SUPPLEMENTARY APPENDIX

International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia

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Supplemental Methods Description

Study Conduct

Based on discussions with the principal investigator (NG) Amgen provided an initial design and statistical analysis plan and through a series of meetings with authors, these plans were further developed and revised. After approval by relevant regulatory authorities and if applicable by local human subjects committees, study implementation was managed by Amgen; anonymized data were assembled by the country study groups or clinical sites and forwarded to Amgen where analyses were conducted according to the analysis plan. All authors had full access to the data they provided and reviewed and approved summaries of their site-specific data and the pooled data. The principal investigator (NG) and Amgen coauthors (MK, VC, AK) developed the initial tables and figures for data summarization. Amgen medical writing staff assisted with editing and formatting of the manuscript.

Study Design

Databases from study groups were extracted from follow-up data of first-line trials that included unselected patients treated according to national protocols. The majority of patients included in this study participated in a clinical trial for their first line therapy, and were then followed for relapse and survival. During their first line treatment, patients generally received protocols adopted at the national level (particularly in the European study groups and centers) whereas salvage therapy was performed according to the decision of individual investigators according to the standard of care. Large individual centers extracted information on relapsed patients from their consecutive databases. Whereas some study groups and centers collected data systematically on response rates, lines of salvage treatments, types of salvage treatments and realization of HSCT, others collected data on overall survival only. Therefore, for analysis of the different outcome parameters, datasets with different patient numbers were created based on availability.

Outcome Measures

Peripheral blood count data were not available at the time of CR after salvage therapy, but CR after salvage therapy was usually defined among European sites as BM blasts <5% and no peripheral blast cells or extramedullary manifestations[3]. Recovery of peripheral blood counts may not have been reached in all cases, particularly if patients received HSCT shortly after achievement of a marrow CR. Among individual US study sites, generally CR criteria were used as published for acute myeloid leukemia, involving the complete recovery of peripheral counts[15]. Two participating study groups did

not provide any CR data because it was not documented in the respective databases (missing on study group level). Among study groups intending to provide CR data, information was not available for a minority of individual patients (missing on patient level). If the salvage start date was missing, then the date of relapse immediately before the start of salvage treatment was used. Patients without a death reported were censored at the date last known to be alive.

As described above for CR data, HSCT data after salvage treatment were sometimes missing either on a study group (n=2) or individual patient level.

Outcomes were stratified by age, sex, WBC count at first diagnosis, and calendar period (based on salvage treatment). In addition, outcomes in relapsed patients in first salvage without prior HSCT were stratified by time from first remission to first relapse, and outcomes in relapsed patients in first salvage with prior HSCT were stratified by time from prior HSCT to first salvage.

Statistical Analysis

Variables included in multivariate analyses included disease status, months from first remission, time to first relapse, age, sex, period of salvage therapy, and WBC count at diagnosis. If data were missing for the outcomes or covariates, the patient was excluded from analyses; there were no attempts to impute the missing data.

Subgroup comparisons of KM curves were performed with the log-rank test. In the analyses by lines of treatment, a patient was included in more than one category if they had multiple documented lines of salvage treatment. To address achievement of CR as a time-dependent covariate, the Mantel-Byar test[18] was used to compare impact on OS resulting from achievement of CR after salvage therapy to those who did not, and the methods of Simon and Makuch[20] were used to plot survival curves from the median time to CR by CR achievement status. Among responders, only patients with a date of CR were included in the time-dependent analyses. The Mantel-Byar test and Simon and Makuch methods were also used to statistically and graphically assess the relationship between the time-dependent variable HSCT (realized after first salvage and before any subsequent salvage therapy) and OS. These survival curves were plotted starting from the median time to transplant. Sensitivity analyses were also conducted to account for potential changes in outcomes across the study time period; analyses were limited to patients who were treated from 2005 onward to provide a cohort of patients receiving current standard of care therapy.

Supplemental Table 1. Number of patients and patient records meeting inclusion criteria by study group (country/site) and line of salvage treatment

Country	Study group	Number of records* meeting inclusion criteria	Number of patients meeting inclusion criteria	Number of patients per line of salvage		
				1st salvage	2nd salvage	3rd salvage+
Czech Republic	CELL	33	19	19	10	4
France** (2 datasets)	GRALL, LALA	293	293	293	--	--
Germany	GMALL	420	314	314	106	--
Italy*** (2 datasets)	NILG	113	99	99	10	3
Poland	PALG	66	63	58	7	1
Spain	PETHEMA	174	110	108	47	15
United Kingdom	UK NCRI	427	427	427	--	--
US (3 sites)	n/a	684	381	310	194	137
Totals		2,210	1,706	1,628	374	160

n/a, not applicable

*****Record refers to the number of salvage lines reported in the dataset; several salvage lines may be included per patient.

