European Review for Medical and Pharmacological Sciences 2022; 26: 975-995

Systematic review and pooled analysis of survival outcomes in patients with relapsed or refractory B-cell acute lymphoblastic leukaemia who have undergone haematopoietic stem cell transplant

T.A. RUSSELL-SMITH[1], S. CHADDA[2], C. LEREUN[3], P. BAJKO[2], E. DOOGAN[2]

[1]Pfizer Inc, New York, NY, USA
[2]Genesis Research, Newcastle upon Tyne, UK
[3]Independent Statistician, Sainte-Anne, Guadeloupe, France

Abstract. – OBJECTIVE: Information about the long-term survival impact of hematopoietic stem cell transplant (HSCT) in adults with relapsed/refractory B-cell acute lymphoblastic leukaemia is limited. The objective was to conduct a systematic review identifying studies reporting survival in HSCT-receiving patients and apply parametric analyses to predict long-term survival.

MATERIALS AND METHODS: Twenty-five relevant studies were identified. Analyses were conducted in 10 studies (n=503; "global" analysis) reporting overall survival (OS) data as Kaplan-Meier curves or at patient level. Four studies (n=217; "subgroup" analysis) measured OS from the point of HSCT. Patient-level data were recreated from Kaplan-Meier curves and pooled, with six models tested for longer-term extrapolation. Additionally, a sensitivity analysis was undertaken involving removal of data from the oldest study cohort (recruited between 1981-1997) to determine if the year which patients received HSCT impacted survival compared to post-2009 data.

RESULTS: Median OS and five-year survival probability were 11.4 months and 24.4% (95% CI, 20.5-28.5%) in the global analysis, and 12.0 months and 28.4% (95% CI, 22.1-34.9%) in the subgroup analysis. The generalised gamma and Gompertz models fit longer-term extrapolation criteria. The generalised gamma model predicted survival at 10.4% *vs.* 14.8% (15 years), 8.3% vs. 12.8% (20 years), and 6.9% *vs.* 11.4% (25 years) for the global and subgroup analysis, respectively. The Gompertz model predicted survival to plateau at 23% *vs.* 25.6% just before 10 years. The sensitivity analysis excluding older data found median survival increased two-fold (25.3 vs. 12 months).

CONCLUSIONS: Results synthesize long-term evidence of outcomes for HSCT-receiving patients, providing a basis for treatment comparison. Risk of death is low beyond four years and newer data appears correlated with improved outcomes.

Key Words:
B-cell acute lymphoblastic leukaemia, Relapsed/refractory, Hematopoietic stem cell transplant, Systematic review, Survival.

Introduction

Acute lymphoblastic leukaemia (ALL) is a haematological cancer that is driven by the proliferation and accumulation of lymphoid progenitor cells in the bone marrow and other tissues[1]. Overproduction of these immature lymphocytes occupies space in the blood and bone marrow, resulting in a reduction in normal white blood cells, red blood cells, and platelets[2]. Signs and symptoms include fatigue, fever/drenching night sweats, bruising or bleeding easily, shortness of breath, weight loss, bone/stomach pain, painless lumps near the lymph nodes, and infections[2].

The incidence of ALL follows a bimodal distribution, whereby the first peak occurs during childhood and a second peak occurs at around the age of 50[3]. In 2017, the age-standardized rate of new ALL cases were 1.1 (95% CI, 1.0-1.2) per 100,000 in the UK[4] and 1.7 per 100,000, with an estimated 100,012 people living with ALL in the US[5]. The 5-year relative survival rate was reported to be 68.8% between 2010-2016 in the US[5].

Among patients with newly diagnosed B-cell ALL, approximately 45% will relapse or become refractory to initial treatment[6]. In relapsed/refractory (R/R) disease, the prognosis is poor[7]. One study reported a 5-year survival rate of 10% and a median overall survival (OS) of 4.5 months after patients experienced relapse[8]. Furthermore, 1- and 3-year OS rates were reported to decrease for adult patients with R/R B-precursor ALL with increasing numbers of salvage therapies[9].

Corresponding Author: S. Chadda, MSc; e-mail: schadda@genesisrg.com

Allogeneic haematopoietic stem cell transplant (alloHSCT) is an important treatment option in ALL for the prevention of relapse. It is the standard of care (SoC) for adult patients with Philadelphia (Ph)-negative ALL who achieve first complete response (CR) and have a high risk of relapse[10]. Autologous HSCT (autoHSCT) has been reported to show comparable survival post-transplant to alloHSCT in patients with Ph-positive ALL[11]. However, a study which evaluated HSCT in adults with ALL in Europe reported a 70% decrease in the use of autoHSCT when comparing the periods of 2013-2015 and 2001-2003, with an increasing trend toward the use of alloHSCT[12].

A key goal of current treatment in patients with R/R B-cell ALL is the achievement of CR/CRi [through application of chemotherapy or targeted therapies such as antibodies and tyrosine kinase inhibitors (TKIs)] followed by HSCT[13]. HSCT is a potentially curative treatment option but is often only used in a subgroup of patients as not all patients achieve CR/CRi, maintain CR/CRi, or are transplant eligible[9]. Appropriate selection of candidate patients for alloHSCT has been highlighted as a challenge in achieving optimal outcomes[14]. Patient risk-stratification is essential to ensure that the benefit of HSCT is not offset by potential toxicity that may occur as a result of the intensity of pre-transplant conditioning therapy, or post-transplant graft *vs.* host disease (GvHD)[14]. Additionally, minimal residual disease (MRD)-positivity may persist in some patients despite achieving a response. Achieving MRD-negativity prior to HSCT may be associated with improved survival outcomes[14].

Several treatments have been recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of R/R ALL in adults including inotuzumab ozogamicin[15], blinatumomab[16], and ponatinib[17]. These treatments have also received approval by the European Medicines Agency (EMA)[18-20] and the US Food and Drug Administration (FDA)[21-23]. They can be used to bridge patients to HSCT with the goal of achieving CR/CRi. They can also be applied to extend life in cases where HSCT is not possible[15-17]. As highlighted by Gokbuget (2016)[9], the investigation of potential new treatments for R/R ALL in adults is challenging due to the rarity of the condition in the adult population, the poor prognostic outcomes, and non-standardised approaches for salvage therapies.

R/R B-cell ALL has poor survival rates with limited alternative treatments. Additionally, there are a number of treatment challenges including achievement of CR/CRi and patient selection for HSCT. Therefore, the investigation and analysis of survival data in patients who have undergone HSCT is important. Such analysis stands to both summarise and predict the potential benefits associated with promising new treatments that increase the number of patients receiving HSCT.

The relationship between HSCT and survival outcomes in adult patients with B-cell ALL, specific to the R/R setting, has not been clearly summarised in any published systematic reviews (SLRs). Additionally, available literature does not concisely report long-term survival in this patient population. Therefore, an objective of this study was to conduct an SLR to identify studies reporting survival in patients with R/R B-cell ALL who have undergone HSCT. The subsequent objective was to pool, analyse, and model survival data to longer-term horizons. The purpose of which was to provide collated and synthesized information for prescribers, transplanters, and formulary decision makers.

Materials and Methods

Search Strategy

This SLR was performed in accordance with established international guidelines for conducting systematic reviews[24-28].

Electronic search strings for Ovid Embase, Ovid Medline, and the Cochrane Library (***Supplementary Data***) were developed using the patient, intervention, comparator, and outcome (PICO) elements described in Table I. Table I also presents the study type, geographic scope, timeframe, and language restrictions. Searches were executed on the 23rd of July 2020. Hand searching of key studies, relevant published SLRs, and key conferences was conducted to supplement the results of the electronic database searches.

Study Selection and Data Extraction

Studies identified through searches were combined into a single EndNote library for de-duplication using a published method[29]. Irrelevant studies were excluded based on the title and abstract by two blinded, independent reviewers using the Rayyan software[30]. Two reviewers screened the remaining full-text articles. Studies had to meet all PICO criteria to be eligible for inclusion in the SLR; reasons for exclusion were recorded. Any disagreements between reviewers were resolved through additional review by a third systematic reviewer.

Relevant information from included studies was extracted including study design, baseline characteristics, and survival outcomes. Secondary outcomes of interest were also collated includ-

Table I. PICO elements. PICO elements, study type, geographic scope, timeframe, and language restrictions used to determine studies eligible for inclusion in the SLR.

Element	Focus	
Patients	Adult patients (15+ years) with R/R B-cell ALL.	
Intervention	Patients who have undergone HSCT.	
Comparison	None.	
Outcomes	• OS. • PFS rates. • Median OS. • Median PFS. • EFS. • Disease-free survival.	• Duration of response. • NRM. • TRM (if related to HSCT). • Overall mortality. • Relapse incidence.
AEs	• Rates of VOD.	• Rates of GvHD.
Publication type	• RCTs. • Non-RCT publications containing registry or hospital record data. • SLRs were excluded unless they contained additional meta-analyses. • Publications comprising <5 patients who received HSCT were excluded.	
Publication timeframe	• Full manuscripts from 1990 to present. • Conference abstracts from 2015 to present.	
Geographic limitations	None.	
Language	• English language abstract. • Non-English publications that were believed to be of interest were translated.	
Databases to search	• Ovid MEDLINE. • Ovid Embase. • Cochrane Library (Reviews and clinical trial databases).	
Other	• Trials registries: Clinicaltrials.gov; clinicaltrialsregister.eu. • Conference abstract databases: ASCO, ASH, EHA, ESMO, EBMT, BSH. • Reference list/ citation checking; key author searching.	

AE, Adverse event; ALL, acute lymphoblastic leukaemia; ASCO, American Society for Clinical Oncology; ASH, American Society of Haematology; BSH, British Society for Haematology; EBMT, European Society for Blood and Marrow Transplantation; EFS, Event-free survival; EHA, European Haematology Association; ESMO, European Society for Medical Oncology; GvHD, graft vs. host disease; HSCT, haematopoietic stem cell transplant; NRM, Non-relapse mortality; OS, Overall survival; PFS, Progression-free survival; RCT, Randomised controlled trial; R/R, relapsed/refractory; TRM, Transplant-related mortality; VOD, veno-occlusive disease.

ing duration of response, rates of veno-occlusive disease (VOD), rates of GvHD, overall mortality, non-relapse mortality (NRM), and transplant-related mortality (TRM). All studies were quality assessed according to an adapted version of the NICE quality appraisal checklist for quantitative intervention studies[31].

Statistical Analysis

There were three main statistical analyses conducted that involved pooling of OS data and parametric modelling to predict long-term survival (Table II).

Analysis of Pooled Survival Data

OS data reported in included studies (either as a Kaplan-Meier survival curve or individual patient data) were collected. Data points from each Kaplan-Meier survival curve were digitised using GetData Graph Digitiser software[32]. Patient-level data were then recreated from the digitised data using the Guyot algorithm[33] – a validated, published method that has been used at conferences and in health technology assessments[16,34,35]. The algorithm was implemented in the software R[36]. The Kaplan-Meier curves drawn from the recreated patient-level data were plotted next to the digitised curves for validation.

