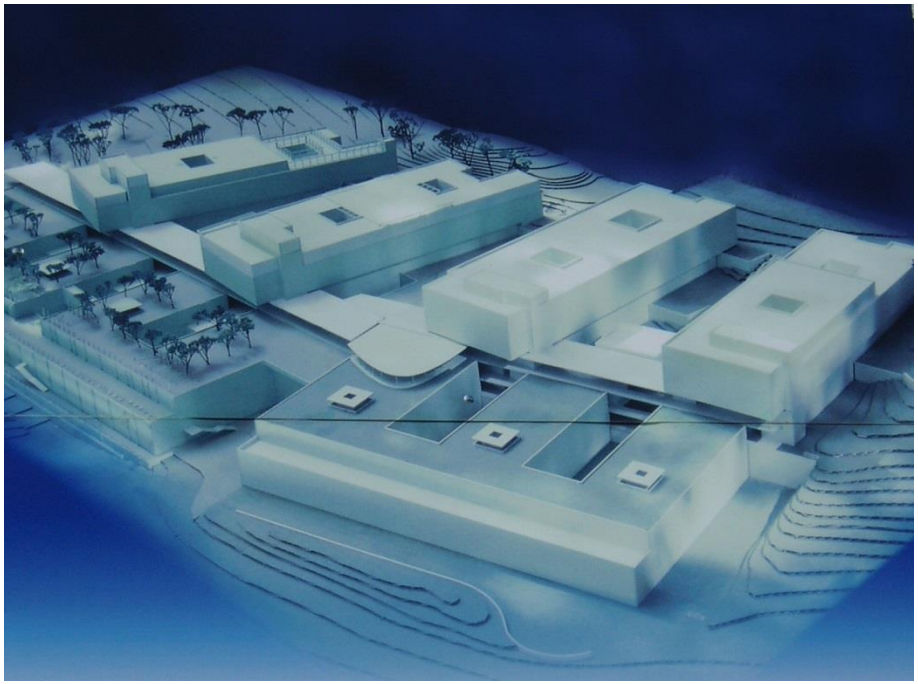
Blinatumomab in Acute lymphoblastic leukemia



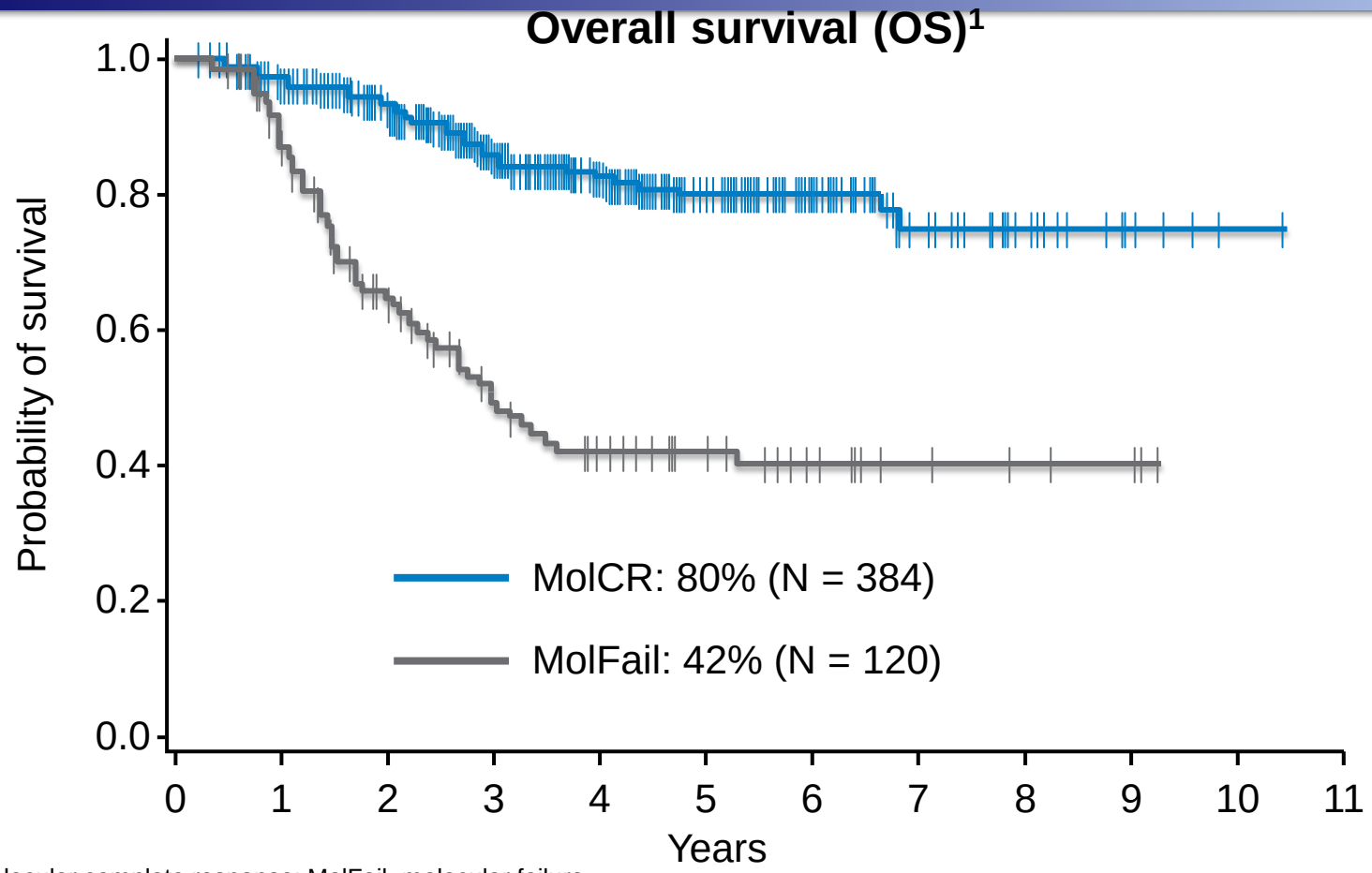
Max S.Topp MD
Würzburg
Germany

Disclosures

- Amgen
- Affimed
- Roche
- Regeneron
- Gilead

PERSISTENT MRD POSITIVITY DURING INDUCTION IN ALL

Minimal residual disease (MRD) is the most important prognostic factor in ALL



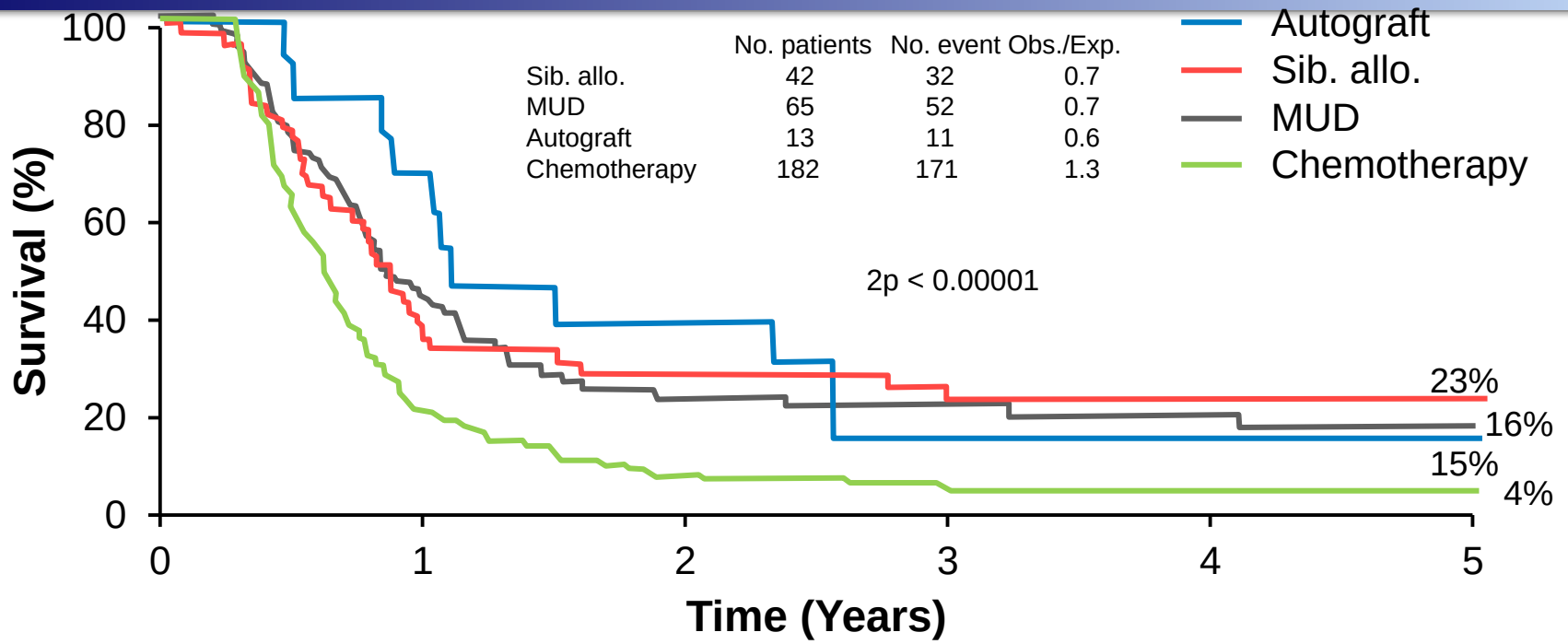
MolCR, molecular complete response; MolFail, molecular failure

- Molecular MRD negativity is associated with significant improvement in DFS[2] and OS[1]
- Molecular MRD status is a predictor of haematological relapse[3]

1. Gökbuget N, et al. *Blood*. 2012;120:1868–1876. 2. Bassan R, et al. *Blood* 2009;113:4153–4162. 3. Raff T, et al. *Blood* 2007;109:910–915.

RELAPSE

Probability of survival by therapy given in relapse



At risk:						
Sib. allo.	42	15	11	9	8	6
MUD	65	26	13	11	8	6
Autograft	13	9	5	2	2	1
Chemotherapy	182	34	11	5	4	2

Sib. allo., sibling allograft; MUD, matched unrelated donor

Fielding A, et al. *Blood* 2007;109:944–950.

