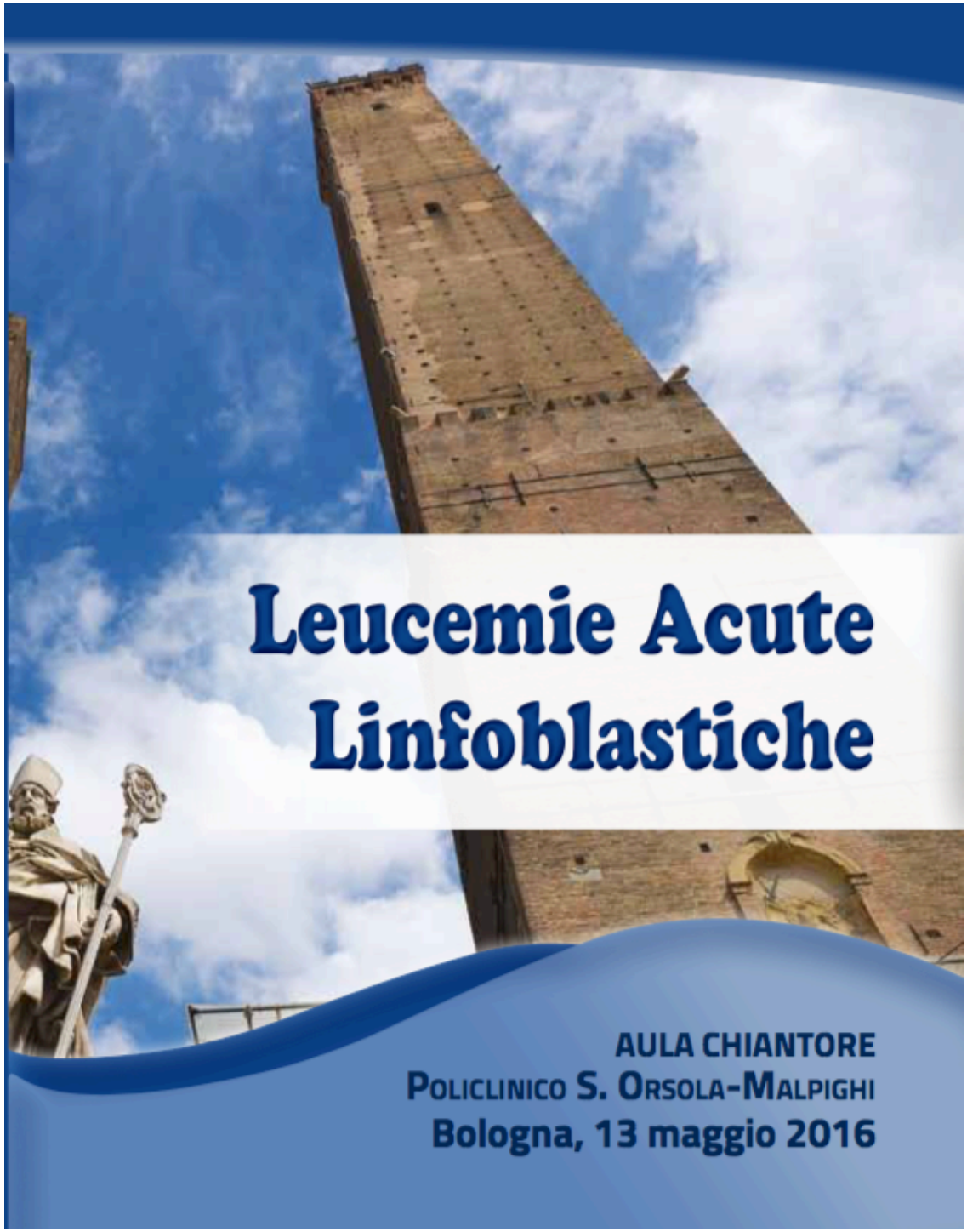
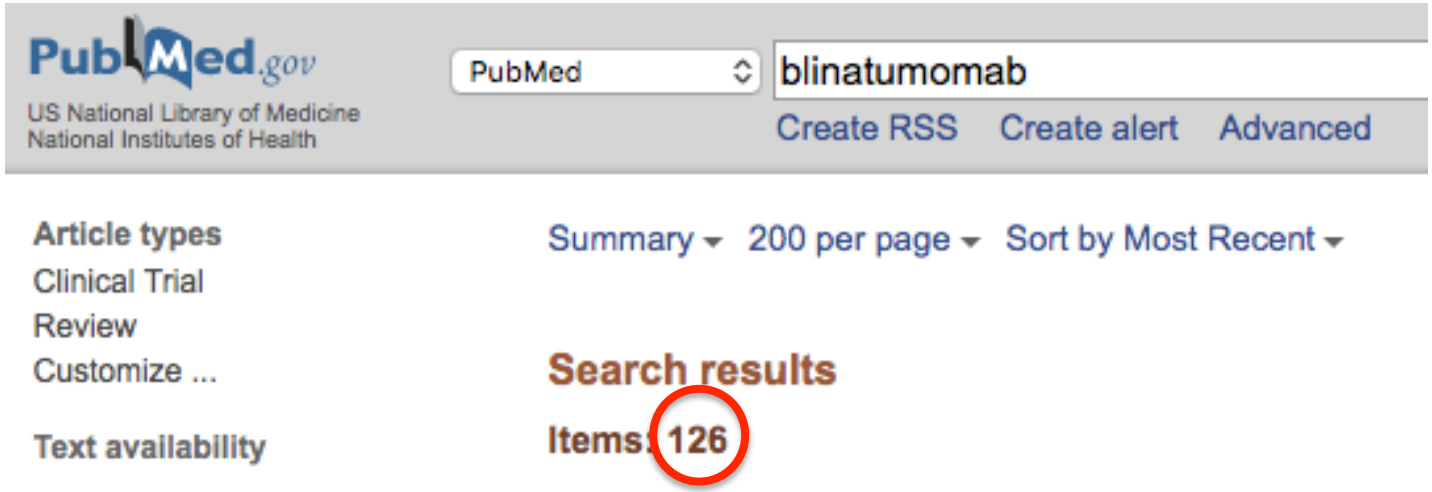


