SUPPLEMENTARY APPENDIX

A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia

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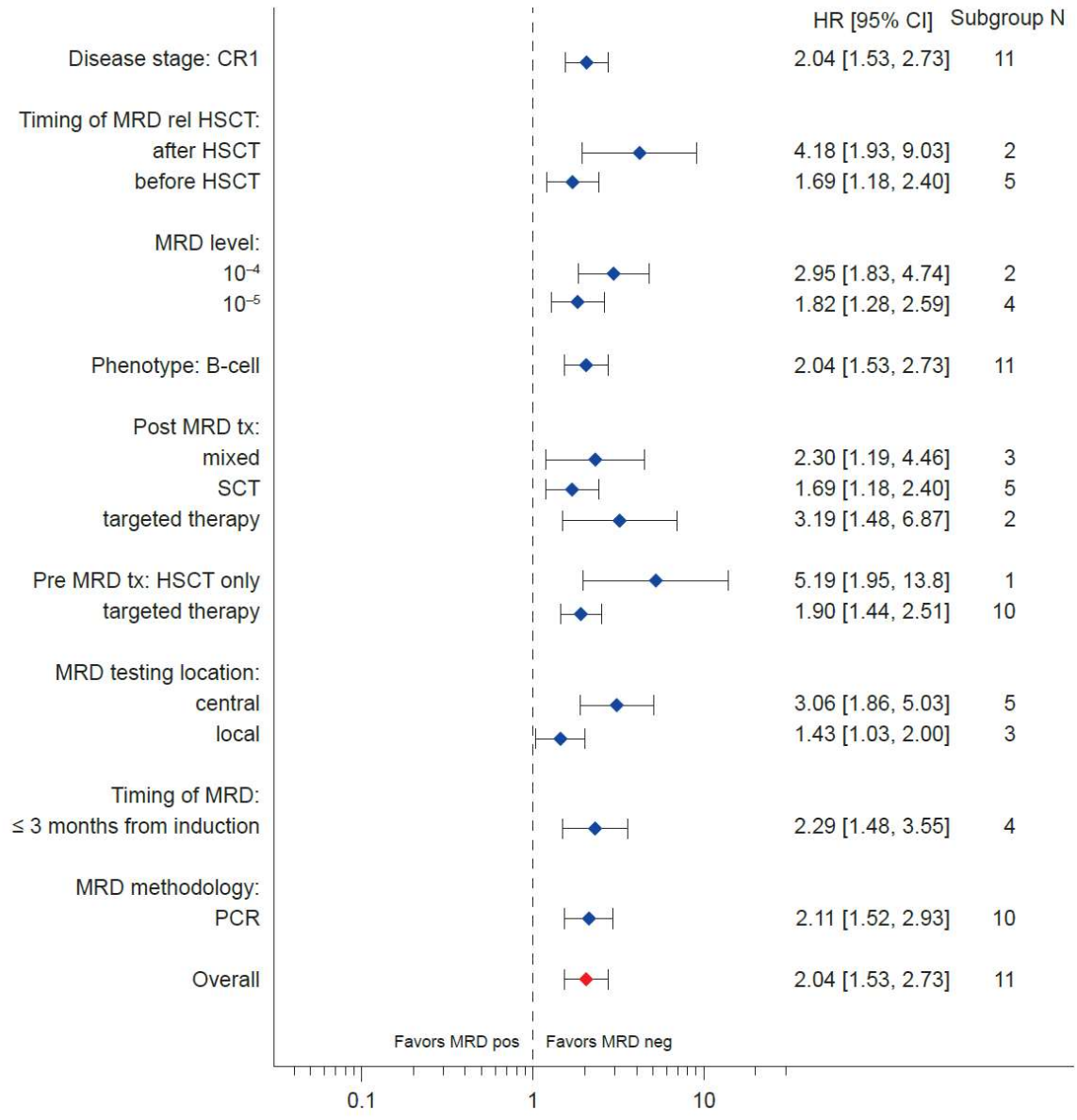
Contents

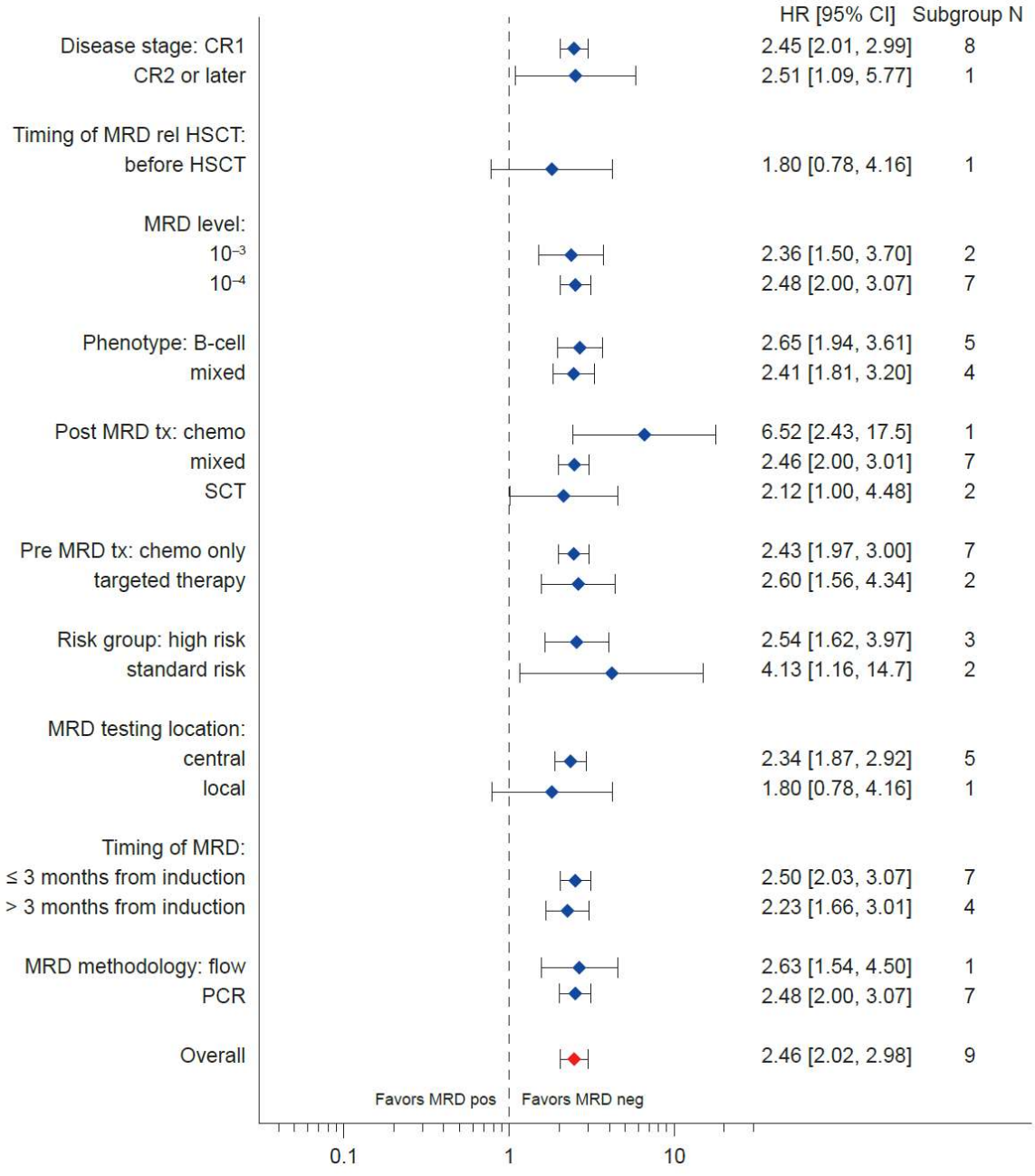
Supplementary Figures

Supplementary Figure 1a. Forest plot: random effects relapse-free survival hazard ratios for Philadelphia chromosome-positive acute lymphoblastic leukemia by subgroup (MRD-positive status vs MRD-negative status).



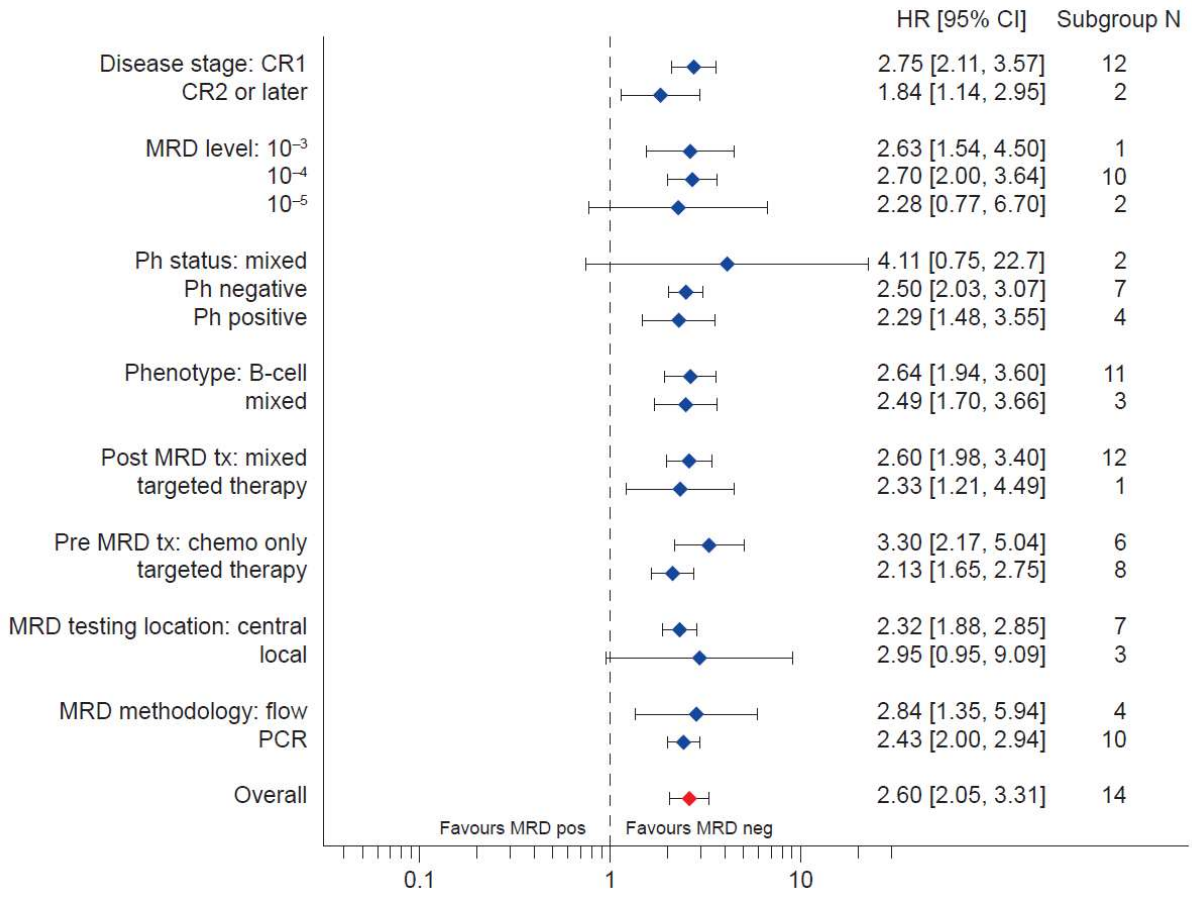
CI, confidence interval; CR1, first complete remission; HR, hazard ratio; HSCT, hematological stem-cell transplantation; MRD, minimal residual disease; MRD neg, minimal residual disease-negative status; MRD pos, minimal residual disease-positive status; N, number of studies; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; SCT, stem cell transplantation; targeted, targeted agent (eg, tyrosine kinase inhibitor, blinatumomab, inotuzumab); tx, treatment.

Supplementary Figure 1b. Forest plot: random effects relapse-free survival hazard ratios for Philadelphia chromosome-negative acute lymphoblastic leukemia by subgroup (MRD-positive status vs MRD-negative status).



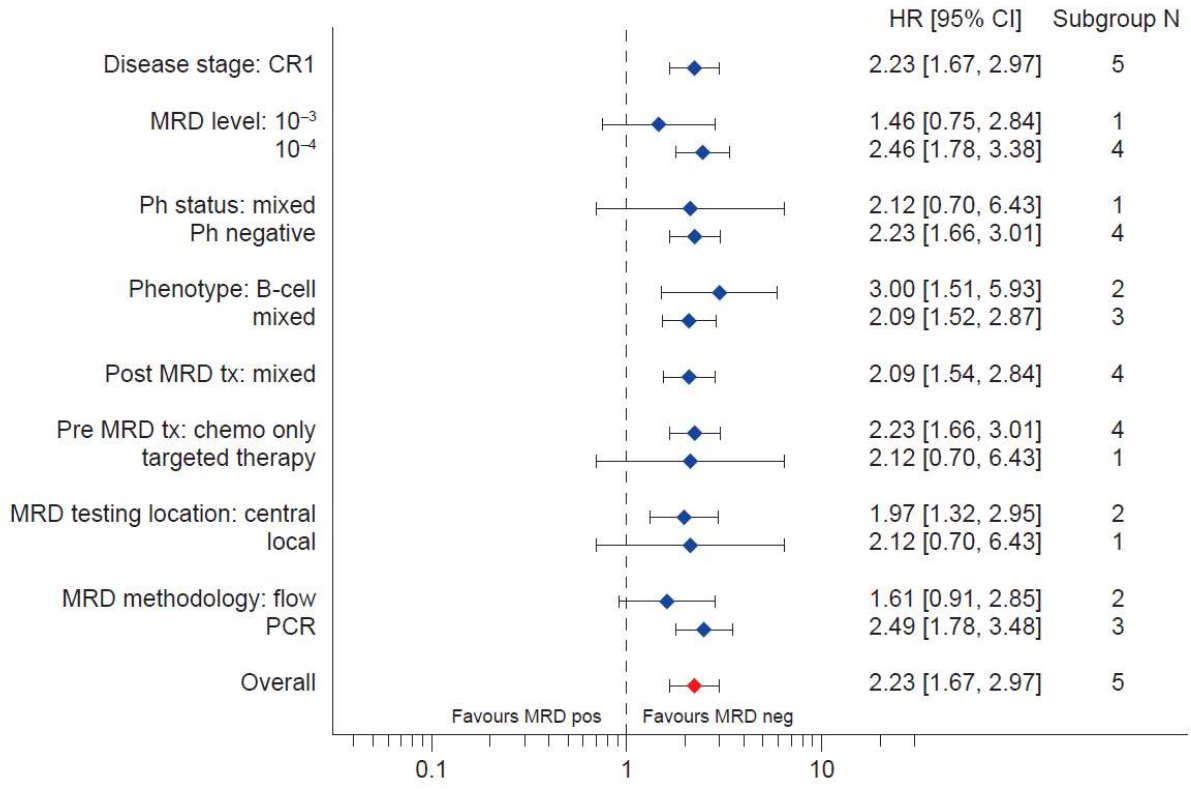
CI, confidence interval; Chemo, chemotherapy; CR1, first complete remission; CR2, second complete remission; Flow, flow cytometry; HR, hazard ratio; HSCT, hematological stem-cell transplantation; MRD, minimal residual disease; MRD neg, minimal residual disease-negative status; MRD pos, minimal residual disease-positive status; N, number of studies; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; SCT, stem cell transplantation; targeted, targeted agent (eg, tyrosine kinase inhibitor, blinatumomab, inotuzumab); tx, treatment.