Recreated patient-level data and published patient-level data were pooled together to produce a single, overall OS curve ("global" analysis). The median survival time and Kaplan-Meier estimates of OS every 6-months, and associated 95% confidence intervals (CIs), were identified and reported. Additionally, a post-hoc "subgroup" analysis

Table II. Summary of the three main statistical analyses. Summary of the three main statistical analyses undertaken in this study that involved pooling of OS data and parametric modelling to predict long-term survival.

Analysis name	Purpose	Study data included
Global analysis	Determine how HSCT impacts long-term survival in patients with R/R B-cell ALL.	Including data from all studies identified that contained OS Kaplan-Meier curves or patient-level data.
Post-hoc subgroup analysis	Determine how HSCT impacts long-term survival in patients with R/R B-cell ALL where baseline measurement is from the point of HSCT.	Including a subgroup of studies from the global analysis that explicitly reported OS from the time of HSCT only (excluding stu dies from the global analysis that reported OS from a baseline point prior to HSCT or following HSCT).
Post-hoc sensitivity analysis according to age of study	Investigate the correlation between survival outcomes and year in which patients received HSCT.	Including the same studies as the subgroup analysis (i.e., those explicitly reporting OS from the time of HSCT only) but excluding data where HSCT was undertaken prior to the year 2000.

ALL, Acute lymphoblastic leukaemia; HSCT, Haematopoietic stem cell transplant; OS, Overall survival; R/R, Relapsed/refractory.

was conducted on included studies that explicitly reported OS from the time of HSCT only (excluding studies from the global analysis that reported OS from a baseline point prior to HSCT or following HSCT; Table II for full description).

Parametric Modelling and Extrapolation

Six standard parametric models were applied to the pooled OS data for the global and subgroup analyses: exponential, Weibull, Gompertz, log-normal, loglogistic, and generalised gamma. The most appropriate model(s) were selected based on three criteria: (1) the value of the Akaike Information Criterion (AIC) statistics the lower the value, the more suitable the model; (2) visual inspection of the fit of the model to the underlying data over the observation period; (3) critical assessment of clinical plausibility of longer-term extrapolation. Survival estimates were then predicted at 15, 20, and 25 years using the selected model.

Post-Hoc Sensitivity Analyses

Transplant practices have likely improved over time due to experience and improvements in

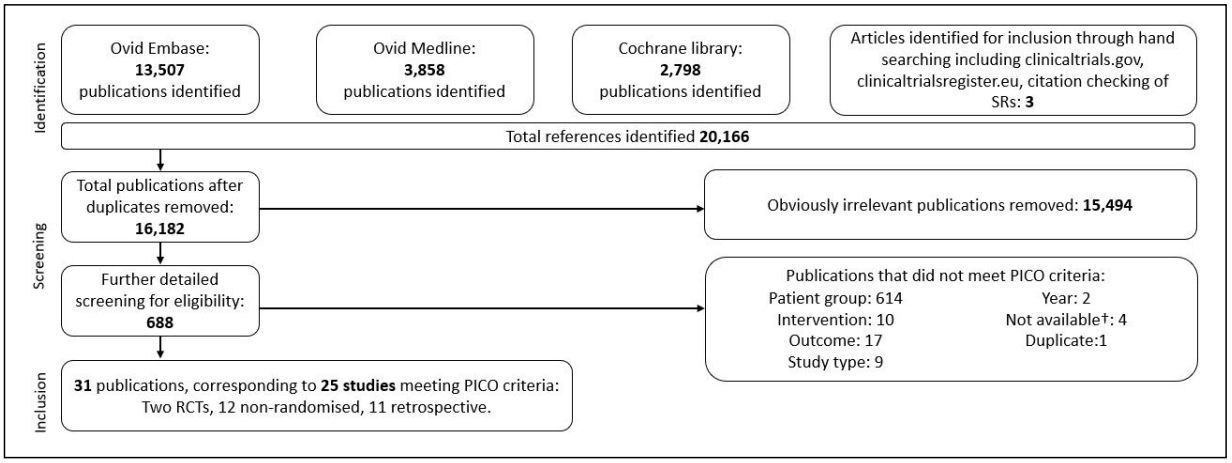

Figure 1. PRISMA diagram. The number of included and excluded publications identified after systematic searching for patients with R/R B-cell ALL who have undergone HSCT.
PICO, patients, interventions, comparators, and outcomes; RCTs, Randomized controlled trials; SR, Systematic review.
†References that were not located online nor available through the British Library as of 11th September 2020.

technology. Therefore, an "age of study" sensitivity analysis was conducted to investigate the correlation between survival outcomes and the year in which patients received HSCT (Table II). Data were excluded from one outlier study in the subgroup analysis whose recruitment period was between 1981-1997[37]. The remaining three studies in the subgroup analysis had a post-2009 recruitment period[38-40]. Additionally, further post-hoc sensitivity analyses were applied to confirm the robustness of the statistical analyses conducted in this study.

Results

Description of Studies Identified in SLR

Searches identified 20,166 records of which 3,984 were duplicates and 15,494 were removed following title/abstract screening, leaving 688 for detailed screening. After full-text review, 31 relevant references were identified for inclusion in the SLR, corresponding to 25 studies in total (see Figure 1 for the PRISMA diagram). Forty-four studies (corresponding to 49 references) containing B-cell ALL patients were excluded because patient cohorts contained de novo patients, patients whose treatment line was unspecified, or a mixture of de novo and R/R patients (with no separation of outcomes between either patient group). Therefore, only studies that reported outcomes solely for R/R patients were included.

A summary of the study design and baseline characteristics for each study is available in Table III. Of the 25 studies included, seven were international/multi-centre registry studies that contained between 84 to 2,150 patients, of which 23 to 309 patients per study matched the PICO criteria. The remaining studies were single centre registries, randomized controlled trials (RCTs), or non-randomized studies. These studies contained 6 to 405 patients, of which 6 to 137 patients matched the PICO criteria. The median age range across studies was 23-59 years. Treatments prior to HSCT included blinatumomab, inotuzumab ozogamicin, total body irradiation, or SoC (typically chemotherapy based). These treatments were sometimes coupled with other induction or consolidation therapies, myeloablative, non-myeloablative, or reduced-intensity conditioning. The baseline timepoints from which outcomes were measured were prior to HSCT in eight studies, from the time of HSCT in seven studies, post-HSCT in five studies, and not specified in 10 studies.

Risk of Bias in SLR Studies

Of the 25 studies included in this SLR, 14 were full manuscripts and 11 were available as conference abstracts only. Quality assessments were only conducted for studies available as full manuscripts. The NICE quality appraisal checklist for quantitative intervention studies was used to assess bias and generalizability of studies[31]. One study fulfilled "all or most of the checklist criteria" for ensuring minimal bias[41], 10 studies were deemed to have met "some of the checklist criteria" for ensuring minimal bias[9,39,40,42-48], and three studies fulfilled "few or no checklist criteria", and were therefore at risk of potential bias[47,49,50]. Regarding generalizability to the source population, 12 studies fulfilled "some of the checklist criteria"[9,39,40,43-51]. The remaining three studies fulfilled "all or almost all the checklist criteria" for ensuring generalisability[41,42].

SLR Outcomes

The main outcomes of interest were OS, progression-free survival (PFS), event-free survival (EFS), and relapse-free survival (RFS). Other outcomes of interest were duration of response, rates of VOD and GvHD, overall mortality, NRM, and TRM, and are reported in ***Supplementary Data***. Disease-free survival, leukaemia-free survival, and relapse incidence were also outcomes of interest. However, none of the included studies reported these outcomes.

Overall Survival

Eighteen studies in the SLR contained OS data (of which 10 contained Kaplan-Meier curves or patient-level data that were used in the analysis of long-term survival) (Table IV). OS was defined in this SLR as the "*time from the start of a given treatment regimen until death or date of last follow-up*". The included studies that reported OS were consistent with this definition[44, 52-57].

The lowest median OS was 4.0 months (95% CI, 1.2-7.0) for patients who had received their third line of salvage therapy prior to HSCT[9]. The highest median OS was 20.2 months (95% CI, 9.1-31.3) in patients who had received inotuzumab ozogamicin prior to HSCT[46].

Generally, OS decreased with increasing lines of salvage treatment. MRD status of patients also had an impact on OS over time. The lowest 2-year OS reported was 0% for patients who had

Table III. Baseline characteristics. Summary of study design and baseline characteristics for studies identified during systematic searching for patients with R/R B-cell ALL who have undergone HSCT.

Author (year), NCT identifier, trial name, Study type	ITT population n PICO population n‡	Median age	Treatments received prior to HSCT	ECOG status/KPS	CR/ CRi/ CRp	Outcome measurement baseline point
Aboudalle (2018)[52], Non-randomised, single arm.	ITT: n=35 PICO: n=17 (49%).	ITT: 28 years (19-76).	≥2 cycles of blinatumomab.	ECOG 0: n=6 1: n=20, 2: n=7 Missing: n=2	CR: n=13 CRi: n=2 CRp: n=4	From the initiation of blinatumomab treatment (i.e. prior to HSCT).
Ali (2018)[70], NCT01564784, INO-VATE, RCT †Kantarjian (2019)[42]	InO: ITT, n=164 PICO, n=79	ITT: 46.5 years (18-78)	≤6 cycles InO combined with: Myeloablative conditioning (67.1%) or RIC (32.9%).	ECOG 0: n=62 1: n=81 2: n=21	PICO CR: n=65 (38.6%).	Not specified.
	SoC: ITT, n=162 PICO, n=36.	ITT: 47.5 years (18-79)	SoC combined with: Myeloablative conditioning (66.7%) or RIC (22.2%).	ECOG 0: n=61 1: n=802: n=20 Missing: n=1	PICO CR: n=17 (10.5%).	
Ansuinelli (2019)[71], Retrospective, single centre.	ITT: n=36 PICO: n=14.	≥18 years	At least one cycle of blinatumomab prior to receiving HSCT.	-	-	Not specified.
Badar (2020)[49], Retrospective multi-centre.	ITT: n=84 PICO: n=23	ITT: 50 years (20-87) PICO: 43 years (20-75)	At least one cycle of InO (100% of patients). Myeloablative conditioning for alloHSCT (in 86% of patients).	KPS (ITT): ≤80: n=11 80-100: n=50 Missing: n=23	-	From time of HSCT.
Badar (2020)[58], Retrospective multi-centre.	ITT: n=309	Blina-tumomab: 59 years (18-72), InO: 43 years (20-75)	None [treatments administered post-HSCT (HSCT occurred prior to study commencement): Blinatumomab: n=233, InO: n=86]	-	-	Measured from initiation of Blinatumomab/InO treatment (i.e. post-HSCT).
	Blinatumomab PICO: n=85					
	InO PICO: n=21					
Boissel (2019)[72], Neuf,Retrospective observational.	ITT: n=373 PICO n=74	ITT: 43 years (IQR = 27-55)	All patients received blinatumomab	-	-	Measured from initiation of blinatumomab treatment (i.e. prior to HSCT).
Boissel (2019)[73], Neuf, Retrospective observational	ITT: n=253 PICO: n=43	ITT: 36.5 years (IQR: 24.0-52.0)	All patients received blinatumomab	-	CR achieved prior to transplant: n=33	Measured from initiation of blinatumomab treatment (i.e. prior to HSCT).
Goekbuget (2018)[41], MT103-203, MT103-211, Non-randomised.	ITT: n=305 PICO: n=108	PICO MT103-211: 31 years (18-65) PICO MT103-203: 43 years (18-67)	All patients received blinatumomab.PICO: Myeloablative conditioning, n=47; RIC/ non-myeloablative conditioning, n=47; unknown, n=14	-	-	Time from initiation of blinatumomab (i.e. prior to HSCT).
†Gokbuget (2020)[38]§ MT103-211 only.	ITT: n=116 PICO: n=74		PICO: Of the 74 HSCT patients: Myeloablative conditioning (n=55), RIC (n=14); conditioning regimen NR (n=5)	-	CR2: n=39 CR3: n=2	Measured from time of HSCT.
Gokbuget (2012)[43], NCT00199056, NCT00198991, Retrospective analysis of non-randomised GMALL 06/99 and 07/03.	ITT: n=169 PICO: n=122	ITT: 34 years	-	-	-	Not specified.