L'esperienza di Verona

Massimiliano Bonifacio



only considering Acute Lymphoblastic Leukemia…

10 • Original reports of clinical trials

11 • Case reports, biological studies, others

98 • Reviews and commentaries

A clinical case

- D. (d.o.b. May 1984) was diagnosed with Philadelphia-neg, standard risk, TEL-AML1+, B-precursor common ALL in April 2009.
- She was treated with a pediatric-like regimen (GIMEMA/AIEOP LAL1308 protocol) obtaining MRD-negative CR after induction.
- She remained in complete MRD response until maintenance therapy completion and she went off-therapy in April 2011.
- In November 2013, during a routine bone marrow check, a **MRD relapse** was documented (both by flow cytometry and molecular analysis) with rapidly raising values (from $1x10^{-4}$ to $5x10^{-2}$)
- She was enrolled in the BLAST trial, obtaining complete MRD response after the 1st cycle. It was decided to not proceed to allogeneic HSCT. She received 3 consolidation cycles of blinatumomab and ended treatment on May 2014.

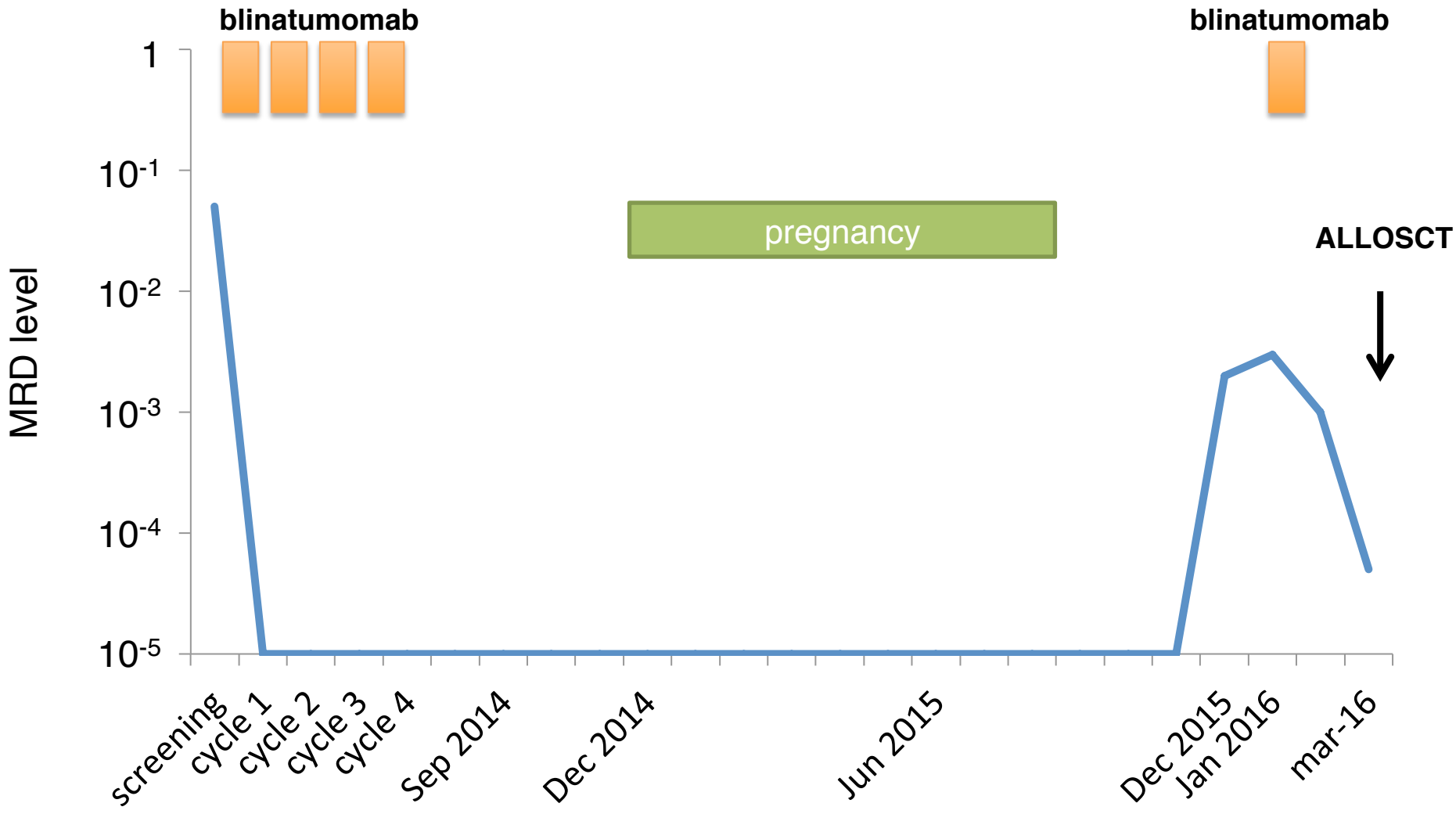
Bonifacio M, Tanasi I, et al. *manuscript in preparation*