Supplementary Figure 2a. Forest plot: random effects relapse-free survival hazard ratios for timing of MRD ≤ 3 months from induction (MRD-positive status vs MRD-negative status).



CI, confidence interval; Chemo, chemotherapy; CR1, first complete remission; CR2, second complete remission; Flow, flow cytometry; HR, hazard ratio; MRD, minimal residual disease; MRD neg, minimal residual disease-negative status; MRD pos, minimal residual disease-positive status; N, number of studies; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; targeted, targeted agent (eg, tyrosine kinase inhibitor, blinatumomab, inotuzumab); tx, treatment.

Supplementary Figure 2b. Forest plot: random effects relapse-free survival hazard ratios for timing of MRD > 3 months from induction (MRD-positive status vs MRD-negative status).



CI, confidence interval; Chemo, chemotherapy; CR1, first complete remission; Flow, flow cytometry; HR, hazard ratio; MRD, minimal residual disease; MRD neg, minimal residual disease-negative status; MRD pos, minimal residual disease-positive status; N, number of studies; PCR, polymerase chain reaction; Ph, Philadelphia chromosome; targeted, targeted agent (eg, tyrosine kinase inhibitor, blinatumomab, inotuzumab); tx, treatment.

Supplementary Tables

Supplementary Table 1. Search terms used for the systematic literature searches.

Database/ source	Search terms
Embase	
1	Acute lymphoblastic leukemia.mp. or acute lymphoblastic leukemia/
2	Acute lymphoblastic leukaemia.mp.
3	Acute lymphocytic leukemia.mp. or acute lymphoblastic leukemia/
4	Acute lymphocytic leukaemia.mp.
5	Minimal residual disease.mp. or minimal residual disease/
6	1 or 2
7	3 or 4
8	6 or 7
9	5 and 8
10	Limit 9 to (human and English language and ed=19950101-20150301)
11	Limit 10 to article
PubMed[a]	
	((("Acute lymphoblastic leukemia"[All Fields] OR "acute lymphoblastic leukaemia"[All Fields]) OR "acute lymphocytic leukemia"[All Fields]) OR "acute lymphocytic leukaemia"[All Fields]) AND "minimal residual disease"[All Fields]
Congresses	
	Minimal residual disease
	MRD
	Acute lymphoblastic leukemia (leukaemia)
	Acute lymphocytic leukemia (leukaemia)

[a]Searches were limited to English language and humans, published between 1 January 1995 and 1 March 2016.

Supplementary Table 2. Study characteristics: acute lymphoblastic leukemia in first complete remission.

Study	Design/location	Treatment protocol	HSCT	MRD methodology and definitions	Time points of MRD testing used for assessments of survival outcomes
Philadelphia chromosome status: negative					
NILG-ALL 09/00 trial Bassan *et al.* (2014)[1]	Prospective; Italy	Chemotherapy (patients who were CD20+ could receive rituximab)	Allogeneic/ autologous	PCR for ≥ 1 MRD probes MRD−: < 10^{-4} PCR signal	Weeks 16 and 22 after initiation of induction/consolidation
GRAALL 2003 and 2005 trials Beldjord *et al.* (2014)[2]	Phase 2 (GRAALL 2003) and Phase 3 (GRAALL 2005); prospective; multicenter; France	Chemotherapy	Allogeneic (administered in first CR)	qRT PCR for ≥ 2 *Ig*/*T-cell receptor* gene rearrangements; bone marrow samples assessed in a central reference laboratory MRD−: < 10^{-4} MRD+: ≥ 10^{-4}	6 weeks after induction therapy initiation
GRAALL 2003 and 2005 trials Dhèdin *et al.* (2015)[3]	Phase 2 (GRAALL 2003) and Phase 3 (GRAALL 2005); retrospective analysis of prospective MRD data; multicenter; Europe	Chemotherapy	Allogeneic (planned after 3 or 6 blocks of consolidation); some patients received UBCT	qRT PCR for ≥ 2 *Ig/T-cell receptor* gene rearrangements; bone marrow samples assessed in a central reference laboratory; sensitivity ≥ 10^{-4}	6 weeks after induction therapy initiation
GMALL 06/99 and 07/03 trials Gökbuget *et al.* (2012)[4]	Retrospective analysis of prospective MRD data; multicenter; Germany	Chemotherapy	Allogeneic (high-risk patients)	qRT PCR for leukemia-specific *Ig/T-cell receptor* gene rearrangements; assessed in a central laboratory Molecular CR: MRD− with assay sensitivity of ≥ 10^{-4}	Before consolidation (Day 71) and after first consolidation at Week 16
PALG ALL 4-2002 trial Holowiecki *et al.* (2008)[5]	Prospective; multicenter; Poland	Chemotherapy	Allogeneic or autologous (high-risk patients)	MFC; assessed at a central laboratory MRD+ defined as expression of ≥ 2 aberrant phenotypes on > 50% leukemic blasts; > 0.1% used as cut-off point	At end of induction and end of consolidation
NILG 09-2000 trial Mannelli *et al.* (2012)[6]	Prospective; Italy	Chemotherapy	Allogeneic (high-risk patients)	qRT PCR for *BCR-ABL* or *Ig* MRD−: < 10^{-4} at Week 16 and negative at Week 22	Weeks 16 and 22 after treatment initiation
UKALL XII trial Mortuza *et al.* (2002)[7]	Prospective; UK	Chemotherapy	Allogeneic (for patients with available donor) or autologous	PCR, α-^{32}P dCTP PCR and ASO PCR MRD+: 1–5 leukemic cells in 10^2–10^3 normal cells	After treatment initiation: 0–2 months; 3–5 months; 6–9 months and 10–24 months
UKALL XII/ ECOG2993 trial Patel *et al.* (2010)[8]	Prospective; multicenter; UK	Chemotherapy	Allogeneic or autologous	qRT PCR for rearrangements in *Ig*/*T-cell receptor* genes among others, ASO PCR MRD−: qRT PCR < 10^{-4}	After Phase 1 and 2 induction and after intensification Some patients had further samples taken at 28 and

Study	Design/location	Treatment protocol	HSCT	MRD methodology and definitions	Time points of MRD testing used for assessments of survival outcomes
					39 weeks from start of treatment and every 6 months thereafter during maintenance
Salah-Eldin *et al.* (2014)[9] Salah-Eldin *et al.* (2014)[10]	Prospective; Egypt	Chemotherapy	None	qRT PCR for rearrangements in *Ig* genes Molecular CR: MRD− (assay sensitivity of ≥ 10^{-3})	After induction and after consolidation
Thomas *et al*. (2012)[11]	Prospective; USA	Chemotherapy + rituximab for patients who were CD20+	None	MFC	Assessed at CR
NILG 10/07 trial Bassan *et al.* (2014)[12]	Pilot study; prospective; Italy	Chemotherapy	Allogeneic (early HSCT for high-risk patients; administered postconsolidation for MRD+ patients) Autologous if allogeneic not feasible	PCR MRD−: < 10^{-4}	Week 10 after initiation of treatment
BLAST Gökbuget *et al.* (2015)[a,13]	Phase 2; prospective; Europe	Blinatumomab	HSCT	PCR (per EuroMRD guidelines) MRD response defined as no PCR amplification at a sensitivity of 10^{-4} or < 10^{-4} leukemic cells; MRD assessed at central reference laboratory	Within the first 2 treatment cycles
Joint analysis of EWALL Giebel *et al*. (2010)[14]	Retrospective; multicenter; pooled analysis; Europe	Chemotherapy	Allogeneic or autologous	MFC or PCR-based MRD−: < 0.1% of bone marrow cells	Measured before HSCT
Philadelphia chromosome status: positive					
NILG 09/00 and 10/07 trial Lussana *et al.* (2016)[15]	Phase 2; pooled analysis of prospective trials; Italy	Chemotherapy + imatinib	Allogeneic (administered in first CR)	qRT PCR; MRD− defined as *BCR-ABL/ABL* < 1 x10^{-5}	Before HSCT
GIMEMA 1509 trial Chiaretti *et al.* (2015)[16]	Phase 2; prospective; multicenter; Italy	Chemotherapy + dasatinib	Allogeneic in some MRD+ patients (administered at CRh)	Molecular testing for *BCR-ABL1*	Day 85 after treatment initiation
Ravandi *et al*. (2015)[a,17]	Phase 2; prospective; multicenter; USA	Chemotherapy + dasatinib	Allogeneic (administered in first CR)	qRT PCR for *BCR-ABL*	"At defined intervals" after treatment initiation

Study	Design/location	Treatment protocol	HSCT	MRD methodology and definitions	Time points of MRD testing used for assessments of survival outcomes
Nishiwaki *et al.* (2016)[18]	Retrospective; Japan	Chemotherapy + imatinib or dasatinib	Allogeneic	qRT PCR MRD−: < 10^{-5}	Within 30 days prior to HSCT
Bachanova *et al.* (2014)[19]	Retrospective; multicenter; matched-pair analysis of registry data; international	Chemotherapy +imatinib, nilotinib or dasatinib	Allogeneic (all patients)	*BCR-ABL* transcript levels or FISH analysis Stringency and sensitivity could not be determined in this analysis	Pre-HSCT
Kim *et al*. (2015)[20]	Prospective; Phase 2; multicenter; Korea	Chemotherapy + nilotinib	Allogeneic	qRT PCR for *BCR-ABL* expression (sensitivity 10^{-5}); measured at the central reference laboratory MRD−: *BCR-ABL*:G6PDH ratio < 10^{-5}	Every 3 months from CRh until end of maintenance therapy. For those who received HSCT, MRD was evaluated within 1 month of the start of conditioning and every 3 months thereafter
Lee *et al* (2012)[21]	Retrospective; single-center; Korea	Chemotherapy + imatinib	Allogeneic	qRT PCR for *BCR-ABL* transcript; measured at a central reference laboratory MRD stratified by 4 groups after 2 courses of consolidation: 1. EMRs (persistent MRD− [*BCR-ABL:ABL* ratio ≤ 0.1%] or CR [undetectable *BCR-ABL*]) 2. LMRs (conversion to MRD− or CR by the end of consolidation) 3. IMRs (MRD levels of > 0.1–1%) 4. PMRs (MRD > 1%) Measured at a central reference laboratory	After 2 courses of chemotherapy, before HSCT
Kim *et al*. (2015)[22]	Prospective; single-center; Korea	Chemotherapy + imatinib	Allogeneic	qRT PCR for *BCR-ABL* transcript; measured at a central reference laboratory MRD stratified by 3 groups after 2 courses of consolidation: 1. EMRs (early and persistent MRD− [*BCR-ABL:ABL* ratio ≤ 0.1% or ≥ 3-log reduction in *BCR-ABL* transcript level from baseline]) 2. LMRs (conversion from MRD+ to MRD−) 3. PMRs (MRD+: MRD levels > 1% or < 3-log reduction in *BCR-ABL* transcript level from baseline)	After 2 courses of chemotherapy

Study	Design/location	Treatment protocol	HSCT	MRD methodology and definitions	Time points of MRD testing used for assessments of survival outcomes
Lee *et al*. (2009)[23]	Prospective; single-center; Korea	Chemotherapy + imatinib	Allogeneic	qRT PCR for *BCR-ABL* transcript (sensitivity 10^{-5})	At 4 weeks after initiation of imatinib therapy
Mizuta *et al*. (2012)[24]	Prospective; multicenter; Japan	Chemotherapy + imatinib	Allogeneic	qRT PCR for *BCR-ABL* transcript) (sensitivity 10^{-5}); measured at a central reference laboratory	Before and at HSCT
Ravandi *et al*. (2013)[25]	Prospective; single-center; USA	Chemotherapy + imatinib or dasatinib	None	MFC or qRT PCR for *BCR-ABL* transcript and IGH PCR	Not reported; median follow-up 1–501 weeks
Tucunduva *et al*. (2014)[26]	Retrospective registry-based analysis; multicenter; multicountry	Some patients received imatinib ± dasatinib; TKI was not specified in some patients	UCBT	Qualitative or quantitative RT PCR (sensitivity 10^{-2} to 10^{-5}) or flow cytometry (sensitivity 10^{-4}); measured at local reference laboratory	Before UCBT
Yanada *et al*. (2008)[27]	Prospective; multicenter; Phase 2; Japan	Chemotherapy + imatinib	Allogeneic	qRT PCR (sensitivity 10^{-5}); measured at a central reference laboratory MRD−: no detectable *BCR-ABL* Low MRD: < 50 copies *BCR-ABL*/μg	End of induction (Days 28 and 63 [only Day 63 for RFS analysis]) and after each consolidation cycle
Wetzler *et al*. (2014)[28]	Prospective; multicenter; USA	Chemotherapy + imatinib	Allogeneic or autologous	qRT PCR; measured at a central reference laboratory	Day 120 following HSCT
Chalandon *et al*. (2012)[29]	Prospective; multicenter; multicountry	Chemotherapy + imatinib	Allogeneic or autologous	qRT PCR; measured at a central reference laboratory	After Cycle 1 and Cycle 2
Kuang *et al*. (2013)[30]	Prospective; multicenter; China	Chemotherapy + imatinib	Allogeneic	*BCR-ABL* fusion gene quantification	6 months of postinduction therapy
Lee *et al*. (2012)[31]	Prospective; Phase 2; Korea	Chemotherapy + imatinib	Allogeneic	qRT PCR for *BCR-ABL* transcript; measured at a central reference laboratory	After Cycle 1 and Cycle 2
Hohtari et al (2016)[32]	Retrospective; multicenter; Finland	Chemotherapy +/- imatinib or dasatinib	Allogeneic	qRT PCR for *BCR-ABL* transcript	At 3 months after initiation of TKI treatment
Lim *et al.* (2016)[33]	Prospective; single-center; Korea	Chemotherapy + imatinib	Allogeneic	qRT PCR for *BCR-ABL* transcript; measured at a central reference laboratory MRD−: < 10^{-5}	Time of diagnosis; at CR and every 3 months thereafter
Short *et al.* (2016)[34]	Prospective; multicenter; USA	Chemotherapy + TKI	None	qRT PCR for *BCR-ABL* transcript MRD−: < 10^{-4}	At CR and every 3 months thereafter
Wassmann *et al*. (2005)[35]	Prospective; multicenter; Germany	Imatinib after SCT	Allogeneic or autologous	qRT PCR; assessed at central reference laboratory	After imatinib treatment initiation, following SCT
Yoon *et al.* (2016)[36]	Prospective; single-center; Korea	Chemotherapy + TKI	Allogeneic	qRT PCR for *BCR-ABL* transcript; measured at a central reference laboratory MRD−: < 10^{-4}	During TKI-based chemotherapy, before HSCT
Philadelphia chromosome status: mixed					
Short *et al.* (2015)[37] Short *et al.* (2016)[38]	Prospective; USA	Chemotherapy ± TKI (imatinib, dasatinib or ponatinib) or ± rituximab, ofatumumab or inotuzumab	HSCT (type not specified)	MFC (4- or 6-color); sensitivity 0.001%	At the time of CR

