
**Anticorpi monoclonali bispecifici**

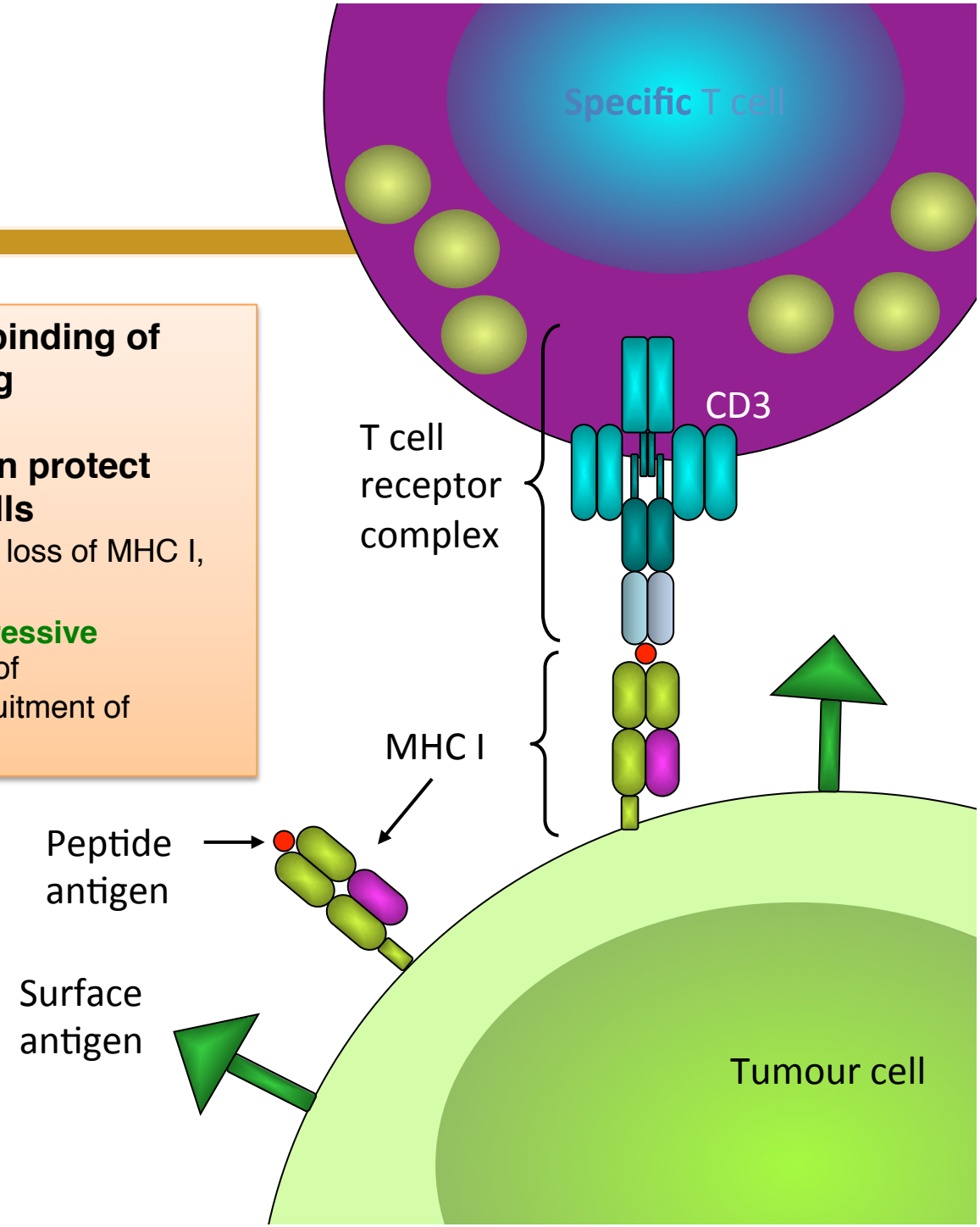
*Massimiliano Bonifacio*
Verona

# T cells and cancer

**T cell receptor recognition and binding of antigen is required for cell killing**

**Multiple escape mechanisms can protect cancer cells from attack by T cells**

- **Reduced immune recognition** (eg loss of MHC I, reduced antigen expression)
- **Development of an immunosuppressive microenvironment** (eg production of immunosuppressive cytokines, recruitment of immunosuppressive $T_{regs}$)