Surface antigens of interest in B-precursor ALL

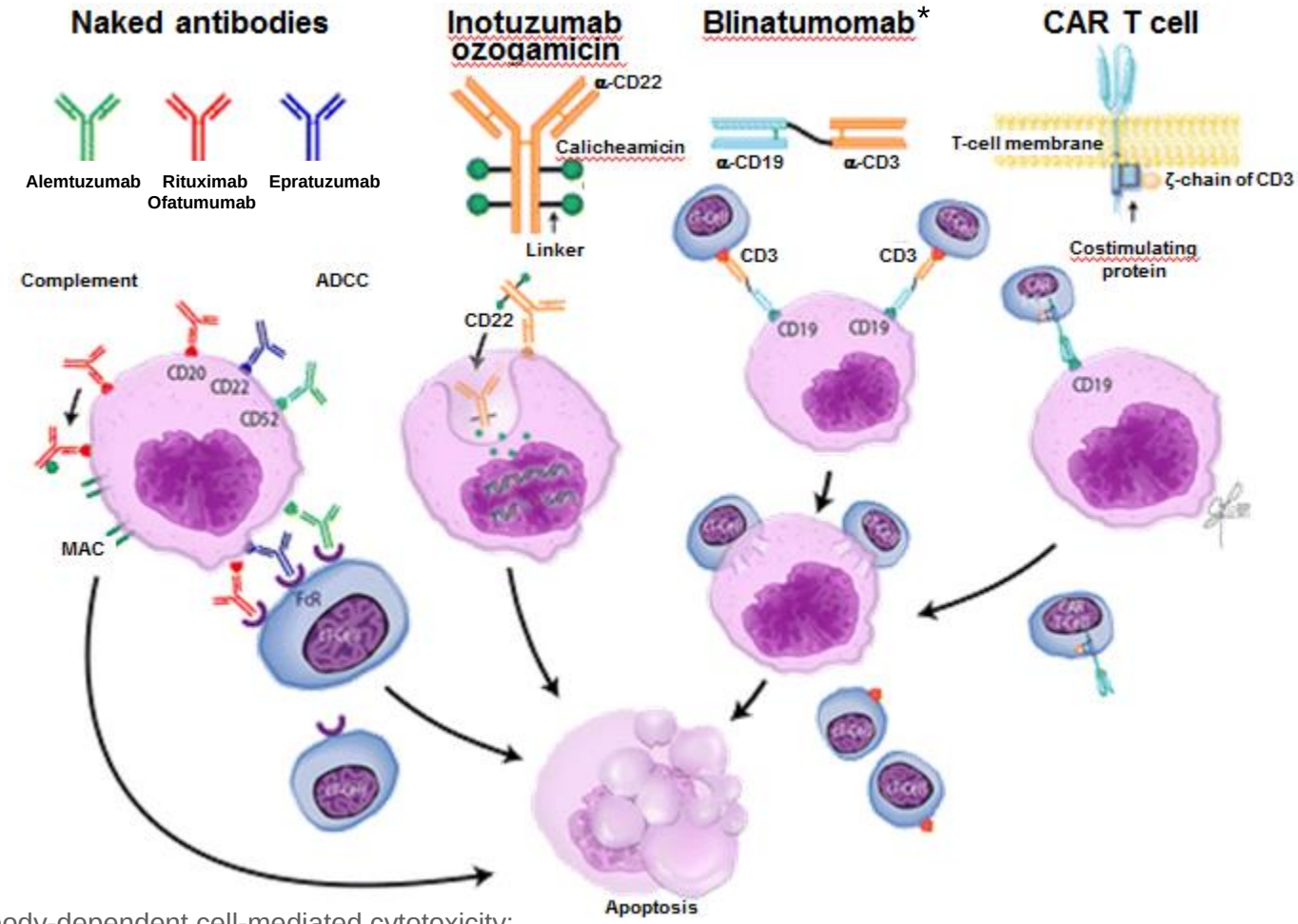
Surface antigen	Expression on precursor B-ALL cells*
CD19	95–100%
CD20	22–41%
CD22	60–96%
CD33	17–23%
CD52	79%

Therapies targeted to specific surface antigens are a novel alternative or complementary approach to chemotherapy

*Surface antigen expression with a cut-off of >20% positive leukaemia blast cells

Hoelzer D. Hematology Am Soc Hematol Educ Program 2011;2011:243–9

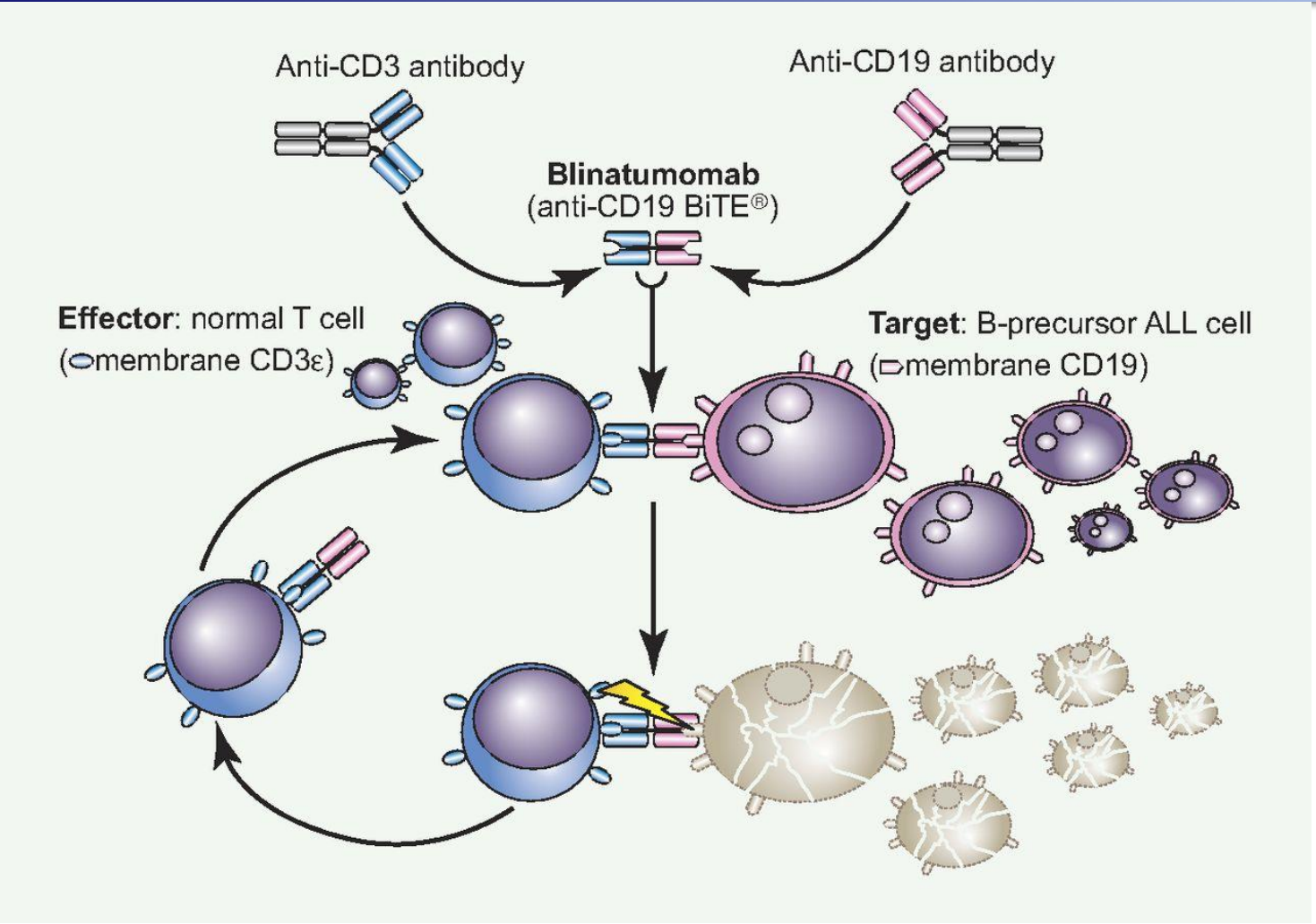
Novel approaches to the treatment of ALL



ADCC, antibody-dependent cell-mediated cytotoxicity;
CAR, chimeric antigen receptor; MAC, membrane attack complex

Portell CA, Advani AS. Leuk Lymphoma 2014;55:737–48

Mode of action of Blinatumomab



Bassan, Blood: 120; 2012

Initial exploratory Phase 2 studies identified efficacious dosing strategies while managing risk of dose-limiting AEs

Adults with MRD+ ALL‡ (n=21)[1]

- Blinatumomab 15 µg/m^2/d cIV, 4 weeks on, 2 weeks off

Key efficacy results

- **80%** molecular CR rate after 2 cycles (1° endpoint)

Key safety results

- Lymphopenia most common grade ≥3 AE (33% pts)
- Grade 3/4 neurological events in 4 pts (19%), including seizure requiring treatment discontinuation in 1 pt (fully reversible)
- No cases of severe cytokine release syndrome (CRS)

Adults with R/R ALL (n=36)[2]

- Blinatumomab 5–15 µg/m^2/d cIV, 4 weeks on, 2 weeks off identified in dose-finding phase, used in extension phase

Key efficacy results

- **69%** CR/CRh* rate after 2 cycles (1° endpoint)
- **88%** molecular CR rate
- **52%** alloSCT realisation rate

Key safety results

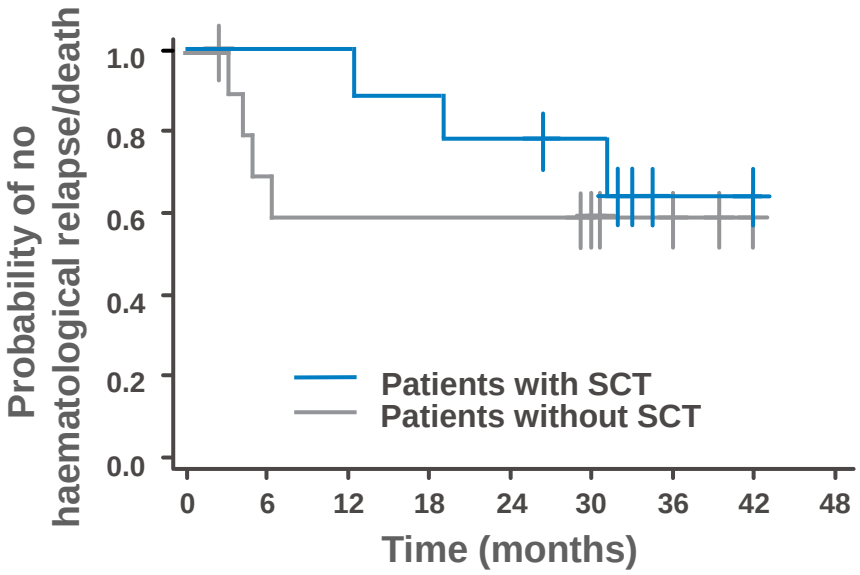
- Leukopenia most common grade ≥3 AE (14% pts)
- Neurological events requiring treatment interruption/discontinuation in 6 pts (17%)
- Disease burden associated with risk of grade ≥3 CRS (n=2); no grade ≥3 CRS with stepped dosing + pre-phase dexamethasone and/or cyclophosphamide† for pts with BMB ≥50%

*CRh, CR with partial haematological recovery (platelets >50,000/µL, haemoglobin >7 g/dL, ANC >500/µL)
† Dexamethasone 10 mg/m^2 (up to 5 days) and/or cyclophosphamide 200 mg/m^2 (up to 3 days);
‡Blinatumomab is not licensed for use in MRD+ ALL
BMB, bone marrow blast; cIV, continuous IV infusion

