XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

# Impatto clinico della MRD nella LLA

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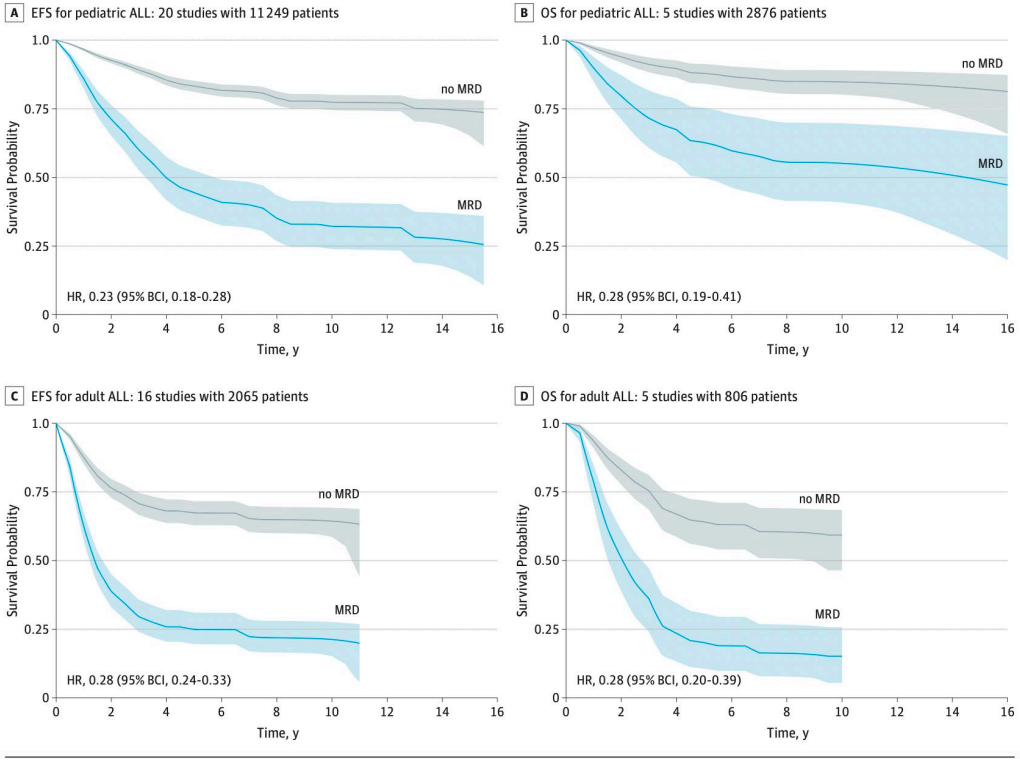
# Disclosures of Daniela Cilloni

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Abbvie | | | | | X | X | |
| Astellas | X | | | | | | |
| BMS | | | | | X | X | |
| Daiichi Sankyo | | | | | | X | |
| GSK | | | | | X | X | |
| Novartis | | | | | X | | |

# Measurable Residual Disease (MRD) in ALL

- 1) Why?
- 2) How?
- 3) Optimal time points and threshold
- 4) How should MRD guide decisions for HSCT during first line therapy?
- 5) How should MRD guide decisions for HSCT undergoing salvage therapy?

# MRD has a strong impact on OS and EFS in ALL

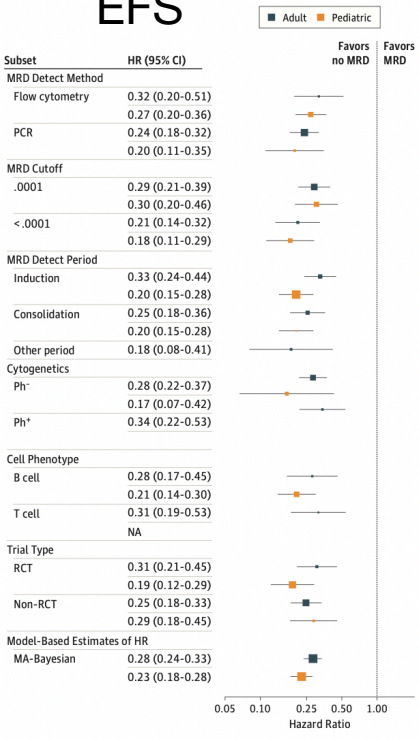



**Meta-analysis** of 39 publications 13637 patients
2076 adult
11249 pediatric

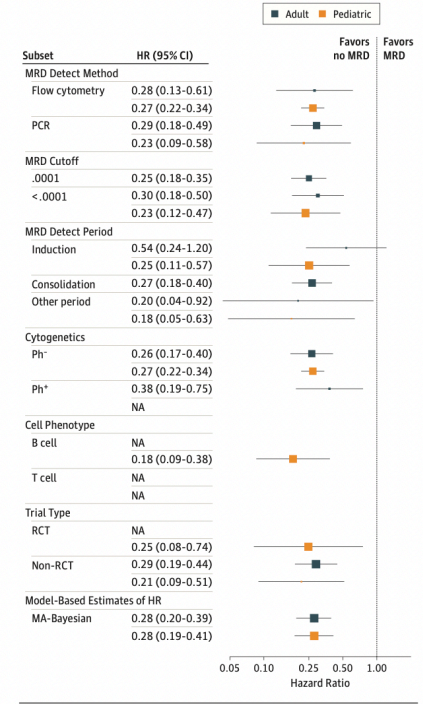
*Berry DA, et al JAMA Oncol*. 2017;

# Prognostic significance is consistent across therapies, methods of detection and times of MRD assessment, cutoff levels, and disease subtypes

