
Progetto Ematologia Romagna

# I nuovi anticorpi monoclonali: Leucemia Acuta Linfoblastica

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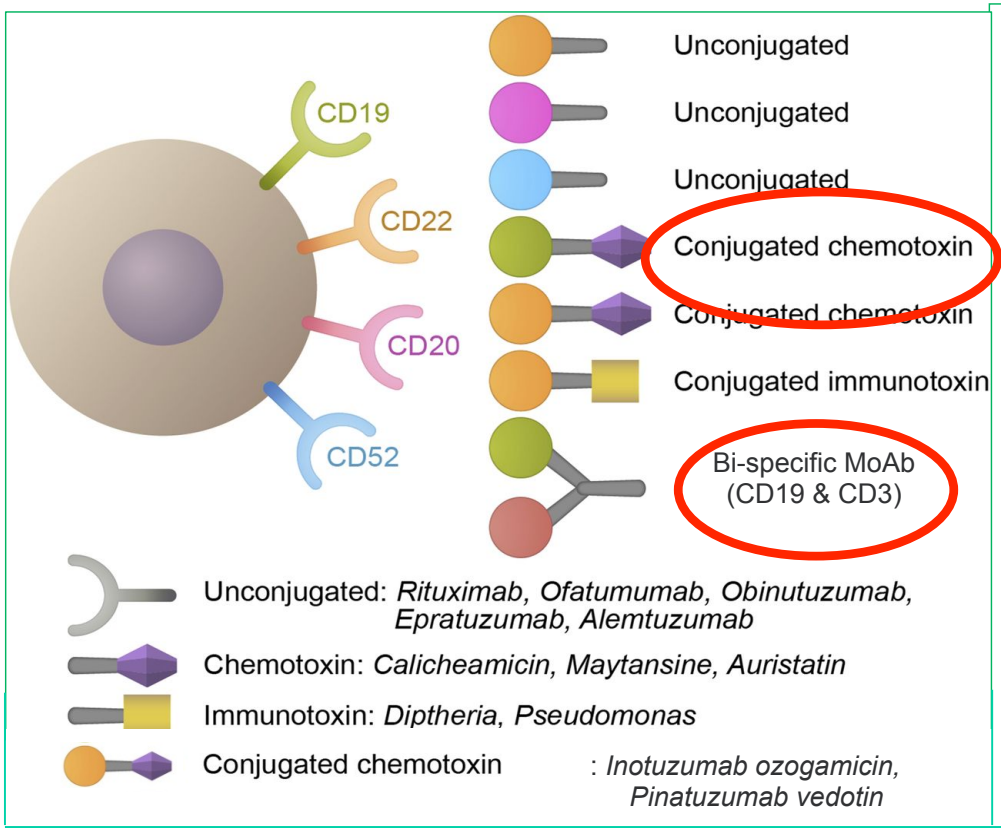
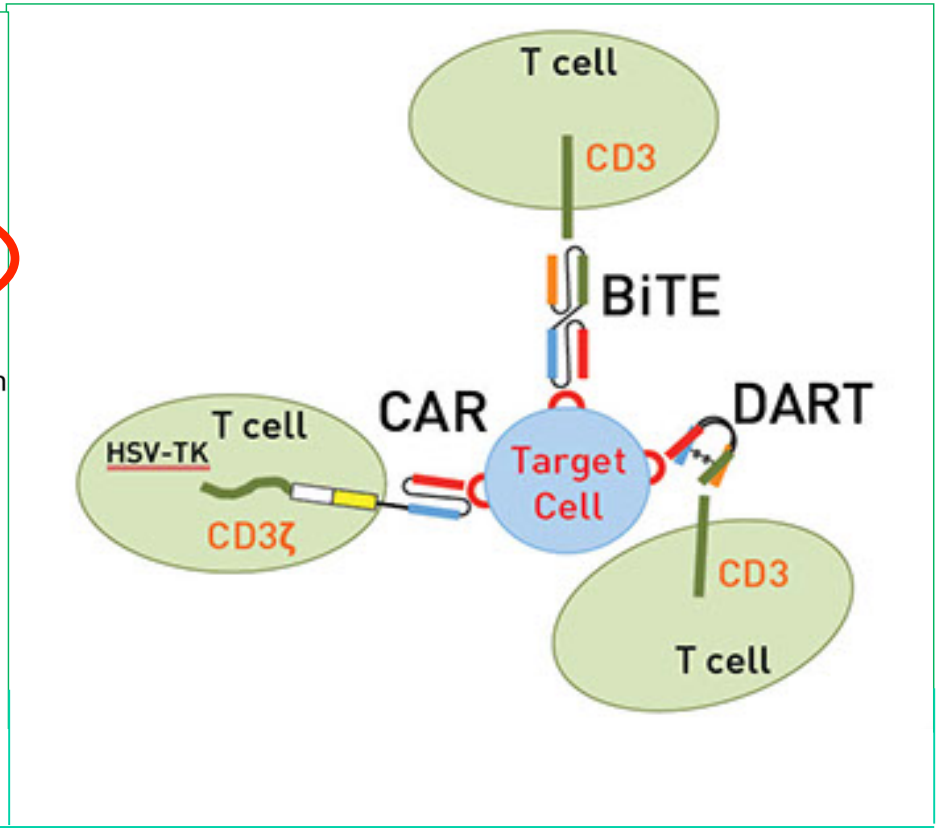
✓ No conflicts of interest to declare

# Immuno-oncology in ALL

## Antibodies, ADCs, immunotoxins, BiTEs, DARTs, CAR-T cells[1,2]




ADC, antibody–drug conjugate; ALL, acute lymphoblastic leukaemia; BiTE, bi-specific T-cell engagers;
CAR, chimeric antigen receptor; DART, dual affinity retargeting molecules; HSV-TK, Herpes Simplex virus thymidine kinase

1. Adapted from Jabbour. Blood 2015;125:4010; 2. http://www.dipersiolab.org/index.html (accessed 20 March 2016)

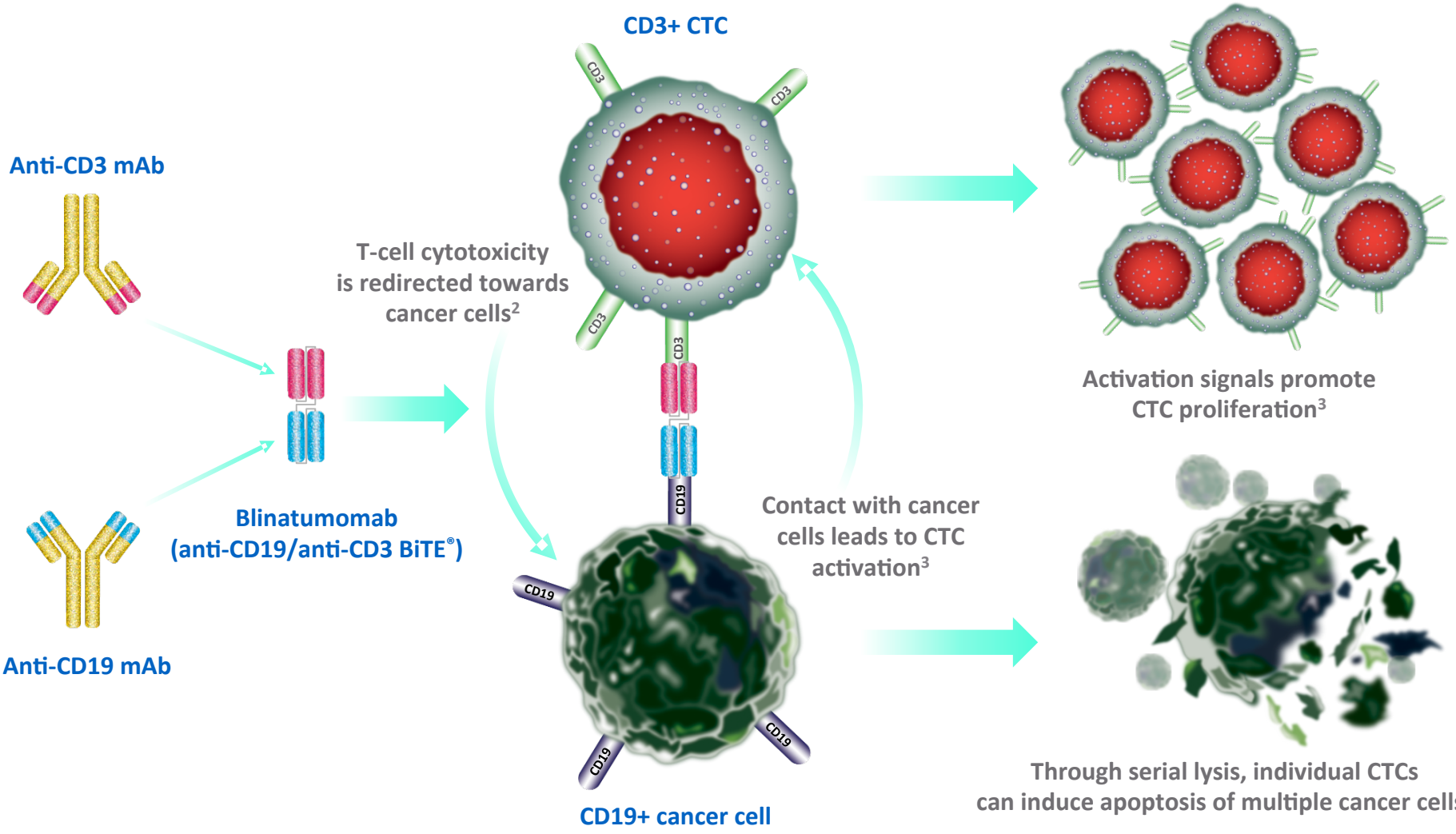
# Expression of antigens in B-cell lineage ALL for potential antibody therapy

| Surface antigen | ALL subtype | Expression on LBC (%) | Monoclonal antibody |
|---|---|---|---|
| CD20 | Burkitt<br>B-precursor | 80–90<br>30–50 | • Rituximab<br>• Ofatumumab |
| CD19 | B-precursor<br>Mature B-ALL | 95–<100<br>94–<100 | T cell-activating therapies<br>• Blinatumomab bispecific CD3/CD19<br>• ADCT-402<br>• CAR T cells |
| CD22 | B-precursor<br>Mature B-ALL | 93–96<br>≈100 | • Inotuzumab ozogamicin<br>• Epratuzumab<br>• Moxetumomab pasudotox |

ALL, acute lymphoblastic leukaemia; CAR T, chimeric antigen receptor T cell; LBC, leukaemia cell line

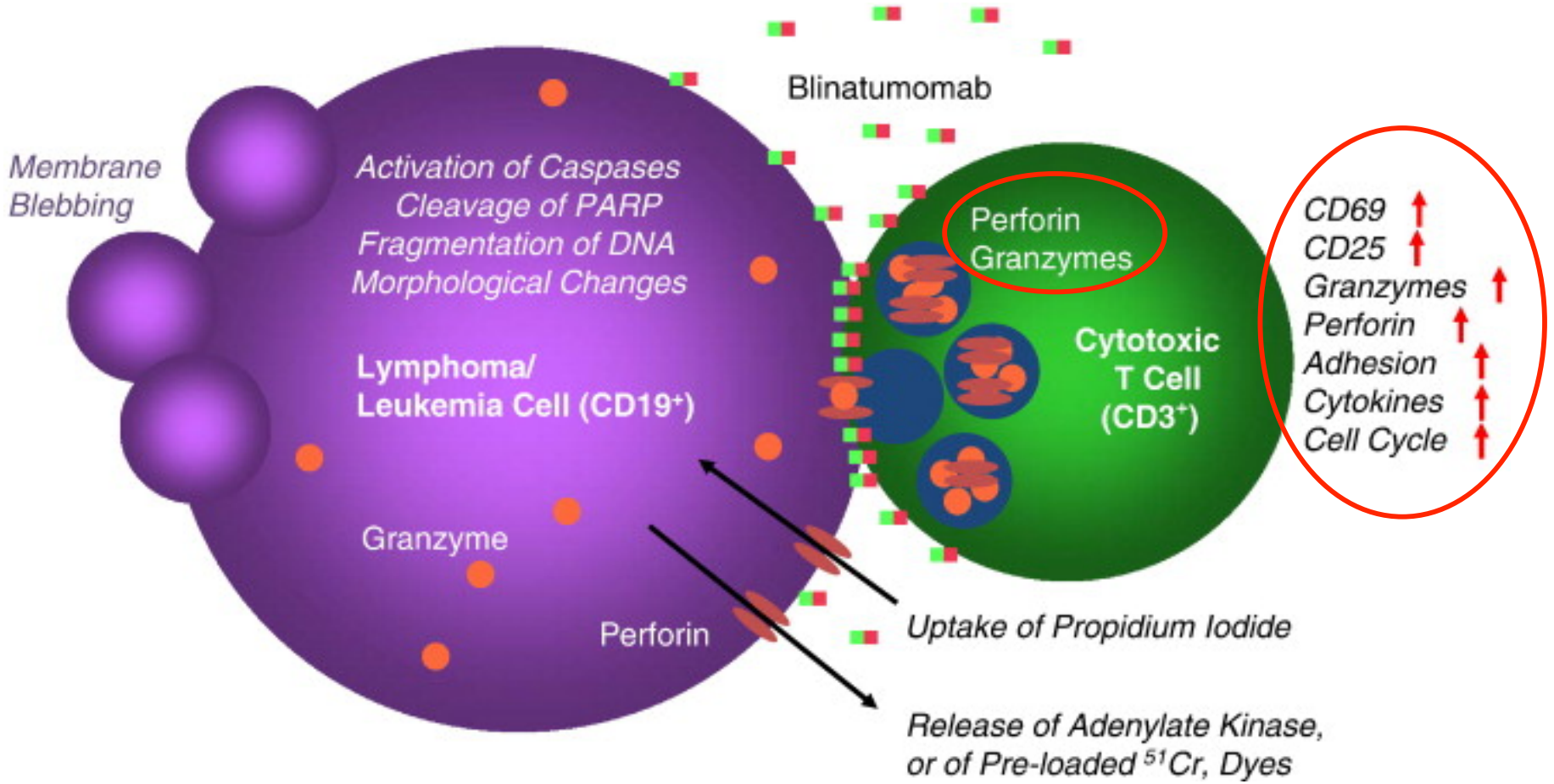
1. Jabbour. *Blood* 2015;125:4010–4016; 2. Hoelzer D *et al Blood Rev* 2012:26–32 ; 3. Gokbuget N *et al. Ann Hematol* 2004;83:201–205. 4. Kumar J *et al. Indian J Hematol Blood Transfus* 2012;30:16–18; 5. Jain N et al Blood 2017;130:1321; 6. Maude SL *et al Blood* 2015;125:4017–4023; Raponi S et al Leuk Lymphoma 2011;52:1098–1107

# 2018 Blinatumomab: A BiTE® antibody designed to direct cytotoxic T-cells to CD19-expressing cancer cells



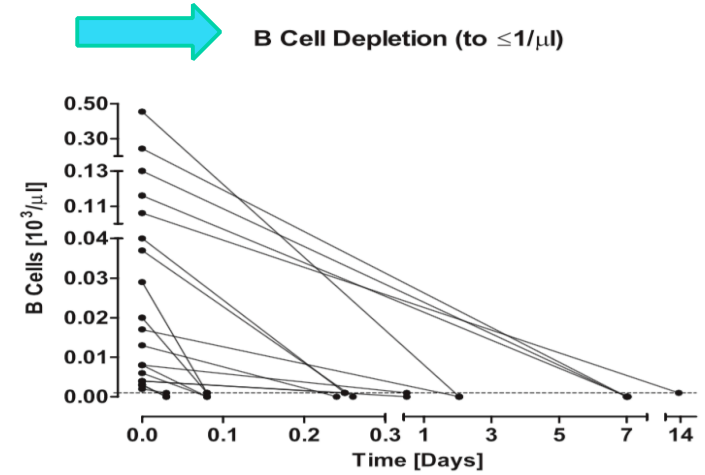

Baeuerle PA, et al. *Cancer Res* 2009;69:4941–44; 2. Bargou R, et al. *Science* 2008;321:974–7; 3. Klinger M, et al. *Blood* 2012;119:6226–33; 4. Hoffmann P, et al. *Int J Cancer* 2005;115:98–104.