Table continued

Table III. Baseline characteristics. Summary of study design and baseline characteristics for studies identified during systematic searching for patients with R/R B-cell ALL who have undergone HSCT.

Author (year), NCT identifier, trial name, Study type	ITT population n PICO population n‡	Median age	Treatments received prior to HSCT	ECOG status/KPS	CR/ CRi/ CRp	Outcome measurement baseline point
Gokbuget (2016)[9], NCT02003612, Retrospective observational.	1st salvage: ITT, n=1,618; PICO, n=210 (13.0%)	-	-	-	-	Measured from time from initiation of last salvage treatment (median time from salvage therapy to HSCT was 100 days).
	2nd salvage: ITT, n=372; PICO n=61 (16.5%)					
	≥3rd salvage: ITT, n=160; PICO, n=17 (10.6%)					
Greil (2019)[59], Retrospective.	ITT: n=180 PICO: n=137	ITT: 37 years	TBI: 61%	-	-	Not specified.
Grigg (1999)[44], Retrospective multi-centre.	TT: n=147 PICO: n=81	ITT: 28 years (17-54)	TBI ITT: n=91 (62%) Non-TBI ITT: n=56 (38%)	-	-	Measured from time of HSCT.
Isufi (2018)[74], Non-randomised.	ITT: n=98 PICO: n=21	ITT: 59 years (20-73)	TBI	-	-	Not specified.
Jabbour (2017)[39], Retrospective.	1st salvage treatment ITT: n=46 MRD +ve PICO: n=12 MRD -ve PICO: n=14	ITT: 38 years (18-87)	InO ITT: n=21 (46%). Blinatumomab ITT: n=4 (9%)	-	-	Measured from time of blinatumomab/ InO treatment initiation (median time to HSCT = 2 months).
	2nd salvage treatment ITT: n=32 MRD +ve PICO: n=10 MRD -ve PICO: n=6	ITT: 38 years (19-79)	InO ITT: n=20 (63%). Blinatumomab ITT: n=7 (22%)	-	-	
Jabbour (2018)[45], NCT01371630, Non-randomised.	ITT: n=59 PICO: n=26	ITT: 35 years (18-87)	All patients received InO	-	-	Not specified.
Jabbour (2019)[46], NCT02013167, TOWER, RCT.	ITT: n=405 PICO: n=97	Blinatumomab PICO: 31 years (18-71)	Blinatumomab: ≥1 cycle of induction therapy; consolidation blinatumomab therapy (in patients achieving BM response)	-	PICO blinatumomab Cri: n=50	Not specified.
		SoC PICO: 29 years (18-70)	SoC: ≥1 cycle of induction therapy; consolidation chemotherapy (in patients achieving BM response)	-	PICO SoC Cri: n=18	
†Kantarjian (2017)[75], NCT02013167, TOWER	-	-	Blinatumomab: Previous alloHSCT n=94 (34.7%) SoC: Previous alloHSCT n=46 (34.3%)	-	-	Not specified.
Jain (2018)[76], CALM, Non-randomised dose finding study.	ITT: n=9 PICO: n=5	23 years (18-49)	Previous alloHSCT with relapse at a median of 5.9 (4-11) months post-transplant: n=7	-	-	Measured from time of HSCT.
Park (2015)[77], NCT01044069, Non-randomised, single arm.	ITT: n=33 PICO: n=11	54 years (22-74)	Prior alloHSCT, n=11 (33%); ≥ 3 prior lines of therapy, n=14 (42%). All patients received conditioning chemotherapy followed by 1-3x106 19-28z CAR-T cells/kg.	-	-	Post-HSCT (exact timing not specified in study).
Stein (2016)[78], Non-randomised open label trial.	ITT: n=189 PICO: n=34	PICO: 31 years (18-65)	All patients received blinatumomab: ≤5 cycles.	-	-	Measured from time of HSCT.

Table continued

Table III. Baseline characteristics. Summary of study design and baseline characteristics for studies identified during systematic searching for patients with R/R B-cell ALL who have undergone HSCT.

Author (year), NCT identifier, trial name, Study type	ITT population n PICO population n‡	Median age	Treatments received prior to HSCT	ECOG status/KPS	CR/ CRi/ CRp	Outcome measurement baseline point
Stelmach (2020)[40], Retrospective single centre.	Blinatumomab ITT: n=18 PICO: n=11	ITT: 32 years (20-73)	All patients received blinatumomab: ≥1 cycle.	-	ITT CR & Cri: 69% (39-91)	- Measured from time of HSCT.
	InO PICO: n=16	ITT: 42 years (18-74)	All patients received InO: ≥1 cycle.	-	ITT CR & Cri = 94% (70-100)	
Topp (2012)[50], NCT00198991, NCT00198978, Non-randomised trial.	ITT: n=20 PICO: n=9	≥18 years	All patients received induction and consolidation chemotherapy, followed by blinatumomab.	-	All patients achieved CR prior to HSCT	Measured from time of blinatumomab initiation (median time from blinatumomab completion to HSCT = 0.7 months).
Topp (2014)[51], NCT01209286, Non-randomised single arm.	ITT: n=36 PICO: n=13	32 years (18-77)	All patients received induction and consolidation chemotherapy, followed by blinatumomab (2 cycles; plus an additional three cycles if CR was not achieved).	-	-	Measured from time of first CR (i.e. prior to HSCT).
†Zugmaier (2015)[67]			-			
Topp (2015)[47]¶, NCT01466179, Non-randomised, single arm.	ITT: n=189 PICO: n=32	ITT: 39 years (18-79)	Dexamethasone (patients with >50% peripheral blood BM blasts). All patients received blinatumomab (≥1 cycle).	-	-	Measured from time of HSCT
Topp (2018)[65], NCT01466179, MT 103-211.	PICO: n=34					Not specified.
†Stein (2019)[64], NCT01466179	PICO: n=64	PICO: 32 years (19-74)	None (conditioning regimens received for previous alloHSCT; HSCT received prior to study commencement).			Post-HSCT (exact timing not specified in study).
Wang (2019)[48], Non-randomised	ITT: n=32 PICO: n=27	PICO: 27 years (15-50)	None (conditioning therapy and CAR-DLI for 5 days; HSCT received prior to study commencement).	-	-	Measured from time of first CAR-DLI infusion (i.e. post-HSCT); median time from HSCT to relapse = 8 months.
Zhang (2018)[66], Non-randomised	PICO: n= 6	18-60 years	None (CAR-T therapy; HSCT received prior to study commencement).	-	-	Post-HSCT (exact timing not specified in study).

AlloHSCT, Allogeneic haematopoietic stem cell transplant; BM, Bone marrow; CAR-DLI, chimeric antigen receptor-modified donor lymphocyte infusion; CAR-T, chimeric antigen receptor T-cell; CR, Complete remission; CRi, Complete remission with incomplete haematologic recovery; CRp, Complete remission with partial recovery; ECOG, Eastern Cooperative Oncology Group, KPS, Karnofsky Performance Status; HSCT, Haematopoietic stem cell transplant; Ino, inotuzumab ozogamicin; IQR, Inter-quartile range; ITT, Intention to treat; MRD -ve, Minimal residual disease-negative; MRD +ve, Minimal residual disease-positive; NR, Not reported; PICO, Patients, Interventions, Comparators and Outcomes; RCT, Randomised controlled trial; RIC, Reduced-intensity conditioning; SoC, Standard of care; TBI, Total body irradiation.
Table III footnotes: - Indicates this figure was not reported by the author in the study. *Indicates follow-up data for the same study from the study above.
†The PICO population n-value is the number of patients within each study population that met PICO criteria. ‡The only relevant outcome reported by Gokbuget (2020)[38] was in the form of a Kaplan-Meier curve, i.e., there are no data points available. §All patients in Topp (2015)[47] were MRD-negative post-treatment with blinatumomab and chemotherapy.

Table IV. Studies reporting OS data. Summary of studies reporting OS data for studies identified during systematic searching in patients with R/R B-cell ALL who received HSCT.

Author (year) / NCT reference	No. patients in analyses	Reported OS outcome	Results	Median follow-up
Aboudalle (2018)[52]	n=17	Patient-level OS data reported.		-
Ali (2018)[70]	InO administered prior to HSCT: n=79	Median OS, months (95% CI).	12.6 (9.3-27.7)	-
		HSCT vs no HSCT, HR, p-value.	0.55 (p=0.0065)	-
†Kantarjian (2019)[42]‡		2-year OS, % (95% CI).	39.4% (28.1-50.5).	-
	SoC administered prior to HSCT: n=36	Median OS, months (95% CI).	-	-
		HSCT vs no HSCT, HR, p-value.	-	-
		2-year OS, % (95% CI).	-	-
Badar (2020)[49]	n=23	Median OS, months (95% CI).	7.5 (3.2-maximum NR)	-
Badar (2020)[58]	Blinatumomab administered prior to HSCT: n=85	Median OS, months (95% CI).	NR	-
		2-year OS, %.	62%	-
	InO administered prior to HSCT: n=21	Median OS, months (95% CI).	NR	-
		12-month OS, %.	53%	-
Goekbuget (2018)[41] NCT01207388 & NCT01466179 †Gokbuget (2020)[38]‡	n=34	Median OS, months (95% CI).	Age >35 years: 15.9 months	-
†Topp (2018)[65] NCT01466179	n=34	Median OS, months (95% CI).	Age >35 years: 15.9	-
†Stein (2019)[64] NCT01466179	n=64	Median OS, months (95% CI).	8.5 (4.2- 11.2).	16.6 months (range: 12.4-23.3).
Gokbuget (2012)[43]‡ NCT00199056 & NCT00198991	n=103	Median OS, months.	13.6	23 months.
		3-year probability.	36% ± 5%	
Gokbuget (2016)[9] NCT02003612	1st salvage n=210	Median OS, months (95% CI).	4.4 (3.7-5.8).	-
		6-month OS, % (95% CI).	42% (36-49).	-
		2-year OS, % (95% CI).	23% (18-29).	-
		36-month OS, % (95% CI).	10% (7-15).	-
	2nd salvage n=61	Median OS, months (95% CI).	4.5 (2.4-5.3).	-
		6-month OS, % (95% CI).	35% (23-47).	-
		2-year OS, % (95% CI).	17% (9-28).	-
		36-month OS, % (95% CI).	4% (1-12).	-
	3rd salvage n=17	Median OS, months (95% CI).	4.0 (1.2-7.0).	-
		6-month OS, % (95% CI).	39% (17-61).	-
		2-year OS, % (95% CI).	20% (5-42).	-
		36-month OS, % (95% CI).	0%	-
Grigg (1999)[44]‡	n=81	Two OS Kaplan-Meier curves contained with the publication.		-

Table continued

Table IV. ***(Continued).*** Studies reporting OS data. Summary of studies reporting OS data for studies identified during systematic searching in patients with R/R B-cell ALL who received HSCT.