## EFS




## OS



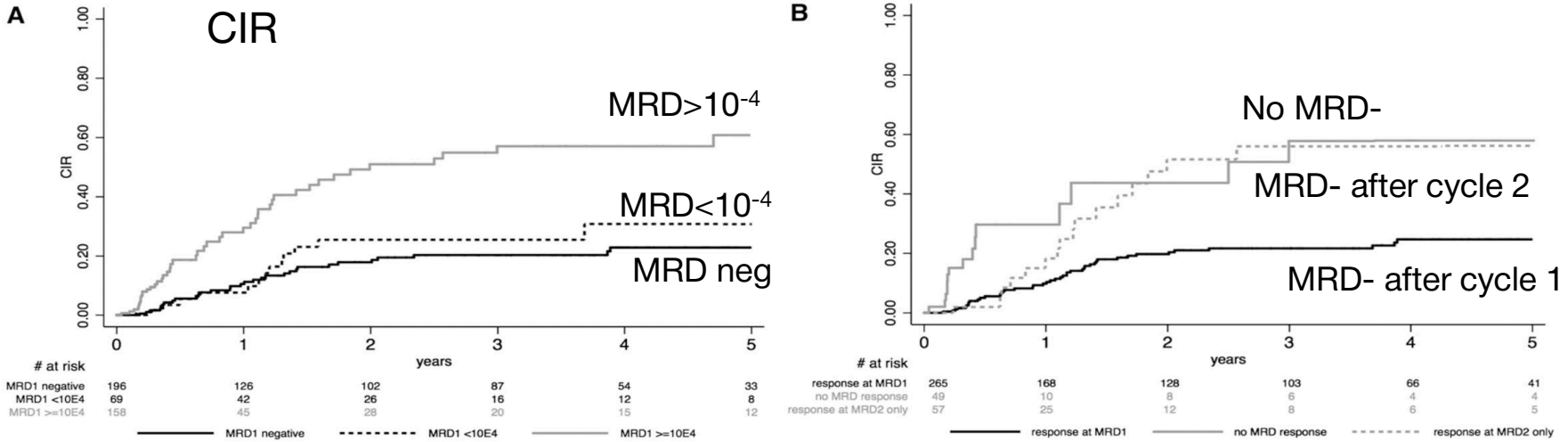

*Berry DA, et al JAMA Oncol*. 2017

**Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia**

Kheira Beldjord,[1] Sylvie Chevret,[2] Vahid Asnafi,[3] Françoise Huguet,[4] Marie-Laure Boulland,[5] Thibaut Leguay,[6] Xavier Thomas,[7] Jean-Michel Cayuela,[1] Nathalie Grardel,[8] Yves Chalandon,[9] Nicolas Boissel,[1] Beat Schaefer,[10] Eric Delabesse,[4] Hélène Cavé,[11] Patrice Chevallier,[12] Agnès Buzyn,[3] Thierry Fest,[5] Oumedaly Reman,[13] Jean-Paul Vernant,[14] Véronique Lhéritier,[15] Marie C. Béné,[12] Marina Lafage,[16] Elizabeth Macintyre,[3] Norbert Ifrah,[17] and Hervé Dombret,[1] on behalf of the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL)

GRAALL 2003
GRAALL 2005

423 B-ALL (Ph-) and T-ALL in 1° CR




Post-induction MRD1 levels (evaluated at week 6)

CIR= cumulative incidence of relapse

*Beldjord K, et al. Blood 12, 2014, 123, 24.*

- 1) Why?
- 2) **How?**
- 3) Optimal time points and threshold
- 4) How should MRD inform decisions for HSCT during first line therapy?
- 5) How should MRD inform decisions for HSCT undergoing salvage therapy?
- 6) How should MRD inform decisions for nontransplant interventions

# Methods for MRD evaluation

| Method | Specimen | Sensitivity | Advantages | Disadvantages |
|---|---|---|---|---|
| MFC for "difference from normal" | Fresh viable cells | ~1 × $10^{-4}$ | • Fast<br>• Relatively inexpensive<br>• Does not require pretreatment specimen | • Lower sensitivity than other available MRD assays<br>• May fail to identify phenotypic shifts<br>• Interlaboratory variability |
| PCR for IG/TR gene rearrangements | DNA | ~1 × $10^{-4}$ to $10^{-5}$ | • Specific for leukemic sequences | • Time-consuming and labor intensive<br>• Requires standardization (not done within the United States)<br>• Requires pretreatment specimen to identify leukemia clonotype<br>• Does not provide information about antigen expression |
| RT-PCR for *BCR*::*ABL1* | RNA | ~1 × $10^{-4}$ to 1 × $10^{-5}$ | • Relatively simple to perform<br>• Uses standard primers used for diagnostic purposes | • Applicable only to Ph-positive ALL (~1/3 of ALL cases)<br>• Not optimal for MRD assessment of multilineage Ph-positive ALL<br>• Does not provide information about antigen expression |
| NGS for IG/TR gene rearrangements | DNA | ~1 × $10^{-6}$ | • More sensitive than other available MRD assays<br>• Specific for leukemic sequences<br>• Only FDA-cleared assay for MRD in B-cell ALL (ie, clonoSEQ) | • Relatively expensive (vs MFC or RT-PCR for *BCR*::*ABL1*)<br>• Requires pretreatment specimen to identify leukemia clonotype<br>• Does not provide information about antigen expression |

- 1) Why?
- 2) How?
- 3) **Optimal time points and threshold**
- 4) How should MRD inform decisions for HSCT during first line therapy?
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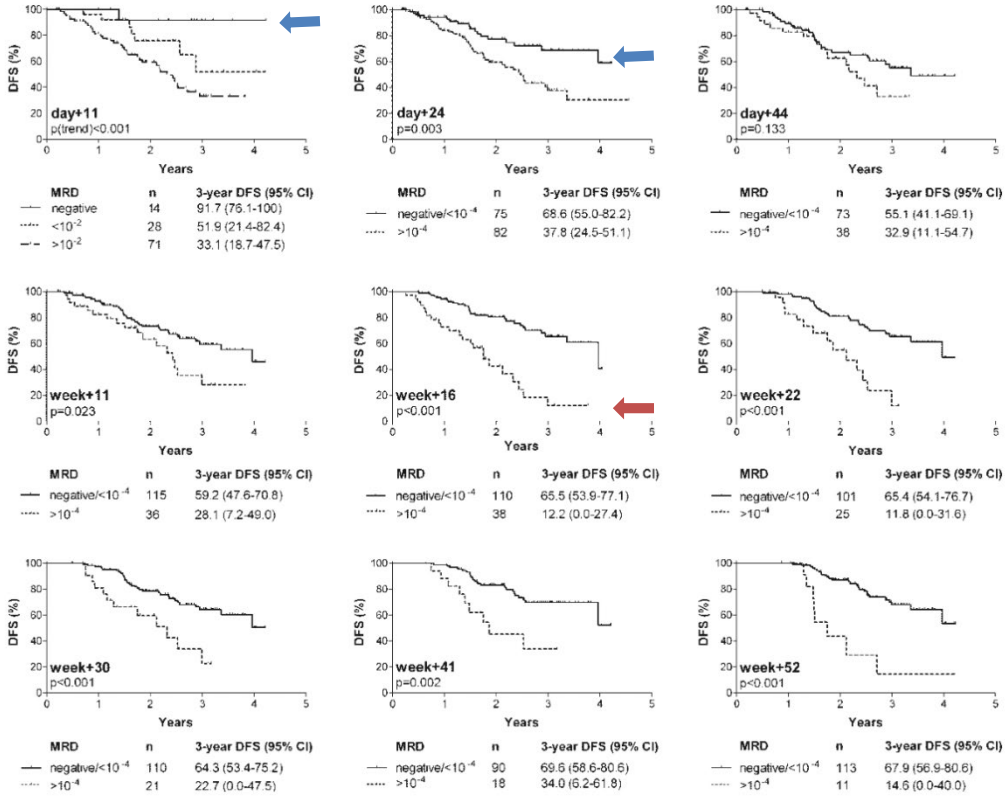
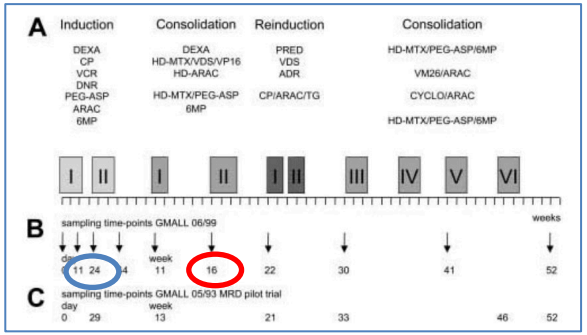
# Probability of disease-free survival (DFS) according to MRD results at 9 time-points during first year of therapy




