Cellex Symposium, September 14th 2018

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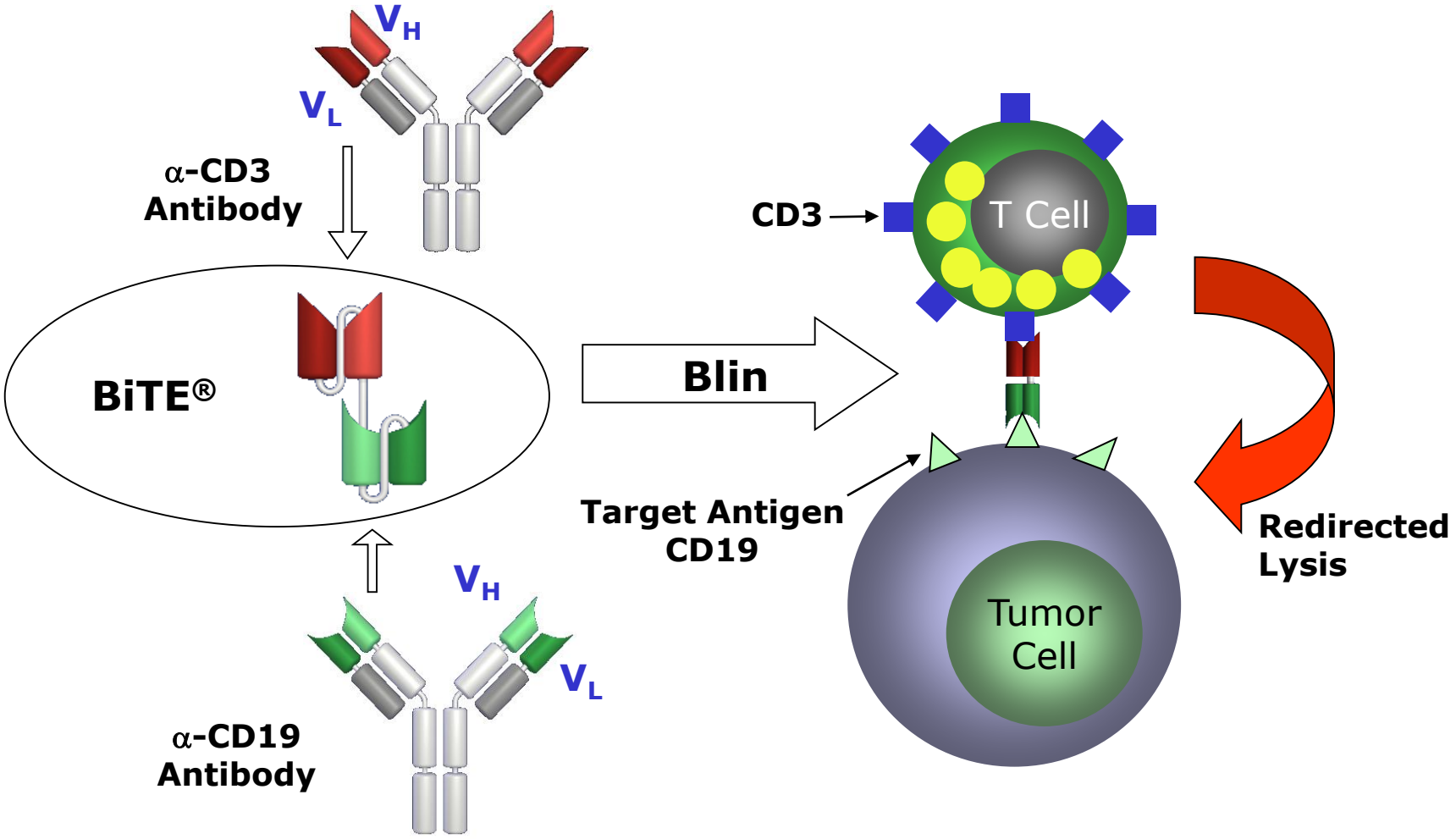
Blinatumomab and beyond

Comprehensive Cancer Center Mainfranken

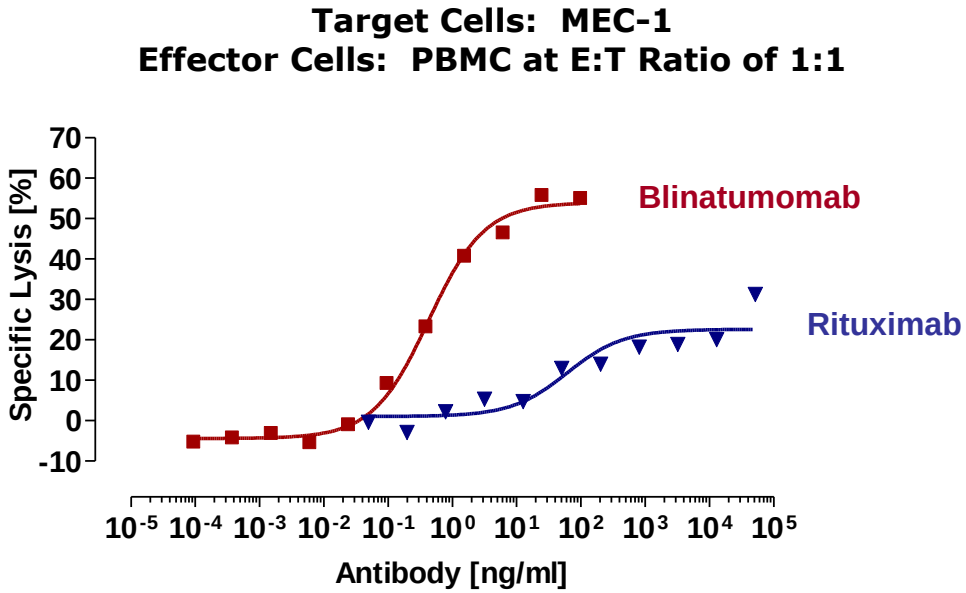
Blinatumomab (MT103), a Bispecific T Cell Engaging Single-chain BiTE® Antibody



