# Blinatumomab for Minimal Residual Disease (MRD) in Adults With B-Cell Precursor Acute Lymphoblastic Leukemia: Median Overall Survival Is Not Reached in Complete MRD Responders at a Median Follow-up of 53.1 Months

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**ASH 2018 Annual Meeting; San Diego, CA; December 1–4, 2018; Presentation #554**

# 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

G Zugmaier *Employment and equity ownership:* Amgen; *Patents:* 20170327581, 9688760, 20170122947, 9486475, 20160208001, 9192665, 20150071928, 8840888, 20140227272, 20140228316, 20130323247, 20130287774, 20130287778, 20110262440, 20100112603, 7700299, 20070037228

M Bonifacio *Research funding:* Novartis; *Consultancy*: Amgen, Pfizer, Incyte

C Graux, C Faul No potential conflicts of interest to disclose

MS Topp *Research funding/travel support/honoraria/advisory committees:* Amgen

M Brüggemann *Research funding:* Affimed, Regeneron; *Consultancy*: Amgen, Incyte, PRMA; *Speakers' bureau*: Amgen, Roche, Pfizer

K Taylor *Employment and equity ownership:* Amgen

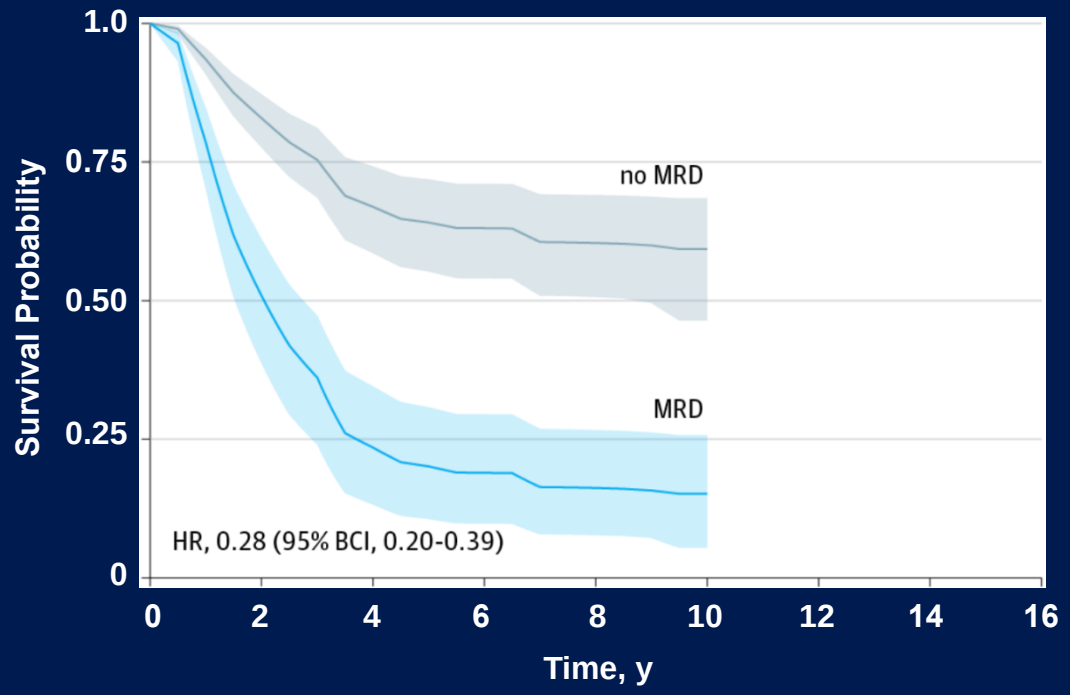
RC Bargou *Consultancy/honoraria:* Amgen, GEMoaB, Cellex, Novartis, Molecular Partners, Pfizer

Amgen Inc. sponsored this study and provided medical writing assistance

# Background: Minimal Residual Disease

- After hematologic 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]