GMALL trials 05/93 and 06/99
196 standard risk pts

The presence of MRD $<10^{-4}$ at any timepoint, was strongly predictive of disease-free survival (DFS)

Very rapid disease clearance (MRD $<10^{-4}$ at day 11 and 24 of induction) was associated with low risk for relapse

*Bruggemann et al. Blood 2006*

| National Study Group | Patient age (y) | Risk stratification criteria* | | | |
|---|---|---|---|---|---|
| | | Postinduction MRD | Cytogenetics/ genetics† | WBC ($\times 10^9$/L) | Miscellaneous |
| GMALL (Germany) | <55 | ≥0.01% after consolidation (wk 16 onward) | *KMT2A*$^+$ | >30 (B) | Late CR, pro-B, early/ mature-T |
| GIMEMA (Italy) | ≤65 | ≥0.01% after early consolidation (wk 10-16), any positivity (wk 22) | Adverse, *KMT2A*$^+$ | >100 | Early/mature-T |
| HOVON (The Netherlands) | <40 | ≥0.01% after consolidation (wk 14-16) | Adverse *KMT2A*, hypodiploidy, complex karyotype | >30 (B), >100 (T) | Late CR |
| PALG (Poland) | <55 | ≥0.1% after induction<br>≥0.01% during/after consolidation | *KMT2A*$^+$ | >30 (B), >100 (T) | CNS$^+$ |
| UK NCRI ALL Group (United Kingdom) | <40 | ≥0.1% after induction and consolidation (mathematical risk model integrating MRD, cytogenetics and WBC) | Adverse | High count | — |
| FALL (Finland) | <45 | ≥0.1% after consolidation block B | Abn11q23, hypodiploidy | >100 | Late CR, d15 BM blasts >25% |
| RALL (Russia) | <55 | Positive during/after consolidation | t(4;11), t(1;19), *KMT2A*$^+$ | — | Age >30 |
| SVALL (Sweden) | <65 | ≥0.1% after consolidation | Hypodiploidy, *KMT2A*$^+$ | — | EOI BM blasts >5% |
| PETHEMA (Spain) | <55 (60 fit) | ≥0.1% after induction<br>≥0.01% during/after consolidation | — | — | — |
| GRAALL (France/ Belgium/ Switzerland) | <60 | ≥0.1% after induction at wk 6 or ≥0.01% after consolidation at wk 12 | — | — | — |
| CELL (Czech Republic) | <65 | ≥0.1% after induction<br>≥0.01% after consolidation | *KMT2A*$^+$ | >30 (B) | Early/mature-T |

- **Good responders** have MRD levels: **<0.01%**

# Optimal time points and thresholds

**MRD<0.01%**

**Pediatric patients:** + **33** (post induction), **+ 78** (post-consolidation)
**Adult patients**: post induction and post consolidation