Study	Design/location	Treatment protocol	HSCT	MRD methodology and definitions	Time points of MRD testing used for assessments of survival outcomes
Ravandi *et al.* (2016)[39]	Retrospective; USA	Chemotherapy ± imatinib, dasatinib ± rituximab, ponatinib ± rituximab, or ofatumumab	Allogeneic	MFC (4-color); aberrant expression of ≥ 2 antigens required for assignment of MRD+; sensitivity 0.01%	At first CR, and at 3 and 6 months after treatment initiation
Study 202 Topp *et al.* (2011)[40] Topp *et al.* (2012)[41]	Phase 2; Prospective; open-label; multicenter; Europe	Blinatumomab	Allogeneic (if donor available; administered any time after first cycle)	qRT PCR for clonally rearranged *Ig/T-cell receptor* genes, *BCR-ABL* or *MLL-AF4* translocation; sensitivity ≥ 10^{-4} MRD response defined as achieving MRD− within 4 cycles of treatment	After each treatment cycle
Weng *et al.* (2013)[42] Weng *et al.* (2012)[43]	Prospective; single-center; China	Induction and consolidation (other details not reported)	Allogeneic	Flow cytometry (8-color) with validation by qRT PCR for *BCR-ABL* fusion gene MRD−: < 10^{-4}	At the end of induction of CR and after Cycle 1 of consolidation

[a]35% of patients were treated in second or later CR.

ABL, *Abelson*; ALL, acute lymphoblastic leukemia; ASO PCR, allele-specific oligonucleotide polymerase chain reaction; *BCR-ABL*, *breakpoint cluster region–Abelson*; BLAST, Confirmatory Phase II Study of Blinatumomab (MT103) in Patients With Minimal Residual Disease of B-precursor Acute Lymphoblastic Leukemia; BM, bone marrow; CMR, complete molecular response; CR, complete remission; CRh, complete hematological remission; dCTP, deoxycytidine triphosphate; EMR, early molecular responder; EuroMRD, European Study Group on MRD detection in ALL; EWALL, European Study Group for Adult ALL; FISH, fluorescent *in-situ* hybridisation; G6PDH, glucose-6-phosphase dehydrogenase; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; GMALL, German Multicenter Study Group for Adult Acute Lymphocytic Leukemia; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; GRAAPH, Group for Research on Adult Acute Lymphoblastic Leukemia Ph+; HSCT, hematological stem cell transplantation; Ig, immunoglobulin; IGH, immunoglobulin heavy chain; IMR, intermediate molecular responder; LMR, late molecular responder; MFC, multiparametric flow cytometry; MMR, major molecular response; MRD, minimal residual disease; MRD−, minimal residual disease negative; MRD+, minimal residual disease positive; NILG, Northern Italy Leukemia Group; NR, not reported; PD, progressive disease; PALG, Polish Adult Leukemia Group; PMR, poor molecular responder; qRT PCR, quantitative reverse transcription polymerase chain reaction; RFS, relapse-free survival; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor; UCBT, umbilical cord blood transplantation; UKALL, United Kingdom Acute Lymphoblastic Leukemia.

Supplementary Table 3. Study characteristics: acute lymphoblastic leukemia in second, or later, complete remission.

Study	Design/location	Treatment protocol	HSCT	MRD methodology	Time points of MRD testing used for assessments of survival outcomes
Philadelphia chromosome status: negative					
Gökbuget *et al.* (2014)[44]	Phase 2; prospective; multicenter; Europe	Blinatumomab	–	ASO qRT PCR MRD response defined as no PCR amplification at a sensitivity of 10^{-4} or < 10^{-4} leukemic cells; MRD assessed at central reference laboratory	Within the first 2 treatment cycles
Philadelphia chromosome status: positive					
Wassmann *et al.* (2003)[45]	Prospective; single-center; Germany	Imatinib + IFN-α	Study conducted in patients who were ineligible for HSCT	qRT PCR (sensitivity 10^{-5})	–
DeBoer *et al.* (2014)[46] DeBoer *et al.* (2016)[47]	Phase 2; prospective; multicenter; USA	Chemotherapy + imatinib	Allogeneic or autologous	*ABL1* kinase mutations: direct sequencing and mutation-specific qRT PCR assays if a mutation was present	At Day 120
Philadelphia chromosome status: mixed					
Park *et al.* (2015)[48]	Phase 1; prospective; USA	Chemotherapy + CART cells	Allogeneic	MFC; MRD defined as < 5% blasts in bone marrow	Days 14–28
Kantarjian *et al.* (2016)[49]	Phase 3; prospective	Inotuzumab ozogamicin or standard therapy (FLAG or cytarabine plus mitoxantrone or high-dose cytarabine)	–	Multicolor MFC MRD defined as 0.01% bone marrow blasts	At screening; between days 16 and 28 of cycles 1– 3 and every 1 to 2 cycles thereafter; at the end-of-treatment visit; during planned follow-up visits; and as clinically indicated
Study 206 Topp *et al.* (2014)[50] Zugmaier *et al.* (2015)[51]	Phase 2; prospective; multicenter; open-label; single-arm; Germany	Blinatumomab	Allogeneic (if patients achieved CR or CRh)	qRT PCR for clonally rearranged *Ig/T-cell receptor* genes; assessed at central reference laboratory MRD response defined as < 10^{-4} detectable blasts of nucleated cells	Assessed on Day 29 of each cycle
Philadelphia chromosome status: not reported					
Jabbour *et al.* (2017)[52]	Retrospective; single-center; USA	Blinatumomab, inotuzumab ozogamicin, or hyper-CVAD + inotuzumab ozogamicin	HSCT (type not specified)	MFC (6-color) MRD−: < 10^{-4}	At time of achievement of CR/CRp/CRi, at approximately 4 weeks and every 2 cycles of therapy
Park *et al.* (2016)[53]	Phase 1; prospective; single-center	Chemotherapy + CART cells	HSCT (type not specified)	Bone marrow blast % MRD defined as < 5% blasts	Immediately before treatment
Yilmaz *et al.* (2015)[54]	Prospective; USA	Inotuzumab ozogamicin ± chemotherapy or blinatumomab	Allogeneic	MFC (6-color); MRD sensitivity 0.01%	At response to salvage therapy

ALL, acute lymphoblastic leukemia; ASO PCR, allele-specific oligonucleotide polymerase chain reaction; *BCR-ABL*, *breakpoint cluster region–Abelson*; CART, chimeric antigen receptor T-cell; CR, complete remission; CRh, complete hematological remission; CRi, complete remission with inadequate count recovery; CRp, complete remission with inadequate

platelet recovery; (hyper)-CVAD, (hyper-fractionated) cyclophosphamide, vincristine, Adriamycin, dexamethasone; FLAG, fludarabine, cytarabine, and granulocyte colony-stimulating factor; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; HSCT, hematological stem-cell transplantation;; IFN-α, interferon-α; Ig, immunoglobulin; MFC, multiparametric flow cytometry; *MLL-AF4*, myeloid/lymphoid or mixed-lineage leukemia-ALL-1 fused gene on chromosome 4; MRD, minimal residual disease; PCR, polymerase chain reaction; qRT PCR, quantitative reverse transcription polymerase chain reaction; RFS, relapse-free survival.

Supplementary Table 4. Patient characteristics: acute lymphoblastic leukemia in first complete remission.

Study	Total number of patients	Number eligible for MRD test/MRD data available	Number of patients receiving HSCT after MRD test	B-ALL or T-ALL	Philadelphia chromosome status	Standard/high risk
Philadelphia chromosome status: negative						
NILG-ALL 09/00 trial Bassan *et al.* (2014)[1]	304	141 (98 included in the analysis)	43 of 60 MRD+ patients	Mixed	Ph−	Mixed
GRAALL 2003 and 2005 trials Beldjord *et al.* (2014)[2]	860	423[a]	158[a]	Mixed B-ALL: 260 (62%) T-ALL: 163 (39%)	Ph−	Mixed High risk: 273 (65%)
GRAALL 2003 and 2005 trials Dhèdin *et al.* (2015)[3]	522[b]	278[b]	282[b] (13 received UBCT HSCT)	Mixed B-ALL: 343 (66%) T-ALL: 179 (34%)	Ph−	High risk
GMALL 06/99 and 07/03 trials Gökbuget *et al.* (2012)[4]	1648	580	57/120 MRD+ patients All "high-risk" patients were candidates for allogeneic SCT. In GMALL 07/03, patients in the standard-risk group with persistent MRD >10^{-4} until week 16 were candidates for transplantation in first CR	Mixed B-ALL: 1076 (65%) T-ALL: 569 (35%)	Ph−	Mixed High risk: 975 (59%) Standard risk: 673 (41%)
PALG ALL 4-2002 trial Holowiecki *et al.* (2008)[5]	131	116	62/131	Mixed B-ALL: 87 (75%) T-ALL: 29 (25%)	Ph−	Mixed High risk: 82 (71.7%) Standard risk: 34 (29.3%)
NILG 09-2000 trial Mannelli *et al.* (2012)[6]	172	172	27/38 MRD+ patients	B-ALL	Ph−	Mixed High risk: 51 (29.7%) Standard risk: 121 (70.3%)
UKALL XII trial Mortuza *et al*. (2002)[7]	110	85	35	B-ALL	Ph−	–
UKALL XII/ECOG2993 trial Patel *et al.* (2010)[8]	161	161	65	Non-T lineage B-ALL: 97% Mixed phenotype: 3%	Ph−	Mixed
Salah-Eldin *et al.* (2014)[9] Salah-Eldin *et al.* (2014)[10]	55	48	No HSCT	B-ALL	Ph−	Standard risk
Thomas *et al*. (2012)[11]	216	216	No HSCT	B-ALL	Ph−	–
NILG 10/07 trial Bassan *et al.* (2014)[12]	159	106[d] (those who achieved CR)	65[d]	Mixed B-ALL: 117 (74%) T-ALL: 42 (26%)	Ph−	Mixed High-risk B-ALL: 62 (53%) Standard-risk B-ALL: 55 (47%)
BLAST Gökbuget *et al.* (2015)[13]	116	112	90	B-ALL	Ph−	–
Joint analysis of EWALL Giebel *et al.* (2010)[14]	123[b]	123[b]	123[b]	Mixed B-ALL: 77 T-ALL: 46	Mixed Ph+: 16%	High risk

Study	Total number of patients	Number eligible for MRD test/MRD data available	Number of patients receiving HSCT after MRD test	B-ALL or T-ALL	Philadelphia chromosome status	Standard/high risk
Philadelphia chromosome status: positive						
NILG 09/00 and 10/07 trials Lussana *et al.* (2016)[15]	106	73	65	B-ALL[c]	Ph+	–
GIMEMA 1509 trial Chiaretti *et al.* (2015)[16]	63	60	60	B-ALL[c]	Ph+	–
Ravandi *et al.* (2015)[17]	97	19	Not reported	B-ALL[c]	Ph+	–
Nishiwaki *et al.* (2016)[18]	432	432	432	B-ALL[c]	Ph+	–
Bachanova *et al.* (2014)[19]	197	185	185	B-ALL[c]	Ph+	–
Kim *et al.* (2015)[20]	91	90	57/82 achieving CR	B-ALL[c]	Ph+	–
Lee *et al.* (2012)[21]	95	95	95	B-ALL[c]	Ph+	–
Kim *et al.* (2015)[22]	118	118	118	B-ALL[c]	Ph+	–
Lee *et al.* (2009)[23]	52	52	52	B-ALL[c]	Ph+	–
Mizuta *et al.* (2012)[24]	100	60	57	B-ALL[c]	Ph+	–
Ravandi *et al.* (2013)[25]	122	76	No HSCT	B-ALL[c]	Ph+	–
Tucunduva *et al.* (2014)[26]	98	98	98	B-ALL[c]	Ph+	–
Yanada *et al.* (2008)[27]	100	85	79	B-ALL[c]	Ph+	–
Wetzler *et al.* (2014)[28]	34	13	0	B-ALL[c]	Ph+	–
Chalandon *et al.* (2012)[29]	270	265	213 after Cycle 1; 205 after Cycle 2	B-ALL[c]	Ph+	–
Kuang *et al.* (2013)[30]	50	50	5	B-ALL[c]	Ph+	–
Lee *et al.* (2012)[31]	95	95	95	B-ALL[c]	Ph+	–
Hohtari et al. (2016)[32]	128	128	64	B-ALL[c]	Ph+	–
Lim *et al.* (2016)[33]	82	78	54	B-ALL[c]	Ph+	–
Short *et al.* (2016)[34]	202	122	0	B-ALL[c]	Ph+	–
Wassmann *et al.* (2005)[35]	27	27	17	B[a]	Ph+	–
Yoon *et al.* (2016)[36]	173	169	169	B-ALL[c]	Ph+	–
Philadelphia chromosome status: mixed						
Short *et al.* (2015)[37] Short *et al.* (2016)[38]	324[a]	272[a]	49/272	Mixed[d] B-ALL (90%) T-ALL (5%)	Mixed Ph+: 44%	–
Ravandi *et al.* (2016)[39]	340	260	40	B-ALL	Mixed Ph+: 43%	–
Study 202 Topp *et al.* (2011)[40]	21	20	8	B-ALL	–	–
Topp *et al.* (2012)[41]	21	20	9	B-ALL	Mixed	–
Weng *et al.* (2013)[42] Weng *et al.* (2012)[43]	125	106	33	B[c]	–	–

[a]Includes patients with B-ALL and T-ALL and Burkitt leukemia.