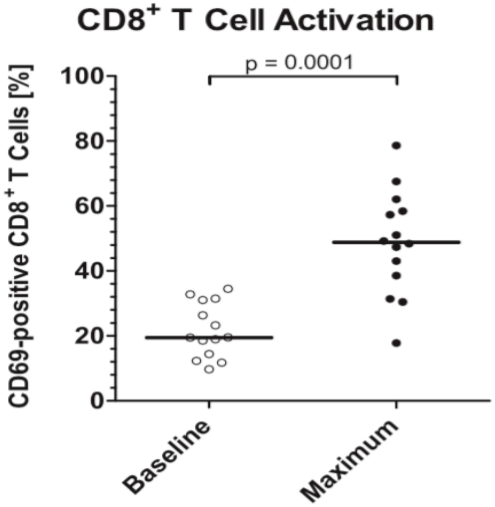
# Mechanism of action



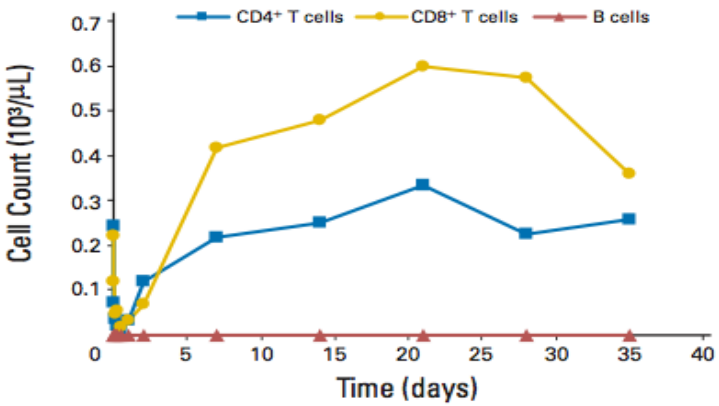

*Nagorsen D et al, Pharmacology & Therapeutics 2012*

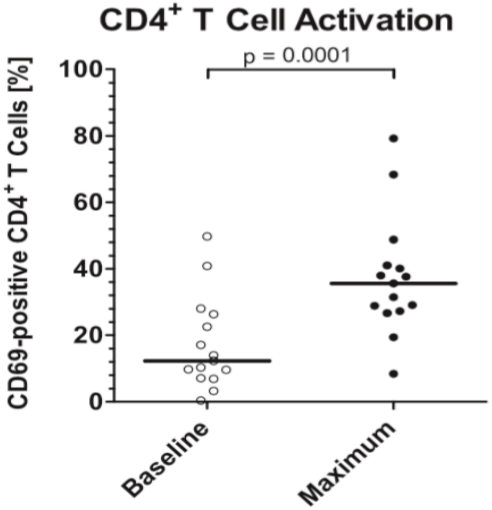
# Immunological response (I)




- ✓ Rapid and durable depletion of target B-cells
- ✓ Initial drop of T-cells with recovery within a few days and then expansion above baseline counts under treatment

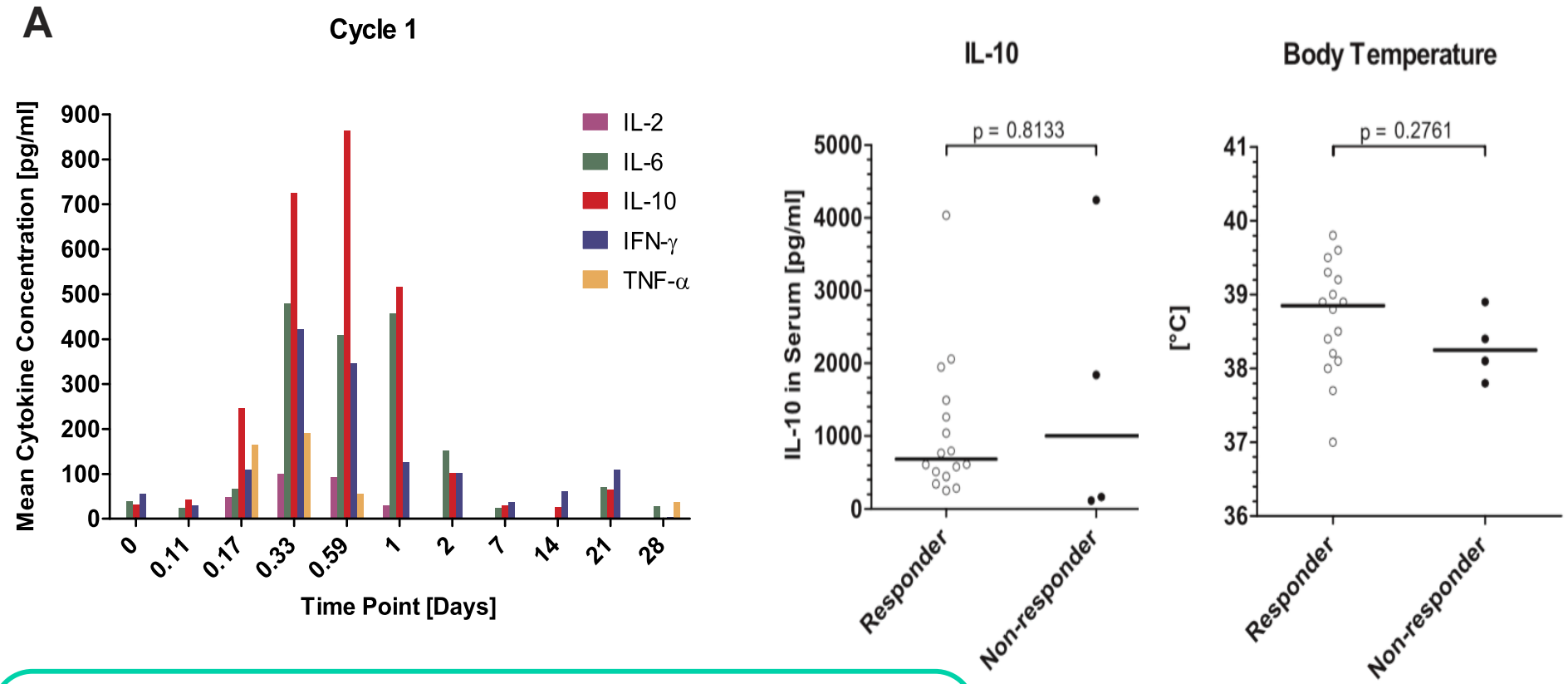



- ✓ A large proportion of recovering T cells up-regulates activation markers (CD25, CD69)

*Klinger M et al. Blood 2012*

# Immunological response (II)



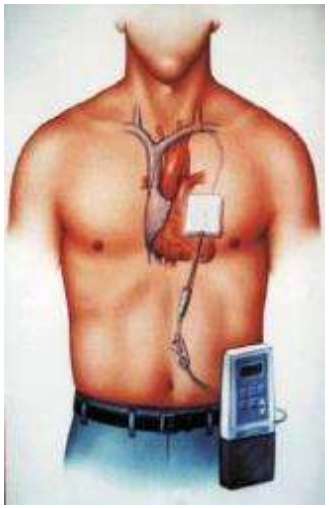

- ✓ Cytokines are transiently released on start of the first infusion and are no longer detected on following cycles
- ✓ The peak levels of cytokines and fever do not correlate with clinical response to Blinatumomab

*Topp M et al, J Clin Oncol 2011;*
*Klinger M et al. Blood 2012*

# A new drug with a new administration schedule

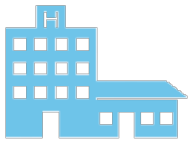
## Continuous IV (cIV) administration via pump

- Inpatient & ambulatory; 24/7 for 4 weeks, 2 weeks off



## Administration in inpatient and ambulatory home settings

- Inpatient: COE, academic centre, community
- Outpatient: hosp. OP, clinic, home



**Hospital**

Minimum of:

- Days 1–9, cycle 1*
- Days 1–2, cycle 2

**Home**

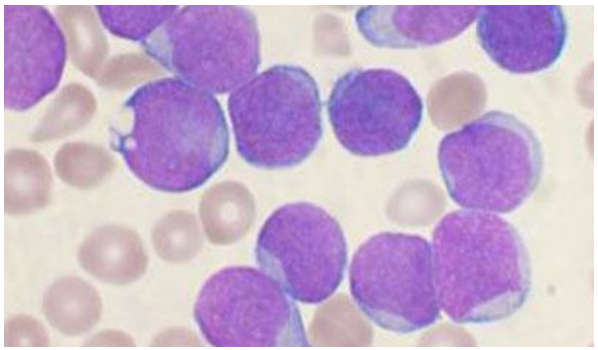
- cIV infusion bag changes every ≤4 days by home healthcare service or in outpatient setting

*14 days in patients with a history or presence of clinically relevant CNS pathology

COE, centre of excellence; OP, outpatient

BLINCYTO® Summary of Product Characteristics Amgen BV, 2015

# Blinatumomab: for which patients?

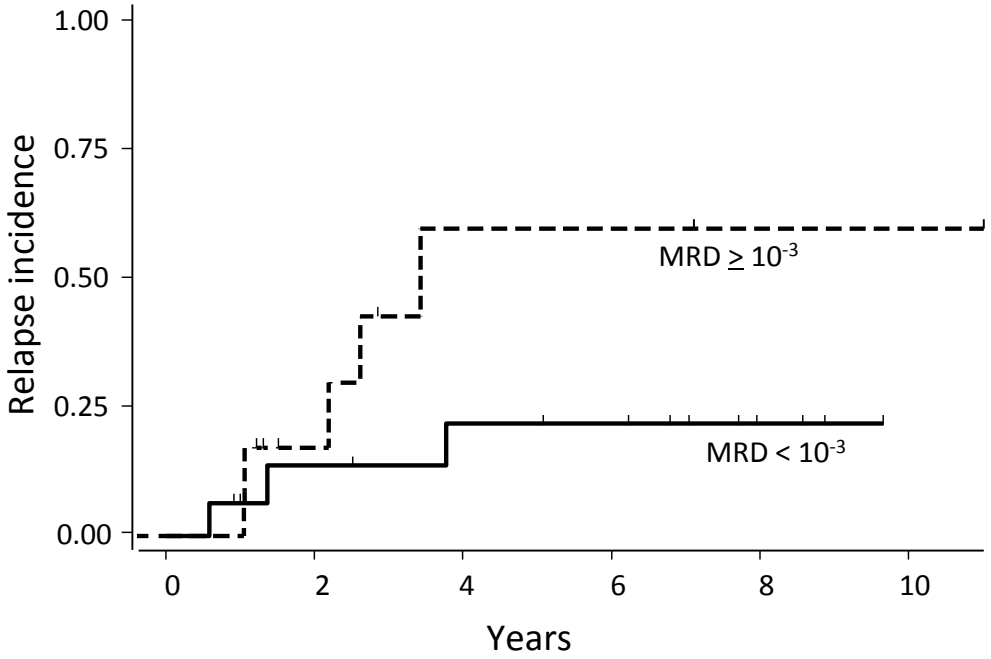


MRD +

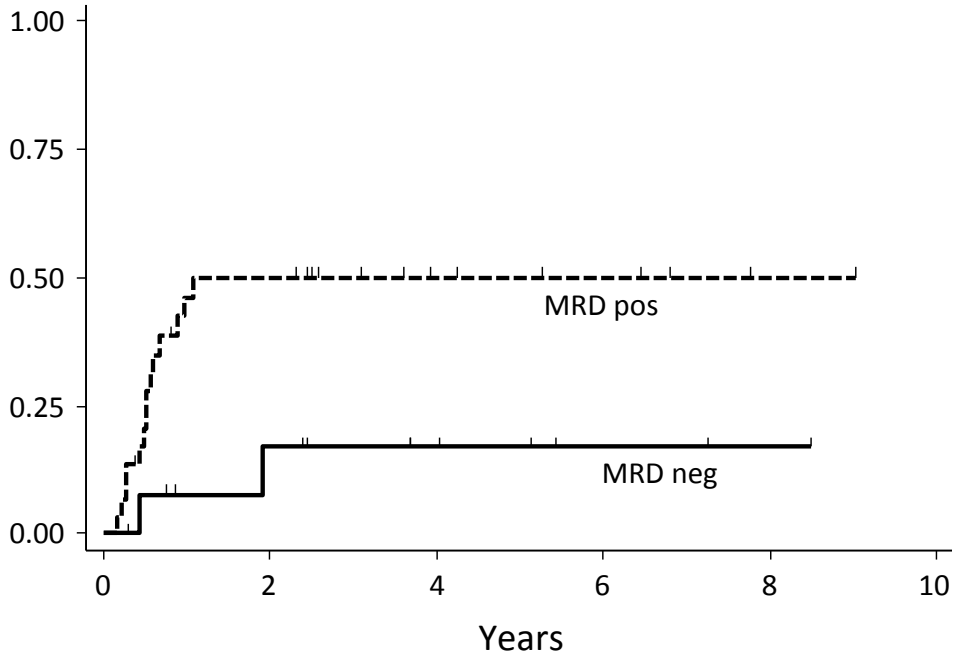
R/R ALL

AIFA Approval: Ph negative relapsed/refractory adult B-ALL patients

# 2018 AlloSCT for adult ALL: impact of MRD status at conditioning




**Ph-**

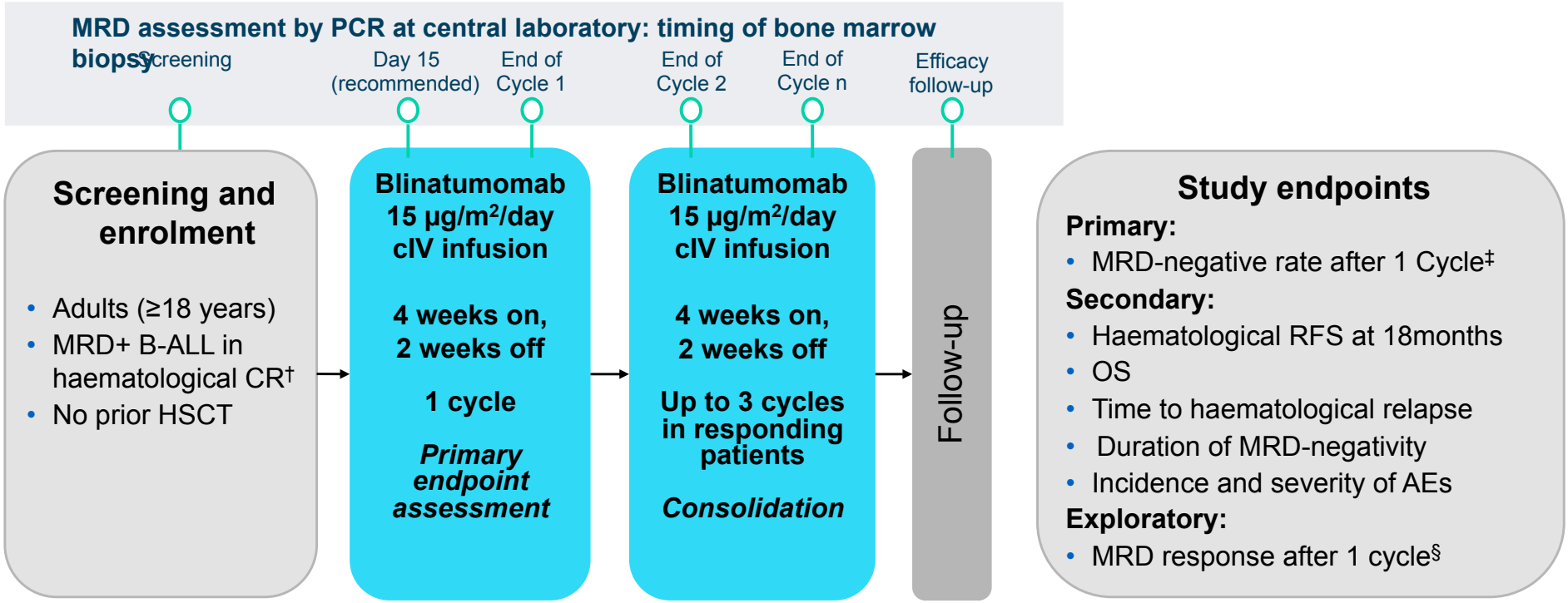



**Ph+**

*Lussana F and Rambaldi A. Haematologica 2015;9:369–76*

haematologica the hematology journal

# Open-label, single-arm, multicentre, Phase 2 study of Blinatumomab in adults with MRD-positive* B-precursor ALL (BLAST)[1,2]




- **AlloHSCT offered to eligible patients when donor available**

**15 µg/m²/day dose used in this study corresponds to 28 µg/day fixed-dosing strategy[3]**

†<5% blasts after three chemotherapy blocks, ANC ≥1,000/µL, platelets ≥50,000/µL, Hb ≥9 g/dL, with MRD ≥$10^{-3}$;
‡MRD-negative, no amplification in PCR (assay sensitivity ≥$10^{-4}$); §Reduction of MRD to <$10^{-4}$ (assay sensitivity ≥$10^{-4}$)

1. Gökbuget N, et al. ASH 2014: Abstract 379 and oral presentation; 2. Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation; 3. Wu B, et al. ASCO 2013: Abstract 30489 and poster presentation.