- 1) Why?
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- **4) How should MRD inform decisions for HSCT during first line therapy?**
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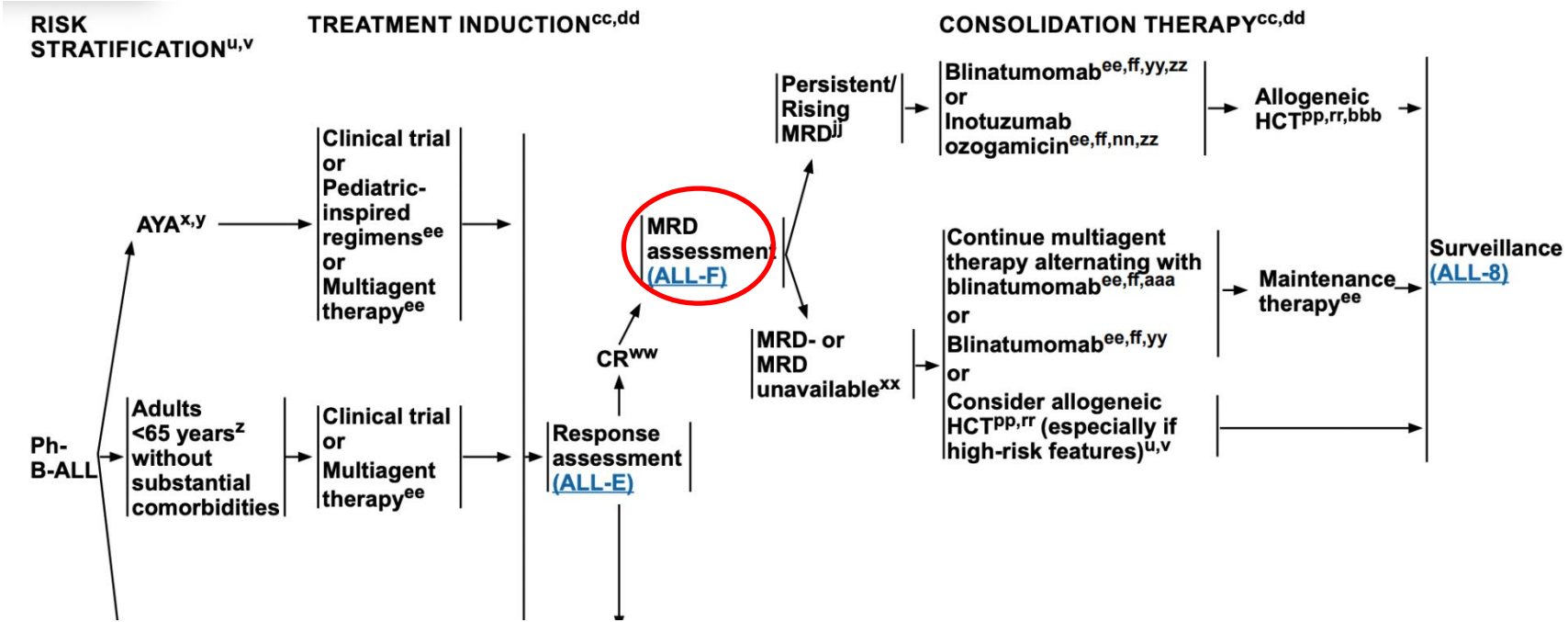
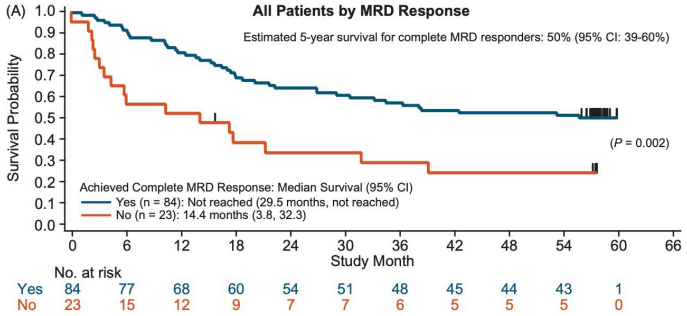
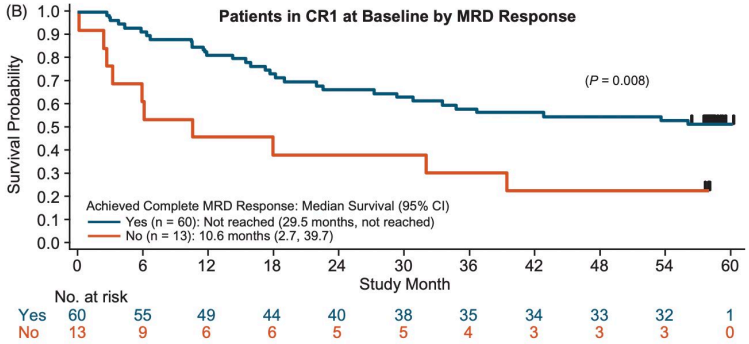
# MRD post induction guides the post remission strategy