[b]Includes patients with B-ALL and T-ALL.

[c]Based on the assumption that Ph+ patients have B-ALL.
[d]Burkitt or Burkitt-like leukemia (4.8%).

ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BLAST, Confirmatory Phase II Study of Blinatumomab (MT103) in Patients With Minimal Residual Disease of B-precursor Acute Lymphoblastic Leukemia; EWALL, European Study Group for Adult ALL; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; HSCT, hematological stem-cell transplantation; MRD, minimal residual disease; MRD−, minimal residual disease negative; MRD+, minimal residual disease positive; NILG, Northern Italy Leukemia Group; PALG, Polish Adult Leukemia Group; Ph−, Philadelphia chromosome negative; Ph+, Philadelphia chromosome positive; SCT, stem cell transplantation; T-ALL, T-cell acute lymphoblastic leukemia; UCBT, umbilical cord blood transplantation; UKALL, United Kingdom Acute Lymphoblastic Leukemia.

Supplementary Table 5. Patient characteristics: acute lymphoblastic leukemia in second, or later, complete remission.

Study	Total number of patients	Number eligible for MRD test/MRD data available	Number of patients receiving HSCT after MRD test	B-ALL or T-ALL	Philadelphia chromosome status	Standard/high risk
Philadelphia chromosome status: negative						
Study 211 Gökbuget *et al.* (2014)[44]	189	73	Not reported	B	Ph−	Mixed
Philadelphia chromosome status: positive						
Wassmann *et al*. (2003)[45]	68	6	No HSCT	Mixed (pre-B-ALL; c-ALL)	Ph+	–
DeBoer *et al*. (2014)[46] DeBoer *et al.* (2016)[47]	99	20	20	B[a]	Ph+	–
Philadelphia chromosome status: mixed						
Park *et al.* (2015)[48]	44	35/43	12/36	B	Mixed; Ph+: 32%	Mixed
Study 206 Topp *et al.* (2014)[50]	36	36	13	B	Mixed; Ph+: 6%	Mixed
Zugmaier *et al.* (2015)[51]	36	25	4	B	Ph−	–
Philadelphia chromosome status: not reported						
Jabbour *et al.* (2017)[52]	78	78	42	B	–	–
Yilmaz *et al.* (2015)[54]	130	78	44	B	–	–

[a]Based on the assumption that most Ph+ patients have B-ALL.

B-ALL, B-cell acute lymphoblastic leukemia; c-ALL, common-type acute lymphoblastic leukemia; HSCT, hematological stem-cell transplantation; MRD, minimal residual disease; Ph−, Philadelphia chromosome negative; Ph+, Philadelphia chromosome positive; T-ALL, T-cell acute lymphoblastic leukemia.

Supplementary Table 6. Clinical outcomes: acute lymphoblastic leukemia in first complete remission.[a]

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
Philadelphia chromosome status: negative			
NILG-ALL 09/00 trial Bassan *et al.* (2014)[1]	CMR (MRD−) 64/136 (47%) MRD− (< 10^{-4}) 21/136 (15%) MRD+ (10^{-4}–< 10^{-3}) 17/136 (13%) MRD+ (≥ 10^{-3}) 34/136 (25%)	**Post-HSCT** Allogeneic HSCT: 26/60 MRD+ patients[b]; autologous HSCT: 17/60 MRD+ patients[b] Data shown for all evaluable patients (n = 136) *6-year OS* MRD−: 64% MRD+ (≥ 10^{-3}): 24%; $p < 0.0001$ *6-year DFS* MRD−: 73% MRD+ (≥ 10^{-3}): 15%; $p < 0.0001$ *6-year OS*[b] Allogeneic/autologous HSCT: MRD− (< 10^{-4})/MRD+ (10^{-4}–10^{-3}): 50% MRD+ (≥10^{-3}): 26%; $p = 0.02$ Allogeneic HSCT: MRD− (< 10^{-4})/MRD+ (10^{-4}–10^{-3}): 60% MRD+ (≥ 10^{-3}): 27%; $p = 0.08$ *6-year DFS*[b] Allogeneic/autologous HSCT: MRD− (< 10^{-4})/MRD+ (10^{-4}–10^{-3}): 46% MRD+ (≥ 10^{-3}): 16%; $p = 0.03$ Allogeneic HSCT: MRD− (< 10^{-4})/MRD+ (10^{-4}–10^{-3}): 60% MRD+ (≥ 10^{-3}): 18%; $p = 0.05$ *6-year relapse*[b] Allogeneic/autologous HSCT: MRD− (< 10^{-4})/MRD+ (10^{-4}–10^{-3}): 43% MRD+ (≥10^{-3}): 69%; $p = 0.16$ Allogeneic HSCT: MRD− (< 10^{-4})/MRD+ (10^{-4}–10^{-3}): 23% MRD+ (≥ 10^{-3}): 64%; $p = 0.09$	Posttransplantation 6-year DFS was improved following allogeneic vs autologous HSCT in patients who were MRD+ (42% vs 18%; $p = 0.035$), but was affected by postinduction MRD level Patients with posttransplantation MRD levels ≥10^{-3} may have worse transplantation outcomes than those with lower levels of MRD Patients with high postinduction MRD may represent a very high-risk subset that may require close MRD monitoring; reducing MRD levels prior to and following HSCT may be beneficial in such patients
GRAALL 2003 and 2005 trials Beldjord *et al.* (2014)[2]	CR after first induction cycle: 100%[b] MRD−: 196/423 (46%)[b] MRD− (< 10^{-4}): 69/423 (16%)[b] MRD+ (≥ 10^{-4}): 158/423 (37%)[b]	**Post-HSCT** Allogeneic HSCT: 107/260 patients Data shown are for all evaluable patients (n = 260) *Cause-specific CIR (MRD+ [≥ 10^{-4}] vs MRD−)*	MRD level is an independent predictor of outcomes and should be used for individual treatment stratification

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		HR 3.46 (95% CI: 2.00–6.00; $p < 0.001$) *Univariate analysis* *Cause-specific CIR* MRD+ (≥ 10^{-4}) vs MRD−: HR 3.07 (95% CI: 1.92–4.90; $p < 0.001$) *Multivariate analysis* *Cause-specific CIR* MRD+ (≥ 10^{-4}) vs MRD−: HR 2.49 (95% CI: 1.43–4.32); $p < 0.001$ *5-year CIR*[b] MRD−: 23% (95% CI: 17–31%) MRD− (< 10^{-4}): 31% (95% CI: 18–49%); $p = 0.24$ MRD+ (≥ 10^{-4}): 60% (95% CI: 48–73%)	MRD− (< 10^{-4}) response was a better predictor of relapse than earlier morphological response assessment MRD− was a significant predictor of higher CIR in patients with B cell ($p < 0.001$) and T-cell ($p = 0.017$) ALL Patients were classified as high-risk if they had MRD levels ≥ 10^{-4} (and/or high-risk oncogenetics)
GRAALL 2003 and 2005 trials Dhèdin *et al.* (2015)[3]	MRD threshold 10^{-3} at Week 6	**<u>Post-HSCT</u>** Allogeneic HSCT: 282/522 *3-year OS (HSCT vs no HSCT)* MRD−: HR 1.13 (95% CI: 0.61–2.11); $p = 0.050$ MRD+ or late CR: HR 0.43 (95% CI: 0.21–0.90) *3-year CIR (HSCT vs no HSCT)* MRD−: HR 0.55 (95% CI: 0.24–1.29); $p = 0.17$ MRD+ or late CR: HR 0.50 (95% CI: 0.24–1.06); $p = 0.099$ *3-year RFS (HSCT vs no HSCT)* MRD−: HR 1.34 (95% CI: 0.70–2.54); $p = 0.38$ MRD+ or late CR: HR 0.36 (95% CI: 0.18–0.73); $p = 0.004$ *Multivariate analysis* *MRD+: RFS* HR 0.27 (95% CI: 0.12–0.60); $p = 0.001$ Interaction between MRD+ and HSCT effect $p = 0.028$ *MRD+: RFS* HR 0.32 (95% CI: 0.14–0.76); $p = 0.01$ Interaction between MRD+ and HSCT effect $p = 0.12$	HSCT benefits patients who were MRD+ but not MRD– Early MRD response is the best and maybe a unique tool to optimally select patients who may benefit from HSCT Being MRD− was associated with significantly prolonged RFS ($p = 0.001$) and OS ($p = 0.048$) vs being MRD+
GMALL 06/99 and 07/03 trials[c] Gökbuget *et al.* (2012)[4]	Cytological CR at Day 71: 961/1076 (89%) Molecular CR (MRD−) at Day 71: 252/383 (66%) Molecular CR (MRD−) at Week 16: 299/383 (78%)	**<u>Pre-HSCT</u>** *5-year continuous CR*[b] MRD− (Day 71): 68% ± 3% MRD+ (Day 71): 26% ± 6%; $p < 0.0001$ MRD− (Week 16): 74% ± 3% MRD+ (Week 16): 12% ± 5%; $p < 0.0001$	Detectable MRD after induction and first consolidation was associated with an unfavorable prognosis, regardless of disease risk Patients who were MRD+ had significantly improved probabilities of continuous CR, DFS and OS if they received HSCT,

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
	Continuous CR[b] MRD− (Day 71): 70% ± 3% MRD+ (Day 71): 39% ± 5%; *p* <0.0001 MRD− (Week 16): 74% ± 3% MRD+ (Week 16): 35% ± 5%; *p* <0.0001	*5-year DFS*[b] MRD− (Day 71): 60% ± 3% MRD+ (Day 71): 20% ± 5%; *p* < 0.0001 MRD− (Week 16): 68% ± 3% MRD+ (Week 16): 10% ± 4%; *p* < 0.0001 *5-year OS*[b] MRD− (Day 71): 80% ± 3% MRD+ (Day 71): 36% ± 6%; *p* < 0.0001 MRD− (Week 16): 81% ± 3% MRD+ (Week 16): 33% ± 7%; *p* < 0.0001 **Post-HSCT** Allogeneic HSCT in MRD+: 56/120 (47%) Data shown for all evaluable patients (n = 580) *5-year continuous CR*[b] MRD− (Day 71): 70% ± 3% MRD+ (Day 71): 39% ± 5%; *p* < 0.0001 MRD− (Week 16): 74% ± 3% MRD+ (Week 16): 35% ± 5%; *p* < 0.0001 *5-year DFS*[b] MRD− (Day 71): 63% ± 3% MRD+ (Day 71): 31% ± 4%; *p* < 0.0001 MRD− (Week 16): 67% ± 3% MRD+ (Week 16): 25% ± 5%; *p* < 0.0001 *5-year OS*[b] MRD− (Day 71): 79% ± 3% MRD+ (Day 71): 47% ± 5%; *p* < 0.0001 MRD− (Week 16): 80% ± 3% MRD+ (Week 16): 42% ± 5%; *p* < 0.0001 With vs without HSCT *5-year continuous CR*[b] MRD+ (Week 16) with HSCT: 66% ± 7% MRD+ (Week 16) without HSCT: 12% ± 5%; *p* < 0.0001 *5-year DFS*[b] MRD+ (Week 16) with HSCT: 44% ± 8% MRD+ (Week 16) without HSCT: 11% ± 4%; *p* < 0.0001	compared with those who did not receive HSCT MRD was shown to directly correlate with clinical outcome, and was therefore suggested to be an appropriate endpoint for future clinical trials

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		5-year OS[b] MRD+ (Week 16) with HSCT: 54% ± 8% MRD+ (Week 16) without HSCT: 33% ± 7%; *p* = 0.06	
PALG ALL 4-2002 trial Holowiecki *et al*. (2008)[5]	CR after Cycle 1: 111/131 (85%) MRD+ after induction: 33% MRD+ after consolidation: 22%	**Pre-HSCT** *3-year LFS* *After induction* MRD−: 68% (95% CI: 54–82%) MRD+: 6% (95% CI: 0–18%); *p* < 0.0001 *After consolidation* MRD−: 53% (95% CI: 37–70%) MRD+: 29% (95% CI: 0–59%); *p* = 0.13 *After induction and consolidation* MRD−: 67% (95% CI: 51–82%) MRD+: 17% (95% CI: 0–35%); *p* = 0.002 *3-year CIR* *After induction* MRD−: 33% (95% CI: 11–35%) MRD+: 94% (95% CI: 82–100%); *p* < 0.0001 *After consolidation* MRD−: 40% (95% CI: 23–57%) MRD+: 71% (95% CI: 41–100%); *p* = 0.06 *After induction and consolidation* MRD−: 23% (95% CI: 65–100%) MRD+: 83% (95% CI: 65–100%); *p* = 0.002 *Univariate analysis*[b] *Association of factors with relapse rate* MRD+ after induction: RR 3.15 (95% CI: 1.75–5.64); *p* = 0.0001 MRD+ after consolidation: RR 1.68 (95% CI: 0.83–3.4); *p* = 0.17 MRD+ after induction and/or consolidation: RR 2.83 (95% CI: 1.51–5.33); *p* = 0.001 *Association of factors with LFS* MRD+ after induction: RR 2.63 (95% CI: 1.54–4.5); *p* = 0.0004 MRD+ after consolidation: RR 1.46 (95% CI: 0.75–2.82); *p* = 0.27 MRD+ after induction and/or consolidation: RR 2.39 (95% CI: 1.36–4.22); *p* = 0.003 *Multivariate analysis*[b] *Association of factors with relapse rate*	MRD evaluation by MFC is applicable for almost all adult patients with Ph− ALL MRD evaluation can be used to identify patients at high risk of relapse and who may benefit from treatment intensification Being MRD+ after induction was the strongest predictor of treatment failure