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

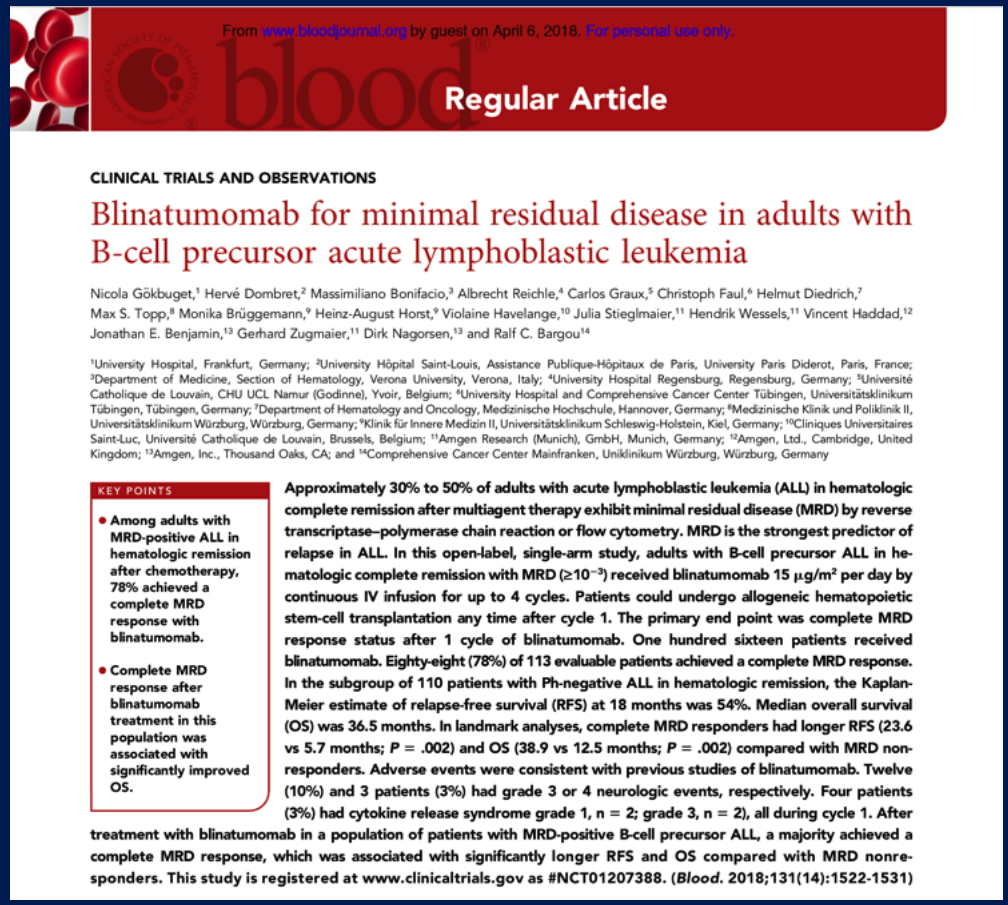



BCI, Bayesian credible intervals; BCP-ALL, B-cell precursor acute lymphoblastic leukemia; HR, hazard ratio; MRD, minimal residual disease

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, a bispecific antibody construct, redirects T cells to kill $CD19^+$ target cells
- A multinational, single-arm study (BLAST; NCT01207388) examined blinatumomab efficacy and safety in adults with BCP-ALL and MRD
- 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)





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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 μg/m² 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

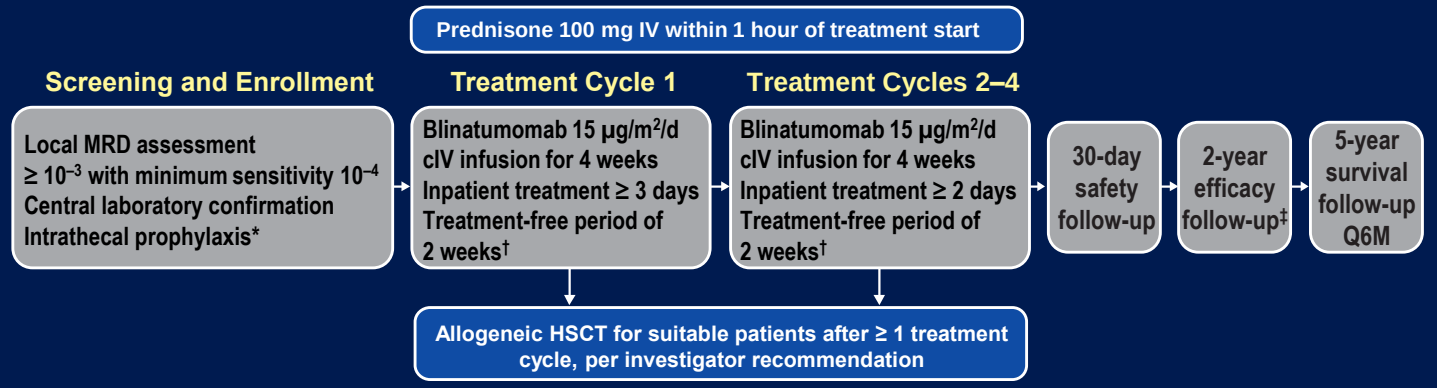
## Key Eligibility Criteria

- 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 hematologic complete remission; CR2+, second or later hematologic complete remission; HSCT, hematopoietic 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

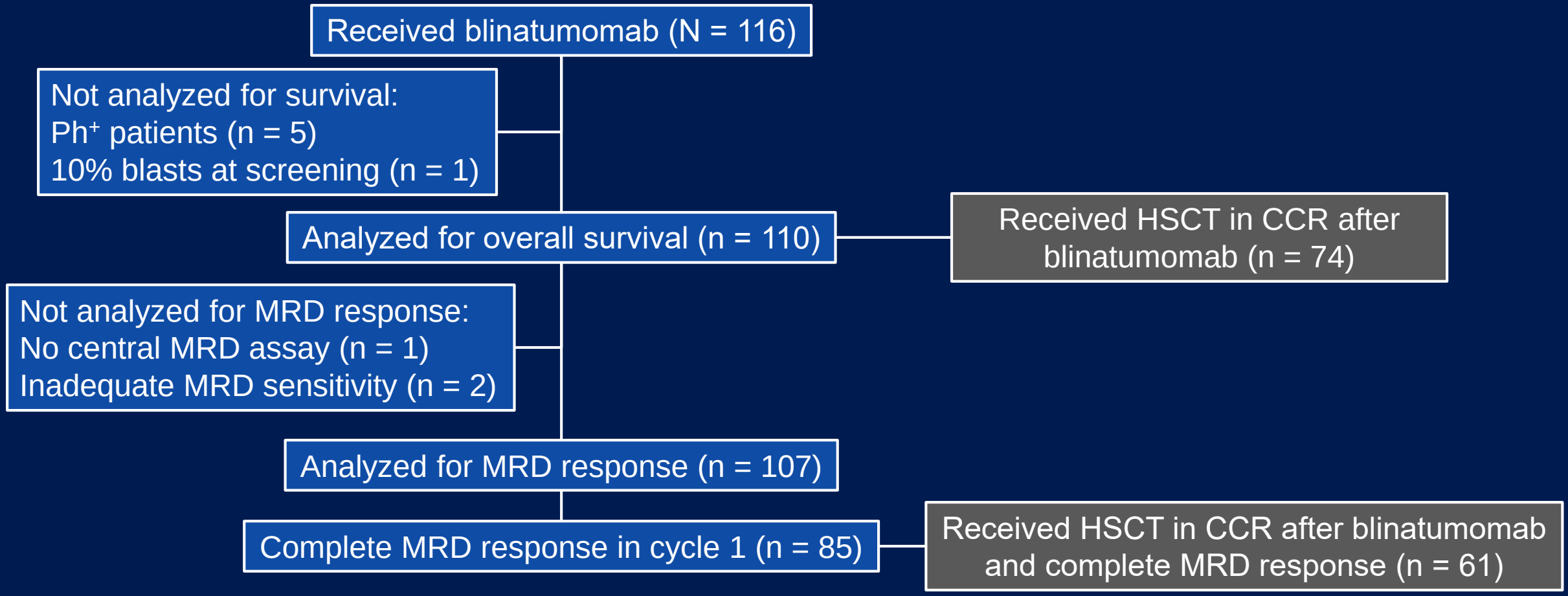
- This report describes long-term overall survival for adults Ph-negative BCP-ALL and MRD, with a minimum patient follow-up of 3 years after blinatumomab treatment