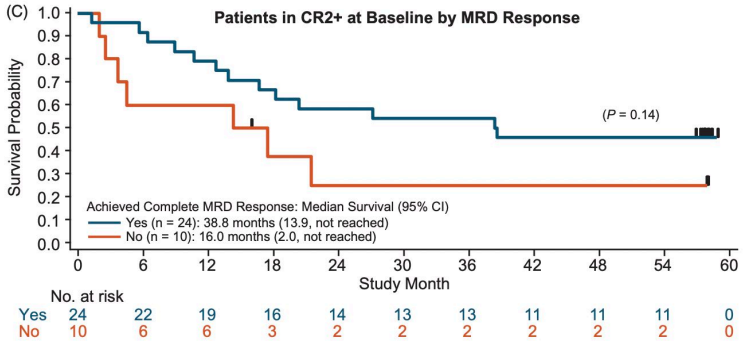



*NCCN 2024*

# Blinatumomab for MRD+ ALL (Blast study)



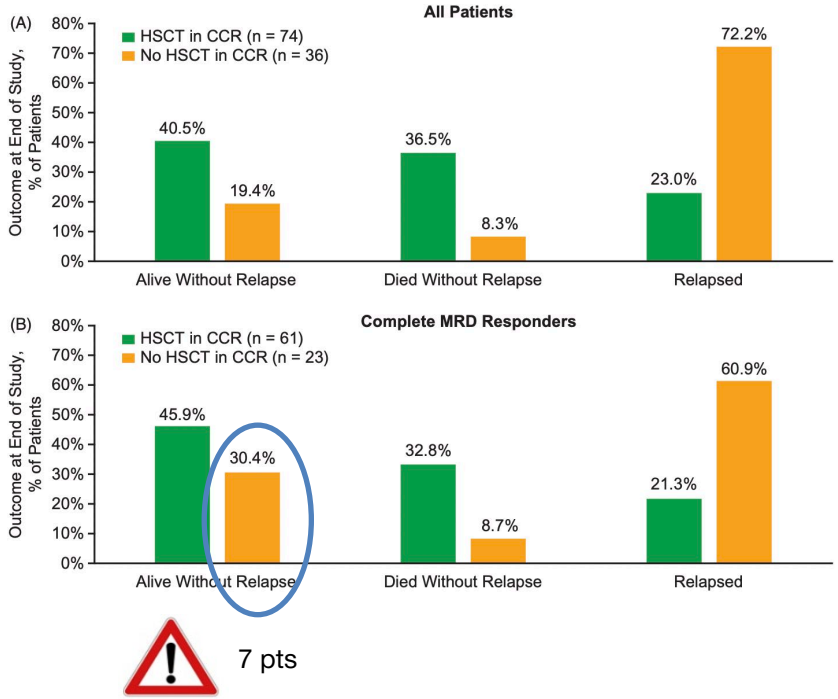



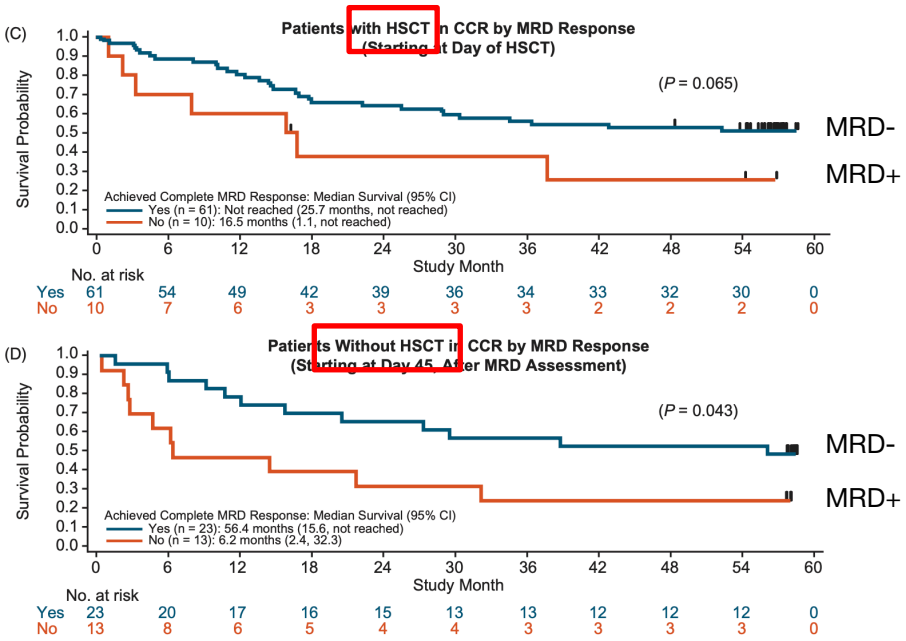

Enrolled pts with MRD>$10^{-3}$

77% of pts obtained MRD neg after 1 cycle of blinatumomab

*Gökbuget N, et al. Leuk Lymph 2020*

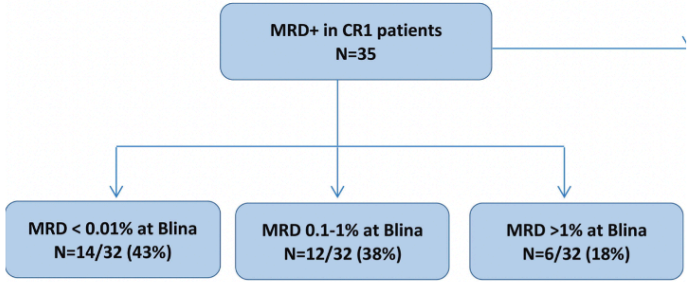
# Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia




*Gökbuget N, et al. Leuk Lymph 2020*

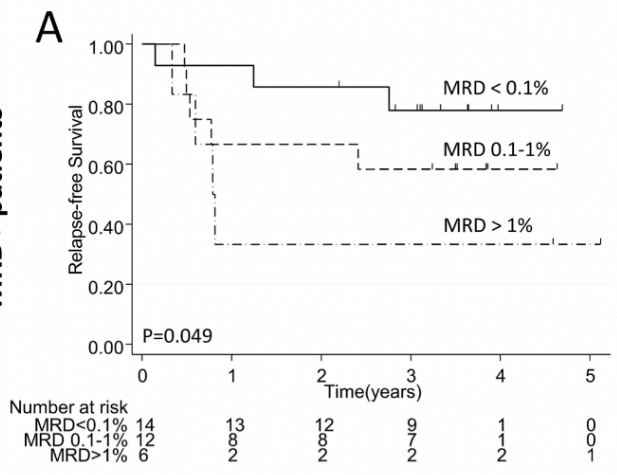
# RFS and OS according to MRD levels before blinatumomab

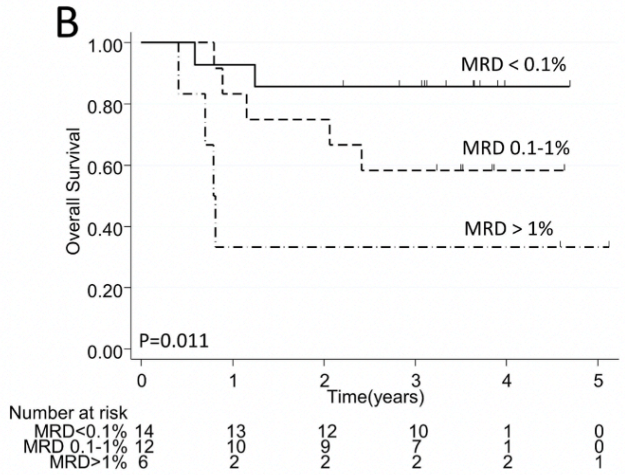



RFS

OS

MRD+ patients



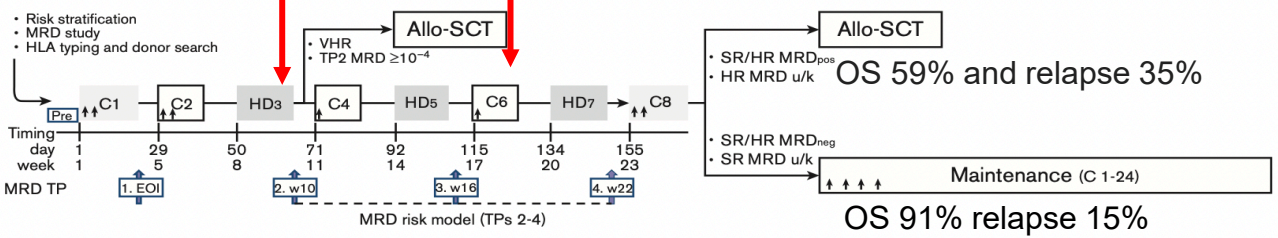




*Cabannes-Hamy A, et al. Haematologica 2022*

# GIMEMA LAL 2317: Primary end-point MRD negativity after cycle 3

blina

blina




| Treatment phase | Drugs | Dosing and administration | Days |
|---|---|---|---|
| **Prephase** | Prednisone<br>Cyclophosphamide | 20 mg/m² PO q12h<br>300 (200 if age >55) mg/m² IV over 30' | −5 to −1<br>−3 to −1 |
| **Course 1** | Idarubicin<br>Vincristine<br>Dexamethasone<br>Pegaspargase<br>IT prophylaxis(†) | 12 (9 if age >55) mg/m² IV over 30'<br>1.4 mg/m² (max. 2 mg) IV push<br>5 mg/m² IV over 5' q12h<br>2000 (1000 if age >55) IU/m² IV over 120' | 1,2<br>1,8,15,22<br>1-5, 15-19<br>10<br>1,15 |
| **Courses 2,4,6** | Vincristine<br>Idarubicin<br>Cyclophosphamide<br>Dexamethasone<br>Cytarabine<br>Pegaspargase<br>6-mercaptopurine<br>IT prophylaxis (†) | 1.4 mg/m² (max. 2 mg) IV push<br>12 (9 if age >55) mg/m² IV over 30'<br>1000 mg/m² IV over 60'<br>5 mg/m² PO q12h<br>75 mg/m² SC<br>2000 (1000 if age >55) IU/m² IV over 120'<br>60 mg/m² PO q12h | 1,8 (no course 2)<br>1<br>1<br>1-5<br>2-5<br>8 (no course 4)<br>1-10<br>1 (and 15, course 2) |
| **HD courses 3,7** | Methotrexate<br><br>Cytarabine | 2500 (B), 5000 (T), 1500 (age >55) mg/m² IV over 24h; FAR<br>2000 mg/m² IV q12h | 1<br><br>3,4 |