1. Topp MS, et al. J Clin Oncol 2011;29:2493–8;
2. Topp MS et al. J Clin Oncol 2014;32:4134–40

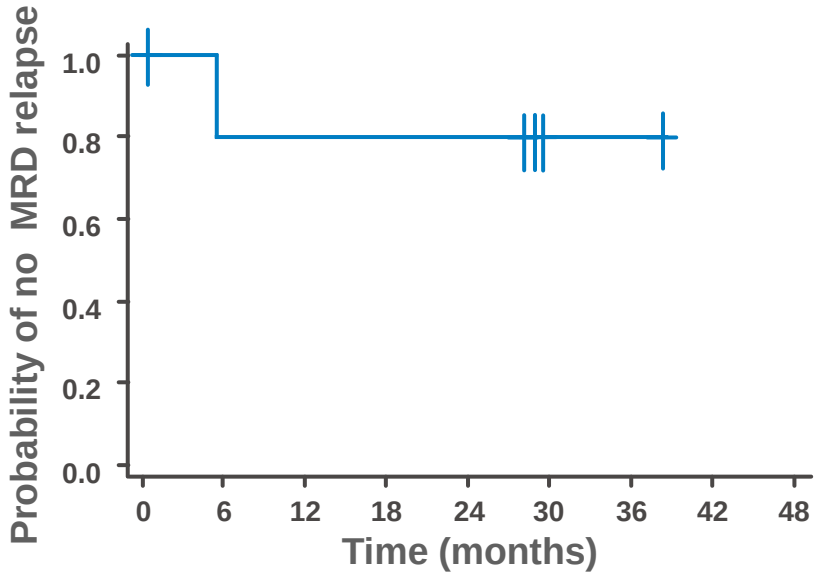
Long-term follow-up of exploratory Phase 2 study of adults with MRD+ ALL

Haematological RFS



- With SCT (n=9): median follow-up = 32.9 months
- Without SCT (n=11): median follow-up = 30.8 months

MRD response duration in Ph- patients who received only blinatumomab

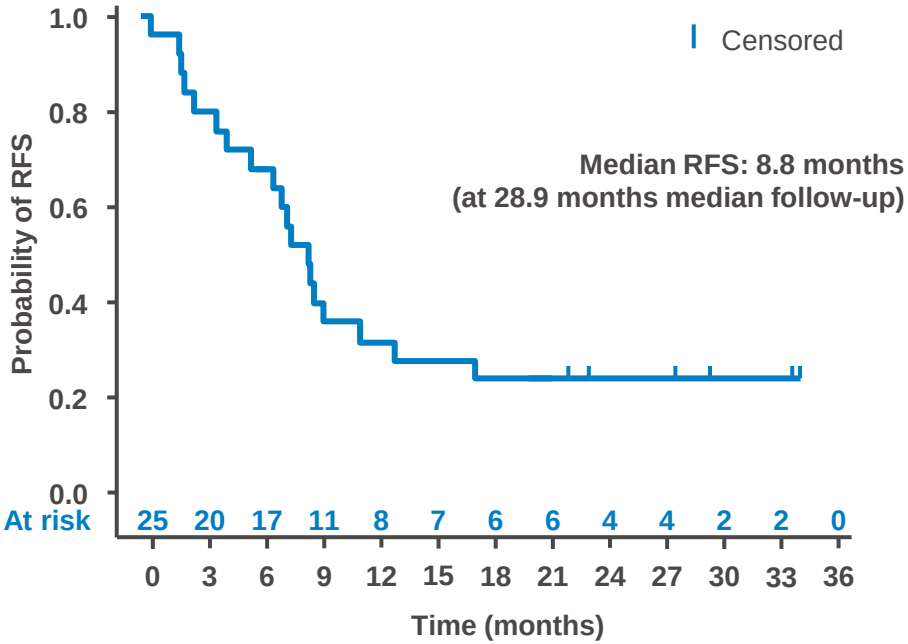


- Median follow-up (n=6) = 29.2 months

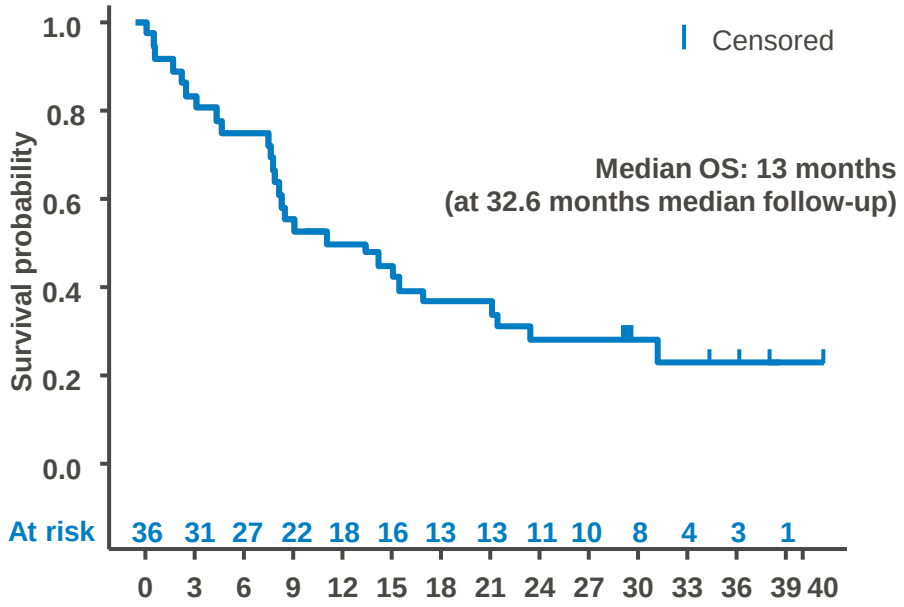
Topp MS, et al. Blood 2012;120:5185–7

Long-term follow-up of exploratory phase 2 study of adults with relapsed/refractory ALL

RFS



OS

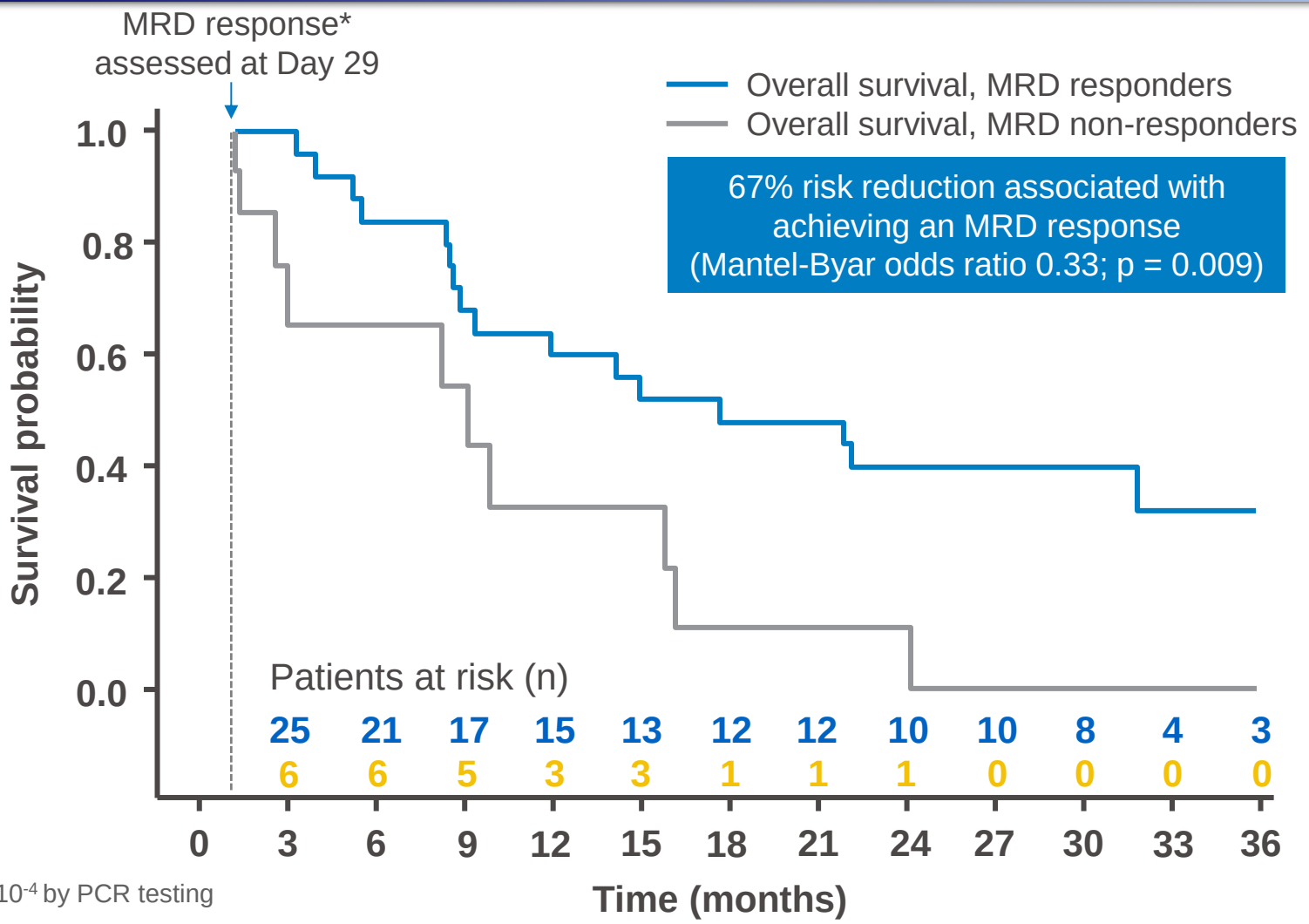


N=10 long-term survivors at the time of data cut-off for these ad hoc analyses

Zugmaier G, et al Topp. Blood 2015;126:2578–84

Long-term follow-up of exploratory phase 2 study of adults with relapsed/refractory ALL

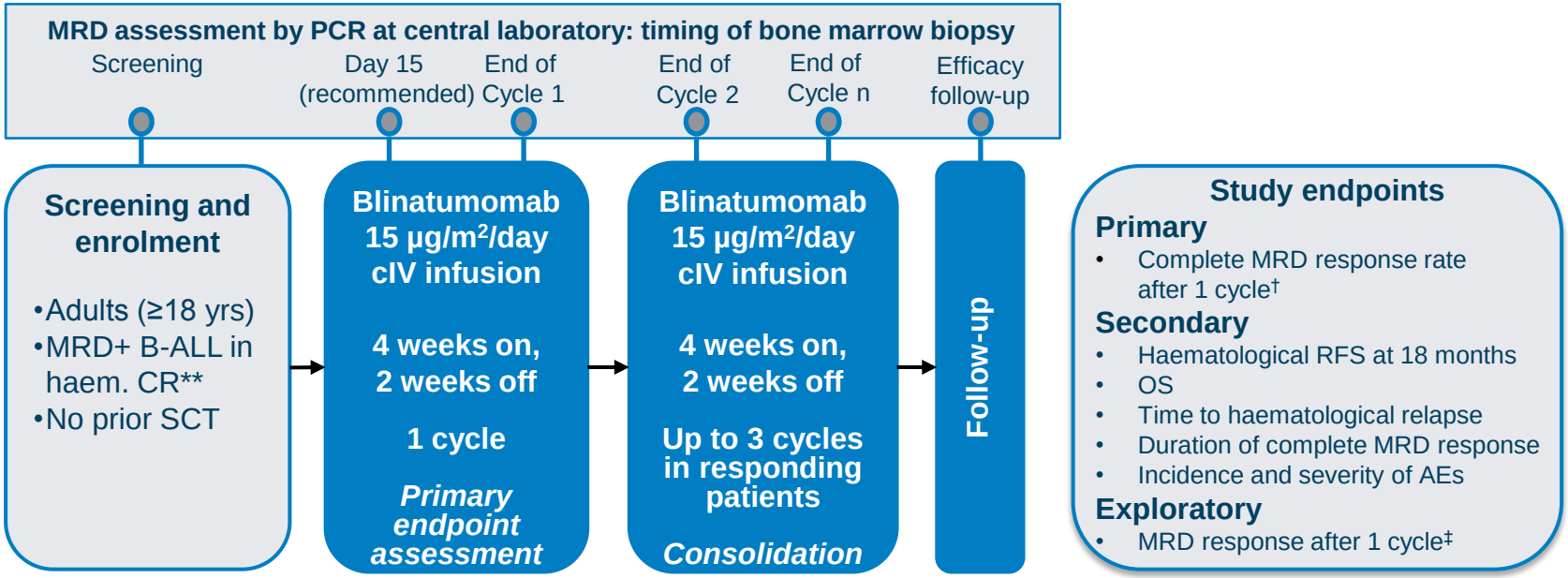
Overall survival by MRD response



*MRD <10^{-4} by PCR testing

Zugmaier G, et al Topp. Blood 2015;126:2578–84

Confirmatory Phase 2 study of blinatumomab in adults with MRD+ B-precursor ALL (BLAST)[1*]