# BLAST – MRD-negativity within 1 cycle

| | Primary endpoint full analysis set* (n=113) | | |
|---|---|---|---|
| | n | % | 95% CI |
| Patients with evaluable MRD | 112 | 99 | |
| Primary endpoint<br>MRD-negativity after Cycle 1 | 88 | 78 | 69–85 |
| Exploratory endpoint<br>MRD response (MRD not detectable or only present at $<10^{-4}$) after Cycle 1 | 96 | 85 | 77–91 |

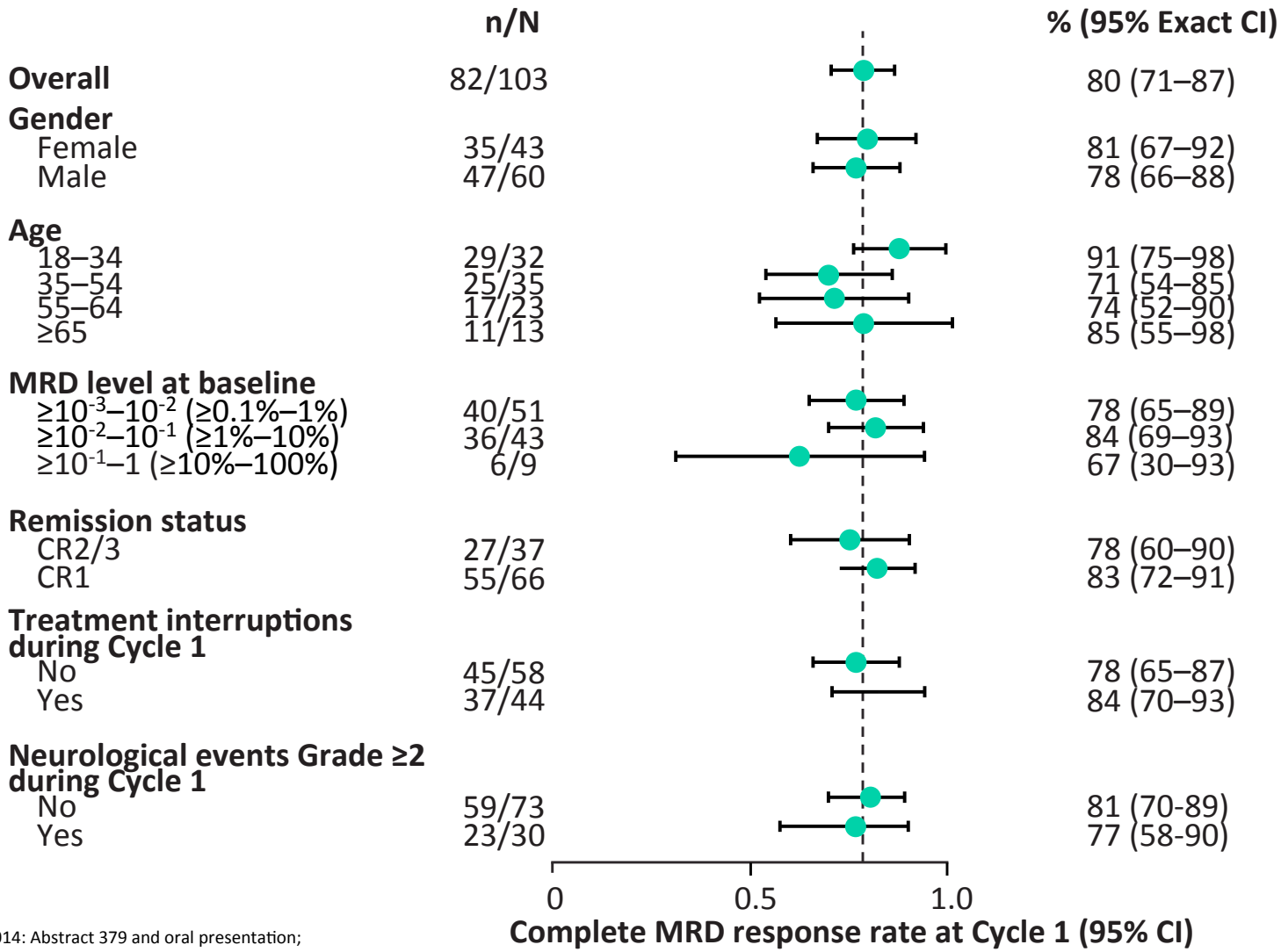
- 2 patients achieving reduction of MRD to below the quantifiable limit during Cycle 1 achieved a MRD-negativity after continued treatment in Cycle 2

*Patients who had an MRD analysis available with an assay sensitivity of $\geq 10^{-4}$ at the central lab

Gökbuget N, et al. ASH 2014: Abstract 379 and oral presentation; Blood 2018

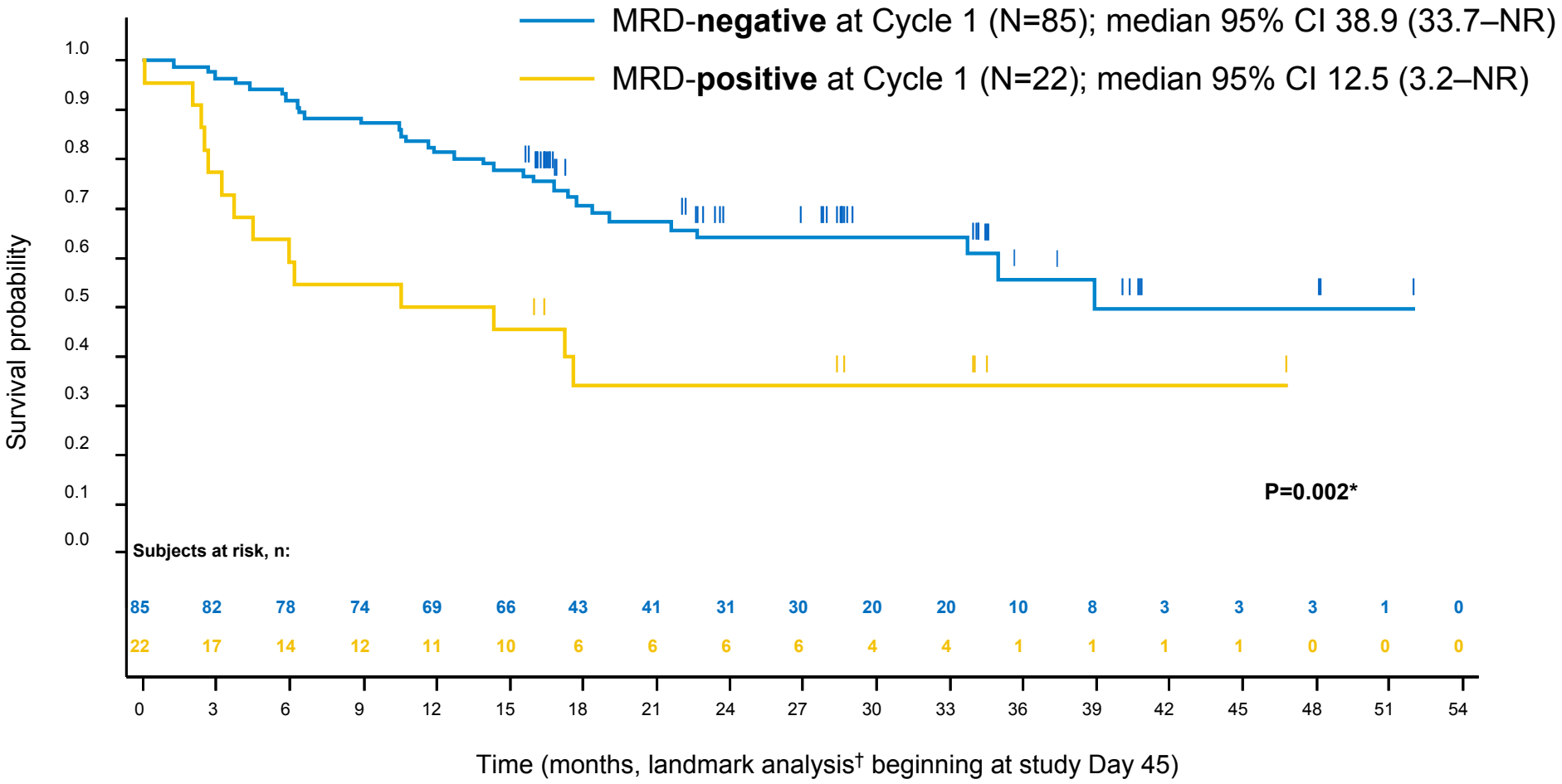
# BLAST – MRD-negativity according to clinical characteristics

## *Primary endpoint efficacy set*




Gökbuget N, et al. ASH 2014: Abstract 379 and oral presentation;
Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation; Blood 2018.

# BLAST – OS according to MRD-negativity
## *Ph-negative patients in haematological CR*




*Log rank P-value for association between OS and MRD response; causality not implied; underlying baseline characteristics may also influence both outcomes;
†The landmark analysis by MRD response included patients with overall survival of ≥45 days Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation.

# BLAST – Neurological AEs

| | All (N=116) | Grade 3 (N=116) | Grade 4 (N=116) |
|---|---|---|---|
| Any neurological event, n (%)* | 61 (53) | 12 (10) | 3 (3) |
| Neurological events in >2% of patients, n (%)* | | | |
| Tremor | 35 (30) | 6 (5) | 0 (0) |
| Aphasia | 15 (13) | 1 (1) | 0 (0) |
| Dizziness | 9 (8) | 1 (1) | 0 (0) |
| Ataxia | 7 (6) | 0 (0) | 0 (0) |
| Paraesthesia | 7 (6) | 0 (0) | 0 (0) |
| Encephalopathy | 6 (5) | 3 (3) | 2 (2) |
| Dysgraphia | 5 (4) | 0 (0) | 0 (0) |
| Intention tremor | 4 (3) | 0 (0) | 0 (0) |
| Convulsion | 3 (3) | 1 (1) | 1 (1) |
| Dysarthria | 3 (3) | 0 (0) | 0 (0) |
| Memory impairment | 3 (3) | 0 (0) | 0 (0) |

- Rates decreased over time (Cycles 1, 2, 3 and 4) for any neurologic event (47%, 24%, 15% and 15%) and any Grade ≥3 neurological event (10%, 4%, 0% and 0%)
- 12 (10%) of patients had treatment interruptions or discontinuations due to Grade 3–4 neurological AEs
  - 5 resumed treatment without another interruption
  - 2 resumed then discontinued treatment for another neurological event
- Median time to resolution of any neurological events was 4 days (Q1, Q3: 2, 8 days)

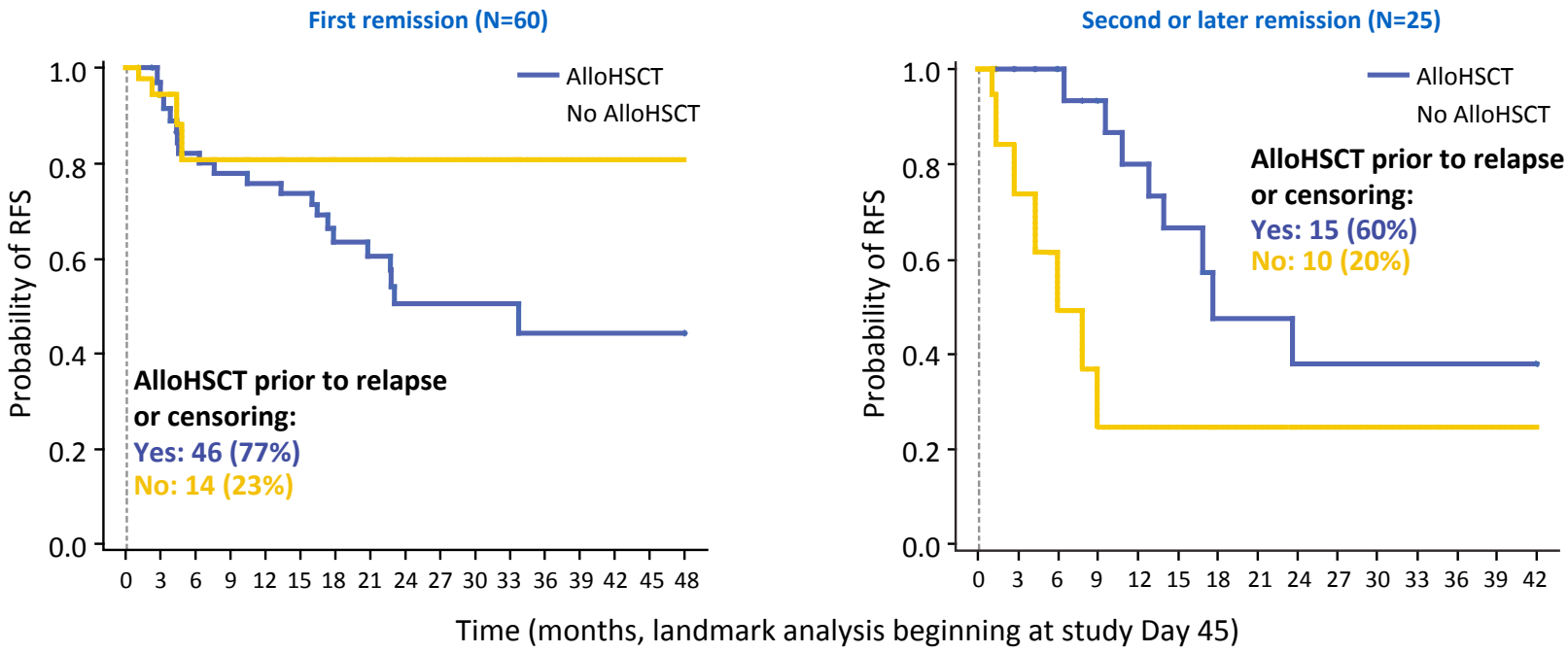
* Including treatment and 30 days after infusion Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation.