** Includes two datasets, from GRAALL (Group for Research on Adult Acute Lymphoblastic Leukemia) and LALA (Lymphoblastic Acute Leukemia in Adults).

***Includes two datasets, from NILG (Northern Italy Leukemia Group) and S Orsola Istituto Seragnoli.

Supplemental Table 2. Complete remission and survival by selected cutpoints for time to first relapse among adult Ph-negative relapsed/refractory B-precursor ALL patients in first salvage treatment who did not receive HSCT prior to salvage therapy

	Complete remission		Overall survival				
	n/N	CRsg % (95% CI)	N	Median OS, in months (95% CI)	6-month OS KM% (95% CI)	12-month OS KM% (95% CI)	36-month OS KM% (95% CI)
Time to first relapse							
< 6 months	78/232	34 (28, 40)	421	4.4 (4.0, 4.9)	38 (34, 43)	18 (14, 21)	6 (4, 9)
≥ 6 months	208/464	45 (40, 49)	854	6.4 (6.0, 7.0)	52 (49, 55)	27 (24, 30)	10 (8, 12)
p-value		<0.001		<0.001			
< 12 months	134/415	32 (28, 38)	725	4.6 (4.1, 5.0)	39 (35, 42)	18 (15, 21)	6 (4, 7)
≥ 12 months	152/281	54 (48, 60)	550	7.8 (6.8, 8.6)	59 (55, 63)	32 (28, 36)	13 (10, 16)
p-value		<0.001		<0.001			
< 18 months	169/502	34 (30, 38)	887	4.9 (4.4, 5.3)	41 (38, 44)	19 (17, 22)	6 (8, 8)
≥ 18 months	117/194	60 (53, 67)	388	8.4 (7.5, 9.3)	62 (57, 67)	35 (30, 40)	15 (12, 19)
p-value		<0.001		<0.001			
< 24 months	199/563	35 (31, 39)	1012	5.1 (4.7, 5.6)	43 (40, 46)	20 (18, 23)	6 (5, 8)
≥ 24 months	87/133	65 (57, 73)	263	9.3 (7.9, 11.2)	65 (59, 71)	38 (33, 44)	19 (14, 23)
p-value		<0.001		<0.001			

p-values were generated using logistic regression models for complete remission and Cox models for survival

Supplemental Table 3. Complete remission and overall survival among adult Ph-negative relapsed/refractory B-precursor ALL patients in first salvage treatment who were treated in 2005 or later by selected demographic and clinical factors

	Complete remission		Overall survival				
	n/N	CRsg % (95% CI)	N	Median OS, in months (95% CI)	6-month OS KM% (95% CI)	12-month OS KM% (95% CI)	36-month OS KM% (95% CI)
Overall	145/324	45 (39, 50)	631	6.5 (5.8, 7.3)	53 (49, 57)	31 (27, 35)	13 (11, 17)
Disease status							
Primary refractory	14/41	34 (20, 51)	41	12.1 (5.8, 19.2)	66 (49, 78)	50 (34, 65)	18 (7, 32)
Relapsed, without prior alloHSCT	113/242	47 (40, 53)	481	6.5 (5.7, 7.4)	53 (49, 58)	30 (26, 34)	13 (10, 17)
Relapsed, with prior alloHSCT	18/41	44 (28, 60)	109	5.1 (4.3, 6.9)	46 (36, 55)	27 (19, 36)	12 (6, 20)
p-value from univariate model		*0.33*		*0.11*			
p-value from multivariate model		*0.92*		*0.031*			
Time from CR1 to first relapse (in months)*							
<6 months	25/78	32 (22, 44)	156	4.6 (3.7, 5.4)	39 (31, 46)	16 (11, 23)	5 (2, 10)
6 to <12 months	18/50	36 (23, 51)	96	5.4 (4.2, 6.7)	46 (36, 56)	20 (13, 30)	3 (0, 11)
12 to <18 months	20/32	63 (44, 79)	61	8.8 (5.7, 11.0)	62 (48, 73)	35 (23, 47)	19 (10, 30)
18 to <24 months	8/20	40 (19, 64)	47	7.9 (5.5, 16.3)	59 (44, 72)	36 (23, 50)	14 (6, 25)
24 or more months	42/57	74 (60, 84)	116	13.6 (8.7, 21.0)	74 (65, 81)	53 (43, 62)	30 (21, 39)
p-value from univariate model		*<0.001*		*<0.001*			
p-value from multivariate model		*0.004*		*<0.001*			
Months from prior HSCT to first salvage							
<12	5/22	23 (8, 45)	67	4.7 (3.7, 6.2)	41 (29, 53)	23 (13, 33)	14 (6, 25)
12 or more months	9/12	75 (43, 95)	36	6.2 (2.9, 8.7)	51 (34, 66)	31 (17, 47)	16 (6, 30)
p-value from univariate model		*0.013*		*0.39*			
*p-value from multivariate model***		*NA*		*NA*			

