Blinatumomab for Minimal Residual Disease (MRD) in Adults with B-cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL): Median Overall Survival (OS) Not Reached at 5 Years for Complete MRD Responders

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Disclosures

N Goekbuget *Research funding/travel support:* Amgen, Pfizer, Novartis; *Consultancy:* Amgen, Pfizer, Novartis, Celgene, Kite/Gilead

H Dombret *Consultancy/honoraria:* Amgen, Pfizer, Roche/Genentech, Ariad (Incyte), Jazz Pharma, Kite Pharma, Novartis, Agios, Sunesis, Ambit (Daiichi Sankyo), Karyopharm, Menarini, Astellas, Janssen, Servier, Seattle Genetics, Cellectis, Celgene, ImmunoGen, Shire-Baxalta, AbbVie, Otsuka; *Research funding*: Amgen, Pfizer, Ariad (Incyte), Jazz Pharma, Kite Pharma, Novartis; *Speakers' bureau*: Amgen, Pfizer, Ariad (Incyte), Celgene; *Travel expenses*: Amgen, Ariad (Incyte), Cellectis, Celgene

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K Taylor *Employment and equity ownership:* Amgen

RC Bargou *Consultancy/honoraria:* Amgen, GEMoaB, Cellex, Novartis, Molecular Partners, Pfizer

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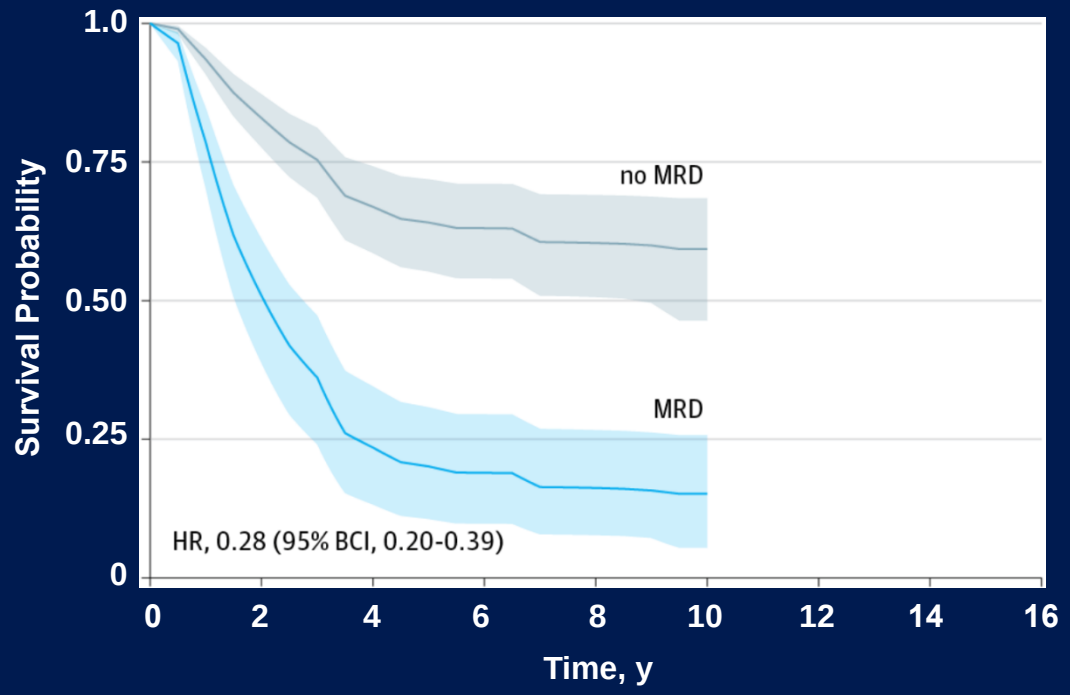
Background: Minimal Residual Disease

- After haematologic complete remission with intense chemotherapy, approximately 30% of adults with BCP-ALL have MRD[1]
- MRD is the strongest predictor of relapse in BCP-ALL[2,3]
- Median overall survival for adults with ALL and MRD after chemotherapy is approximately 2 years[3]
- The likelihood of MRD response during chemotherapy consolidation is low[1]

Overall survival for adults with ALL in five studies with 806 patients[3]

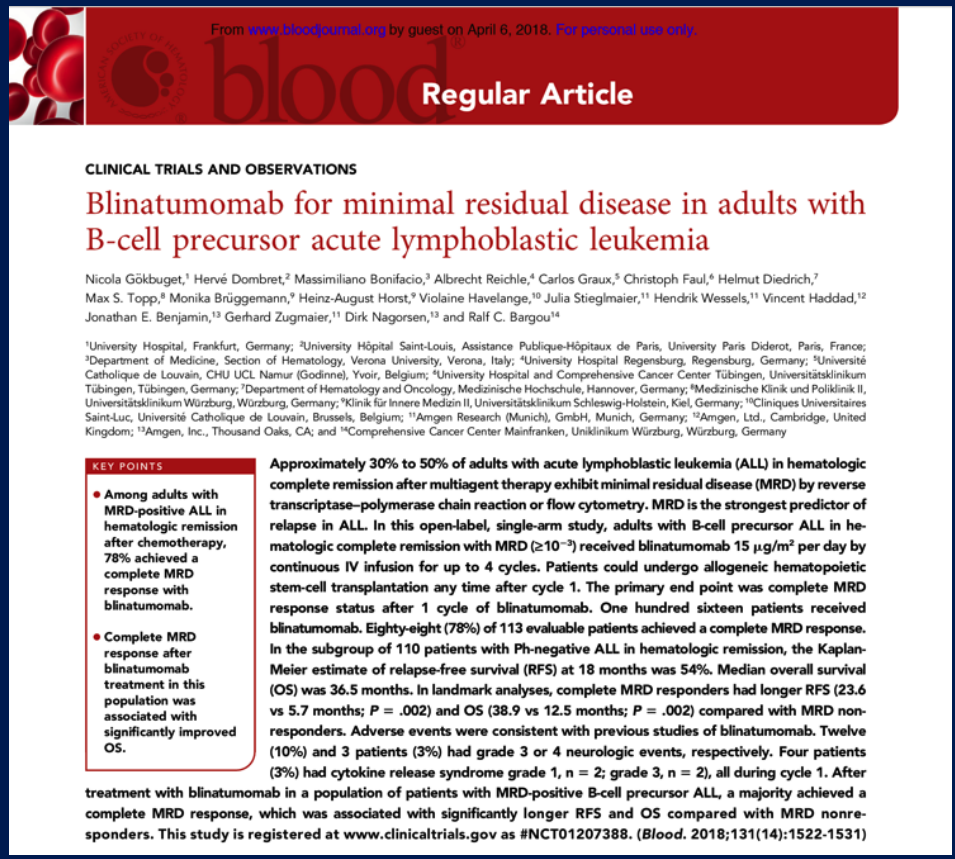


BCI, Bayesian credible intervals; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; HR, hazard ratio; MRD, minimal residual disease