## 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

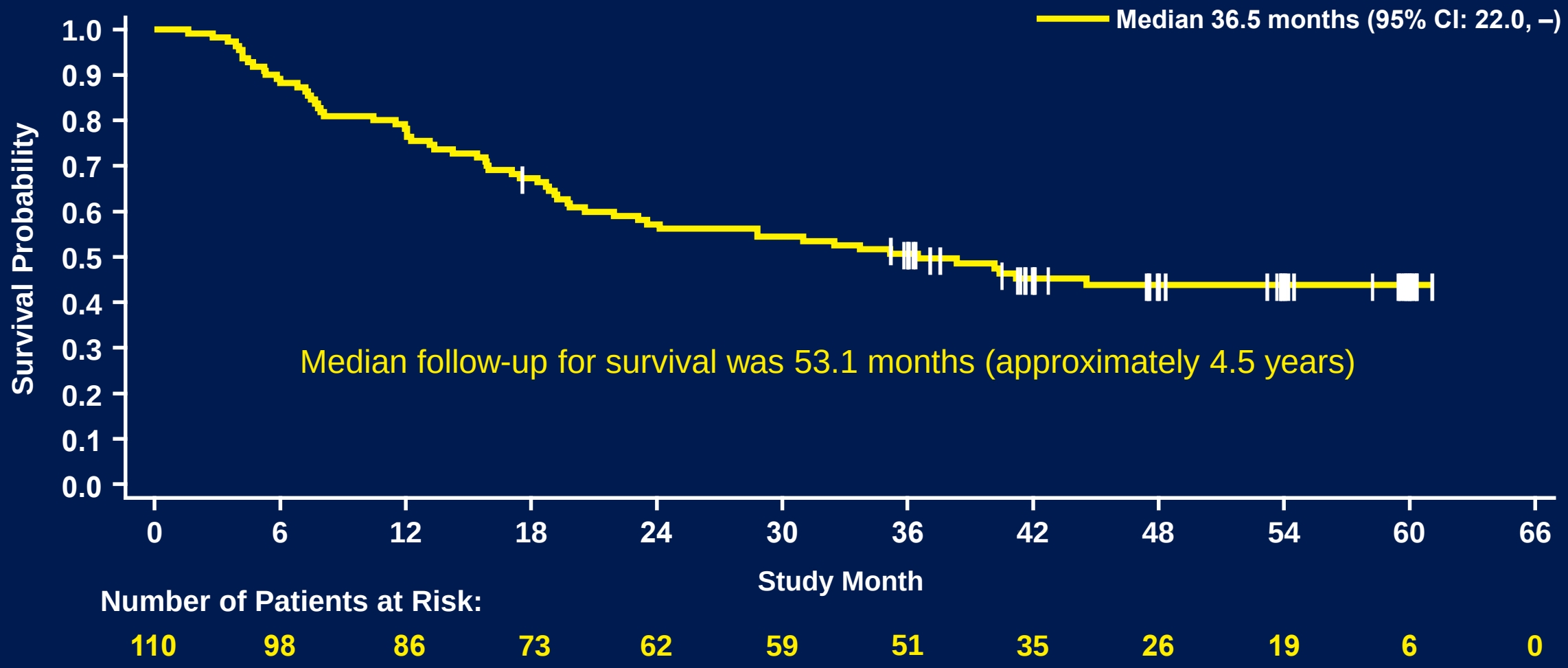
BCP-ALL, B-cell precursor acute lymphoblastic leukemia; MRD, minimal residual disease

