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

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ABSTRACT

Adults with relapsed/refractory acute lymphoblastic leukemia have an unfavourable prognosis, which is influenced by disease and patient characteristics. To further evaluate these characteristics, a retrospective analysis of 1,706 adult patients with Ph-negative relapsed/refractory B-precursor acute lymphoblastic leukemia diagnosed between 1990-2013 was conducted using data reflecting the standard of care from 11 study groups and large centers in Europe and the United States. Outcomes included complete remission, overall survival, and realization of stem cell transplantation after salvage treatment. The overall complete remission rate after first salvage was 40%, ranging from 35%-41% across disease status categories (primary refractory, relapsed with or without prior transplant), and was lower after second (21%) and third or greater (11%) salvage. The overall complete remission rate was higher for patients diagnosed from 2005 onward (45%, 95% CI: 39%-50%). One- and three-year survival rates after first, second, and third or greater salvage were 26% and 11%, 18% and 6%, and 15% and 4%, respectively, and rates were 2%-5% higher among patients diagnosed from 2005. Prognostic factors included younger age, longer duration of first remission, and lower white blood cell counts at primary diagnosis. This large dataset can provide detailed reference outcomes for patients with relapsed/refractory Ph-negative B-precursor acute lymphoblastic leukemia. *clinicaltrials.gov identifier: 02003612*

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Introduction

Overall prognosis among adult acute lymphoblastic leukemia (ALL) patients has improved by optimisation of front-line therapy,¹ but outcomes remain poor for patients who relapse or are refractory to initial treatment. Reported rates of complete remission (CR) after salvage treatment range from 18%-45%, and median survival times range from 2-8 months, with less than 10% survival after 5 years in most studies.^{2,7} Achievement of CR and subsequent HSCT is the only curative option in relapsed adult ALL;^{2,3,6} however, this can only be achieved in a subgroup

of patients. Longer duration of first CR is associated with improved survival; however, there is no established cut-off point for CR duration that predicts long-term survival.^{2,4-6} Options are even more limited for patients who do not respond to first-line of salvage, and probabilities of survival decline substantially with successive lines of treatment.^{3,4,7}

For these reasons, new treatment options are needed for adult patients with relapsed/refractory (r/r) ALL, and a number of promising compounds are currently under clinical evaluation.^{8,9} The rarity of adult r/r ALL,¹⁰ combined with the very poor outcomes and non-standardised approaches of salvage therapies, make it difficult to conduct randomised trials of new compounds. Approvals of new treatments are therefore often based on evidence from phase 2 single-arm trials.¹¹⁻¹⁴

To attain a more precise estimate of clinical practice outcomes in adult r/r ALL, and to evaluate important patient subgroups, we pooled data from major national study groups and large individual sites treating adult ALL from Europe and the United States to create the most extensive clinical dataset available in this population.

The analysis aimed to describe patient characteristics and outcome parameters (achievement of CR, overall survival [OS] and realization of allogeneic HSCT) among adult patients with Ph-negative B-precursor r/r ALL treated according to standard of care in Europe and the United States before the introduction of new targeted therapies, such as blinatumomab. Additional objectives were to evaluate prognostic factors, define subgroups, and to provide a reference population for the assessment of new compounds in this setting.

Methods

Study conduct

This observational study was designed jointly by the sponsor, Amgen and the authors. All authors were involved in the preparation, revision, and formal approval of the manuscript. All authors met the criteria of the International Committee of Medical Journal Editors (<http://www.icmje.org>) for authorship, and take responsibility for the content and accuracy of data presented. Co-author roles are described in the *Appendix*.

Study design

Details of the study design, outcomes, and analyses procedures are described in the *Appendix*. Briefly, individual databases were prepared by the participating study groups or centers to include all consecutive adult patients with r/r ALL. These databases were transferred and evaluated centrally for inclusion in the pooled analysis. After individual database review for data coding, consistency, and characterization of missing data, the clinical data were then harmonized.

All patients provided informed consent to each study site investigator to use their data for clinical research purposes.

Eligibility criteria

Eligibility criteria were defined across the databases as follows: adult patients with r/r B-precursor ALL; age ≥ 15 years at time of first diagnosis; Ph/BCR-ABL negative; initial diagnosis of ALL in the year 1990-2013; no isolated extramedullary relapse or central nervous system (CNS) involvement at relapse; and available endpoint data (CR, HSCT, or OS). Other than Ph/BCR-ABL chromosome status, no other cytogenetics data were collected.

Patients in relapse or in the refractory setting were included, independent of treatment strategy. Patients treated with blinatumomab were excluded, but all other regimens were permitted, including palliative care; type of salvage therapy was not recorded in all databases. Primary refractory disease was defined by study group criteria as persistent disease after standard induction and consolidation therapy. Relapse was defined by standard criteria as reappearance of disease after previous achievement of CR.

Outcome measures

The primary outcome measure was the rate of CR after salvage therapy. CR was defined by the study groups/sites based on general clinical practice guidelines, with some variation across the individual study groups.

Secondary outcomes included OS and realization of HSCT after salvage treatment (allogeneic HSCT only). OS was defined as the time from the start of last salvage therapy to death from any cause.

Subgroups and covariates

For analysis of outcomes, three clinically-relevant patient "disease status" subgroups were defined: "Primary Refractory", "Relapsed, with prior HSCT", and "Relapsed, without prior HSCT". Four study groups did not have eligible patients with primary refractory disease in their database. Patients were also grouped according to their line of salvage treatment, classified as first, second, or third or greater salvage.

Statistical analysis

Generalized estimating equations were used to compare CR proportions across lines of salvage. For OS, the Kaplan Meier (KM) median and KM proportions at 6, 12, and 36 months were estimated with corresponding 95% CI.^{15,16}

Univariate and multivariate logistic regression models were used to evaluate the potential relationships between patient and disease characteristics. CR and Cox models were used to evaluate relationships for OS. Mantel-Byar¹⁷ and Simon-Makuch methods were used for statistical evaluation of time-dependent variables (*see Appendix*). Sensitivity analyses were conducted to account for potential changes in outcomes across the study time period; these analyses were limited to patients who were diagnosed from 2005 onward to provide a cohort of patients receiving current standard of care therapy.