Löffler....and Bargou, Blood, 2000

Mack, Riethmüller, Kufer, PNAS, 1995

Preclinical Characterization Blinatumomab



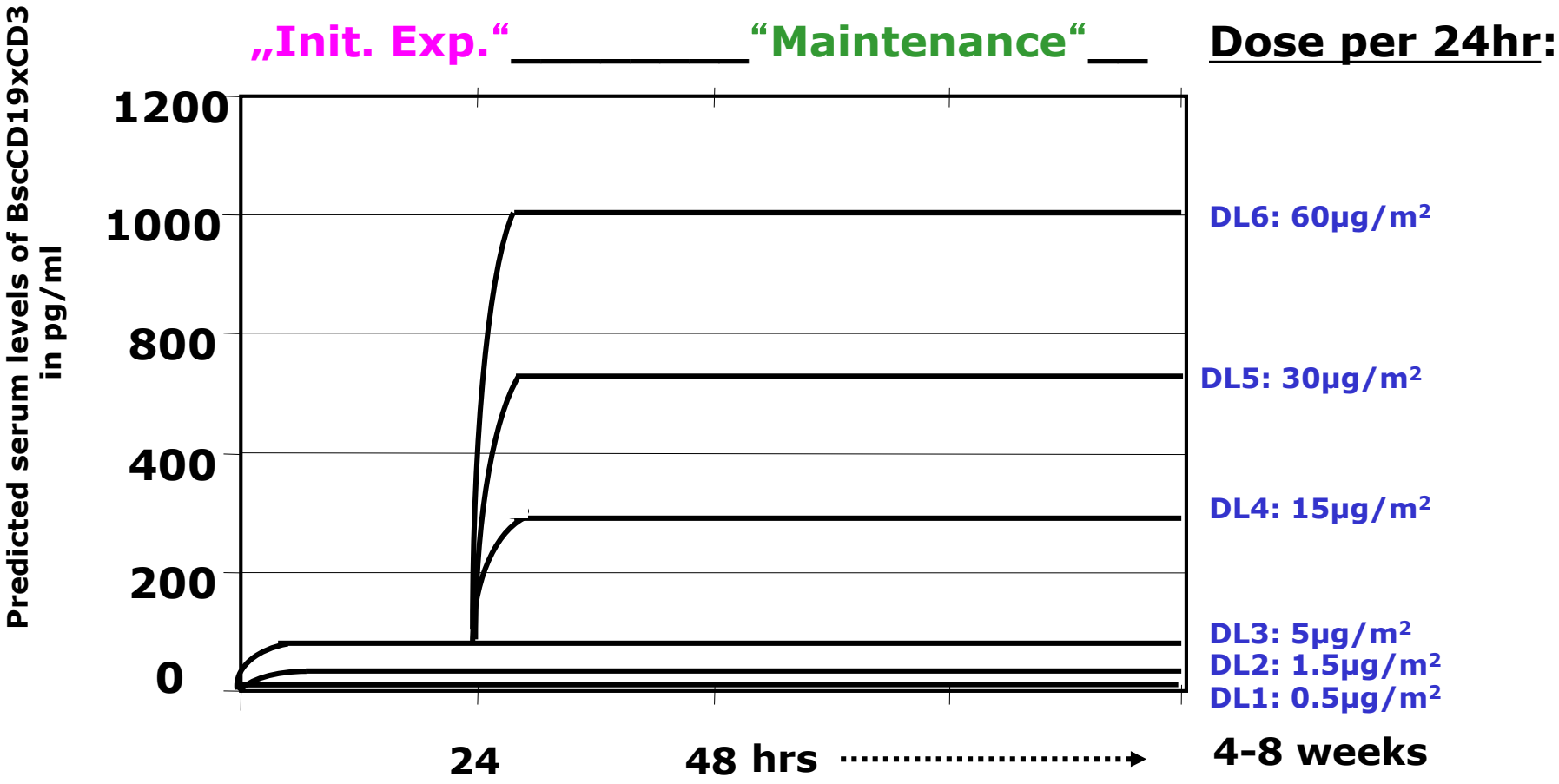
- **Blinatumomab is active at very low concentrations (pg/ml) *in vitro***
- **Blinatumomab-activated T cells do strongly proliferate and perform serial lysis at very low E:T ratios (1:90)**
- **Blinatumomab does not require T cell costimulation**
- **Has anti-tumor activity in animal models at very low concentrations (0.1 µg i.v./day)**
- **Serum half time 2-3 hrs**

Löffler et al., ***Blood***, 2000
Dreier et al., ***Int.J. Cancer,*** 2002
Löffler et al., ***Leukemia,*** 2003
Dreier et al., ***J. Immunol.,*** 2003

Grün et al., ***Cancer Immunol. Immunther.****, 2004*
Hoffmann et al., ***Int.J. Cancer,*** 2005
Schlereth et al, ***Cancer Immunol. Immunther.,*** 2006
Brandl et al., ***Cancer Immunol. Immunther.,*** 2007

D´Argouges et al., ***Leuk Res****, 2008*
Baeuerle et al., ***Cur Opin Mol Ther***, 2009
Nagorsen et al., ***Leukemia Lymphoma*** 2009
Nagorsen et al., ***Pharmacol Ther*** 2012