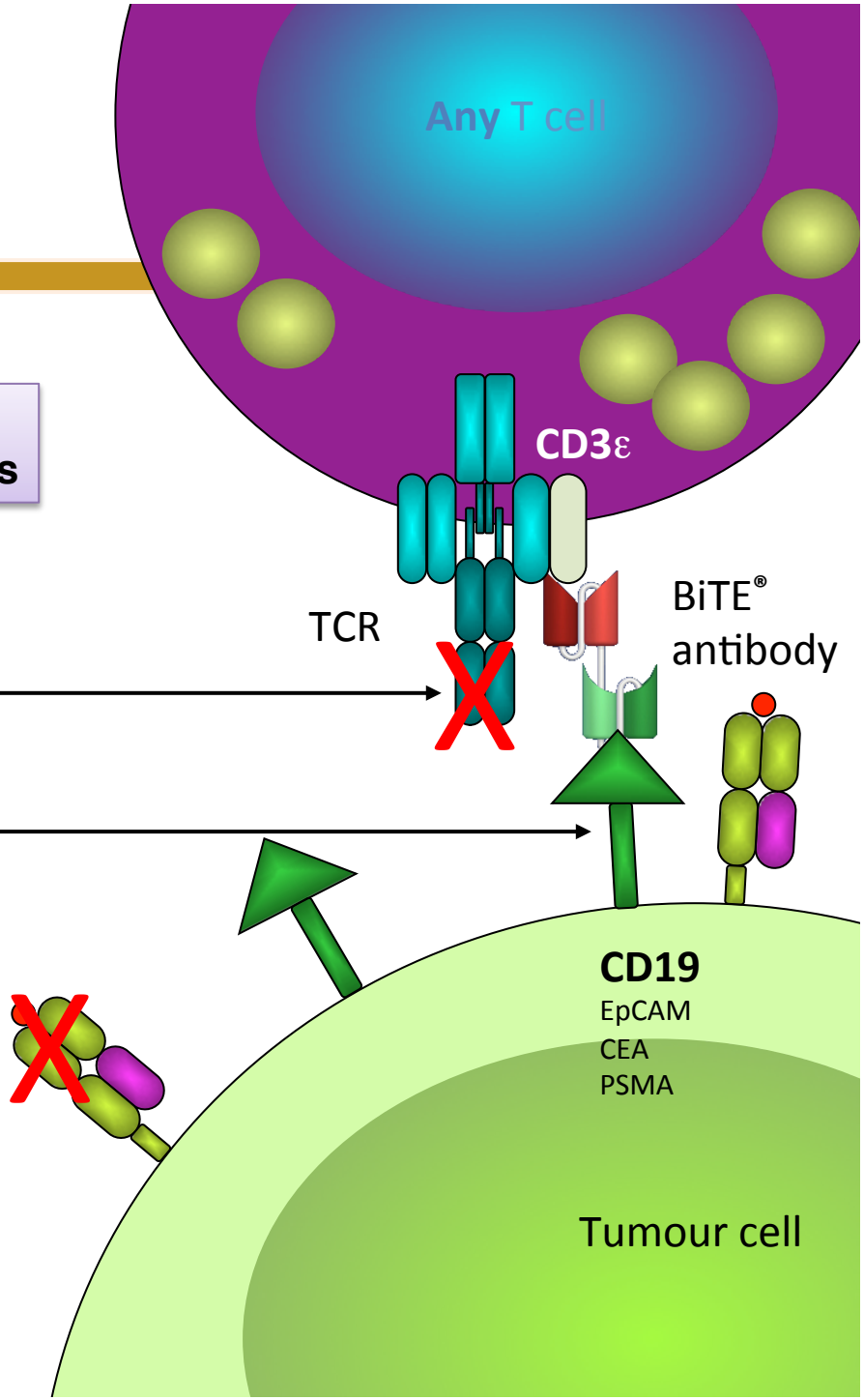
# BiTE® antibodies

**BiTE® (Bispecific T-cell Engager) antibodies may circumvent frequent escape mechanisms**

Do not require T-cell clone with specific T cell receptor

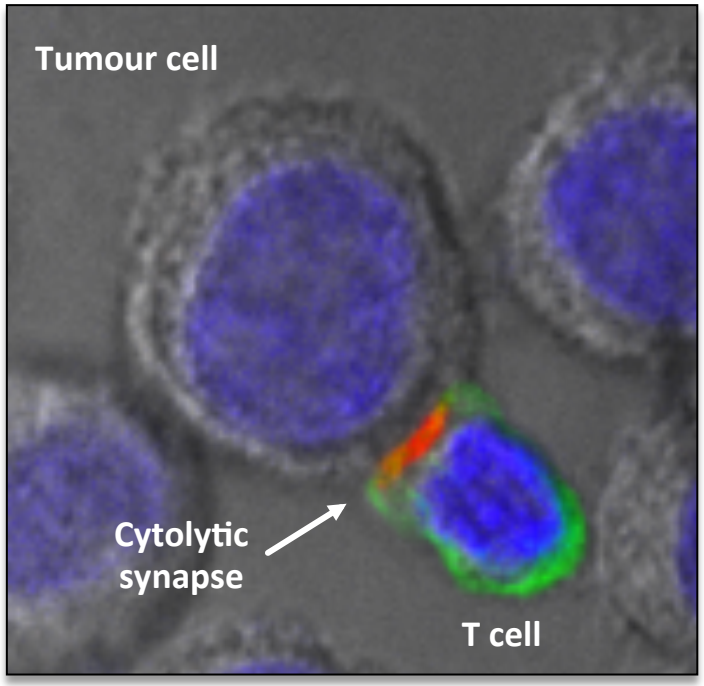
Can make any T cell recognise a surface antigen

Do not require MHC I and peptide antigen for recognition by T cell



# BiTE® antibodies unleash the immune system on cancer cells

**T cell kills tumour cell via BiTE bridge**




- BiTE®-activated cytotoxic T cells release cytokines and produce additional **perforin** and **granzymes**[1,2]
- A single BiTE®-activated cytotoxic T cell can engage target antigen-binding regions of multiple cancer cells and initiate lysis and apoptosis[3]
- BiTE®-activated cytotoxic T cells enter the cell cycle, resulting in local T-cell proliferation and a polyclonal expansion of **memory CD8⁺ T cells**[1,2]

1. Baeuerle PA, et al. Curr Opin Mol Ther 2009;11:22–30;
2. Nagorsen D, Baeuerle PA. Exp Cell Res 2011;317:1255–60;
3. Hoffmann P, et al. Int J Cancer 2005;115:98–104

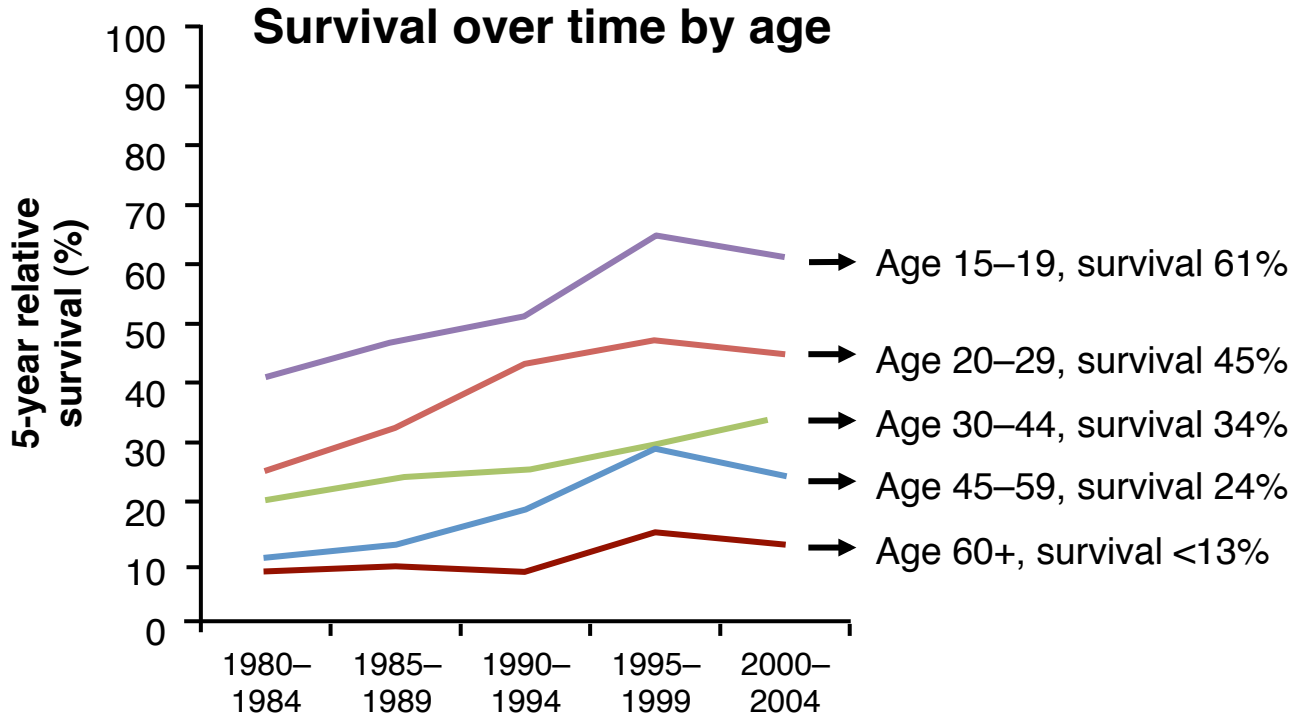
# BiTE® antibodies for cancer immunotherapy

| Drug | Target | Setting | Phase of development |
|---|---|---|---|
| Blinatumomab | CD19 | Relapsed/refractory Ph- B-ALL | FDA- and EMA-approved |
| | | Relapsed/refractory Ph+ B-ALL | Phase II (completed) |
| | | $MRD^+$ B-ALL | Phase II (completed) |
| | | Relapsed/refractory DLBCL | Phase II (ongoing) |
| AMG330 | CD33 | Acute myeloid leukemia | Preclinical |
| AMG110 | EpCAM | Lung cancer, gastric cancer, colorectal cancer, breast cancer, prostate cancer, ovarian cancer | Phase I (completed) |
| MEDI-565 | CEA | Gastrointestinal adenocarcinoma | Phase I (completed) |
| BAY2010112 (subcutaneous) | PSMA | Prostate cancer | Phase I (ongoing) |

Stieglmaier J, et al. Expert Opin Biol Ther 2015;15:1093-1099.