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

15 µg/m²/day dose used in this study corresponds to 28 µg/day fixed dosing strategy[2]

*__Blinatumomab is not licensed for use in MRD+ ALL__
**<5% blasts after 3 chemotherapy blocks; ANC ≥1,000/µL; platelets ≥50,000/µL; Hb ≥9 g/dL; MRD ≥10^{-3}
†MRD negative, no amplification in PCR (minimum sensitivity 10^{-4}); ‡ MRD <10^{-4} (minimum sensitivity 10^{-4})

1. Gökbuget N, et al. Oral presentation at ASH, San Francisco, CA; December 6–9 2014, Abstract 37;
2. Wu B, et al. Poster presented at ASCO May 31 – June 4 2013, Chicago, Illinois. Abstract 30489

Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL

Complete MRD response within 1 cycle

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

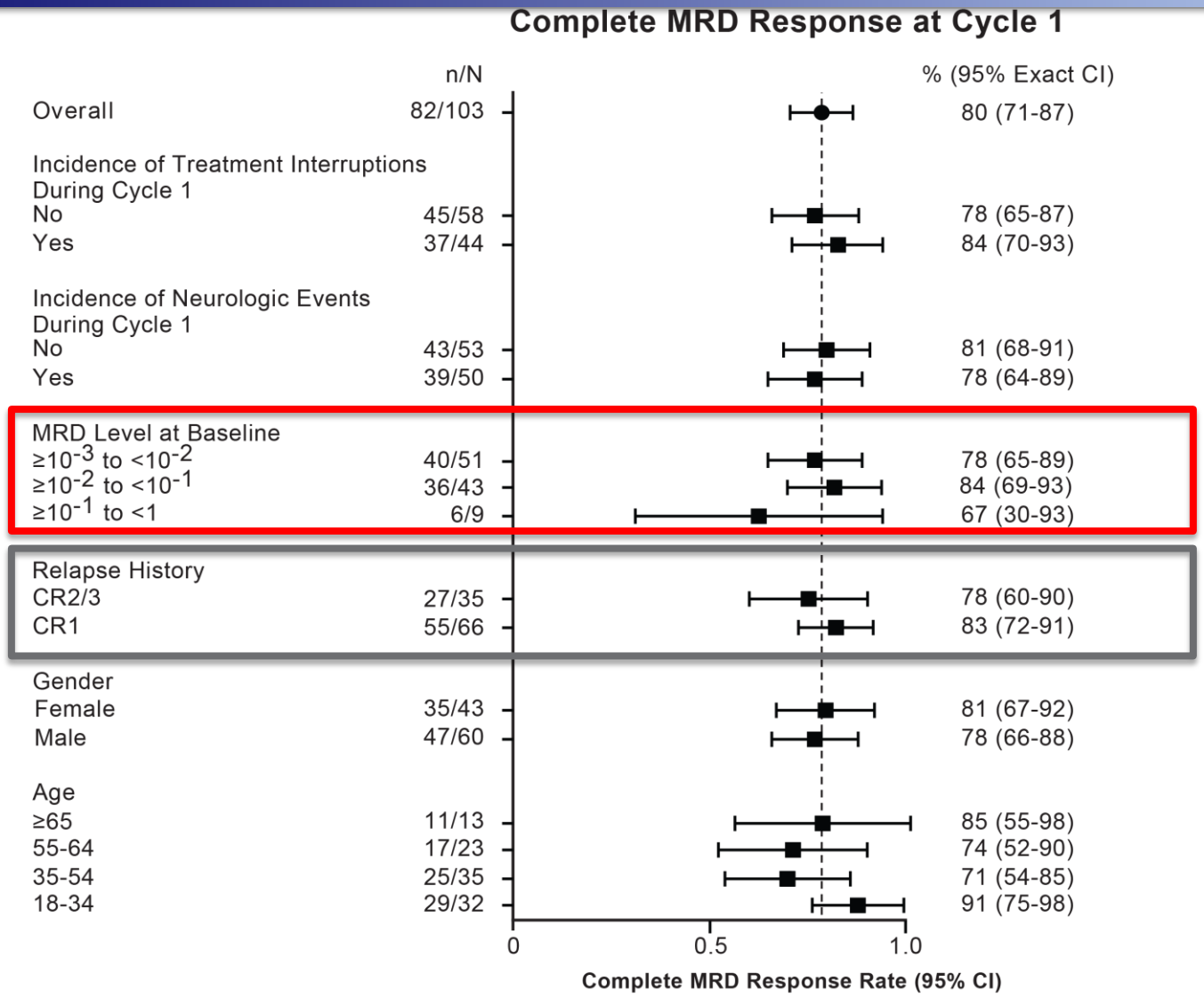
- 2 patients achieving reduction of MRD to below the quantifiable limit during Cycle 1 achieved a complete MRD response after continued treatment in Cycle 2

*Patients who had an MRD assay available with a sensitivity $<10^{-4}$ at the central lab

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

Complete MRD Response by Clinical Characteristics

Primary Endpoint Efficacy Set (N=103)



Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL

Overview of AEs

	AE (n=116)	Treatment-related AE† (n=116)
Any AE,* n (%)	116 (100)	112 (97)
Serious AE	73 (63)	60 (52)
Grade 3 AE	38 (33)	34 (29)
Grade 4 AE	31 (27)	25 (22)
Fatal AE	2 (2)	1 (<1)
AE leading to interruption of treatment	36 (31)	33 (28)
AE leading to permanent discontinuation of treatment	20 (17)	14 (12)

- **Treatment interruption due to AE** (>2% of patients): pyrexia (8%); chills, alanine aminotransferase or aspartate aminotransferase increases, overdose, tremor, aphasia, encephalopathy (3% for each)
- **Permanent discontinuation due to AE** (>2% of patients): tremor (4%); aphasia, encephalopathy and seizure (3% for each)

*Including treatment and 30 days after last infusion;
†Investigator judged that it was reasonably possible that the event was related to treatment with investigational product

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

Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL

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 neurologic 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

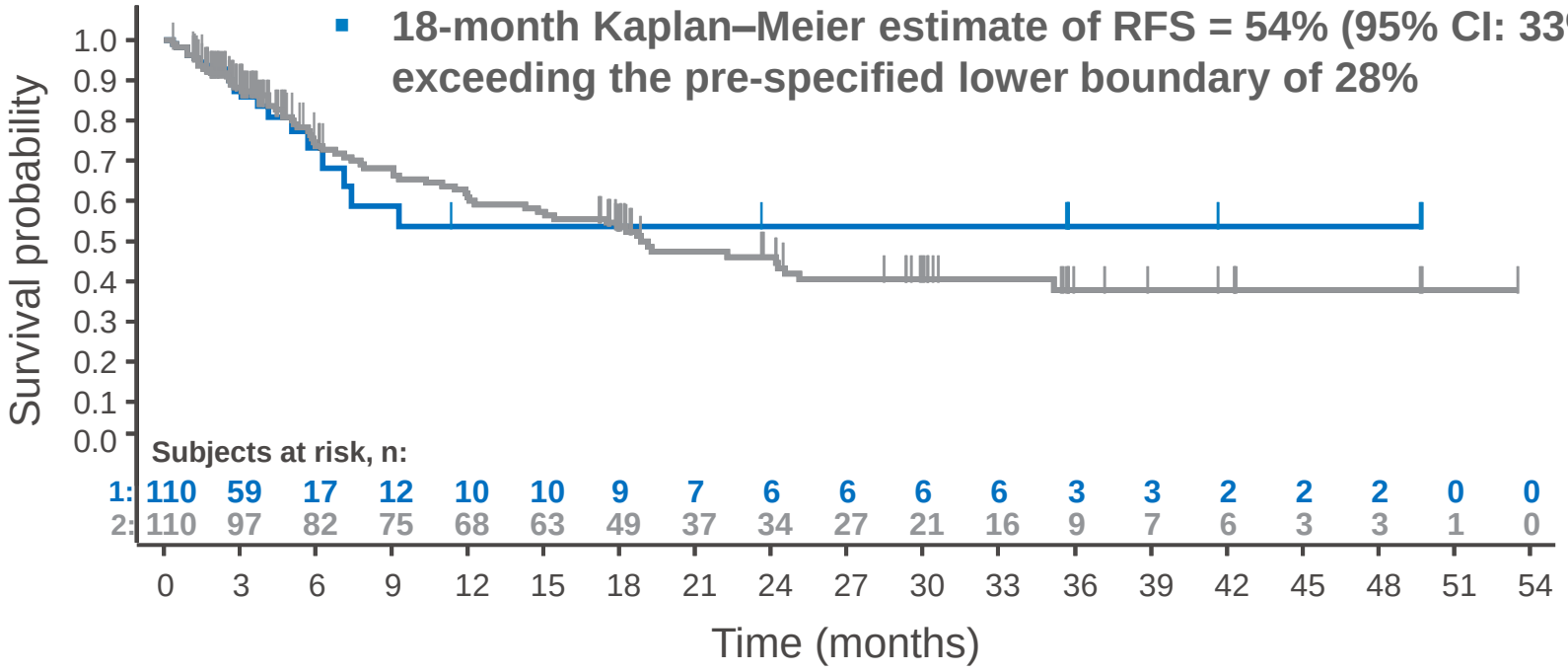
Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL: relapse-free survival

Ph-negative patients in haematological CR

Median (95% CI) follow-up: 29.9 (24.2, 30.6) months

The key secondary endpoint was met:

- **18-month Kaplan–Meier estimate of RFS = 54% (95% CI: 33%, 70%) exceeding the pre-specified lower boundary of 28%**