Author (year) / NCT reference	No. patients in analyses	Reported OS outcome	Results	Median follow-up
Jabbour (2017)[39]‡	First salvage treatment, MRD +ve: n=12	Median OS, months.	8	-
		2-year OS, %.	38%	-
	First salvage treatment, MRD -ve: n=14	Median OS, months (95% CI).	NR	-
		2-year OS, %.	65%	-
	Second salvage treatment, MRD +ve: n=10	Median OS, months.	10	-
		2-year OS, %.	0%	-
	Second salvage treatment, MRD -ve: n=6	Median OS, months.	12	-
		2-year OS, %.	33%	-
Jabbour (2018)[45] NCT01371630	n=17	Median OS, months.	25	24 months.
		12-month OS, %.	63%	
Jabbour (2019)[46] NCT02013167	n=97	Median OS, months (95% CI).	Blinatumomab: NE	-
			InO: 20.2 (9.1-31.3)	-
Park (2015)[77] NCT01044069	n=11	6-month OS, % (95% CI).	70% (33-89).	-
Stein (2016)[78]‡	n=34	12-month OS, % (95% CI).	73% (55-85).	13.4 months
Stelmach (2020)[40]‡	Blinatumomab administered prior to HSCT: n=11	12-month OS, % (95% CI).	31% (2-59).	-
	InO administered prior to HSCT: n=16	-	-	-
Wang (2019)[48]‡	n=32	One OS Kaplan-Meier curves contained with the publication.		-
Zhang (2018)[66]‡	n=6	Patient-level OS data reported.		243.5 days
Zugmaier (2015)[67]‡ NCT01209286	n=13	Long-term survival, n (%).	6 (46.2%).	-

ALL, Acute lymphoblastic leukaemia; CI, Confidence interval; HSCT, Haematopoietic stem cell transplant; InO, Inotuzumab ozogamicin; MRD -ve, Minimal residual disease-negative; MRD +ve, Minimal residual disease-positive; OS, Overall survival; R/R, Relapsed/refractory; NE, not evaluable; NR, Not reached; SoC. Standard of care.
- indicates this figure was not reported by the author in the study.
*Indicates follow-up data for the same study from the publication above.
†Indicates studies that contained Kaplan-Meier or patient-level OS data and were therefore included in long-term survival analyses.

Table V. Studies reporting PFS, EFS and RFS data. Summary of studies reporting PFS, EFS and RFS data for studies identified during systematic searching in patients with R/R B-cell ALL who received HSCT.

Author (year)/ NCT reference	No. patients in analyses	Reported outcome	Results	Median follow-up
Progression-free survival				
Badar (2020)[49]	n=23	Median PFS, months (range)	3.5 (2.3-maximum NR)	-
Badar (2020)[58]	n=309	2-year PFS (blinatumomab administered prior to HSCT), %	66%	-
		6-month PFS (InO administered prior to HSCT), %	53%	
Greil (2019)[59]	n=137	10-year PFS, %	Ph +ve B-cell ALL: 33%	-
			Ph -ve B-cell ALL: 27%	
Event-free survival				
Jabbour (2017)[39]	First salvage treatment and were MRD +ve (prior to HSCT): n=12	Median EFS, months	6	-
		2-year EFS, %	19%	
	First salvage treatment and were MRD -ve (prior to HSCT): n=14	Median EFS, months	NR	
		2-year EFS	65%	
	Second salvage treatment and were MRD +ve (prior to HSCT): n=10	Median EFS, months	7	
		2-year EFS	0%	
	Second salvage treatment and were MRD -ve (prior to HSCT): n=6	Median EFS, months	12	
		2-year EFS	17%	
Relapse-free survival				
Stein (2016)[78]	n=34	12-month RFS, % (95% CI)	53% (34-69).	13.4 months.
Topp (2018)[65] NCT01466179	n=34	Median RFS, months	Age ≤35 years: 16.4 Age >35 years: 15.9	-
†Stein (2019)[64] NCT01466179	n=29	Median RFS, months	7.4 (5-10.1)	12.4 months (11.5-18).
Zugmaier (2015)[67] NCT01209286	n=13	Patients with long-term RFS	n=4	28.9 months (0.5-34.5).

ALL, Acute lymphocytic leukaemia; EFS, Event-free survival; InO, Inotuzumab ozogamicin; HSCT, Haematopoietic stem cell transplant; MRD -ve, Minimal residual disease-negative; MRD +ve, Minimal residual disease-positive; NR, Not reported; PFS, Progression-free survival; Ph -ve, Philadelphia-negative; Ph +ve, Philadelphia-positive; R/R, Relapsed/refractory; RFS, Relapse-free survival.
Indicates this data was not reported by the author in the study.
*Indicates follow-up data for the same study from the publication above.

MRD-positive status at the time of transplant and had received their second salvage treatment[39]. The highest 2-year OS reported was 65% for patients who had MRD-negative status at the time of transplant and had received their first salvage treatment[39].

Progression-Free Survival

Three studies in the SLR reported PFS data (Table V) but none provided a definition[49,58,59]. The MeSH definition used to classify studies in Medline states PFS as *"Length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but the disease does not get worse"*[60]. For ALL, PFS has been defined as *"time to disease progression or death following transplant"*[61].

PFS was reported at different timepoints between studies. In one study, median PFS was reported at 3.5 months (range: 2.3-maximum not reached) in patients following HSCT[49]. A 2-year PFS rate of 66% was reported for patients who received blinatumomab then underwent HSCT. A 6-month PFS rate of 53% was reported for patients who received inotuzumab ozogamicin then underwent HSCT[58]. A higher 10-year PFS was reported for Ph-positive B-cell ALL (33%) than Ph-negative B-cell ALL (27%)[59]. The length of follow-up was not reported for any of these studies.

Event-Free Survival

One study in the SLR reported EFS data in patients who received HSCT (Table V). EFS was defined in this study as *"time of treatment initiation until treatment failure, relapse, or death from any cause"*[39]. A higher 2-year EFS was reported for patients who received only one salvage treatment prior to HSCT (MRD-positive, 19%; MRD-negative, 65%) compared with those who had received two salvage treatments prior to HSCT (MRD-positive, 0%; MRD-negative, 17%)[39]. The length of follow-up was not reported.

Relapse-Free Survival

Three studies in the SLR reported RFS data in patients who received HSCT (Table V). These studies defined RFS as *"time from graft infusion/ achievement of CR/MRD to relapse, death, or censoring at last date of remission"*[47,62,63]. The lowest median RFS was 7.4 months (range: 5-10.1), after a median follow-up of 12.4 months[64]. The highest median RFS was 16.4 months for patients aged ≤35 years and 15.9 months for patients aged >35 years. However, the follow-up time was not reported in this study[65].

Analysis of Long-Term Overall Survival

Selection of studies: global vs. post-hoc subgroup analysis

Of studies identified in the SLR that reported OS data, 10 of the 18 studies contained OS Kaplan-Meier curves or patient-level data. These 10 studies were eligible for inclusion in analyses of long-term survival. Of these studies, one was a conference abstract[66] and nine were full-text manuscripts that were quality assessed [38-40, 42-44, 48, 64, 67]. One study was deemed to have fulfilled "all or almost all of the checklist criteria" for ensuring minimal bias[38], six studies met "some of the criteria"[39,40,42-44,64], and two studies met 'few or none of the criteria'[48, 67]. Regarding generalizability, two studies fulfilled "all or almost all of the checklist criteria"[38,42], and seven studies fulfilled "some of the criteria"[39,40,43,44,48,64,67].

Studies in the global analysis could be grouped into three categories. Only studies in the first category were included in the subgroup analysis, whilst the global analysis included studies from all three categories:

1. Studies which explicitly stated that HSCT was received at the start of follow-up and the baseline for measuring OS was from the point of HSCT[38,40,44]. To note, the Jabbour (2017)[39] study was assumed to fall within this category as the median time to HSCT was 2 months and outcome measurement began 2 months post-randomisation.

2. Studies in which HSCT occurred during follow-up and OS was measured from time of study inclusion, with HSCT occurring at an unspecified point during observation[42,43].

3. Studies in which HSCT occurred prior to study initiation and OS was measured from time of study inclusion of patients having previously received HSCT at some point[48,64,66,67].

Pooled Analysis of OS Data

When all the recreated patient-level data were pooled, OS data were available for 503 and 217 patients for the global and subgroup analyses, respectively. In the global analysis, the median follow-up was 10.8 months (range: 0.5 month-13 years). During follow-up, a total of 361 deaths were observed, representing 71.8% of the total sample. The median OS was 11.4 months (95% CI, 9.5-12.6). In the subgroup analysis, the median follow-up was 11.4 months (range: 0.2 months-13 years). During follow-up in the subgroup analysis, a total of 147 deaths were observed, representing 67.7% of the total sample. The median OS was 12.0 months (95% CI, 9.7-16.6).

Table VI shows the observed survival at six-month intervals for both analyses. Figure 2 shows the pooled OS Kaplan-Meier curves (solid lines). Survival decreased over the first five years in patients who had undergone HSCT, before plateauing in both the global and subgroup analyses. No deaths were observed during the sixth and seventh year of follow-up. However, the number of patients remaining in the pooled cohort decreased between these timepoints as the majority of studies had completed their follow-up. At eight years, only two patients were left in the cohort in both analyses.

The curves generated for both the global and subgroup analyses were similar, with the subgroup analysis reporting marginally superior survival from six months onwards. The magnitude of the difference varied but was generally around four percentage points throughout. In the first part of the observation period there appeared to be a delay of approximately six months between global and subgroup analysis curves.