1. Brüggemann M, et al. *Blood.* 2006;107:1116-1123. 2. Beldjord K, et al. *Blood.* 2014;123:3739-3749. 3. Berry DA, et al. *JAMA Oncol.* 2017;3:e170580.

Background: BLAST Study Primary Results

- Blinatumomab, the first and only approved bispecific T-cell engager (BiTE®) therapy, redirects T cells to kill $CD19^+$ target cells
- A multinational, single-arm study (BLAST; NCT01207388) examined the efficacy and safety of blinatumomab to achieve complete MRD response in MRD-positive adults with BCP-ALL
- Complete MRD response rate after cycle 1 was 78% (88/113) among MRD-evaluable patients
- Grade 3 or 4 adverse events during blinatumomab treatment included neurologic events (13%) or cytokine release syndrome (2%)
- After a minimum patient follow-up of 18 months, median overall survival was 36.5 months (95% CI: 19.8, not estimable) and not reached in MRD responders



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Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia

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KEY POINTS

- Among adults with MRD-positive ALL in hematologic remission after chemotherapy, 78% achieved a complete MRD response with blinatumomab.
- Complete MRD response after blinatumomab treatment in this population was associated with significantly improved OS.

Approximately 30% to 50% of adults with acute lymphoblastic leukemia (ALL) in hematologic complete remission after multiagent therapy exhibit minimal residual disease (MRD) by reverse transcriptase–polymerase chain reaction or flow cytometry. MRD is the strongest predictor of relapse in ALL. In this open-label, single-arm study, adults with B-cell precursor ALL in hematologic complete remission with MRD ($\geq 10^{-3}$) received blinatumomab 15 $\mu g/m^2$ per day by continuous IV infusion for up to 4 cycles. Patients could undergo allogeneic hematopoietic stem-cell transplantation any time after cycle 1. The primary end point was complete MRD response status after 1 cycle of blinatumomab. One hundred sixteen patients received blinatumomab. Eighty-eight (78%) of 113 evaluable patients achieved a complete MRD response. In the subgroup of 110 patients with Ph-negative ALL in hematologic remission, the Kaplan-Meier estimate of relapse-free survival (RFS) at 18 months was 54%. Median overall survival (OS) was 36.5 months. In landmark analyses, complete MRD responders had longer RFS (23.6 vs 5.7 months; $P = .002$) and OS (38.9 vs 12.5 months; $P = .002$) compared with MRD nonresponders. Adverse events were consistent with previous studies of blinatumomab. Twelve (10%) and 3 patients (3%) had grade 3 or 4 neurologic events, respectively. Four patients (3%) had cytokine release syndrome grade 1, n = 2; grade 3, n = 2), all during cycle 1. After treatment with blinatumomab in a population of patients with MRD-positive B-cell precursor ALL, a majority achieved a complete MRD response, which was associated with significantly longer RFS and OS compared with MRD nonresponders. This study is registered at www.clinicaltrials.gov as #NCT01207388. (*Blood*. 2018;131(14):1522-1531)

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CI, confidence interval; MRD, minimal residual disease
Gökbuget N, et al. Blood. 2018;131:1522-1531.

Study Methods

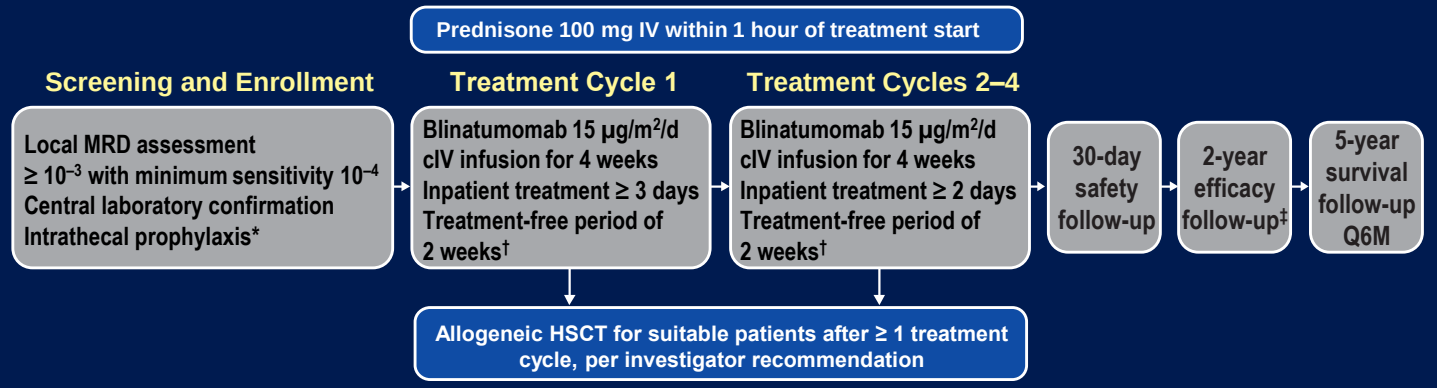
Key Eligibility Criteria

- Adults with Ph$^-$ BCP-ALL
- CR1 or CR2+ (< 5% blasts) after ≥ 3 intensive chemotherapy blocks
- MRD (at least 10^{-3}) ≥ 2 weeks after the last chemotherapy

Assessments

- Complete MRD response at cycle 1
  - No target amplification by real-time quantitative polymerase chain reaction
  - Minimum sensitivity of 10^{-4}
- Overall survival

Treatment



Baseline bone marrow aspirations were obtained during screening or within 4 weeks prior to treatment start. Confirmatory bone marrow aspirations were performed on day 43 of cycle 1 if the central MRD result was not yet available or if there was an unclear MRD result (between LLOQ and sensitivity).