SCT in continuous CR: 67%

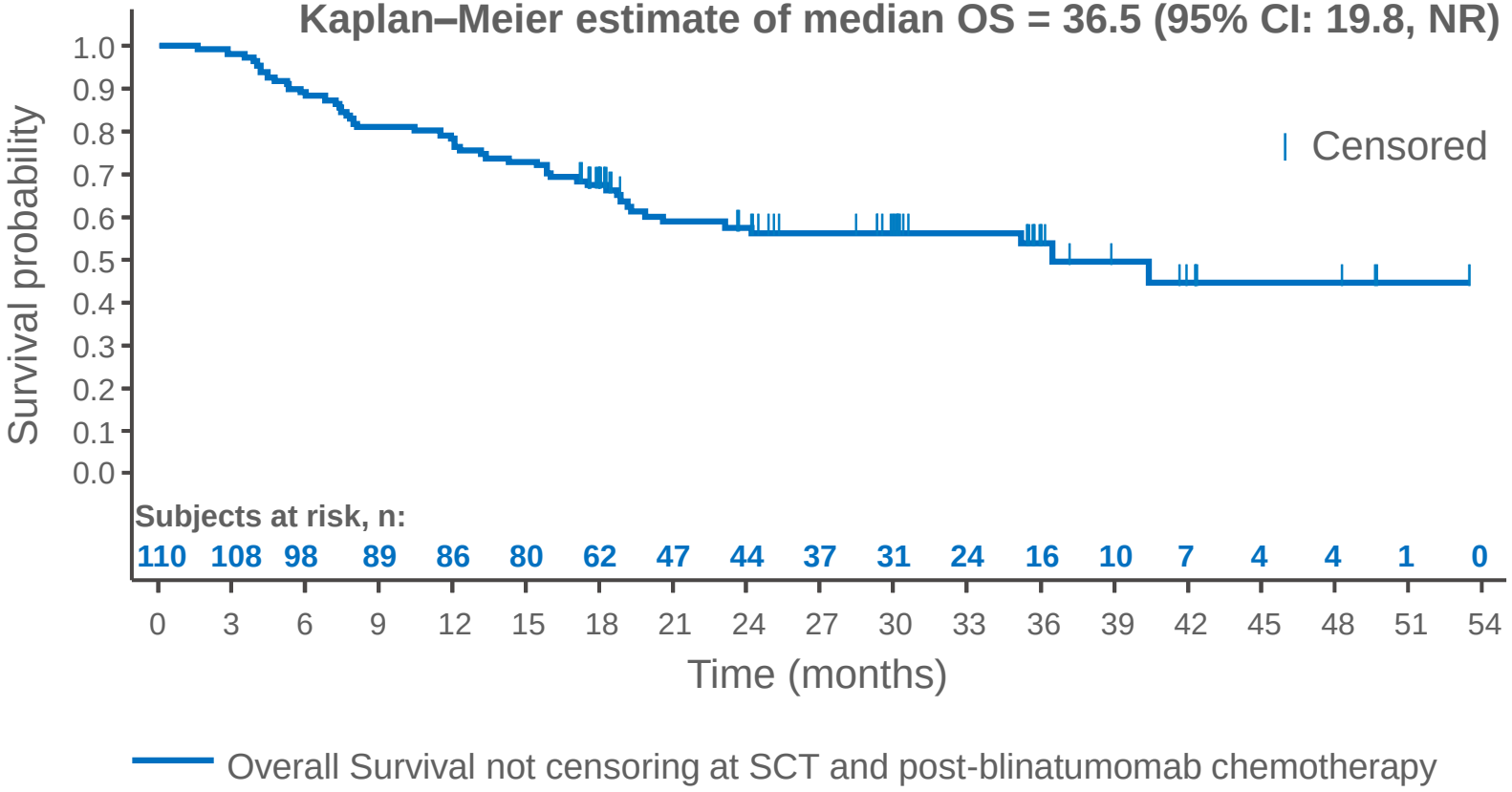
Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation

Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL: overall survival

Ph-negative patients in haematological CR (median age 45 [18–76] years)

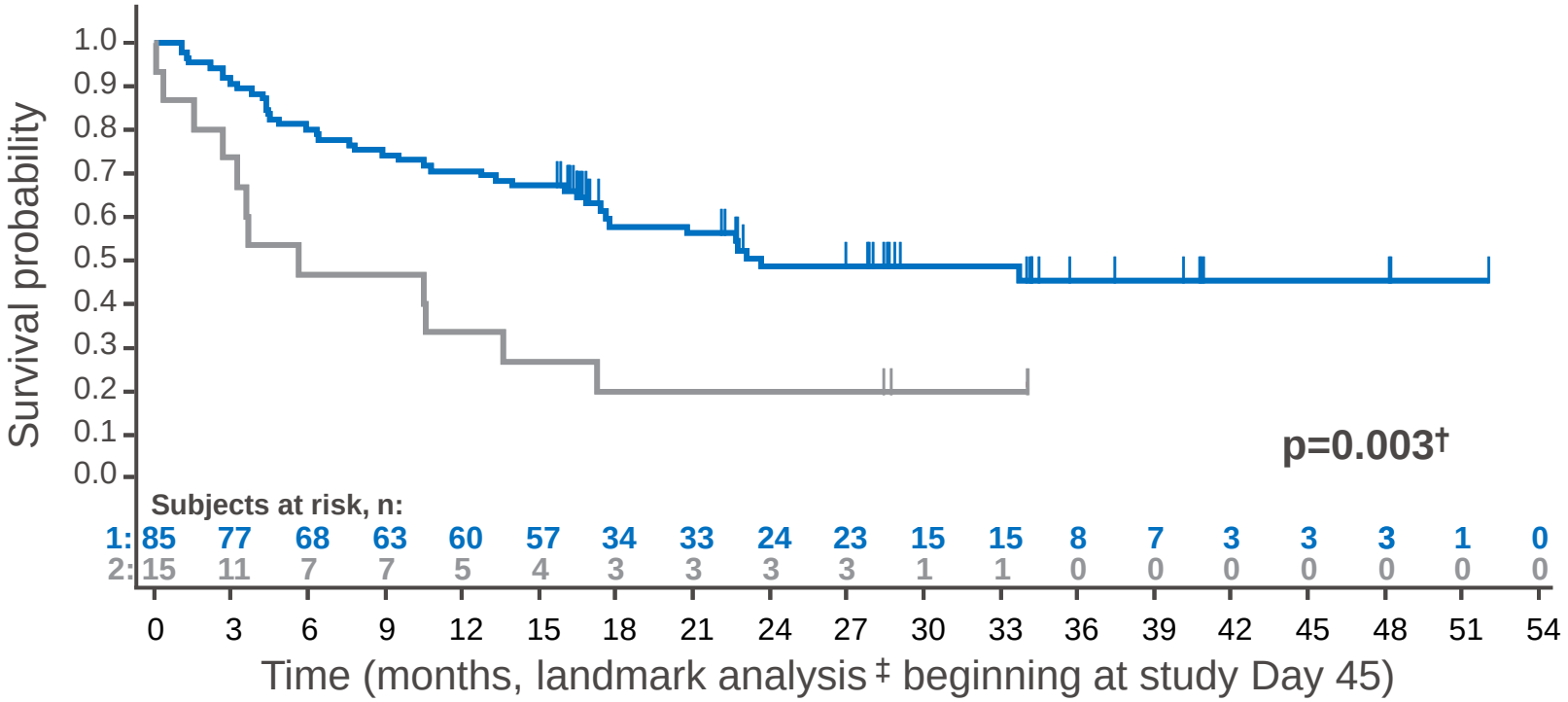
Median (95% CI) follow-up: 30.0 (25.1, 35.4) months

Kaplan–Meier estimate of median OS = 36.5 (95% CI: 19.8, NR) months



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

Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL: relapse-free survival by complete MRD response*

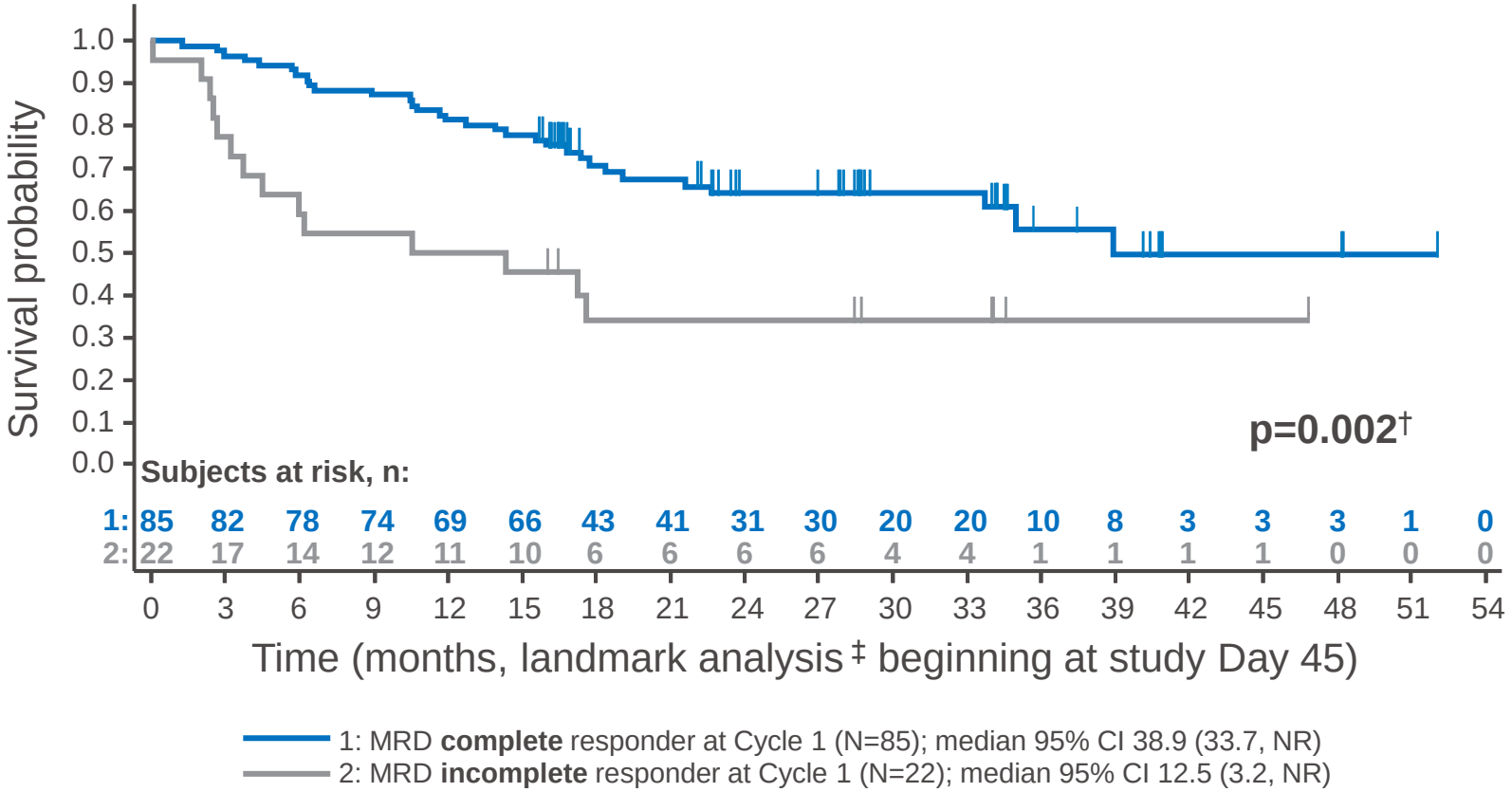


100 patients with data on MRD response according to the primary endpoint efficacy set

*Complete MRD response (primary endpoint): MRD-negative, no amplification in PCR (minimum sensitivity 10^{-4})
†Log rank p-value for association between RFS 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

Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL: overall survival by complete MRD response*



*Complete MRD response (primary endpoint): MRD-negative, no amplification in PCR (minimum sensitivity 10^{-4})
†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

Confirmatory Phase 2 study of blinatumomab in adults with MRD-positive B-precursor ALL