# Complete MRD Responses and HSCT



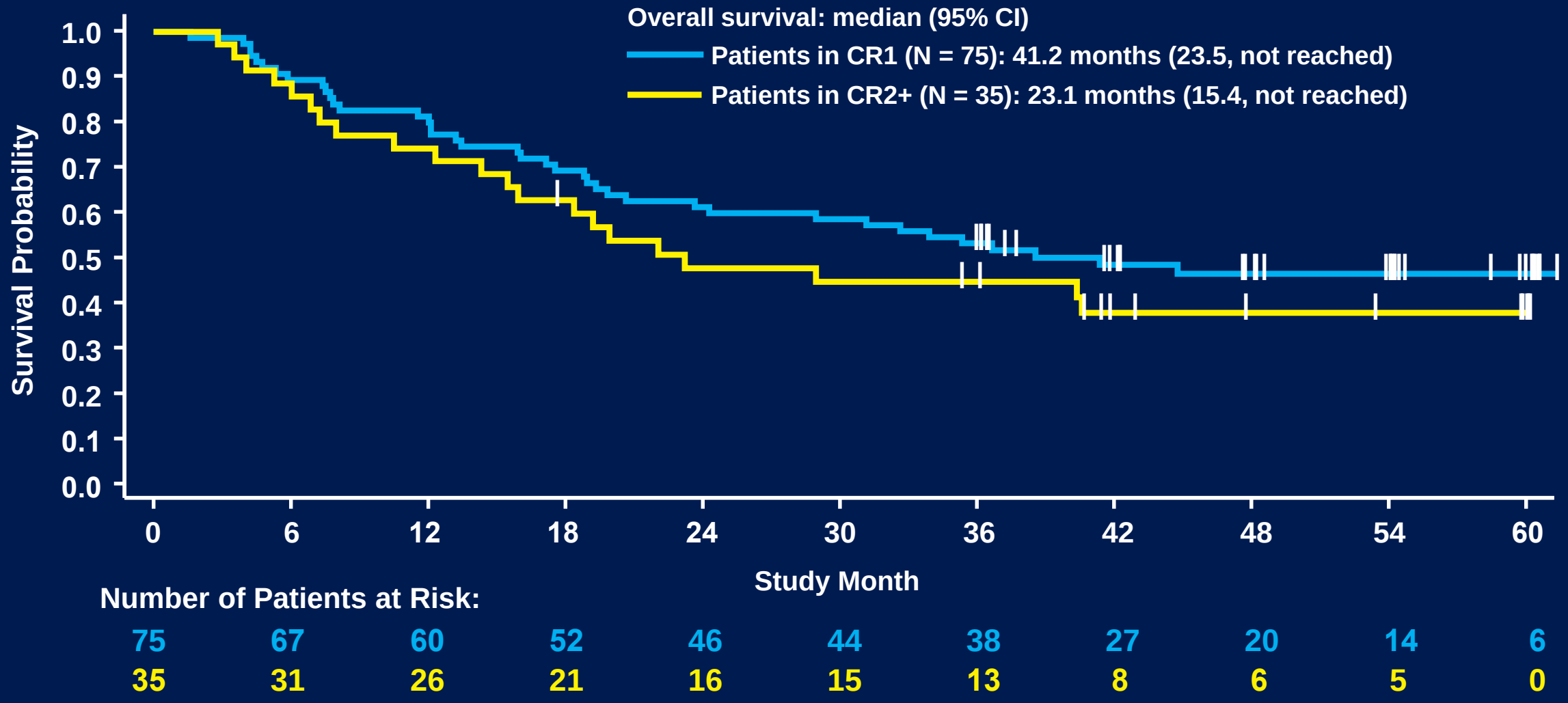

CCR, continuous complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; Ph+, Philadelphia chromosome positive
Complete MRD response was defined as no target amplification, with a minimum sensitivity of $10^{-4}$

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



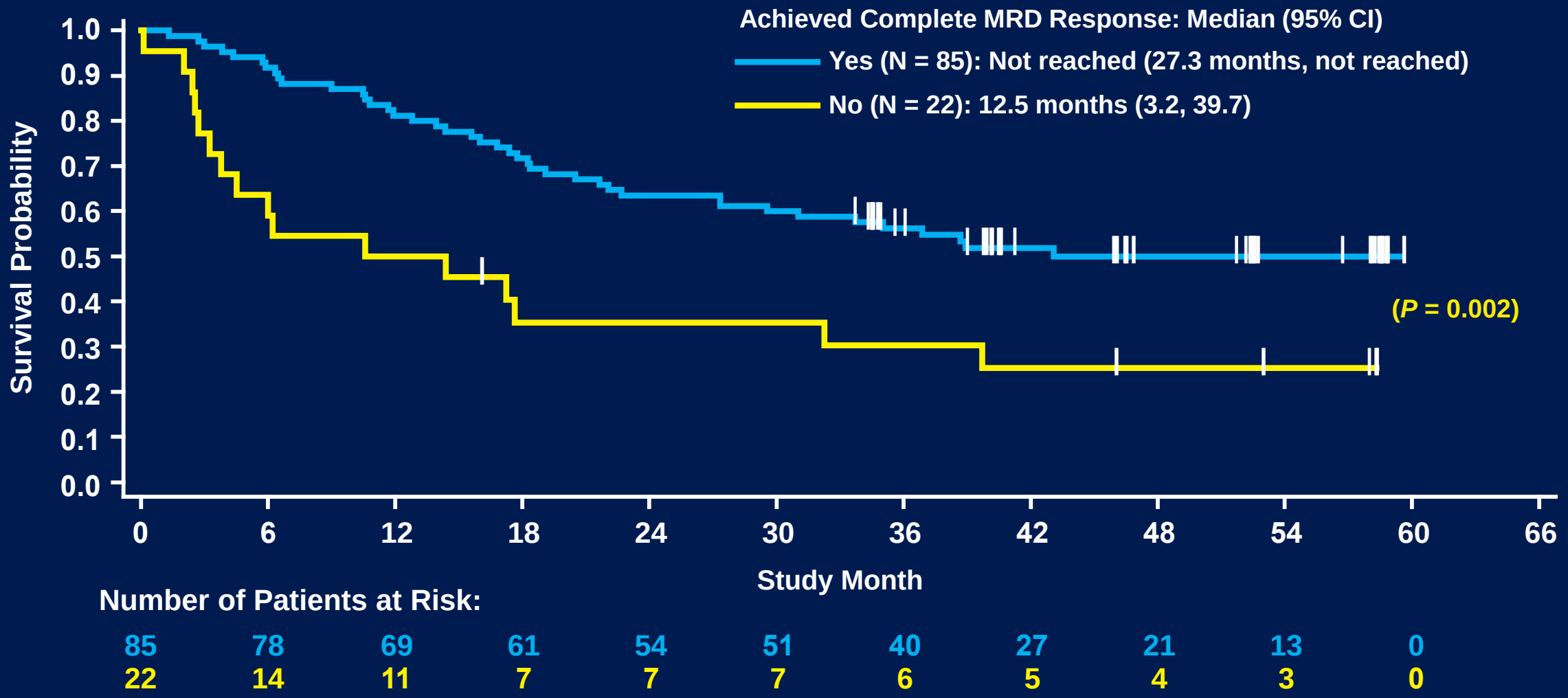

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; CI, confidence interval
Includes patients analyzed for overall survival (N = 110)