# Acute Lymphoblastic Leukemia in adults: scenario

Despite improvements in paediatric patients, survival remains poor in adults with Acute Lymphoblastic Leukemia



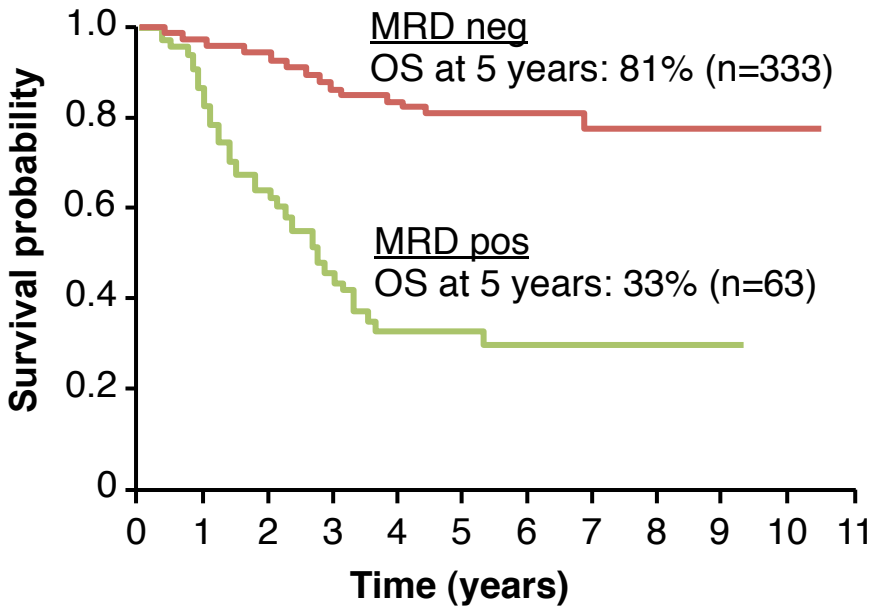

**Since 1980, there has been no significant improvement in survival rates in patients >60 years of age**

Pulte et al. *Blood* 2009;113:1408–11

# Particularly critical areas in therapy of adult ALL

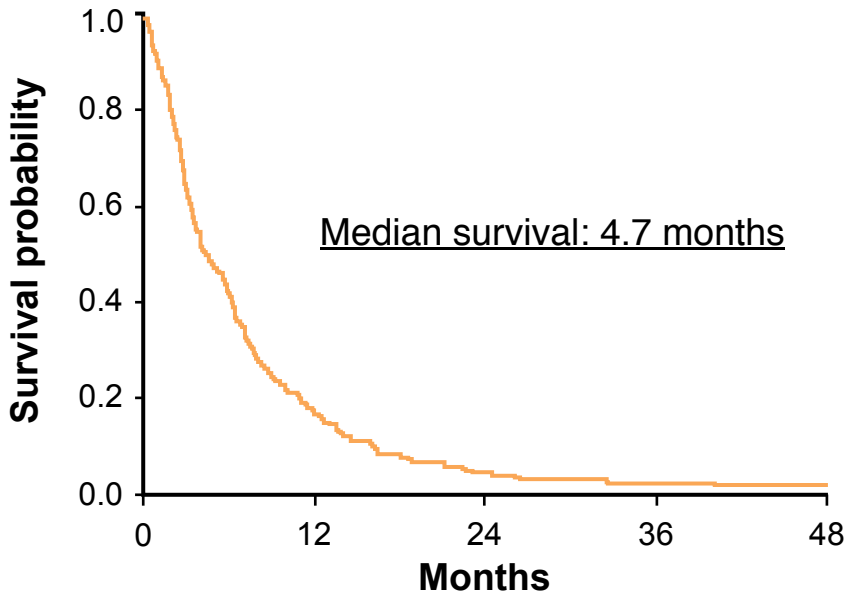
## Minimal Residual Disease (MRD+) patients

**Probability of survival in GMALL studies according to MRD status at week 16 of induction treatment [1]**




## Patients relapsed after / refractory to frontline treatment

**Probability of survival in patients with primary failure on frontline induction or early relapse (within 12 months) [2]**



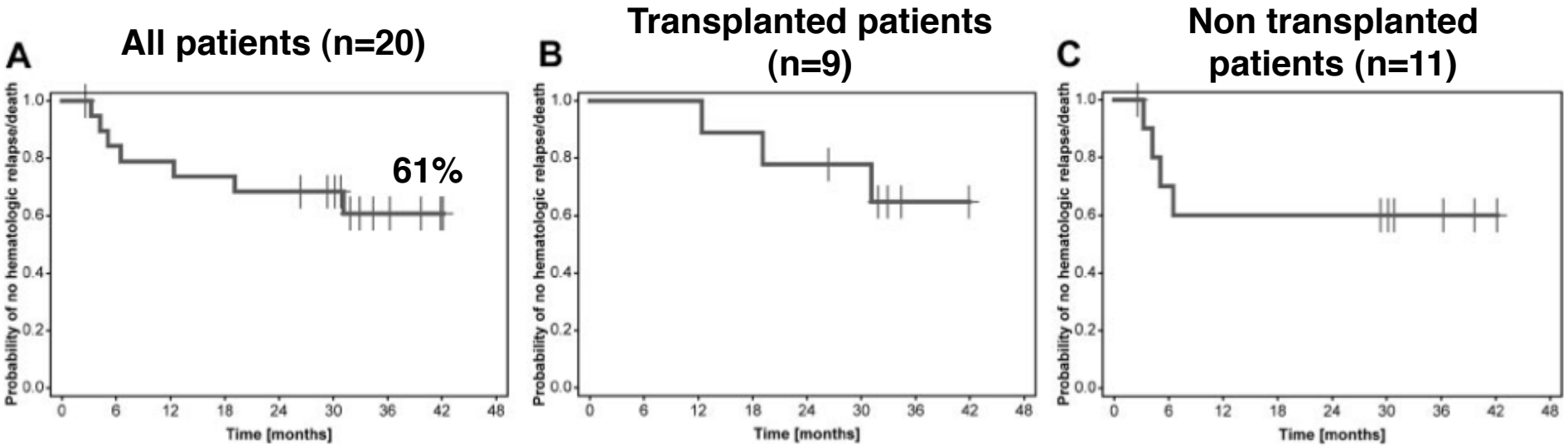

[1] Gokbuget et al. *Blood* 2012;120:1868-1876. [2] Kantarjian et al. Cancer 2010;116:5568-5574.

# Blinatumomab in MRD$^{+}$ B-ALL
## *Pilot experience (MT103-202 German study)*

- Patients with B-precursor ALL in hematological CR with molecular failure (n=21)
- MRD >$10^{-4}$ (after standard induction and consolidation)