A clinical case

- In December 2014 (during the regular 6-month follow-up visit after blinatumomab end) she reported the suspicion of an unplanned pregnancy, which was confirmed by lab tests.
- On 14th August 2015 she delivered a healthy male baby.
- In December 2015 a **second MRD relapse** was documented (both by flow cytometry and molecular analysis, 2x10^{-3}) and confirmed 1 month apart with slightly rising levels (3x10^{-3}).
- She was treated with another cycle of blinatumomab between February and March 2016, obtaining a MRD response (positive below LLOQ).
- She underwent allogeneic HSCT from sibling donor on 19 Apr 2016 (Endoxan – TBI as conditioning regimen).

Bonifacio M, Tanasi I, et al. *manuscript in preparation*

A clinical case



Blinatumomab in MRD^{+} B-ALL
Inclusion criteria

Pilot experience (German multicenter MT103-202 trial – n=21)

- Patients with B-precursor ALL in first hematological CR with molecular failure or molecular relapse
- MRD >10^{-4}

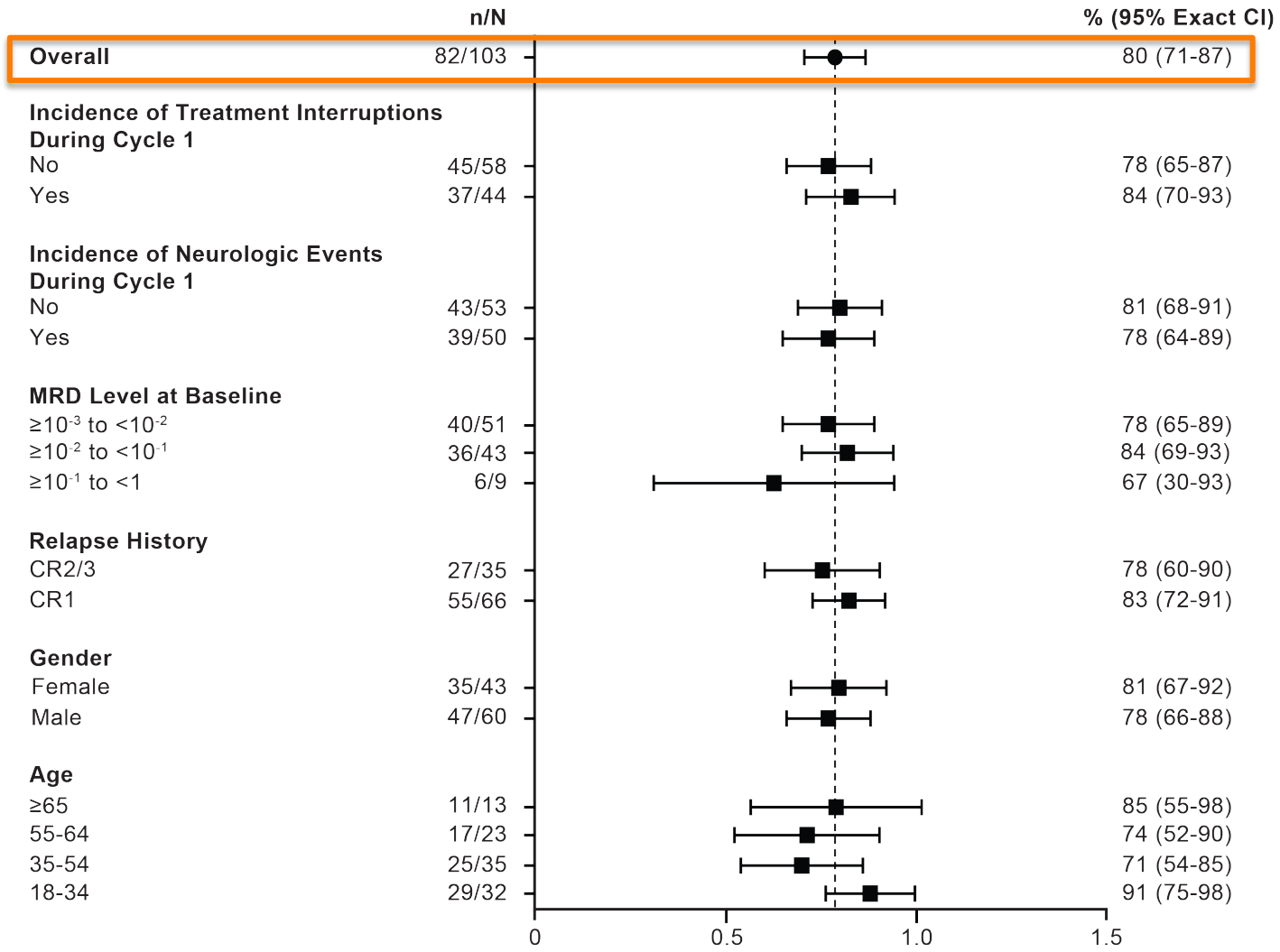
Confirmatory study (International multicenter MT103-203 trial – n=116)