Results

Patient population: demographic and clinical characteristics

Adult Ph-negative, B-precursor r/r ALL patient data were pooled across 11 groups or sites (6 European study groups and 2 centers, and 3 US centers). The number of patients provided by groups or sites that met the inclusion criteria ranged from 33 to 427 (*Online Supplementary Table S1*), with 1706 patients providing data for at least one outcome (CR, OS, or HSCT). Survival data were available for 1695 patients. Information was available on results from first salvage in 1628 patients, second salvage in 374 patients, and from third or greater salvage in 160 patients. A single salvage record was available from 1336 patients (which could be from first or later salvage) and multiple records were available from 370 patients. Overall, 2210 salvage records were included (Figure 1, *Online Supplementary Table S1*). Information on treatment intensity was not available for most patients (68% with OS data and 47% with CR data in first salvage), and only 8 patients

Table 1. Adult Ph-negative relapsed/refractory B-precursor ALL patient data by selected demographic and clinical factors, summarized by outcomes and HSCT status.

	All patients			Patients with CR data available			Patients with information on HSCT status after salvage available
	In 1 st salvage (N=1 618)	In 2 nd salvage (N=372)	In 3 rd or greater salvage (N=160) **	In 1 st salvage (N=901)	In 2 nd salvage (N=332)	In 3 rd or greater salvage (N=159)	In 1 st salvage (N=1 337)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age at salvage treatment, years							
15-17	65 (4.0)	12 (3.2)	4 (2.5)	39 (4.3)	11 (3.3)	4 (2.5)	59 (4.4)
18-34	758 (46.8)	182 (48.9)	88 (55.0)	399 (44.3)	163 (49.1)	87 (54.7)	618 (46.2)
35-54	578 (35.7)	125 (33.6)	43 (26.9)	320 (35.5)	107 (32.2)	43 (27.0)	490 (36.6)
55-64	170 (10.5)	33 (8.9)	15 (9.4)	97 (10.8)	31 (9.3)	15 (9.4)	126 (9.4)
≥65	47 (2.9)	20 (5.4)	10 (6.3)	46 (5.1)	20 (6.0)	10 (6.30)	44 (3.3)
Sex							
Male	950 (58.7)	225 (60.5)	99 (61.9)	536 (59.5)	201 (60.5)	98 (61.6)	790 (59.1)
Female	668 (41.3)	147 (39.5)	61 (38.1)	365 (40.5)	131 (39.5)	61 (38.4)	547 (40.9)
WBC at diagnosis							
<30,000/μL	918 (69.3)	125 (69.1)	19 (65.5)	428 (69.5)	98 (68.5)	18 (64.3)	744 (70.4)
≥30,000/μL	406 (30.7)	56 (30.9)	10 (34.5)	188 (30.5)	45 (31.5)	10 (35.7)	313 (29.6)
Period of salvage treatment							
1990-1994	107 (6.6)	44 (11.8)	26 (16.3)	85 (9.4)	44 (13.3)	26 (16.4)	100 (7.5)
1995-1999	342 (21.1)	71 (19.1)	48 (30.0)	178 (19.8)	71 (21.5)	48 (30.2)	323 (24.2)
2000-2004	538 (33.3)	102 (27.4)	32 (20.0)	314 (34.9)	80 (24.2)	32 (20.1)	491 (36.7)
2005 or later	631 (39.0)	155 (41.7)	34 (33.8)	324 (36.0)	137 (41.1)	53 (33.3)	423 (31.6)
Disease status							
Primary refractory	115 (7.1)	69 (18.6)	35 (21.9)	111 (12.4)	57 (17.3)	34 (21.4)	105 (7.9)
Relapsed, without prior HSCT	1291 (79.9)	240 (64.9)	108 (67.5)	707 (78.6)	223 (67.6)	108 (67.9)	1074 (80.4)
Relapsed, with prior HSCT	210 (13.0)	61 (16.5)	17 (10.6)	81 (9.0)	50 (15.1)	17 (10.7)	157 (11.7)
Time from CR1 to first relapse (in months) *							
<12 months	725 (56.9)	118 (66.7)	58 (55.2)	415 (59.6)	115 (65.7)	58 (55.2)	588 (55.4)
≥12 months	550 (43.1)	59 (33.3)	47 (44.8)	281 (40.4)	60 (34.3)	47 (44.8)	473 (44.6)
<6 months	421 (33.0)	60 (33.9)	32 (30.5)	232 (33.3)	57 (32.6)	32 (30.5)	334 (31.5)
6 to <12 months	304 (23.8)	58 (32.8)	26 (24.8)	183 (26.3)	58 (33.1)	26 (24.8)	254 (23.9)
12 to <18 months	162 (12.7)	23 (13.0)	17 (16.2)	87 (12.5)	23 (13.1)	17 (16.2)	137 (12.9)
18 to <24 months	125 (9.8)	11 (6.2)	8 (7.6)	61 (8.8)	11 (6.3)	8 (7.6)	100 (9.4)
24 or more months	263 (20.6)	25 (14.1)	22 (20.9)	133 (19.1)	26 (14.9)	22 (20.9)	236 (22.2)
Time from prior alloHSCT to first salvage ***							
<12 months	151 (71.9)	47 (77.1)	13 (65.0)	57 (70.4)	38 (76.0)	13 (65.0)	108 (68.8)
≥12 months	59 (28.1)	14 (22.9)	7 (35.0)	24 (29.6)	12 (24.0)	7 (35.0)	49 (31.2)

No significant differences in patient characteristics were observed between the different analysis groups defined by availability of data on response to salvage or subsequent HSCT, or for the analysis groups defined by different lines of salvage. *excludes refractory patients and those with prior HSCT ** Earliest of 3rd or greater salvage treatment. *** Among the 217 patients who had a prior HSCT.

were documented as receiving palliative care.