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		MRD+ after induction: RR 3.07 (95% CI: 1.71–5.51); *p* = 0.0002 *Association of factors with LFS* MRD+ after induction: RR 2.57 (95% CI: 1.5–4.39); *p* = 0.0006 **Post-HSCT** Allogeneic HSCT: 35/131 patients Autologous HSCT: 27/131 patients *3-year CIR after induction*[b] Autologous HSCT MRD−: 31% (95% CI: 6–56) MRD+: 91% (95% CI: 74–100%); *p* = 0.05 Allogeneic HSCT MRD−: 11% (95% CI: 0–22%) MRD+: 20% (95% CI: 0–55%); *p* = 0.27 *3-year LFS after induction*[b] Autologous HSCT MRD−: 58% (95% CI: 28–87%) MRD+: 9% (95% CI: 0–24%); *p* = 0.04 Allogeneic HSCT MRD–: 73% (95% CI: 55–90%) MRD+: 60% (95% CI: 17–100%); *p* = 0.47	
NILG 09-2000 trial Mannelli *et al.* (2012)[6]	Overall CR rate: 84% (n = 145) MRD− in patients with CD20 > 20% Week 10: 16/29 (55%) Week 16: 15/28 (54%) Week 22: 15/25 (60%) MRD− in patients with CD20 ≤ 20% Week 10: 29/64 (45%) Week 16: 37/60 (62%) Week 22: 36/61 (59%)	**Post-HSCT** Allogeneic HSCT: 27/38 (MRD+ patients) Data for all evaluable patients shown *Median OS (estimated)* CD20 > 20% MRD+: 21 months MRD: not reached CD20 ≤ 20% MRD+: 18 months MRD−: not reached	MRD is relevant for prognosis assessment
UKALL XII trial Mortuza *et al*. (2002)[7]	*Chemotherapy + autologous HSCT group* *0–2 months* *CCR* MRD−: 13/18 (72%) MRD+: 5/18 (28%) *Relapsed*	**Post-HSCT** Autologous HSCT: 16/35 Allogeneic HSCT: 19/35 Pooled data shown for patients who received autologous HSCT or chemotherapy (n = 35) *Multivariate analysis (effect of MRD status at different time points; Wald statistic shown)*	MRD is a strong predictor of outcomes in adults with B-ALL and becomes progressively more predictive with time, particularly during the first year of treatment For patients receiving autologous HSCT, but not allogeneic HSCT, clinical outcome

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
	MRD−: 6/18 (33%) MRD+: 12/18 (67%); *p* = 0.043 *3–5 months* *CCR* MRD−: 22/25 (88%) MRD+: 3/25 (12%) *Relapsed* MRD−: 7/23 (30%) MRD+: 16/23 (70%); *p* < 0.0001 *6–9 months* *CCR* MRD−: 13/13 (100%) MRD+: 0–13 (0%) *Relapsed* MRD−: 3/14 (21%) MRD+: 11/14 (79%); *p* < 0.0001 *10–24 months* *CCR* MRD−: 15/16 (94%) MRD+: 1/16 (6%) *Relapsed* MRD−: 5/10 (50%) MRD+: 5/10 (50%); *p* = 0.018	0–2 months: 6.159; *p* = 0.013 3–5 months: 10.082; *p* = 0.001 6–9 months: 9.308; *p* = 0.002 10–24 months: 4.280; *p* = 0.039 *DFS stabilized* *0–2 months* MRD−: 65% MRD+: 22%; *p* = 0.016 *3–5 months* MRD−: 74% MRD+: 11%; *p* <0.0001 *6–9 months* MRD−: 80% MRD+: 0%; *p* <0.0001 *Relative risk of relapse* *0–2 months* MRD−: 0.61 MRD+: 1.36; *p* = 0.16 *3–5 months* MRD−: 0.47 MRD+: 1.62; *p* < 0.0001 *6–9 months* MRD−: 0.36 MRD+: 1.92; *p* < 0.0001 *10–24 months* MRD−: 0.48 MRD+: 1.6; *p* = 0.0019	is linked to MRD status before transplantation
UKALL XII/ECOG2993 trial[c] Patel *et al.* (2010)[8]	–	**<u>Pre-HSCT</u>** *5-year RFS* *Postinduction 1* MRD−: 70% (95% CI: 55–83%) MRD+: 42% (95% CI: 23–61%); *p* = 0.07 *Postinduction 2* MRD−: 71% (95% CI: 58–85%) MRD+: 15% (95% CI: 0–40%); *p* = 0.002 *Postintensification* MRD−: 70% (95% CI: 55–86%) MRD+: 33% (95% CI: 8–59%); *p* = 0.02	MRD detection at the time of stem-cell collection or just before autologous HSCT, but not before allogeneic HSCT, was associated with a higher rate of treatment failure due to relapse MRD status in standard-risk patients was a strong adverse predictor for relapse

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		6–9 months MRD−: 76% (95% CI: 55–97%) MRD+: 33% (95% CI: 0–69%); *p* = 0.03 *9–24 months* MRD−: 77% (95% CI: 59–96%) MRD+: 0% *Relative risk of relapse (MRD+ vs MRD−)* *Postinduction 1* 2.13 (95% CI: 0.95–4.97); *p* = 0.07 *Postinduction 2* 8.95 (95% CI: 2.85–28.09); *p* = 0.002 *Postintensification* 3.65 (95% CI: 1.33–10.02); *p* = 0.02 *6–9 months* 5.27 (95% CI: 1.15–24.09); *p* = 0.03 *5-year risk of relapse* MRD−: 50% (95% CI: 46–54%) MRD+: 43% (95% CI: 34–51%); *p* = 0.07 **Post-HSCT** Autologous HSCT: 25/161 Allogeneic HSCT: 40/161 Data shown for all evaluable patients (n = 161) *5-year OS* MRD−: 51% (95% CI: 43–60%) MRD+: 43% (95% CI: 39–47%); *p* = 0.02 *5-year EFS* MRD−: 47% (95% CI: 39–55%) MRD+: 39% (95% CI: 35–43%); *p* = 0.007 *5-year risk of relapse* MRD−: 43% (95% CI: 34–51%) MRD+: 50% (95% CI: 46–54%); *p* = 0.07 *5-year RFS* MRD assessed prior to autologous HSCT; n = 25 MRD−: 77% (95% CI: 54–100%) MRD+: 25% (95% CI: 0–55%); *p* = 0.01 *5-year RFS*	

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		MRD assessed prior to allogeneic HSCT; n = 36 MRD−: 79% (95% CI: 61–97%) MRD+: 79% (95% CI: 52–100%); *p* > 0.1 *5-year EFS* MRD assessed prior to allogeneic HSCT; n = 36 MRD–: 50% (95% CI: 26–75%) MRD+: 52% (95% CI: 24–80%); *p* > 0.1	
Salah-Eldin *et al.* (2014)[9,c] Salah-Eldin *et al.* (2014)[10,c]	Cytological CR after induction: 92% Molecular CR after induction: 74% MRD− After induction: 74% After consolidation: 77%	**Pre-HSCT** *3-year relapse rate* *After induction* MRD−: 21% MRD+: 69%; *p* = 0.005 *3-year DFS* *After induction* MRD−: 79% MRD+: 31%; *p* = 0.001 *After consolidation* MRD−: 76% MRD+: 20%; *p* < 0.001 *3-year OS* *After induction* MRD−: 82% MRD+: 42%; *p* < 0.004 *After consolidation* MRD−: 83% MRD+: 30%; *p* < 0.0001	MRD+ status at the end of induction and consolidation was predictive of relapse and poor survival MRD quantification identified prognostic subgroups within the standard-risk Ph− patient population who may benefit from individualized treatment options
Thomas *et al*. (2012)[11]	–	–	MRD+ after induction was associated with a higher relapse rate and lower 3-year CR compared with being MRD– at the time of CR
NILG 10/07 trial Bassan *et al.* (2014)[12]	CR: 83% MRD−: 77/102 (72%)[a]	**Post-HSCT** Allogeneic HSCT[b]: 57/65 patients Autologous HSCT[b]: 8/65 patients Data shown for all evaluable patients (n = 106) *4-year DFS*[b] MRD−: 74% MRD+: 30%; *p* < 0.0001	HSCT treatment decision was based on MRD status and resulted in promising survival results
BLAST Gökbuget *et al.* (2015)[13]	All patients who achieved CR were evaluated	**Post-HSCT** HSCT: 90/116 patients Data shown for all evaluable patients (n = 112)	MRD was associated with longer OS and RFS, compared with no MRD response

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		Median OS MRD−: 40.4 months MRD+: 12.0 months; *p* = 0.001 *Median RFS (patients who were RFS after 45 days)* MRD−: 35.2 months (95% CI: 18.9 months–NR) MRD+: 7.1 months (95% CI: 3.1–15.0 months); *p* = 0.002 *Median DOR (patients with DOR ≥ 45 days)* MRD−: NR MRD+: 15.0 months; *p* = 0.015)	
Philadelphia chromosome status: positive			
NILG 09/00 and 10/07 trials Lussana *et al.* (2015)[55]	MRD− at conditioning: 24/65 (37%) MRD+ at conditioning: 41/65 (63%)	**Post-HSCT** Allogeneic HSCT: 72/72 patients MRD status before HSCT was available for 65/72 patients *5-year LFS* MRD−: 58% MRD+: 41%; *p* = 0.17 *5-year OS* MRD−: 58% MRD+: 49%; *p* = 0.55 *CIR* MRD−: 8% MRD+: 39%; *p* = 0.007	Patients who were MRD+ and underwent allogeneic HSCT showed a significant increased risk of relapse after transplant compared with those who were MRD−
GIMEMA 1509 trial Chiaretti *et al.* (2015)[16]	–	**Pre-HSCT** *DFS at Day 85* MRD−: 75% MRD+: 44%; *p* = 0.06	A better DFS was observed in patients who were MRD− compared with those who were MRD+
Ravandi *et al.* (2015)[17]	MRD− at first CR: 6/19 (32%) MRD+ at first CR: 13/19 (68%)	**Post-HSCT** Allogeneic HSCT: 41 (in first CR)/94 patients	There was no difference in RFS by the MRD status at CR (p = 0.52)
Nishiwaki *et al.* (2016)[18]	–	**Post-HSCT** Allogeneic HSCT: 432/432 patients Post-HSCT MRD data available for 388 patients *4-year LFS* MRD−: 60% MRD+: 46%; *p* = 0.0004 *4-year CIR* MRD−: 19% MRD+: 29%; *p* = 0.006	MRD− status at the time of allogeneic HSCT is one of the most important prognostic factors for survival for Ph− patients who received HSCT during first CR

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		LFS *Univariate analysis (MRD+ vs MRD−):* HR: 1.69 (95% CI: 1.28–2.24); *p* < 0.0001 *Multivariate analysis (MRD+ vs MRD−):* HR: 1.69 (95% CI: 1.27–2.24); *p* < 0.0001 *Relapse risk* *Univariate analysis (MRD+ vs MRD−):* HR: 1.18 (95% CI: 1.18–2.58); *p* = 0.006 *Multivariate analysis (MRD+ vs MRD−):* HR: 1.74 (95% CI: 1.18–2.58); *p* = 0.006 *OS* *Univariate analysis (MRD+ vs MRD−):* HR: 1.59 (95% CI: 1.17–2.16); *p* = 0.003 *Multivariate analysis (MRD+ vs MRD−):* HR: 1.58 (95% CI: 1.16–2.15); *p* = 0.003 For patients who received post-HSCT TKI (n = 103) *Multivariate analysis (MRD+ vs MRD−)* *LFS:* HR: 1.70 (95% CI: 1.22–2.35); *p* = 0.001 *Relapse:* HR : 1.52 (95% CI: 1.02–2.23); *p* = 0.05 *OS:* HR: 1.63 (95% CI: 1.16–2.32); *p* = 0.005 For patients aged < 55 years who underwent myeloablative conditioning (n = 324) *4-year LFS* MRD−: 65% MRD+: 48%; *p* = 0.0002 *4-year OS* MRD−: 72% MRD+: 58%; *p* = 0.002	
Bachanova *et al.* (2014)[19]	–	**Post-HSCT** Allogeneic HSCT: 197/197 patients; MRD status available for 185/197 *Multivariate analyses* *(MRD status pre-HSCT)* *OS* MRD− (reference): HR 1.00 MRD+: HR 0.94 (95% CI: 0.65–1.34); *p* = 0.71	Achieving MRD– status pre-HSCT may lead to low relapse rate and prolonged survival

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		DFS MRD− (reference): HR 1.00 MRD+: HR: 1.06 (95% CI: 0.75–1.48); *p* = 0.75 *Relapse* MRD− (reference): HR 1.00 MRD+: HR: 1.60 (95% CI: 0.96–2.67); *p* = 0.070 *3-year CIR* *RIC group* MRD−: 31% (95% CI: 15–50%) MRD+: 61% (95% CI: 45–76%); *p* = 0.070 *MAC group* MRD−: 21% (95% CI: 11–32%) MRD+: 35% (95% CI: 24–48%); *p* = 0.070	
Kim *et al.* (2015)[20]	CRh: 82/90 (91%) MRD−: 64% MRD+: 0%; *p* < 0.001	**Pre-HSCT** *Hematological relapse* *(MRD+ vs MRD−):* HR 6.3; *p* = 0.001 *2-year RFS* MRD−: 85% MRD+: 49% HR: 3.8; *p* = 0.024 **Post-HSCT** Allogeneic HSCT: 57/82 (63%) patients Data shown for all evaluable patients (n = 90) *Achievement of MRD−* With HSCT: 89% Without HSCT: 56% MRD− before allogeneic HSCT: 84% MRD– 3 months after allogeneic HSCT: 82%	MRD status just before allogeneic HSCT and at 3 months after allogeneic HSCT were predictive of 2-year RFS MRD status at early postremission was also predictive of RFS
Lee *et al.* (2012)[21]	MRD− (EMR): 33/95 (35%) MRD− (LMR): 35/95 (37%) MRD+ (IMR): 9/95 (10%) MRD+ (PMR): 18/95 (19%)	**Post-HSCT** Allogeneic HSCT: 95/95 patients *After first course of imatinib* *Univariate analysis* *5-year DFS* MRD−: 95% MRD+ (IMR): 69%; *p* = 0.0048 MRD+ (PMR): 30%; *p* = 0.001 *5-year CIR* MRD−: 5%	MRD monitoring is useful in identifying transplant patients at a high risk of relapse as there is a strong correlation between MRD status and long-term outcomes post-HSCT