# BLAST – Role of HSCT in MRD-negative patients

## Transplant realisation rate: 72%

| Cox model analyses of HSCT as time-dependent covariate for RFS | | |
|---|---|---|
| | First remission | Second or later remission |
| Hazard ratio: | **2.26** (95% CI: 0.73–6.97) | **0.33** (95% CI: 0.11–0.98) |
| P-value | 0.15 | 0.046 |

## Simon–Makuch plot of RFS (Landmark 45 days)




Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation.

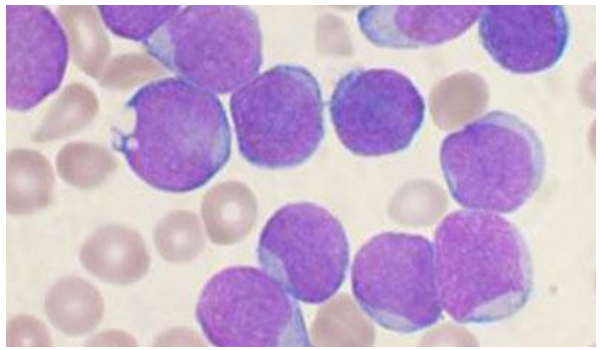
# 2018 Summary: blinatumomab for adult patients with MRD-positive B-precursor ALL

- Blinatumomab induced a high rate of MRD-negativity (78%)
  - 67% of patients received HSCT in continuous CR after blinatumomab
  - MRD response was associated with improved OS, RFS and response duration
  - Patients treated in first remission had improved RFS and response duration compared with those treated in subsequent remission
- Among patients who experienced neurological events on study, most had a worst event grade of ≤2[2]
  - 12 (10%) patients interrupted or discontinued treatment due to Grade ≥3 neurological events. There were no reported cases of CRS in this study

Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation, Blood 2018

# Blinatumomab: for which patients?

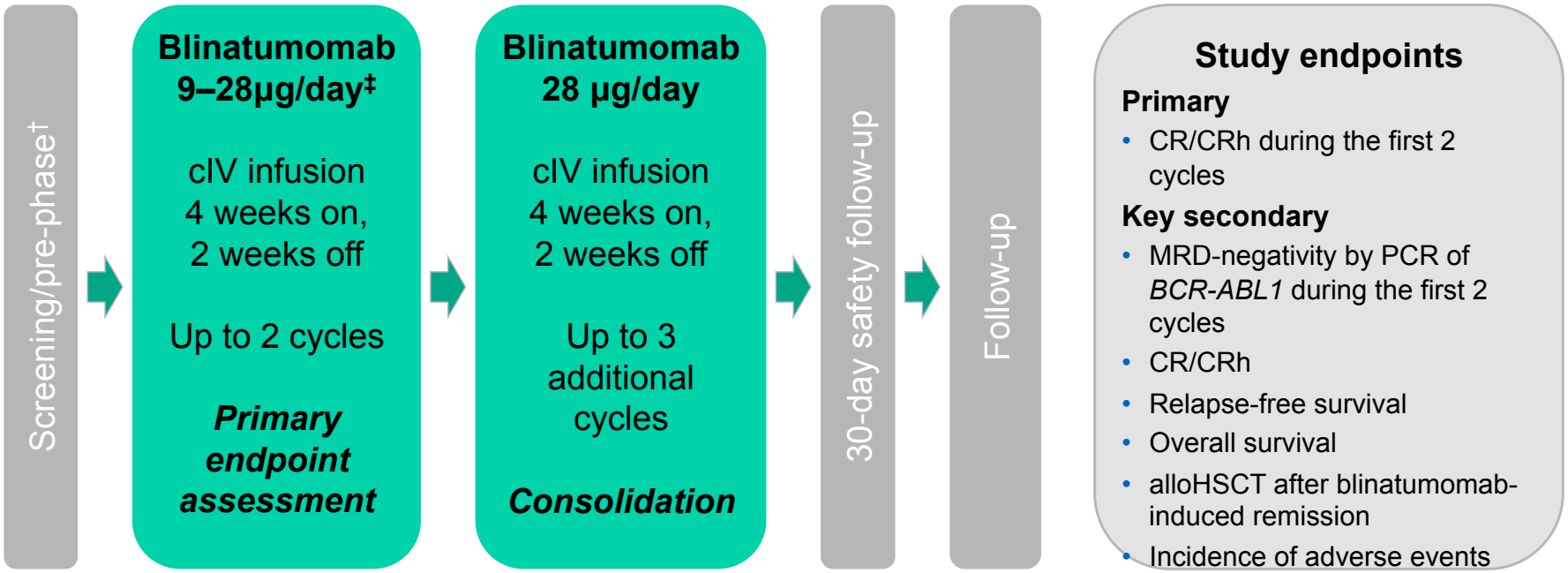
MRD +



R/R ALL

AIFA Approval: Ph negative relapsed/refractory adult B-ALL patients

# Open-label, single-arm, multicentre, Phase 2 study of blinatumomab in adult patients with Ph-positive* r/r B-precursor




To reduce tumour burden and CRS, patients with a high baseline blast count received pre-phase treatment with dexamethasone 10 mg/m²/day (for up to 5 days) up to a maximum of 24 mg/day (absolute);
‡9 µg/day in Week 1 of Cycle 1, followed by 28 µg/day from Weeks 2–4

**Martinelli G, et al. *J Clin Oncol* 2017;35:1795–802.**

# ALCANTARA – Patient demographics and clinical characteristics

| | n/N | % |
|---|---|---|
| Male sex | 24/45 | 53 |
| Median age, years (range) | 55 (23–78) | - |
| Age group | | |
| 18 to <55 years | 22/45 | 49 |
| ≥55 years | 23/45 | 51 |
| Cytogenetics and molecular analyses | | |
| Ph-positive *and* other cytogenetic abnormalities | 22/38 | 58 |
| ABL kinase domain mutations | 17/37 | 46 |
| T315I mutation | 10/37 | 27 |
| Bone marrow blasts | | |
| <10% | 2/45 | 4 |
| 10% to <50% | 9/45 | 20 |
| 50% to <75% | 6/45 | 13 |
| ≥75% | 28/45 | 62 |

Martinelli G, et al. *J Clin Oncol* 2017;35:1795–802.

# ALCANTARA – Prior treatments

| | n/N | % |
|---|---|---|
| Number of prior TKIs* | | |
| 1 | 7/45 | 16 |
| 2 | 21/45 | 47 |
| 3 | 13/45 | 29 |
| 4 | 4/45 | 9 |
| Prior allogeneic HSCT | 20/45 | 44 |
| Prior TKIs† | 45/45 | 100 |
| Imatinib | 25/45 | 56 |
| Dasatinib | 39/45 | 87 |
| Nilotinib | 16/45 | 36 |
| Ponatinib | 23/45 | 51 |

One patient had ALL that was resistant to imatinib and never exposed to a 2+ generation TKI (protocol deviation);
†Prior TKI use was not mutually exclusive;
TKI, tyrosine kinase inhibitor

Martinelli G, et al. *J Clin Oncol* 2017;35:1795–802.

# ALCANTARA – Response during first 2 cycles and transplant realisation

| Primary endpoint | n/N1 | % (95% CI) |
|---|---|---|
| CR/CRh during the first two cycles | 16/45 | 36 (22–51) |
| **Secondary endpoints** | **n/N1** | **% (95% CI)** |
| Best response during the first two cycles | | |
| CR | 14/45 | 31 (18–47) |
| CRh | 2/45 | 4 (1–15) |
| MRD-negativity* | 14/16 | 88 (62–98) |
| Allogeneic HSCT after blinatumomab-induced remission† | 4/16 | 25 (7–52) |
| Age 18 to <55 years | 2/8 | 25 (3–65) |
| Age ≥55 years | 2/8 | 25 (3–65) |
| 100-day post-transplant mortality rate† | 1/4 | 25 (4–87) |

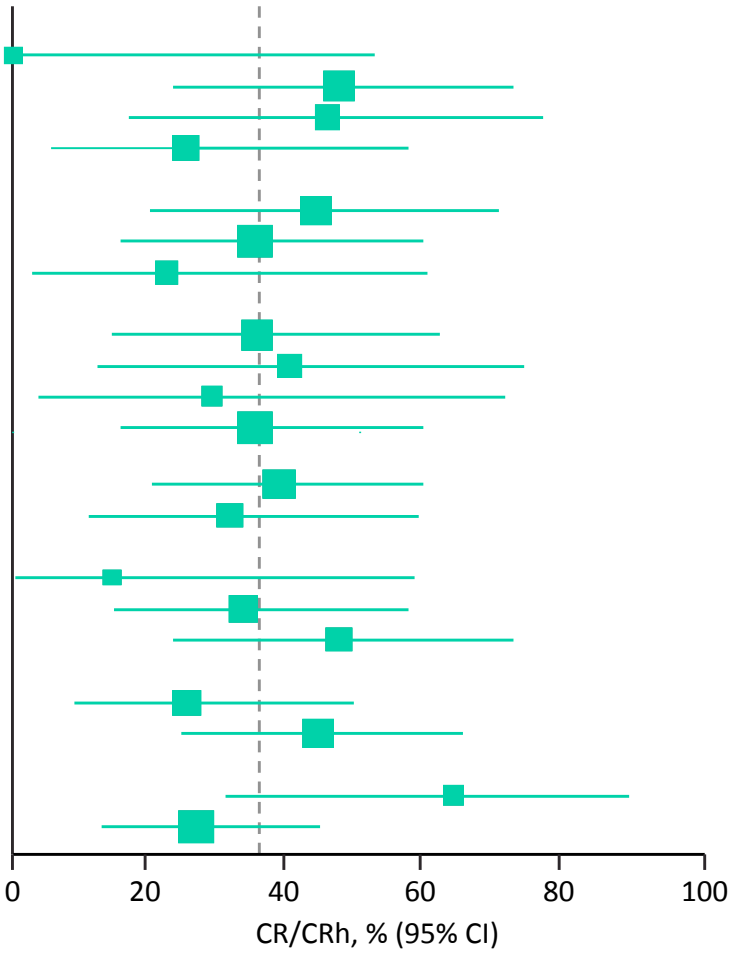
Among CR/CRh responders only; includes all four CR/CRh patients with the T315I mutation. MRD-negativity was defined as no detectable PCR amplification of *BCR-ABL1* genes in a central laboratory with an assay sensitivity of $\geq 10^{-5}$;
†For patients who received alloHSCT during blinatumomab-induced remission without other anti-leukaemia therapy;
N1, number of patients with evaluable data under each category

Martinelli G, et al. *J Clin Oncol* 2017;35:1795–802.

# ALCANTARA – Response during first 2 cycles

## *Subgroup analysis of CR/CRh*

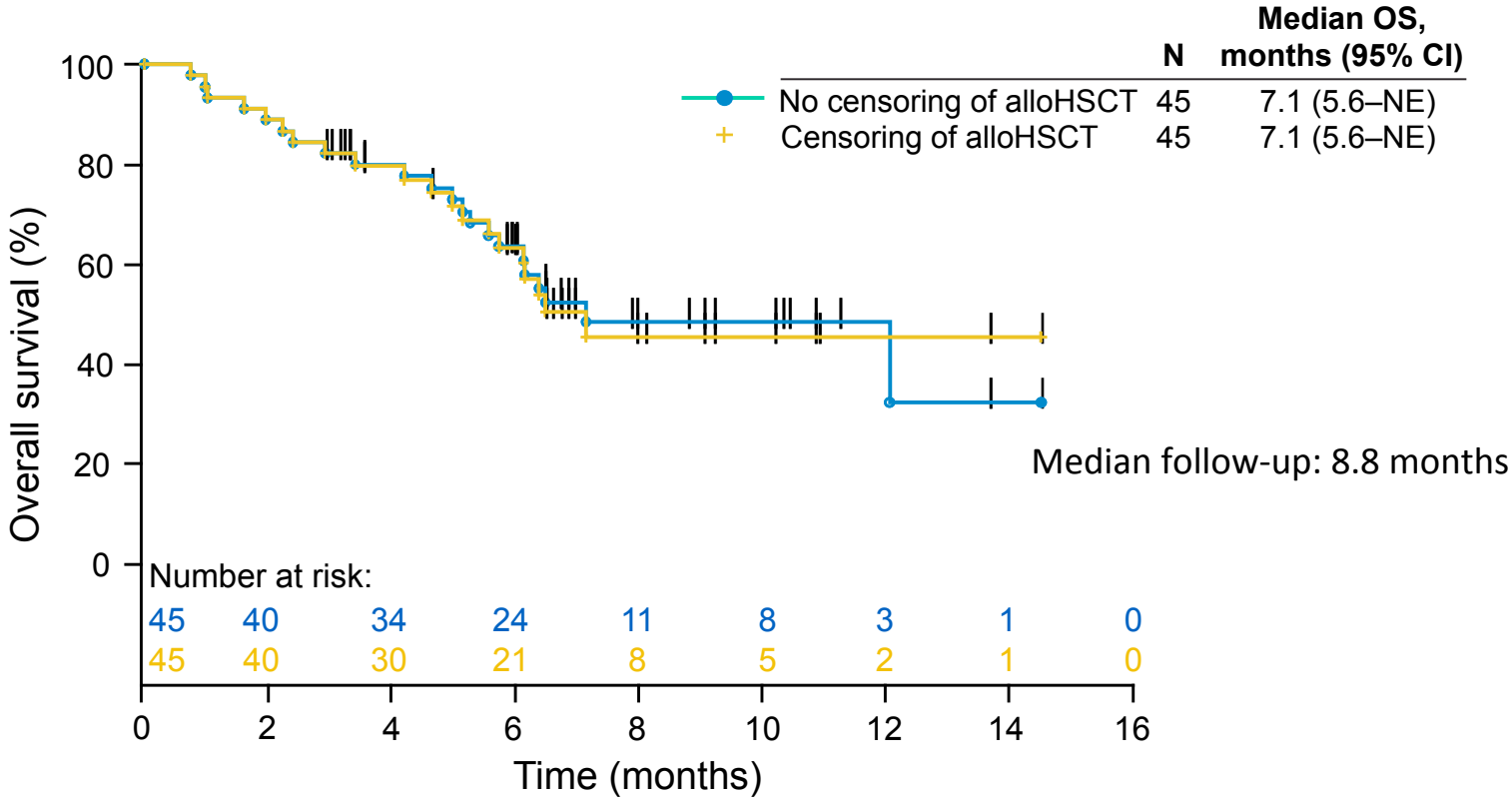
| | n | N | % | 95% CI |
|---|---|---|---|---|
| **Age group, years** | | | | |
| ≥18 to <35 | 0 | 5 | 0 | 0–52 |
| ≥35 to <55 | 8 | 17 | 47 | 23–72 |
| ≥55 to <65 | 5 | 11 | 46 | 17–77 |
| ≥65 | 3 | 12 | 25 | 6–57 |
| **ECOG status** | | | | |
| 0 | 7 | 16 | 44 | 20–70 |
| 1 | 7 | 20 | 35 | 15–59 |
| 2 | 2 | 9 | 22 | 3–60 |
| ***BCR-ABL1* mutations** | | | | |
| Yes | 6 | 17 | 35 | 14–62 |
| T315I mutation | 4 | 10 | 40 | 12–74 |
| Other | 2 | 7 | 29 | 4–71 |
| No | 7 | 20 | 35 | 15–59 |
| ***BCR-ABL1* isoform (baseline)** | | | | |
| *p190* | 10 | 26 | 39 | 20–59 |
| *p210* | 5 | 16 | 31 | 11–59 |
| **Previous TKI therapies** | | | | |
| 1 | 1 | 7 | 14 | <1–58 |
| 2 | 7 | 21 | 33 | 15–57 |
| ≥3 | 8 | 17 | 47 | 23–72 |
| **Prior alloHSCT** | | | | |
| Yes | 5 | 20 | 25 | 9–49 |
| No | 11 | 25 | 44 | 24–65 |
| **Bone marrow blasts** | | | | |
| <50% | 7 | 11 | 64 | 31–89 |
| ≥50% | 9 | 34 | 27 | 13–44 |




The dashed line represents the point estimate for CR or CRh for the entire patient population. Size of square corresponds to number of patients in subgroup

Adapted from Martinelli G, et al. *J Clin Oncol* 2017;35:1795–802.