*During screening or within 4 weeks of treatment initiation; at day 29 of cycles 2 and 4; and every 3 months following treatment for up to 18 months. Treatment comprised dexamethasone 4 mg (or equivalent), methotrexate 15 mg, and cytosine arabinoside 40 mg.
†May be extended by up to 7 days.
‡At 3, 6, 9, 12, 18, and 24 months after treatment start.

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; cIV, continuous IV; CR1, first haematologic complete remission; CR2+, second or later hematologic complete remission; HSCT, haematopoietic stem cell transplantation; IV, intravenous; LLOQ, lower limit of quantitation; MRD, minimal residual disease; Ph$^-$, Philadelphia chromosome negative; Q6M, once every 6 months

Objective and Statistical Methods

Objective

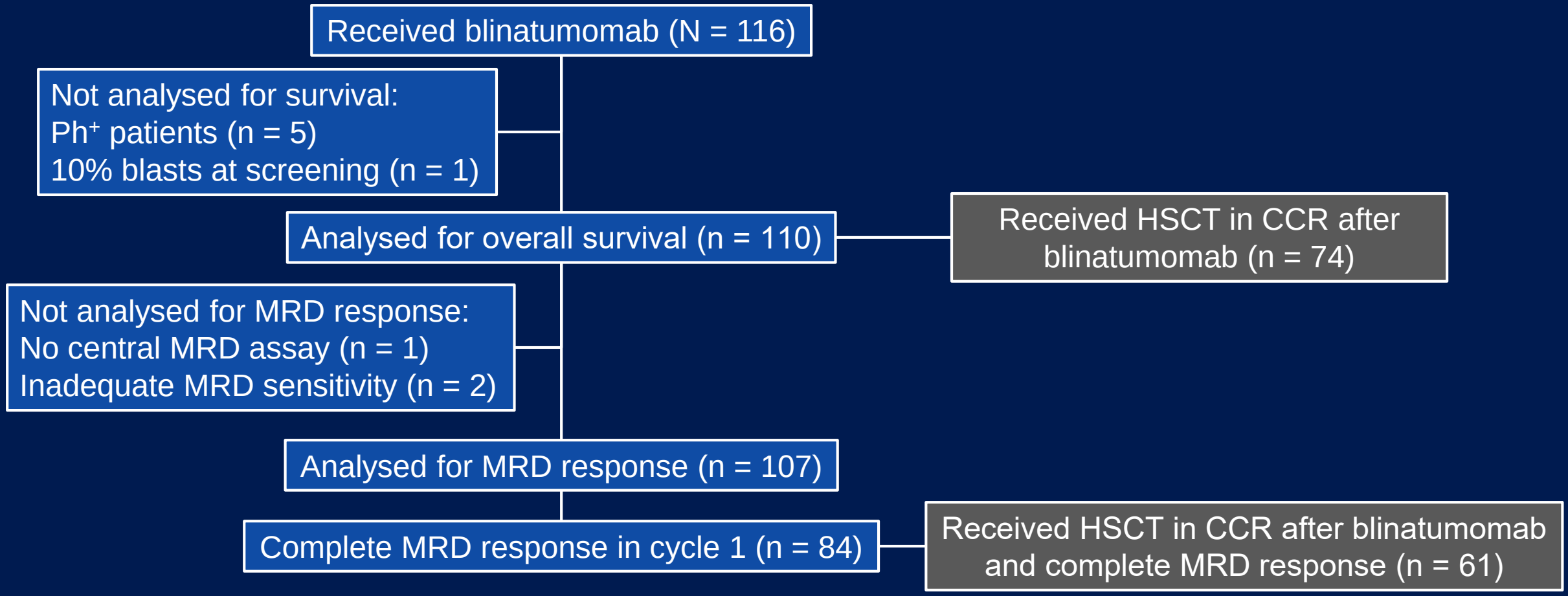
- This report describes the final analysis of long-term overall survival for adults with Ph-negative BCP-ALL and MRD, 5 years after blinatumomab treatment

Statistical Analysis

- Kaplan-Meier estimates of overall survival were determined:
  - Overall
  - By complete MRD response in cycle 1
- A conditional landmark of 45 days (the end of cycle 1) was used for subgroup analyses by complete MRD response

