37 (42)	51 (41)	6 (46)	4 (67)	3 (8)	6 (43)	26 (44)	<.001†
2	215 (34)	84 (33)	18 (47)	35 (39)	40 (33)	4 (31)	0	13 (34)	4 (29)	17 (29)	
3	101 (16)	43 (17)	8 (21)	7 (8)	16 (13)	1 (8)	2 (33)	15 (39)	0	9 (15)	
4	15 (2)	8 (3)	2 (5)	0	0	0	0	4 (11)	0	1 (2)	
Not available	289	154	30	49	0	6	7	0	27	16	
Extranodal involvement, n (%)	608 (67)	259 (65)	55 (85)	93 (67)	82 (67)	12 (63)	8 (67)	25 (66)	23 (56)	51 (70)	
Not available	20	14	3	0	0	0	1	0	0	2	.1†
>1 site, n (%)	312 (35)	111 (28)	28 (44)	45 (33)	69 (56)	9 (47)	6 (55)	14 (37)	5 (12)	25 (35)	
Not available	25	15	5	0	0	0	2	0	0	3	<.001†
Bone marrow involvement, n (%)	271 (33)	123 (35)	26 (42)	43 (44)	32 (26)	7 (41)	2 (17)	8 (21)	14 (36)	16 (22)	.01†
Not available	112	59	6	40	0	2	1	0	2	2	
ECOG, n (%)											
0	348 (41)	138 (39)	27 (47)	52 (38)	70 (57)	8 (50)	1 (11)	2 (5)	37 (90)	13 (19)	<.001†
1	370 (44)	168 (47)	24 (42)	58 (42)	44 (36)	6 (38)	5 (56)	17 (45)	4 (10)	44 (64)	
2	93 (11)	40 (11)	4 (7)	19 (14)	9 (7)	2 (12)	3 (33)	9 (24)	0	7 (10)	
3	30 (4)	8 (2)	2 (4)	7 (5)	0	0	0	9 (24)	0	4 (6)	
4	5 (1)	1 (<1)	0	2 (1)	0	0	0	1 (3)	0	1 (1)	
Not available	79	55	11	0	0	3	4	0	0	6	
LDH >ULN, n (%)	513 (68)	203 (63)	33 (70)	71 (59)	93 (76)	14 (78)	9 (100)	32 (84)	7 (47)	51 (84)	<.001†
Not available	173	89	21	18	0	1	4	0	26	14	
β2M >ULN, n (%)	188 (62)	46 (69)	2 (11)	39 (70)	61 (56)	–	–	30 (81)	2 (40)	8 (73)	<.001†
Not available	622	343	50	82	14	19	13	1	36	64	

PIT score is determined based on the presence of the 4 variables: age (≤60 vs >60 years), performance status (ECOG ≤1 vs >2), LDH level (low vs high), and BM involvement (negative vs positive). Depending on the number of adverse prognostic factors (0, 1, 2, or ≥3), patients were classified into LR, low-IR, high-IR, or HR groups, respectively. IPI score is determined based on the presence of 5 dichotomous variables (age, stage, LDH, ECOG performance status, and number of involved extranodal sites). Depending on the number of adverse prognostic factors (0-1, 2, 3, or >3), patients were classified into LR, low-IR, high-IR, or HR groups, respectively.

β2M, beta-2 microglobulin; CRP, C-reactive protein; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HSTCL, hepatosplenic T-cell lymphoma; IQR, interquartile range; IgG, immunoglobulin G; Ki-67, proliferation index; LDH, lactate dehydrogenase; LLN, lower limit of normal; PIT, prognostic index for T-cell lymphoma; T-PLL, T-cell prolymphocytic leukemia; ULN, upper limit of normal.

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CRP >ULN, n (%)	216 (63)	44 (79)	6 (22)	53 (84)	51 (42)	2 (67)	6 (100)	36 (95)	2 (17)	16 (94)	<.001†
Not available	582	354	41	75	2	16	7	0	29	58	
Absolute lymphocyte count <LLN, n (%)	315 (42)	117 (38)	21 (43)	36 (31)	91 (74)	10 (56)	4 (33)	15 (39)	5 (36)	16 (26)	<.001†
Not available	182	99	19	21	0	1	1	0	27	14	
Albumin <LLN, n (%)	259 (38)	123 (37)	6 (75)	25 (27)	32 (26)	3 (43)	8 (67)	35 (92)	12 (100)	15 (25)	<.001†
Not available	238	75	60	47	0	12	1	0	29	14	
IgG <LLN, n (%)	32 (12)	16 (14)	0	–	10 (10)	0	0	5 (13)	1 (9)	0	.95
Not available	653	296	67	138	23	16	12	0	30	71	
Ki67 ≥40%, n (%)	297 (68)	128 (59)	4 (50)	62 (87)	31 (69)	6 (86)	5 (62)	28 (80)	21 (64)	12 (71)	<.001†
Not available	485	194	60	67	78	12	5	3	8	58	
Time to follow-up since diagnosis, median (IQR), y	1.92 (0.94-3.94)	2.69 (1.35-5.02)	1.11 (0.72-3.42)	1.27 (0.82-2.20)	1.80 (0.98-3.87)	1.07 (0.62-4.19)	1.25 (0.68-2.57)	1.35 (0.60-2.51)	2.67 (1.64-3.94)	1.89 (0.67-3.11)	<.001
Current status, n (%)											
Alive	303 (33)	153 (37)	21 (31)	48 (35)	43 (35)	5 (26)	7 (54)	1 (3)	13 (32)	12 (16)	<.001†
Dead	515 (56)	238 (58)	35 (51)	82 (59)	77 (63)	13 (68)	5 (38)	34 (89)	28 (68)	3 (4)	
Lost to follow-up	107 (12)	19 (5)	12 (18)	8 (6)	3 (2)	1 (5)	1 (8)	3 (8)	0	60 (80)	

PIT score is determined based on the presence of the 4 variables: age (≤60 vs >60 years), performance status (ECOG ≤1 vs >2), LDH level (low vs high), and BM involvement (negative vs positive). Depending on the number of adverse prognostic factors (0, 1, 2, or ≥3), patients were classified into LR, low-IR, high-IR, or HR groups, respectively. IPI score is determined based on the presence of 5 dichotomous variables (age, stage, LDH, ECOG performance status, and number of involved extranodal sites). Depending on the number of adverse prognostic factors (0-1, 2, 3, or >3), patients were classified into LR, low-IR, high-IR, or HR groups, respectively.

β2M, beta-2 microglobulin; CRP, C-reactive protein; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; HSTCL, hepatosplenic T-cell lymphoma; IQR, interquartile range; IgG, immunoglobulin G; Ki-67, proliferation index; LDH, lactate dehydrogenase; LLN, lower limit of normal; PIT, prognostic index for T-cell lymphoma; T-PLL, T-cell prolymphocytic leukemia; ULN, upper limit of normal.

**P* values for the comparison between patients in different national cohorts were calculated using Kruskal-Wallis and χ^2 tests for nonnormally distributed continuous variables and categorical variables, respectively.

†*P* values based on Fisher exact test due to some small cell counts; χ^2 test for the *P* value calculation of all other categorical variables.

Table 2. Treatment characteristics for the global cohort (training and test)

Characteristic	All (n = 925)	United States (n = 410)	Australia (n = 68)	Brazil (n = 138)	South Korea (n = 123)	South Africa (n = 19)	Saudi Arabia (n = 13)	Japan (n = 38)	Italy (n = 41)	India (n = 75)	*P* value*
Relapsed	468 (51)	258 (63)	26 (39)	39 (28)	63 (52)	6 (32)	2 (17)	15 (39)	10 (24)	49 (65)	<.001
Primary refractory	452 (49)	151 (37)	40 (61)	99 (72)	59 (48)	13 (68)	10 (83)	23 (61)	31 (76)	26 (35)	
Not available	5	1	2	0	1	0	1	0	0	0	
First-line therapy											
Treatment, n (%)											
CHOP based	320 (35)	132 (32)	30 (47)	35 (26)	76 (62)	5 (26)	3 (23)	7 (18)	11 (27)	21 (28)	<.001†
CHOEP based	269 (29)	140 (34)	18 (28)	66 (49)	4 (3)	13 (68)	3 (23)	0	18 (44)	7 (9)	<.001†
EPOCH based	48 (5)	38 (9)	1 (2)	5 (4)	3 (2)	0	0	1 (3)	0	0	-
CHP-BV based	19 (2)	14 (3)	0	1 (1)	0	0	3 (23)	0	1 (2)	0	-
Alemtuzumab based	15 (2)	14 (3)	0	0	0	0	1 (8)	0	0	0	-
Other‡	248 (27)	72 (18)	15 (23)	29 (21)	40 (33)	1 (5)	3 (23)	30 (79)	11 (27)	47 (63)	<.001†
NA	6	0	4	2	0	0	0	0	0	0	
Treatment response, n (%)											
Complete response	410 (45)	218 (55)	22 (33)	39 (28)	49 (40)	6 (32)	2 (17)	15 (39)	13 (32)	46 (61)	<.001†
Partial response	161 (18)	34 (9)	18 (27)	35 (25)	29 (24)	8 (42)	10 (83)	10 (26)	7 (17)	10 (13)	
Stable disease	36 (4)	17 (4)	7 (11)	1 (1)	4 (3)	2 (11)	0	2 (5)	3 (7)	0	
Progressive disease	298 (33)	125 (32)	19 (29)	63 (46)	40 (33)	3 (16)	0	11 (29)	18 (44)	19 (25)	
NA	20	16	2	0	1	0	1	0	0	0	
Underwent auto-HSCT consolidation, n (%)	186 (21)	122 (30)	6 (19)	11 (8)	32 (26)	2 (11)	5 (50)	0	7 (17)	1 (2)	<.001†
Not available	50	1	36	0	1	0	3	0	0	9	
Received radiation in first line, n (%)	121 (14)	35 (10)	6 (9)	19 (14)	32 (26)	1 (5)	5 (62)	2 (5)	1 (2)	20 (27)	<.001†
NA	70	64	0	0	0	0	5	0	0	1	
Second-line therapy											
Commonly used therapy, n (%)											<.001†
SA	323 (35)	219 (53)	24 (35)	9 (7)	18 (15)	1 (5)	1 (8)	9 (24)	13 (32)	29 (39)	
CC	559 (60)	154 (38)	43 (63)	125 (91)	104 (85)	18 (95)	12 (92)	29 (76)	28 (68)	46 (61)	
Both	11 (1)	5 (1)	1 (1)	4 (3)	1 (1)	0	0	0	0	0	
Excluded§	32 (3)	32 (8)	0	0	0	0	0	0	0	0	
Achieved complete remission, n (%)	258 (35)	137 (39)	18 (35)	24 (29)	31 (28)	8 (57)	4 (44)	6 (16)	9 (22)	21 (45)	
NA	180	58	16	56	13	5	4	0	0	28	.008†

Exhibited characteristics apply to the entire global data set of 925 patients.