Phase I dose escalation study with MT103 (blinatumomab) as continous infusion in relapsed/refractory B-NHL



Baseline patient characteristics

Baseline demographic and clinical characteristics	Overall (n=76)	Extension phase* (n=34)
Median age, y (range)	65 (20–80)	62 (20–80)
Male sex, n (%)	57 (75)	23 (68)
Median time from diagnosis, y (range)	4 (1–28)	2.3 (1–28)
Median time from last chemotherapy regimen, months (range)	8.3 (0–100)	6.1 (1–81)
Median number of prior treatment regimens (range)	3 (1–10)	3 (1–8)
Type of prior treatment regimen†		
Prior rituximab, n (%)	71 (93)	33 (97)
Prior fludarabine, n (%)	23 (30)	5 (15)
Prior autoSCT, n (%)	23 (30)	9 (26)
Lymphoma histology, n (%)		
Indolent lymphoma	52 (68)	18 (53)
FL	28 (37)	10 (29)
MCL	24 (32)	8 (24)
Refractory to prior rituximab treatment‡	20 (26)	8 (24)
DLBCL	14 (18)	13 (38)
Relapsed after therapy with CHOP	10 (13)	10 (29)
Relapsed after autoSCT	9 (12)	9 (26)
Other§	10 (13)	3 (9)

Goebeler ME, et al. J Clin Oncol 2016;34:1104–11

Blinatumomab: Toxicity Profile

MTD reached at **60 µg/m²/24 h**

Dose Limiting Toxicity at 90 µg/m²/24 h: neurol. side effects (toxic encephalopathy like syndrom)

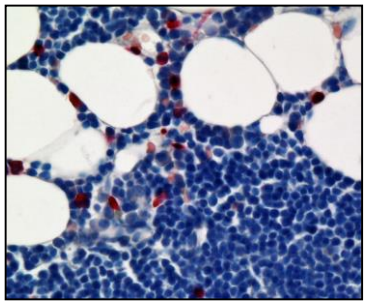
- **Clinically relevant and dose-limiting toxicities**
  - Flu-like symptoms (fever, chills, fatigue)
  - Neurological AEs: toxic encephalopathy-like syndrome - reversibel
  - Majority of side effects within 72 h after treatment start

- **CRS**
  - Dose-limiting in rr ALL with high tumor load
  - Clinically manageable (prephase, stepwise dose escalation, anti-pyretics, hydration, steroids, IL-6 blockade)
  - No severe CRS in NHL and MRD ALL

Clinical activity of blinatumomab in patients with relapsed/refractory B-Non-Hodgkin Lymphoma

Baseline

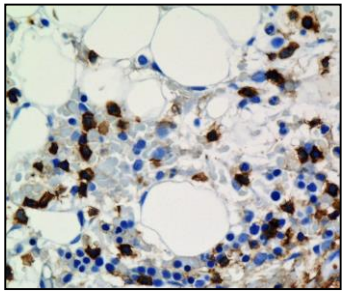
After Treatment

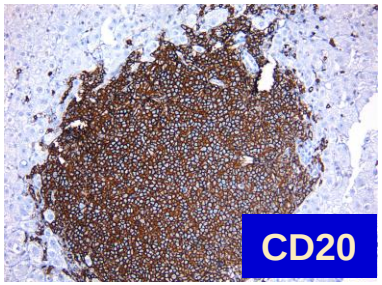


MT103
15 µg/m²/24 h

Bone marrow biopsy

Small lymphocytic lymphoma

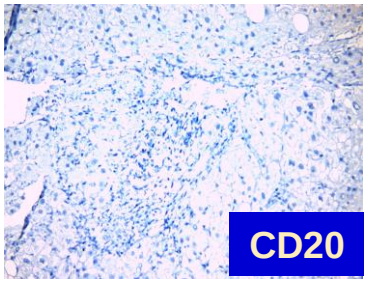


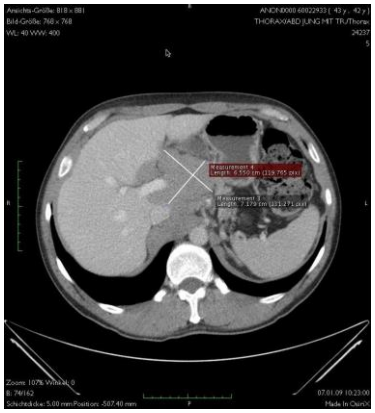


MT103
60 µg/m²/24 h

Liver biopsy

Mantle cell lymphoma

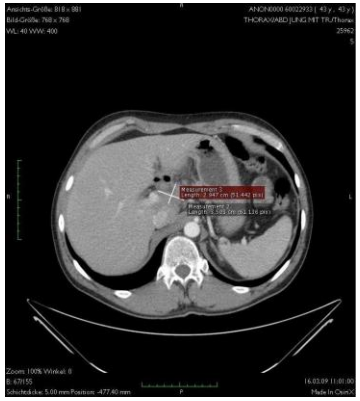




MT103
60 µg/m²/24 h

CT scan bulky disease

Mantle cell lymphoma



Bargou et al. *Science* 2008

Ph I Dose Escalating Trial in Patients with rr B Cell Non Hodgkin Lymphoma

4 – 8 week continous iv adminstration per cycle

Dose Level	Patients evaluable for response (n=70)	Complete Response	Partial Response	Overall Response Rate
0.5 – 5 µg/m^2/24 h	13	0	0	0/13
15 & 30 µg/m^2/24 h	20	2	2	4/20
60 µg/m^2/24 h	**35**	**13**	**11**	**24/35**
90 µg/m^2/24 h	2	1	1	2/2