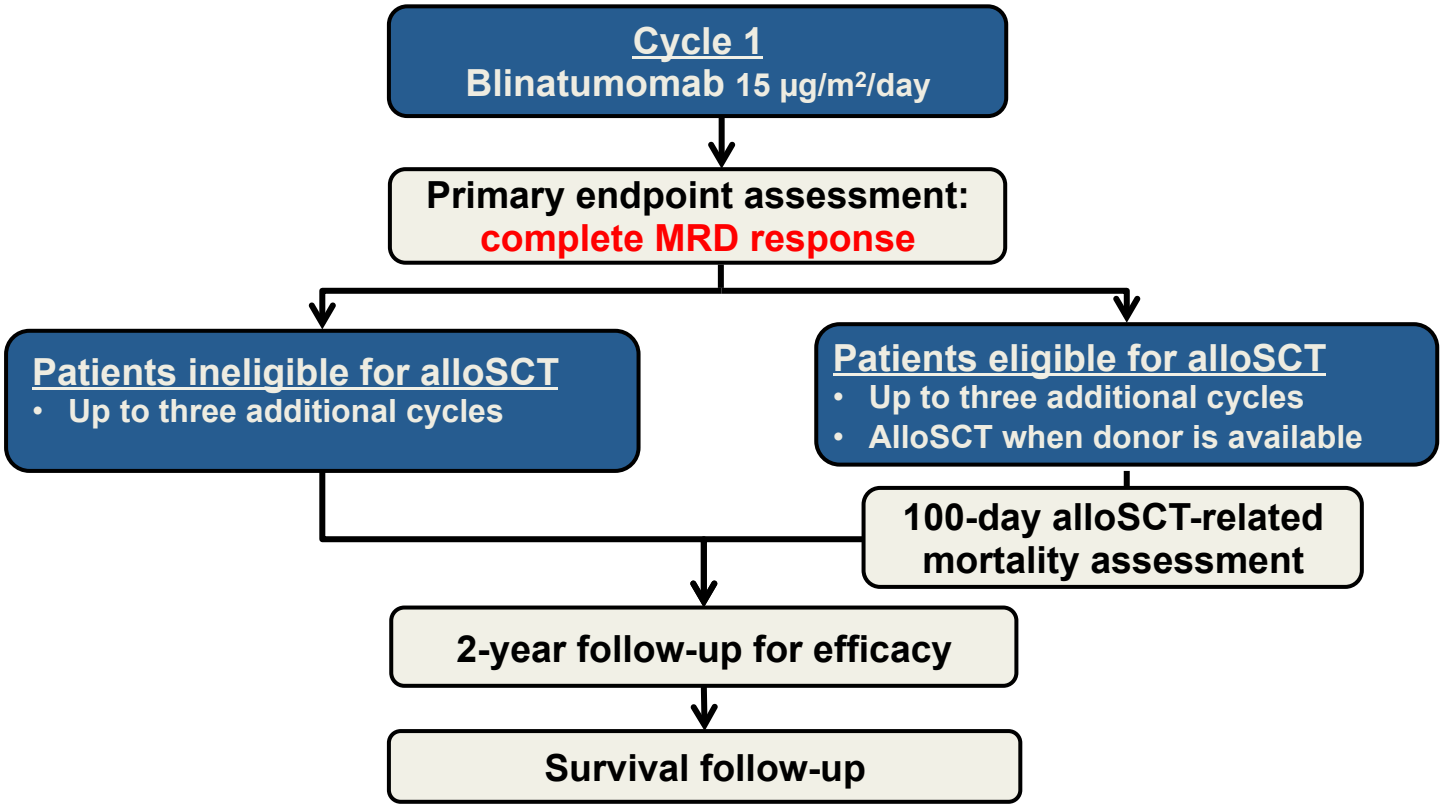
**MRD complete response rate: 80%**

*All responses within the first cycle of treatment*




Topp et al. *J Clin Oncol* 2011;29:2493-2498. Topp et al. *Blood* 2012;120:5185-5187.

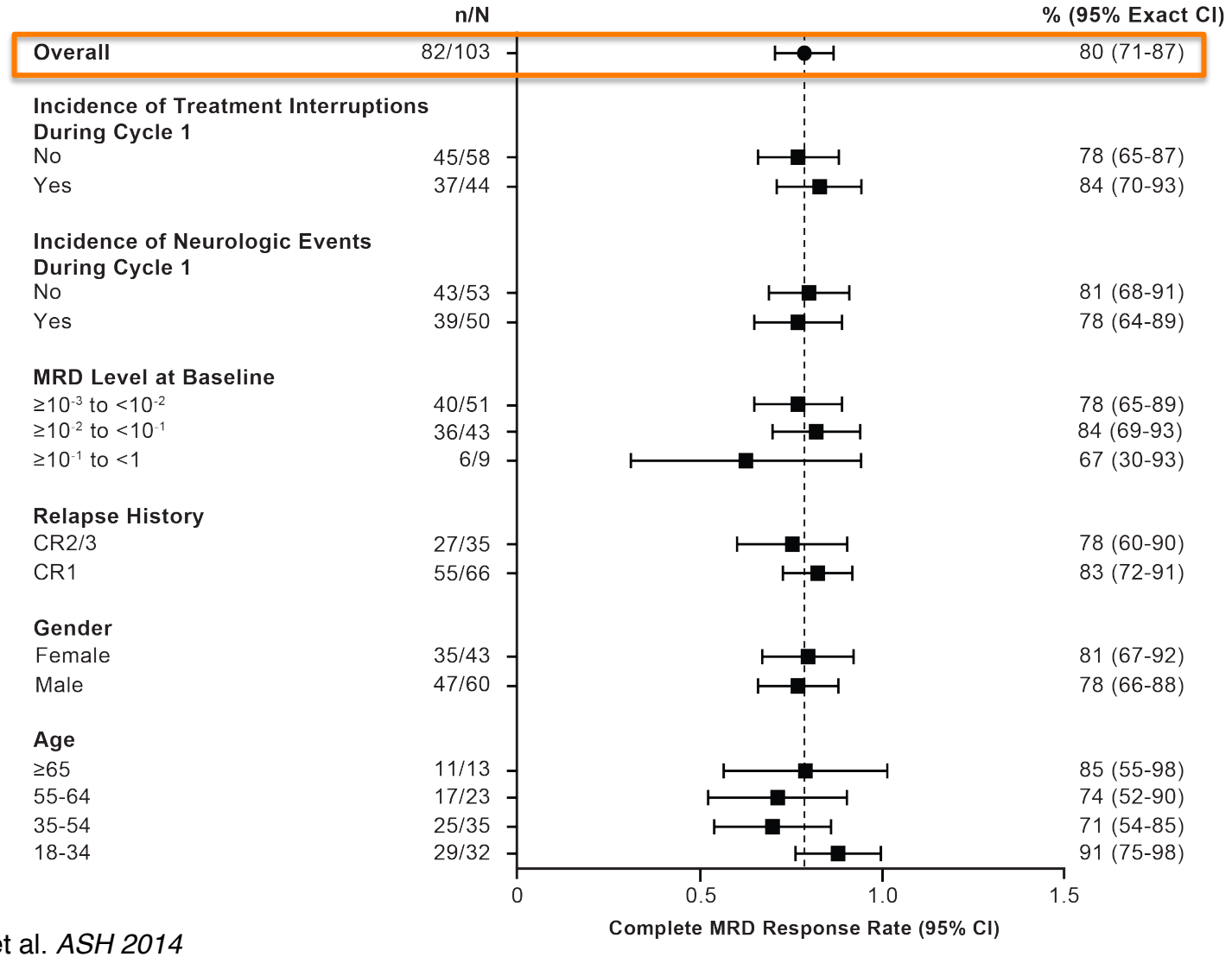
# Blinatumomab in MRD+ B-ALL
## *Confirmatory multicenter MT103-203 study*




- Blinatumomab was given by continuous IV infusion, **15 µg/m²/d** x 28 days per cycle, for 4 weeks on/2 weeks off (one cycle) for a maximum of up to four cycles.
- A MRD level of ≥ $10^{-3}$ was required for study entry.

Gokbuget N et al. *ASH 2014*

# BLAST multicenter MRD study
## *Complete MRD response after cycle 1*




Gokbuget N et al. *ASH 2014*

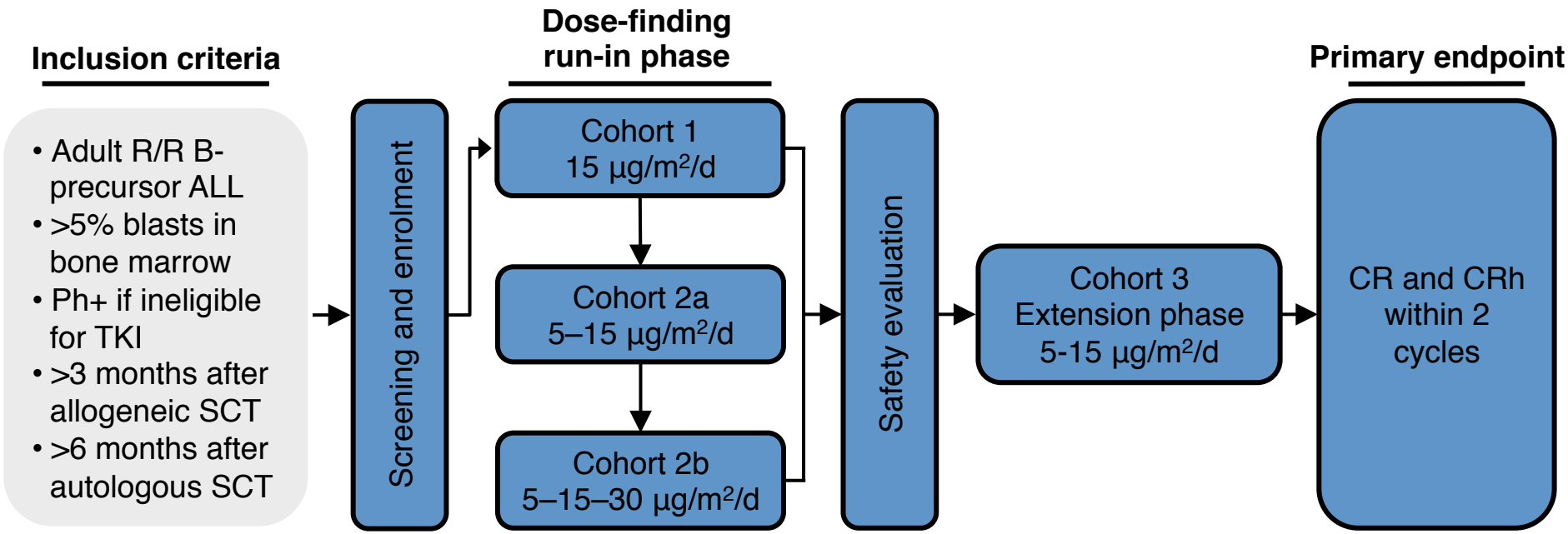
# BLAST multicenter MRD study
## *Long-term outcome*