CHP-BV, cyclophosphamide + doxorubicin + prednisone + brentuximab; NA, information not available.

**P* values for the comparison between patients in different national cohorts were calculated using χ^2 tests for categorical variables.

†*P* values based on Fisher exact test due to some small cell counts.

‡Lymphoma subtypes for the patients receiving "other" first-line therapies include PTCL-NOS (n = 94), ENKTCL (n = 70), AITL (n = 49), ALK$^-$ ALCL (n = 23), ATLL (n = 13), HSTCL (n = 10), T-PLL (10), ALK$^+$ALCL (n = 6), other (n = 6), and EATL (n = 5).

§Patients receiving the following therapies as second line were excluded from various subanalyzes comparing effects of SA with those of CC: bexarotene, investigational study drug, methotrexate, and allo-HSCT.

Table 2 (continued)

Characteristic	All (n = 925)	United States (n = 410)	Australia (n = 68)	Brazil (n = 138)	South Korea (n = 123)	South Africa (n = 19)	Saudi Arabia (n = 13)	Japan (n = 38)	Italy (n = 41)	India (n = 75)	*P* value*
Underwent HSCT consolidation, n (%)	159 (20)	91 (23)	13 (38)	19 (14)	18 (21)	6 (33)	0	3 (8)	7 (17)	2 (4)	
NA	114	12	34	0	36	1	7	0	0	24	<.001†
Auto-HSCT	78 (49)	27 (30)	11 (85)	15 (79)	13 (72)	3 (50)	0	2 (67)	6 (86)	1 (50)	
Allo-HSCT	81 (51)	64 (70)	2 (15)	4 (21)	5 (28)	3 (50)	0	1 (33)	1 (14)	1 (50)	<.001†
Total no. of lines of therapy, median (IQR)	3 (2-4)	3 (2-4)	3 (3-4)	2 (2-2)	3 (2-4)	2 (2-3)	2 (2-3)	2 (2-3)	4 (3-5)	2 (2-3)	<.001
Year of start date, n (%)											<.001†
2010	7 (1)	4 (1)	1 (2)		0	0	0	2 (5)	0	0	
2011	24 (3)	19 (5)	2 (3)		0	1 (5)	0	1 (3)	1 (2)	0	
2012	49 (6)	39 (10)	5 (8)		0	0	0	3 (8)	1 (2)	1 (1)	
2013	47 (6)	29 (7)	3 (5)		8 (7)	1 (5)	0	2 (5)	1 (2)	3 (4)	
2014	65 (9)	42 (11)	5 (8)		8 (7)	4 (21)	0	1 (3)	2 (5)	3 (4)	
2015	58 (8)	29 (7)	5 (8)	-	11 (9)	2 (11)	0	3 (8)	1 (2)	7 (9)	
2016	74 (10)	33 (8)	1 (2)		18 (15)	2 (11)	1 (11)	6 (16)	2 (5)	11 (15)	
2017	108 (14)	47 (12)	9 (14)		26 (21)	2 (11)	3 (33)	7 (18)	1 (2)	13 (17)	
2018	88 (12)	40 (10)	10 (16)		19 (15)	1 (5)	0	4 (11)	7 (17)	7 (9)	
2019	93 (12)	30 (8)	15 (24)		13 (11)	2 (11)	2 (22)	6 (18)	9 (22)	15 (20)	
2020	84 (11)	41 (10)	6 (10)		15 (12)	4 (21)	1 (11)	2 (5)	8 (20)	7 (9)	
2021	50 (7)	35 (9)	1 (2)		4 (3)	0	2 (22)	0	5 (12)	3 (4)	
2022	16 (2)	7 (2)	0		1 (1)	0	0	0	3 (7)	5 (7)	
NA	162	15	5	138	0	0	4	0	0	0	

Exhibited characteristics apply to the entire global data set of 925 patients.

CHP-BV, cyclophosphamide + doxorubicin + prednisone + brentuximab; NA, information not available.

**P* values for the comparison between patients in different national cohorts were calculated using χ^2 tests for categorical variables.

†*P* values based on Fisher exact test due to some small cell counts.

‡Lymphoma subtypes for the patients receiving "other" first-line therapies include PTCL-NOS (n = 94), ENKTCL (n = 70), AITL (n = 49), ALK^- ALCL (n = 23), ATLL (n = 13), HSTCL (n = 10), T-PLL (10), ALK^+ALCL (n = 6), other (n = 6), and EATL (n = 5).

§Patients receiving the following therapies as second line were excluded from various subanalyzes comparing effects of SA with those of CC: bexarotene, investigational study drug, methotrexate, and allo-HSCT.

estimates from the start of second-line treatment is based on 763 patients for whom the start dates of second-line treatments were available.

Relapsed patients have superior survival compared with primary refractory patients in MTCL subtypes

We compared median OS from the time of second-line treatment for patients with relapsed vs primary refractory disease, stratified by lymphoma subtype. The Kaplan-Meier estimate of OS was longer for relapsed patients than refractory patients in PTCL-NOS (1.97 years [95% confidence interval (CI), 1.27-2.69] vs 0.89 years [95% CI, 0.66-1.20]; $P = .01$) and ALK^- ALCL (4.22 years [95% CI, 1.52 to infinite (inf)] vs 1.36 years [95% CI, 0.38-2.84]; $P = .01$). The difference in OS from second-line treatment was not statistically significant in AITL (2.84 years [95% CI, 1.77-3.40] vs 2.25 years [95% CI, 1.08-5.69]; $P = .98$), ENKTCL (1.30 years [95% CI, 0.84 to inf] vs 1.17 years [95% CI, 0.49-7.10]; $P = .35$), or ALK^+ ALCL (3.40 years [95% CI, 1.94 to inf] vs inf years [95% CI, 0.09 to inf]; $P = .48$; Figure 2). In addition, the OS from second-line treatment was not statistically significant ($P = .065$) between patients with different histological subtypes with ALK^- ALCL (2.49 years; 95% CI, 1.05-4.22), ALK^+ ALCL (inf years; 95% CI, 1.54 to inf), PTCL-NOS (1.21 years; 95% CI, 1.04-1.65), ENKTCL (1.23 years; 95% CI, 0.77 to inf), and AITL (2.58 years; 95% CI, 1.89-3.40; supplemental Figure 1).

Prognostic factors in patients with R/R MTCL and MNKCL

Although multiple prognostic factors and models have been proposed to risk stratify patients with MTCL and MKNCL, they were mostly developed for newly diagnosed patients. Thus, a new prognostic model is needed to further refine subgroups with varied outcomes within the R/R population in light of the above distinct outcomes and wide ranges of OS demonstrated above.

We thus split our global cohort of 763 patients into a training set (80%) and a test set (20%) and systematically evaluated 21 available features that were clinically relevant and easy to use in a global real-world data set. These included demographics, histological, laboratory, radiologic, and treatment characteristics (Figure 3A). We identified 11 nontreatment factors on univariable analysis to be associated with an inferior OS from the start of second-line treatment ($P \leq 0.3$). Based on the step-by-step selection in multivariable Cox regression and clinical considerations, our final model that combined 6 of the 11 features was chosen based on the highest training C-index among the models that incorporated covariates retaining an independent prognostic value ($P \leq .05$) and based on Akaike information criterion. The final 6 features included were age >60 years, primary refractory, not AITL subtype, >1 extranodal site involvement, Ki67 ≥40%, and absolute lymphocyte count below the lower limit of normal, and each was associated with a P value of ≤.05 in the final multivariable Cox model (Figure 3B). Based on heterogeneous scoring of the Ki67 proliferation index (265 patients had Ki67 ≥40% and 94 with <40%), the cutoff of 40% was chosen, which gave us the optimal C-index in combination with other factors on the training and test cohorts. Because the relative risks associated with each of these 6 factors are similar, we assigned a score of 1 to each unfavorable feature. We then developed a novel prognostic model for 248 patients with R/R MTCL and MNKCL to estimate their OS from the start of second-line treatment and named it the prognostic index for R/R TCL (PIRT) score (Table 3). There was a clear trend of declining OS with an increasing score (Figure 4A-B). Patients were initially categorized into 6 subgroups because they had separate outcomes based on their scores (supplemental Figure 2A). For practical considerations, including ease of use as a tool to aid clinicians in the real world, we ultimately consolidated the 6 groups into 3 final risk groups: low risk (LR; 0-1), IR (2-3), and HR (4-6), with marked similarity between their predicted and actual survival (supplemental Figure 2B). On the training data set, the median 3-year OS was 75.2% for the LR group (95% CI, 29.7-85.2) vs 50.6% for the IR group (95% CI, 37.7-58.9) vs 16% for the HR group (95% CI, 7.7-26.9; Table 3). The PIRT score was associated with a lower Akaike information criterion and higher C-index when its performance was compared with the IPI and PIT scores. We were also able to segregate the test data set into 3 risk groups with disparate 3-year OS: LR (57.1%; 95% CI, 17.1-83.7) vs IR (23.3%; 95% CI, 8.7-41.9) vs HR (7%; 95% CI, 0.4-26.9; Figure 4C), similar to the training cohort. Based on the evaluation of 1000 bootstrapped test sets, our PIRT score demonstrated an improved prediction probability with a higher average C-index (0.7; 95% CI, 0.63-0.76) than IPI (0.56; 95% CI, 0.5-0.63) and PIT (0.59; 95% CI, 0.52-0.65) on the test data set (Table 3). Based on paired t tests between IPI vs PIRT and PIT vs PIRT scores, we confirmed that this distinction of performance was statistically significant.