Patient demographic data are presented in Table 1. The median age of the overall population was 34 years (range, 15-83), and approximately one-third were aged 35-54 years. Most patients (59%) were male, and over 70% received salvage therapy after the year 2000. A large majority of patients (80%) had relapsed ALL without prior HSCT; 13% had relapse after HSCT, and 7% had primary refractory disease. In patients who had relapsed without prior HSCT, 30% relapsed within six months, 24% within 6-12 months and 21% after more than two years from diagnosis. In patients who had relapsed after HSCT, 69% relapsed within one year.

No differences in patient characteristics were observed between the analysis groups defined by availability of data on response to salvage or subsequent HSCT, or for the analysis groups defined by different lines of salvage (Table 1).

Response to salvage therapy

Response to first salvage. Data on CR following first salvage therapy were available for 901 patients. In total, 361 patients achieved a CR after first salvage (40%; 95% CI: 37%-43%). CR rates in first salvage ranged from 35%-41% depending on disease status (primary refractory, relapsed with or without prior HSCT; Table 2), but these differences were not statistically significant.

Prognostic factors for response to first salvage. Significantly higher CR rates were observed among younger patients ($P=0.008$) and patients with longer times to relapse from either prior HSCT ($P<0.001$) or remission ($P<0.001$) (Table 2 and *Online Supplementary Table S2*). Interestingly, patients with a WBC count of $>30,000/\mu\text{L}$ at first diagnosis had a significantly lower CR rate after first salvage (34% vs. 45%; $P=0.011$). CR rates increased during each 5-year period from 1990 onward, from 29% in patients who received salvage therapy from 1990-1994 to 45% in

Table 2. Complete remission and overall survival among adult Ph-negative relapsed/refractory B-precursor ALL patients in first salvage treatment by selected demographic and clinical factors.

	n/N	Complete remission		Overall survival			
		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	361/901	40 (37, 43)	1618	5.8 (5.5, 6.2)	49 (46, 51)	26 (24, 28)	11 (10, 13)
Disease status							
Primary refractory	44/111	40 (30, 49)	115	8.2 (6.6, 11.0)	64 (55, 72)	38 (29, 47)	11 (6, 18)
Relapsed, without prior alloHSCT	289/707	41 (37, 45)	1291	5.8 (5.4, 6.2)	49 (46, 51)	25 (23, 28)	11 (10, 13)
Relapsed, with prior alloHSCT	28/81	35 (24, 46)	210	4.4 (3.7, 5.8)	42 (36, 49)	23 (18, 29)	10 (7, 15)
<i>P</i> -value from univariate model		0.55		0.03			
<i>P</i> -value from multivariate model		0.37		<0.001			
Time from CR1 to first relapse (in months)*							
<6 months	78/232	34 (28, 40)	421	4.4 (4.0, 4.9)	39 (34, 43)	18 (15, 22)	8 (5, 11)
6 to <12 months	56/183	31 (24, 38)	304	5.0 (4.1, 5.6)	40 (35, 46)	19 (15, 24)	6 (4, 10)
12 to <18 months	35/87	40 (30, 51)	162	6.1 (5.2, 7.3)	52 (44, 59)	26 (19, 33)	10 (6, 16)
18 to <24 months	30/61	49 (36, 62)	125	7.4 (5.6, 8.3)	57 (47, 65)	29 (21, 37)	10 (6, 16)
24 or more months	87/134	65 (56, 73)	264	9.3 (8.1, 11.2)	68 (62, 73)	42 (36, 48)	24 (19, 30)
<i>P</i> -value from univariate model		<0.001		<0.001			
<i>P</i> -value from multivariate model		<0.001		<0.001			
Months from prior HSCT to first salvage							
<12	12/57	21 (10, 32)	151	4.2 (3.2, 4.6)	36 (28, 44)	19 (13, 26)	5 (2, 10)
12 or more months	16/24	67 (48, 86)	59	7.5 (4.3, 11.2)	58 (44, 70)	34 (22, 47)	15 (7, 27)
<i>P</i> -value from univariate model		<0.001		0.014			
<i>P</i> -value from multivariate model**		NA		NA			
Period of salvage treatment							
1990-1994	25/85	29 (20, 40)	107	3.5 (2.7, 6.6)	42 (33, 51)	21 (14, 29)	7 (3, 13)
1995-1999	65/178	37 (29, 44)	342	4.6 (4.1, 5.3)	38 (33, 43)	17 (13, 21)	5 (3, 8)
2000-2004	126/314	40 (35, 46)	538	6.3 (5.6, 6.7)	53 (48, 57)	27 (24, 31)	13 (11, 16)
2005 or later	145/324	45 (39, 50)	631	6.5 (5.8, 7.3)	53 (49, 57)	31 (27, 35)	13 (11, 17)
<i>P</i> -value from univariate model***		0.003		<0.001			
<i>P</i> -value from multivariate model***		0.025		<0.001			
Age at salvage treatment (in years)							
15-17	22/39	56 (40, 72)	65	7.6 (6.0, 13.0)	62 (49, 72)	43 (31, 55)	16 (8, 26)
18-34	176/399	44 (39, 49)	758	6.7 (6.3, 7.4)	56 (52, 60)	30 (27, 34)	15 (12, 18)
35-54	118/320	37 (32, 42)	578	4.6 (4.2, 5.2)	42 (38, 46)	21 (18, 25)	8 (6, 11)
55-64	33/97	34 (25, 44)	170	4.8 (3.7, 5.9)	41 (34, 49)	18 (13, 25)	6 (3, 11)
≥65	12/46	26 (14, 41)	47	2.9 (2.0, 4.7)	34 (21, 47)	17 (8, 29)	3 (0, 12)
<i>P</i> -value from univariate model		<0.001		<0.001			
<i>P</i> -value from multivariate model		0.008		<0.001			
Sex							
Male	202/536	38 (34, 42)	950	6.1 (5.6, 6.6)	51 (47, 54)	28 (25, 31)	12 (10, 15)
Female	159/365	44 (38, 49)	668	5.5 (4.8, 6.1)	47 (43, 50)	24 (20, 27)	9 (7, 12)
<i>P</i> -value from univariate model		0.078		0.034			
<i>P</i> -value from multivariate model		0.56		0.045			
WBC at diagnosis							
<30,000/μL	193/428	45 (40, 50)	918	6.3 (5.8, 6.7)	52 (49, 56)	29 (26, 32)	13 (11, 16)
≥30,000/μL	63/188	34 (27, 41)	406	4.6 (4.2, 5.3)	41 (36, 46)	20 (17, 25)	9 (6, 12)
<i>P</i> -value from univariate model		0.013		0.006			
<i>P</i> -value from multivariate model		0.011		0.001			