- Patients with B-precursor ALL in hematological CR with molecular failure or molecular relapse, including patients in 2nd or later remission
- MRD, defined as a level of ≥ 10^{-3} in an assay with a minimum sensitivity of 10^{-4}

BLAST multicenter MRD study
Causes of screening failure

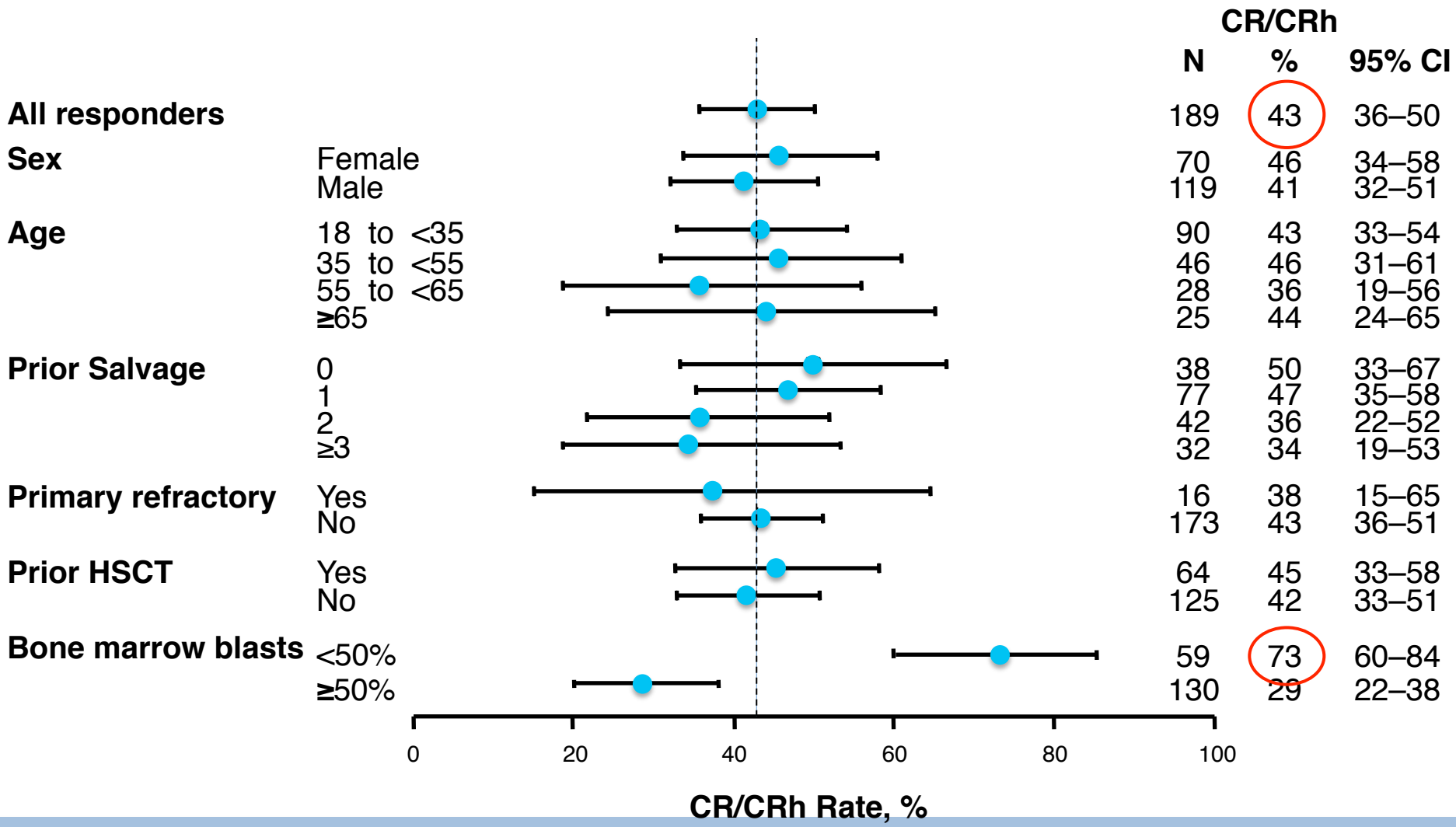
Active Infection	2
Alternative Therapy	2
CD19 Negative	1
CNS Relapse	2
Consent Withdrawn	1
Hepatic	1
MRD < 10^-3	48
Neurologic Disorder	2
Overt Relapse	31
Technical	5
Grand Total	95