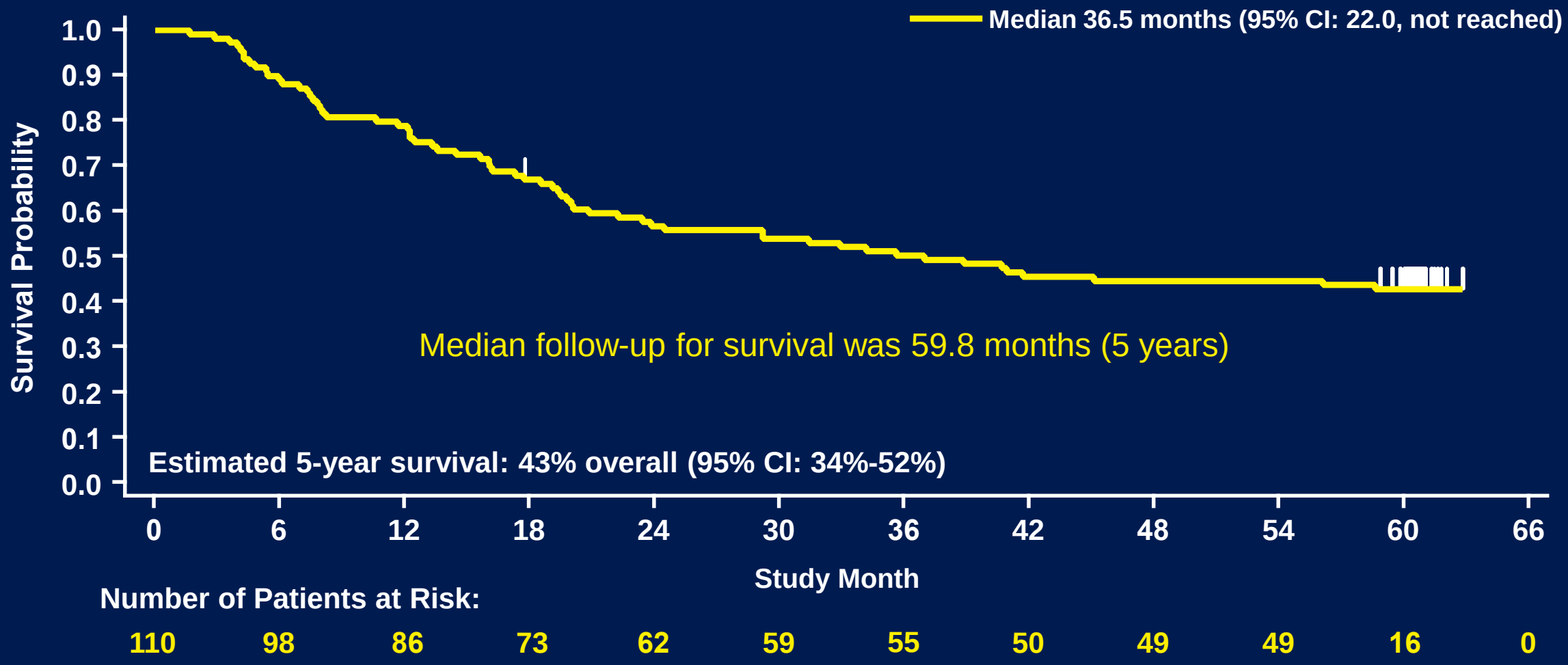
BCP-ALL, B-cell precursor acute lymphoblastic leukemia; MRD, minimal residual disease

Complete MRD Responses and HSCT



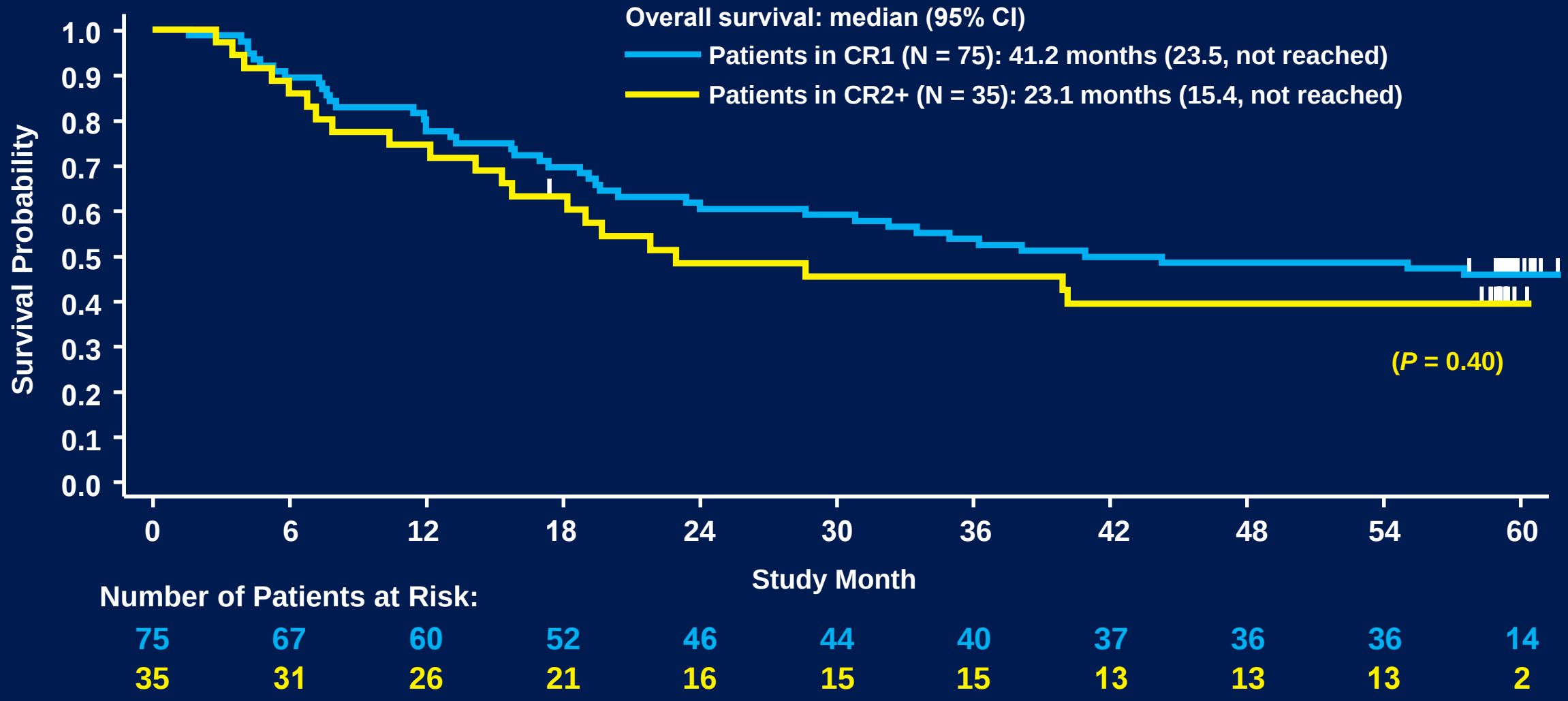
CCR, continuous complete remission; HSCT, haematopoietic stem cell transplantation; MRD, minimal residual disease; Ph+, Philadelphia chromosome positive
Complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}