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. ***Calendar period categorized as 1990-1999 and 2000 or later in univariate and multivariate models.

patients who received therapy from 2005-2013 ($P=0.025$) (Table 2). Three study groups/sites provided data across all four calendar periods, and for these the increase in CR over time was not significant ($P=0.077$). In sensitivity analyses (Online Supplementary Table S3) limited to patients treated for r/r ALL from 2005-2013, the overall CR was slightly higher at 45% (95% CI: 39%-50%) than for the entire cohort of patients treated from 1990 onward. Time from CR to first relapse and from HSCT to first salvage remained significant prognostic factors for CR in this sub-

group. Most importantly, there was little improvement for unfavourable subtypes of relapse – e.g., relapses within 6 months from diagnosis with 34% CR rate in the whole cohort, and 32% CR rate in the more recent cohort.

Response to second or later salvage. Data on response to second salvage were available in 332 patients, and on third or later salvage in 159 patients. The overall CR rates (excluding patients refractory to primary treatment) decreased with line of salvage, from 40% (95% CI: 37%-44%) in first salvage to 21% (95% CI: 16%-26%) in sec-

ond salvage and 11% (95% CI: 6%-18%) in third or greater salvage (Table 3). Similarly, CR rates decreased with line of salvage in patients without prior HSCT: 41% (95% CI: 37%-44%) for first salvage, 19% (95% CI: 14%-24%) for second salvage, 11% (95% CI: 6%-19%) for third or later salvage ($P < 0.001$), and in patients with prior HSCT: 35% (95% CI: 24%-46%) for first salvage, 32% (95% CI: 20%-47%) for second salvage, 12% (95% CI: 1%-36%) for third or later salvage ($P = 0.367$). In the cohort of patients treated from 2005 onward, CR was slightly higher in the second (27%; 95% CI: 19%-37%) and third or greater salvages (14%; 95% CI: 5%-29%) than for the overall patient cohort (Online Supplementary Table S4).

Overall survival after salvage therapy

Survival after first salvage. The median duration of OS among the 1618 patients in first salvage with available survival data was 5.8 months (95% CI: 5.5-6.2 months; Figure 2A). The proportion of patients alive after 6 months was 49% (95% CI: 46%-51%), after 1 year 26% (95% CI: 24%-28%), and after 3 years 11% (95% CI: 10%-13%) (Table 2), while the median length of follow up in the 193 patients alive at last observation was 43.6 months (range, < 1-247 months). The median OS was 8.2 months (95% CI: 6.6-11.0 months) in refractory patients, 5.8 months (95% CI: 5.4-6.2 months) in patients who had relapsed without prior HSCT, and 4.4 months (95% CI: 3.7-5.8 months) in patients who had relapsed with prior HSCT

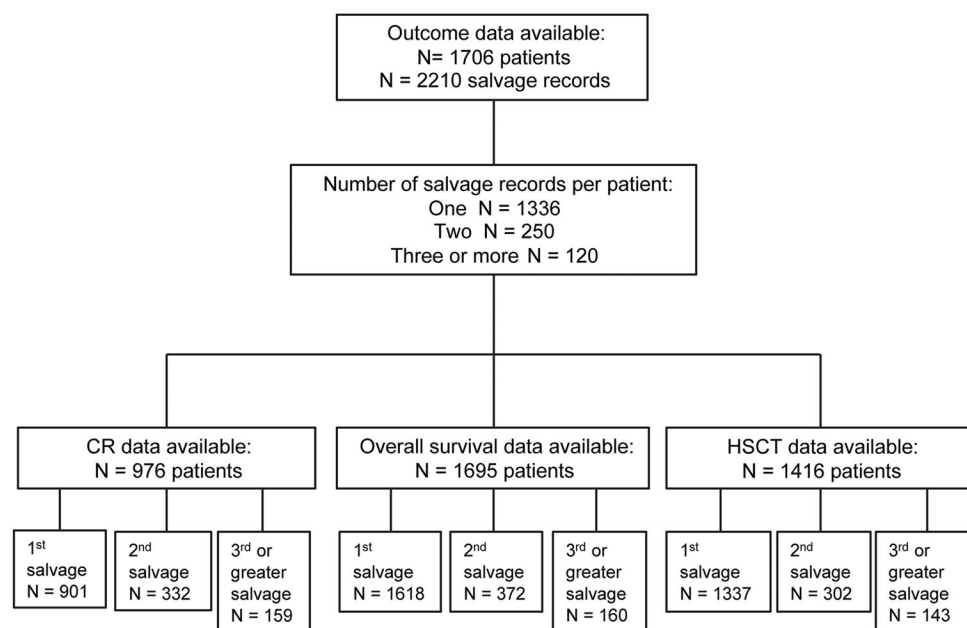


Figure 1. Flow chart of patients and patient records analysed. Patients with more than one line of salvage in the dataset could contribute multiple records; the numbers in the bottom row correspond to the number of records available for each line of salvage. There were 11 patients without survival information that were included in the analysis: 10 had CR information only and 1 had HSCT information only. The total number of patients (who met eligibility criteria and had outcome data available) was 1706. Overall survival data was missing from 11 patients. Two study group databases did not collect information on CR (n = 590 patients); CR data was missing from a further 140 patients. HSCT data were missing from 290 patients.