BLAST multicenter MRD study
Complete MRD response after cycle 1



Gokbuget N et al. *ASH 2014*

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



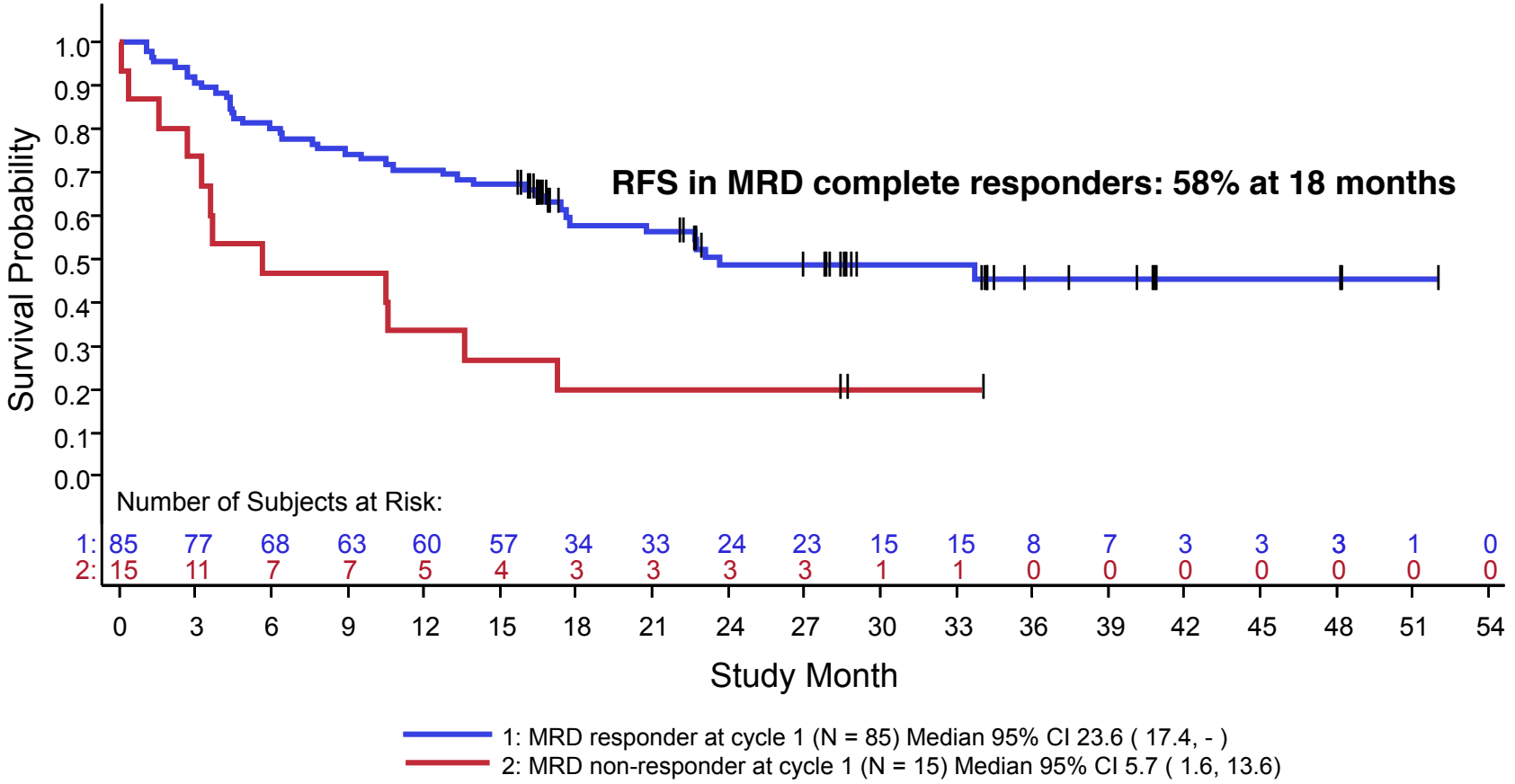
Topp et al. *Lancet Oncol* 2015;16:57-66.

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.

BLAST multicenter MRD study
Relapse free survival



Complete MRD response (primary endpoint): MRD negative, no amplification in PCR (minimum sensitivity 10^{-4})
NR = not reached. The landmark analysis by MRD response included patients with overall survival of ≥ 45 days

Gokbuget N et al. *ASH 2015*

Our experience in MRD^{+} B-ALL
Patient characteristics

Patient	Age	Cytogenetics Molecular	Previous treatments	MRD	Level of MRD at study entry
#001 female	35y	t(14;19?)(q32;q?)	GIMEMA induction / 2 consolid / mainten	relapse	$1.8x10^{-2}$
#002 male	51y	normal	GIMEMA induction (*res*) FLAI salvage (*CR MRD+*)	failure	$3.8x10^{-2}$
#003 male	46y	normal	NILG induction / 1 consolid (*CR MRD+*)	failure	$2.2x10^{-3}$
#004 male	22y	normal	AIEOP induction (*late CR*) / 1 consolid (*CR MRD+*)	failure	$3x10^{-3}$
#005 male	52y	normal	GIMEMA induction / 2 consolid (*CR MRD+*)	failure	$1.3x10^{-2}$
#006 female	19y	TEL/AML1+	AIEOP induction / consolid (standard risk) / maintenance	late relapse (>3 yrs)	$5x10^{-2}$
#007 male	32y	normal	NILG induction / reinduction (*late CR*)	failure	$6x10^{-2}$