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		MRD+ (PMR): 54%; *p* = 0.007 *After second course of imatinib* *Univariate analysis* *5-year DFS* MRD− (EMR): 88% MRD− (LMR): 64%; *p* = 0.043 MRD+ (IMR): 56%; *p* = 0.009 MRD+ (PMR): 8%; *p* < 0.001 *5-year CIR* MRD− (EMR): 7% MRD− (LMR): 13%; *p* = NS (vs EMR) MRD+ (IMR): 37%; *p* = 0.012 (vs EMR) MRD+ (PMR): 86%; *p* < 0.001 (vs IMR) *Multivariate analysis* *5-year DFS* MRD+ (IMR) vs MRD− (EMR): RR: 4.67 (95% CI: 1.16–18.79); *p* = 0.030 MRD+ (PMR) vs MRD− (EMR): RR: 26.07 (95% CI: 7.93–85.69); *p* < 0.001 MRD− (LMR) vs MRD− (EMR): RR: 3.15 (95%CI: 1.00–9.92); *p* = 0.050 *5-year relative risk of relapse* MRD+ (IMR) vs MRD− (EMR): RR: 9.01 (95% CI: 1.63–49.69); *p* = 0.012 MRD+ (PMR) vs MRD− (EMR): RR: 32.95 (95%CI: 6.78–160.21); *p* < 0.001 MRD− (EMR) vs MRD− (LMR): RR 2.17 (0.39–11.89); *p* = 0.374	
Kim *et al*. (2015)[22]	*MRD status after treatment* MRD− (EMR): 40/118 (34%) MRD− (LMR): 42/118 (36%) MRD+ (PMR): 36/118 (31%)	**Post-HSCT** Allogeneic HSCT: 118/118 patients *Univariate analysis* 6-year DFS MRD– (EMR): 74% ± 7% MRD– (LMR): 64% ± 8% MRD+ (PMR): 24% ± 7% *6-year CIR*s MRD− (EMR): 14% ± 6% MRD− (LMR): 20% ± 7% MRD+ (PMR): 71% ± 8% *Relapse* MRD kinetics were a potential predictor of disease relapse (MRD− [EMR] vs MRD− [LMR] vs MRD+ [PMR]); *p* < 0.001	MRD status was the most powerful factor predicting relapse risk MRD+ (PMR) patients had higher CIR and shorter DFS than those achieving MRD−

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		Multivariate analysis *6-year DFS* MRD− (LMR) vs MRD− (EMR): HR: 1.26 (95% CI: 0.55–2.93); $p = 0.585$ MRD+ (PMR) vs MRD− (EMR): HR: 4.18 (95% CI: 1.96–8.90); $p < 0.001$ *CIR at 6 years* MRD− (LMR) vs MRD− (EMR): HR: 1.68 (95% CI: 0.55–5.13); $p = 0.365$ MRD+ (PMR) vs MRD− (EMR): HR: 7.41 (95% CI: 2.76–19.88); $p < 0.001$ *6-year relapse rate* MRD− (EMR): 14% ± 6%; HR: 1 MRD− (LMR): 20% ± 7%; HR: 1.68 (95% CI: 0.55–5.13); $p = 0.365$ MRD+ (PMR): 71% ± 8%; HR: 7.41 (95% CI: 2.76–19.88); $p < 0.001$	
Lee *et al*. (2009)[23]	CR (after 4 weeks' imatinib): 11/52 (21%)	**Post-HSCT** Allogeneic HSCT: 52/52 patients *Multivariate analysis* *4-year OS* MRD < 3 log reduction vs MRD ≥ 3 log reduction: RR: 4.8 (95% CI: 1.5–14.7); $p = 0.007$ *4-year DFS* MRD < 3 log reduction vs MRD ≥ 3 log reduction: RR: 4.6 (95% CI: 1.5–14.6); $p = 0.009$ *4-year relapse* MRD < 3 log reduction vs MRD ≥ 3 log reduction: RR: 5.3 (95% CI: 1.5–19.0); $p = 0.011$	There was a significant correlation between the extent of MRD reduction after the first 4 weeks of therapy and allogeneic HSCT outcome Early MRD evaluation may allow the identification of HSCT patients at high risk of relapse and allow the introduction of MRD-based therapeutic approaches
Mizuta *et al*. (2012)[24]	–	**Post-HSCT** Allogeneic HSCT: 60/60 patients (MRD data available for 57/60 patients) *Univariate analysis (MRD− vs MRD+)* *OS:* RR: 1.32 (95% CI: 0.52–3.35); $p = 0.562$ *DFS:* RR: 1.47 (95% CI: 0.64–3.36); $p = 0.361$ *Relapse rate:* RR: 4.82 (95% CI: 1.20–19.4); $p = 0.027$ *Multivariate analysis (MRD− vs MRD+)* *OS:* RR: 1.12 (95% CI: 0.33–3.83); $p = 0.860$	Achieving MRD negativity before allogeneic HSCT resulted in significantly lower relapse rate after HSCT Univariate analysis found that MRD status at the time of HSCT had a significant influence on relapse rate ($p = 0.015$) Prospective monitoring of MRD could identify patients at risk of relapse

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		DFS: RR: 1.27 (95% CI: 0.46–3.48); *p* = 0.642 *Relapse rate:* RR: 7.34 (95% CI: 0.54–99.4); *p* = 0.134	
Ravandi *et al*. (2013)[25]	*CR duration* (*MRD assessed by MFC*) MRD+ at time of CR: no effect on CR duration MRD+ at 3 months: significantly shorter CR duration (*p* = 0.04) MRD−at 12 months: significantly longer CR duration (*p* = 0.001) *CR duration* (*MRD assessed by BCR-ABL ratio)* MRD− (< 0.1%) at time of CR: longer OS (*p* = ns) MRD− (< 0.1%) at 3 and 6 months: significantly higher likelihood of longer CR duration (*p* = 0.04) MRD− (< 0.1%) or better at 9 and 12 months: longer CR duration (*p* = ns)	**Pre-HSCT** *Univariate analysis (MRD− vs MRD+)* *EFS:* HR: 0.41; *p* = 0.002 *MRD measured by IGH PCR (MRD− vs MRD+):* HR: 1.96; *p* = 0.037 *MRD measured by MFC (MRD− vs MRD+):* HR: 3.27; *p* = 0.001 *Multivariate analysis* *Association of factors with EFS* MRD−: HR: 0.248 (95% CI: 0.110–0.559); *p* = 0.001 MRD+ by IGH PCR: HR: 1.651 (95% CI: 0.714–3.819); *p* = 0.242 MRD+ by MFC: HR: 1.464 (95% CI: 0.583–3.679); *p* = 0.418 *DFS and OS (MRD+ by IGH PCR)* No association with improved DFS or OS at any time point *OS* (*MRD assessed by MFC*) MRD+ at time of CR: no effect on OS MRD+ at 3 months: significantly shorter OS; *p* = 0.04 MRD−at 12 months: significantly longer OS; *p* = 0.001 *OS* (*MRD* assessed *by BCR-ABL ratio*) MRD− at time of CR: longer OS; *p* = ns MRD− at 3 and 6 months: significantly higher likelihood of longer survival; *p* = 0.04 MRD– at 9 and 12 months: longer CR duration; *p* = ns *CIR* No difference according to MRD status at any time point, except for achieving a flow-negative status by 3 months (associated with lower incidence of relapse)	MRD is an important predictor of outcomes Patients with MRD− had a better survival than those who did not achieve such a response
Tucunduva *et al*. (2014)[26]	–	**Post-UCBT** UCBT: 98/98 patients *3-year LFS* MRD− at UCBT: 49% ± 8% MRD+ at UCBT: 27% ± 6% *3-year CIR (patients transplanted in first CR only; n = 79/98)*	MRD+ before UCBT is associated with increased relapse

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		MRD−: 14% ± 6% MRD+: 41% ± 8% HR (MRD− vs MRD+) 0.33 (95% CI: 0.12–0.89); *p* = 0.02 *Univariate analysis of 3-year LFS (MRD− vs MRD+):* HR: 0.58 (95% CI: 0.34–1.0); *p* = 0.05 *Multivariate analysis of 3-year RFS (MRD− vs MRD+):* HR: 0.64 (95% CI: 0.37–1.12); *p* = 0.12 *3-year CIR* MRD− at UCBT: 16% ± 6% MRD+ at UCBT: 45% ± 7% *Univariate analysis of 3-year CIR (MRD− vs MRD+):* HR: 0.31 (95% CI: 0.13–0.76); *p* = 0.0073 *Multivariate analysis of 3-year CIR (MRD− vs MRD+):* HR: 0.33 (95% CI: 0.13–0.79); *p* = 0.013	
Yanada *et al*. (2008)[27]	CR: 97 (97%) Proportion of MRD− patients during early-treatment courses Day 28: 24% Day 63: 48% First consolidation (Cycle 1): 68% Cycle 2: 67% 1 and 2 years: nearly all samples (n = 2–11)	**Post-HSCT** Allogeneic HSCT: 60/100 patients (first CR) 19/100 patients (beyond first CR) Data shown for all evaluable patients (n = 85) *3-year RFS* MRD− (at Day 63) vs MRD+: 46% vs 42%; *p* = 0.800 MRD− (at Day 28) vs MRD+: *p* = 0.867 MRD− (at first consolidation) vs MRD+: *p* = 0.549 MRD levels >1000 copies/μg vs MRD levels <1000 μg (at Day 63): trend towards lower RFS; *p* = 0.092 *Relapse rate* MRD− (at Day 63) vs MRD+: 40% vs 41%; *p* = 0.964 MRD− (at Day 28) vs MRD+: *p* = 0.796 MRD− (at first consolidation) vs MRD+: *p* = 0.667 MRD levels >1000 copies/μg vs MRD levels <1000 μg (at Day 63): trend towards higher relapse rate; *p* = 0.070	MRD is strongly predictive of subsequent relapse but allogeneic HSCT can override its adverse effect
Wetzler *et al*. (2014)[28]	–	**Post-HSCT** Autologous HSCT: 19/34 patients (3 converted from MMR to MRD−) Allogeneic HSCT: 15/34 patients (5 converted from MMR to MRD−) *Autologous HSCT* DFS and OS of patients who achieved at least a MMR (n = 8) at Day +120 were longer than those for patients who were MRD+ (*p* = 0.092 and *p* = 0.026, respectively)	–

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		Allogeneic HSCT Sample size too small to analyse effect of MRD on outcome	
Chalandon *et al*. (2012)[29]	CR: 251/265 (95%) patients *MRD− (< 0.1%) after Cycle 1* Imatinib: 44% Imatinib plus hyper-CVAD: 46%; *p* = 0.79 *MRD− (< 0.1%) after Cycle 2* Imatinib: 68% Imatinib plus hyper-CVAD: 63.5%; *p* = 0.56 *MRD− (undetectable)* Imatinib: 28% Imatinib plus hyper-CVAD: 22%; *p* = 0.33	**Post-HSCT** Allogeneic HSCT: 157/251 patients (imatinib, 80; plus hyper-CVAD, 77) Autologous HSCT: 34/251 patients (17 in each arm) *Allogeneic HSCT* MRD− (< 0.1%) in Cycle 2: 89/133 (67%) patients *Autologous HSCT* MRD− (< 0.1%) in Cycle 2: 28/31 (90%) patients *3-year RFS (in patients achieving MRD− < 0.1% in Cycle 2)* Allogenic HSCT: 49% Autologous HSCT: 63%; *p* = 0.35 *3-year OS (in patients achieving MRD− < 0.1% in Cycle 2)* Allogenic HSCT: 58% Autologous HSCT: 69%; *p* = 0.08	No significant effect of MRD after Cycle 2 on response (including MRD− < 0.1%) on posttransplant RFS or OS
Kuang *et al*. (2013)[30]	CR rate (4 weeks' postinduction therapy) Overall: 49/50 (98%)	**Post-HSCT** Allogeneic HSCT (in first CR): 5/50 patients Data shown for all evaluable patients (n = 50) Median DFS (post hoc analysis; all patients) MRD−: not reached MRD+: 11 months; *p* = 0.001	MRD status at 6 months is an important prognostic indicator
Lee *et al*. (2012)[31]	*Cycle 1* Molecular response ≥ MMR: 33/95 (35%) patients MRD− (> 0.1–1%): 27/95 (28%) patients MRD− (< 1%): 35/95 (37%) patients CR: 12/95 (13%) patients *Cycle 2* Molecular response ≥ MMR (MRD− < 0.1%–<1%): 68/95 (72%) patients MRD− (> 0.1–1%): 9/95 (10%) patients MRD− (< 1%): 18 (19%) patients CR: 27 (28%) patients	**Post-HSCT** Allogeneic HSCT: 88/95 (93%) patients in first CR	The most powerful predictive factor affecting relapse, DFS and OS was achievement of MMR or CMR (MRD−) after second imatinib cycle (*p* < 0.001) Assessment of MRD reduction may allow the identification of patients who have received HSCT and are at high risk of relapse; this could lead to potential guidelines for the development of new risk-adapted, MRD-based therapeutic approaches
Hohtari *et al.* (2016)[32]	In TKI-treated patients there was a trend for better OS in patients who were MRD− at 3 months (*p* = 0.144)	OS at 5 years was better in the allogeneic HSCT group (62% vs 48%, *p* = 0.004)	
Lim *et al.* (2016)[33]	CMR rate 88.5%	Allogeneic HSCT associated with improved RFS (HR = 0.264, *p* = 0.032)	Patients who lost CMR had significantly inferior RFS and OS. Early CMR