Overall, estimation proved more precise in the global analysis with narrower CIs. This was due

Table VI. Observed and predicted survival in global, subgroup, and sensitivity analysis. Observed survival was recorded at six-month intervals based on the OS Kaplan-Meier curves. Curves were constructed from pooled OS data from 10 studies that reported OS for patients with R/R B-cell ALL that had received HSCT ("global" analysis). Four of these studies reported OS data from the point of HSCT procedure ("subgroup" analysis). Additionally, an "age of study" sensitivity analysis reported OS from three studies whose patient recruitment was post-2009 with the removal of patient data between 1981-1997. Long-term predicted survival data from the generalized gamma and Gompertz parametric models is shown at five-year intervals.

Time point (in years)	Patients still in cohort			Survival probability (95% confidence interval)					
				Global		Subgroup		Sensitivity†	
	Global	Sub-group	Sensitivity†	Gompertz	Generalised gamma	Gompertz	Generalised gamma	Gompertz	Generalised gamma
0	503	217	136	100% (-)		100% (-)		100% (-)	
0.5	343	144	117	69.0% (64.8-72.9)		67.6% (60.9-73.4)		87.4% (80.6-92.0)	
1.0	227	102	89	47.0% (42.6-51.3)		49.8% (42.9-56.4)		69.8% (61.2-76.8)	
1.5	169	79	68	37.5% (33.2-41.8)		40.7% (34.0-47.3)		55.9% (46.9-64.0)	
2.0	145	68	60	33.9% (29.6-38.1)		37.0% (30.4-43.6)		51.7% (42.7-60.0)	
2.5	128	57	49	31.2% (27.1-35.4)		33.6% (27.1-40.2)		46.3% (37.3-54.8)	
3.0	115	50	44	29.7% (25.6-33.9)		32.3% (25.9-38.9)		44.3% (35.3-52.9)	
3.5	109	47	41	28.4% (24.3-32.6)		30.4% (24.0-37.0)		41.3% (32.4-50.0)	
4.0	95	45	40	24.8% (20.8-28.9)		29.1% (22.8-35.7)		40.3% (31.4-49.0)	
4.5	77	38	33	24.4% (20.5-28.5)		28.4% (22.1-34.9)		39.1% (30.2-47.9)	
5.0	44	5	-	24.4% (20.5-28.5)		28.4% (22.1-34.9)		38.7%	35.6%
10.0	-	-	-	12.2% (1.7-33.9)		14.1% (1.8-38.5)		34.2%	22.6%
15.0	-	-	-	23%	10.4%	25.6%	14.8%	33.7%	16.6%
20.0	-	-	-	23%	8.3%	25.6%	12.8%	33.6%	13.1%

†Sensitivity analysis where Grigg (1999)[44] OS data was excluded.

to the global analysis including a larger patient cohort than the subgroup analysis.

Extrapolation Of Long-Term Survival Using Parametric Modelling

Of the six parametric models fitted, the Gompertz and generalised gamma models were considered most suitable for extrapolation of long-term OS in the global and subgroup analysis. The parameters for the selected models are presented in ***Supplementary Data***.

Figure 2 shows the pooled OS Kaplan-Meier curves (solid lines) and long-term fitted Gompertz and generalised gamma (dashed lines) for both analyses. As observed with the pooled OS Kaplan-Meier curves, the predicted survival was marginally superior from six months onwards in the subgroup compared with the global analysis for both models. This difference was also observed in the corresponding long-term extrapolations.

Table VI shows the predicted survival probabilities for the global and subgroup analyses from 10 years onwards for both models. Just prior to 10 years, both Gompertz curves reached a plateau at 23% and 25.6% and remained at those values even when extrapolated to much longer time horizons. Conversely, the survival predicted by the generalised gamma models continued to decline and reached 6.9% and 11.4% at 25 years in the global and subgroup analysis, respectively.

Post-Hoc Sensitivity Analyses to Test Robustness

A sensitivity analysis was performed to assess the extent of the impact of the artificially inflated drop toward the end of the observation period in the Kaplan-Meier curves. This was done by censoring all patients just before the eight-year timepoint in the global analysis (Figure 2, solid lines). When parametric models were fit to the new data, the results obtained were similar. The same models were chosen, and the long-term predictions were almost identical, confirming the robustness of the analysis (data not shown).

A separate sensitivity analysis was performed to establish the impact of including the Jabbour (2017)[39] study in the subgroup analysis. The other three included studies explicitly stated that the baseline for measuring OS was from the point of HSCT[38, 40, 44]. Whereas the Jabbour (2017)[39] study was only assumed to fall within this category. This is because median time to HSCT was 2 months and outcome measurement began 2 months post-randomisation. Excluding Jabbour (2017)[39] did not have a considerable impact on the results, which validated the assumption to include it within the subgroup analysis (data not shown).

Post-Hoc Sensitivity Analysis of Long-Term Survival According to Age of Study

Pooled OS curve

An "age of study" sensitivity analysis was conducted which excluded data from one outlier study [Grigg (1999)[44]] in the subgroup analysis whose recruitment period was between 1981-1997. The remaining three studies recruited patients post-2009[38-40]. When OS data from these three studies were pooled, survival data were available for 136 patients. The median follow-up was 17.9 months (range: 0.2 months-4.9 years). This was shorter than in the subgroup analysis as all the data after 5-years came from Grigg (1999)[44]. During follow-up, a total of 75 deaths were observed, representing 55.1% of the total sample. The median survival time was 25.3 months (95% CI, 16.8-39.4) post-HSCT.

Table VI shows the observed and predicted survival outcomes for the subgroup compared to the age of study sensitivity analysis. Figure 3 shows the age of study sensitivity analysis curve compared with the subgroup analysis curve. The shape of the sensitivity analysis curve differs from the subgroup analysis curve as the decline in survival rate is slower. In both curves, the decline in survival remains more pronounced in the initial 1.5 years than in subsequent years. However, this difference is less prominent in the age of study sensitivity analysis. Similarly, the survival rate appears to reach a plateau around four years at 40.3% (31.4-49.0) compared to 29.1% (22.8-35.7) in the age of study sensitivity analysis *vs.* subgroup analysis, respectively. The analyses showed that pooled studies containing data from the last 12 years were associated with more favourable survival compared to the study containing data from 24-30 years ago.

Parametric Modelling

The Gompertz, generalised gamma, lognormal and, loglogistic models were all considered suitable models for the pooled OS curve for the age

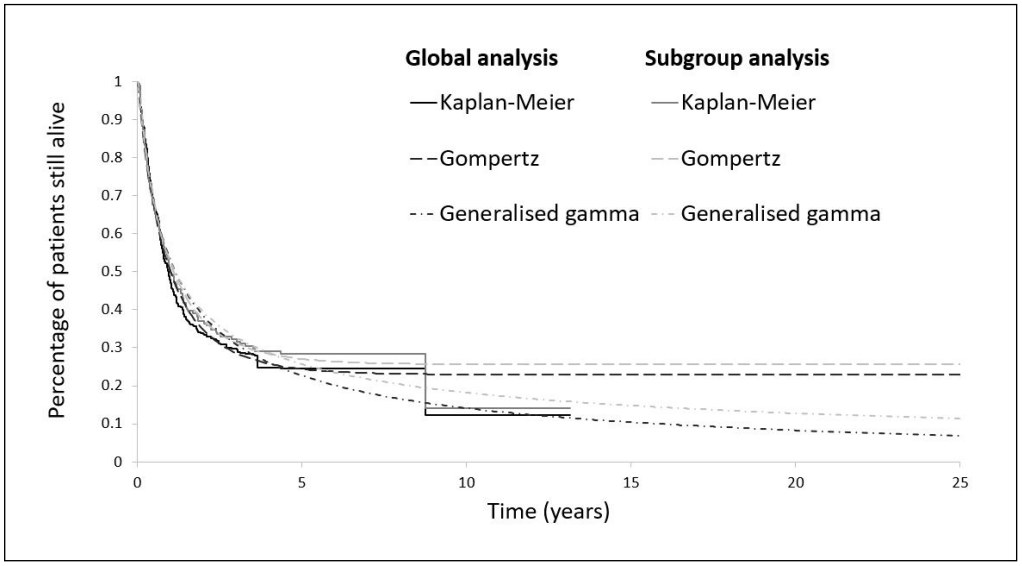

Figure 2. Observed and predicted survival in global and subgroup analysis. Kaplan-Meier curves constructed from pooled OS data from 10 studies that reported OS for patients with R/R B-cell ALL that had undergone HSCT ("global" analysis; n=503). Four of these studies reported OS data from the point of HSCT procedure ("subgroup" analysis; n=217). Both Kaplan-Meier curves were fitted with Gompertz and generalised gamma parametric curves used to predict survival up to 25 years.

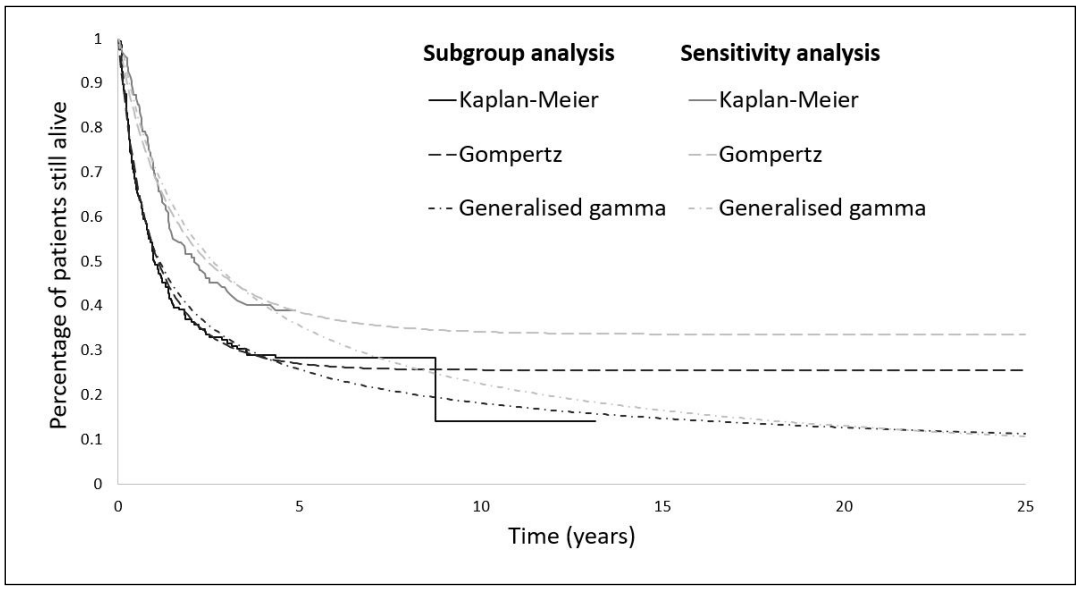

Figure 3. Observed and predicted survival in subgroup and age of study sensitivity analysis. Kaplan-Meier curves constructed from pooled OS data from four studies which reported OS data from the point of HSCT procedure for patients with R/R B-cell ALL ("subgroup" analysis; n=217). The "age of study" sensitivity analysis curve reported OS from three studies whose patient recruitment was post-2009 (n=136) with the removal of patient data between 1981-1997. Both Kaplan-Meier curves were fitted with Gompertz and generalised gamma parametric curves used to predict survival up to 25 years.

of study sensitivity analysis. However, the generalised gamma and lognormal models had the best curve fit overall. ***Supplementary Data*** shows the model parameters.