Our experience in MRD$^+$ B-ALL
Outcome

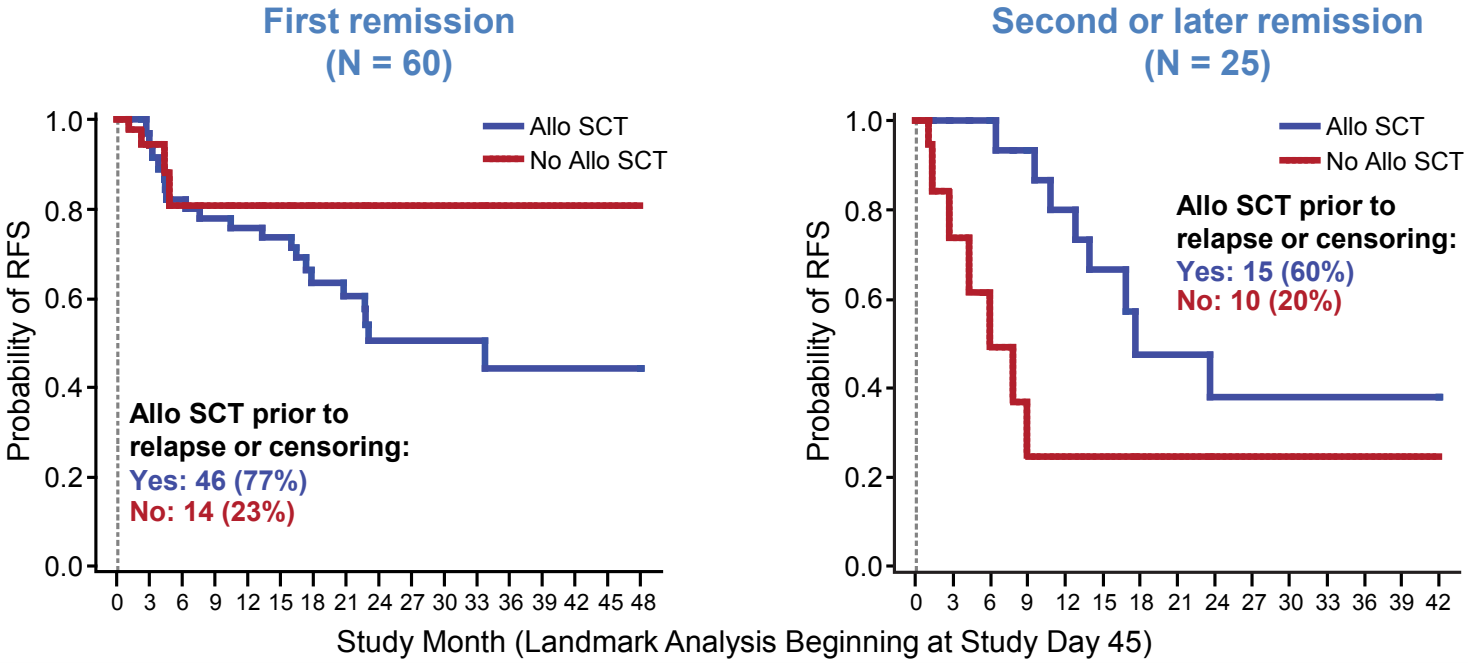
Patient	N° of cycles	Complete MRD Response after C1	Status at transplant	Outcome
#001 female	2	Yes	Hematologic relapse → chemotx → CR	**Death in remission** (at d+77 after HSCT due to acute GVHD)
#002 male	3	Yes	Complete MRD response	**Death in remission** (at d+102 after HSCT due to wasting encephalopathy of unknown origin)
#003 male	2	n.v.	Complete MRD response (*flow cytometry*)	**Relapse and death** (after a second HSCT)
#004 male	2	Yes	MRD response (positive below LLOQ)	**Relapse – alive in CR (chemotx + blina + DLI)** (+27 months after transplant)
#005 male	3	Yes	Complete MRD response	**Death in remission** (at +18 months after HSCT due to rapidly fatal multifocal cerebral astrocytoma)
#006 female	4	Yes	MRD relapse	**Alive** (severe pneumonia after HSCT)
#007 male	3	Yes	Complete MRD response	**Alive in CR** (+7 months after transplant)

BLAST multicenter MRD study
Role of SCT in pts with complete MRD response

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	**0.15**	**0.046**

Simon-Makuch Plot of RFS
(Landmark 45 days)