Table 3. Complete remission and overall survival among adult Ph-negative relapsed* B-precursor ALL patients by line of salvage treatment by selected clinical factors.

	n/N	Complete remission			Overall survival		
		CRsg %	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	289/709	41 (37, 44)	1293	5.8 (5.4, 6.2)	49 (46, 51)	25 (23, 28)	11 (10, 13)
With prior HSCT	28/81	35 (24, 46)	210	4.4 (3.7, 5.8)	42 (36, 49)	23 (18, 29)	10 (7, 15)
Combined	317/790	40 (37, 44)	1503	5.7 (5.2, 6.0)	48 (45, 50)	25 (23, 27)	11 (10, 13)
P-value		0.28		0.17			
In 2nd salvage							
Without prior HSCT	42/225	19 (14, 24)	242	3.3 (2.5, 4.0)	30 (25, 36)	14 (10, 19)	6 (3, 10)
With prior HSCT	16/50	32 (20, 47)	61	4.5 (2.4, 5.3)	35 (23, 47)	17 (9, 28)	4 (1, 12)
Combined	58/275	21 (16, 26)	303	3.4 (2.8, 4.2)	31 (26, 36)	14 (11, 19)	5 (3, 8)
P-value		0.04		0.50			
In 3rd+ salvage							
Without prior HSCT	12/108	11 (6, 19)	108	2.8 (2.2, 3.1)	22 (14, 30)	11 (6, 17)	5 (2, 11)
With prior HSCT	2/17	12 (1, 36)	17	4.0 (1.2, 7.0)	39 (17, 61)	20 (5, 42)	0
Combined	14/125	11 (6, 18)	125	2.9 (2.6, 3.4)	24 (17, 32)	12 (7, 18)	4 (1, 9)
P-value		0.94		0.41			

*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.

($P < 0.001$ for the difference between the groups; Figure 2B and Table 2). In patients without prior HSCT, median survival was longer in patients with a longer time to relapse after first CR (Figure 2C), increasing from 4.4 months (95% CI: 4.0-4.9 months) in patients with a first CR lasting < 6 months to 9.3 months (95% CI: 8.1-11.2 months) in patients with a first CR lasting ≥ 24 months.

Simon-Makuch curves depict the impact of CR after first salvage on survival (Figure 3). There was a significant association between achieving CR and improved overall survival (Mantel-Byar, $P < 0.001$).

Prognostic factors for survival after first salvage

Factors associated with OS in a multivariate analysis of patients in first salvage followed similar patterns to those observed for CR. Time to relapse after first CR was significantly associated with survival, with median OS increasing with each additional 6 months of remission (Table 2; $P < 0.001$). Different cut-offs for time to first relapse all showed a significantly improved OS with longer duration of first remission (*Online Supplementary Table S2*). Similarly, in patients who had previously received HSCT, a remission duration of > 12 months was significantly