There was little difference between the results of the four parametric models, as shown in Figure 4. Figure 3 shows long-term survival predictions of the Gompertz and the generalised gamma for the age of study sensitivity analysis compared with the same models for the subgroup analysis. As observed in the subgroup analysis, the Gompertz model for the sensitivity analysis reached a plateau just prior to 13 years at 33.7%. This plateau remained even when extrapolated to much longer time horizons. The generalised gamma model may be considered as a suitable alternative because its long-term predictions decreased with time. The predicted survival rate was 16.6% at 15 years, 13.1% at 20 years and 10.7% at 25 years. The loglogistic and lognormal models gave similar but slightly lower survival predictions.

Discussion

This study provides insight into published data on survival after HSCT in adult patients with R/R B-cell ALL. In the SLR, 25 studies were identified that met PICO criteria for inclusion. The SLR was limited by the quality of some included studies. 11 of the 25 included studies were only available as abstracts, which were limited in length and so likely contained incomplete or immature data. Additionally, there was not enough information provided in these abstracts to allow quality assessment. Therefore, the risk of bias for all studies could not be determined. The most frequently reported outcome was OS, with 16 studies providing relevant data. Other survival outcomes were inconsistently reported and included PFS, EFS, and RFS.

Long-term survival was predicted by pooling OS data in a global analysis (10 studies; n=503) and subgroup analysis (four studies; n=217). The pooled Kaplan-Meier survival curves were extrapolated using parametric modelling. In all Kaplan-Meier and associated parametric curves (global, subgroup, and age of study sensitivity analysis), the survival of patients who had undergone HSCT appears significantly more stable after four years, with the risk of death low for patients who had survived past that point.

A small improvement in OS was observed for the subgroup analysis (OS measured from time of HSCT) from six months onwards compared with the global analysis. The magnitude of the differ-

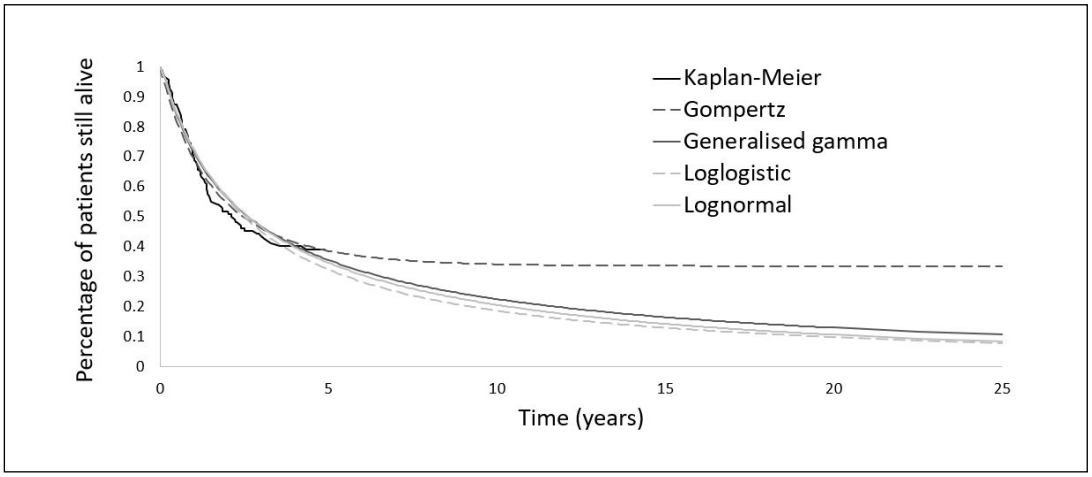

Figure 4. Observed and predicted survival in the age of study sensitivity analysis. A Kaplan-Meier curve constructed from pooled OS data from three studies which reported OS data from the point of HSCT procedure for patients with R/R B-cell ALL. Patients included in this curve were recruited post-2009 (n=136), with data from 1981-1997 excluded. The Kaplan-Meier curve was fitted with Gompertz, generalised gamma, loglogistic and lognormal parametric curves used to predict survival up to 25 years.

ence varied between global and subgroup OS Kaplan-Meier curves but was generally around four percentage points throughout. This was also the case for long-term OS extrapolations. The reduced OS was expected in the global analysis as HSCT occurred prior to the start of the observation period in four of the six additional studies. Therefore, a delay between receiving HSCT and the baseline point for measuring OS would naturally lead to lower survival estimates. The precise magnitude of that shift in time between the baseline measurement points of the global *vs.* the subgroup analysis is unknown. However, there appeared to be a delay of approximately six months between estimates (Figure 2).

An age of study sensitivity analysis was performed to remove patients from the subgroup analysis who underwent HSCT between 1981-1997[44], leaving only patients who underwent HSCT from 2009 onwards. The resulting median OS was increased by more than two-fold (25.3 months *vs.* 12 months for the age of study sensitivity and subgroup analyses, respectively). The Gompertz model predicted a relative increase in the long-term survival probability, with the curve plateauing at 34%, as opposed to 25.6%, after year 12. The generalised gamma model also reflected an increase in survival probability for the age of study sensitivity analysis compared with the subgroup analysis (22.6% *vs.* 14.1% at 10 years). However, the magnitude of the difference between curves decreased from 15 years (16.6% *vs.* 14.8%) and thereafter. This analysis is limited in that it is driven by the removal of only one study without formal control for confounding factors. However, there exists a correlation between the substantial improvement in OS in the group which excluded the older data. This may be a result of improvements in transplant practice, technology, understanding and/or SoC that come with time. Similarly, Gooley (2010)[68] reported substantial reductions in patient mortality post-HSCT in 2003-2007 *vs.* 1993-1997. This was due to a decrease in organ damage, improved prophylaxis, and improved techniques for the prevention and management of GvHD.

In all three analyses (global, subgroup, and the age of study sensitivity analysis) the Gompertz and generalised gamma models met criteria for long-term survival extrapolation and were both considered a good fit to the pooled Kaplan-Meier curves. Whilst the Gompertz visually fit the pooled Kaplan-Meier curves well in all three analyses, it reached an indefinite plateau (just prior to 10 years in the global and subgroup analysis, and just prior to 13 years in the sensitivity analysis). This is a known limitation of the model. In contrast, the generalised gamma models suffer from the opposite limitation in that they fail to maintain a plateau into the longer-term, which is what was observed in the pooled Kaplan-Meier curves. To resolve this and generate long-term survival predictions between the two curves, predictions using the Gompertz curves could be adjusted with general population mortality data. Long-term survival data could then be compared to the generalised

gamma curves. Indeed, NICE have previously accepted the use of an adjusted Gompertz model for assessing long-term survival in patients with R/R ALL treated with blinatumomab[69].

Conclusions

To our knowledge, this study is the first to systematically identify, pool study data, and predict long-term OS using parametric modelling in studies reporting survival data for adult patients with R/R B-cell ALL who have undergone HSCT. The study used a systematic approach to identify all relevant studies. It tested numerous parametric models to select the most suitable models for the pooled data according to pre-defined criteria. Furthermore, sensitivity analyses were conducted to test the experimental robustness and plausibility of included data. HSCT (combined with the prior achievement of CR or CRi) is a potentially curative treatment[9] for patients with R/R B-cell ALL. Findings from this study suggest that HSCT provides promising survival outcomes, especially once patients are past the initial four years post-HSCT.

This analysis provides global insight into the long-term survival of patients with R/R B-cell ALL who have undergone HSCT and addresses a gap in the current clinical evidence. Key findings include the risk of death being reduced beyond four years compared to the first four years after HSCT. Additionally, more modern data appears correlated with improved survival. The results deliver long-term evidence of the impact of HSCT on survival and provide a basis for comparison with other treatments for this patient population. Furthermore, this study emphasises the importance developing effective treatments that allow patients to achieve CR/ CRi and proceed to HSCT.

Authors' Contributions

TA Russell-Smith and S. Chadda contributed to research design, synthesis and interpretation of findings, and critically reviewed draft manuscripts. C. Le Reun contributed to research design, acquisition, analysis, and interpretation of statistical analysis data, and critically reviewed draft manuscripts. P. Bajko and E. Doogan contributed to acquisition, analysis, and interpretation of SLR data and contributed to drafting and critical revision of the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

The authors would like to thank Caroline von Wilamowitz Moellendorff for her contribution to the SLR, who was previously employed by SIRIUS Market Access, Newcastle upon Tyne, UK. Additionally, the authors would like to acknowledge that Pfizer Inc. provided the project funding. TA Russell-Smith is an employee of Pfizer. S. Chadda, E. Doogan, and P. Bajko disclose that they are employees of Genesis Research, a company that received funding from Pfizer for its role in conducting the study and developing the manuscript. C. Le Reun received consulting fees from Genesis Research for her role in conducting the study and performing the statistical analyses.

References

1) Jabbour E, O'Brien S, Konopleva M, Kantarjian H. New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia. Cancer 2015; 121: 2517-2528.
2) NIH National Cancer Institute. Adult Acute Lymphoblastic Leukemia Treatment (PDQ®)–Patient Version 2020 [Available from: https://www.cancer.gov/types/leukemia/patient/adult-all-treatment-pdq].
3) Paul S, Kantarjian H, Jabbour EJ. Adult Acute Lymphoblastic Leukemia. Mayo Clin Proc 2016; 91: 1645-1666.
4) Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence statistics 2017 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/leukaemia-all/incidence#heading-Zero].
5) NIH National Cancer Institute. Cancer Stat Facts: Leukemia — Acute Lymphocytic Leukemia (ALL) 2020 [Available from: https://seer.cancer.gov/statfacts/html/alyl.html].
6) NICE [ID893]. Final scope for the appraisal of inotuzumab ozogamicin for treating relapsed or refractory B cell acute lymphoblastic leukaemia. National Institute for Health and Care Excellence; 2016.
7) Paul S, Rausch CR, Nasnas PE, Kantarjian H, Jabbour EJ. Treatment of relapsed/refractory acute lymphoblastic leukemia. Clin Adv Hematol Oncol 2019; 17: 166-175.
8) Oriol A, Vives S, Hernández-Rivas J-M, Tormo M, Heras I, Rivas C, Bethencourt C, Moscardó F, Bueno J, Grande C, del Potro E, Guardia R, Brunet S, Bergua J, Bernal T, Moreno M-J, Calvo C, Bastida P, Feliu E, Ribera J-M, Programa Español de Tratamiento en Hematologia G. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. Haematologica 2010; 95: 589-596.
9) Gokbuget N, Dombret H, Ribera JM, Fielding AK, Advani A, Bassan R, Chia V, Doubek M, Giebel S,

Hoelzer D, Ifrah N, Katz A, Kelsh M, Martinelli G, Morgades M, O'Brien S, Rowe JM, Stieglmaier J, Wadleigh M, Kantarjian H. International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractor y acute lymphoblastic leukemia. Haematologica 2016; 101: 1524-1533.