MTD reached at **60 µg/m^2/24 h**

Dose Limiting Toxicity at 90 µg/m^2/24 h: neurol. side effects (toxic encephalopathy like syndrom)

Göbeler et al. *J. Clin. Oncol.* 2016

Bargou et al. *Science* 2008

Phase-I trial with blinatumomab in rr NHL: efficacy at MTD level (60 μg/m²/d)

Median number of previous treatment regimens: 3 (1–10)

Actually Exposed to 60 μg/m²/d – N = 35			
Histologic subtype	**CR + CRu n (%)**	**PR n (%)**	**ORR n (%)**
All patients	13/35	11/35	24/35 (69)
FL	6/15	6/15	12/15 (80)
DLBCL	4/11	2/11	6/11 (55)
MCL	3/7	2/7	5/7 (71)
Other (MZL, LPL)	0/2	1/2	1/2 (50)

Efficacy in rr DLBCL confirmed in a phase II trial

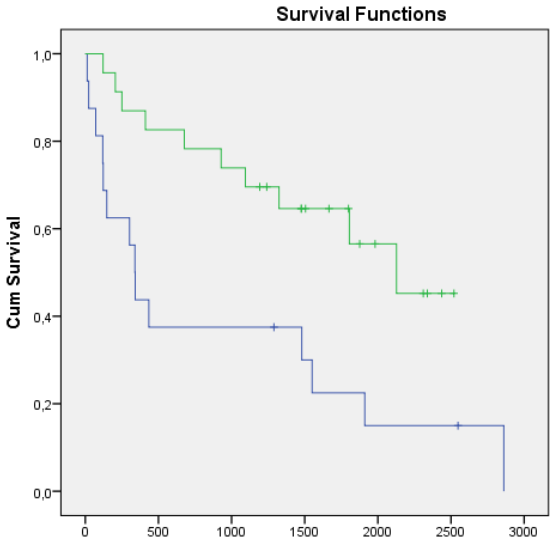
Viardot et al. *Blood* 2016

Göbeler et al. *J. Clin. Oncol.* 2016

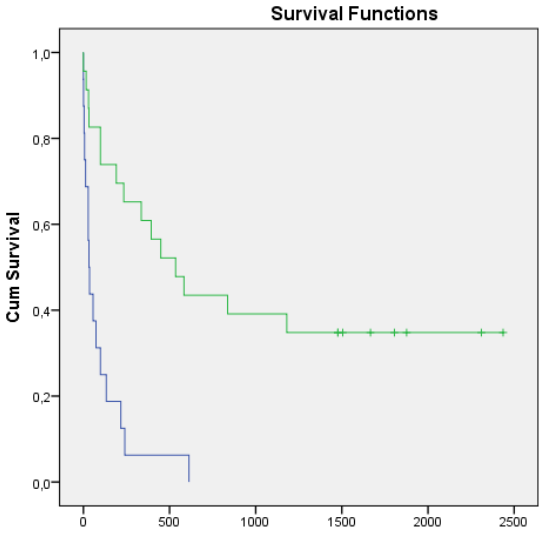
Bargou et al. *Science* 2008

Long Term Remission in Patients with r/r NHL treated with single-agent treatment with blinatumomab

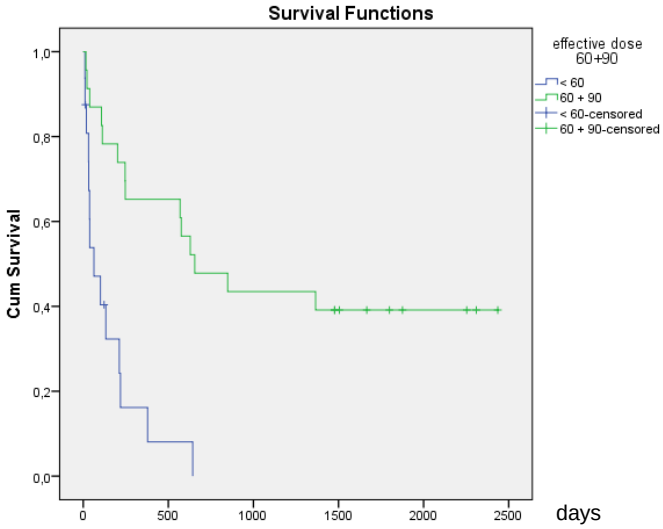
Overall Survival



Progression-Free Survival



Treatment-Free Survival



effective dose 60 + 90 μg/m^2/day

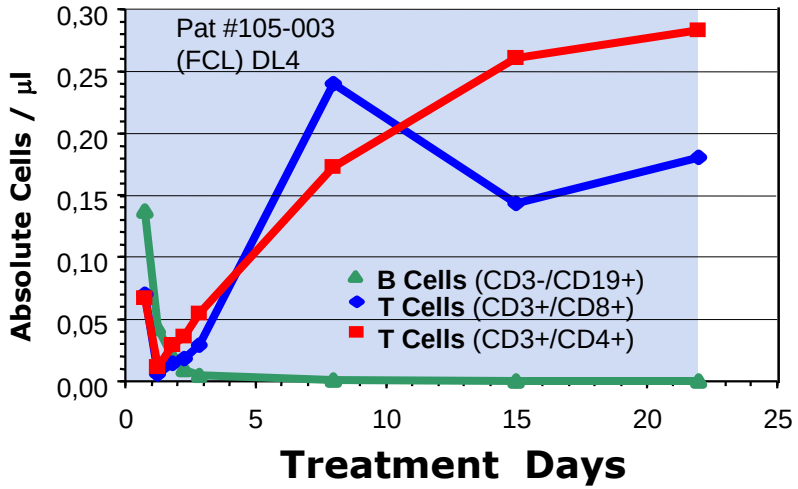
effective dose < 60 μg/m^2/day

[Study MT103-104, single-center long term remission data in patients with r/r NHL].
Unpublished raw data.