Overall Survival: Ph-Negative Patients With BCP-ALL and MRD



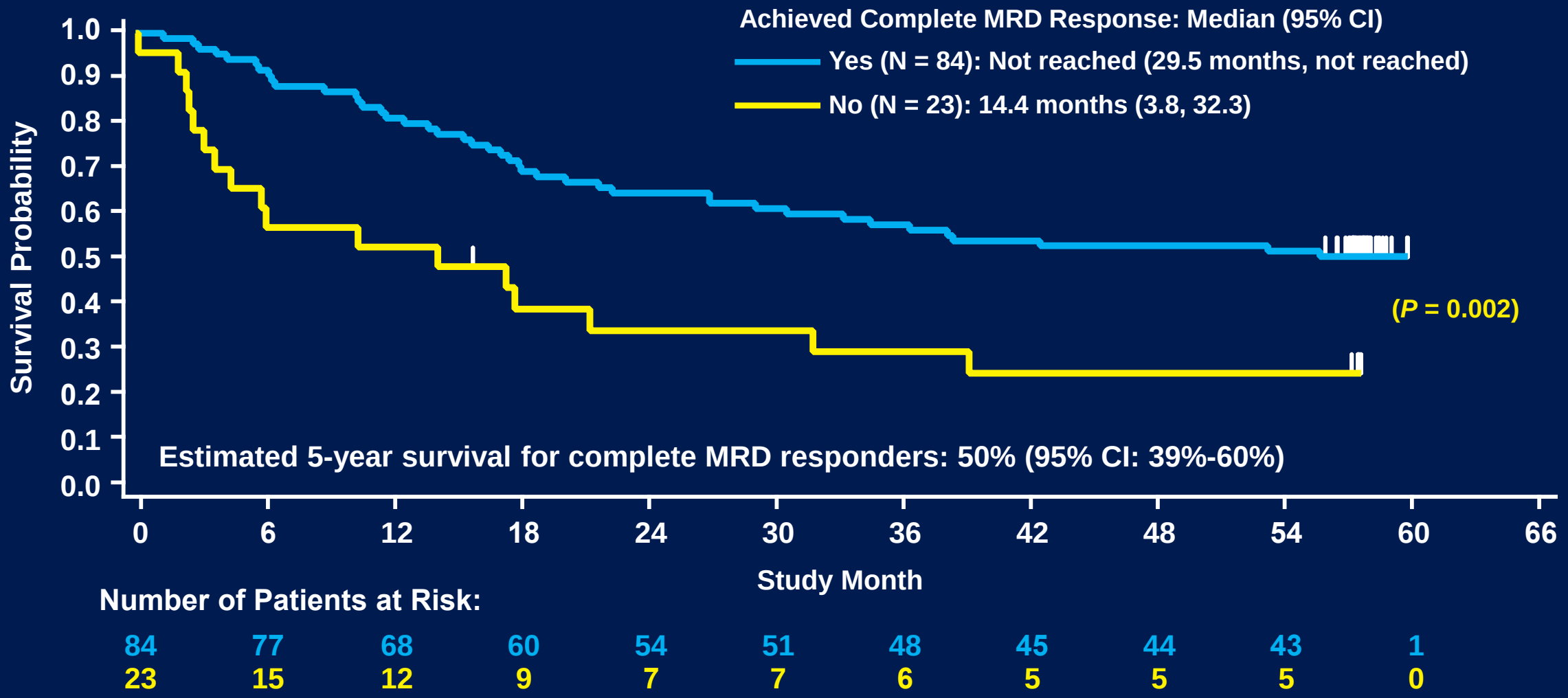
BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CI, confidence interval
Includes patients analysed for overall survival (N = 110)

Overall Survival: By CR1 or CR2+



CR1, first complete remission; CR2+, second or later complete remission

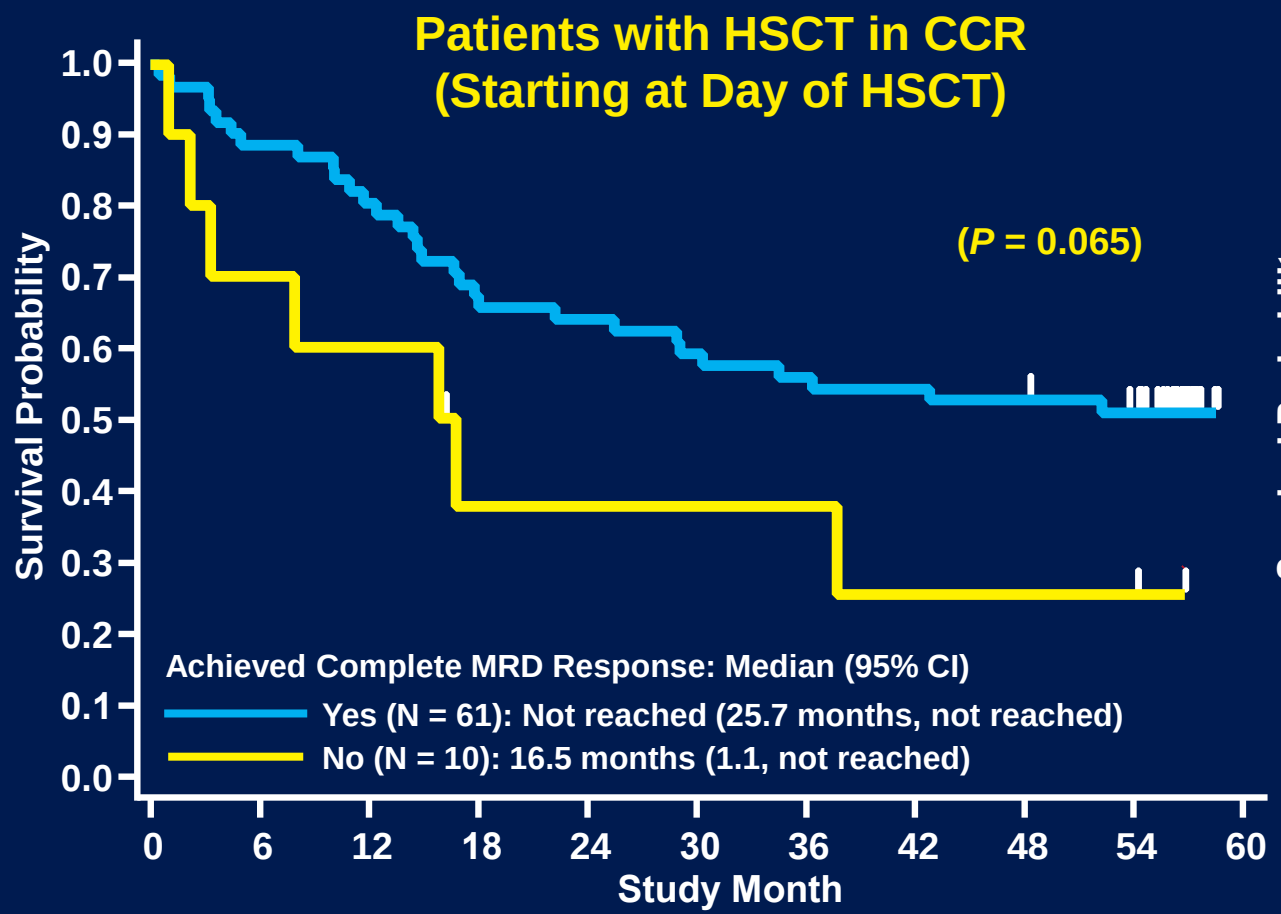
Overall Survival by Complete MRD Response: All Patients Analysed