10) Giebel S, Marks DI, Boissel N, Baron F, Chiaretti S, Ciceri F, Cornelissen JJ, Doubek M, Esteve J, Fielding A, Foa R, Gorin NC, Gokbuget N, Hallbook H, Hoelzer D, Paravichnikova E, Ribera JM, Savani B, Rijneveld AW, Schmid C, Wartiovaara-Kautto U, Mohty M, Nagler A, Dombret H. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 2019; 54: 798-809.
11) Giebel S, Labopin M, Potter M, Poiré X, Sengeloev H, Socié G, Huynh A, Afanasyev BV, Schanz U, Ringden O, Kalhs P, Beelen DW, Campos AM, Masszi T, Canaani J, Mohty M, Nagler A. Comparable results of autologous and allogeneic haematopoietic stem cell transplantation for adults with Philadelphia-positive acute lymphoblastic leukaemia in first complete molecular remission: An analysis by the Acute Leukemia Working Party of the EBMT. Eur J Cancer 2018; 96: 73-81.
12) Giebel S, Boumendil A, Labopin M, Seesaghur A, Baron F, Ciceri F, Esteve J, Gorin NC, Savani B, Schmid C, Wetten S, Mohty M, Nagler A. Trends in the use of hematopoietic stem cell transplantation for adults with acute lymphoblastic leukemia in Europe: a report from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Ann Hematol 2019; 98: 2389-2398.
13) Hoelzer D, Bassan R, Dombret H, Fielding A, Ribera JM, Buske C. Acute lymphoblastic leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2016; 27: v69-v82.
14) Saadeh SS, Litzow MR. Hematopoietic stem cell transplant in adults with acute lymphoblastic leukemia: the present state. Expert Rev Hematol 2018; 11: 195-207.
15) NICE [TA541]. Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia. National Institute for Health and Care Excellence; 2018.
16) NICE [TA450]. Blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. National Institute for Health and Care Excellence; 2017.
17) NICE [TA451]. Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia. National Institute for Health and Care Excellence; 2017.
18) EMA. Besponsa 2020 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/besponsa].
19) EMA. Iclusig 2019 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/iclusig].
20) EMA. Blincyto 2021 [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto].
21) FDA. FDA approves new treatment for adults with relapsed or refractory acute lymphoblastic 2017 [Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-relapsed-or-refractory-acute-lymphoblastic].
22) FDA. Ponatinib (marketed as Iclusig) Informaton 2015 [Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/ponatinib-marketed-iclusig-informaton].
23) FDA. FDA granted accelerated approval to blinatumomab (Blincyto, Amgen Inc.) for the treatment of adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia 2018 [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-accelerated-approval-blinatumomab-blincyto-amgen-inc-treatment-adult-and-pediatric].
24) Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009; 339: b2700.
25) [PMG24]. N. Single technology appraisal: User guide for company evidence submission template. National Institute for Health and Care Excellence; 2015.
26) CRD. CRD's guidance for undertaking systematic reviews in health care.: Centre for Reviews and Dissemination; 2009.
27) Higgins J, Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, MJ., Welch, VA. Cochrane handbook for systematic reviews of interventions version 6.0 (updated July 2019). Cochrane 2019.
28) NICE [PMG10]. The social care guidance manual. Appendix B Methodology Checklist: systematic reviews and meta-analyses. National Institute for Health and Care Excellence; 2016.
29) Bramer WM, Giustini D, de Jonge GB, Holland L, Bekhuis T. De-duplication of database search results for systematic reviews in EndNote. Journal of the Medical Library Association : JMLA 2016; 104: 240-243.
30) Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev 2016; 5: 210.
31) NICE. Quality appraisal checklist – quantitative intervention studies [online]. National Institute for Health and Care Excellence; 2020.
32) GetData. GetData Graph Digitizer version 2.26.0.20 [software] 2013 [Available from: http://getdata-graph-digitizer.com/].
33) Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol 2012; 12: 9.

34) NICE (TSD19). NICE DSU Technical Support Document 19: Partitioned survival analysis for decision modelling in health care: a criticial review. National Institute for Health and Care Excellence; 2017.
35) NICE (TSD16). NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. National Institute for Health and Care Excellence; 2014.
36) R-Core-Team. R: A Language and Environment for Statistical Computing Vienna, Austria2016 [Available from: www.R-project.org/].
37) Grigg A, Morton J, Durrant S, Bardy P, Szer J. Factors influencing the outcome of donor marrow transplantation in adults from less than ideal donors: experience from two Australian centres. Aust N Z J Med 1997; 27: 311-318.
38) Gokbuget N, Zugmaier G, Dombret H, Stein A, Bonifacio M, Graux C, Faul C, Bruggemann M, Taylor K, Mergen N, Reichle A, Horst HA, Havelange V, Topp MS, Bargou RC. Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. Leukemia lymphoma 2020: 1-9.
39) Jabbour E, Short NJ, Jorgensen JL, Yilmaz M, Ravandi F, Wang SA, Thomas DA, Khoury J, Champlin RE, Khouri I, Kebriaei P, O'Brien SM, Garcia-Manero G, Cortes JE, Sasaki K, Dinardo CD, Kadia TM, Jain N, Konopleva M, Garris R, Kantarjian HM. Differential impact of minimal residual disease negativity according to the salvage status in patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Cancer 2017; 123: 294-302.
40) Stelmach P, Wethmar K, Groth C, Wenge DV, Albring J, Mikesch JH, Schliemann C, Reicherts C, Berdel WE, Lenz G, Stelljes M. Blinatumomab or Inotuzumab Ozogamicin as Bridge to Allogeneic Stem Cell Transplantation for Relapsed or Refractory B-lineage Acute Lymphoblastic Leukemia: A Retrospective Single-Center Analysis. Clin Lymph Myelom Leuk 2020: e724-e733.
41) Goekbuget N, Stein A, Zugmaier G, Dombret H, Brueggemann M, Bonifacio M, Dong X, Kantarjian H, Bargou R, Topp M. Long-term survival of adults with b-cell precursor acute lymphoblastic leukemia (BCP-ALL) after treatment with blinatumomab and subsequent allogeneic hematopoietic stem cell transplantation. HemaSphere 2018; 2 (Supplement 2): 43.
42) Kantarjian HM, DeAngelo DJ, Stelljes M, Liedtke M, Stock W, Gökbuget N, O'Brien SM, Jabbour E, Wang T, Liang White J, Sleight B, Vandendries E, Advani AS. Inotuzumab ozogamicin *vs.* standard of care in relapsed or refractory acute lymphoblastic leukemia: Final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer 2019; 125: 2474-2487.
43) Gokbuget N, Stanze D, Beck J, Diedrich H, Horst HA, Huttmann A, Kobbe G, Kreuzer KA, Leimer L, Reichle A, Schaich M, Schwartz S, Serve H, Starck M, Stelljes M, Stuhlmann R, Viardot A, Wendelin K, Freund M, Hoelzer D. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood 2012; 120: 2032-2041.
44) Grigg AP, Szer J, Beresford J, Dodds A, Bradstock K, Durrant S, Schwarer AP, Hughes T, Herrmann R, Gibson J. Factors affecting the outcome of allogeneic bone marrow transplantation for adult patients with refractory or relapsed acute leukaemia. Brit J Haematol 1999; 107: 409-418.
45) Jabbour E, Ravandi F, Kebriaei P, Huang X, Short NJ, Thomas D, Sasaki K, Rytting M, Jain N, Konopleva M, Garcia-Manero G, Champlin R, Marin D, Kadia T, Cortes J, Estrov Z, Takahashi K, Patel Y, Khouri MR, Jacob J, Garris R, O'Brien S, Kantarjian H. Salvage chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD for patients with relapsed or refractory philadelphia chromosome-negative acute lymphoblastic leukemia: A phase 2 clinical trial. JAMA Oncol 2018; 4: 230-234.
46) Jabbour EJ, Gokbuget N, Kantarjian HM, Thomas X, Larson RA, Yoon SS, Ghobadi A, Topp MS, Tran Q, Franklin JLF, S. J. Stein, A. S. . Transplantation in adults with relapsed/refractory acute lymphoblastic leukemia who are treated with blinatumomab from a phase 3 study. Cancer 2019: 4181-4192.
47) Topp MS, Gökbuget N, Stein AS, Zugmaier G, O'Brien S, Bargou RC, Dombret H, Fielding AK, Heffner L, Larson RA, Neumann S, Foà R, Litzow M, Ribera JM, Rambaldi A, Schiller G, Brüggemann M, Horst HA, Holland C, Jia C, Maniar T, Huber B, Nagorsen D, Forman SJ, Kantarjian HM. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol 2015; 16: 57-66.
48) Wang T, Gao L, Hu X, Liu B, Chen J, Zhang W, Wang J, Yu X, Feng D, Chang AE, Max W, Tang G, Li Q, Yang J. Chimeric Antigen Receptor-modified Donor Lymphocyte Infusion Improves the Survival of Acute Lymphoblastic Leukemia Patients With Relapsed Diseases After Allogeneic Hematopoietic Stem Cell Transplantation. J Immunother 2019; 42: 81-88.
49) Badar T, Szabo A, Wadleigh M, Liedtke M, Arslan S, Siebenaller C, Aldoss I, Schultz E, Hefazi M, Litzow MR, Kuo E, Wang A, Curran E, Shallis RM, Podoltsev N, Balasubramanian S, Yang J, Mattison R, Burkart M, Dinner S, Advani A, Atallah E. Real-World Outcomes of Adult B-Cell Acute Lymphocytic Leukemia Patients Treated With Inotuzumab Ozogamicin. Clin Lymph Myelom Leuk 2020; 20: 556-560.
50) Topp MS, Gokbuget N, Zugmaier G, Degenhard E, Goebeler ME, Klinger M, Neumann SA, Horst HA, Raff T, Viardot A, Stelljes M, Schaich M, Kohne-Volland R, Bruggemann M, Ottmann OG, Burmeister T, Baeuerle PA, Nagorsen D, Schmidt M, Einsele H, Riethmuller G, Kneba M, Hoelzer D, Kufer P, Bargou RC. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood 2012; 120: 5185-5187.
51) Topp MS, Gokbuget N, Zugmaier G, Klappers P, Stelljes M, Neumann S, Viardot A, Marks R, Died-