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
	CMR within 3 months associated with improved RFS (HR = 0.251, *p* = 0.001)		significantly associated with RFS in multivariate analysis
Short *et al.* (2016)[34]	CMR at 3 months vs no CMR associated with longer median OS (127 vs 38 months, *p* = 0.009) and RFS (126 vs 18 months, *p* = 0.007) Multivariate showed CMR at 3 months was prognostic for OS (HR = 0.42, *p* = 0.01)	No HSCT	Patients who achieve CMR at 3 months have superior survival that those who do not, and have excellent long-term outcomes even without HSCT
Yoon *et al.* (2016)[36]	EMRs, n = 59; LMRs, n = 57; PMRs, n = 53 DFS EMR vs LMR: HR = 2.02, *p* = 0.046 EMR vs PMR: HR = 3.79, *p* < 0.001	Conditioning regimen with RIC or MAC: 5-year DFS was 49.7% vs 56.6% (p = 0.296) 5-year OS was 59.3% vs 62.1% (p = 0.540) No difference between RIC and MAC within different MRD response groups	Patients with EMR had better outcomes than those with LMR or PMR
Wassmann *et al.* (2005)[35]	MR: 14/27 (52%)	**<u>Post-HSCT</u>** Allogeneic HSCT: 3/27 Autologous HSCT: 24/27 (MRD data available for 17/27 patients) *Median DFS* MRD–: 28.6 months MRD+: 3.6 months; *p* < 0.001 *1-year DFS* MRD–: 91% ± 9% MRD+: 8% ± 7%; *p* < 0.001 *2-year DFS* MRD−: 55% ± 21% MRD+: only 1 patient survived 13 months *Median TTP from start of imatinib* MRD−: 28.6 months MRD+: 3.6 months; *p* < 0.001 *Estimated 1-year PFS* MRD−: 91% ± 9% MRD+ (13 months): 8% ± 7% *Estimated 2-year PFS* MRD−: 68% ± 21% *1-year OS* MRD−: 100% MRD+: 23% ± 13%; *p* < 0.001 *2-year OS*	Early MRD analysis provides critical information for guiding therapeutic intervention at the level of low leukemic cell burden

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		MRD−: 80.0% ± 18% MRD+: only 1 patient survived 13 months	
Philadelphia chromosome status: mixed			
Short *et al.* (2015)[37] Short *et al.* (2016)[38]	All patients (227/227) achieved CR MRD− at CR: 78/227 (34%) patients MRD+ at CR: 149/227 (66%) patients; $p = 0.47$	**Post-HSCT** HSCT: 49/272 patients Data shown for all eligible patients (n = 227) *Median RFS* MRD−: 99 months (95% CI: 45 months–NR) MRD+: 22 months (95% CI: 17–48 months); $p < 0.01$ *Median OS* MRD−: 137 months (95% CI: 87 months–NR) MRD+: 33 months (95% CI: 23–73 months); $p < 0.01$	Combining cytogenetic abnormalities with MRD status (assessed by MFC) did not offer additional prognostic information
Ravandi *et al.* (2016)[39]	All patients had CR at study entry MRD− at CR: 166/260 (64%) patients MRD− at 3 months: 201/215 (93%) patients MRD− at 6 months: 160/166 (96%) patients	**Post-HSCT** Allogeneic HSCT in first CR: 40/323 patients Data shown for all eligible patients (n = 260) *MRD– was associated with a statistically significant improvement in OS* MRD– at CR: $p = 0.03$ MRD− at 3 months: $p = 0.004$ MRD− at 6 months: $p < 0.0001$ *Multivariate analysis of OS (MRD− vs MRD+)* MRD− at CR: HR: 1.4 (95% CI: 0.94–2.10); $p = 0.1$ MRD− at 3 months from therapy initiation: HR: 1.96 (95% CI: 0.85–4.50); $p = 0.12$ MRD− at 6 months from therapy initiation: HR: 2.68 (95% CI: 0.89–8.06); $p = 0.08$ *MRD− associated with significant improvements in DFS* MRD− at CR: $p = 0.004$ MRD− at 3 months: $p = 0.004$ MRD− at 6 months: $p < 0.0001$ *Multivariate analysis of DFS (MRD− vs MRD+)* MRD− at CR: HR: 1.47 (95% CI: 1.003–2.153); $p = 0.048$ MRD− at 3 months from therapy initiation: HR: 1.72 (95% CI: 0.79–3.73); $p = 0.17$ MRD− at 6 months from therapy initiation: HR: 2.12 (95% CI: 0.70–6.44); $p = 0.18$ *Multivariate analysis of time to relapse (MRD− vs MRD+)*	MRD− status at CR was an independent predictor of DFS ($p < 0.05$) Achievement of MRD– is an important predictor of DFS and OS and may allow de-intensification of treatment

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		MRD− at CR: HR: 2.263 (95% CI: 1.432–3.576); *p* = 0.0005 MRD− at 3 months: HR: 1.976 (95% CI: 0.790–4.944); *p* = 0.145 MRD− at 6 months: HR: 2.969 (95% CI: 1.214–12.691); *p* = 0.02	
Joint analysis of EWALL Giebel *et al.* (2010)[14]	MRD− at HSCT[b]: 93/123 (76%) patients MRD+ at HSCT[b]: 30/123 (24%) patients	**Post-HSCT** Allogeneic or autologous HSCT: 123/123 patients *5-year LFS* (B-ALL cohort) MRD−: 54% ± 8% MRD+: 26% ±13%; *p* = 0.17 *5-year LFS* (whole cohort)[b] MRD−: 57% ± 2% MRD+: 17% ± 8%; *p* = 0.0002 *Multivariate analysis of risk of relapse or death in remission (MRD+ vs MRD−)[b]:* RR 2.8 (95% CI: 1.6–5.0); *p* = 0.0005	MRD status was the most important determinant of LFS MRD determines the outcome of high-risk patients who received autologous HSCT in first CR
Study 202 Topp *et al.* (2011)[40] Topp *et al.* (2012)[41]	MRD response rate[b]: 16/20 (80%) patients	**Post-HSCT** Allogeneic HSCT: 9/20 patients Data for all evaluable patients shown (n = 20) *RFS at 33 months (interim analysis)* MRD− lower limit of 95% CI: 19.1 months MRD+ lower limit of 95% CI: 3.2 months	Blinatumomab-induced MRD negativity translates into favorable RFS
Philadelphia chromosome status: not reported			
Weng *et al.* (2013)[42] Weng *et al.* (2012)[43]	Patients achieving CR ≥ 1 MRD− result: 58/106 (55%) patients Maintaining MRD−: 30/106 (28%) patients ≥ 1 MRD+ result: 76/106 (72%) patients Maintaining MRD+: 48/106 (45%) patients	**Post-HSCT** HSCT: 33/106 patients Data shown for all evaluable patients (n = 106) *RFS at end of induction of CR* MRD−: 65% ± 9% MRD+: 12% ± 5%; *p* < 0.001 MRD− (undetectable): 79% ± 10% MRD− (0.001% –< 0.01%): 37% ± 15%; *p* = 0.002 MRD+ (≥ 0.01%–< 0.1%): 29% ± 13% MRD+ (≥ 0.1%–< 1.0%): 15% ± 9%; *p* = 0.014 MRD+ (≥ 1.0%): 100%; *p* = 0.004 (vs MRD+ [≥ 0.1%–< 1.0%]) *2-year OS at end of induction of CR* MRD−: 69% ± 8% MRD+: 25% ± 6%; *p* < 0.001 MRD− (undetectable): 82% ± 9% MRD– (0.001%–< 0.01%): 46% ± 16%; *p* = 0.071 MRD+ (≥ 0.01%–< 0.1%): 50% ± 13% MRD+ (≥ 0.1%–< 1.0%): 11% ± 9%; *p* = 0.070	MRD status was independently associated with RFS and OS Positive MRD status after induction and 1 consolidation was associated with an increased risk of relapse MRD status could be measured by 8-color MFC and could potentially become an important tool to assess treatment response and prognosis

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
		MRD+ (≥ 1.0%): 22% ± 9%; *p* = 0.411 (vs MRD+ [≥ 0.1%–< 1.0%]) *2-year RFS after 1 consolidation* MRD−: 65%% ± 8% MRD+: 0%; *p* < 0.001 *2-year OS after 1 consolidation* MRD−: 68% ± 8% MRD+: 19% ± 6%; *p* < 0.001 MRD+ (≥ 0.01%–< 0.1%): 13% ± 12% MRD+ (≥ 0.1%–< 1.0%): 31% ± 11%; *p* = 0.859 MRD+ (≥ 1.0%): 10% ± 7%; *p* = 0.056 (vs MRD+ [≥ 0.1%–< 1.0%]) *2-year RFS according to dynamic MRD* ≥ 1 MRD− result: 58% ± 8% Never achieving MRD−: 2% ± 2%; *p* < 0.001 ≥ 1 MRD+ result: 10% ± 5% Maintaining MRD−: 83% ± 8%; *p* < 0.001 *Univariate analysis* *RFS (vs MRD−)* MRD+ at end of induction: *p* < 0.001 MRD+ after 1 consolidation: *p* < 0.001 *Multivariate analysis* *RFS (vs MRD−)* MRD+ at the end of induction: OR: 4.427 (95% CI: 1.750–11.197); *p* < 0.001 MRD+ after 1 consolidation: OR: 9.832 (95% CI: 4.545–21.268); *p* < 0.001	

[a]B-ALL phenotype unless otherwise stated.

[b]Patients with B-ALL and T-ALL included in the analysis.

[c]Data for patients with standard-risk disease shown.

ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; *BCR-ABL*, *breakpoint cluster region–Abelson*; CCR, continuous clinical remission; CI, confidence interval; CIR, cumulative incidence of relapse; CMR, complete molecular response; CR, complete remission; CRh, complete hematological remission; (hyper)-CVAD, (hyper-fractionated) cyclophosphamide, vincristine, Adriamycin, dexamethasone; DFS, disease-free survival; DOR, duration of response; EFS, event-free survival; EMR, early molecular responder; EWALL, European Study Group for Adult ALL; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; HR, hazard ratio; HSCT, hematological stem-cell transplantation; IGH, immunoglobulin heavy chain; IMR, intermediate molecular responder; LMR, late molecular responder; LFS, leukemia-free survival; MAC, myeloablative conditioning; MMR, major molecular response; MR, molecular response; MFC, multiparametric flow cytometry; MRD, minimal residual disease; MRD−, minimal residual disease negative; MRD+, minimal residual disease positive; NILG, Northern Italy Leukemia Group; NS, not significant; OR, odds ratio; OS, overall survival; PALG, Polish Adult Leukemia Group; Ph−, Philadelphia

chromosome negative; PMR, poor molecular responder; RIC, reduced intensity conditioning; RFS, relapse-free survival; T-ALL, T-cell acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor; UCBT, umbilical cord blood transplantation; UKALL, United Kingdom Acute Lymphoblastic Leukemia.

Supplementary Table 7. Other clinical outcomes: acute lymphoblastic leukemia in second or later complete remission.

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
Philadelphia chromosome status: negative			
Study 211 Gökbuget *et al.* (2014)[44]	CR: 63/189 (33%)	**Pre-HSCT** *Median OS* MRD−: 11.4 months (95% CI: 8.5 months–NE) MRD+: 6.7 months (95% CI: 2.0 months–NE) *Median RFS* MRD−: 6.9 months (95% CI: 5.5–10.1 months) MRD+: 2.3 months (95% CI: 1.2 months–NE)	Patients who did not achieve MRD responses tended to have shorter durations of OS and RFS
Philadelphia chromosome status: positive			
Wassmann *et al*. (2003)[45]	Sustained MR was achieved in 3/6 patients	**Pre-HSCT** *DFS* MRD− (n = 3) range: 6.4–20.8+ months MRD+ (n = 1): 21.4+ months *OS* MRD− (n = 3): range: 19.1–20.8+ months MRD+ (n = 1): 21.4+ months	–
DeBoer *et al*. (2014)[46] DeBoer *et al*. (2016)[47]	–	**Post-HSCT** Autologous HSCT: 15/57 Allogeneic HSCT: 19/57 Transplanted in first CR off-study: 9/57 Data for all evaluable patients shown (n = 20) MRD− (≤ 0.001) at Day 120 following autologous HSCT was significantly associated with prolonged DFS and OS (p = 0.01) MRD+ (> 0.001) at Day 120 was associated with significantly worse DFS than MRD−; HR 7.84; p = 0.013	MRD was associated with worse DFS
Philadelphia chromosome status: mixed			
Park *et al*. (2015)[48]	CR: 36/43 (84%) MRD−: 29/35 (83%) MRD+: 6/35 (17%)	**Pre-HSCT** *6-month OS* MRD−: 76% (95% CI: 51–89%) MRD+: 14% (95% CI: 8–45%) **Post-HSCT** Allogeneic HSCT at CR (12/36 [33%]) Allogeneic HSCT after CR did not affect survival rate	MRD negativity following treatment is highly predictive of survival

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
Topp *et al.* (2014)[50] Zugmaier *et al.* (2015)[51]	CR/CRh: 25/36 (69%) CR MRD−: 15/25 (60%) MRD+ [a]: 2/11(18%) CRh MRD−: 7/25 (28%) MRD+ [a]: 1/11 (9%) MRD− after blinatumomab treatment: 25/36 (69%) MRD− at end of Cycle 1: 18/25 (72%) MRD− at end of Cycle 2: 3/25 (12%) MRD− at end of Cycle 3: 1/25 (4%)	**Pre-HSCT** *Relapse-free after blinatumomab* MRD– (OS ≥ 30 months): 2 (8%) MRD+: 0 (0%) **Post-HSCT** Allogeneic HSCT: 6/10 long-term survivors (≥ 30 months) Data for all evaluable patients shown (n = 25) *OS (MRD+ vs MRD−):* OR 0.33 (95% CI: 0.144–0.771); *p* = 0.009 *Relapse-free after HSCT* MRD−: 4 (16%) MRD+: 0 (0%)	MRD response to blinatumomab treatment was associated with significantly longer OS compared with OS in patients who did not achieve an MRD response All 10 long-term survivors (OS ≥ 30 months) after the start of blinatumomab treatment were MRD−; none of the MRD+ patients were long-term survivors A 67% reduction in the risk of death was associated with MRD response
Philadelphia chromosome status: not reported			
Jabbour *et al.* (2016)	*2-year EFS :* MRD−: 31% MRD+: 12% *p* = 0.09 *2 -year OS* MRD− 40% MRD+ 26% *p* = 0.18	**Post-HSCT** *2-year EFS* MRD−: 46% MRD+: 11% *2-year OS* MRD−: 55% MRD+: 22%	MRD negativity associated with improved RFS and OS for patients in first salvage. Patients in second salvage have poor outcomes regardless of MRD status
Yilmaz *et al.* (2015)[54]	Responding patients: 78/130 MRD−: 41/78 (53%) MRD+: 37/78 (47%) *CR* MRD−: 24/42 (57%) MRD+: 18/42 (43%) *CR (without platelet recovery)* MRD−: 16/30 (35%) MRD+: 14/30 (47%) *CR (without platelet recovery ± neutrophil recovery)* MRD−: 1/6 (17%) MRD+: 5/6 (83%) *Median CR* MRD−: 17 months MRD+: 8 months; *p* = 0.63	**Post-HSCT** Allogeneic HSCT: 44/78 (56%) Data shown for all evaluable patients shown (n = 78) *Median EFS* MRD−: 12 months MRD+: 6 months; *p* = 0.06 *2-year EFS* MRD−: 32% MRD+: 8% *Median OS* MRD−: 17 months MRD+: 9 months; *p* = 0.18 *2-year OS* MRD−: 36% MRD+: 27%	MRD negativity in addition to the morphologic response improves response duration and survival

Study	CR or molecular response	Outcomes pre-/post-HSCT	MRD as a predictor of outcomes
	2-year CR MRD−: 47% MRD+: 28%		

[a]All MRD+ patients had an OS < 30 months.