We pooled eligible patients (not previously included in the global training and test data set) from the T-Cell Project (TCP) 2.0 registry and from 1 of the US institutions (Massachusetts General Hospital) to form the independent validation cohort. After harmonizing the data and applying the same inclusion criteria for the training and test populations, there were 102 and 45 eligible patients in the TCP 2.0 and MGH cohorts, respectively. The clinical characteristics of the combined validation cohort are summarized in the supplemental Table 6. In the combined cohort, after applying the PIRT score, patients were classified as LR (n = 7), IR (n = 60), and HR groups (n = 80). The PIRT was prognostic for 3-years OS, with a median of 85.7% (95% CI, 33.4-97.8), 29.9% (95% CI, 12.1-50.2), and 26.2% (95% CI, 15.9-37.7) for LR, IR, and HR groups, respectively (Figure 4D). To emphasize, our PIRT score demonstrated an improved prediction probability with a higher average C-index (0.62; 95% CI, 0.57-0.67) than IPI (0.51; 95% CI, 0.46-0.57) and PIT (0.55; 95% CI, 0.5-0.61) on the validation data set ($P < .01$). It is worth noting that the prognostic order of the risk groups defined by the score was maintained in the external validation cohort. We have developed a web-based survival risk calculator that uses the PIRT prognostic model to aid clinicians in predicting survival estimates, which will be free for use for any audience (https://www.petalconsortium.org/pirt-calculator).

Comparative outcomes of patients receiving SA vs CC as second-line treatment

Having observed heterogenous outcomes between R/R patients, we wanted to interrogate the impact of different therapies. In our cohort, R/R patients received either SA (323/925 [35%]) or CC (559/925 [60%]) for their second-line treatment, with higher proportions receiving SA in the United States (219/410 [53%]) and lower proportions in South Korea (18/123 [15%]), Saudi Arabia

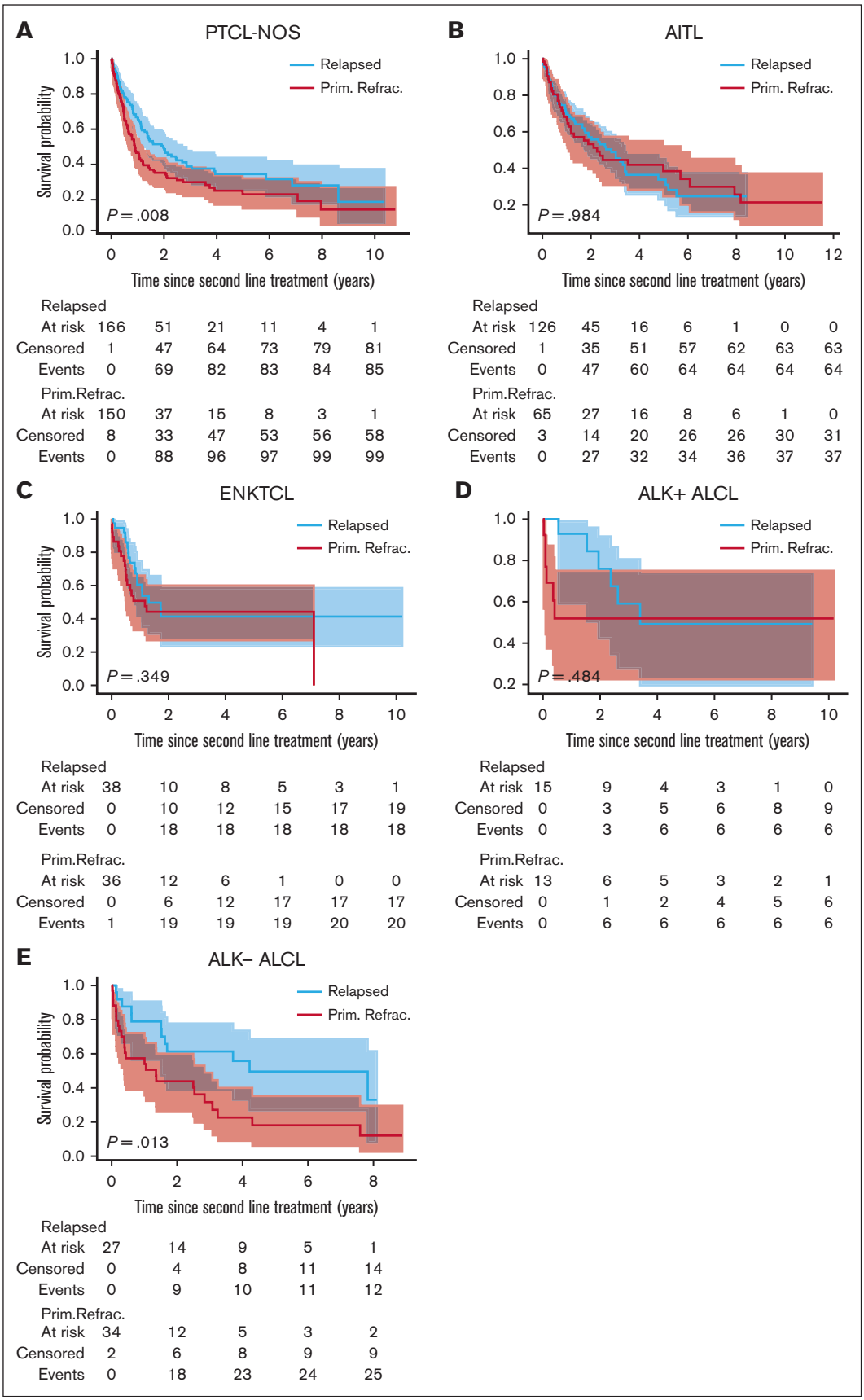
A
PTCL-NOS
Relapsed
Prim. Refrac.
Survival probability
P = .008
Time since second line treatment (years)
Relapsed
At risk 166 51 21 11 4 1
Censored 1 47 64 73 79 81
Events 0 69 82 83 84 85
Prim.Refrac.
At risk 150 37 15 8 3 1
Censored 8 33 47 53 56 58
Events 0 88 96 97 99 99
B
AITL
Relapsed
Prim. Refrac.
P = .984
Time since second line treatment (years)
Relapsed
At risk 126 45 16 6 1 0 0
Censored 1 35 51 57 62 63 63
Events 0 47 60 64 64 64 64
Prim.Refrac.
At risk 65 27 16 8 6 1 0
Censored 3 14 20 26 26 30 31
Events 0 27 32 34 36 37 37
C
ENKTCL
Relapsed
Prim. Refrac.
Survival probability
P = .349
Time since second line treatment (years)
Relapsed
At risk 38 10 8 5 3 1
Censored 0 10 12 15 17 19
Events 0 18 18 18 18 18
Prim.Refrac.
At risk 36 12 6 1 0 0
Censored 0 6 12 17 17 17
Events 1 19 19 19 20 20
D
ALK+ ALCL
Relapsed
Prim. Refrac.
P = .484
Time since second line treatment (years)
Relapsed
At risk 15 9 4 3 1 0
Censored 0 3 5 6 8 9
Events 0 3 6 6 6 6
Prim.Refrac.
At risk 13 6 5 3 2 1
Censored 0 1 2 4 5 6
Events 0 6 6 6 6 6
E
ALK– ALCL
Relapsed
Prim. Refrac.
Survival probability
P = .013
Time since second line treatment (years)
Relapsed
At risk 27 14 9 5 1
Censored 0 4 8 11 14
Events 0 9 10 11 12
Prim.Refrac.
At risk 34 12 5 3 2
Censored 2 6 8 9 9
Events 0 18 23 24 25

Figure 2.

(1/13 [8%]), and Brazil (9/138 [7%]). Globally, 258 of 745 patients (35%) achieved a second complete response upon second-line treatment, with higher rates in South Africa (8/14 [57%]). A total of 159 of 811 patients (20%) proceeded to HSCT after second-line treatment; of these 159 patients, 78 (49%) received consolidative auto-HSCT, and 81 (51%) received allogeneic HSCT (allo-HSCT). Consolidative HSCT after second-line treatment was more common in Australia (13/34 [38%]) and South Africa (6/18 [33%]) and less common in Japan (3/38 [8%]). With the exception of the United States (27/91 [30%]), the percentage of patients bridged to auto-HSCT was higher or comparable with allo-HSCT even after second-line treatment, highlighting the differences in clinical practice globally. The distribution of patients bridged to auto-HSCT or allo-HSCT by SA or CC across various lymphoma subtypes is summarized in supplemental Table 7. Although an overall greater number of patients underwent HSCT after CC than after SA treatment, the proportion of patients undergoing allo-HSCT was comparable between the 2 treatment groups, likely secondary to heterogeneity in treatment paradigms globally.