| | Median (95% CI), Months | |
|---|---|---|
| | **Relapse-free Survival*** | **Overall Survival** |
| Overall (n=112) | 18.9 (12.3 - 35.2) | 36.5 (19.2 - NR) |
| By MRD complete response | | |
| MRD complete responders (n=88) | NR (6.0 - NR) | 38.9 (33.7 - NR) |
| MRD non-responders (n=24) | 3.6 (1.6 - 5.7) | 10.5 (3.8 - NR) |
| By remission status | | |
| First CR (n=75) | 24.6 (18.7 - NR) | 36.5 (20.6 - NR) |
| Second/third CR (n=35) | 11.0 (6.8 - 15.4) | 19.1 (11.9 - NR) |

CR = complete remission; MRD = minimal residual disease; NR = not reached
MRD response was defined as MRD < $10^{-4}$ (minimum sensitivity $10^{-4}$)
*RFS censoring at HSCT or post-blinatumomab chemotherapy.

Gokbuget N et al. *ASH 2015*

# Blinatumomab in relapsed/refractory B-ALL
## *Pilot experience (MT103-206 German study)*




**Blinatumomab cIV, 4 weeks on/2 weeks off, for up to 5 cycles**
Consolidation after CR/CRh* within the first 2 cycles:

- 3 more cycles of blinatumomab *or*
- allogeneic SCT

Topp et al. *J Clin Oncol* 2014;32:4134-4140.

# Blinatumomab in relapsed/refractory B-ALL
## *Patient characteristics (MT103-206 German study)*

| | All cohorts n=36 (%) |
|---|---|
| Median age, years (range) | 32 (18-77) |
| Gender female/male, n | 14/22 |
| No prior HSCT, n (%) | 21 (58) |
| Primary refractory | 3 (8) |
| Salvage 1 after CR1 | |
| ≤18 months from initial diagnosis | 8 (22) |
| >18 months from initial diagnosis | 8 (22) |
| ≥2nd salvage | 2 (6) |
| Prior HSCT, n (%) | 15 (42) |
| Ph+, n (%) | 2 (6) |
| t(4;11), n (%) | 4 (11) |

Topp et al. *J Clin Oncol* 2014;32:4134-4140.

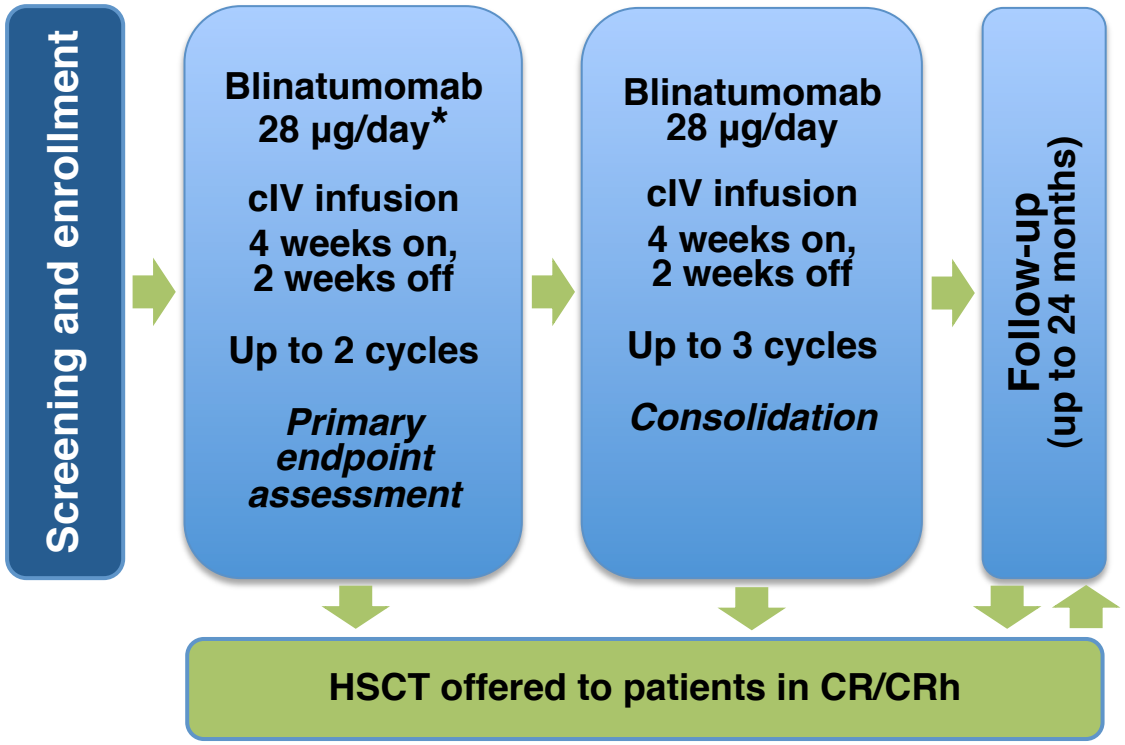
# Blinatumomab in relapsed/refractory B-ALL
## *Response rates (MT103-206 German study)*

| | Overall | No prior HSCT | | | Prior HSCT (n=15) |
|---|---|---|---|---|---|
| | | Salvage 1 after CR1 ≤18 mo (n=8) | Salvage 1 after CR1 >18 mo (n=8) | ≥2nd salvage or refractory (n=5) | |
| CR/CRh, n (%) | 25 (69) | 7 (88) | 8 (100) | 2 (40) | 8 (53) |
| CR | 15 (42) | 3 (38) | 6 (75) | 2 (40) | 4 (27) |
| CRh | 10 (28) | 4 (50) | 2 (25) | 0 | 4 (27) |
| Blast-free hypoplastic bone marrow, n (%) (platelets <50,000/μL and/or neutrophils <500/μL) | 3 (8) | 0 | 0 | 0 | 3 (20) |
| No remission, n (%) | 6 (17) | 1 (13) | 0 | 1 (20) | 4 (27) |
| Not evaluable,*n (%) | 2 (6) | 0 | 0 | 2 (40) | 0 |

- **88% of all responders (22/25) achieved molecular remission (MRD negative) and the majority demonstrated MRD response in cycle 1**

Topp et al. *J Clin Oncol* 2014;32:4134-4140.