# ALCANTARA – Overall survival




| Patient subgroup | Median OS, months (95% CI) |
|---|---|
| All patients | 7.1 (5.6–NE) |
| MRD-negative | NR |
| MRD-positive | 3.9 (3.0–NE) |

# ALCANTARA – Adverse events (regardless of causality)

| Adverse events, n (%) | Any grade | Grade 1–2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Any adverse event** | 45 (100) | 45 (100) | 33 (73) | 16 (36) |
| **Grade ≥3 adverse events occurring in ≥5% patients*** | | | | |
| Pyrexia | 26 (58) | 24 (53) | 5 (11) | 0 |
| Febrile neutropenia | 18 (40) | 9 (20) | 12 (27) | 0 |
| Headache | 14 (31) | 13 (29) | 3 (7) | 0 |
| Anaemia | 13 (29) | 9 (20) | 7 (16) | 1 (2) |
| Thrombocytopenia | 10 (22) | 4 (9) | 5 (11) | 7 (16) |
| Pain | 7 (16) | 4 (9) | 4 (9) | 0 |
| Aspartate aminotransferase increased | 6 (13) | 3 (7) | 3 (7) | 2 (4) |
| Alanine aminotransferase increased | 5 (11) | 1 (2) | 5 (11) | 0 |
| Device-related infection | 5 (11) | 3 (7) | 3 (7) | 0 |
| Neutropenia | 3 (7) | 0 | 0 | 3 (7) |

# ALCANTARA – Neurological events and CRS (regardless of causality)

| Neurological events, n (%) | Any grade | Grade 1–2 | Grade 3 | Grade 4/5 |
|---|---|---|---|---|
| **Any neurological event** | 21 (47) | 20 (44) | 3 (7) | 0 |
| **Neurological events occurring in ≥2 patients** | | | | |
| Paresthesia | 6 (13) | 6 (13) | 0 | 0 |
| Confusional state | 5 (11) | 5 (11) | 0 | 0 |
| Dizziness | 4 (9) | 4 (9) | 0 | 0 |
| Tremor | 4 (9) | 4 (9) | 0 | 0 |
| Aphasia | 2 (4) | 1 (2) | 1 (2) | 0 |
| Cerebellar syndrome | 2 (4) | 2 (4) | 0 | 0 |
| Memory impairment | 2 (4) | 2 (4) | 0 | 0 |
| Nervous system disorder | 2 (4) | 1 (2) | 1 (2) | 0 |

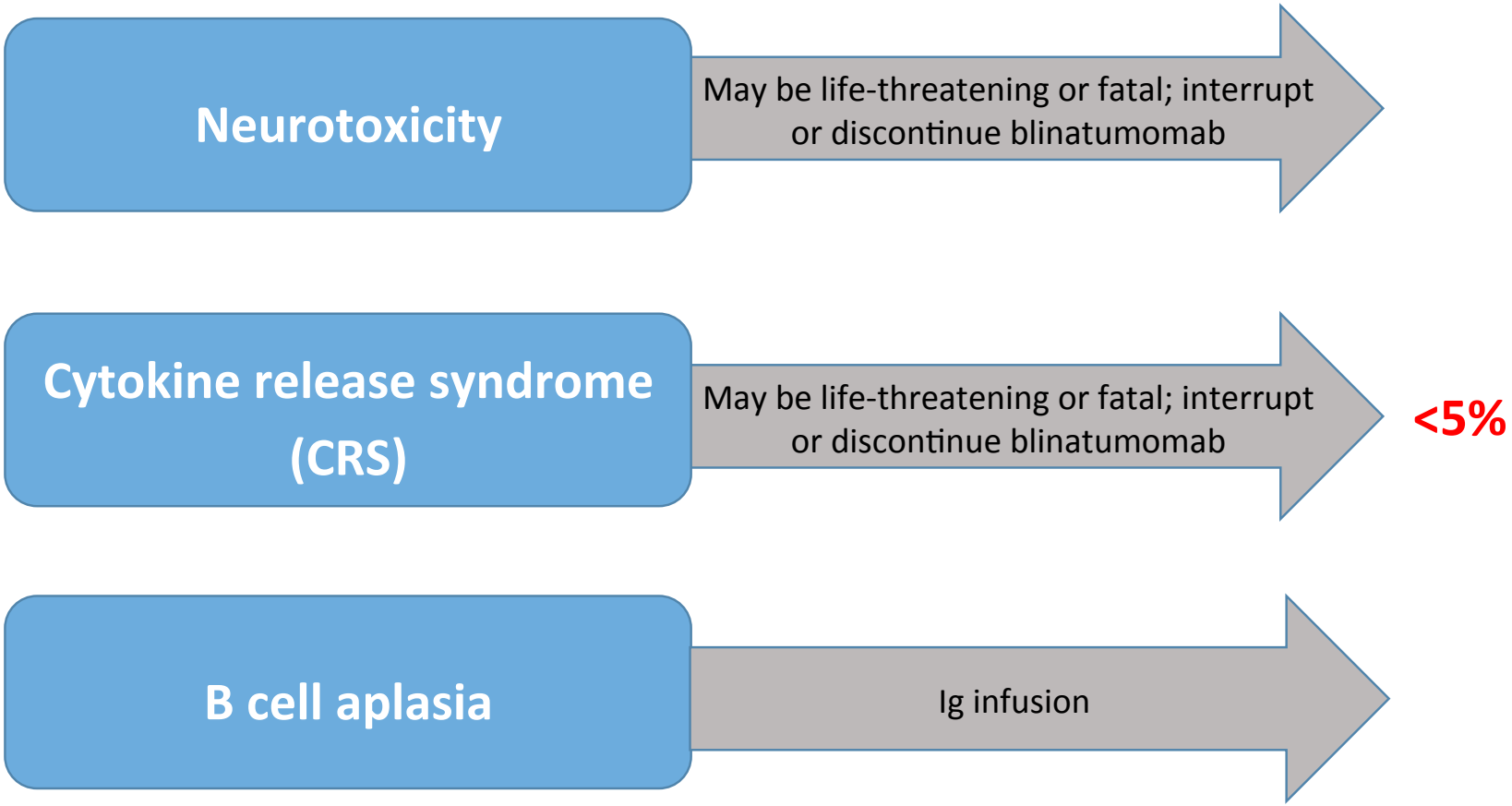
- No patients had Grade 4 or 5 neurological events
- CRS occurred in three patients (all Grade 1 or 2)
  - None of the CRS events led to treatment discontinuation or interruption

# Summary: blinatumomab for adult patients with r/r Ph-positive B-precursor ALL

- Single-agent blinatumomab demonstrated anti-leukaemia activity in high-risk patients with Ph-positive ALL who had relapsed or were refractory to TKIs
  - 36% of patients (16/45) achieved CR/CRh during the first two cycles
  - Among responders, 88% (14/16) achieved MRD-negativity
- Median OS of 7.1 months was observed in this patient population with poor prognosis
- Haematological and MRD responses were independent of mutational status, including presence of the T315I mutation
  - Equivalent CR/CRh and RFS observed in patients aged <55 and ≥55 years
- Adverse events were consistent with previous blinatumomab treatment experience in the setting of r/r Ph-negative B-precursor ALL

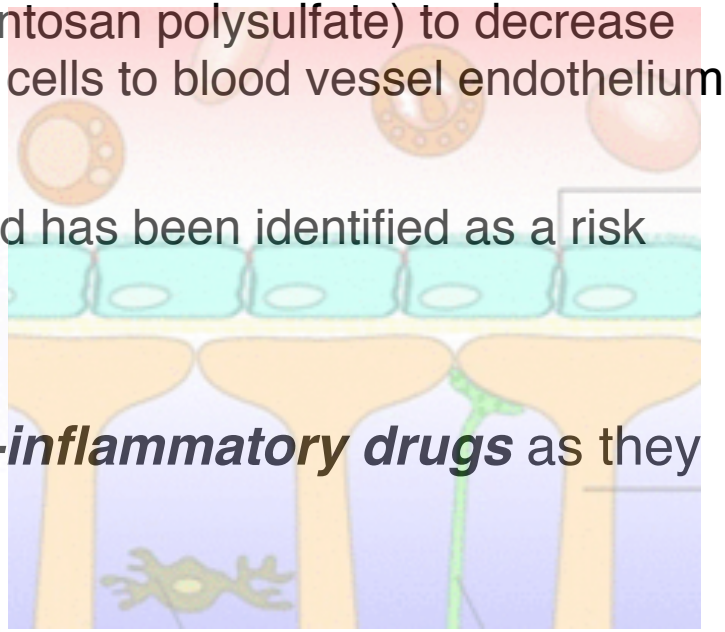
Martinelli G, et al. *J Clin Oncol* 2017;35:1795–802.

# Blinatumomab: toxicity



# Neurological toxicity

- **Postulated mechanism: T-cell migration and activation into CNS**
  - Mitigation of CNS events with the use of ***corticosteroids***
  - Use of ***heparin-like agents*** (PPS, pentosan polysulfate) to decrease Blinatumomab-induced adhesion of T cells to blood vessel endothelium through P-selectin blocking
  - A B:T cell ratio <1:8 in peripheral blood has been identified as a risk factor for neurotoxicity



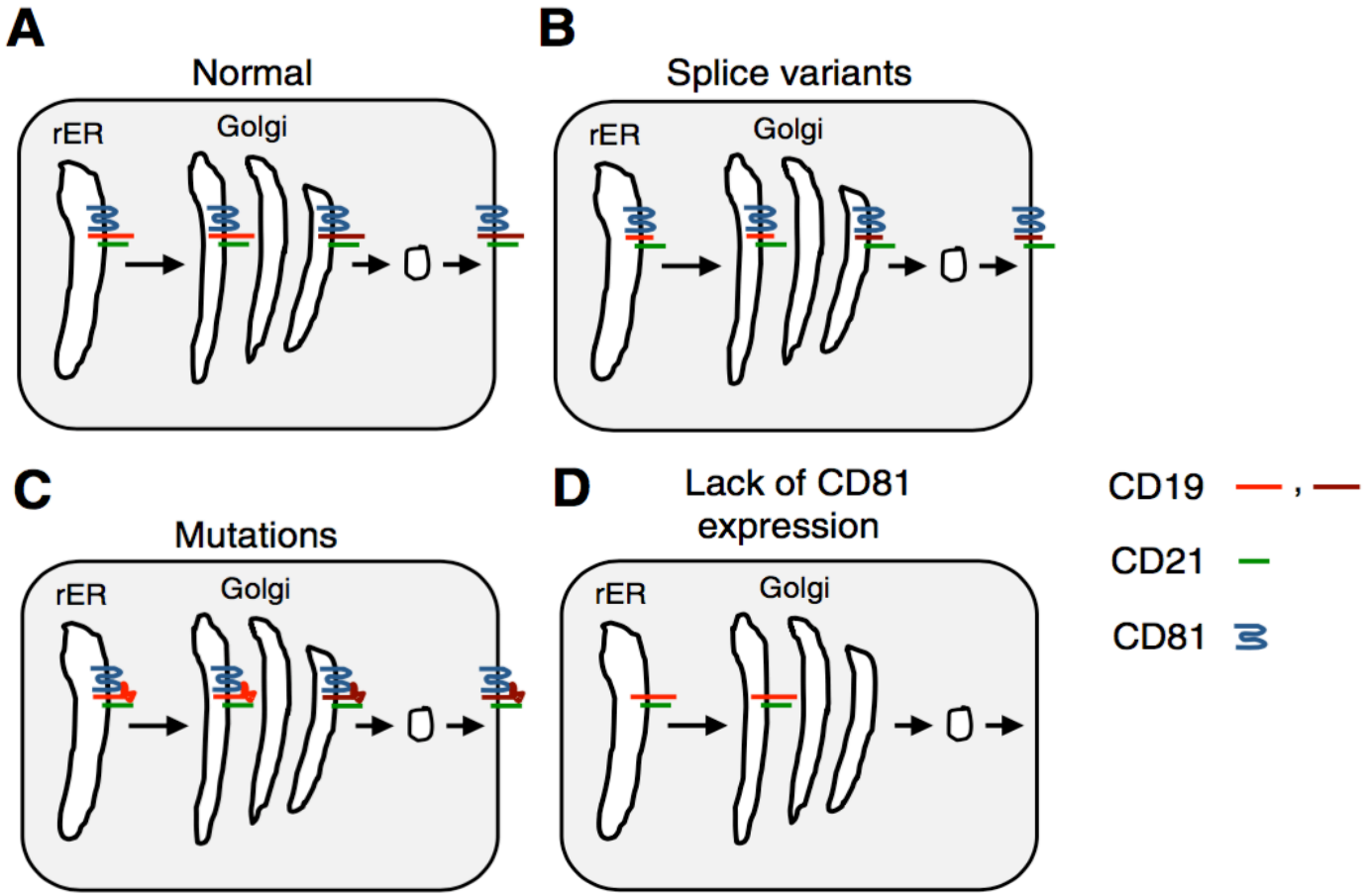
- **Avoid the use of *Non-steroidal anti-inflammatory drugs*** as they may increase vascular permeability
- **Role of prophylaxis with anticonvulsants (i.e. *levetiracetam*?)**

# Mechanisms of resistance

- CD19 loss / reduced expression / mutation
- Lymphoid to myeloid lineage switch
- Induction of checkpoint molecules / T-cell exhaustion
- Impaired $T_{reg}/T_{eff}$ ratio
- … and (probably) many others

Duell J et al. Leukemia 2017 [e-pub ahead of print]
Velasquez MP and Gottschalk S. Blood 2017;129:9-10.
Jacoby E et al. Nat Commun 2016;7:12320. Gardner R et al. Blood;2016:127:2406-10.
modified from Lesokhin AM et al. Sci Transl Med 2015;7:280sr1. Feucht J et al. Oncotarget 2016;7:76902-19.