We next sought to compare the OS of patients receiving SA vs CC across subtypes from the start of second-line treatment. The number of patients included in this analysis was 763, for whom the dates of start of second-line treatment were available. For PTCL-NOS (1.42 years [95% CI, 0.92-2.14] vs 1.14 years [95% CI, 0.91-1.59]; $P = .63$) and ALK$^+$ ALCL (inf years [95% CI, 0.12 to inf] vs 1.94 years [95% CI, 0.09 to inf]; $P = .41$), OS from the time of second-line treatment was comparable between those treated with SA and CC. In AITL (3.40 years [95% CI, 2.58 to inf] vs 1.71 years [95% CI, 0.96-2.49]; $P = .004$) and ALK$^-$ ALCL (3.08 years [95% CI, 1.05 to inf] vs 1.36 years [95% CI, 0.30-3.71]; $P = .06$), the OS for patients treated with SA was superior compared with those treated with CC (Figure 5). However, for ENKTCL, CC-treated patients (7.10 years [95% CI, 0.77 to inf] vs 0.84 years [95% CI, 0.43-1.73]; $P = .04$) experienced longer OS than those treated with SA. The 3-year and 5-year OS for patients treated with SA in comparison with CC confirmed these results as well and are exhibited in supplemental Table 8A-C.

We evaluated the PFS for patients who achieved response (complete response + partial response + stable disease) to SA and CC by calculating the time from the start of SA or CC treatment to the start of third-line treatment, death, or loss of follow-up (Figure 6A). We observed a statistically significant PFS advantage achieved with the use of SA over CC regardless of transplantation status after second-line therapy. This was observed even after adjusting for important prognostic factors such as PIT score, primary refractory status, and lymphoma subtype (average hazard ratio (aHR), 0.69; 95% CI, 0.51-0.95; $P = .02$). This was also true when transplant was considered as an event but not censored (aHR, 0.64; 95% CI, 0.49-0.85; $P < .005$; Figure 6B) and when transplant was used as a censoring event (aHR, 0.78; 95% CI, 0.55-1.11; $P = .17$; Figure 6C). When we investigated OS for patients who were administered SA vs CC but did not undergo auto-HSCT or allo-HSCT, the HR was 0.62 (95% CI, 0.42-0.91; $P = .01$), whereas the HR for those who proceeded to transplant receiving SA vs CC was 0.55 (95% CI, 0.29-1.03; $P = .06$; Figure 6D).

We then stratified analysis by specific SA subclasses based on the mechanism of action of the drugs including epigenetic modifiers (EMs), ADCs, AFs, and small-molecule signaling inhibitors (SMIs). For PTCL-NOS, there was no difference in OS from the time of second-line treatment across patients treated with CC (1.14 years; 95% CI, 0.91-1.59), EM (1.09 years; 95% CI, 0.85 to inf), ADC (2.69 years; 95% CI, 1.37 to inf), AF (0.65 years; 95% CI, 0.23-1.46), and SMI (0.87 years; 95% CI, 0.15-2.04; Figure 7A). This result was consistent when EM group only included HDACi (1.12 years; 95% CI, 0.82 to inf; supplemental Figure 3A). Patients with AITL treated with SMI had improved OS (95% CI, 8.17 to inf) compared with those treated with CC (95% CI, 0.96-2.49; $P < .0005$) and EM (95% CI, 1.04-3.46; $P = .001$) and comparable OS with those treated with ADC (95% CI, 0.01 to inf; $P = .11$; Figure 7B). The SMI treatments consisted mostly of alisertib, duvelisib, cerdulatinib, and cyclosporine. The distribution of SMI and number of patients specifically with AITL receiving it included anti-cyclin-dependent kinase 9 (CDK9) inhibitor (n = 1), alisertib (n = 6), duvelisib alone and its combination with romidepsin or bortezomib (n = 7), cerdulatinib (n = 4), cyclosporine (n = 4), ruxolitinib (n = 1), and tipifarnib (n = 2). In patients with AITL, patients treated with CC or ADC did not have significant difference in OS compared with the EM group, which only included HDACi (2.11 years; 95% CI, 0.88-2.84; $P = .7$; supplemental Figure 3B). For ENKTCL, there was no difference in OS between those treated with CC and those treated with monoclonal antibody (7.1 years [95% CI, 0.77 to inf] vs 1.07 years [95% CI, 0.33 to inf]; $P = .1$). For ALK$^+$ ALCL, there was no difference in OS between those treated with CC and those treated with ADC (1.94 years [95% CI, 0.09 to inf] vs inf years [95% CI, 2.37 to inf]; $P = .48$). Importantly, for ALK$^-$ ALCL, the OS was inferior in those treated with CC compared with ADC (1.36 years [95% CI, 0.30-3.71] vs 4.22 years [95% CI, 1.05 to inf]; $P = .03$; Figure 7C-E).

We also compared the median time to the next therapy for SA vs CC in the second-line setting. For the combined cohort, the time to next therapy was comparable between the 2 groups (HR, 0.81; 95% CI, 0.60-1.09; $P = .16$; HR with adjustment for lymphoma subtype, PIT score, and primary refractory disease, 0.83; 95% CI, 0.57-1.21; $P = .34$). Supplemental Figure 4 illustrates the number of patients receiving CC vs SA over time across countries. We also evaluated the OS of SA vs CC across the 3 risk groups defined by PIRT score in the combined training and test population, and once again, SA was at least comparable in all risk groups and even superior in some relative to CC (supplemental Figure 5). A summary of start and stop time points and of events for various survival analyses for the global cohort is depicted in supplemental Table 9. A summary table that highlights differences in baseline, demographic, clinical, and treatment characteristics of the SA and

Figure 2. OS for relapsed and primary refractory (R/R) patients with MTCL and MNKCL stratified by histological subtype comparing relapsed vs primary refractory disease. (A-E) Kaplan-Meier curves show OS estimates since the start of second-line treatment for patients with PTCL-NOS (A), AITL (B), ENKTCL (C), ALK$^+$ ALCL (D), and ALK$^-$ ALCL (E). Results depicted apply to the global data set of 763 patients for whom information on the start of second-line treatment was available. *P* values calculated by log-rank test. Prim. Refrac., primary refractory.

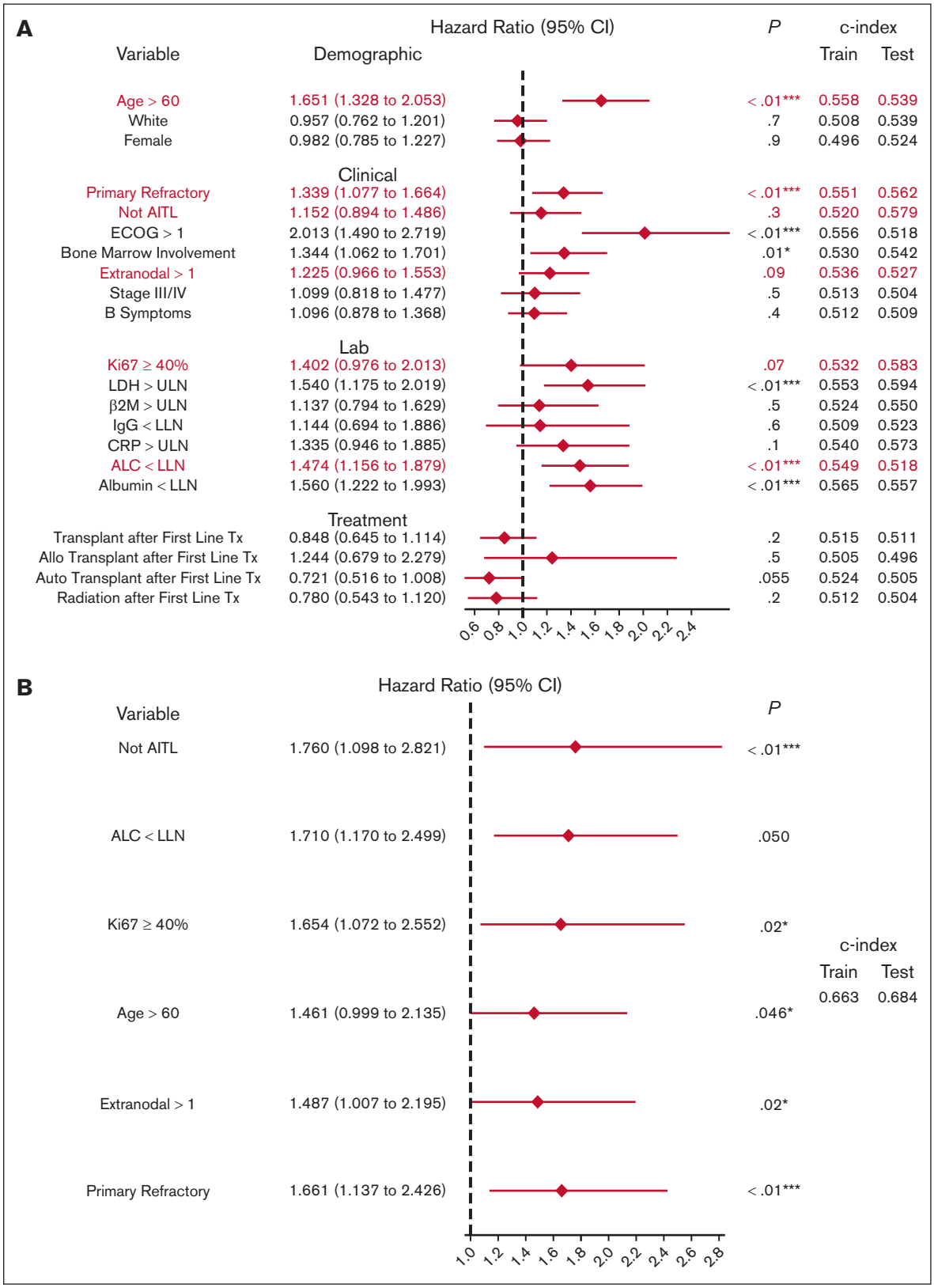

Figure 3. Cox proportional hazards regression analysis for OS from risk-defining events of patients with relapsed and primary refractory (R/R) MTCL and MNKCL. Forest plot of univariable and multivariable analysis for risk factors associated with survival. (A) Univariable analysis performed systematically on 21 clinically relevant factors on the global training and test data sets and C-index reported. The 6 features used in the final multivariable model are highlighted in red. (B) Final multivariable model selected based on the highest training C-index among the models that incorporated covariates retaining an independent prognostic value ($P \leq .05$). Included covariates were age >60 years, primary refractory, not AITL subtype, >1 extranodal site involvement, Ki67 ≥40%, and ALC less than LLN. ALC, absolute lymphocyte count; β2M, beta-2 microglobulin; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; IgG, Immunoglobulin G; LLN, lower limit of normal; Tx, treatment; ULN, upper limit of normal.