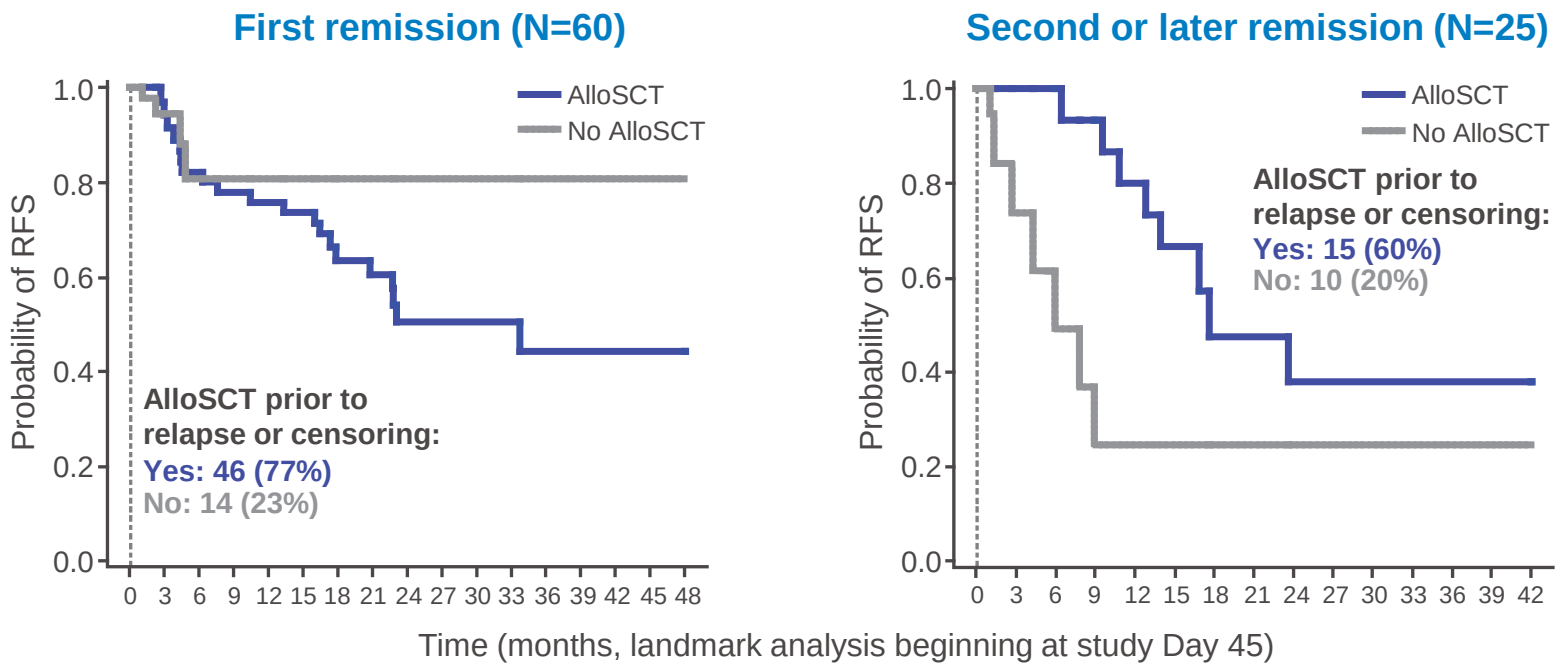
Role of SCT in patients with complete MRD response

Transplant realisation rate: 72%

Cox model analyses of SCT as time-dependent covariate for RFS

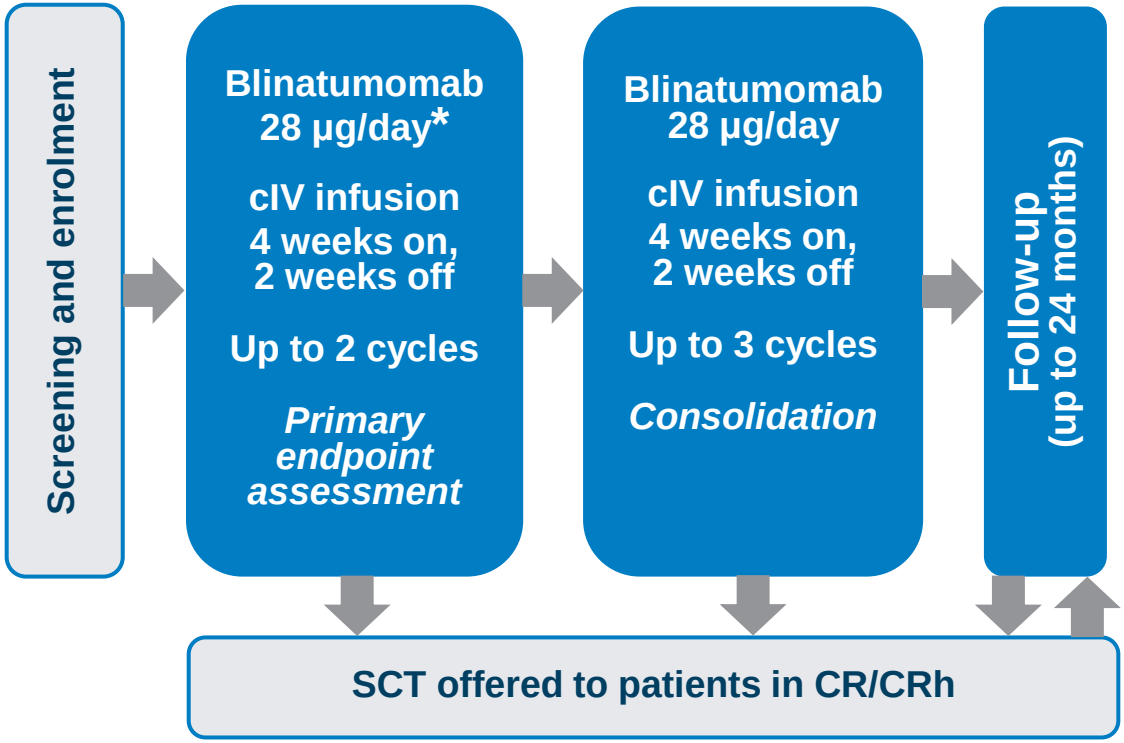
	First remission	Second or later remission
Hazard ratio:	**2.26** (95% CI: 0.73, 6.97)	**0.33** (95% CI: 0.11, 0.98)
p	0.15	0.046

Simon–Makuch plot of RFS (Landmark 45 days)



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

Confirmatory, multicentre, Phase 2 trial of blinatumomab in adults with Ph-negative r/r B-ALL



*9 µg/day in cycle 1 (days 1 to 7)

Study endpoints

Primary
- CR/CRh during the first 2 cycles

Secondary included
- CR, CRh
- RFS
- OS
- AlloSCT realisation rate
- 100-day mortality after alloSCT
- Incidence of AEs

Exploratory included
- MRD response by PCR during the first 2 cycles

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

Topp MS, et al. Lancet Oncol 2015;16:57–66 and supplementary appendix

Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r B-ALL: key inclusion criteria

- Adults (≥18 years) with Ph(-) B-precursor ALL relapsing after prior therapy* or who have refractory disease
  - Primary refractory disease after induction
  - Early relapse: duration of CR1 ≤12 months
  - Relapse within first 12 months post-alloSCT
  - Second or later salvage therapy
- ≥10% blasts in bone marrow ± measurable extramedullary disease
- ECOG PS ≤2

Population selected for negative prognostic factors

*Prior therapy includes induction, consolidation, and/or alloSCT

Topp MS, et al. Lancet Oncol 2015;16:57–66

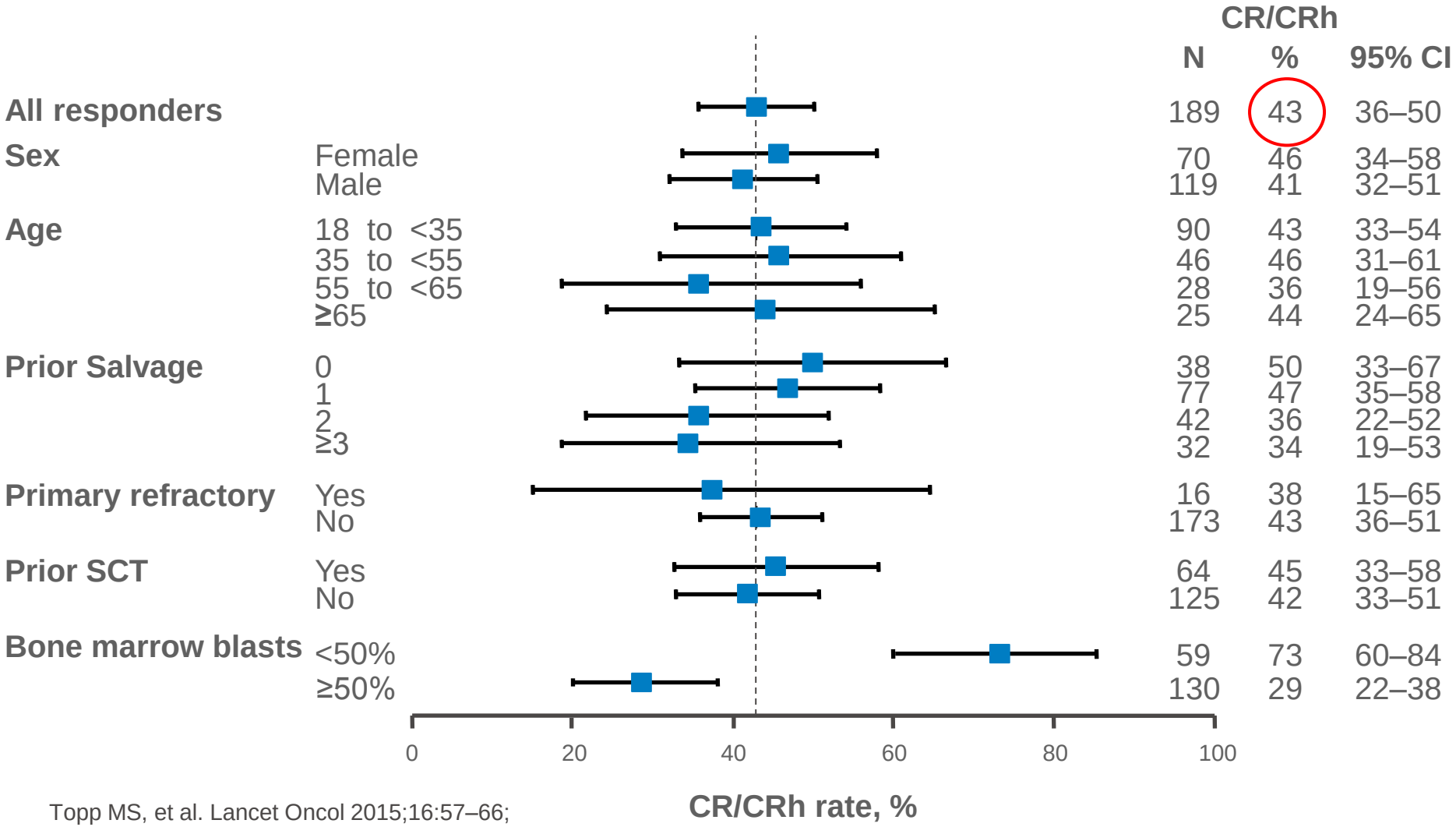
Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r ALL: response and SCT

	n/N	% patients	95% CI
Primary endpoint			
CR/CRh during the first 2 cycles	81/189	43%	36–50
Secondary endpoints			
Best response during the first 2 cycles			
CR	63/189	33%	27–41
CRh	18/189	10%	6–15
Blast-free hypoplastic or aplastic bone marrow	17/189	9%	5–14
Failure to respond to therapy*	73/189	39%	
No response data available†	18/189	10%	
AlloSCT after CR/CRh in first 2 cycles	32/81	40%	
AlloSCT after CR	28/63	44%	
AlloSCT after CRh	4/18	22%	
100-day transplant-related mortality	NA‡	11%	0–23
Exploratory endpoints			
MRD response during the first two cycles			
CR/CRh (evaluable for MRD assessment)	60/73	82%	72–90