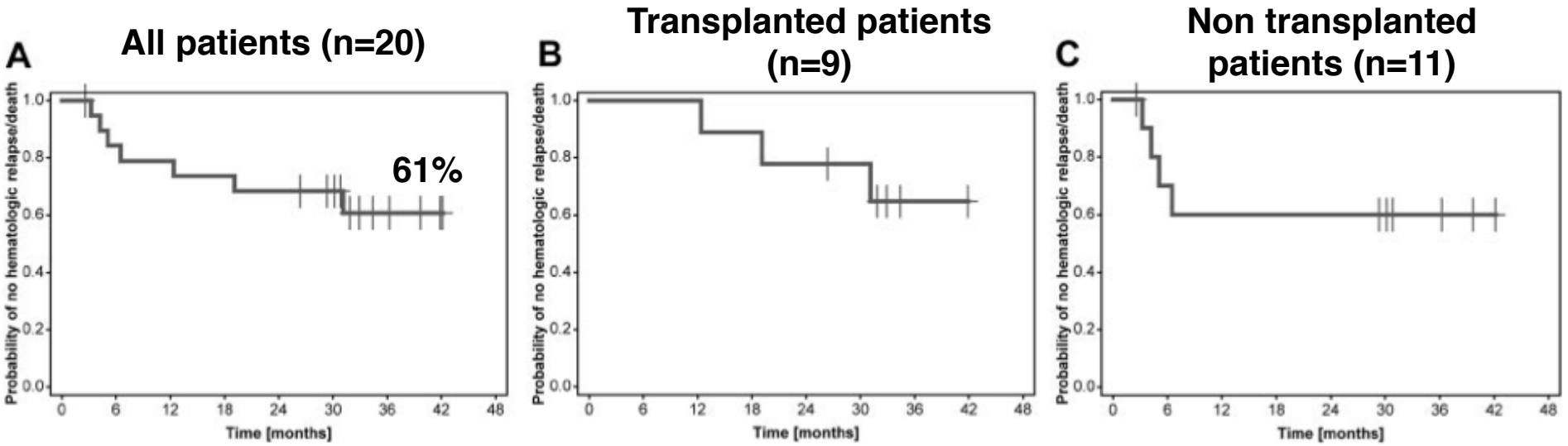
Gokbuget N et al. *ASH 2015*

Blinatumomab and transplant: an open question

First Blinatumomab Phase 2 Study in MRD-Positive ALL

MRD complete response rate: 80%

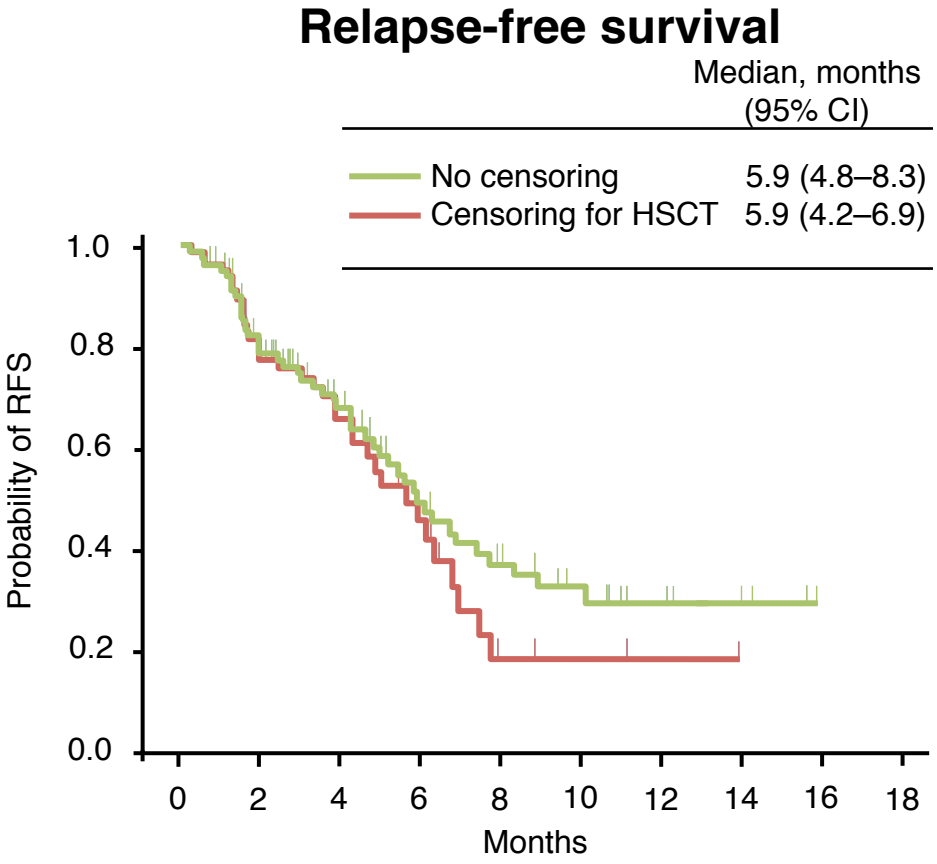
All responses within the first cycle of treatment