Age at salvage treatment (in years)							
15-17	6/11	55 (23, 83)	12	15.4 (2.6, 19.8)	75 (41, 91)	58 (27, 80)	11 (1, 38)
18-34	64/135	47 (39, 56)	281	7.4 (6.5, 9.0)	60 (54, 66)	35 (29, 41)	18 (14, 23)
35-54	52/124	42 (33, 51)	235	5.2 (4.5, 6.2)	45 (38, 51)	26 (20, 32)	11 (7, 15)
55-64	20/42	48 (32, 64)	90	5.8 (4.7, 7.6)	49 (38, 59)	26 (18, 36)	6 (2, 14)
≥65	3/12	25 (5, 57)	13	2.2 (1.1, 15.9)	38 (14, 63)	31 (9, 55)	12 (1, 38)
p-value from univariate model		*0.25*		*<0.001*			
p-value from multivariate model		*0.37*		*<0.001*			
Sex							
Male	81/193	42 (35, 49)	370	6.5 (5.7, 7.7)	54 (48, 59)	33 (28, 38)	15 (12, 20)
Female	64/131	49 (40, 58)	261	6.4 (5.3, 7.4)	52 (46, 58)	28 (22, 34)	11 (7, 15)
p-value from univariate model		*0.22*		*0.31*			
p-value from multivariate model		*0.36*		*0.13*			
WBC at diagnosis							
<30,000/µl	84/177	47 (40, 55)	388	7.3 (6.2, 8.8)	56 (51, 61)	36 (31, 41)	18 (14, 22)
≥30,000/µl	33/88	38 (27, 48)	183	5.5 (4.5, 6.3)	46 (39, 53)	23 (17, 30)	8 (4, 13)
p-value from univariate model		*0.19*		*0.46*			
p-value from multivariate model		*0.17*		*0.27*			

p-values were generated from univariate and multivariate logistic regression models for complete remission and Cox models for survival

*excludes refractory patients and those with prior HSCT. ** not included in the multivariable models due to small patient numbers.

Supplemental Table 4. Complete remission and overall survival among adult Ph-negative relapsed* B-precursor ALL patients by line of salvage treatment who were treated in 2005 or later by selected clinical factors

	Complete remission		Overall survival				
	n/N	CRsg % (95% CI)	N	Median OS, in months (95% CI)	6-month OS KM% (95% CI)	12-month OS KM% (95% CI)	36-month OS KM% (95% CI)
In 1st salvage							
Without prior HSCT	111/236	47 (41, 54)	475	6.5 (5.7, 7.4)	53 (49, 58)	30 (26, 34)	13 (10, 17)
With prior HSCT	18/41	44 (28, 60)	109	5.1 (4.3, 6.9)	46 (36, 55)	27 (19, 36)	12 (6, 20)
Combined	129/277	47 (41, 53)	584	6.3 (5.7, 7.0)	52 (48, 56)	30 (26, 33)	13 (10, 16)
p-value		*0.71*		*0.28*			
In 2nd salvage							
Without prior HSCT	18/79	23 (14, 34)	85	4.0 (2.5, 5.0)	34 (24, 44)	15 (8, 23)	10 (4, 17)
With prior HSCT	12/31	39 (22, 58)	39	4.4 (2.4, 6.0)	33 (19, 48)	17 (7, 30)	3 (0, 14)
Combined	30/110	27 (19, 37)	124	4.4 (3.1, 4.9)	34 (26, 42)	15 (9, 22)	8 (4, 14)
p-value		*0.09*		*0.94*			
In 3rd+ salvage							
Without prior HSCT	5/31	16 (5, 34)	31	3.1 (2.0, 5.4)	29 (15, 45)	16 (6, 31)	12 (3,27)
With prior HSCT	1/11	9 (0, 41)	11	4.6 (0.2, 10.9)	44 (15, 70)	11 (1, 38)	0
Combined	6/42	14 (5, 29)	42	3.5 (2.3, 5.4)	33 (19, 47)	15 (6, 28)	9 (3, 21)
p-value		*0.57*		*0.70*			

*excludes primary refractory patients

p-values comparing patients without prior HSCT to those with prior HSCT were generated from logistic regression models for complete remission and Cox models for survival