# Blinatumomab in relapsed/refractory B-ALL
## *Confirmatory multicenter MT103-211 study*




*9 µg/day in cycle 1 (days 1 to 7)

**Primary endpoint**

- CR/CRh during the first 2 cycles

**Key inclusion criteria**

Ph- R/R B-ALL with any of:

- primary resistance to frontline therapy
- if Salvage 1, CR1 duration <12 months
- ≥2nd salvage
- Post HSCT relapse

>10% blasts in bone marrow

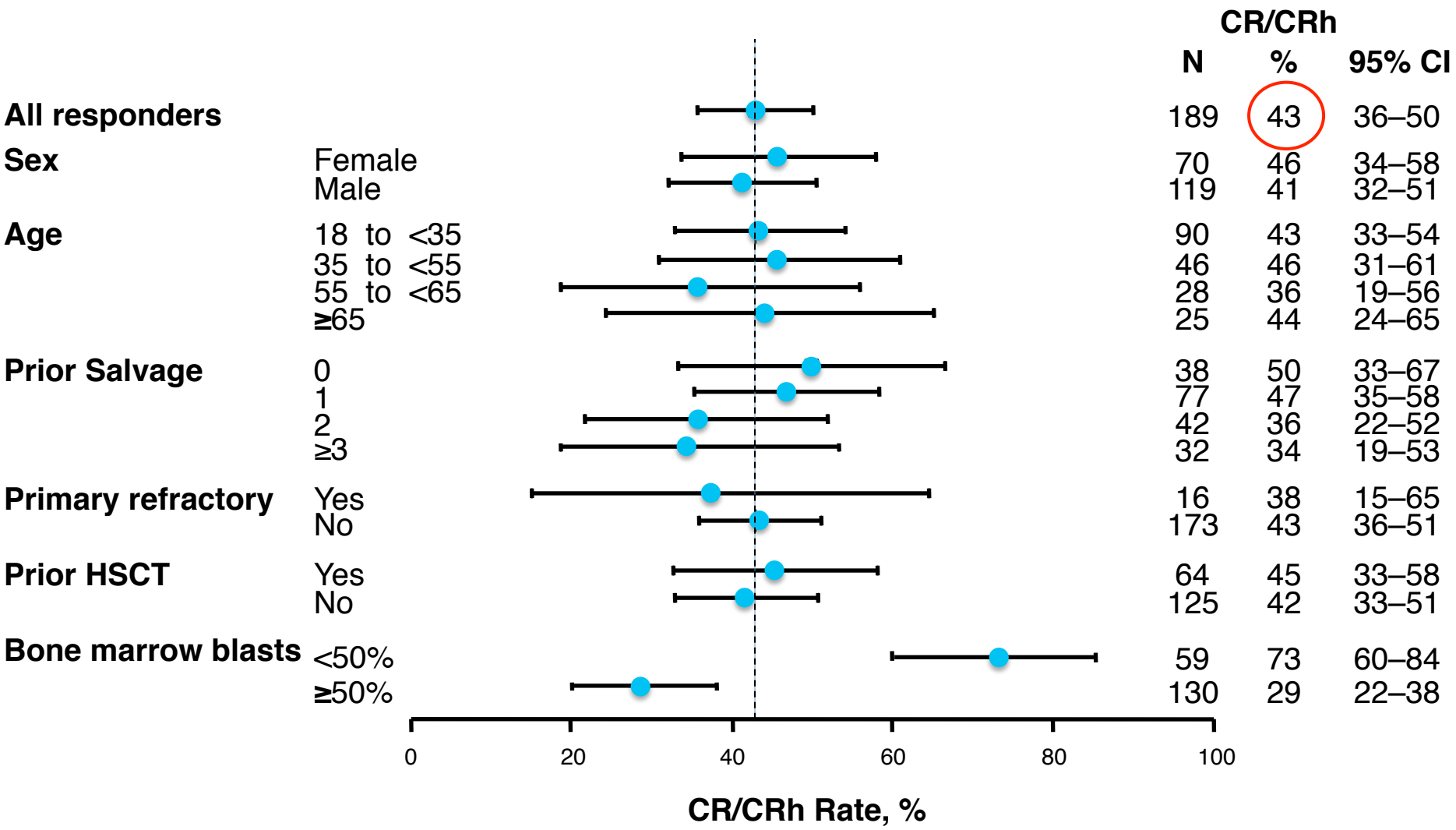
ECOG PS ≤2

Age ≥18 years

CR, complete remission (≤5% bone marrow blasts, platelets >100,000/µL, ANC >1,000/µL) ;
CRh, complete remission with partial recovery of peripheral blood counts (≤5% bone marrow blasts, platelets >50,000/µl and ANC >500/µl)

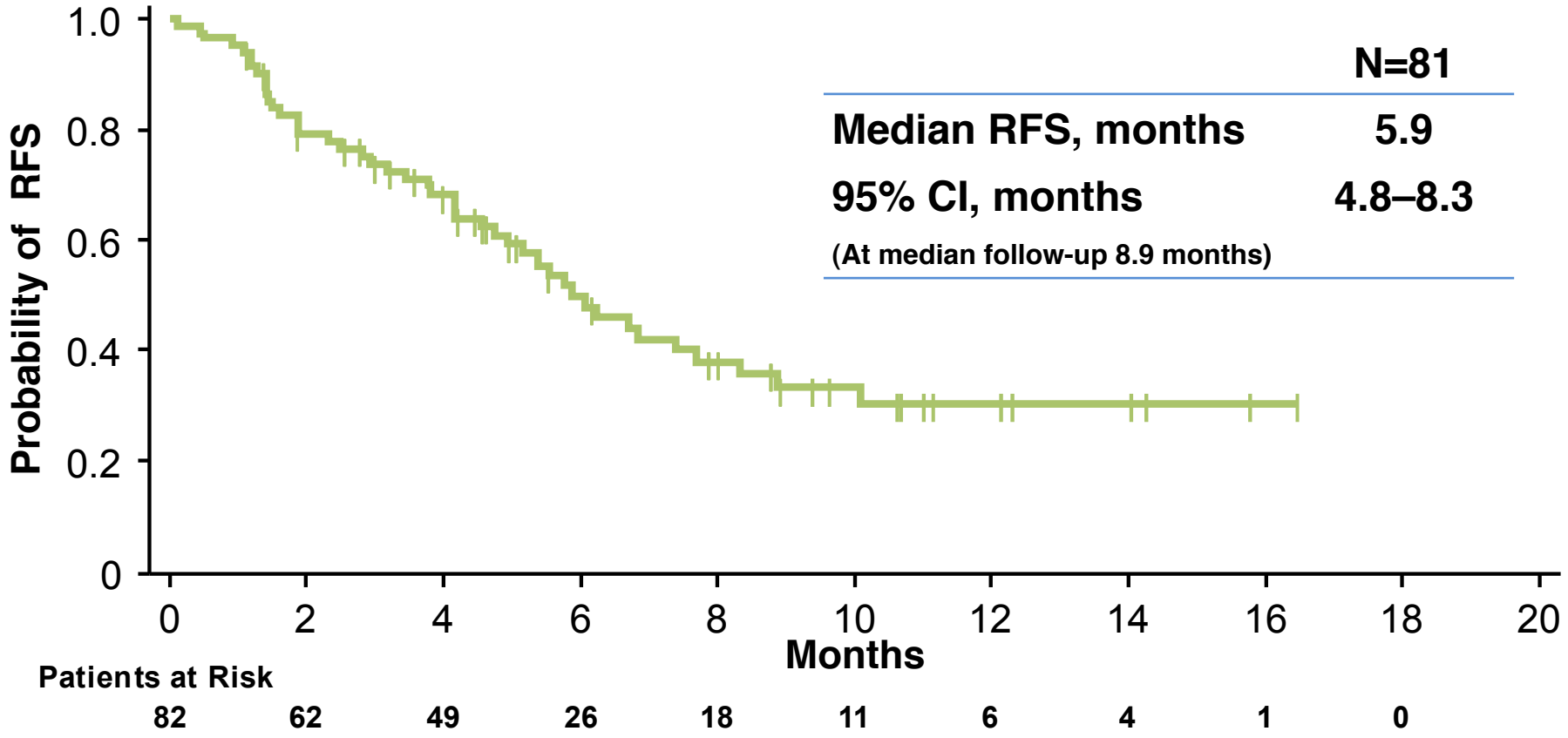
Topp et al. *Lancet Oncol* 2015;16:57-66.