Table 3. Summary of comparative performance of the new PIRT score for patients with R/R MTCL and MNKCL (0-6) against conventional IPI and PIT score across the global (training and test data sets) and the combined TCP 2.0 and MGH cohorts (external validation data set)

Prognostic index	IPI		PIT		PIRT		
Risk group (score)	LR (0-2)	HR (3-5)	LR (0-1)	HR (2-4)	LR (0-1)	IR (2-3)	HR (4-6)
Training set							
n (%)	191 (48)	208 (52)	204 (47)	229 (53)	14 (7)	106 (54)	76 (39)
Median OS since second-line Tx (95% CI)*	2.53 (1.71-4.22)	1.01 (0.65-1.21)	2.62 (1.65-4.30)	1.08 (0.87-1.30)	inf (2.31 to inf)	3.05 (1.65-6.08)	0.65 (0.40-1.07)
P value	<.005		<.005			<.005	
AIC	2437.55		2628.41			1057.53	
Training C-index	0.58		0.57			0.65	
Test set							
n (%)	40 (43)	54 (57)	50 (48)	55 (52)	7 (13)	27 (52)	18 (35)
Median OS since second-line Tx (95% CI)*	1.13 (0.77-3.03)	0.64 (0.32-1.41)	1.46 (0.96-3.40)	0.59 (0.28-1.20)	inf (0.96 to inf)	1.30 (0.54-2.36)	0.28 (0.16-0.68)
Bootstrap testing, C-index average (95% CI)†	0.56 (0.50-0.63)		0.59 (0.52-0.65)			0.70 (0.63-0.76)	
			$C\text{-index}_{\text{test, IPI}} < C\text{-index}_{\text{test, PIRT}}$ (paired *t* test *P* value <.001) $C\text{-index}_{\text{test, PIT}} < C\text{-index}_{\text{test, PIRT}}$ (paired *t* test *P* value <.001)				
External validation set							
n (%)	95 (65)	52 (35)	80 (54)	67 (46)	7 (5)	60 (41)	80 (54)
Median OS since second-line Tx (95% CI)*	1.06 (0.66-2.35)	0.67 (0.48-1.08)	1.90 (0.77 to inf)	0.65 (0.38- 0.94)	NR (0.07 to inf)	1.59 (0.70 to inf)	0.50 (0.23-0.83)
Bootstrap external validation C-index average (95% CI)†	0.51 (0.46-0.57)		0.55 (0.50-0.61)			0.62 (0.57-0.67)	
			$C\text{- index}_{\text{external validation, IPI}} < C\text{- index}_{\text{external validation PIRT}}$ (paired *t* test *P* value <.001) $C\text{- index}_{\text{external validation, PIT}} < C\text{- index}_{\text{external validation, PIRT}}$ (paired *t* test *P* value <.001)				

PIRT score, for the number of selected adverse factors, ranged from 0 to 6. PIRT score was developed after selecting the final MVC model based on 80% (training data set) of 763 patients for whom information on the start of second-line treatment and complete data for the selected risk factors of the final MVC model was available. We tested the final model on 1000 bootstraps of 20% (test data set) of the global data set and used an external validation/independent cohort of 147 patients (T-Cell Project (TCP) 2.0 and Massachusetts General Hospital (MGH) cohorts pooled) to confirm the performance of the PIRT score. The C-index is a widely used metric for the global evaluation of prognostic models in survival analysis.

AIC, Akaike information criterion; MVC, multivariable Cox; NR, not reached; Tx, treatment.

*OS estimates calculated from the start of second-line treatment to death or loss of follow-up.

†Average = 1000 times bootstrapped.

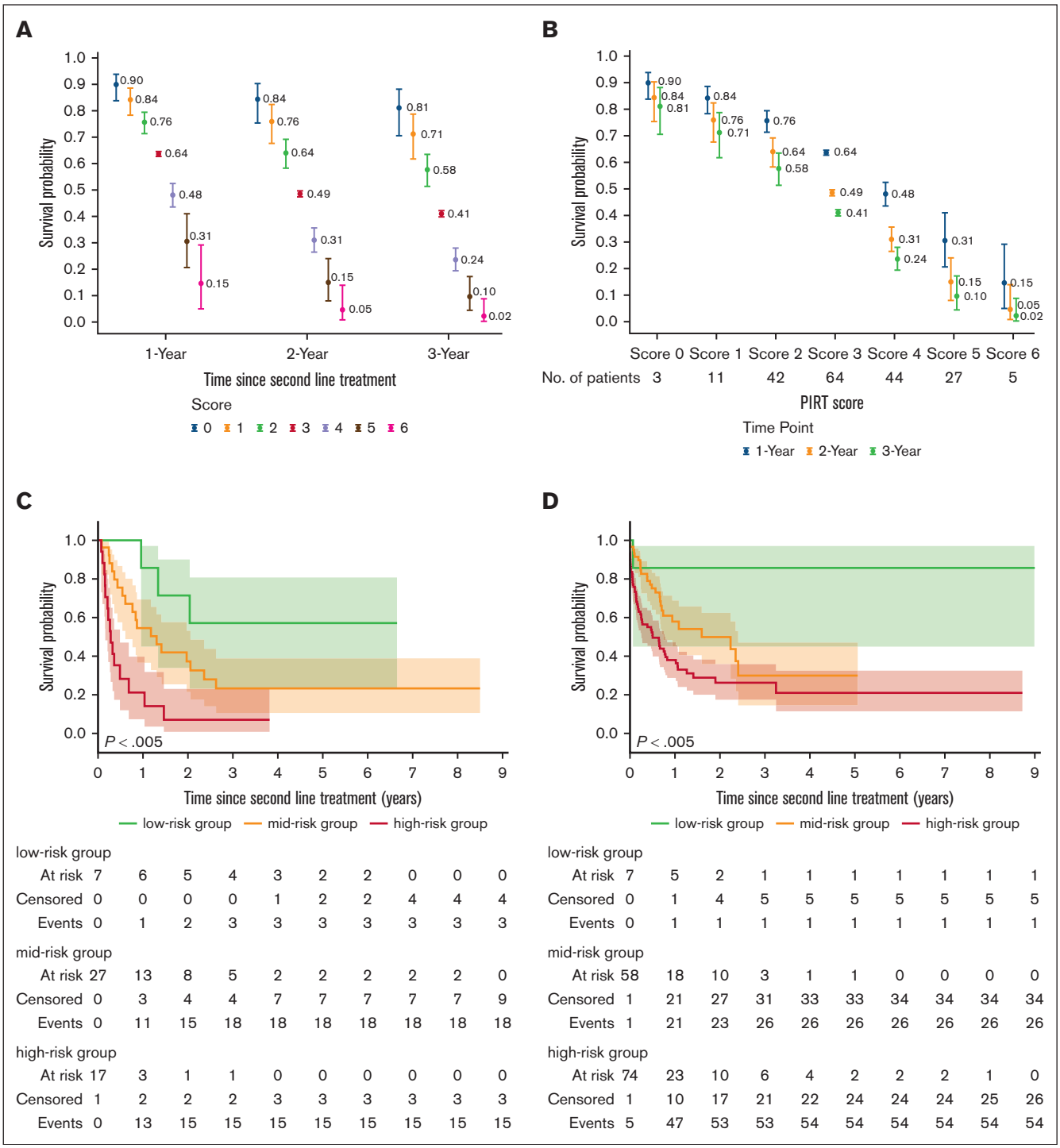

Figure 4. Risk stratification and OS by number of PIRT risk factors in the training, test, and validation cohorts. (A-B) Risk stratification and OS by number of PIRT score risk factors in the training cohort. (C-D) OS by PIRT score categorized risk group in the test and validation cohorts.