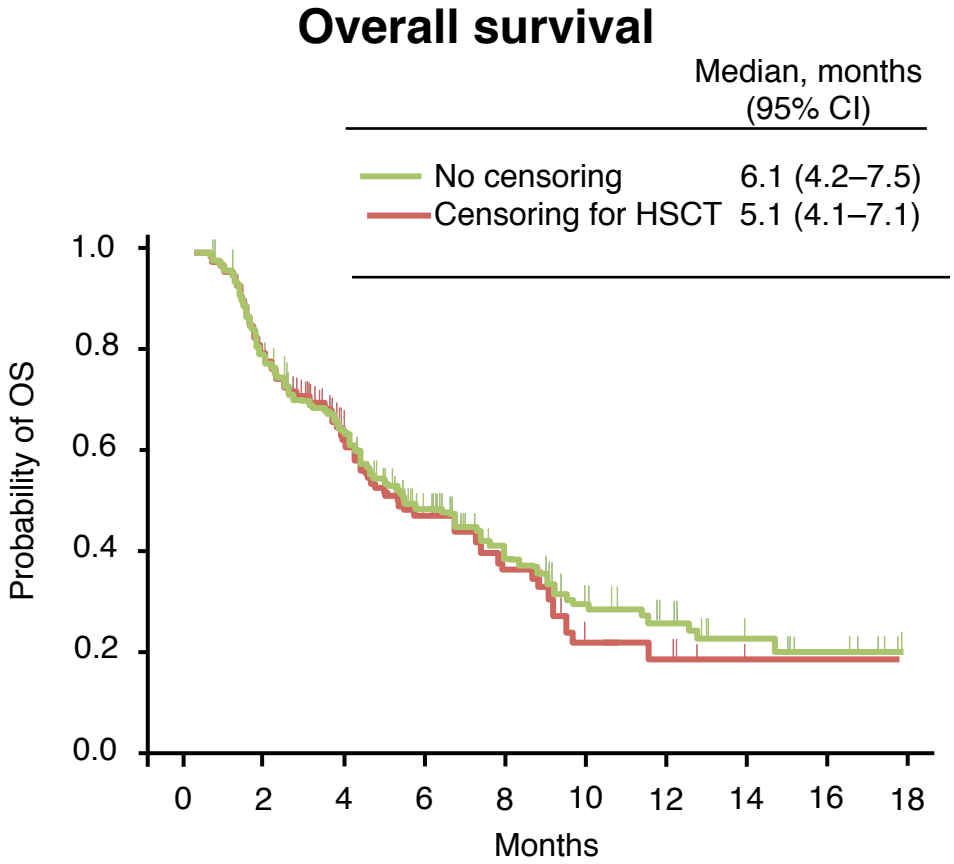


Topp et al. *J Clin Oncol* 2011;29:2493-2498. Topp et al. *Blood* 2012;120:5185-5187.

Blinatumomab and transplant: an open question

in relapsed/refractory patients



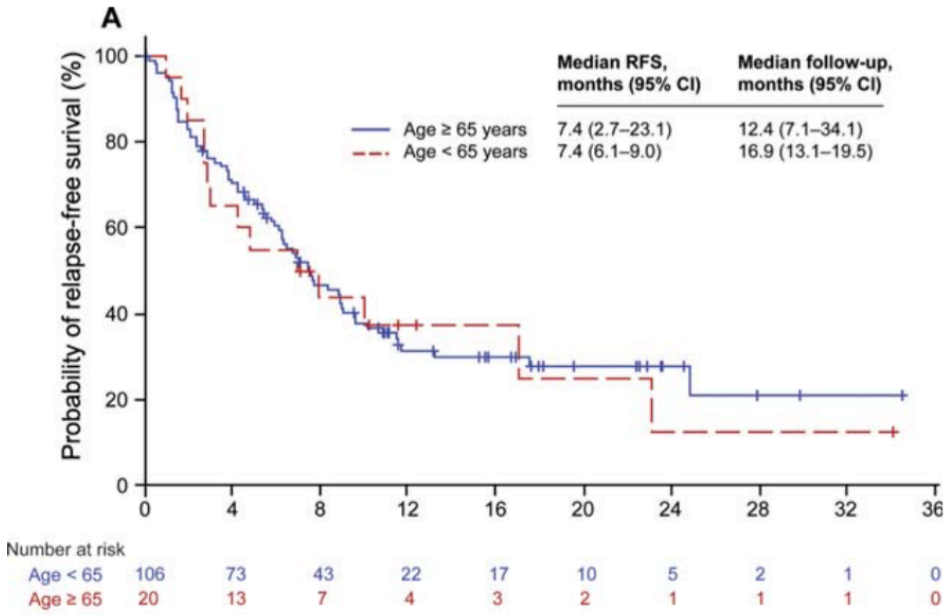


Topp et al. *Lancet Oncol* 2015;16:57-66.

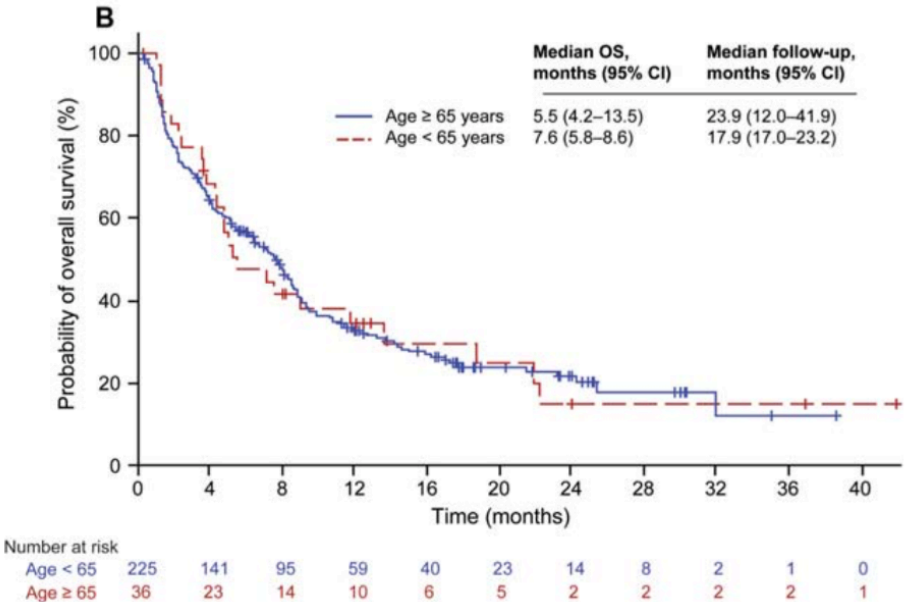
Blinatumomab and transplant: an open question

in relapsed/refractory patients

Relapse-free survival



Overall survival



Kantarjian et al. *Cancer* 2016 [epub]

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)

Some considerations from our experience

- No severe / unexpected toxicities during treatment (absence of neurological events, systematic use of levetiracetam prophylaxis).
- Despite deep molecular responses in all patients, there are early relapses, in patients planned for allogeneic transplantation.
- It is unknown what it the ideal compromise between wash-out after blinatumomab treatment and no transplant delay.
- Infections after HSCT occur and influence outcome.

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 clones – can avoid HSCT to some patients?
- Maintenance treatment is safe? may prolongs survival?