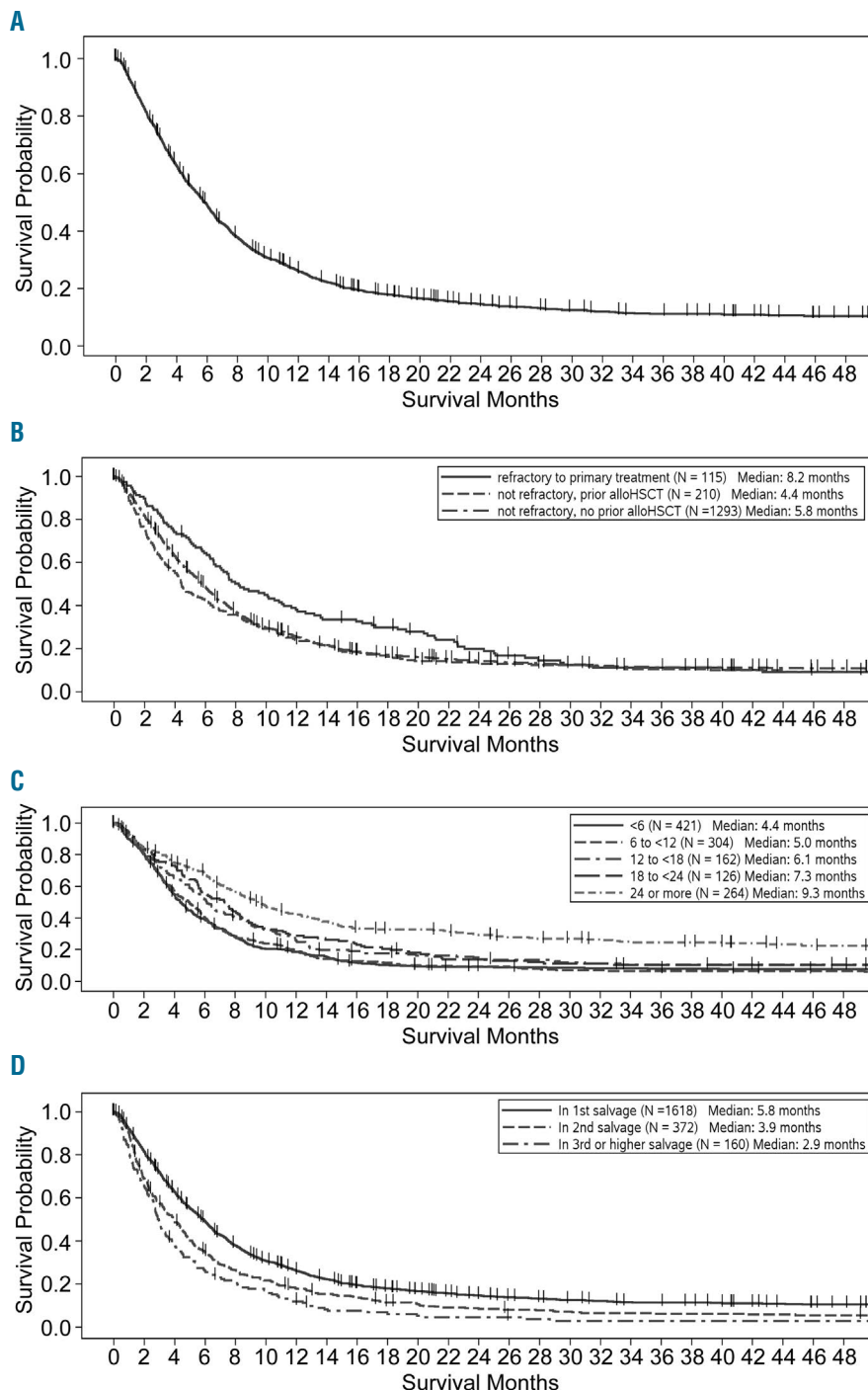


Figure 2. (A) Overall survival from time of first salvage among adult Ph-negative relapsed/refractory B-precursor ALL patients. (B) Overall survival from time of first salvage among adult Ph-negative relapsed/refractory B-precursor ALL patients, by disease status at the time of salvage. (C) Overall survival from time of first salvage among adult Ph-negative relapsed B-precursor ALL patients without prior HSCT, by time to relapse (refractory patients excluded). (D) Overall survival from time of salvage among adult Ph-negative relapsed/refractory B-precursor ALL patients, by line of salvage (all disease statuses included).

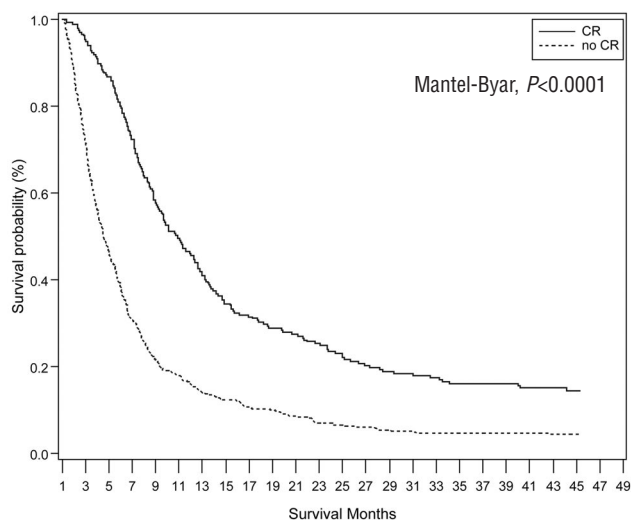


Figure 3. Overall survival by CR status among adult Ph-negative relapsed/refractory B-precursor ALL patients in first salvage. The CR survival curve includes only those patients who achieved CR with the first salvage therapy. Patients who achieved CR but for whom no date of CR was available were excluded from the analysis. Survival between groups is assessed beginning at 36 days after the start of first salvage (the median time to CR) and therefore patients who died or whose data were censored before 36 days are not included in the comparison. At 36 days, 137 patients had achieved CR with first salvage and 563 patients had not. Thirty patients who achieved CR with first salvage and 17 patients who did not remained alive and uncensored at 4 years.

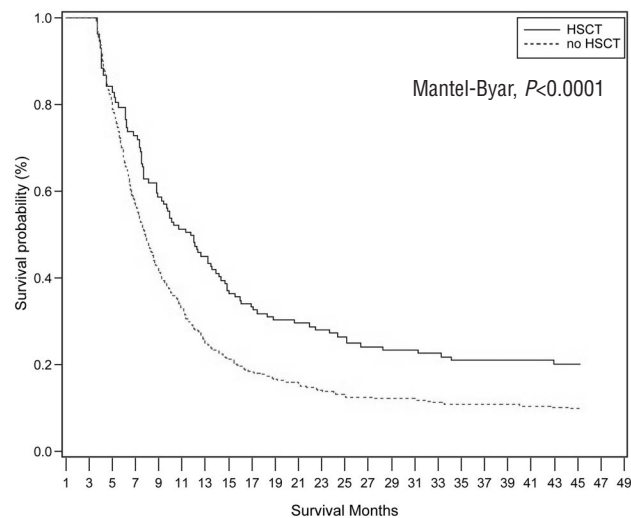


Figure 4. Overall survival among adult R/R ALL patients by receipt of HSCT during first salvage. The HSCT survival curve includes only those patients who received HSCT following first salvage and before any subsequent salvage treatment. Patients who received HSCT but for whom no date of HSCT was available were excluded from the analysis. Survival between groups is assessed beginning at 110 days after the start of first salvage (the median time to HSCT); therefore, patients who died or whose data were censored before 110 days are not included in the comparison. At 110 days, 67 patients had received HSCT following first salvage and 581 patients had not. Twenty-two patients who received HSCT following first salvage and 40 patients who did not remained alive and uncensored at 4 years.

associated with longer median OS (7.5 months vs. 4.2 months; $P=0.014$). Median OS increased over time, and was greater in patients who received first salvage therapy from the year 2000 onward than those who received it from 1990-1999 (6.4 vs. 4.5 months; $P<0.001$). As with CR, the increase in median OS among the three study groups/sites that provided data across all four calendar periods was not significant ($P=0.14$). Survival was better in younger patients ($P<0.001$) and the difference in median OS between males and females was significant (6.1 vs. 5.5 months; $P=0.045$). Finally, the better outcome of patients with lower WBC counts ($<30,000/\mu\text{L}$ at first diagnosis) that was observed for CR rates was also apparent for OS (6.3 vs. 4.6 months; $P=0.001$). In sensitivity analyses (*Online Supplementary Table S3*) limited to patients treated for r/r ALL from 2005-2013, the overall median survival was higher at 6.5 months (95% CI: 5.8-7.3 months) than for the entire cohort of patients treated from 1990 onward. Disease status, time from CR to first relapse, and age remained significant prognostic factors for survival in this subgroup.