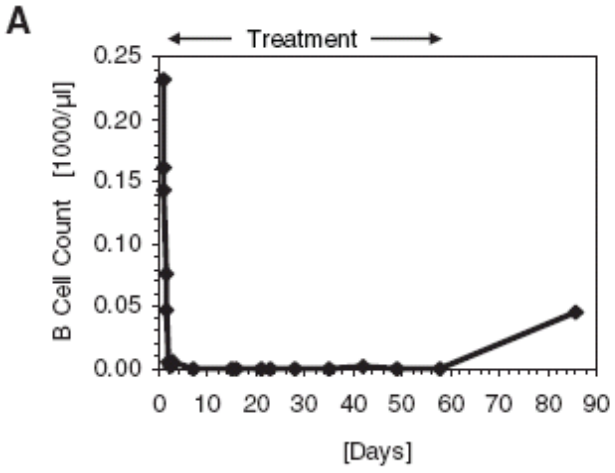
Dufner et al. *in preparation* 2018

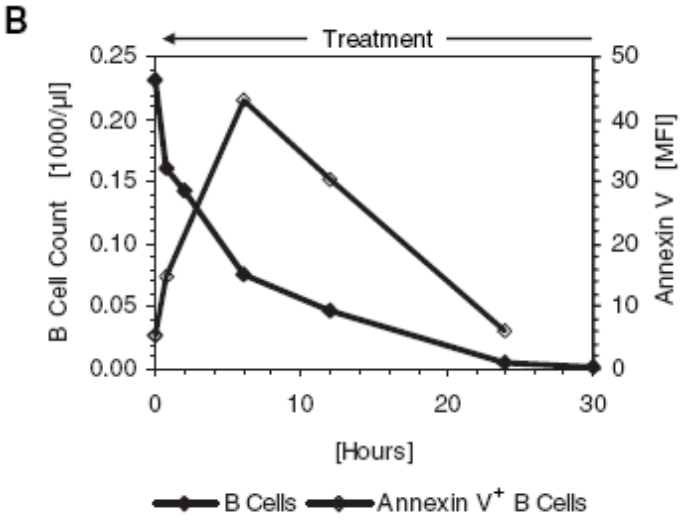
A pathogenetic model and development of mitigation strategies for blinatumomab-associated neurologic events

Pharmacodynamics: Blinatumomab phase I dose escalation study



Blin induces B cell depletion and T Cell expansion

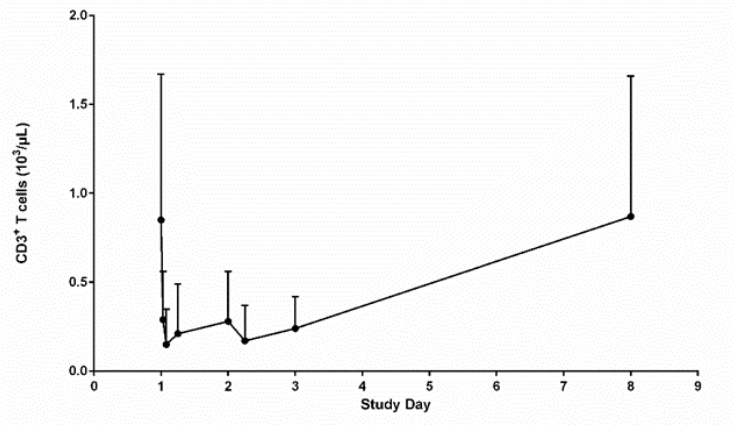




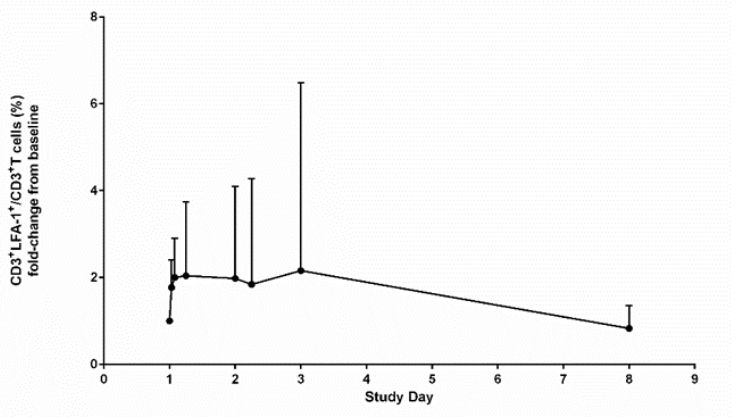
Blin induces apoptosis of circulating B cells

Blinautomab induces rapid T cell adherence to endothelial blood vessels cells in patients