# Multicenter MT103-211 study in rel/ref B-ALL
## *Subgroup analyses of CR/CRh*



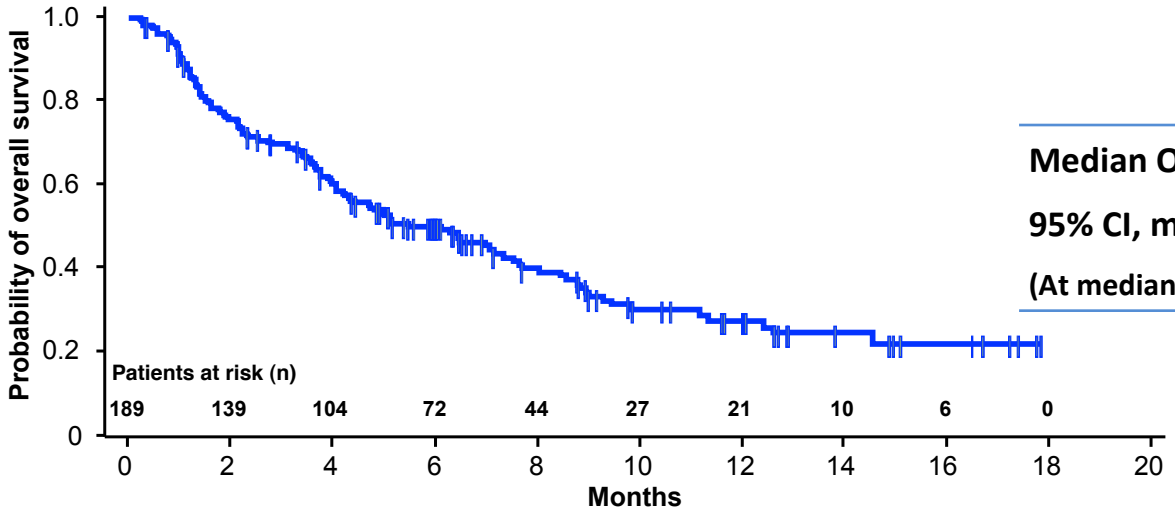

Topp et al. *Lancet Oncol* 2015;16:57-66.

# Multicenter MT103-211 study in rel/ref B-ALL
## *Relapse-free survival*

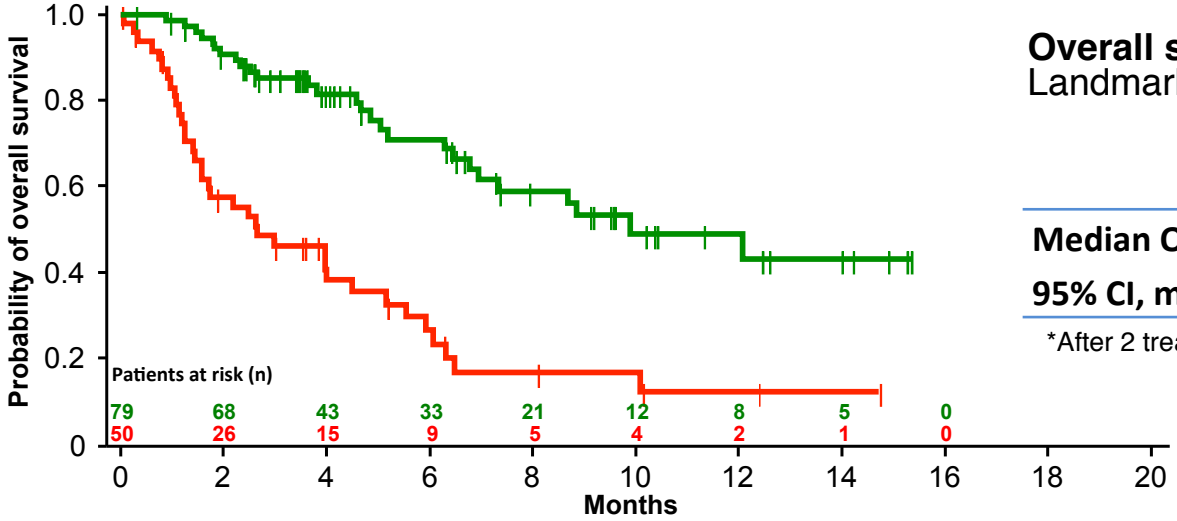



Topp et al. *Lancet Oncol* 2015;16:57-66.

# Multicenter MT103-211 study in rel/ref B-ALL
## *Overall survival*




| | N=189 |
|---|---|
| Median OS, months | 6.1 |
| 95% CI, months | 4.2–7.5 |
| (At median follow-up 9.8 months) | |




**Overall survival**
Landmark analysis Day 77*

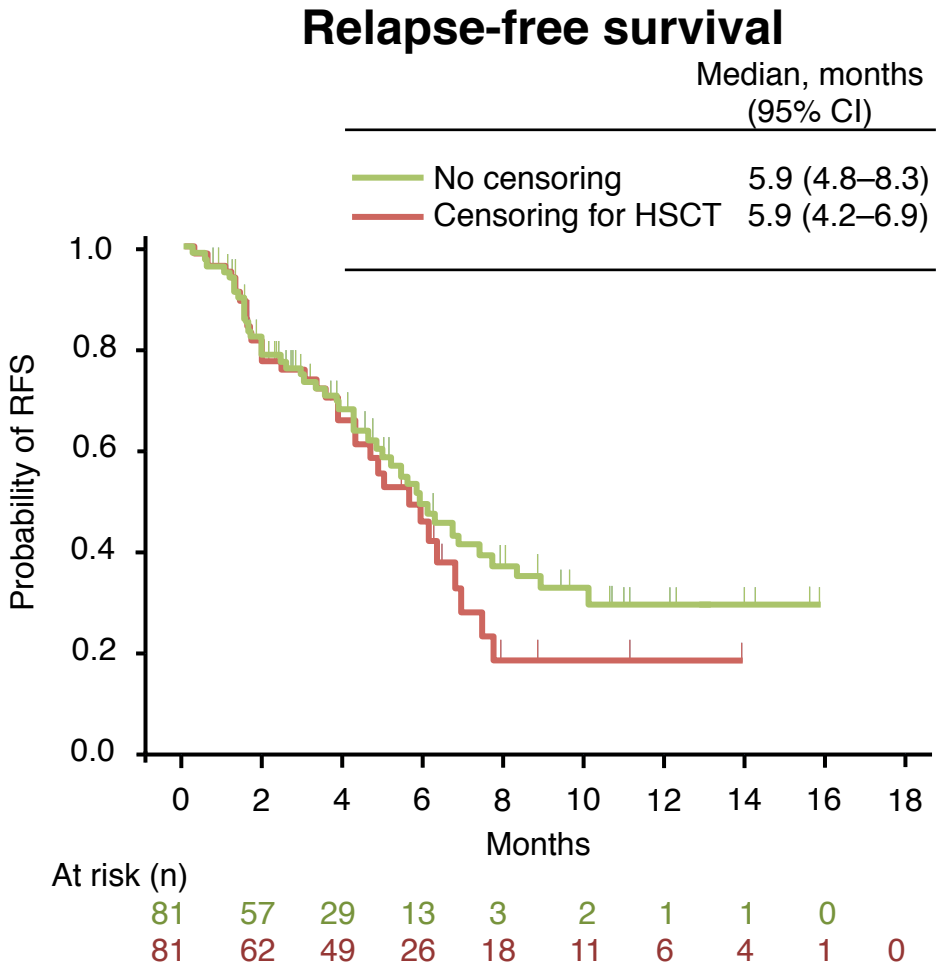
| | CR/CRh N=79 | No CR/CRh N=50 |
|---|---|---|
| Median OS, months | 9.9 | 2.7 |
| 95% CI, months | 6.8–NE | 1.6–4.5 |