† Methotrexate 12.5 mg, Cytarabine 50 mg, Dexamethasone 4 mg (or Methylprednisolone 40 mg)

| Treatment phase | Drugs | Dosing and administration | Days |
|---|---|---|---|
| **HD course 5** | Methotrexate<br><br>Pegaspargase<br>6-mercaptopurine | 2500 (B), 5000 (T), 1500 (age >55) mg/m² IV over 24 h; FAR<br>2000 (1000 if age >55) IU/m² IV over 120'<br>25 mg/m² PO | 1<br><br>3<br>8-18 |
| **Course 8** | Vincristine<br>Idarubicin<br>Dexamethasone<br>Cyclophosphamide<br>Prednisone<br>IT prophylaxis (†) | 1.4 mg/m² (max. 2 mg) IV push<br>10 (7.5 if age >55) mg/m² IV over 30'<br>5 mg/m² PO q12h<br>300 (200 if age >55) mg/m² IV over 30'<br>20 mg/m² PO q12h | 1,8<br>1,8<br>1-5<br>1-3<br>8-12<br>1,15 |
| **Maintenance** courses 1,3,5,7,9,11 | Cyclophosphamide<br>6-mercaptopurine<br>Methotrexate<br>IT prophylaxis (†) | 100 mg/m² PO<br>75 mg/m² PO<br>15 mg/m² PO/IM | 1-4<br>8-28<br>8,15,22<br>1 (courses 3,5) |
| courses 2,4,6,8,10,12 | Vincristine<br>Prednisone<br>6-mercaptopurine<br>Methotrexate<br>IT prophylaxis (†) | 1 mg/m² (max. 2 mg) IV push<br>20 mg/m² PO q12h<br>75 mg/m² PO<br>15 mg/m² PO/IM | 1<br>1-5<br>8-28<br>8,15,22<br>1 (courses 2,4) |
| courses 13-24 | 6-mercaptopurine<br>Methotrexate | 75 mg/m² PO<br>15 mg/m² PO/IM | 8-28<br>1,8,15,22 |

Backbone of LAL1913 protocol

MRD negativity increased from 72% to 93% (P<0.001) after blinatumomab

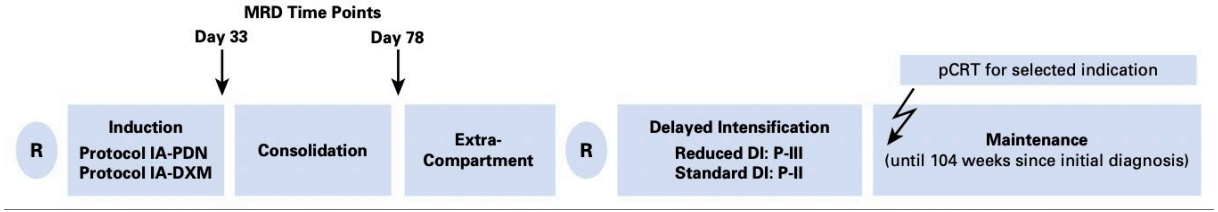
23/30 MRD+ (73%) became MRD-

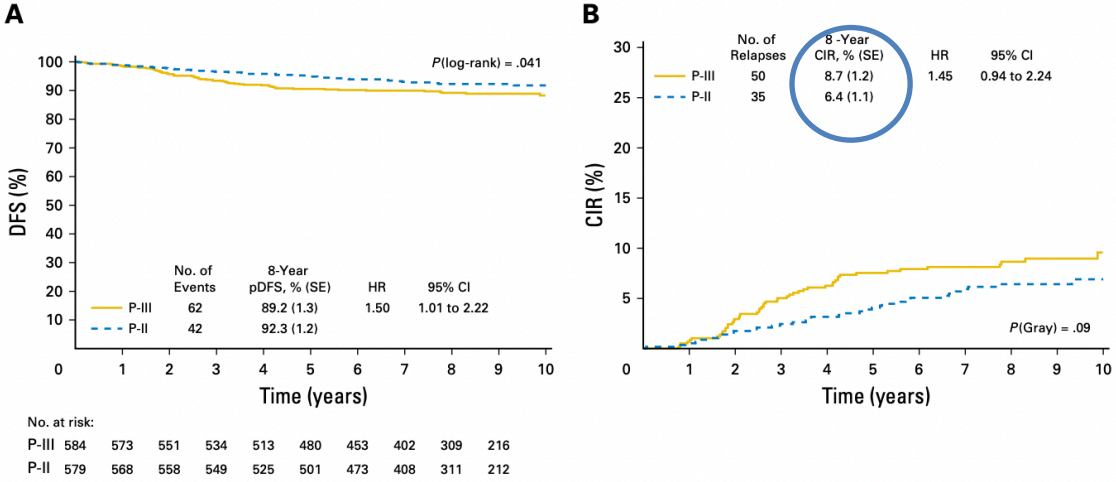
*Bassan R. et al Blood 2025*

MRD positivity identifies patients who can benefit from dose intensification

Treatment de-intensification is allowed in patients with early and deep MRD negativity?

# Reduced-Intensity Delayed Intensification in Standard-Risk Pediatric Acute Lymphoblastic Leukemia Defined by Undetectable Minimal Residual Disease: Results of an International Randomized Trial (AIEOP-BFM ALL 2000)




- Patients with ETV6-RUNX1–positive ALL
- 1 to 6 years of age

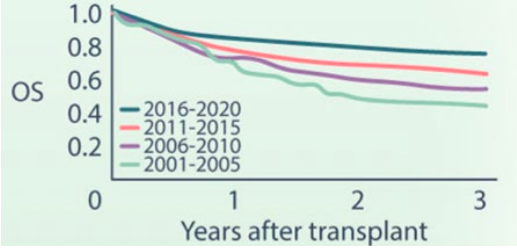
performed equally well in both arms.