Survival after second or later salvage

Median duration of OS after salvage therapy decreased with each subsequent line of therapy (Figure 2D), from 5.8 months (95% CI: 5.5-6.2 months) after first salvage, to 3.4 months (95% CI: 2.8-4.2 months) after second salvage, and 2.9 months (95% CI: 2.6-3.4 months) after third or greater salvage. Among patients who were not refractory to primary treatment, one- and three-year survival rates also decreased with each subsequent salvage therapy, from 25% (95% CI: 23%-27%) and 11% (95% CI: 10%-

13%) for first salvage to 14% (95% CI: 11%-19%) and 5% (95% CI: 3%-8%) for second salvage and 12% (95% CI: 7%-18%) and 4% (95% CI: 1%-9%) for third or greater salvage. No statistically significant difference was detected for OS comparing patients with or without prior HSCT (Table 3). In the cohort of patients treated from 2005 onward, median survival was slightly higher in the second (4.4 months; 95% CI: 3.1-4.9) and third or greater salvages (3.5 months; 95% CI: 2.3-5.4) than for the overall cohort of patients (*Online Supplementary Table S4*).

HSCT after relapse

Realization of HSCT after relapse. Information on HSCT realization after relapse was available for 1337 patients in first salvage. Twenty-eight percent of patients received HSCT after their first salvage treatment, with a range of HSCT in different countries between 15% and 54% (Table 4). The median time from first salvage treatment to HSCT was 3.6 months (range, <1 -15 months). HSCT realization was more common in younger patients, and the proportion of patients who received HSCT increased over time (Table 4). Approximately half the patients who received HSCT were known to be in CR at the time of transplant (183/375 patients, 49%). A similar proportion of patients who achieved a CR received HSCT after their first salvage (183/337 patients, 54%; Table 4). Patients with a prior HSCT were less likely to receive a HSCT after salvage treatment; however, if they achieved CR, they received a second HSCT as often as all other patients.

Overall survival according to receipt of HSCT after relapse. Simon-Makuch curves were used to graphically depict the effect on survival of HSCT during first salvage, using

Table 4. HSCT after salvage therapy in Ph-negative relapsed/refractory B-precursor ALL patients in first salvage treatment only.

	n/N	Among all patients receiving salvage treatment Proportion of any patients with HSCT received after first salvage treatment (%, 95% CI)	n/N	Among patients achieving CR Proportion of patients receiving HSCT in CR after first salvage treatment* (%, 95% CI)
In 1 st salvage				
All countries	375/1 337	28 (26, 31)	183/337	54 (49, 60)
Ranges across all countries	--	15-54	--	40-83
Period of salvage treatment				
1990-1994	15/100	15 (9, 24)	5/24	21 (7, 42)
1995-1999	59/323	18 (14, 23)	20/63	32 (21, 45)
2000-2004	151/491	31 (27, 35)	70/118	59 (50, 68)
2005 or later	150/423	35 (31, 40)	88/132	67 (58, 75)
<i>P</i> -value		<0.001		<0.001
Disease status				
Relapsed without prior HSCT	318/1 074	30 (27, 33)	150/271	55 (49, 61)
Relapsed with prior HSCT	27/157	17 (12, 24)	13/26	50 (30, 70)
<i>P</i> -value		<0.001		0.63
Age at salvage treatment (in years)				
15-17	19/59	32 (21, 46)	10/20	50 (27, 73)
18-34	204/618	33 (29, 37)	96/162	59 (51, 67)
35-54	128/490	26 (22, 30)	61/112	54 (45, 64)
55-64	23/126	18 (12, 26)	15/31	48 (30, 67)
≥65	1/44	2 (0, 12)	1/12	8 (0, 38)
<i>P</i> -value		<0.001		0.01

P-values were generated from univariate Cox models. *Number of patients who achieved CR and who had data on HSCT after salvage.

HSCT as a time-dependent covariate (Figure 4). Duration of survival from 110 days (the median time to transplant) was significantly longer if HSCT was received after first salvage (Mantel-Byar, $P < 0.001$). In this analysis, 40 patients who did not receive HSCT during first salvage were still alive after 3 years; of these, 18 patients were transplanted after a subsequent salvage therapy. This method does not account for differences in patient characteristics that are associated with receiving HSCT.

Discussion

This pooled historical data analysis summarizes the largest dataset on patient outcomes for adults with Ph-negative, B-precursor r/r ALL assembled so far, thereby providing a comprehensive benchmark for standard of care in Europe and the US against which emerging therapies can be judged. By harmonising and pooling the data we were able to obtain more precise estimates, and the relatively large size of the dataset for this rare disease provides greater opportunity for comparing outcomes between important patient subgroups. Rates of remission and survival were found to vary significantly across lines of salvage and between other clinically-relevant subgroups.

Among patients in first salvage, 40% achieved a CR, and the median duration of overall survival was 5.8 months. The one- and three-year survival rates were 26% and 11%, respectively, indicating that one-year of follow-up may be informative to detect a potential survival difference with novel agents, although longer follow up is required to provide full information on prognosis in r/r ALL. Patients receiving therapy 2005 or later had modest-

ly better CR and OS outcomes. After failure of first salvage, outcomes declined significantly. This reflects the likelihood that with each line of salvage, more chemotherapy-resistant subpopulations of ALL blasts will be selected. For clinical trials with new compounds, patients refractory to one or more lines of salvage are usually chosen; our analysis provides the appropriate comparator data for each subset of patients. It furthermore confirms that achievement of CR with the first salvage approach is prognostic: OS was significantly longer in patients who responded to their first salvage treatment than those who did not ($P < 0.001$). It remains to be demonstrated whether the poor prognostic impact of refractory relapses may change when more potent, targeted therapies become available.