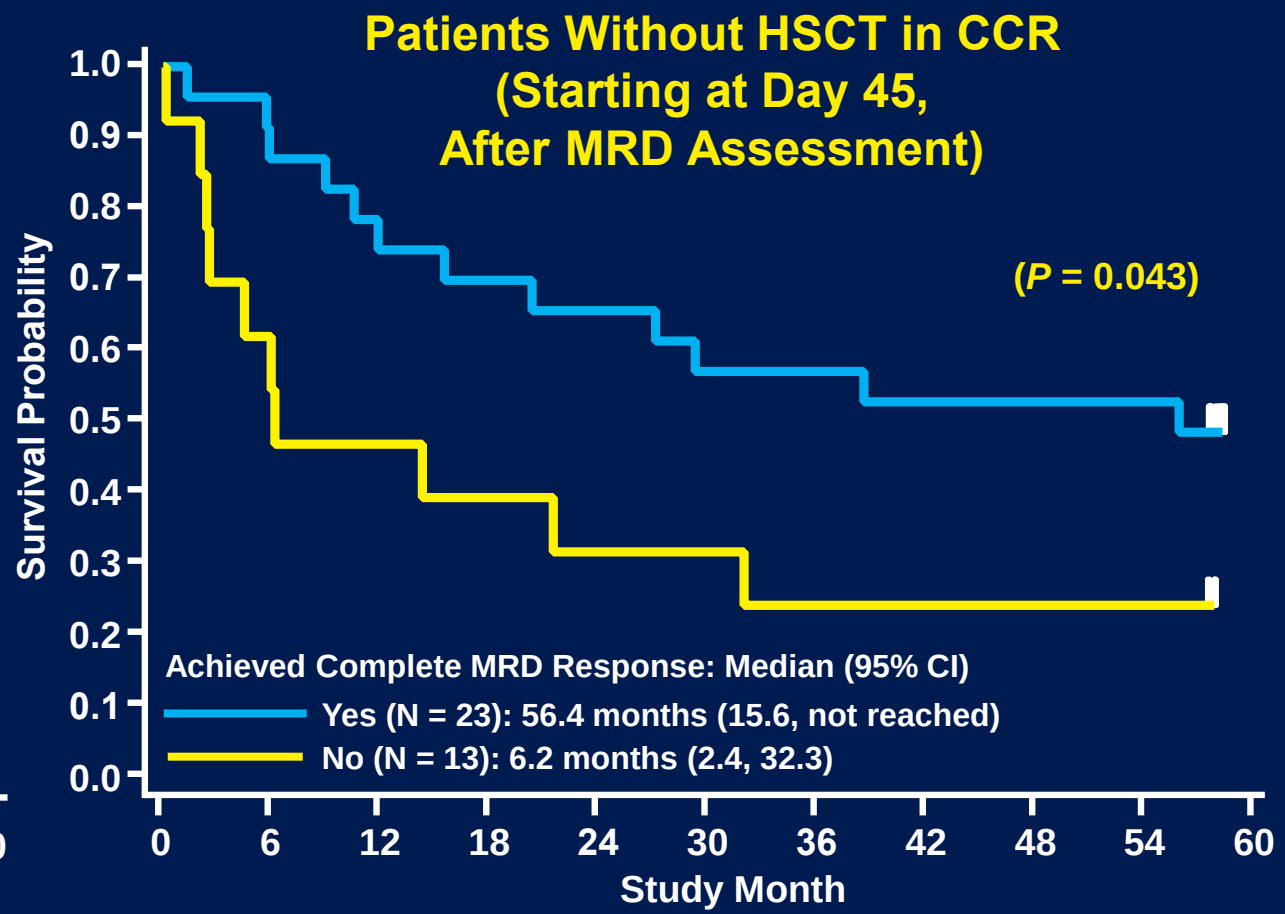


CI, confidence interval; MRD, minimal residual disease

Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}

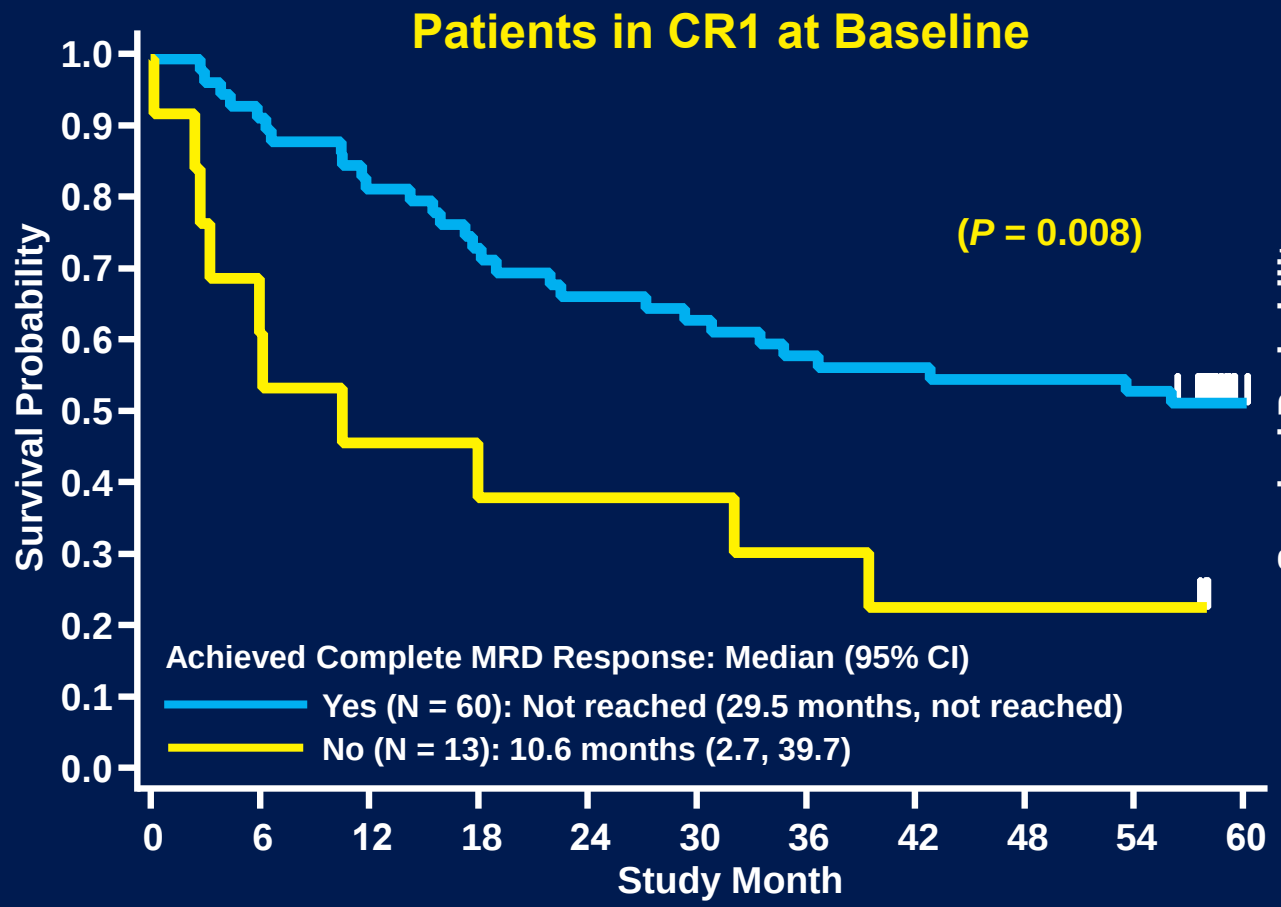