NOTE: % are rounded. *No response to blinatumomab (n=41), progressive disease (n=27), or partial remission (n=5)
†Death before the first response assessment (n=9) or AEs leading to treatment discontinuation before the first response assessment (n=9); ‡Not applicable – rate assessed from Kaplan-Meier estimate; CI, confidence interval

Topp MS, et al. Lancet Oncol 2015;16:57–66

Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r B-ALL: subgroup analyses of CR/CRh



Topp MS, et al. Lancet Oncol 2015;16:57–66;
Topp MS, et al. EHA 2014, Abstract S722 and oral presentation

Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r ALL: adverse events (regardless of causality)*

Adverse events, n (%)†	All patients (N=189)
Worst grade 1 or 2	33 (17)
Worst grade 3 or 4	127 (67)
Worst grade 5 (death)	28 (15)
Grade ≥3 occurring in ≥5% of patients†	
Febrile neutropenia	48 (25)
Neutropenia	30 (16)
Anaemia	27 (14)
Pneumonia	17 (9)
Thrombocytopenia	16 (8)
Hyperglycaemia	15 (8)
Leukopenia	15 (8)
Alanine aminotransferase increased	13 (7)
Hypokalemia	13 (7)
Pyrexia	13 (7)
Sepsis	11 (6)
Hypophosphataemia	10 (5)

*During treatment until 30 days post treatment; †CTCAE v4.0

- 3 patients (2%) had grade 3 CRS (no grade 4 or 5 CRS)
- No patients in remission died during blinatumomab treatment

Topp MS, et al. Lancet Oncol 2015;16:57–66

Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r ALL: neurological events

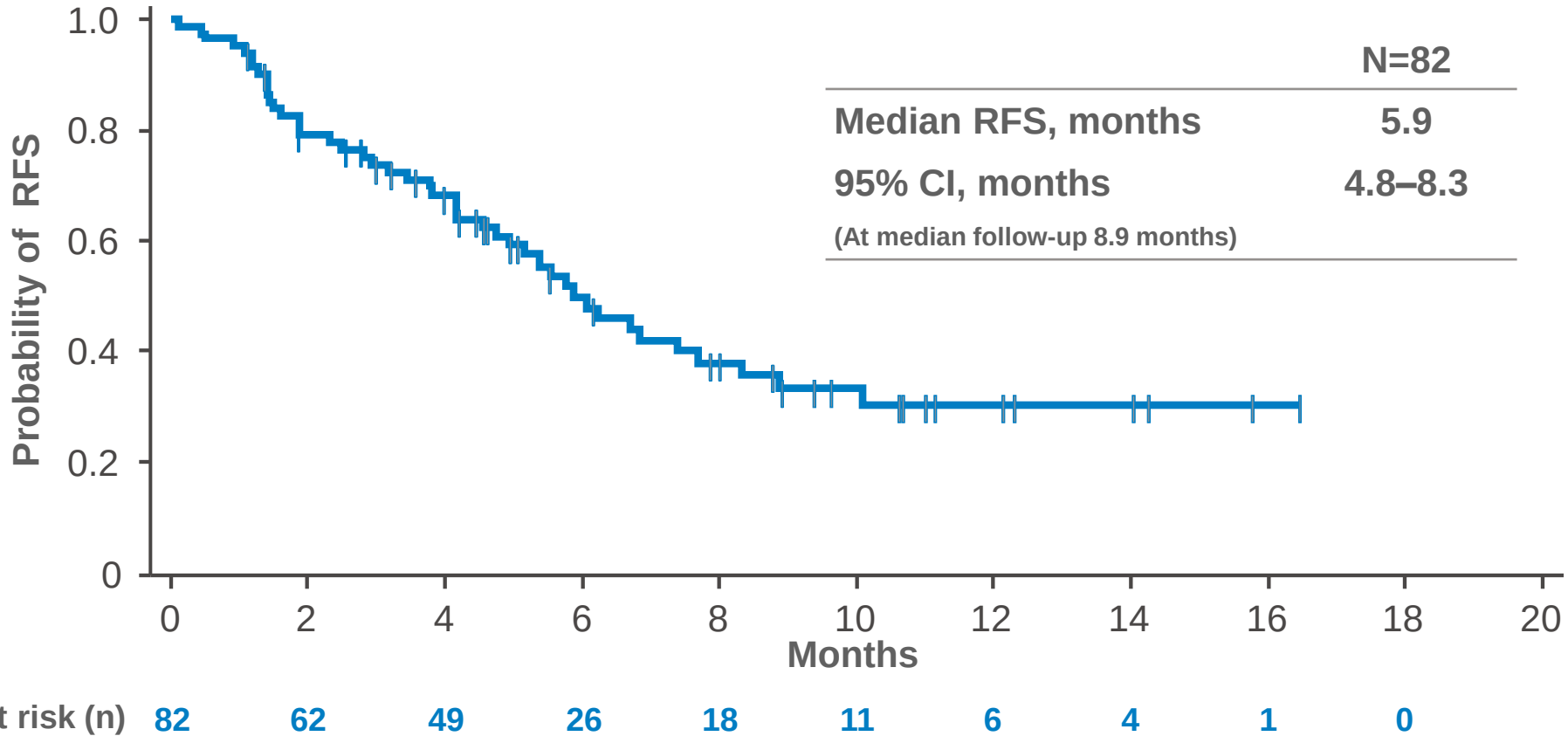
	All patients N=189	
	Grade ≥3*	Any Grade (in ≥2% of patients)
Nervous system/psychiatric disorders, n (%)†	24 (13)	98 (52)
Encephalopathy	6 (3)	10 (5)
Confusional state	3 (2)	14 (7)
Ataxia	3 (2)	9 (5)
Nervous system disorder‡	3 (2)	3 (2)
Aphasia	2 (1)	7 (4)
Mental status changes	2 (1)	7 (4)
Neurotoxicity‡	2 (1)	5 (3)
Tremor	1 (<1)	33 (17)
Dizziness	1 (<1)	26 (14)
Somnolence	1 (<1)	9 (5)
Dysarthria	1 (<1)	6 (3)
Convulsion	1 (<1)	4 (2)
Dysaesthesia	1 (<1)	3 (2)
Cognitive disorder	1 (<1)	3 (2)

†CTCAE v4.0; *Grade 4: n=4 patients; no Grade 5;
‡Terms provided by study sites with no further specification

- 85/98 (87%) of neurological events occurred in cycle 1

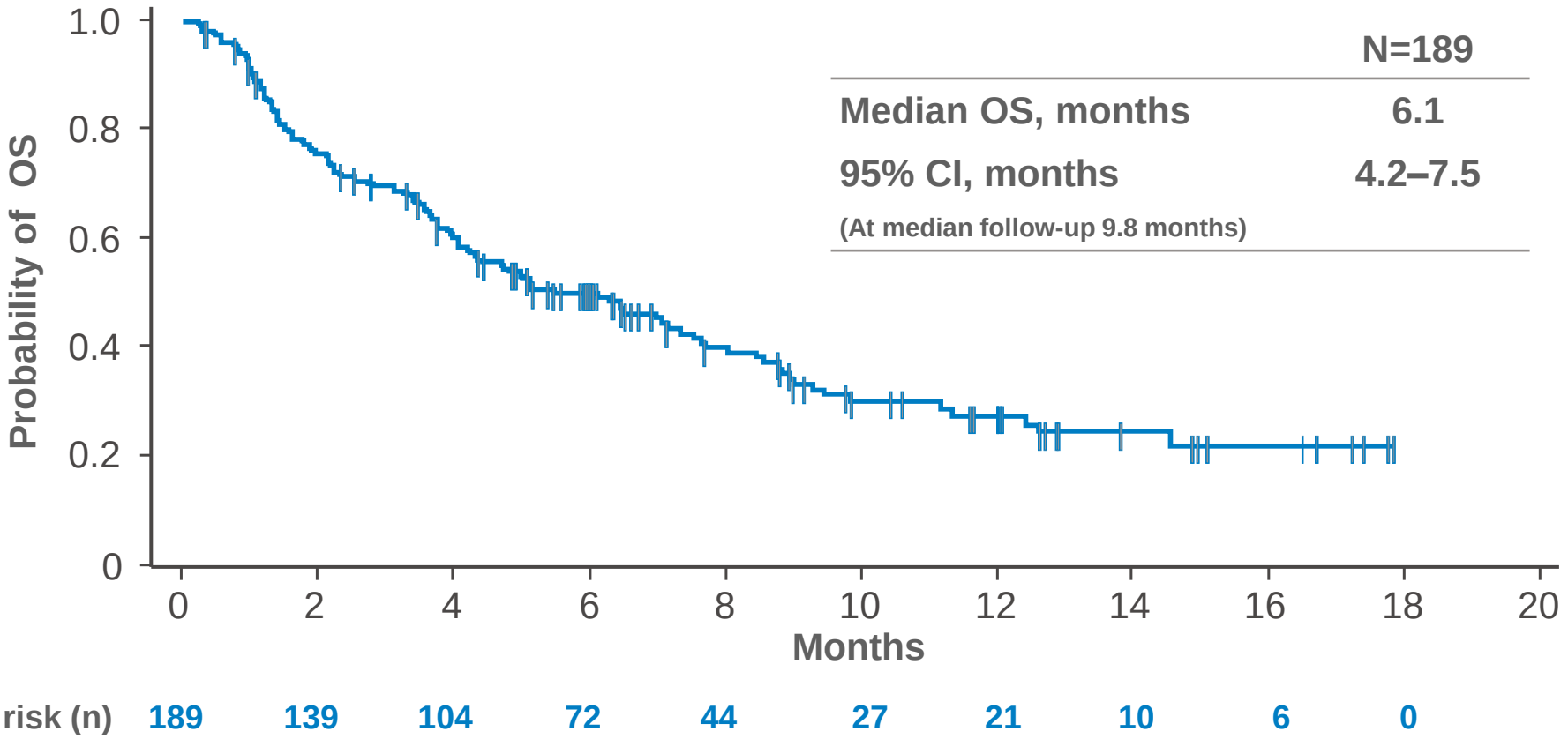
Topp MS, et al. Lancet Oncol 2015;16:57–66

Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r ALL: relapse-free survival



Topp MS, et al. Lancet Oncol 2015;16:57–66

Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r ALL: Overall survival



Topp MS, et al. Lancet Oncol 2015;16:57–66

Confirmatory Phase 2 trial of blinatumomab in adults with Ph-negative r/r ALL: Overall results of MRD evaluation

CR/CRh within 2 cycles and MRD data, n	73†
Patients with MRD response*, n (%)	60 (82)
MRD response in cycle 1	59
MRD response in cycle 2	1

Survival by MRD response

	Median (months) (95% CI)	
	Relapse-free survival	Overall survival
CR\CRh MRD+	2.3 (1.2, NE)	6.7 (2.0, NE)
CR\CRh MRD-	6.9 (5.5, 10.1)	11.5 (8.5, NE)