Overall, the data underline that relapses in adult ALL typically occur early – more than half occurring within 1 year, during ongoing intensive treatment. Duration of first CR is a known prognostic factor for achievement of subsequent responses to salvage therapy and for survival outcomes^{2-5,7,18} and was confirmed here, independently of the cutpoints selected for analysis. This was demonstrated for patients with relapse after chemotherapy, and in patients with relapse after HSCT. In both settings, patients with very late relapse—more than 24 months after first diagnosis—represent a favourable subgroup with better chances to achieve a CR and to obtain long-term survival. The reason for the poor prognosis of early relapses is probably different disease biology.¹⁹ Whereas late relapses may arise from slowly-cycling still chemotherapy-sensitive subclones of ALL, early relapses probably arise from selected, chemotherapy-resistant subclones that proliferate despite ongoing standard chemotherapy.^{19,20}

Interestingly, the rate of CR and OS among patients

receiving salvage therapy after first relapse increased over the calendar period (1990–2013), although no new compounds with extraordinary performance entered the market during this period. The observed improvements over time may be the result of various factors including the more frequent application of more intensive treatments, better supportive care, more aggressive use of HSCT, and more attempts to treat. Sensitivity analyses, limited to patients treated from 2005 onward, showed improvements in CR and survival compared with the entire cohort. However, an analysis limited to those study groups or sites that provided data over the entire calendar period (i.e., from 1990 onward) showed no significant trends over time. CR and OS also differed between study groups or centers, which may be due to differences in the distribution of patient or prognostic factors, such as US sites having patients with more lines of salvage and more patients treated from 1990–2000 than the European study groups or centers.

An association with lower WBC counts at first diagnosis and increased chance of CR has been found in some studies⁶ but no significant association was found with either CR or OS in others.^{2,5} Higher WBC counts reflect a more aggressive disease biology, which is associated with higher relapse rates; patients with higher WBC are therefore considered as high-risk in many study groups. The inferior rates of CR and OS associated with this biologic subtype of B-precursor ALL has now also been confirmed for the r/r setting. Gender has been investigated as a prognostic factor with conflicting results: no significant relationship was observed with OS in some studies,^{3,6,18} but our analysis was consistent with previous findings that although females have no significant difference in probability of achieving CR,^{3,5} they may have a shorter duration of survival than males.^{2,5} The reasons for this are unclear, but an increased mortality rate during or after re-induction may be a contributing factor.⁵ Limited or missing data did not allow us to examine CR or OS results by specific type of induction or salvage therapy.

The overall rate of HSCT after relapse was 28% and ranged from 15% to 54% across different study groups/centers, likely reflecting different practices between countries, donor availabilities and options provided by healthcare systems. However, it reached 50% in patients achieving a CR after first salvage. It is also noteworthy that the rate of HSCT increased over time. This is clinically important because our analysis, although potentially limited by selection factors of who receives and who does not receive HSCT, confirms the long-term benefits of HSCT after relapse from initial therapy. We considered HSCT as a time-dependent covariate to account for the positive selection bias that applies to patients who survive long enough to receive HSCT. Based on these analyses, we show that receipt of HSCT during first salvage significantly increased OS and confirmed that long-term survival in r/r ALL is strongly influenced by whether or not a patient receives HSCT. However, the observed difference in survival may also be influenced by differences in patient characteristics, which may have influenced receipt of HSCT, and which were not collected in this study. These potential factors, such as presence of comorbidities or poor performance status, may also be strong predictors of survival.

A significant association of older age with decreased CR

and poorer survival was confirmed in our pooled analysis, consistent with published findings.^{2,3,7,18} This may reflect the reduced use of intensive chemotherapy, which has expected toxicities and is not needed for older patients who are likely to be ineligible for transplant. These patients have a specific need for less toxic, targeted therapies with the option to obtain prolonged survival without subsequent HSCT.

In the conduct of pooled analysis across different countries and clinical centers, heterogeneity between measured and unmeasured variables may have influenced our findings. The definition of CR, as described in the supplementary material, was based on general clinical practice guidelines and could have varied across the study groups or centers. Our pooled analysis was also limited by data availability on HSCT realization and date of HSCT for a number of patients. If patients with missing HSCT data were different from patients with available data this could introduce bias, but comparisons of the distribution of available demographic and clinical factors between groups with and without HSCT data did not reveal meaningful differences. Additional limitations of patient or prognostic factors included lack of information on minimal residual disease, high-risk biomarkers, or other indications of upfront HSCT which may have decreased the incidence of relapse.

The vast majority of ALL relapses occur in the bone marrow. Patients with CNS involvement or other isolated extramedullary relapses were not included in the analysis because these patients typically receive different treatments and represent a subgroup often reported separately in prospective or retrospective studies, and are usually excluded from trials of new drugs in r/r ALL.

This pooled retrospective analysis is the largest to date that characterizes outcomes among patients with Ph-negative, B-precursor r/r ALL. The rates of CR and OS were comparable with published studies, which is not unexpected since several of the datasets included have already been published separately.^{2,5,18} Newly-approved and emerging therapies offer the promise of improved response rates and opportunities for long-term survival, with the potential for less toxicity than chemotherapy.^{21–23} The data underline the necessity to closely describe subgroups of r/r ALL in clinical trials with new drugs in order to make published results comparable. Our results will therefore be important to provide context when evaluating outcomes with these new therapies, particularly with respect to the important role of composition of patient characteristics in different published trials for r/r ALL. However, investigators should carefully consider selection bias and other limitations of historical data when making such comparisons. These historical real-world clinical data are not equivalent to clinical trial data; nonetheless, by pooling datasets we were able to provide a more accurate estimate of patient outcomes among different subgroups of patients receiving salvage chemotherapy, which can be valuable across all stages of drug development to assess outcomes with current standard of care.

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