[b]Conversion to MRD− after 1 treatment cycle.

ALL, acute lymphoblastic leukemia; CI, confidence interval; CR, complete remission; CRh, complete hematological remission; DOR, duration of response; EFS, event-free survival; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; HR, hazard ratio; HSCT, hematological stem-cell transplantation; MR, molecular remission; MRD, minimal residual disease; MRD−, minimal residual disease negative; MRD+, minimal residual disease positive; NE, not estimable; NR, not reached; OS, overall survival; Ph, Philadelphia chromosome; RFS, relapse-free survival; TTP, time to progression.

Supplementary Table 8a. Inclusion and exclusion of studies in the meta-analysis from studies identified in the systematic literature review: acute lymphoblastic leukemia in first complete remission.

Study	Total number of patients	Inclusion / Exclusion from meta-analysis (reasons for exclusion)
Philadelphia chromosome status: negative		
NILG-ALL 09/00 trial Bassan *et al.* (2014)[1]	304	Included
GRAALL 2003 and 2005 trials Beldjord *et al.* (2014)[2]	860	Included
GRAALL 2003 and 2005 trials Dhèdin *et al.* (2015)[3]	522[b]	Excluded (Uses Simon Makuch plots and it was not possible to estimate HR from these using the methods from Tierney *et al.* prespecified in the protocol)
GMALL 06/99 and 07/03 trials Gökbuget *et al.* (2012)[4]	1648	Included
PALG ALL 4-2002 trial Holowiecki *et al.* (2008)[5]	131	Included
NILG 09-2000 trial Mannelli *et al.* (2012)[6]	172	Excluded (RFS not reported)
UKALL XII trial Mortuza *et al*. (2002)[7]	110	Excluded (data reported in Patel[8])
UKALL XII/ECOG2993 trial Patel *et al.* (2010)[8]	161	Included
Salah-Eldin *et al.* (2014)[9] Salah-Eldin *et al.* (2014)[10]	55	Excluded (unable to calculate HR for RFS)
Thomas *et al*. (2012)[11]	216	Excluded (RFS not reported)
NILG 10/07 trial Bassan *et al.* (2014)[12]	159	Included
BLAST Gökbuget *et al.* (2015)[13]	116	Included
Joint analysis of EWALL Giebel *et al*. (2010)[14]	123[b]	Included
Philadelphia chromosome status: positive		
NILG 09/00 and 10/07 trials Lussana *et al.* (2016)[15]	106	Included

Study	Total number of patients	Inclusion / Exclusion from meta-analysis (reasons for exclusion)
GIMEMA 1509 trial Chiaretti *et al.* (2015)[16]	63	Included
Ravandi *et al*. (2015)[17]	97	Excluded (insufficient data to calculate HR)
Nishiwaki *et al.* (2016)[18]	432	Included
Bachanova *et al.* (2014)[19]	197	Included
Kim *et al*. (2015)[20]	91	Excluded (insufficient data to calculate HR for RFS)
Lee *et al.* (2012)[21]	95	Excluded (insufficient data to calculate HR for RFS)
Kim *et al*. (2015)[22]	118	Excluded (insufficient data to calculate HR for RFS)
Lee *et al*. (2009)[23]	52	Excluded (insufficient data to calculate HR for RFS)
Mizuta *et al*. (2012)[24]	100	Excluded (data reported in Yanada[27] and Nishiwaki[18])
Ravandi *et al*. (2013)[25]	122	Excluded (insufficient data to calculate HR for RFS)
Tucunduva *et al.* (2014)[26]	98	Included
Yanada *et al*. (2008)[27]	100	Included
Wetzler *et al*. (2014)[28]	34	Included
Chalandon *et al*. (2012)[29]	270	Excluded (RFS not reported by MRD status)
Kuang *et al*. (2013)[30]	50	Excluded (insufficient data to calculate HR for RFS)
Lee *et al.* (2012)[31]	95	Excluded (insufficient data to calculate HR for RFS)
Hohtari et al. (2016)[32]	128	Excluded (insufficient data to calculate HR for RFS)
Lim *et al.* (2016)[33]	82	Included
Short *et al.* (2016)[34]	202	Included
Wassmann *et al*. (2005)[35]	27	Included
Yoon *et al.* (2016)[36]	173	Included
Philadelphia chromosome status: mixed		
Short *et al.* (2015)[37] Short *et al.* (2016)[38]	324[a]	Included
Ravandi *et al.* (2016)[39]	340	Included
Study 202 Topp *et al.* (2011)[40]	21	Excluded (RFS not reported by MRD status)
Topp *et al.* (2012)[41]	21	Excluded (RFS not reported by MRD status)
Weng *et al*. (2013)[42] Weng *et al*. (2012)[43]	125	Included

Supplementary Table 8b. Inclusion and exclusion of studies in the meta-analysis from studies identified in the systematic literature review: acute lymphoblastic leukemia in second or later complete remission.

Study	Total number of patients	Number eligible for MRD test/MRD data available
Philadelphia chromosome status: negative		
Study 211 Gökbuget *et al.* (2014)[44]	189	Included
Philadelphia chromosome status: positive		
Wassmann *et al*. (2003)[45]	6	Excluded (small number of patients)
DeBoer *et al*. (2014)[46] DeBoer *et al.* (2016)[47]	99	Excluded (insufficient data to calculate HR for RFS)
Philadelphia chromosome status: mixed		
Park *et al.* (2015)[48]	44	Excluded (RFS not reported by MRD status)
Study 206 Topp *et al.* (2014)[50]	36	Excluded (RFS not reported by MRD status)
Zugmaier *et al.* (2015)[51]	36	Excluded (insufficient data to calculate HR for RFS)
Philadelphia chromosome status: not reported		
Jabbour *et al*. (2017)[52]	78	Included
Yilmaz *et al.* (2015)[54]	130	Excluded (data reported in Jabbour[52])

Supplementary Table 9. Meta-regression for RFS.
The “b” stands for between-group and is the test of whether it is plausible that all levels of the covariate are equal – i.e. how much of the variation (heterogeneity) can be explained by the covariate.

The “w” stands for within-group and is the test of heterogeneity after adjusting for the covariate – i.e. the remaining unexplained variation. For this we used a $p < 0.1$ level of significance as a cut-off.

If the Qb is significant then it means that the covariate had a statistically significant effect on the treatment difference.

If Qw is significant then there is still evidence of heterogeneity between the studies even after adjusting for the covariate.

The meta-regression was only performed on studies where the covariate information could be extracted, which can bias the results. In addition, some covariates were only reported in a small number of studies which will reduce the power to detect a significant difference.

Covariates are color-coded to note the strength of evidence (**green** = strong, **orange** = intermediate, **red** = weak).

	Qw significant	Qw not significant
Qb significant	**Median age** 24 years (HR = 3.33; 95% CI: 2.09–5.30) 41 years (HR = 2.29; 95% CI: 1.87–2.81) 55 years (HR = 1.68; 95% CI: 1.11–2.55) **Ph status** Ph-negative (HR = 2.58; 95% CI: 1.91–3.50) Ph-positive (HR = 2.02; 95% CI: 1.53–2.66) **Post-MRD treatment** Chemo (HR = 6.52; 95% CI: 2.03–20.90) Mix (HR = 2.58; 95% CI: 2.01–3.32) SCT (HR = 1.75; 95% CI: 1.26–2.42) Targeted therapy (HR = 3.15; 95% CI: 1.55–6.42) **Pre-MRD treatment** HSCT only (HR = 5.19; 95% CI: 1.66–16.20) Chemo only (HR = 2.94; 95% CI: 2.17–4.00) Targeted therapy (HR = 1.93; 95% CI: 1.53–2.44) **Test location** Central (HR = 2.69; 95% CI: 1.95–3.71) Local (HR = 1.88; 95% CI: 1.32–2.68) **MRD level** 10^{-3} (HR = 2.29; 95% CI: 1.25–4.18) 10^{-4} (HR = 2.73; 95% CI: 2.14–3.48) 10^{-5} (HR = 1.84; 95% CI: 1.24–2.73)	

	Median follow-up duration **Timing of MRD relative to HSCT**	
Qb not significant	**% male** 47% (HR = 2.66; 95% CI: 1.50–4.70) 56.5% (HR = 2.21; 95% CI: 1.72–2.82) 64% (HR = 1.91; 95% CI: 1.17–3.11) **MRD method** Flow (HR = 2.77; 95% CI: 1.67–4.60) PCR (HR = 2.35; 95% CI: 1.83–3.01) **Tierney method** Method 03 (HR = 2.41; 95% CI: 1.81–3.21) Method 09 (HR = 2.46; 95% CI: 1.68–3.61) Method 10 (HR = 1.72; 95% CI: 0.96–3.11) **Timing of MRD (from induction)** ≤ 3 months (HR = 2.59; 95% CI: 2.07–3.22) > 3 months (HR = 2.24; 95% CI: 1.53–3.29) **Disease stage** **Phenotype**	**Risk group**

CI, confidence interval; HR, hazard ratio; HSCT, hematological stem cell transplantation; MRD, minimum residual disease; PCR, polymerase chain reaction; RFS, relapse-free survival; SCT, stem cell transplantation.

Supplementary Methods

Eligibility criteria

Studies (randomized and nonrandomized) were included regardless of study design or treatment protocol (chemotherapy, targeted agents, hematological stem cell transplantation [HSCT] or a combination) both before and after minimal residual disease (MRD) assessment. Studies had to include patients aged 15 years or older and contain a population with precursor B-cell acute lymphoblastic leukemia (B-ALL) who had undergone MRD testing. Patients could be in first or later complete remission (CR). Studies had to compare the clinical outcomes between patients who were MRD-positive and MRD-negative. All studies that assessed MRD prospectively were included; for studies that assessed MRD retrospectively, only those with 50 or more patients with B-ALL and an evaluable MRD status were included. Studies with Ph-negative patients were included if data could be extracted for patients with B-ALL specifically. Studies with Philadelphia chromosome (Ph)-positive patients were included because it was assumed that all Ph-positive patients had B-ALL.

Data extraction

Data were extracted into a Microsoft® Excel® spreadsheet for the following parameters if available: sample size; median age; percentage male; median follow-up duration; methodology used to assess MRD, including sensitivity and the timing of the assessment; Ph status; histology; risk group; disease stage (first CR or later); and treatment received before and after MRD assessment. Hazard ratios (HRs) for survival outcomes (relapse-free survival [RFS] or equivalent, and overall survival [OS]) were extracted comparing MRD-positive with MRD-negative status.[56] The HRs for the time-to-event outcomes of RFS and OS were used in the meta-analyses (extracted as HRs with 95% confidence intervals [CIs] and *p* values). If HRs comparing MRD status were not reported, they were calculated using the available data according to the hierarchical approach described by Tierney *et al.* (2007).[56]

Meta-analysis methodology

The meta-analyses of HRs were conducted using SAS®, version 9.2.

When selecting studies for inclusion in the meta-analysis, if there was partial overlap in patient populations between publications (i.e. the same study group included in multiple publications), only 1 publication was used in the primary analysis set but the other publications could be included in the subgroup analyses. If outcomes reported for MRD were taken at different time points, then the survival outcomes closest to the time point of 3 months after induction were selected for the primary analysis set. Additional MRD timepoints

from the same study could be included in the subgroup analyses, so a single study could contribute data to both MRD timing subgroups. If multiple levels of MRD were tested, the difference between the highest and lowest MRD level was used.

The following prespecified subgroups were included in the meta-analysis: Ph status (negative or positive), MRD methodology (polymerase chain reaction [PCR] or flow cytometry), MRD level (10^{-3}, 10^{-4}, or 10^{-5}), MRD testing location (central or local laboratory), ALL histological phenotype (B-cell only or mixed B-cell and T-cell), timing of MRD assessment (≤ 3 months or > 3 months after starting therapy, or before or after transplantation), pre-MRD therapy (chemotherapy only, included a targeted agent, and/or HSCT), post-MRD therapy (chemotherapy only, included a targeted agent, and/or HSCT), disease stage (first CR or later), risk group (high, standard, or mixed risk).

The analysis of HRs used unadjusted measures of treatment effect, where available. Meta-analysis was performed using the random effects model.[57,58] Heterogeneity between studies was assessed statistically using the I^2 and Cochran's Q tests.[59,60] Meta-regression was performed to investigate the relationships between covariates (Ph status, median follow-up time, MRD cut-off sensitivity threshold, post-MRD treatment, disease stage, sex and age) and study-level HRs.[58]

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