CC cohorts is included as supplemental Table 10. Patients in the SA cohort were older. There was a higher incidence of the AITL histological subtype, fewer patients had >1 extranodal site involvement, fewer patients had lactate dehydrogenase above the upper limit of normal at baseline, fewer patients had Ki67 ≥40%, and more patients had relapsed disease than the CC cohort, and hence, it is feasible that these factors could have contributed to their better outcomes. To assess the impact of location of diagnosis and treatment on OS, we performed additional univariable Cox analysis. When comparing being diagnosed and treated in the United States vs not, *P* value was .1, training C-index was 0.52, and testing C-index was 0.54, suggesting that the country of

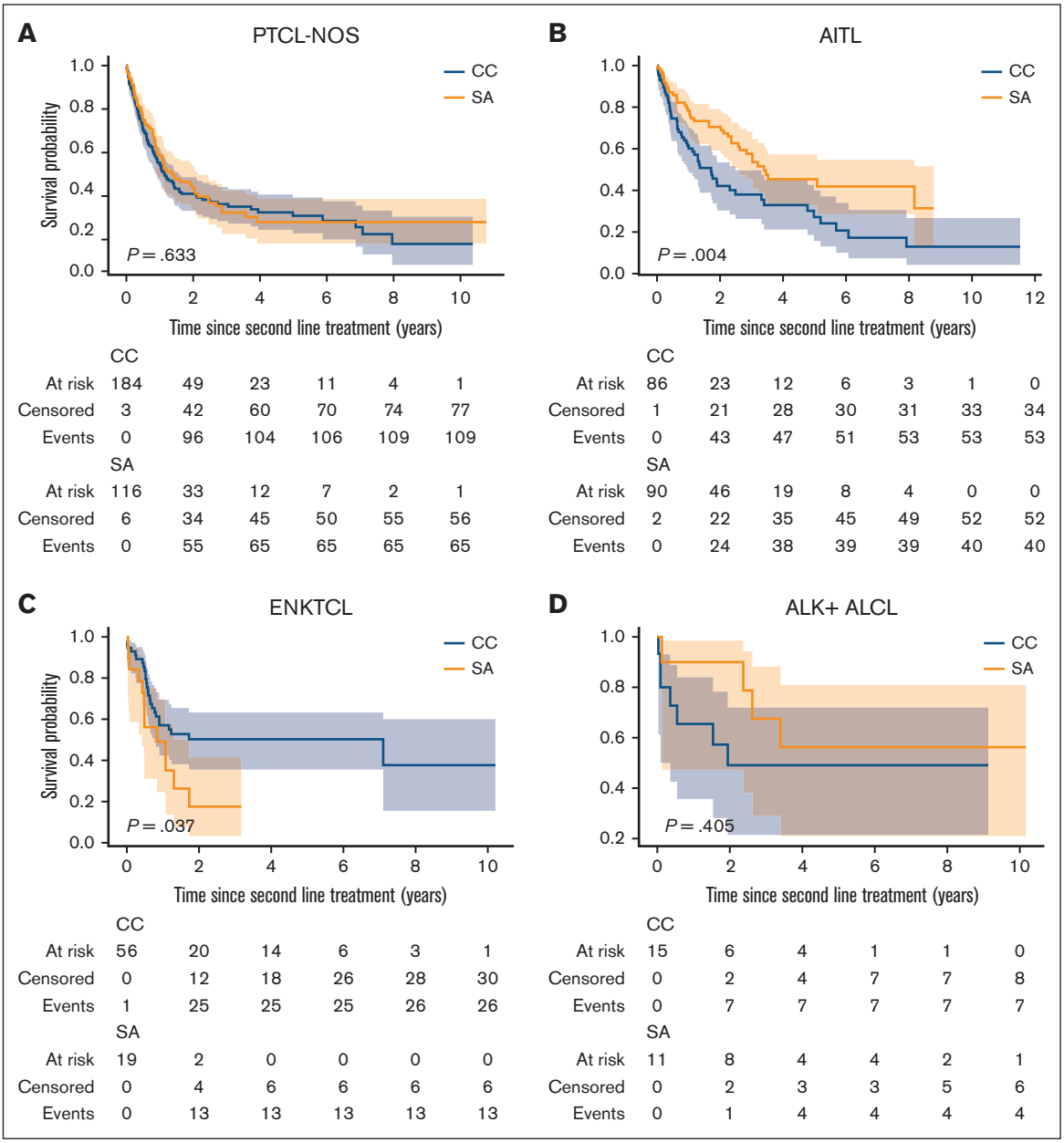

Figure 5. OS for relapsed and primary refractory (R/R) patients with MTCL and MNKCL stratified by histological subtype comparing second-line treatment with CC vs "novel" SA. Kaplan-Meier curves show OS estimates since the start of second-line treatment for patients with PTCL-NOS (A), AITL (B), ENKTCL (C), ALK$^+$ ALCL (D), and ALK$^-$ ALCL (E). Results depicted apply to the global data set of 763 patients for whom information on start dates of second-line treatment was available. *P* values calculated by log-rank test.

diagnosis and treatment is unlikely to affect OS (supplemental Table 11).

Discussion

To the best of our knowledge, this retrospective study represents the largest cohort of patients with R/R aggressive MTCL and MNKCL and reflects outcomes for this specific subset of patients treated according to the standards of care in each country. In this study, we sought to analyze and compare the efficacy of the treatment patterns around the world between SA and CC in the second-line setting and define prognostic factors influencing the survival of patients with R/R lymphoma in a global setting. Previous reports comparing outcomes of patients with R/R lymphoma have largely focused on the combined cohort of all T-cell lymphoma subtypes, thus limiting their generalizability to individual lymphoma subtypes.[1,2] Our relatively large sample size enabled us to interrogate the common nodal lymphoma subtypes with statistical power and observe that outcomes for patients with refractory disease are not necessarily worse when estimating outcomes since the initiation of second-line treatment for subtypes such as AITL, ENKTCL, and ALK$^+$ ALCL. One potential explanation could be

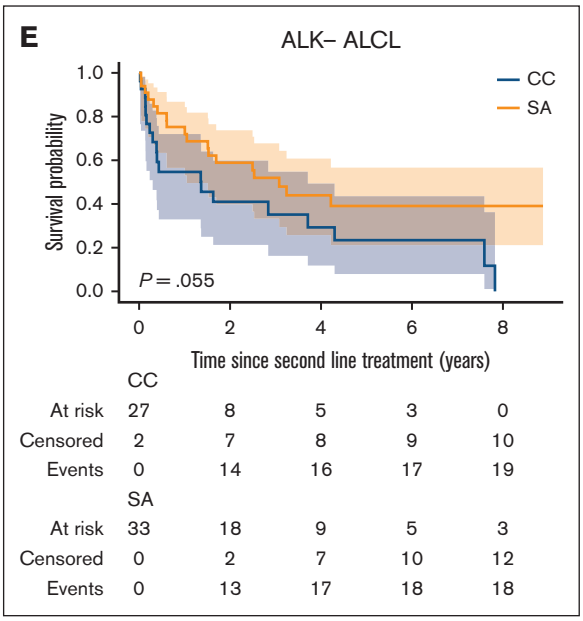

Figure 5 (continued)

access to contemporary drugs such as EMs, SMIs, immune checkpoint blockades, and ADCs, such as BV, that mitigate the effects of initial chemo-refractoriness to some degree.

Several research groups including us have reported on the comparable efficacy and ability to bridge R/R patients to consolidative HSCT with SA over CC. However, studies have been largely restricted to a single institution or multicenter studies within a country or metanalyzes.[4-6] Clinical observations that treatment with HDACi appears to achieve higher responses in patients with T-follicular helper (TFH) phenotype lymphoma (AITL and TFH-PTCL) than those with PTCL-NOS have triggered tremendous interest and guidance on using specific strategies more frequently and earlier in the treatment course of certain PTCL subtypes.[7] In our global data set with well-characterized second-line treatments, we observed that, within the combined cohort, the use of SA in the second-line setting was associated with statistically significant improvement in PFS regardless of transplantation status after the treatment. Unlike the PTCL-NOS subtype, in which no difference in OS was observed between CC and EM or SMI, we observed an OS advantage with the use of SMI over CC but did not see an OS advantage of EM over CC in AITL. This intriguing finding calls for attention to continued investigation of this class of drugs in tailored clinical trials enriched with patients with specific lymphoma subtypes to fully understand its efficacy and potentially a favorable prognosis of this subtype with modern drugs. Our results confirmed in a global data set and outside of a clinical trial scenario that ADC was associated with superior OS compared with CC in the second-line setting for patients with ALK$^-$ ALCL. Thus, we have generated, to our knowledge, the largest global evidence of real-world data that suggest that patients who receive novel agents have comparable and, in certain scenarios, superior outcomes compared with patients who receive chemotherapy-predicated treatments. This calls for the attention of clinicians, regulatory agencies, and pharmaceutical companies to facilitate discussions around expanded access to active drugs worldwide and also might inform the next generation of trial designs.

Although multiple prognostic indices such as IPI, PIT, modified version of PIT (m-PIT), International Peripheral T-Cell Lymphoma Project Score (IPTCLP), and Prognostic Index of Natural Killer Lymphoma (PINK) scores exist for patients with newly diagnosed MTCL and MNKCL, a systematic analysis of independent predictors of outcome in the R/R setting and a risk score for such patients is lacking.[8-12] This is inherently a challenging question because R/R patients are typically associated with a poor prognosis, making further stratification of this subset into defined risk groups with differing outcomes difficult. Through a comprehensive and structured approach, we analyzed the independent effects of all frequently available covariates in a real-world scenario on the outcomes for patients with R/R MTCL and MKNCL. We identified several known and new clinical features to be predictive of inferior survival. However, in the final multivariable model that was associated with the highest C-index in the training data set, age >60 years at diagnosis, primary refractory disease, histological subtype other than AITL, >1 extranodal site involvement, Ki67 ≥40%, and ALC below the lower limit of normal emerged as the most significant predictors of OS, forming the basis for our new score, the PIRT score, for patients with R/R MTCL and MNKCL. This score stratified patients into 3 distinct risk groups with differing outcomes and was validated in a second independent cohort, thereby conforming to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines. Of note, we primarily relied on results from the independent and test cohorts rather than the training cohort. To our knowledge, this is the first report of a prognostic score to estimate survival outcomes for patients with R/R MTCL and MNKCL that has been verified in training, test, and validation cohorts. We had access to a cohort of patients with MTCL and MNKCL with diverse demographic and clinical backgrounds and varying responses to heterogeneous treatment lines, which is a strength of our study and representative of scenarios outside of clinical trials. Our new prognostic model might be of use to medical professionals in real time across the globe, and hence, we developed a web-based calculator and have made it available for public use to qualified personnel with the obvious disclaimers that this is not approved for clinical use by National Comprehensive Cancer Network (NCCN) or the Food and Drug Administration (FDA) and needs to be verified in a future prospective study.