# Overall Survival: By CR1 or CR2+




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

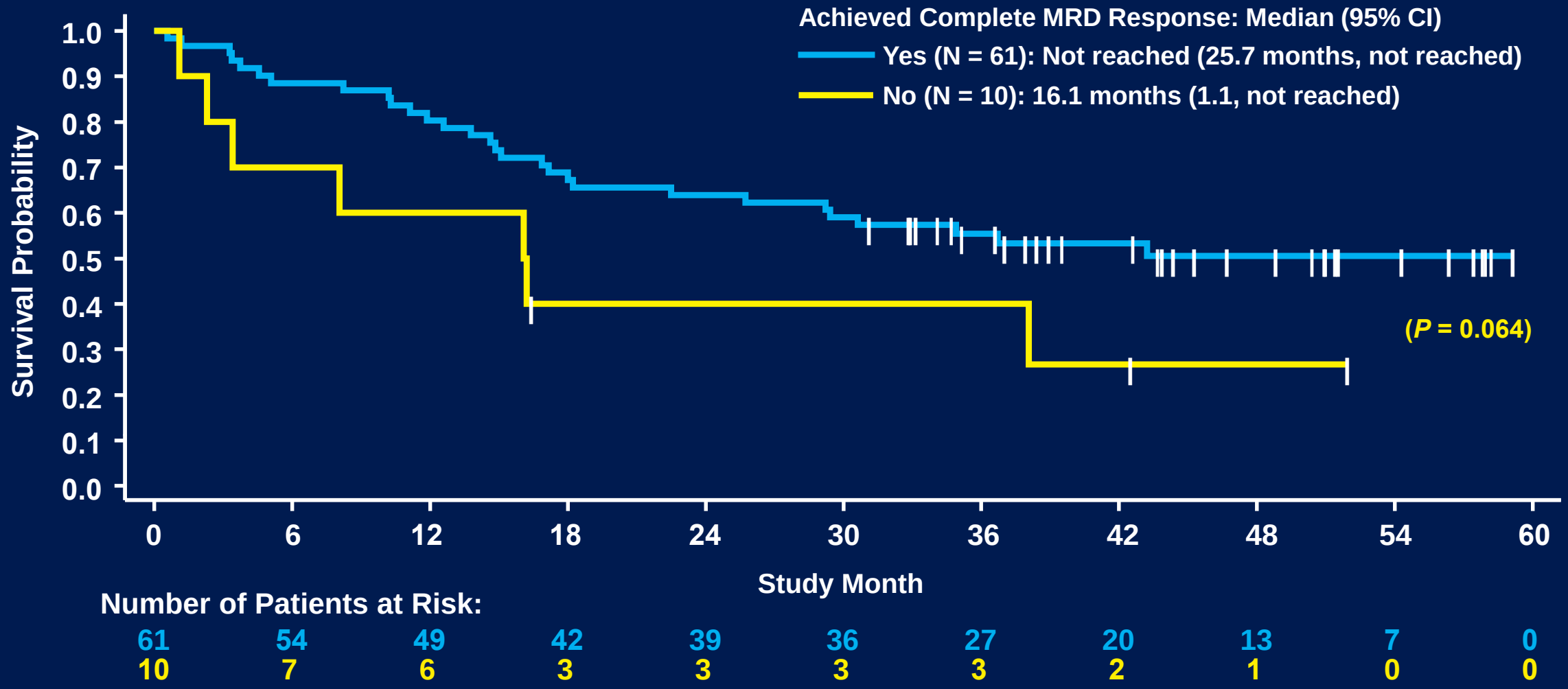
# Overall Survival by Complete MRD Response: All Patients Analyzed




CI, confidence interval; MRD, minimal residual disease

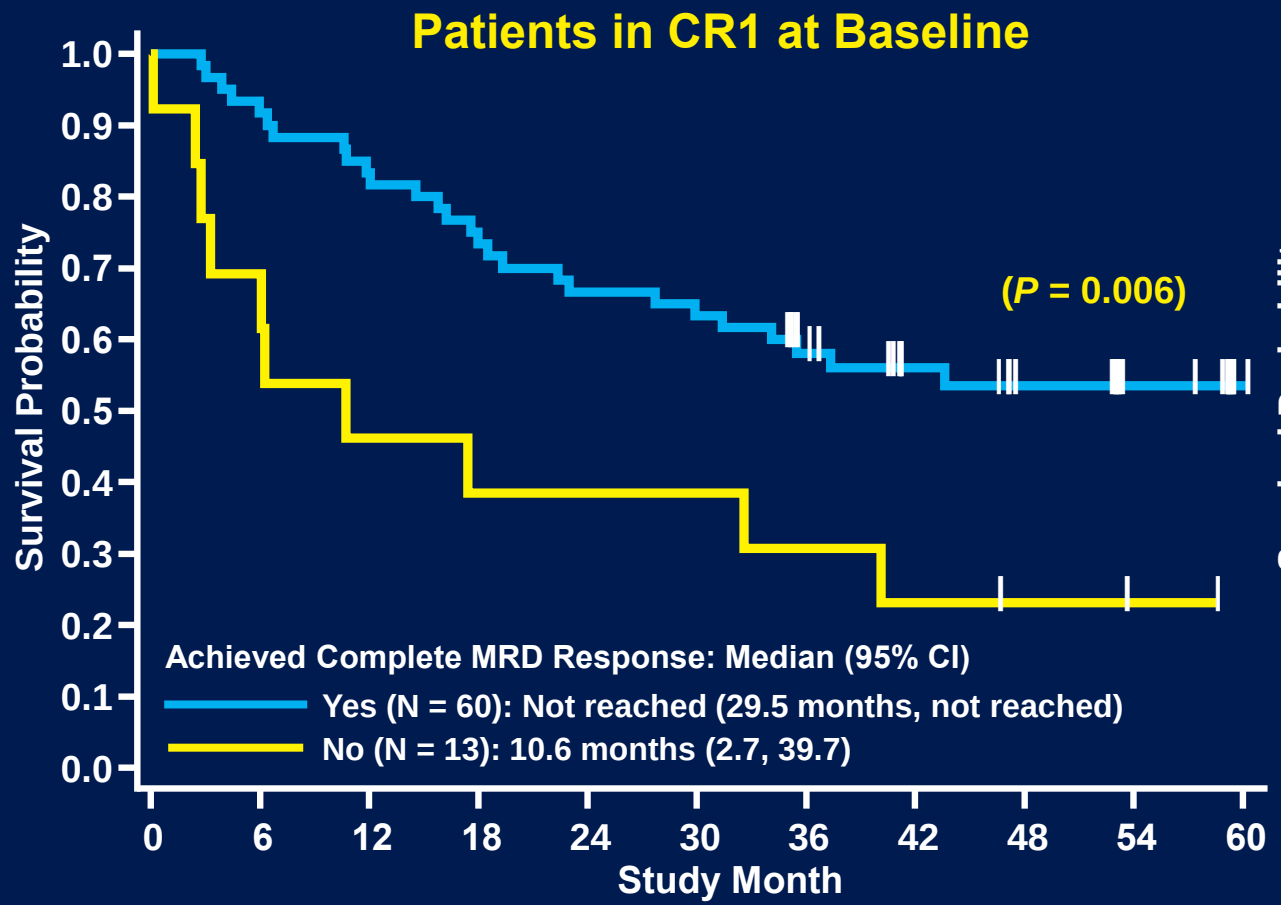
Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of $10^{-4}$