Incidence of death during remission was comparable equivalent toxicity

*Schrappe M, et al. JCO 2018*

# Improved post-transplant outcomes since 2000 for Ph-positive acute lymphoblastic leukemia in first remission: A study from the EBMT Acute Leukemia Working Party

Ali Bazarbachi[1] | Myriam Labopin[2] | Iman Abou Dalle[1] | Ibrahim Yakoub-Agha[3] | Gérard Socié[4] | Thomas Schroeder[5] | Didier Blaise[6] | Xavier Poiré[7] | Marie Balsat[8] | Urpu Salmenniemi[9] | Nicolaus Kröger[10] | Alexander Kulagin[11] | Eva Maria Wagner-Drouet[12] | Depei Wu[13] | Eolia Brissot[14] | Arnon Nagler[15] | Sebastian Giebel[16] | Fabio Ciceri[17] | Mohamad Mohty[14]

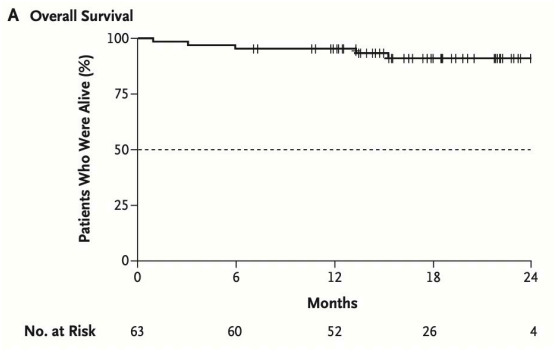



| 3 years | | Relapse | NRM | LFS | OS | chronic GVHD | Ext. chronic GVHD | GRFS |
|---|---|---|---|---|---|---|---|---|
| MRD-negative | 2001–2005 | 34% [26–43] | 25% [18–33] | 41% [32–49] | 52% [43–60] | 47% [37–55] | 26% [18–34] | 34% [26–43] |
| | 2006–2010 | 30% [25–35] | 24% [20–29] | 46% [41–51] | 57.5% [52–62] | 47% [41–52] | 25% [21–30] | 36% [31–41] |
| | 2011–2015 | 24% [21–28] | 23% [20–27] | 52% [48-56.5] | 64% [60–68] | 47% [43–51] | 23% [19–27] | 40% [35–43] |
| | 2016–2020 | 17% [14–20] | 17% [14.5–20] | 66% [62–70] | 77% [73.5–80] | 39% [35–42] | 16% [13–19] | 53% [49–57] |
| | *p* value | <0.001 | 0.013 | <0.001 | <0.001 | 0.006 | 0.001 | 0.001 |
| MRD-positive | 2001–2005 | 48% [39–57] | 25% [17–33] | 27% [19–35] | 41% [32–49] | 55% [45–64] | 29% [20.5–38] | 18% [11–25] |
| | 2006–2010 | 34% [28.5–40] | 24% [19.5–29.5] | 42% [36–47] | 53% [47-59.] | 43% [37–49] | 18% [14–23] | 31% [26–37] |
| | 2011–2015 | 32% [27–37] | 21% [17–26] | 47% [42–52] | 66% [61–70] | 46% [41–51] | 21% [17–26] | 35% [30–40] |
| | 2016–2020 | 23% [19–27] | 17% [14–21] | 60% [55–65] | 73% [68–77] | 40% [35–44] | 22% [18–25.5] | 44% [39–48] |
| | *p* value | 0.001 | 0.047 | <0.001 | <0.001 | 0.036 | 0.12 | <0.001 |

*Hemasphere 2025 Apr*

# Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, M.D., Paolo Di Bartolomeo, M.D., Alessandra Mancino, M.S., Maria-Stefania De Propris, Ph.D., Marco Vignetti, M.D., Anna Guarini, Ph.D., Alessandro Rambaldi, M.D., and Sabina Chiaretti, M.D., Ph.D., for the GIMEMA Investigators*



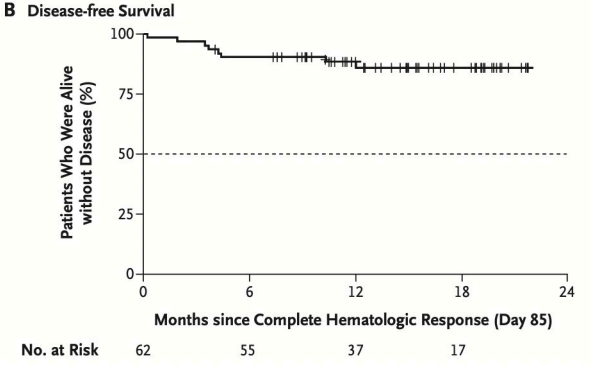
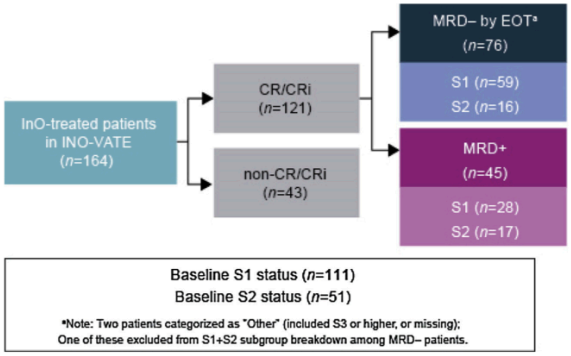



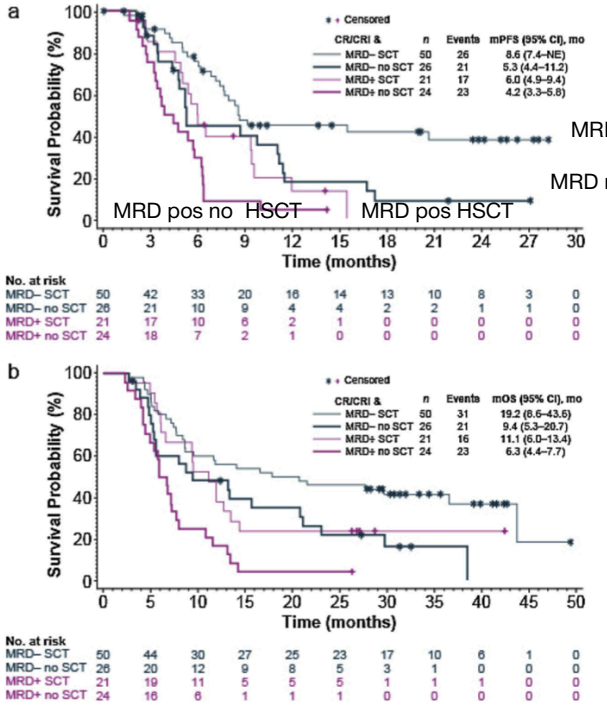

**Table 2. Molecular Responses during Induction Therapy, at the End of Induction Therapy (Day 85), and after Each Blinatumomab Cycle.**