Limitations of the study include systematic error based on the retrospective nature of these analyses, specifically with varied documentation over the span of 10 years. Varied treatment practices in the second-line setting among different academic centers worldwide based on restricted access to SA might underestimate its effects. Although the high proportion of patients from the United States included in the analysis and their access to SA might bias the results of the global cohort, CC was the most commonly used second-line treatment overall, and hence, we believe that the observed benefit of SA over CC cannot be entirely attributed to geographic dominance of patients from the United States within the cohort. Although we organized various drugs as SA or CC based on their mechanism of action, certain drugs such as pralatrexate and BV were categorized under SA and not CC due to their mostly SA use in the R/R setting. Nevertheless, such a bias would equally affect all subgroups; additionally, only a small proportion of patients (n = 23) received pralatrexate in our cohort. Our study lacked central pathology and radiology review and involved data

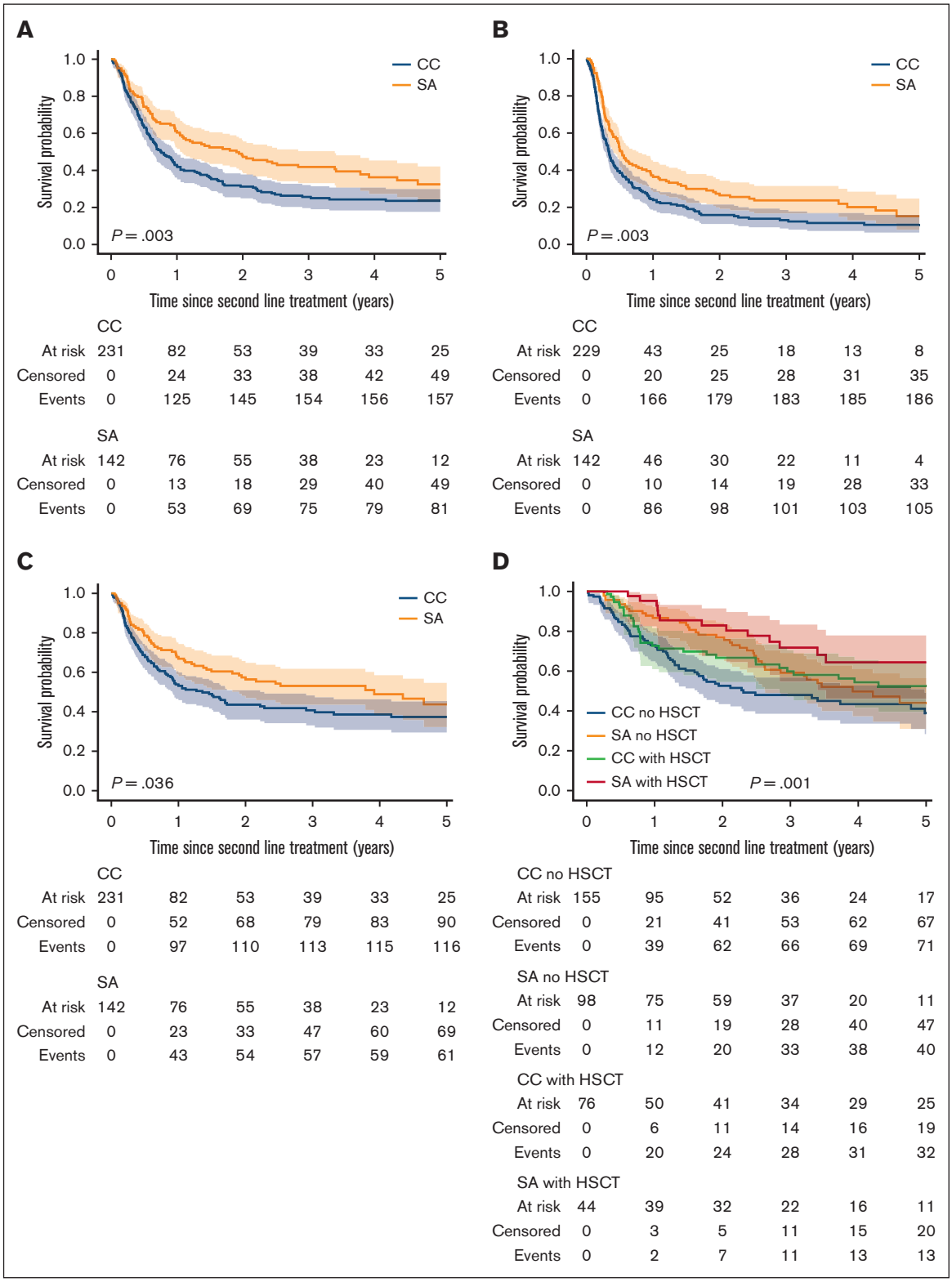

Figure 6. Survival for relapsed and primary refractory (R/R) patients with MTCL and MNKCL who had response to second-line treatment (complete response + partial response + stable disease) comparing second-line treatment with CC vs "novel" SA with and without HSCT. Kaplan-Meier curves show survival estimates. (A) PFS since the start of second-line treatment to the start of third-line therapy, death, or lost to follow-up without counting HSCT as an event or a censoring event. (B) PFS since the start of second-line treatment to the start of third-line therapy, death, or lost to follow-up but counting HSCT as an event. (C) PFS since the start of second-line treatment to transplant, start of third-line therapy, death, or lost to follow-up with the counting of HSCT as a censoring event. (D) OS since the start of second-line treatment to death or lost to follow-up, stratified by HSCT vs no HSCT. Results depicted apply to the global data set of 397 patients for whom information on the start of second-line treatment was available and had response to second-line treatment. *P* values calculated by log-rank test.

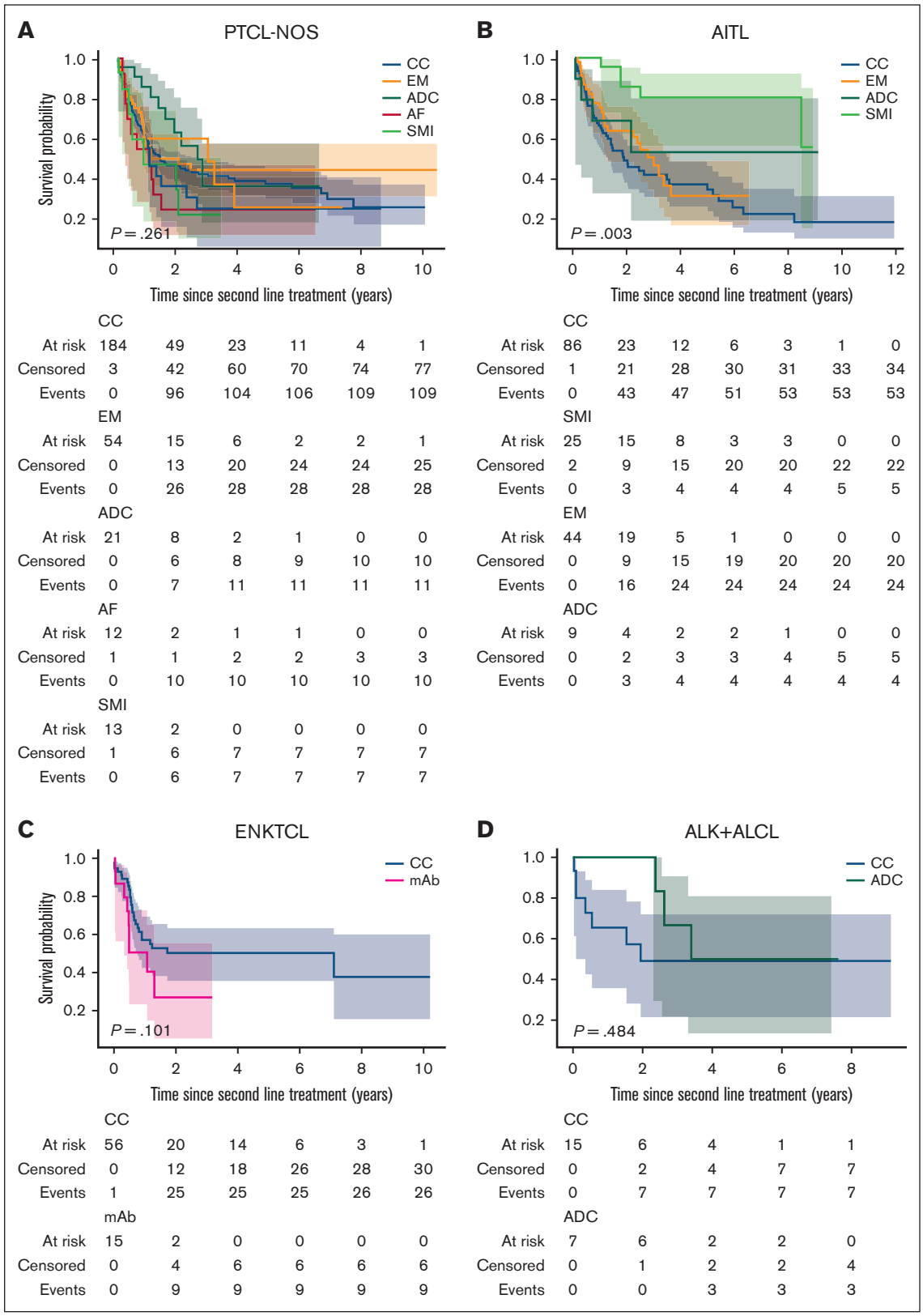

Figure 7. OS for relapsed and refractory (R/R) patients with MTCL and MNKCL stratified by histological subtype comparing second-line treatment with CC or a "novel" SA, which includes EM, ADC, AF, SMI, or a mAb. Kaplan-Meier curves show OS estimates since start of second-line treatment for patients with PTCL-NOS (A),