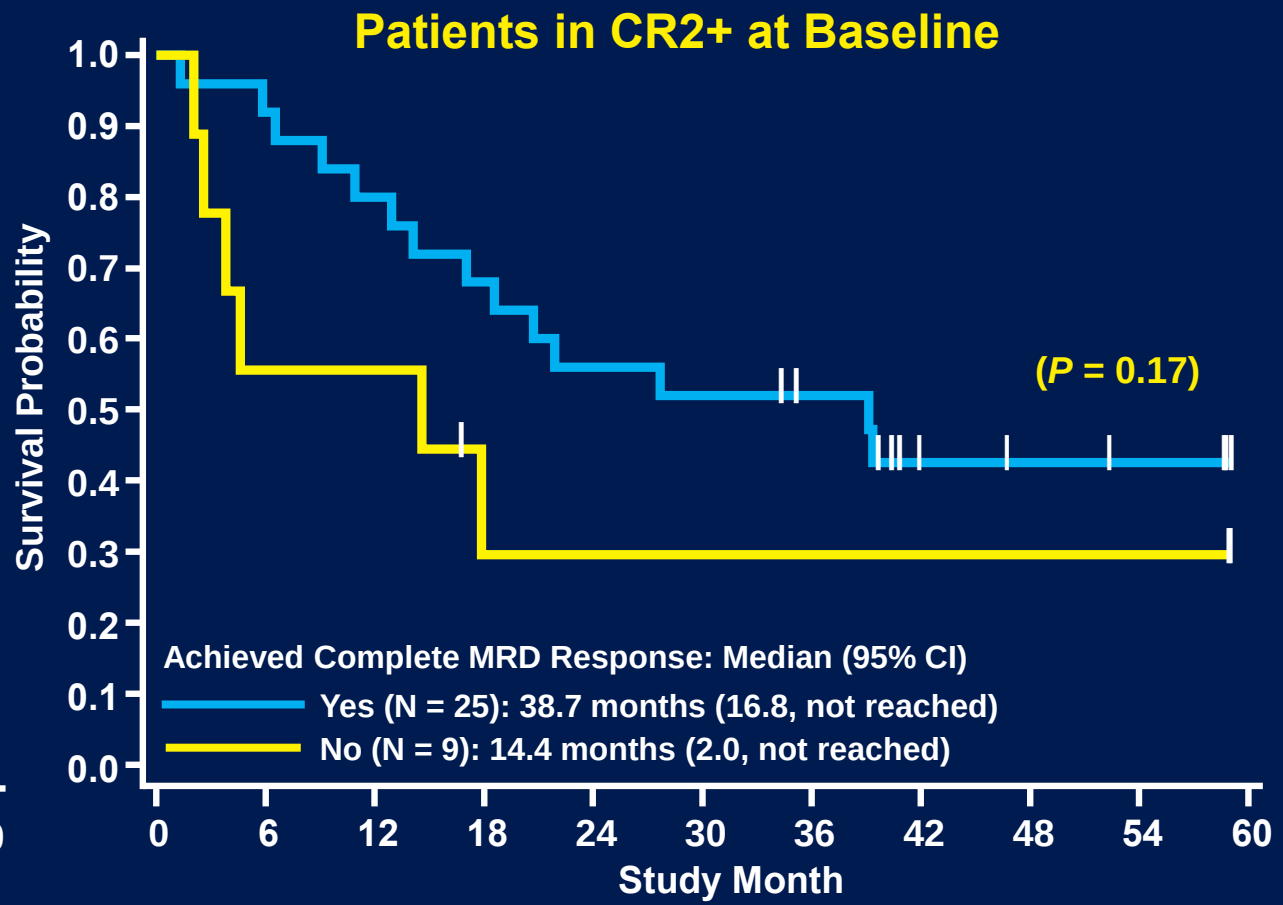
# Overall Survival After HSCT by Complete MRD Response: Patients Who Received HSCT in CCR




CI, confidence interval; CCR, continuous complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease
Includes patients analyzed for MRD response who received HSCT in continuous complete remission (N = 71)