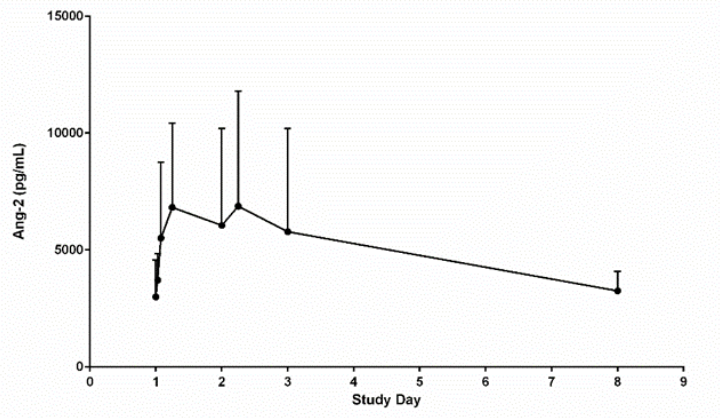
T redistribution



Induction of activated LFA-1 on T cells



Induction of endothelial activation (Ang-2)



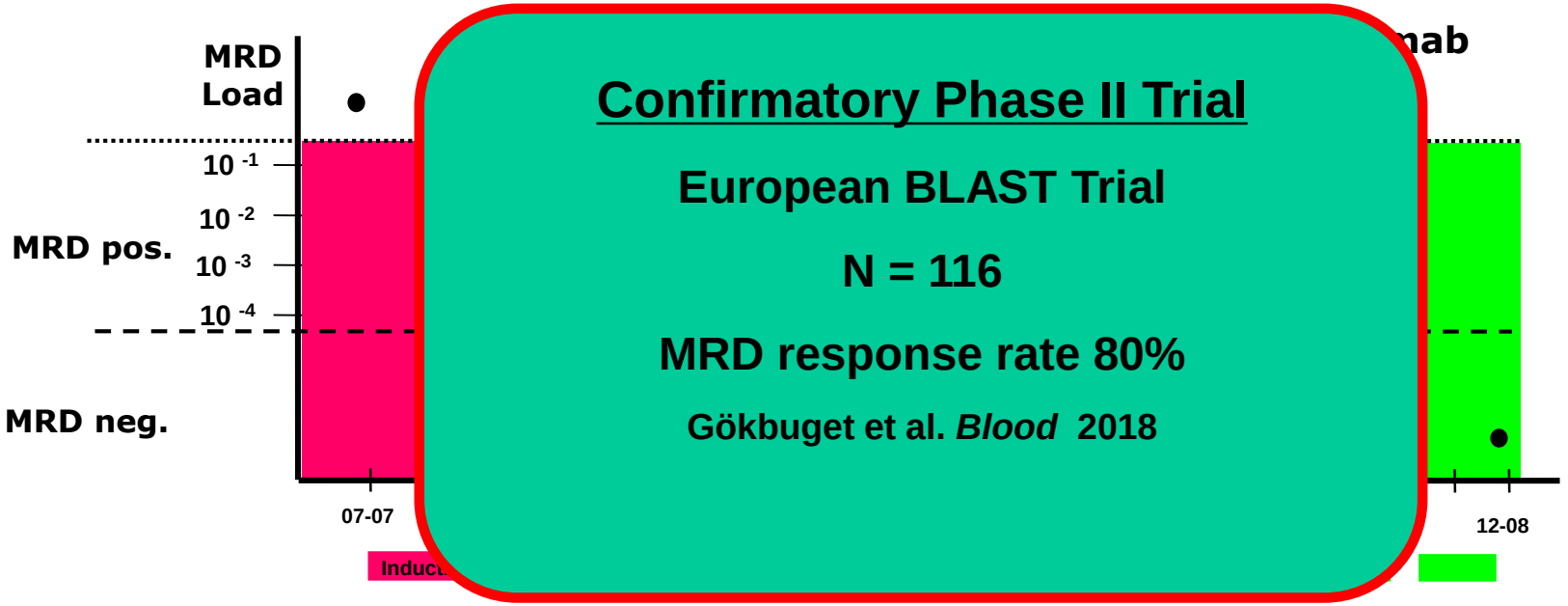
Three high-risk patients treated with blinatumomab (60 μg/m²/day) plus PPS

Patient	Sex	Age	Diagnosis	Prior Lines of Treatment	B/T-cell ratio	Treatment Duration	Best Response	Neurologic Events
1	male	63 years	relapsed FCL grade I, stage IV-AE	2	73/1649	57 days	CRu	grade I tremor, ataxia
2	male	51 years	refractory immunocytoma stage IV-B	5	20/2535	30 days	PD	not observed
3	female	49 years	refractory FCL grade I, stage III-B	1	4/332	56 days	CRu	not observed

=> effective mitigation of neurotox might allow for higher dosing and might imrove efficacy and long-term outcome

Blinatumomab in B Lineage Acute Lymphoblastic leukemia

Blinatumomab (Anti-CD19 BiTE®) for Targeted Therapy of Minimal Residual Disease (MRD) in Patients with B-Precursor Acute Lymphoblastic Leukemia (ALL)



Response Rate (MRD negativity): 80% (16/20)

Topp et al. *J Clin Oncol* 2011

BLAST Trial: Median Overall Survival (OS) Is Not Reached in Complete MRD Responders at a Median Follow-up of 53.1 Months