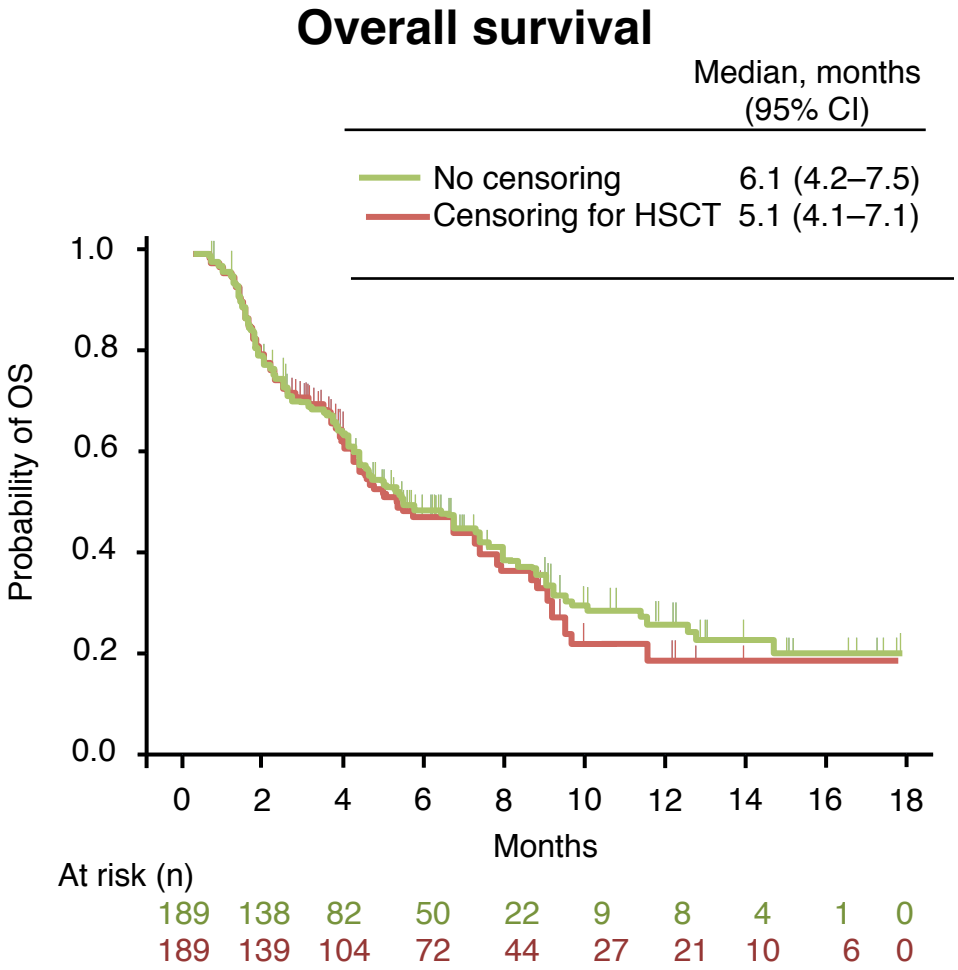
*After 2 treatment cycles

NE, not estimable

Topp et al. *Lancet Oncol* 2015;16:57-66.

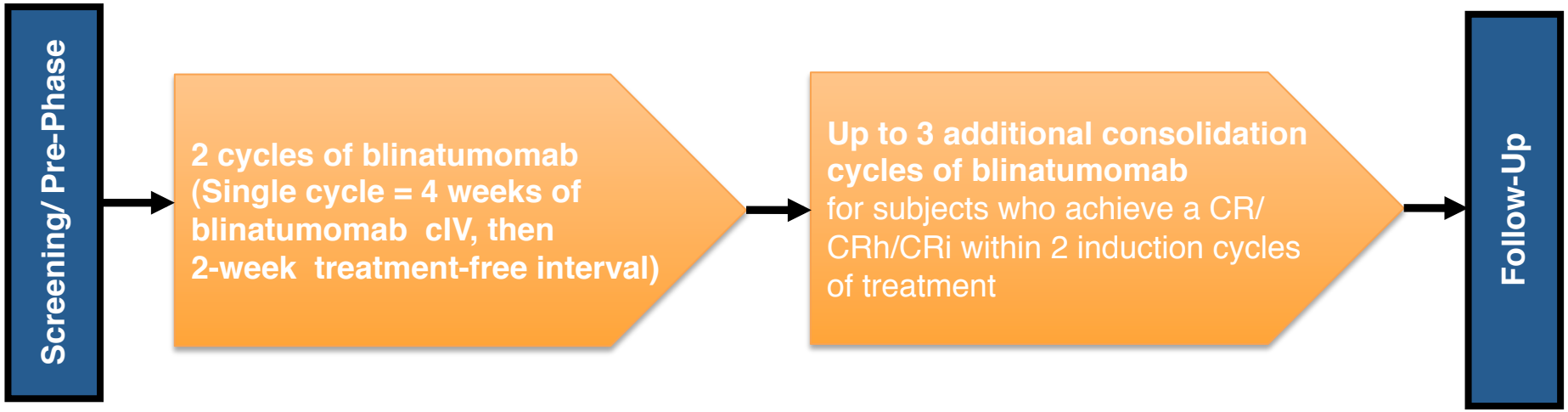
# Multicenter MT103-211 study in rel/ref B-ALL
## *Survival censored for on-study SCT*




Topp et al. *Lancet Oncol* 2015;16:57-66.

# Blinatumomab in Philadelphia+ rel/ref B-ALL
## *The ALCANTARA study*




| | All patients (n=45) |
|---|---|
| CR/CRh, n (%) | 16 (36) 95%CI: 22-51% |
| T315I mutation (n=10) | 4 (40) |
| ≥2 prior 2nd/3rd generation TKI (n=27) | 11(41) |
| Prior ponatinib treatment (n=23) | 8 (35) |
| Complete MRD response, n (%) | 14 (88) |

Martinelli G et al. *ASH 2015*

# Safety profile of blinatumomab

**Most common clinical AE are early, transient, reversible and do not require discontinuation of treatment**

- Pyrexia (60-90%)
- Headache (38-47%)
- Tremor (29-36%)
- Fatigue (24-50%)

**Laboratory abnormalities** (lymphopenia, leukopenia, C-reactive protein increase, decrease of immunoglobulins) **are common.**

**Fatal cases of infections occurred during or after treatment with blinatumomab,** mainly in rel/ref patients and before that response could be assessed or in non-responder patients.

**Dose-dependent CNS adverse events occurred in all clinical studies:**

- Seizure, encephalopathy, ataxia, apraxia, aphasia, tremor
- Reversible, no sequelae, no pathological changes in MRI
- Main cause of treatment interruption in 31% of MRD+ and 15% of rel/ref pts
- Predictive marker identified: low B:T cell ratio in peripheral blood (B:T<1:8)

# Conclusions and open questions

- Blinatumomab demonstrated to be effective in patients with particularly unfavourable characteristics, both in MRD (i.e. high MRD burden) and relapsed/refractory setting (i.e. primary refractory, early relapse, and relapse after HSCT).
- However, the median duration of response and OS obtained in these conditions is far from optimal, and at present the role of blinatumomab is essentially “a bridge to transplant”.

- Open questions:

- How to combine blinatumomab with chemotherapy (concurrent or sequential use)?
- Sequential combination with other novel drugs (inotuzumab)?
- Earlier treatment with blinatumomab – before selection of genetically unstable, resistant subclones – can avoid HSCT to some patients?
- Maintenance treatment is safe? may prolongs survival?