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




**Number of Patients at Risk:**

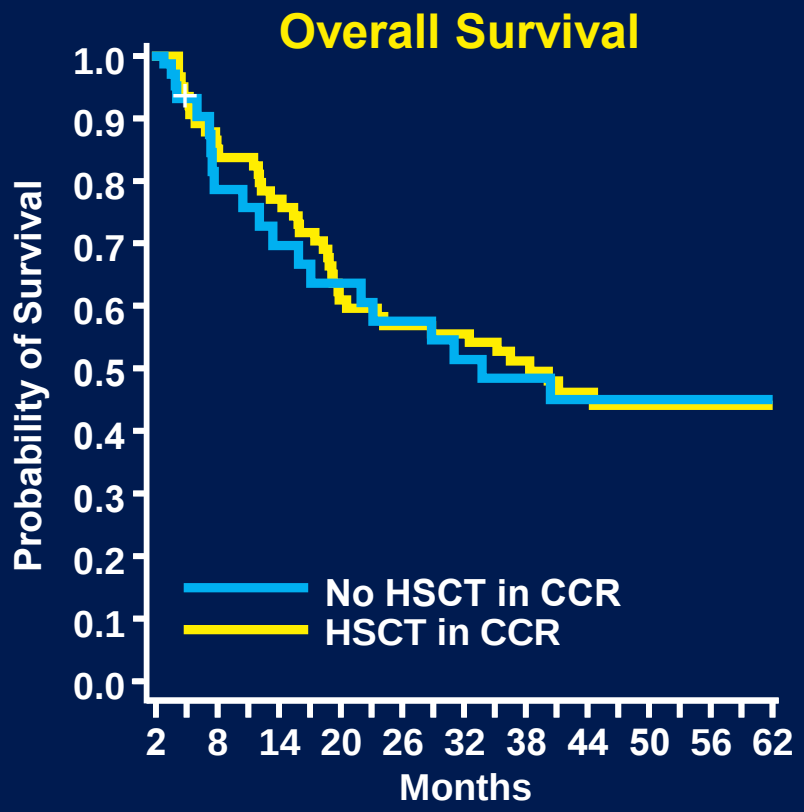
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 60 | 55 | 49 | 44 | 40 | 38 | 29 | 22 | 17 | 10 | 0 |
| 13 | 9 | 6 | 5 | 5 | 5 | 4 | 3 | 2 | 1 | 0 |

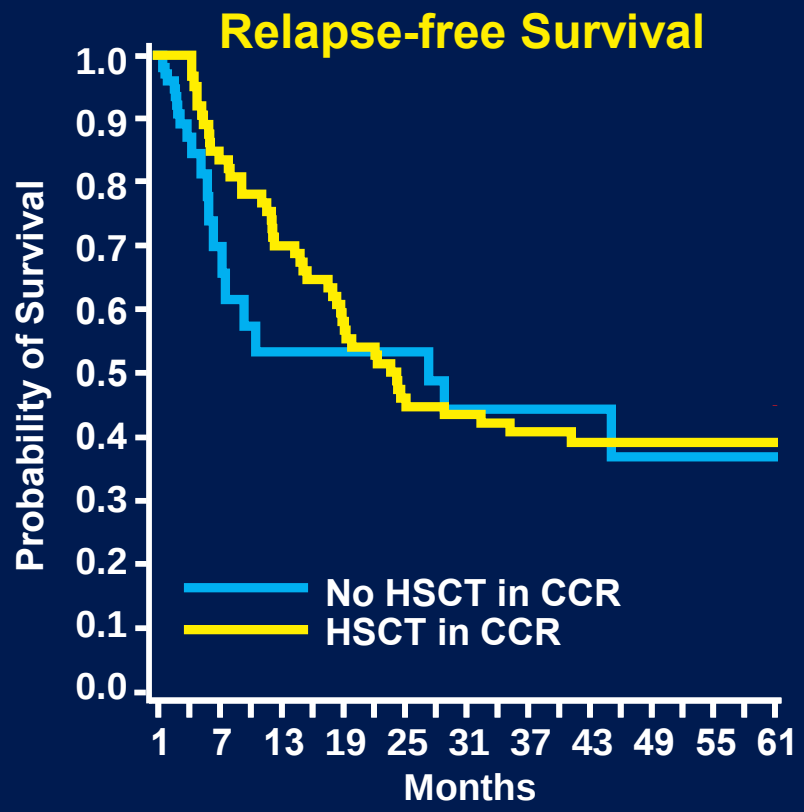
**Number of Patients at Risk:**

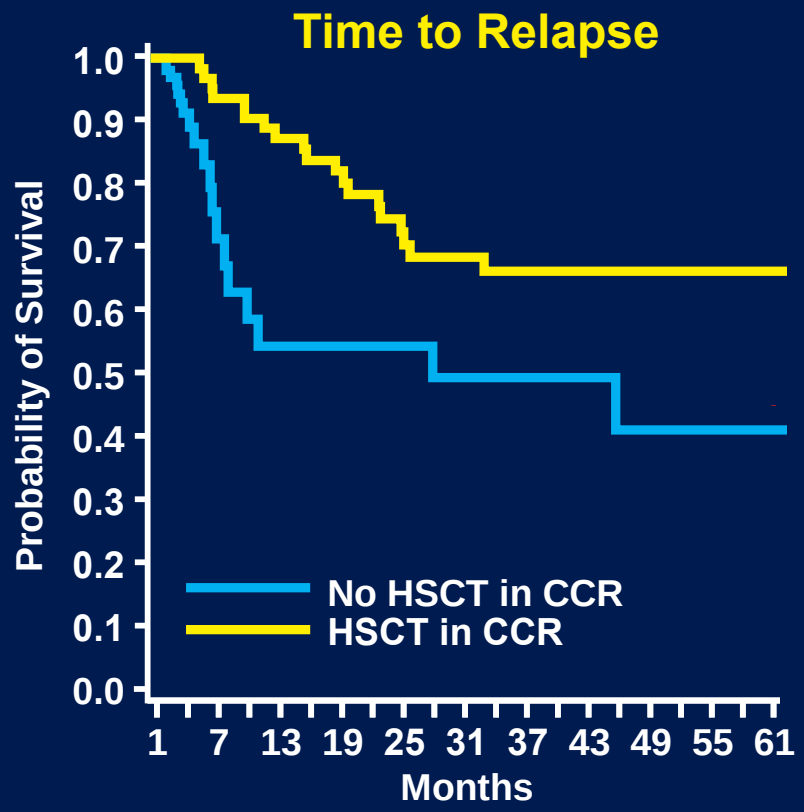
| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 25 | 23 | 20 | 17 | 14 | 13 | 11 | 5 | 4 | 3 | 0 |
| 9 | 5 | 5 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 |