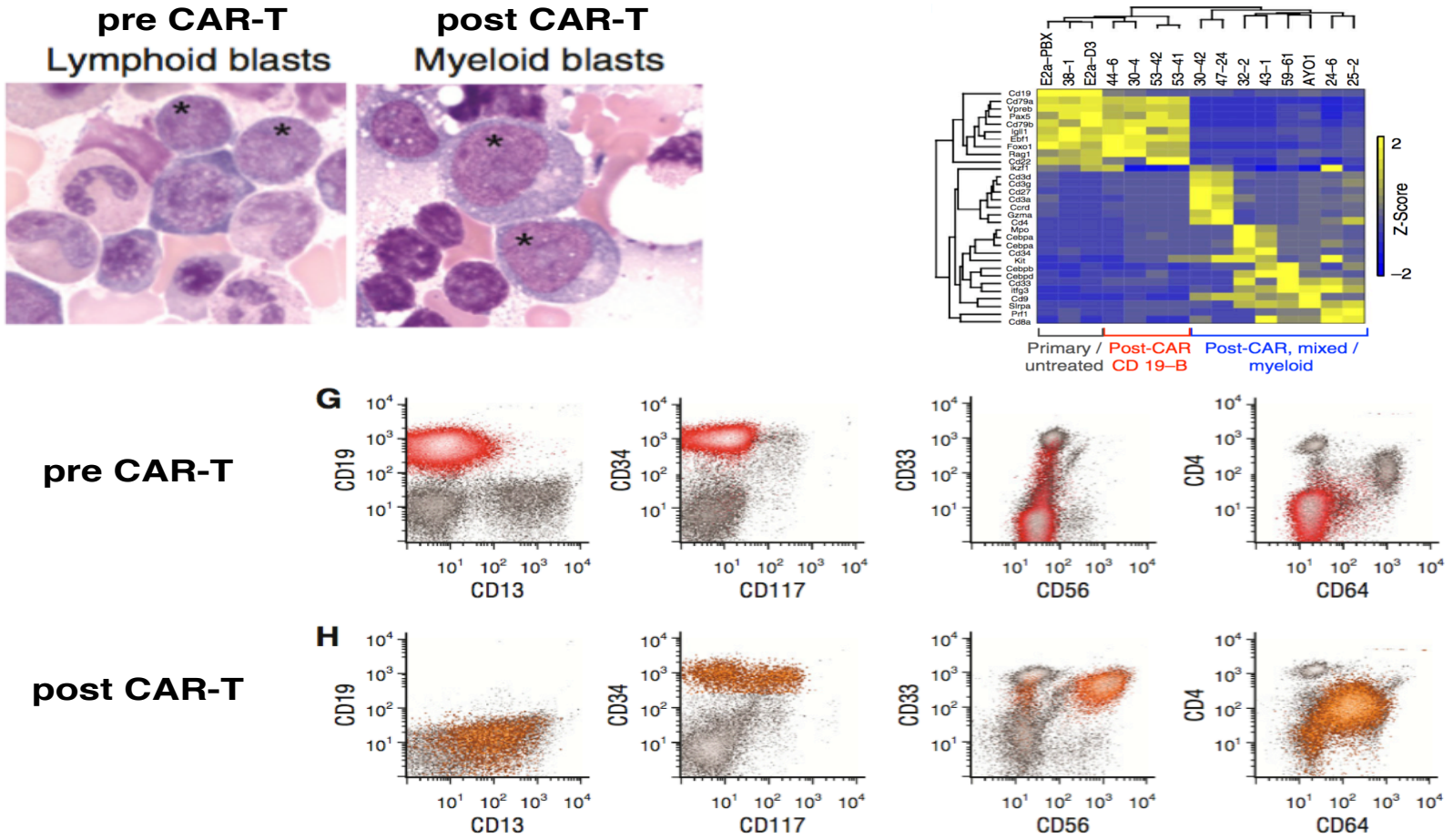
# Impairment of CD19 expression




Velasquez MP and Gottschalk S. Blood 2017:129:9-10.

Braig F et al, Blood 2017

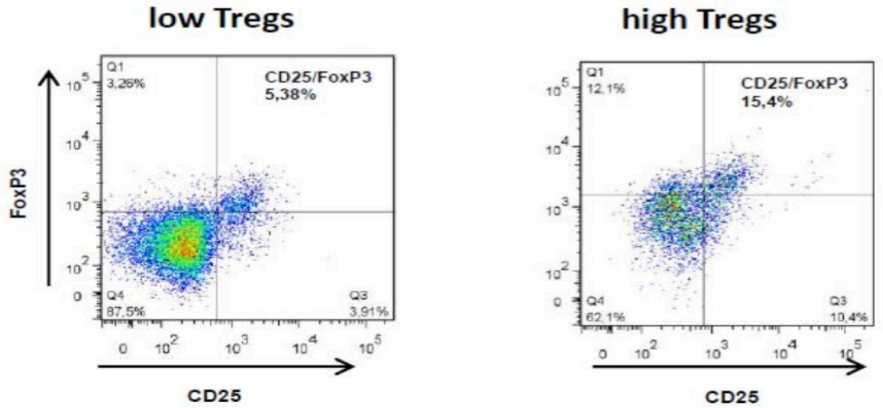
# Lymphoid to myeloid lineage switch




Jacoby E et al. Nat Commun 2016;7:12320. Gardner R et al. Blood;2016:127:2406-10.

# Impaired T reg/ T eff ratio

| Variable | Responders | Non responders | p |
|---|---|---|---|
| Age (years) | 38 (21-77) | 34 (20-69) | ns |
| LDH (U/L) | 211 (119-904) | 402 (182-1860) | **.003** |
| Blast in perip.blood (%) | 0.4 (0.04-1) | 0.78 (0.2-0.95) | **.009** |
| $CD3^+$ total cells ($x10^6$/uL) | 56.9 (0.1-1400) | 84.5 (0-1077) | ns |
| $T_{reg}$ (% of T-cells) | 8.75 (3.2-14.2) | 14.25 (5.65-73) | **.0002** |
| $T_{reg}/T_{eff}$ ratio | 0.045 (0.018-0.112) | 0.077 (0.023-1.985) | **.012** |




Duell J et al. Leukemia 2017 [e-pub ahead of print]

# How can we improve Blinatumomab efficacy?

## →Consider lymphocyte amounts

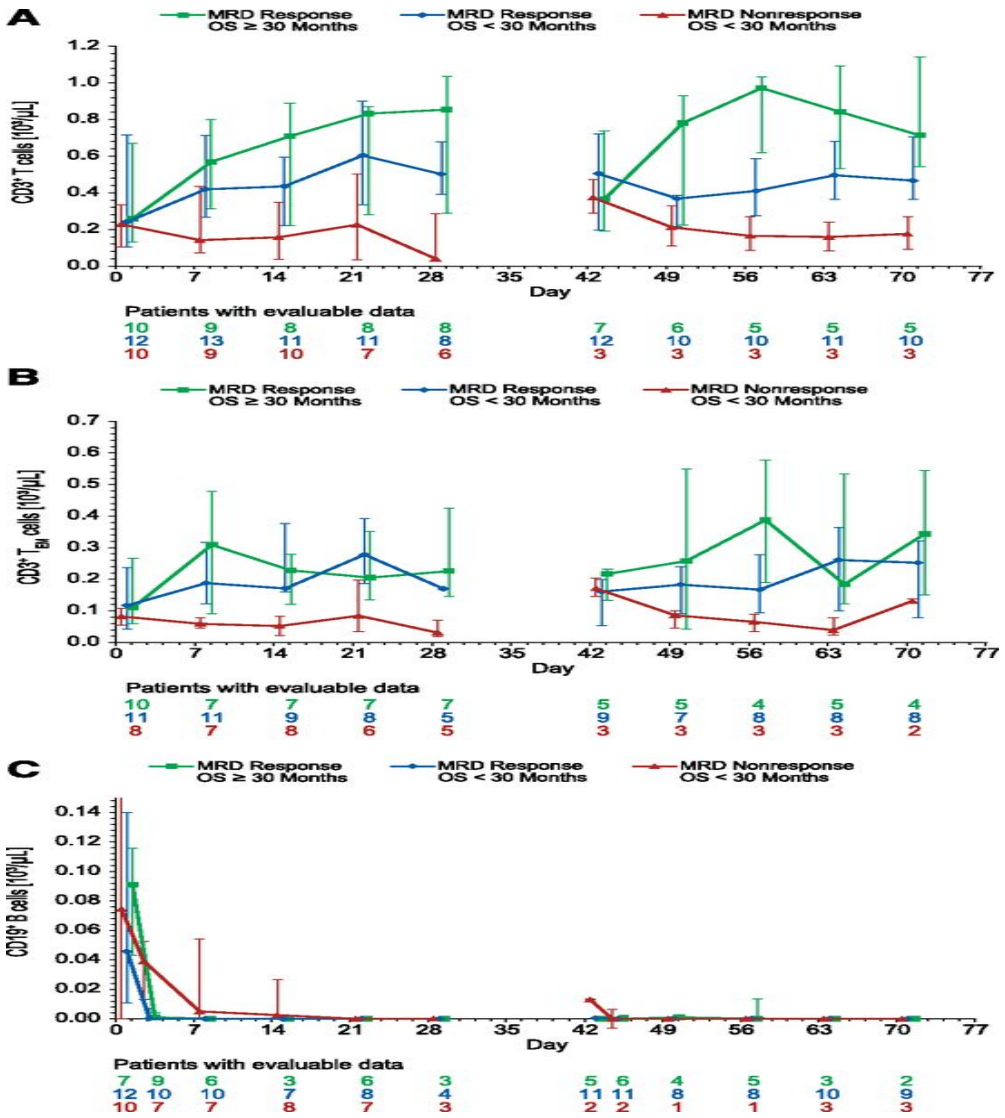
blood

Prepublished online October 19, 2015;
doi:10.1182/blood-2015-06-649111 originally published online
October 19, 2015

**Long-term survival and T-Cell kinetics in adult patients with relapsed/refractory B-precursor acute lymphoblastic leukemia who achieved minimal residual disease response following treatment with Anti-CD19 BiTE® antibody construct blinatumomab**

Gerhard Zugmaier, Nicola Gökbuget, Matthias Klinger, Andreas Viardot, Matthias Stelljes, Svenja Neumann, Heinz-A. Horst, Reinhard Marks, Christoph Faul, Helmut Diedrich, Albrecht Reichle, Monika Brüggemann, Chris Holland, Margit Schmidt, Hermann Einsele, Ralf C. Bargou and Max S. Topp

# T-cell and B-cell kinetics during cycle 1 (day 1 to 29) and cycle 2 (day 43 to 71) of blinatumomab treatment




Gerhard Zugmaier et al. Blood 2015;126:2578-2584

# Baseline biomarkers influencing clinical outcomes in adults with relapsed/refractory B-precursor acute lymphoblastic leukemia (r/r ALL) treated with blinatumomab versus standard-of-care chemotherapy (SOC) from a randomized Phase 3 study

*Wei A, Ribera JM, Martinelli G, Larson RA, Ritchie D, Ghobadi A, Chen Y, Dos Santos CE, Zimmerman ZF, Kantarjian HM.*

*ASH 2017; Abstract 2556*

SC-EU-AMG103-00376-12.17

# Baseline biomarkers associated with clinical outcomes

| Baseline biomarker | CR, Odds ratio (95% CI) | CR/CRh/CRi, Odds ratio (95% CI) | MRD response, Odds ratio (95% CI) | OS, Hazard ratio for death (95% CI) | Effect |
|---|---|---|---|---|---|
| Granulocytes (/µL log10 transformed) | – | – | – | **0.75** (0.57–0.99) | Prognostic |
| Platelets ($10^9$/L log10 transformed) | **4.12** (2.04–8.33) | **1.64** (0.90–2.99) | – | **0.43** (0.29–0.65) | Prognostic |
| CD45+ CD3+ CD8+ (%) / 10 | | | – | – | Predictive |
| Blinatumomab | **1.39** (1.18–1.65) | **1.44** (1.22–1.70) | | | |
| SOC | **1.04** (0.75–1.43) | **1.06** (0.82–1.38) | | | |
| CD45+ CD3- CD19+ (%) / 10 | – | – | – | | Predictive |
| Blinatumomab | | | | **1.19** (1.09–1.29) | |
| SOC | | | | **1.03** (0.93–1.15) | |
| BM blasts (%) / 10 | **0.90** (0.82–0.97) | **0.87** (0.80–0.95) | – | **1.04** (0.98–1.09) | Prognostic |
| CD3+ (/µL log10 transformed) | – | – | **1.75** (0.99–3.08) | – | Prognostic |

**Green:** better outcome
**Black:** no effect
**Red:** worse outcome

NOTE: Odds ratios and hazard ratio are associated with **increased** count/percentage of evaluated biomarkers.
CRi, CR with incomplete haematological recovery; MRD, minimal residual disease.

Wei A, et al. ASH 2017; Abstract 2556.

# Summary

- Biomarkers predictive or prognostic of clinical outcomes were identified in patients with
  r/r Ph-negative B-ALL who received blinatumomab or SOC chemotherapy on the Phase 3 TOWER study
  - Higher platelet and granulocyte counts were prognostic of improved OS
  - Lower BM blast counts were prognostic of increased haematological response
  - Higher numbers of CD3+ T cells were prognostic of increased rate of MRD response
  - Higher frequency of CD45+ CD3+ CD8+ T cells was predictive of increased haematological response to blinatumomab
  - Higher frequency of CD45+ CD3- CD19+ B cells was predictive of decreased OS
  - BM blast percentage and lymphocyte markers were not associated with AEs of interest
- These data demonstrate that responses to blinatumomab can be seen across a variety of subgroups
  - Further study needed to identify subgroups most likely to benefit from blinatumomab therapy

Wei A, et al. ASH 2017; Abstract 2556.

# Expression of antigens in B-cell lineage ALL for potential antibody therapy

| Surface antigen | ALL subtype | Expression on LBC (%) | Monoclonal antibody |
|---|---|---|---|
| CD20 | Burkitt<br>B-precursor | 80–90<br>30–50 | • Rituximab<br>• Ofatumumab |
| CD19 | B-precursor<br>Mature B-ALL | 95–<100<br>94–<100 | T cell-activating therapies<br>• Blinatumomab bispecific CD3/CD19<br>• ADCT-402<br>• CAR T cells |
| CD22 | B-precursor<br>Mature B-ALL | 93–96<br>≈100 | • Inotuzumab ozogamicin<br>• Epratuzumab<br>• Moxetumomab pasudotox |

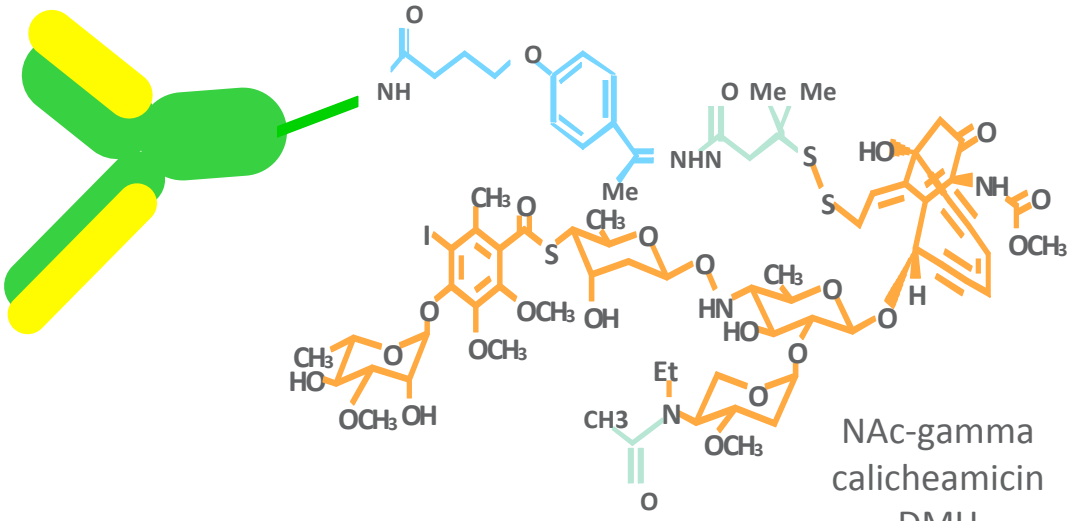
ALL, acute lymphoblastic leukaemia; CAR T, chimeric antigen receptor T cell; LBC, leukaemia cell line

1. Jabbour. *Blood* 2015;125:4010–4016; 2. Hoelzer D *et al Blood Rev* 2012:26–32 ; 3. Gokbuget N *et al. Ann Hematol* 2004;83:201–205. 4. Kumar J *et al. Indian J Hematol Blood Transfus* 2012;30:16–18; 5. Jain N et al Blood 2017;130:1321; 6. Maude SL *et al Blood* 2015;125:4017–4023; Raponi S et al Leuk Lymphoma 2011;52:1098–1107