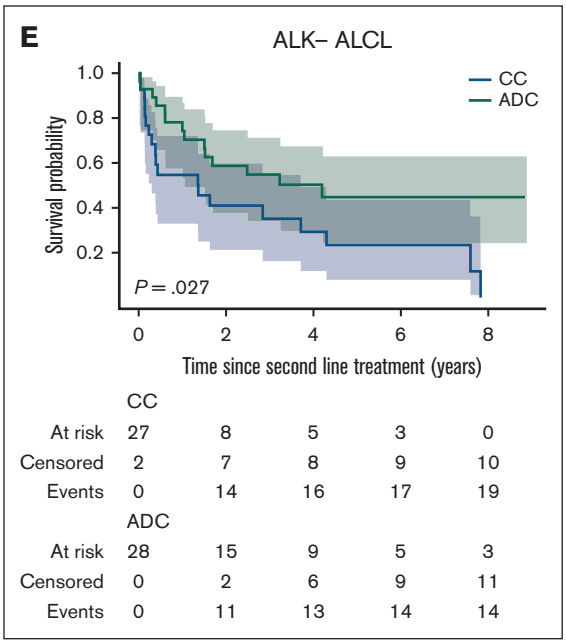

Figure 7 (continued) AITL (B), ENKTCL (C), ALK$^+$ ALCL (D) and, ALK$^-$ ALCL (E). Results depicted apply to the global data set of 763 patients for whom information on the start of second-line treatment was available. *P* values calculated by log-rank test. mAb, monoclonal antibody.

collection across multiple different sources internationally ranging from single institutions to registry cohorts. Another major limitation of our study is that we used variables from the time of diagnosis to generate the PIRT score, which was used to predict survival estimates for patients with R/R MTCL and MNKCL from the time of second-line treatment. It is feasible that variables such as ALC and the number of extranodal sites of involvement changes over time from the point of diagnosis to the start of second-line treatment, and hence, incorporating factors closer to the start of the second-line treatments could be more informative. However, re-evaluation of many of the factors in real-world practices is often not possible. Despite the potential change in some of these variables over their first-line treatment course, we observed a clear separation of survival estimates between the 3 defined risk groups as stratified by the PIRT score in all training, test, and validation cohorts. This underscores the robustness of the model and its generalizability despite the incorporation of limited information around the world. Although the PIRT score can predict survival for a combined cohort of patients with R/R lymphoma, more development, training, and fine tuning of this approach is required for subgroup analyses and individual-level predictions. Thus, personalized survival estimates to chart out patients' trajectories to specific common interventions are the focus of our ongoing research efforts. PETAL consortium investigators are now focused on integrating clinical and molecular information and harnessing artificial intelligence for precision medicine on prospectively enrolled patients. Finally, we recognize that comparisons of treatments reported in our study may not have sufficiently accounted for potential confounders, and as such, the results are subject to potential bias. A future direction is to take an in-depth approach to carefully account for potential confounders to reduce bias. Another area of active research in our group involves the generation of novel causal inference approaches and its potential to provide a natural framework to make forecasts more accurate.

In conclusion, we characterized and benchmarked outcomes for the largest global cohort of patients with R/R MTCL and MNKCL in the era of contemporary therapies. We demonstrated that although CC remains the most frequently used treatment regimen for patients, SA is at least comparable and, in specific subtypes and scenarios, superior to CC, thereby warranting their earlier use in treatment paradigms. Our study also underscores an unmet need for expanded access to SA worldwide. A novel prognostic score such as PIRT highlights patients with poor prognosis, such as R/R MTCL and MNKCL, to have varied outcomes to conventional and recent therapies and might benefit clinicians when faced with accurately determining their prognosis.

Acknowledgments

This work was supported by Daiichi Sankyo, Acrotech Biopharma, and the Center for Lymphoma Research Funds. S.J. is supported by the National Cancer Institute K08 Career Development Award (K08CA230498) and MGH Lymphoma Research Funds. E.J. is supported by the Reid Family Fund for Lymphoma Research.

Authorship

Contribution: S.J. designed the research; J.X.H., Min Jung Koh, L.B., M. Sorial, S.M.M., L.P., S. Singh, I.J.E.-U., J.G., M.J.F.T., C.T.M., A.G., A.D., K.C., A. Lenart, E.N., J.B., Min Ji Koh, E. Miranda, C.C., R.S., S.M.H., M. Merrill, E.J., M. Manni, M.C., T. Skrypets, A. Lymboussaki, M.F., Y.K., J.S.K., J.Y.C., T.E., T. Shet, E.S., A. Shetty, S. Saha, H.J., M. Sengar, C.V.D.W., H.M.P., R.H., T.M., F.F., M.G., B.C., P.L.Z, T.O., N.Y., S.E.Y., W.-S.K., G.P., Z.M., E.V., J.C.A., M.A., J.F., M.E.C., A.K., G.B., H.M., A. Sawas, K.M.K., M.I., F.B., O.A.O., C.S., E. Marchi, D.S., and S.J. performed the research; J.X.H., Min Jung Koh, L.B., M.S., C.S., E. Marchi, D.S., and S.J. analyzed data; C.C., S.M.H., E.J., Y.K., H.J., M.S., H.M.P., F.F., P.L.Z., W.-S.K., O.A.O., C.S., E. Marchi, and D.S. reviewed the manuscript; J.X.H., Min Jung Koh, L.B., D.S., and S.J. wrote the manuscript; and J.X.H., Min Jung Koh, and L.B. were assigned equal authorship based on their equal time and effort spent on this manuscript.

Conflict-of-interest disclosure: C.C. treports honoraria and consultancy fees from Roche, AbbVie, Janssen, AstraZeneca (AZ), Eli Lilly and Company (Lylli), and Takeda. S.M.H. reports consultancy fees from ONO Pharmaceuticals, Tubulis, Abcuro Inc, Cimieo Therapeutics, Auxilius Pharma, Secura Bio, Shoreline Biosciences, Inc, and Yingli Pharma Limited; research funding from Affimed, Celgene, ADC Therapeutics, Millenium, CRISPR Therapeutics, Seattle Genetics, and Verastem/Secura Bio; and consultancy fees and research funding from Daiichi Sankyo, Trillium Therapeutics, Kyowa Hakko Kirin, and Takeda. E.J. reports research funding from Celgene, Pharmacyclics, and Hoffmann-LaRoche; honoraria and research funding from Merck; honoraria from Daiichi, Bristol Myers Squibb (BMS), and Bayer; and patents and royalties with UpToDate. H.J. reports research funding from ImmunoACT, Zydus Pharmaceuticals, and Intas Pharmaceuticals. C.V.D.W. reports ending employment in the past 24 months and membership on an entity's board of directors or advisory committees of Cartherics Pty Ltd. H.M.P. reports speakers bureau fees from Takeda, Merck, Mallinkrodt, and Mundipharma. F.F. reports honoraria from Secura Bio, Daiichi Sankyo, Kyowa, Conjupro, and

Astex; and speakers bureau fees from Seagen and Acrotech. B.C. reports membership on an entity's board of directors or advisory committees in Kite-Gilead, AbbVie, Janssen, Celgene-BMS, BeiGene, and Takeda; and speakers bureau fees from Kite-Gilead, AbbVie, Janssen, Novartis, Lilly, and Roche. P.L.Z. reports membership on an entity's board of directors or advisory committees in Servier, Celltrion, Sandoz, Gilead, Secura Bio, Janssen-Cilag, BMS, Novartis, Antibody-drug conjugate (ADC) Therapeutics, Incyte, AstraZeneca, Merck Sharp & Dohme (MSD), EUSA Pharma, Takeda, Roche, Kyowa Kirin, and BeiGene; speakers bureau fees from Servier, Celltrion, Gilead, Janssen-Cilag, BMS, Novartis, Incyte, AstraZeneca, MSD, Takeda, Roche, EUSA Pharma, Kyowa Kirin, and BeiGene; and consultancy fees from Novartis, MSD, and EUSA Pharma. W.-S.K. reports research funding from Sanofi, BeiGene, Boryong, Roche, Kyowa Kirin, and Donga. E.V. reports research funding from MSD. C.S. reports current employment with Biogen Digital Health. E. Marchi reports research funding from Merck, Celgene/BMS, Astex Pharmaceutical/Myeloid Pharmaceuticals, and Dren Bio; membership on an entity's board of directors or advisory committees in Dren Bio; and other interests including data safety monitoring committee fees from Everest Clinical Research. S.J. reports consultancy fees from Mersana Therapeutics, Myeloid Therapeutics, SIRPant Immunotherapeutics, and Abcuro Inc; membership on an entity's board of directors or advisory committees in Mersana Therapeutics, Myeloid Therapeutics, SIRPant Immunotherapeutics, Abcuro Inc, Secura Bio, Daiichi Sankyo, and CRISPR Therapeutics; and research funding from Daiichi Sankyo, SIRPant Immunotherapeutics, Acrotech Limited Liability Company (LLC), and Abcuro Inc. The remaining authors declare no competing financial interests.

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