†Missing diagnostic and/or follow-up sample in 8/81 responders (10%)
*MRD $<10^{-4}$ by PCR

Topp MS, et al. Lancet Oncol 2015;16:57–66

Summary of blinatumomab efficacy in adult ALL

Relapsed/refractory ALL

	CR/CRh after 2 cycles	MRD response (in responders)	Allo SCT (in responders)	Median RFS	Median OS
206 (n=36)[1,2]	69%	88%†	52%	7.6 mo (at 9.7 mo follow-up) 8.8 mo (at 28.9 mo follow-up)	9.8 mo (at 12.1 m follow-up) 13 mo (at 32.6 mo follow-up)
211 (Ph-; n=189)*[3]	43%	82%†	40%	5.9 mo (at 8.9 mo follow-up)	6.1 mo (9.8 mo follow-up)
Alcantara (Ph+; n=45)[4]	36%	88%‡	25%	6.7 mo (at 8.8 mo follow-up)	7.1 mo (at 8.8 mo follow-up)

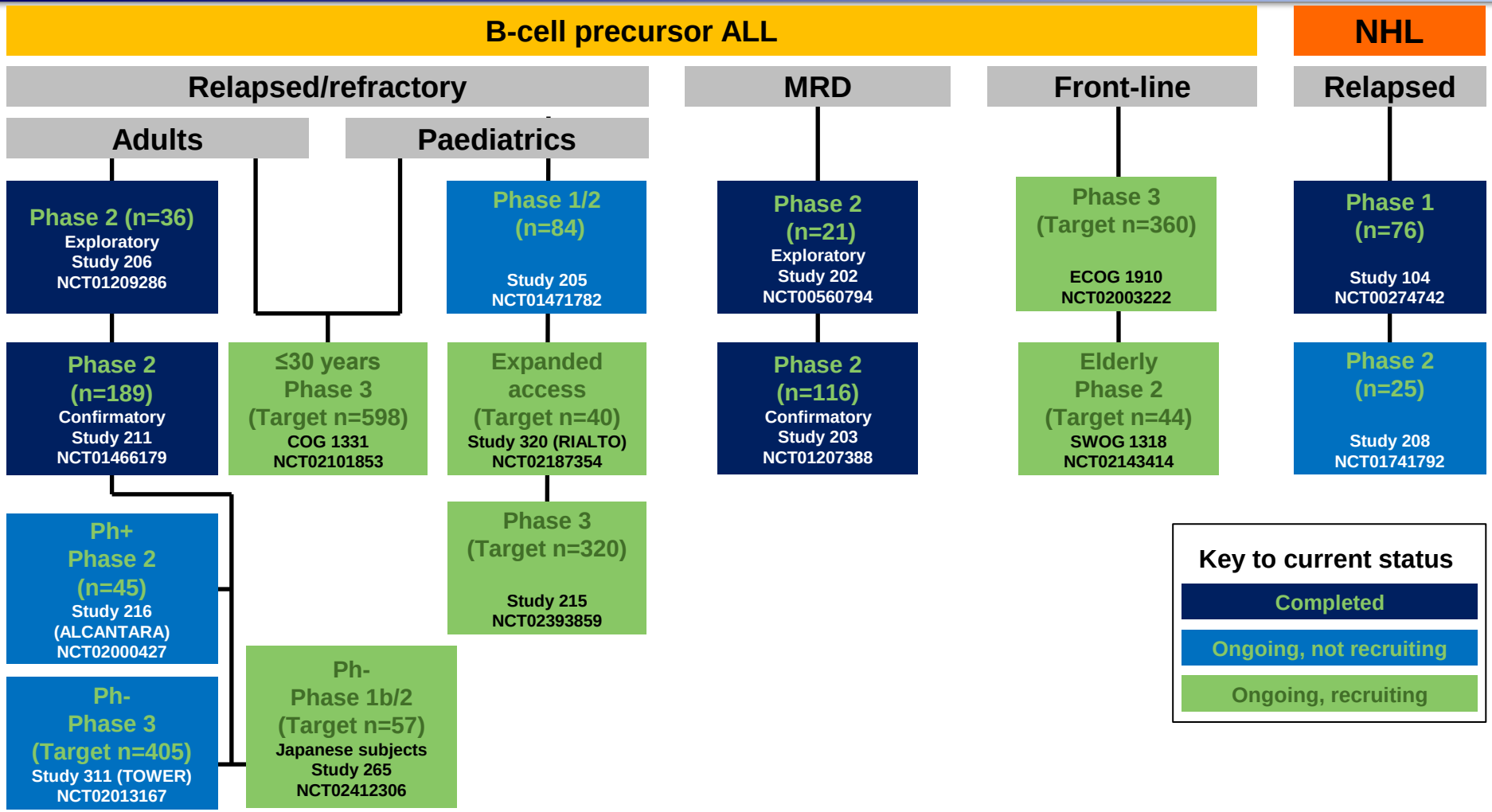
MRD-positive ALL

	Complete MRD response‡	MRD response†	RFS	Median OS
202 (n=20)[5,6]	NA	80% (within 1 cycle)	KM estimate median 61% (at 32.9 mo follow-up)	NA
BLAST[7,8]	78% (within 1 cycle; n=113)[7]	85% (within 1 cycle; n=113)[7]	KM estimate 54% at 18 mo (Ph- in CR; median follow-up 29.9 mo; n=110)[8]	KM estimate 36.5 mo (Ph- in CR; median follow-up 30.0 mo; n=110)[8]

*Patients selected for particularly poor prognosis;
†MRD $<10^{-4}$ (minimum sensitivity 10^{-4});
‡MRD-negative, no amplification in PCR, minimum sensitivity 10^{-4} (10^{-5} in Alcantara)
KM, Kaplan–Meier

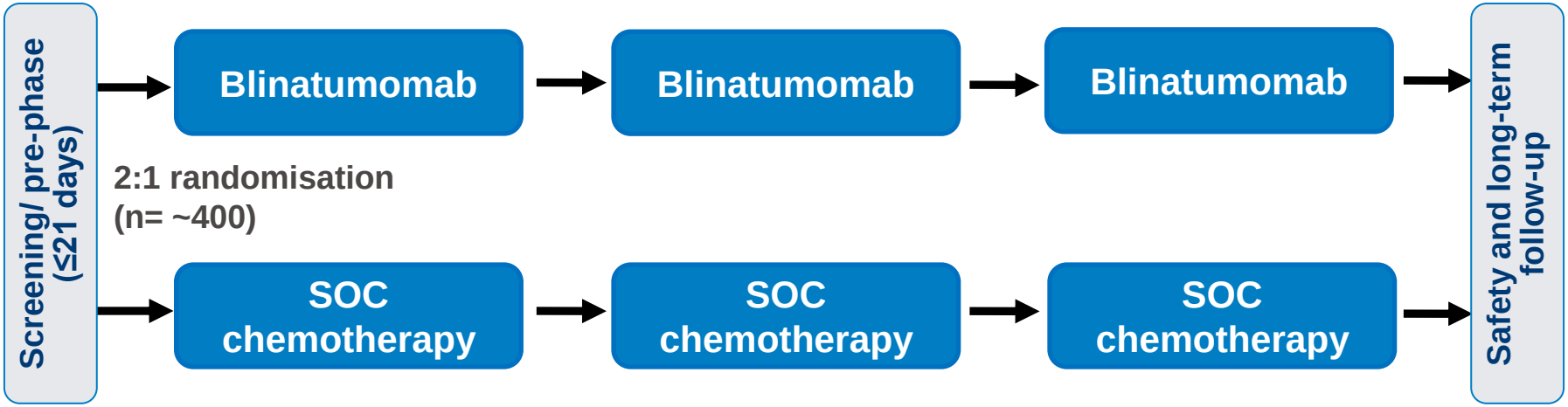
1. Topp MS et al. J Clin Oncol 2014;32:4134–40; 2. Zugmaier G, et al. Blood 2015;126:2578-84;
3. Topp MS, et al. Lancet Oncol 2015;16:57–66; 4. Martinelli G, et al. ASH 2015: Abstract 679 and oral presentation;
5. Topp MS, et al. J Clin Oncol 2011;29:2493–8; 6. Topp MS, et al. Blood 2012;120:5185–87;
7. Gökbuget N, et al. ASH 2014: Abstract 379 and oral presentation;
8. Gökbuget N, et al. ASH 2015: Abstract 680 and oral presentation

Blinatumomab clinical development programme



BLINCYTO® is indicated for the treatment of adults with Philadelphia chromosome-negative r/r B-precursor ALL. Blinatumomab is investigational in all other settings. MRD, minimal residual disease; NHL, non-Hodgkin's lymphoma. Ph-, Philadelphia chromosome negative. Trial information at: https://clinicaltrials.gov/ accessed January 2015.

Phase III, randomized, open-label study of blinatumomab vs. standard of care chemotherapy in adults with r/r B-ALL (TOWER study)



Primary endpoint	• Overall survival	
Key secondary endpoints	• CR and CR/CRh/CRi within 12 weeks • Duration of CR/CRh/CRi • MRD remission ($<10^{-4}$ by PCR or flow cytometry)	• Rate of alloSCT ± blinatumomab • Event Free Survival (EFS) • Safety

Key inclusion criteria	• Ph- B-ALL with any of:
	  • Refractory to primary induction therapy or salvage therapy
	  • If Salvage 1: CR1 duration <12 months
	  • ≥2nd salvage
	  • Relapse at any time after alloSCT
		• >5% blasts in the bone marrow
		• ECOG PS ≤2
		• Age ≥18 years

Conclusions

- Single-agent blinatumomab has demonstrated efficacy in large, multicentre, Phase 2 confirmatory studies in adult ALL
  - **In r/r Ph-negative B-ALL** patients selected for negative prognostic factors: associated with a high CR/CRh rate of 43%, enabling transplant in 40% of responders[1]
  - **In r/r Ph-positive B-ALL** patients who had failed 2+ generation TKI therapy: associated with a high CR/CRh rate of 36% and a complete MRD response in 88% of responders, independent of mutational status including presence of T315i mutation[2]
  - **In MRD+ B-ALL**: associated with a high complete MRD response rate (78% within 1 cycle of treatment), and may contribute to prolonged RFS and OS[3]

- Adverse events consistent with known pharmacological effects of T-cell engagement[1–3]
  - Neurological events observed as a clinically significant AE in 13–14% of patients (as also seen with CAR T-cell therapy)
  - Risk of grade ≥3 CRS with blinatumomab in adults with r/r ALL 2%; managed with stepped-dosing and pre-phase dexamethasone; severe CRS not seen in patients in MRD+ studies

- Optimal position of blinatumomab in the ALL treatment paradigm currently unknown
  - Studies in the front-line setting ongoing

1. Topp MS, et al. Lancet Oncol 2015;16:57–66; 2. Martinelli G, et al. Oral presentation at ASH, Orlando, FL; December 5-8 2015. Abstract 679;
3. Gökbuget N, et al. Oral presentation at ASH, Orlando, FL; December 5-8 2015, Abstract 680

Acknowledgements

- All of the participating patients and their families
- The study groups France (GRAAL), Germany (GMALL), Italy (NILG), Spain (PETHEMA), UK (NCRI Adult ALL Subgroup) and USA
- Central diagnostics: M. Brüggemann and H.Horst, Kiel