# 2018 Inotuzumab Ozogamicin: an ADC Designed to Direct Cytotoxic Payload to CD22-Expressing Cancer Cells

**Humanised IgG4 anti-CD22**[1]

AcBut linker



NAc-gamma calicheamicin DMH

## Favourable antigenic features of CD22…

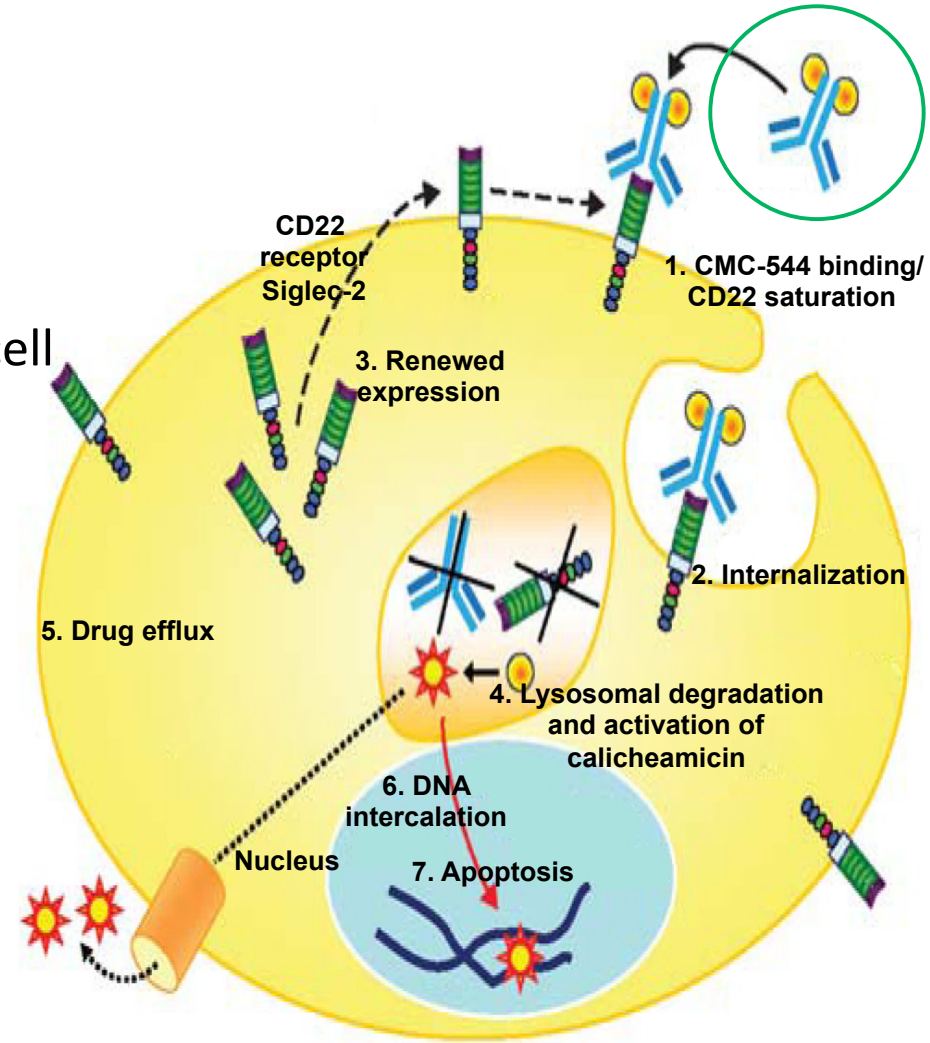
- Expressed by >90% of leukaemic blasts in patients with ALL[2]
- Expressed on B cells during maturation, lost on differentiation to plasma cells[3]
- Not expressed on haematopoietic stem cells or other normal tissues[2]
- Internalised via endocytosis on binding, not shed into the extracellular environment[2]

ADC, antibody–drug conjugate; ALL, acute lymphoblastic leukaemia

1. Advani A *et al. J Clin Oncol* 2010;28:2085-2093; 2. Dahl J *et al. Expert Rev Hematol* 2016;9:329–34; 3. Shor B *et al. Mol Immunol* 2015;67;107–116

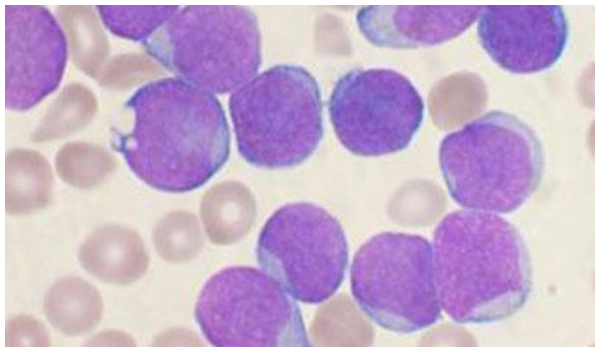
# Inotuzumab Ozogamicin: mechanism of action

- ✓ The antibody-antigen complex is rapidly internalised upon binding to CD22
- ✓ Calicheamicin is released inside the tumour cell
- ✓ Calicheamicin is more potent than other cytotoxic chemotherapeutic agents
- ✓ Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- ✓ Development of DNA breaks is followed by apoptosis of the tumour cell




*de Vries. Leukemia 2012; 26:255*

# Inotuzumab Ozogamicin: for which patients?



R/R ALL

MRD+

# Phase I/II trials with inotuzumab in R/R ALL

## Phase II MDACC trial (single-institution)[1,2]

**N=90**
- Patients with R/R ALL
- CD22-positive
- Salvage status:
- **68% ≥ Salvage 2**

→ Inotuzumab ozogamicin **0.8 mg/m²** (Day 1), **0.5 mg/m²** (Day 8 and Day 15), every 4 weeks (n=41)

→ Inotuzumab ozogamicin **1.8 mg/m²** every 3–4 weeks (n=49)

**ORR: 58%**
**MRD: 72%**

## Phase I/II B1931010 trial (multi-institution)[2,3]

**N=35**
- Patients with R/R ALL
- CD22-positive
- **Second and later salvage settings**

→ **Part 1** Inotuzumab ozogamicin* **0.8–2.0 mg/m²** per cycle (2–3 weekly doses per 28-day cycle for a maximum of six cycles)

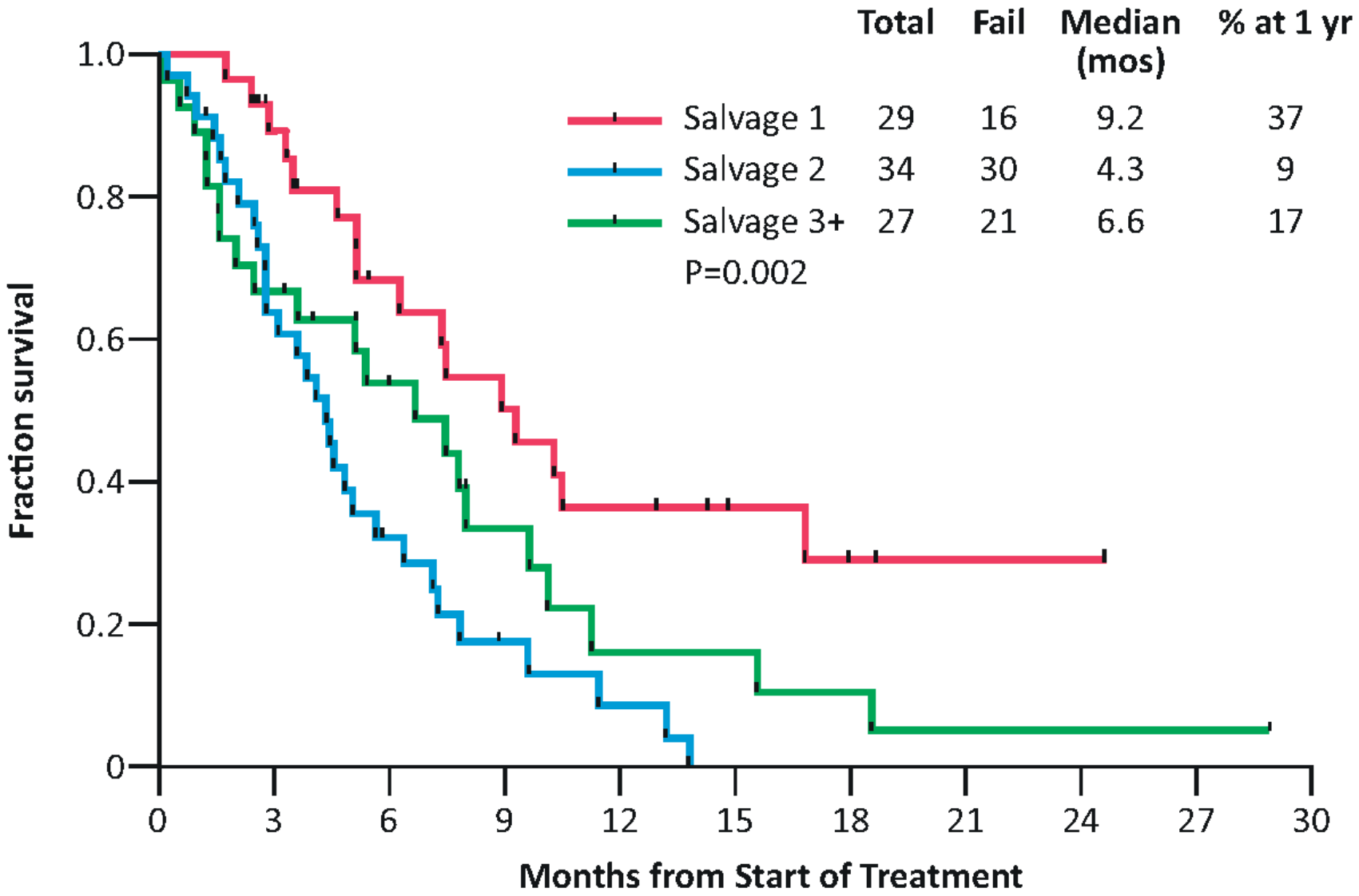
→ **Part 2** Inotuzumab ozogamicin* **1.8 mg/m²** per cycle (3-weekly doses per 28-day cycle for a maximum of six cycles)

**CR + CRi: 65.7%**
**MRD: 78%**

*Fractionated dosing only
ADC, antibody–drug conjugate; CR, complete remission; CRi, complete remission with incomplete haematological recovery of peripheral blood counts; MRD, minimal residual disease; ORR, overall response rate; R/R, relapsed/refractory

1. Kantarjian H *et al. Cancer* 2013;119:2728-2736; 2. Dahl J *et al. Expert Rev Hematol* 2016 [Epub); 3. clinicaltrials.gov (NCT01363297) accessed February 2018

# MDACC Phase II study of InO in R/R ALL: Survival by salvage status




Kantarjian H *et al*. *Cancer* 2013;119:2728–2736

The NEW ENGLAND JOURNAL of MEDICINE

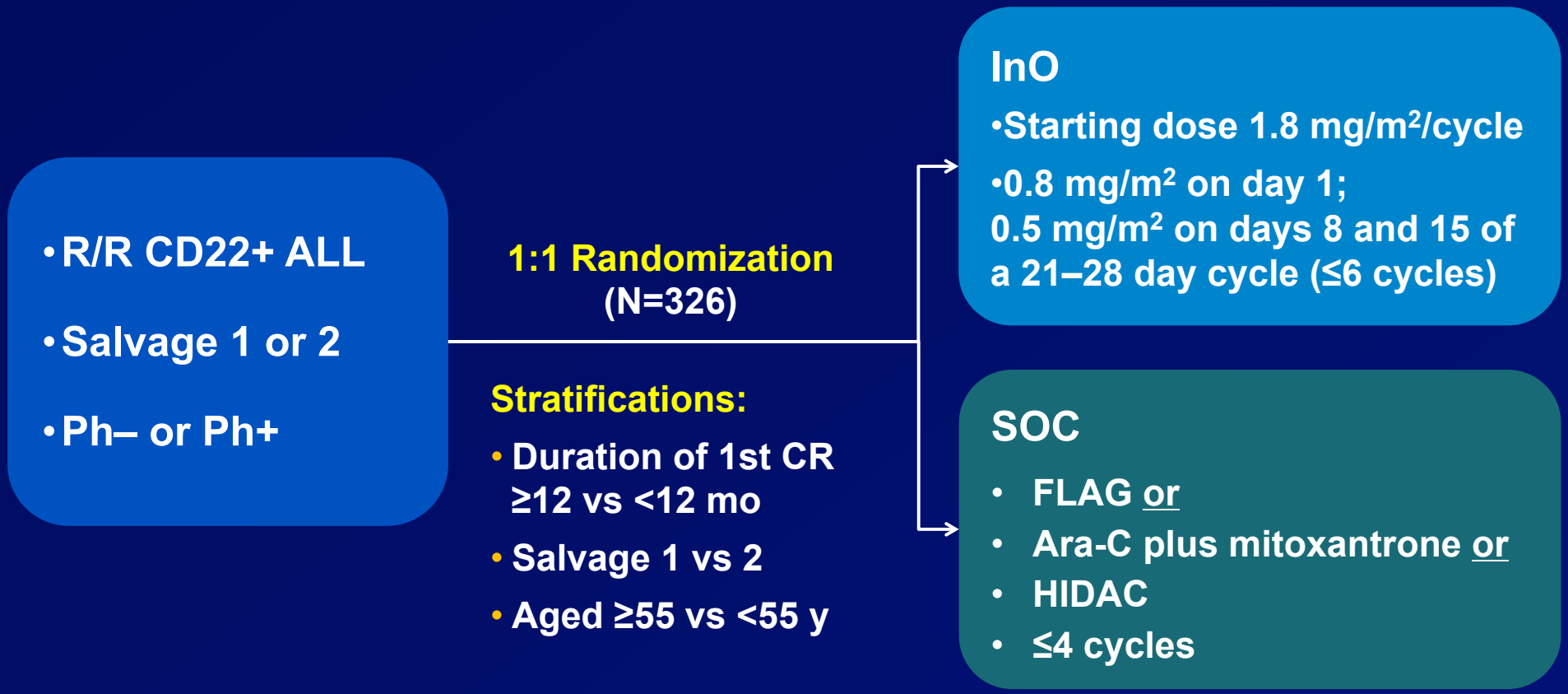
ORIGINAL ARTICLE

# Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., Erik Vandendries, M.D., Ph.D., and Anjali S. Advani, M.D.