CI, confidence interval; CR1, first complete remission; CR2+ second or later complete remission; MRD, minimal residual disease
Includes patients analyzed for MRD response (N = 107)

# Outcomes by HSCT Use in CCR: Simon-Makuch Analyses; Landmark of 2 Months




**Number of Patients at Risk:**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| non-HSCT | 94 | 27 | 23 | 21 | 19 | 17 | 14 | 10 | 10 | 9 | 0 |
| HSCT | 15 | 63 | 58 | 45 | 42 | 41 | 31 | 22 | 15 | 7 | 0 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| non-HSCT | 103 | 16 | 12 | 12 | 12 | 10 | 8 | 6 | 5 | 5 | 0 |
| HSCT | 2 | 62 | 53 | 42 | 34 | 33 | 25 | 19 | 14 | 7 | 0 |

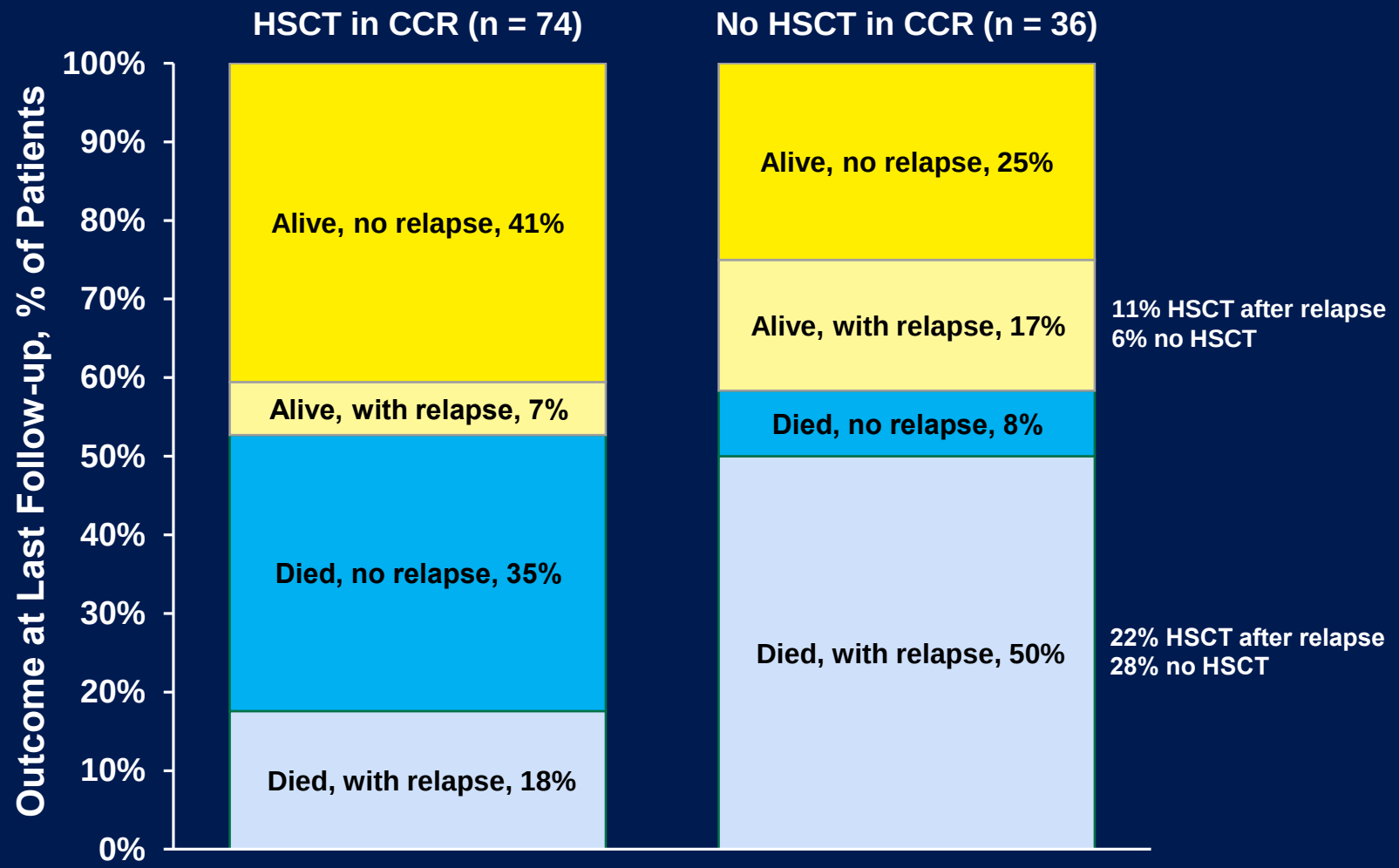
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| non-HSCT | 101 | 16 | 12 | 12 | 11 | 10 | 8 | 6 | 5 | 5 | 0 |
| HSCT | 2 | 61 | 53 | 42 | 34 | 33 | 25 | 19 | 14 | 7 | 0 |

Landmark of 2 months for overall survival and 40 days for other analyses was used to ensure non-zero number of patients in the HSCT group
CCR, continuous complete remission; HSCT, hematopoietic stem cell transplantation

# 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, hematopoietic stem cell transplantation
Includes patients analyzed for overall survival (N = 110)

# Conclusions

- This multinational study included adults with BCP-ALL in hematologic complete remission with persistent MRD or MRD relapse
- Median long-term follow-up was 53.1 months after blinatumomab treatment
- Median overall survival was 36.5 months
- Overall survival reached a plateau >50% at ~48 months (overall and CR1 or CR2+)
- 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
- 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, hematopoietic stem cell transplantation; MRD, minimal residual disease; $Ph^-$, Philadelphia-negative