Overall Survival by Complete MRD Response: With or Without HSCT in CCR

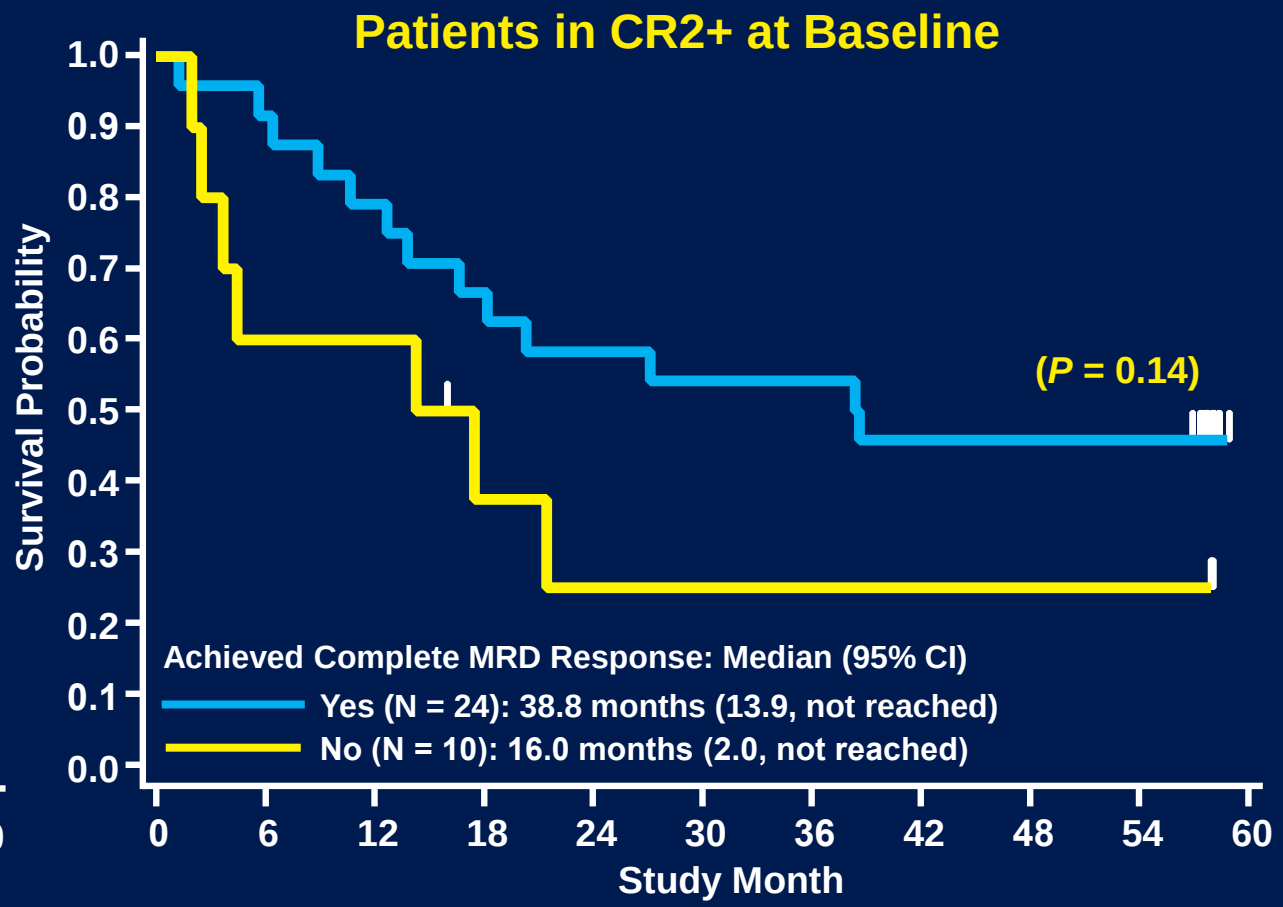




CI, confidence interval; CCR, continuous complete remission; HSCT, haematopoietic stem cell transplantation; MRD, minimal residual disease