# Study Design

- Open-label, phase 3 study: 326 patients randomized at 117 sites in 19 countries




- InO dose was reduced to 1.5 mg/m$^2$/cycle once the patient achieved CR/CRi



Ara-C=cytarabine; CR=complete remission; CRi=CR with incomplete hematologic recovery; FLAG=fludarabine/ara-C/granulocyte colony-stimulating factor; HIDAC=high-dose ara-C; Ph=Philadelphia chromosome

# CR/CRi Results (ITT218)

| Response,* n (%) [95% CI] | InO (n=109) | SOC (n=109) | 1-Sided *P* Value |
|---|---|---|---|
| CR/CRi | 88 (80.7) [72–88] | 32 (29.4) [21–39] | <0.0001 |
| MRD negative† | 69/88 (78.4) [68–87] | 9/32 (28.1) [14–47] | <0.0001 |

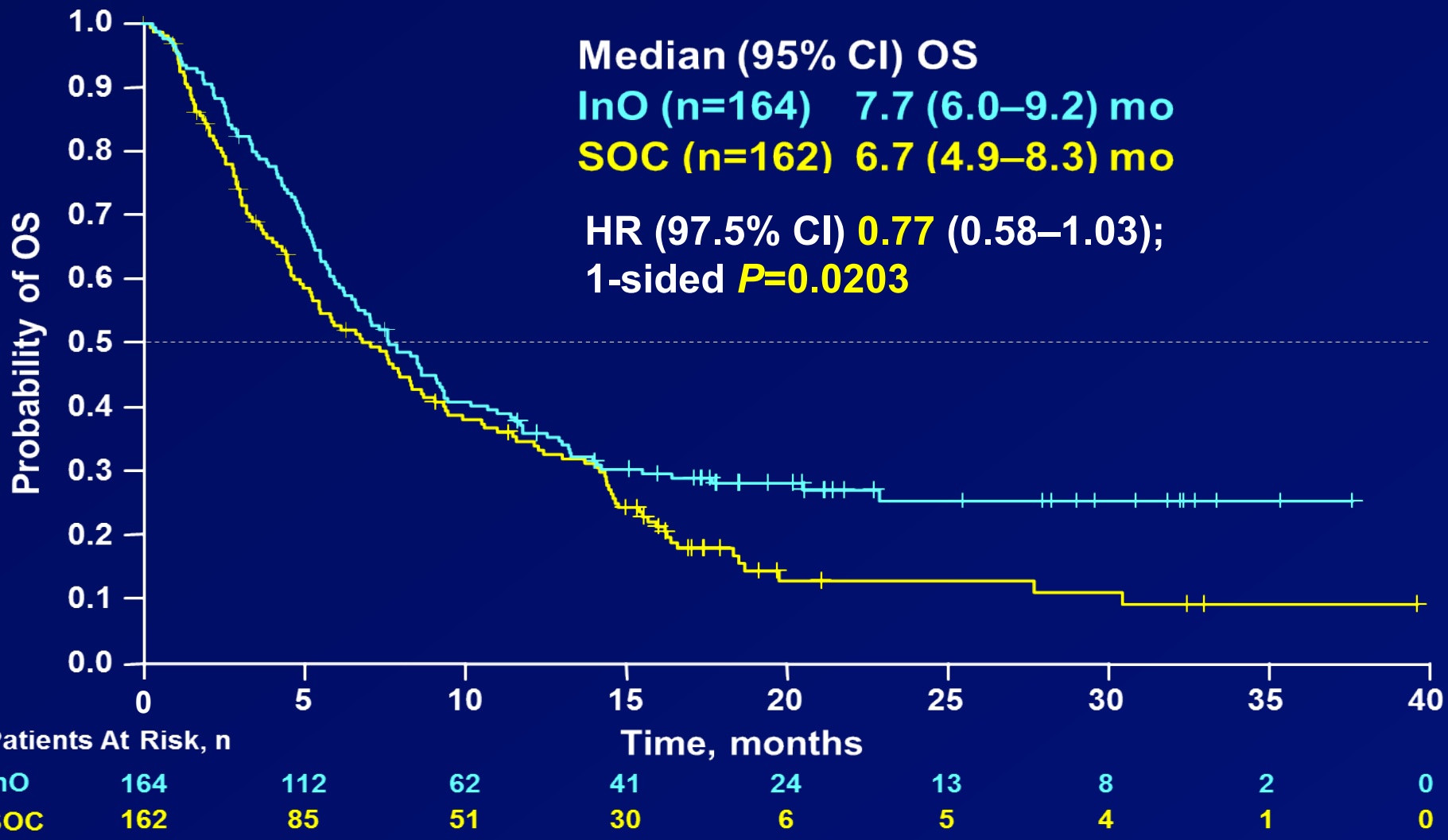
- Among the first 218 patients randomized, over 4X more achieved CR/CRi and proceeded directly to SCT after CR/CRi with InO vs SOC (n=41/109 vs n=10/109; *P*<0.0001)‡

*Cutoff date: October 2, 2014 (database unlocked), per EAC; †Among responders; 13 SOC patients who withdrew before dosing were considered nonresponders; ‡Per investigator's assessment



Kantarjian HM, et al. *N Engl J Med*. 2016;375(8):740-53

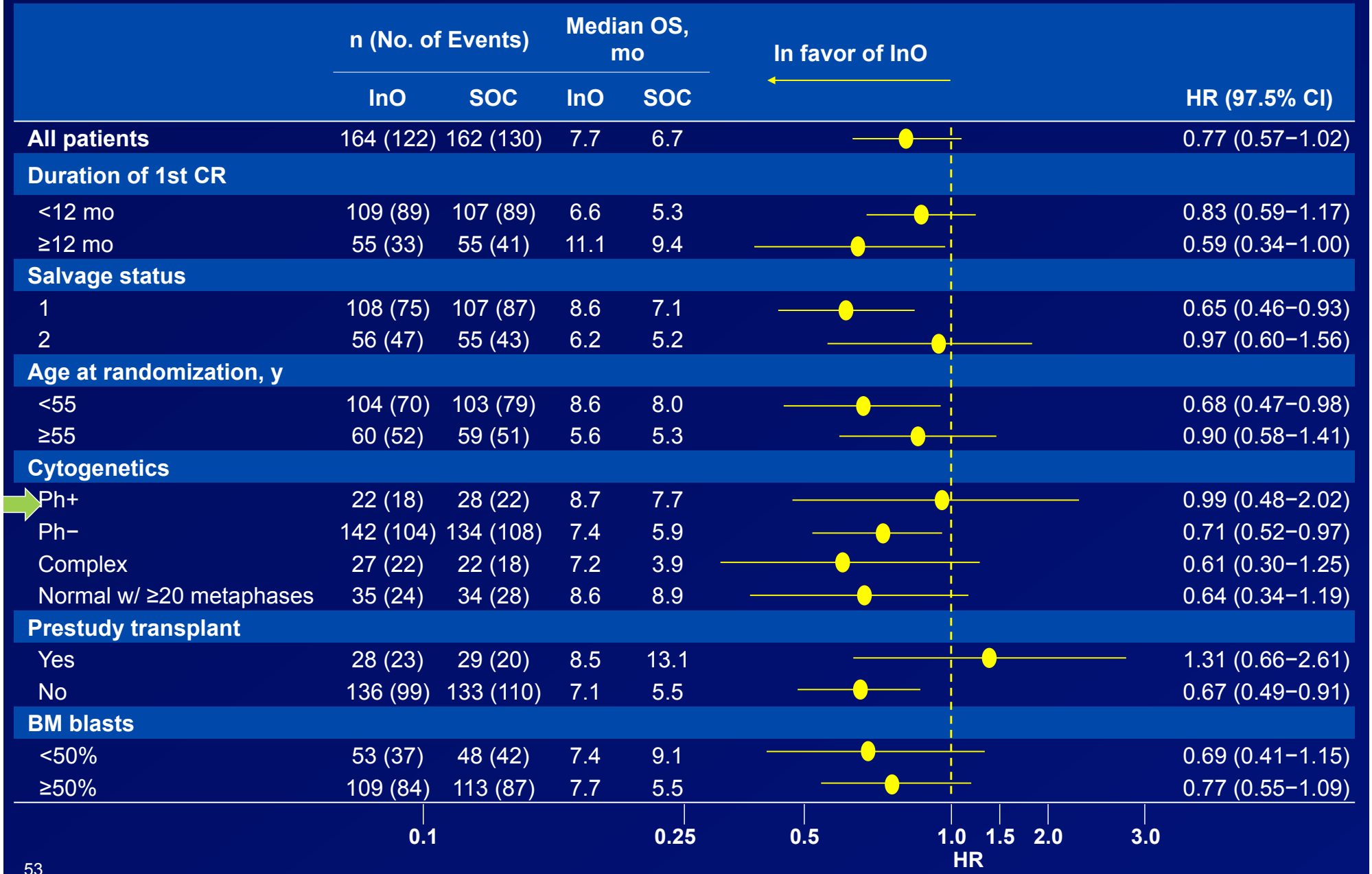
# Overall Survival




- 2-year survival probability higher with InO (23% [95% CI: 16–30] vs 10% [5–16])
- Primary objective to demonstrate significantly improved OS with InO at the prespecified boundary of *P*=0.0104 not met

# Subgroup Analysis of OS (ITT)

| | n (No. of Events) | | Median OS, mo | | HR (97.5% CI) |
|---|---|---|---|---|---|
| | InO | SOC | InO | SOC | |
| **All patients** | 164 (122) | 162 (130) | 7.7 | 6.7 | 0.77 (0.57−1.02) |
| **Duration of 1st CR** | | | | | |
| <12 mo | 109 (89) | 107 (89) | 6.6 | 5.3 | 0.83 (0.59−1.17) |
| ≥12 mo | 55 (33) | 55 (41) | 11.1 | 9.4 | 0.59 (0.34−1.00) |
| **Salvage status** | | | | | |
| 1 | 108 (75) | 107 (87) | 8.6 | 7.1 | 0.65 (0.46−0.93) |
| 2 | 56 (47) | 55 (43) | 6.2 | 5.2 | 0.97 (0.60−1.56) |
| **Age at randomization, y** | | | | | |
| <55 | 104 (70) | 103 (79) | 8.6 | 8.0 | 0.68 (0.47−0.98) |
| ≥55 | 60 (52) | 59 (51) | 5.6 | 5.3 | 0.90 (0.58−1.41) |
| **Cytogenetics** | | | | | |
| Ph+ | 22 (18) | 28 (22) | 8.7 | 7.7 | 0.99 (0.48−2.02) |
| Ph− | 142 (104) | 134 (108) | 7.4 | 5.9 | 0.71 (0.52−0.97) |
| Complex | 27 (22) | 22 (18) | 7.2 | 3.9 | 0.61 (0.30−1.25) |
| Normal w/ ≥20 metaphases | 35 (24) | 34 (28) | 8.6 | 8.9 | 0.64 (0.34−1.19) |
| **Prestudy transplant** | | | | | |
| Yes | 28 (23) | 29 (20) | 8.5 | 13.1 | 1.31 (0.66−2.61) |
| No | 136 (99) | 133 (110) | 7.1 | 5.5 | 0.67 (0.49−0.91) |
| **BM blasts** | | | | | |
| <50% | 53 (37) | 48 (42) | 7.4 | 9.1 | 0.69 (0.41−1.15) |
| ≥50% | 109 (84) | 113 (87) | 7.7 | 5.5 | 0.77 (0.55−1.09) |






BM=bone marrow. Based on March 8, 2016, cutoff date from an unlocked database

# Summary of Hepatic AEs (Safety Population)

- Grade ≥3 hepatic AEs:
  - Less frequent in S1 vs S2 (7% vs 26%) and in patients without prior SCT (25% vs 10%)
  - Incidence similar in patients aged <55 vs ≥55 y (14% vs 11%)
- VOD during InO therapy or in follow-up without intervening SCT:
  - More frequent in S2 (2% [n=2/94] vs 7% [n=3/45]) and in patients with prior SCT (3% [n=3/115] vs 8% [n=2/24])
  - Incidence similar in both age groups (3% [3/86] vs 4% [2/53])
- VOD after poststudy SCT:
  - More frequent in S2 (17% [n=6/36 ] vs 33% [n=4/12]), in patients with prior SCT (43% [n=3/7] vs 17% [n=7/41]), and in older patients (17% [6/36] vs 33% [4/12])



VOD=veno-occlusive disease.

# Take home messages: Inotuzumab Ozogamicin

- InO demonstrated **significantly improved rates of CR/CRi vs SOC in patients with R/R ALL, regardless of salvage status, age (<55 vs ≥55 years), or prior SCT status**
- Overall, over 4X more patients proceeded directly to SCT after InO vs SOC (41 vs 10)
- DoR was significantly longer with InO vs SOC for patients treated with S2, those without prior SCT, and those ≥55 years
- InO safety profile was generally similar across all subgroups
- Incidence of liver **toxicities**, including **VOD**, increased with salvage status and prior SCT but was similar in patients <55 years
  - Post-SCT VOD was more common in patients aged ≥55 years
- InO may represent an important new treatment option in R/R ALL

2018

# Coming soon…
# Inotuzumab Ozogamicin in MRD+ ALL

**PROTOCOL TITLE:** A PHASE IIA STUDY OF FEASIBILITY AND EFFECTIVNESS OF INOTUZUMAB OZAGOMICIN (IO) IN ADULT PATIENTS WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA WITH POSITIVE MINIMAL RESIDUAL DISEASE BEFORE ANY HEMATOPOIETIC STEM CELL TRANSPLANTATION

GIMEMA

**D-ALBA Front-Line Sequential Treatment of Adult Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Patients with Dasatinib and the Bispecific Monoclonal Antibody Blinatumomab**

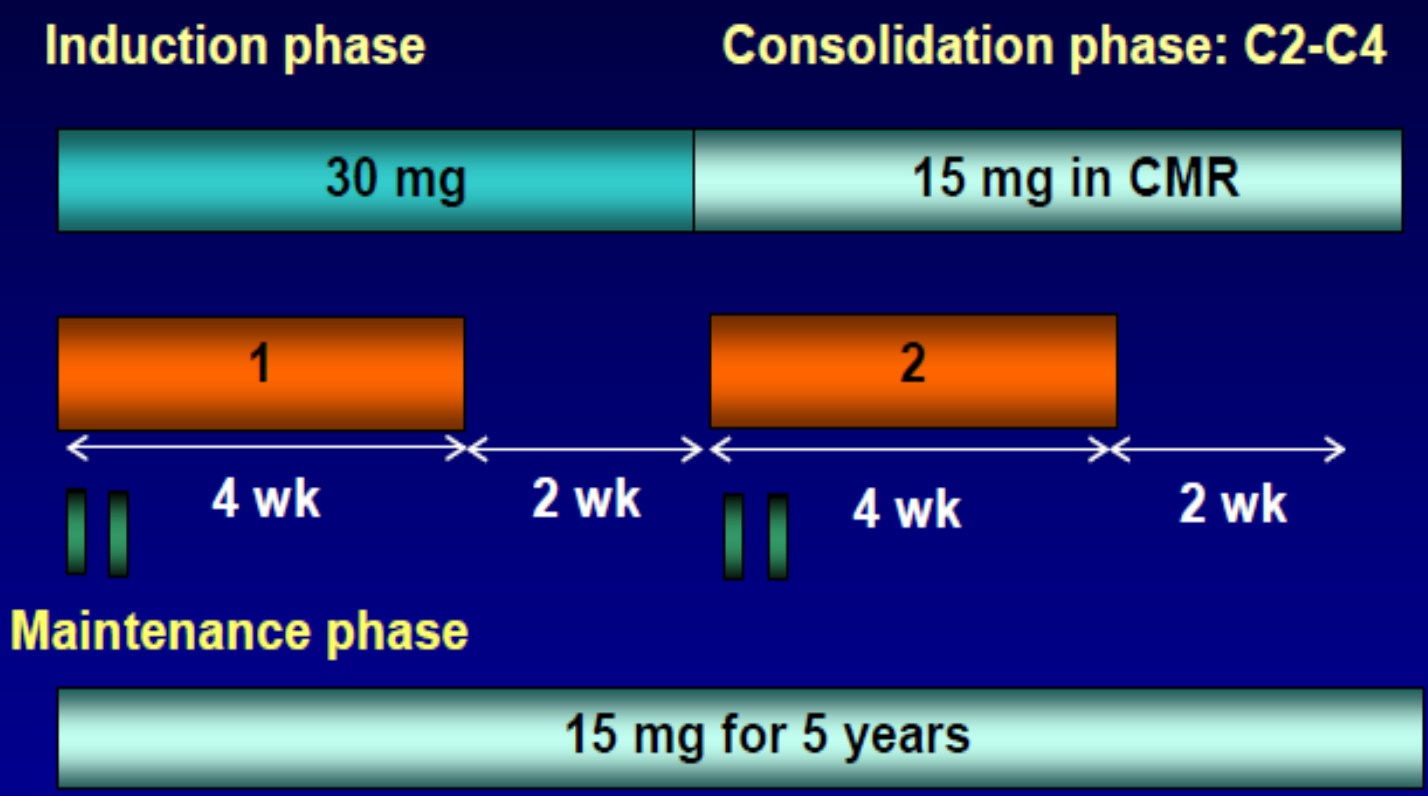
**GIMEMA LAL2116**

**EudraCT number 2016-001083-11**

## GIMEMA LAL 2317:

Blinatumomab incorporated in first line chemotherapy in newly diagnosed Ph neg B ALL

# Blinatumomab-ponatinib in Ph-Positive ALL




Blinatumomab IT MTX, Ara-C Ponatinib 30 mg Ponatinib 15 mg

# Open Questions

- How should we best incorporate these therapies into ALL treatment?
  - Frontline vs relapsed/refractory
- Their incorporation in a concomitant or sequential fashion may:
  - induce higher rates of MRD negativity
  - reduce the need for intensive and prolonged chemotherapy schedules
  - avoid alloHSCT
- Mechanisms of resistance? Combinations to avoid resistance?

# Acknowledgments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Prof G.Martinelli