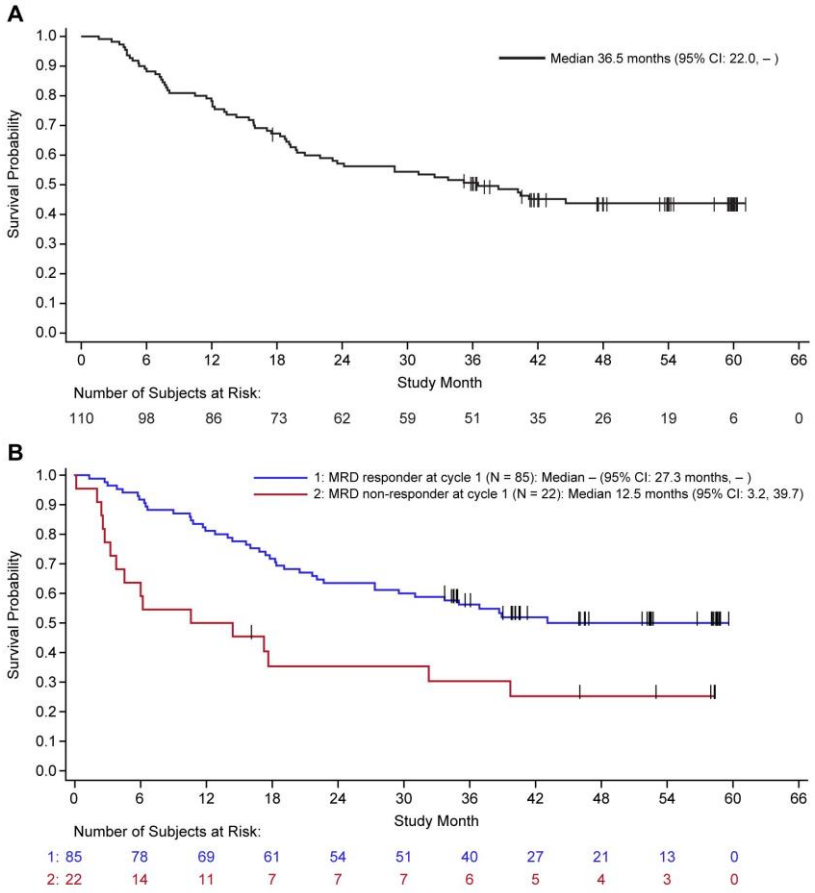


Figure 1. Overall survival. (A) Evaluable patients (Ph– BCP-ALL and <5% blasts at baseline; n = 110). (B) Evaluable patients with adequate MRD response assessment at cycle 1 (n = 107).
Vertical bars indicate censoring; –, not estimable.

Approval of Blin in MRD ALL:

FDA 29th March 2018

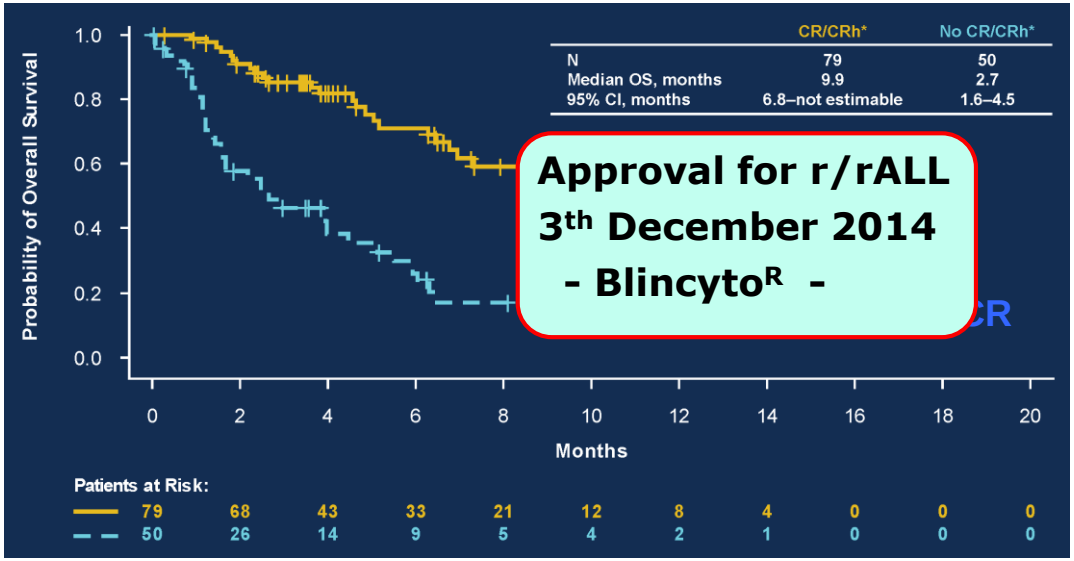
Gökbuget et al. *Blood* 2018

r/rALL: Confirmatory Open-label, Single-arm, Multicenter Phase 2 Study: N=189

- ≥ 2nd Relapse: 80%
  <-> 19% in the exploratory phase II trial
- Post Allo: 34%

CR/CRh: 81/189 (43%)