| Assessment | No Molecular Response | Complete Molecular Response | Positive Nonquantifiable Response | Overall Molecular Response |
|---|---|---|---|---|
| | *number of patients/total number (percent)* | | | |
| Induction period | | | | |
| Day 22 | 48/58 (83) | 3/58 (5) | 7/58 (12) | 10/58 (17) |
| Day 45 | 43/60 (72) | 9/60 (15) | 8/60 (13) | 17/60 (28) |
| Day 57 | 38/56 (68) | 11/56 (20) | 7/56 (12) | 18/56 (32) |
| Day 85 | 42/59 (71) | 6/59 (10) | 11/59 (19) | 17/59 (29) |
| Blinatumomab cycle | | | | |
| After cycle 1 | 20/55 (36) | 19/55 (35) | 16/55 (29) | 35/55 (64) |
| After cycle 2 | 22/55 (40) | 23/55 (42) | 10/55 (18) | 33/55 (60) |
| After cycle 3 | 12/40 (30) | 20/40 (50) | 8/40 (20) | 28/40 (70) |
| After cycle 4 | 7/36 (19) | 17/36 (47) | 12/36 (33) | 29/36 (81) |
| After cycle 5 | 8/29 (28) | 16/29 (55) | 5/29 (17) | 21/29 (72) |

- 1) Why?
- 2) How?
- 3) Optimal time points and threshold
- 4) How should MRD inform decisions for HSCT during first line therapy?
- **5) How should MRD inform decisions for HSCT undergoing salvage therapy?**

# MRD negativity impacts on the outcome of ALL patients in the INOVATE trial



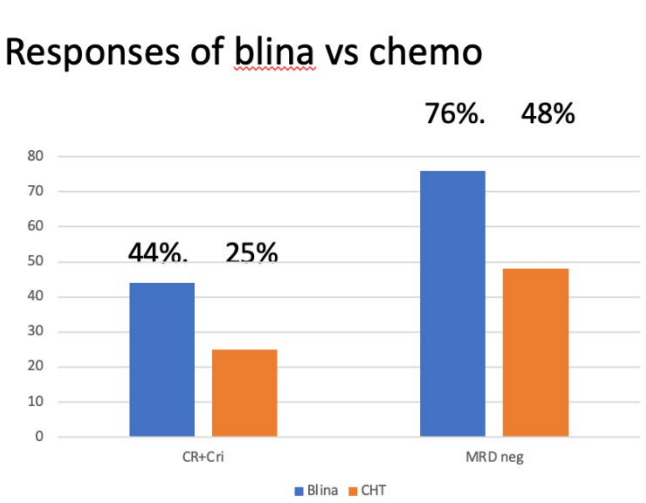



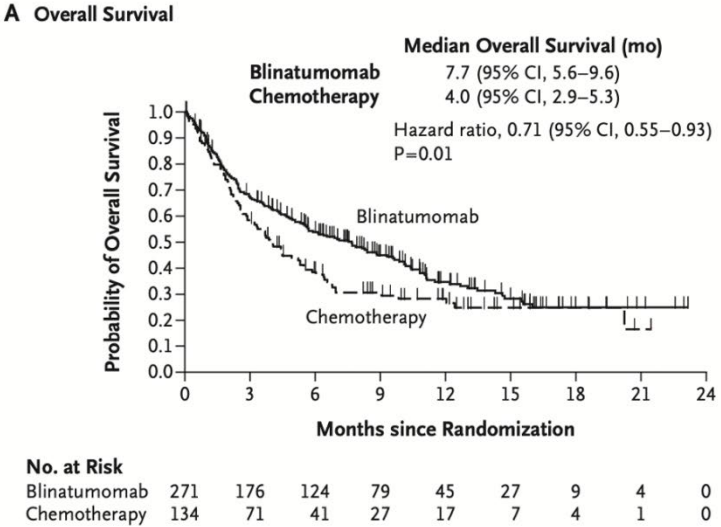

Median PFS

Median OS

*Jabbour et al. Leuk Res 2020*

# Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia




Kantarjian H. et al. N Engl J Med 2017;376:836-47

# MRD in the setting of R/R ALL: Antibodies based study

| Reference | Study | Eligibility | Patients, N | Median age (y) | Prior alloHSCT | ORR | Molecular response | Bridge to alloHSCT | OS estimate or median |
|---|---|---|---|---|---|---|---|---|---|
| **Multicenter antibody-based studies** | | | | | | | | | |
| Kantarjian et al, 2016[122] | INO phase 3 (INO-VATE) | ≥18 years R/R CD22$^+$ ALL | 109 (67% salvage 1) | 47 | 16% | 81% | 63% | 40% | 7.7 mo |
| Topp et al, 2015[191] | Blinatumomab phase 2 | ≥18 years Ph-neg R/R ALL CR1 <12 months | 189 (61% salvage 1) | 36 | 34% | 43% | 35% | 40% | 6.1 months |
| Kantarjian et al, 2017[192] | Blinatomomab phase 3 (TOWER) | ≥18 years Ph-neg R/R ALL CR1 <12 months | 271 (42% salvage 1) | 37 | 35% | 44% | 36% | 14% | 7.7 months |
| Gokbuget et al, 2018[67] | Blinatumomab phase 2 (BLAST) | ≥18 years ALL in HCR MRD ≥ 0.1% | 116 (65% CR1) | 45 | NR | NR | 80% complete MRD response | 67% | 36.5 months |
| Brown et al, 2021[193] | Blinatumomab COG AALL1331 | 1-30 years HR/IR ALL in first relapse | 105 (all salvage 1) | 9 | NR | NR | 79% | 73% | 79% at 24 months |

*Adapted from Gokbuget N et al. Blood 2024*

# Open issues

Significato della MRD positiva non quantificabile

Ruolo delle nuove tecniche: ddPCR, NGS

Significato della MRD misurata con tecniche molto sensibili $10^{-6}$

I pazienti che ottengono una negativizzazione profonda della MRD possono evitare il trapianto?

# **MRD**: **M**isura, **R**ifletti, **D**ecidi