Overall Survival by Complete MRD Response: Patients in CR1 or CR2+





Number of Patients at Risk:

60	55	49	44	40	38	35	34	33	32	1
13	9	6	6	5	5	4	3	3	3	0

Number of Patients at Risk:

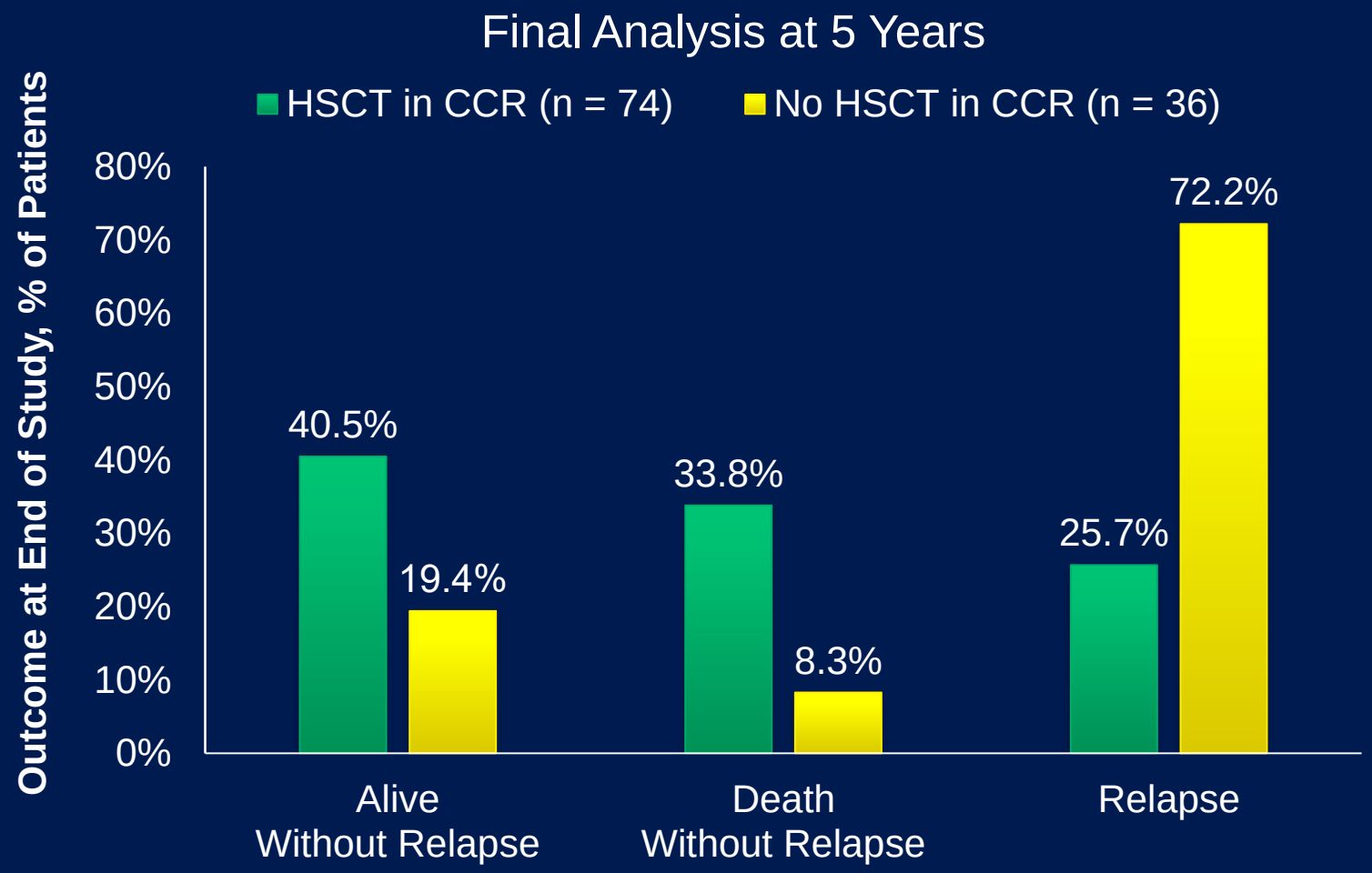
24	22	19	16	14	13	13	11	11	11	0
10	6	6	3	2	2	2	2	2	2	0

CI, confidence interval; CR1, first complete remission; CR2+ second or later complete remission; MRD, minimal residual disease
Includes patients analysed for MRD response (N = 107). Starts at Day 45, after MRD assessment.

Relapse or Death After HSCT in CCR

Characteristics of Patients Receiving HSCT in CCR

	HSCT in CCR (n = 74)
Age, years	
Median (range)	42 (18–67)
> 35	48 (65%)
Conditioning	
Myeloablative	55 (74%)
Reduced intensity	14 (19%)
Missing	5 (7%)
HSCT donor	
Matched, sibling	17 (23%)
Matched, unrelated	20 (27%)
Mismatched	25 (34%)
Missing	12 (16%)



CCR, continuous complete remission; HSCT, haematopoietic stem cell transplantation
Includes patients analysed for overall survival (N = 110)

Conclusions

- This multinational study included adults with BCP-ALL in haematologic complete remission with persistent MRD or MRD relapse
- Median overall survival was 36.5 months with 5 years of follow-up
- Median overall survival was not reached among:
  - Patients who achieved a complete MRD response after cycle 1 of blinatumomab
  - Patients who achieved a complete MRD response with blinatumomab in CR1
  - Patients who received HSCT in CCR after blinatumomab
- This analysis has provided the longest follow-up for any immunotherapy to date
- These results provide further support for the long-term benefits in overall survival associated with blinatumomab treatment in adults with Ph^- BCP-ALL and MRD

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CCR, continuous complete remission; CR1, first complete remission; CR2+, second or greater complete remission; HSCT, haematopoietic stem cell transplantation; MRD, minimal residual disease; Ph^-, Philadelphia-negative