rich H, Faul C, Reichle A, Horst HA, Bruggemann M, Wessiepe D, Holland C, Alekar S, Mergen N, Einsele H, Hoelzer D, Bargou RC. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. J Clin Oncol 2014; 32: 4134-4140.
52) Aboudalle I, Kantarjian HM, Short NJ, Ravandi F, Sasaki K, Garcia-Manero G, Montalban-Bravo G, Cortes JE, Benton CB, Issa GC, Khouri M, Nasnas P, O'Brien SM, Jabbour EJ. Long term follow-up on phase 2 study on the efficacy and safety of blinatumomab in adult patients with relapsed refractory B-precursor acute lymphoblastic leukemia. Blood Conf 60th Ann ASH 2018; 132: S1.
53) Thyagu S, Minden MD, Gupta V, Yee KW, Schimmer AD, Schuh AC, Lipton JH, Messner HA, Xu W, Brandwein JM. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukaemia with imatinib combined with a paediatric-based protocol. Br J Haematol 2012; 158: 506-514.
54) Al Malki MM, Yang D, Labopin M, Afanasyev B, Angelucci E, Bashey A, Socie G, Karduss-Urueta A, Helbig G, Bornhauser M, Niittyvuopio R, Ganser A, Ciceri F, Brecht A, Koc Y, Bejanyan N, Ferraro F, Kebriaei P, Mokhtari S, Ghobadi A, Nakamura R, Forman SJ, Champlin R, Mohty M, Ciurea SO, Nagler A. Comparing transplant outcomes in ALL patients after haploidentical with PTCy or matched unrelated donor transplantation. Blood Adv 2020; 4: 2073-2083.
55) Ludwig WD, Rieder H, Bartram CR, Heinze B, Schwartz S, Gassmann W, Loffler H, Hossfeld D, Heil G, Handt S, Heyll A, Diedrich H, Fischer K, Weiss A, Volkers B, Aydemir U, Fonatsch C, Gokbuget N, Thiel E, Hoelzer D. Immunophenotypic and genotypic features, clinical characteristics and treatment outcome of adult pro-B acute lymphoblastic leukemia: Results of the German multicenter trials GMALL 03/87 and 04/89. Blood 1998; 92: 1898-1909.
56) Mannis GN, Martin TG, Damon LE, Andreadis C, Olin RL, Kong KA, Faham M, Hwang J, Ai WZ, Gaensler KML, Sayre PH, Wolf JL, Logan AC. Quantification of Acute Lymphoblastic Leukemia Clonotypes in Leukapheresed Peripheral Blood Progenitor Cells Predicts Relapse Risk after Autologous Hematopoietic Stem Cell Transplantation. Biol Blood Marrow TR 2016; 22: 1030-1036.
57) Kiehl MG, Kraut L, Schwerdtfeger R, Hertenstein B, Remberger M, Kroeger N, Stelljes M, Bornhaeuser M, Martin H, Scheid C, Ganser A, Zander AR, Kienast J, Ehninger G, Hoelzer D, Diehl V, Fauser AA, Ringden O. Outcome of allogeneic hematopoietic stem-cell transplantation in adult patients with acute lymphoblastic leukemia: No difference in related compared with unrelated transplant in first complete remission. J Clin Oncol 2004; 22: 2816-2825.
58) Badar T, Advani AS, Liedtke M, Arslan S, Khan MA, Aldoss I, Sienbenaller C, Schultz E, Hefazi M, Shallis RM, Yurkiewicz I, Podoltsev N, Patel A, Curran E, Kuo E, Wang A, Balasubramanian S, Yang J, Mattison R, Burkart M, Dinner S, Litzow MR, Wadleigh M, Atallah E. Clinical Outcome with Allogeneic Hematopoietic Stem Cell Transplantation after Blinatumomab or Inotuzumab Ozogamicin in Patients with B-Cell Acute Lymphoblastic Leukemia: Real World Experience. Biol Blood Marrow TR 2020; 26 (3 Supplement): S101-S102.
59) Greil C, Engelhardt M, Ihorst G, Bertz H, Marks R, Zeiser R, Duyster J, Finke J, Wasch R. Prognostic factors for survival after allogeneic transplantation in acute lymphoblastic leukemia. Blood Conf 61st Ann ASH 2019; 134: S1.
60) MeSH. Progression-Free Survival 2019 [Available from: https://www.ncbi.nlm.nih.gov/mesh/?term=progression+free+survival].
61) Clay-Gilmour AI, Hahn T, Preus LM, Onel K, Skol A, Hungate E, Zhu Q, Haiman CA, Stram DO, Pooler L, Sheng X, Yan L, Liu Q, Hu Q, Liu S, Battaglia S, Zhu X, Block AW, Sait SNJ, Karaesmen E, Rizvi A, Weisdorf DJ, Ambrosone CB, Tritchler D, Ellinghaus E, Ellinghaus D, Stanulla M, Clavel J, Orsi L, Spellman S, Pasquini MC, McCarthy PL, Sucheston-Campbell LE. Genetic association with B-cell acute lymphoblastic leukemia in allogeneic transplant patients differs by age and sex. Blood advances 2017; 1: 1717-1728.
62) Dhedin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, Thomas X, Chevallier P, Nguyen S, Coiteux V, Bourhis JH, Hichri Y, Escoffre-Barbe M, Reman O, Graux C, Chalandon Y, Blaise D, Schanz U, Lheritier V, Cahn JY, Dombret H, Ifrah N. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood 2015; 125: 2486-2496.
63) Gokbuget N, Dombret H, Giebel S, Bruggemann M, Doubek M, Foa R, Hoelzer D, Kim C, Martinelli G, Parovichnikova E, Rambaldi A, Ribera JM, Schoonen M, Stieglmaier JM, Zugmaier G, Bassan R. Minimal residual disease level predicts outcome in adults with Ph-negative B-precursor acute lymphoblastic leukemia. Hematology UK 2019; 24: 337-348.
64) Stein AS, Kantarjian H, Gokbuget N, Bargou R, Litzow MR, Rambaldi A, Ribera JM, Zhang A, Zimmerman Z, Zugmaier G, Topp MS. Blinatumomab for Acute Lymphoblastic Leukemia Relapse after Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow TR 2019; 25: 1498-1504.
65) Topp M, Stein AS, Zugmaier G, Dombret H, Brueggemann M, Bonifacio M, Dong X, Kantarjian HM, Bargou RC, Gokbuget N. Long-term survival of adults with B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) after treatment with blinatumomab and subsequent allogeneic hematopoietic stem cell transplantation (HSCT). J Clin Oncol Conf 2018; 36: S1.
66) Zhang R, He Y, Yang D, Wang Y, Feng S, Wang J, Han MZ. Donor-derived second generation of CD19 CAR-T cell therapy for relapsed B-cell acute lymphoblastic leukemia after allogenic stem cell transplantation. Blood Conf 60th Ann ASH 2018; 132: S1.
67) Zugmaier G, Gokbuget N, Klinger M, Viardot A, Stelljes M, Neumann S, Horst HA, Marks R, Faul C, Diedrich H, Reichle A, Bruggemann M, Holland

C, Schmidt M, Einsele H, Bargou RC, Topp MS. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. Blood 2015; 126: 2578-2584.
68) Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, Martin PJ, Sandmaier BM, Marr KA, Appelbaum FR, Storb R, McDonald GB. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med 2010; 363: 2091-2101.
69) NICE [ID804]. Single Technology Appraisal: Blinatumomab for treating Philadelphia chromosome-negative relapsed or refractory acute lymphoblastic leukaemia. National Institute for Health and Care Excellence; 2017.
70) Ali S, Stelljes M, DeAngelo DJ, Liedtke M, Stock W, Gokbuget N, O'Brien S, Jabbour E, Wang T, White JLS, B. Vandendries, E. Avvani, A. S. Kantarjian, H. M. Long-term outcomes in patients with relapsed/refractory acute lymphoblastic leukemia treated with inotuzumab ozogamicin: results from the phase 3 ino-vate study. Brit J Haematol 2018; 181: 38.
71) Ansuinelli M, Vitale A, Pecoraro G, Capria S, Trisolini SM, Minotti C, Cartoni C, Testi AM, Moleti ML, Iori AP, Barberi W, Starza ID, Elia L, Mancini F, De Propris MS, Guarini A, Chiaretti S, Foa R. Role of blinatumomab in minimal residual disease and hematologic relapsed/refractory adult acute lymphoblastic leukemia patients treated over 5 years. A single center experience. Blood Conf 61st Ann ASH 2019; 134.
72) Boissel N, Bassan R, Ribera JM, Chiaretti S, Foa R, Papayannidis C, Alam N, Brescianini A, Pezzani I, Kreuzbauer G, Rambaldi A. Treatment of adults with minimal residual disease (MRD) positive acute lymphoblastic leukemia with blinatumomab in a real-world setting: Results from the neuf study. Blood Conf 61st Ann ASH 2019; 134.
73) Boissel N, Ribera JM, Chiaretti S, Rambaldi A, Bassan R, Papayannidis C, Alam N, Brescianini A, Pezzani I, Kreuzbauer G, Foa R. Treatment of adults with relapsed/refractory philadelphia chromosome negative acute lymphoblastic leukemia with blinatumomab in a real-world setting: results from the NEUF study. Blood Conf 61st Ann ASH 2019; 134.
74) Isufi I, Seropian SE, Cooper DL, Roberts K, Wilson LD, Girardi M, Perreault S, Foss FM. Reduced intensity conditioning with pentostatin and low-dose tbi in patients with relapsed hematologic malignancies. Biol Blood Marrow TR 2018; 24 (3 Supplement 1): S307.
75) Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, Wei A, Dombret H, Foa R, Bassan R, Arslan O, Sanz MA, Bergeron J, Demirkan F, Lech-Maranda E, Rambaldi A, Thomas X, Horst HA, Bruggemann M, Klapper W, Wood BL, Fleishman A, Nagorsen D, Holland C, Zimmerman Z, Topp MS. Blinatumomab *vs.* chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017; 376: 836-847.
76) Jain N, Graham C, Konopleva M, Yallop D, Jozwik A, Patten P, Ellard R, Stewart O, Cuthill K, Potter V, Kassam S, Devereux S, Pagliuca A, Mufti G, Kantarjian H, Jabbour E, Zinai A, Dupouy S, Balandraud S, Poirot C, Philippe A, Simon F, Konto C, Bermingham C, Benjamin R. UCART19, an allogeneic anti-CD19 car T-cell product, in high risk adult patients with CD19+ relapsed/refractory B-cell acute lymphoblastic leukemia: Preliminary results of phase i calm study. HemaSphere 2018; 2 (Supplement 2): 43.
77) Park JH, Riviere I, Wang X, Bernal Y, Purdon T, Halton E, Curran KJ, Sauter CS, Sadelain M, Brentjens RJ. Efficacy and safety of CD19-targeted 19-28z CAR modified T cells in adult patients with relapsed or refractory B-ALL. J Clin Oncol Conf 2015; 33.
78) Stein AS, Topp MS, Gokbuget N, Bargou RC, Dombret H, Larson RA, Rambaldi A, Schiller GJ, Zugmaier G, Sterling L, Benjamin J, Kantarjian H, Forman SJ. Outcomes of hematopoietic stem cell transplantation (HSCT) among adults with relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL) achieving remission with blinatumomab. Biol Blood Marrow TR 2016; 22: S35-S36.