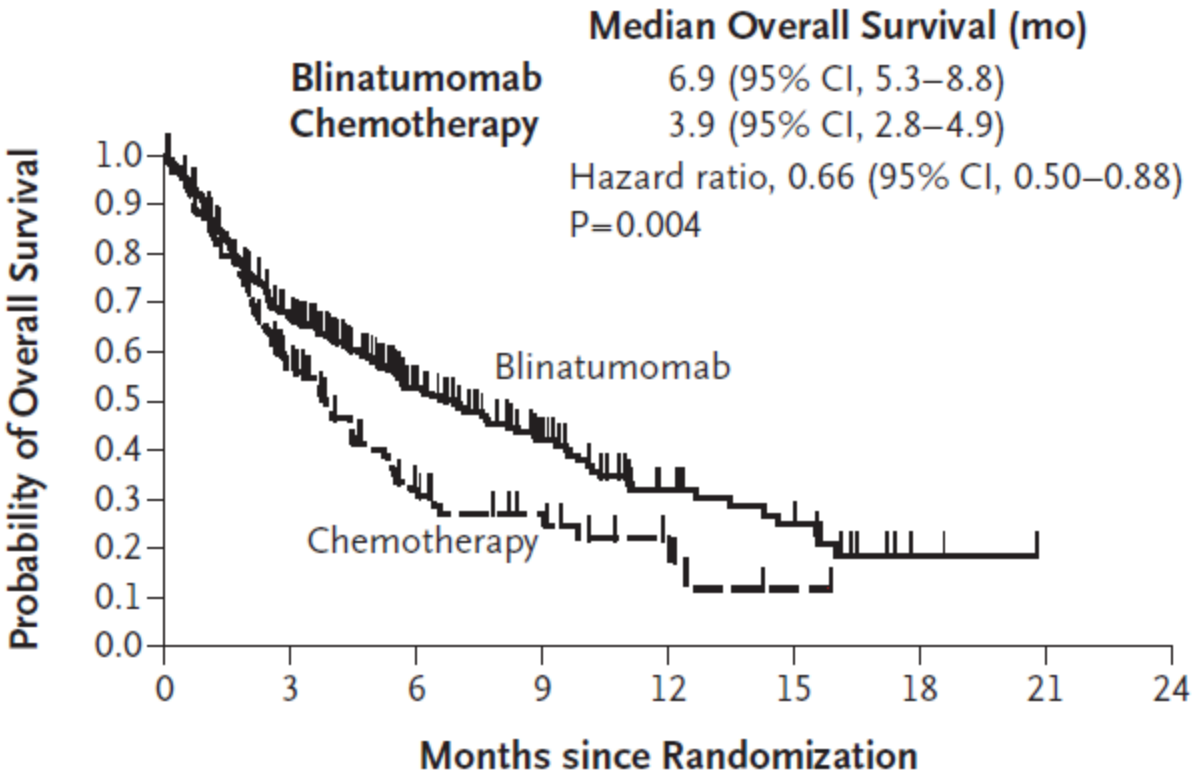
Overall Survival



At median follow up of 8.9 months 45% of the responders are alive and in remission

Topp et al. *Lancet Oncology* 2015

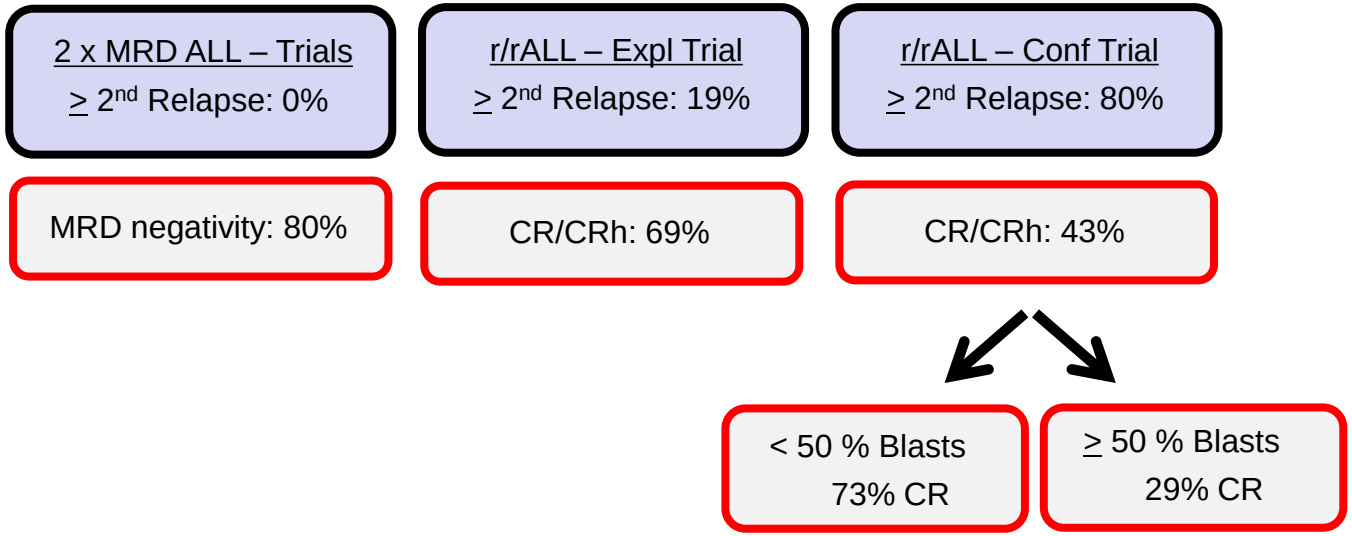
Phase III Trial in rr ALL: Superior OS of blinatumomab compared with chemo - TOWER TRIAL -



Blinatumomab: improved QoL

Kantarjian et al *NEJM* 2017

Efficacy of Blinatumomab in Acute Lymphpblastic Leukemia: results from four ph II trials



Gökbuget et al. *Blood* 2018

Gökbuget et al. *Haematol.* 2017

Topp et al. *Lancet Oncol.* 2015

Zugmaier et al. *Blood* 2015

Topp et al. *J Clin Oncol* 2014

Topp et al. *J Clin Oncol* 2011

Blinatumomab : Better Outcome in the MRD Setting

	MRD ALL BLAST N = 116	rrALL Expl Phase II N = 36	rrALL Conf Phase II N = 189	rr ALL TOWER N = 271
	Phase II	Phase II	Phase II	Phase III
RFS	18.9 months	7.6 months	5.9 months	-
OS	36.5 months	9.8 months	6.1 months	7.7 months

⇒ **Next steps**

⇒ **Integrating Blin into 1st line treatment to target MRD: ALL, DLBCL, MCL**

Gökbuget et al. *Blood* 2018

Kantarjian et al. *NEJM* 2017

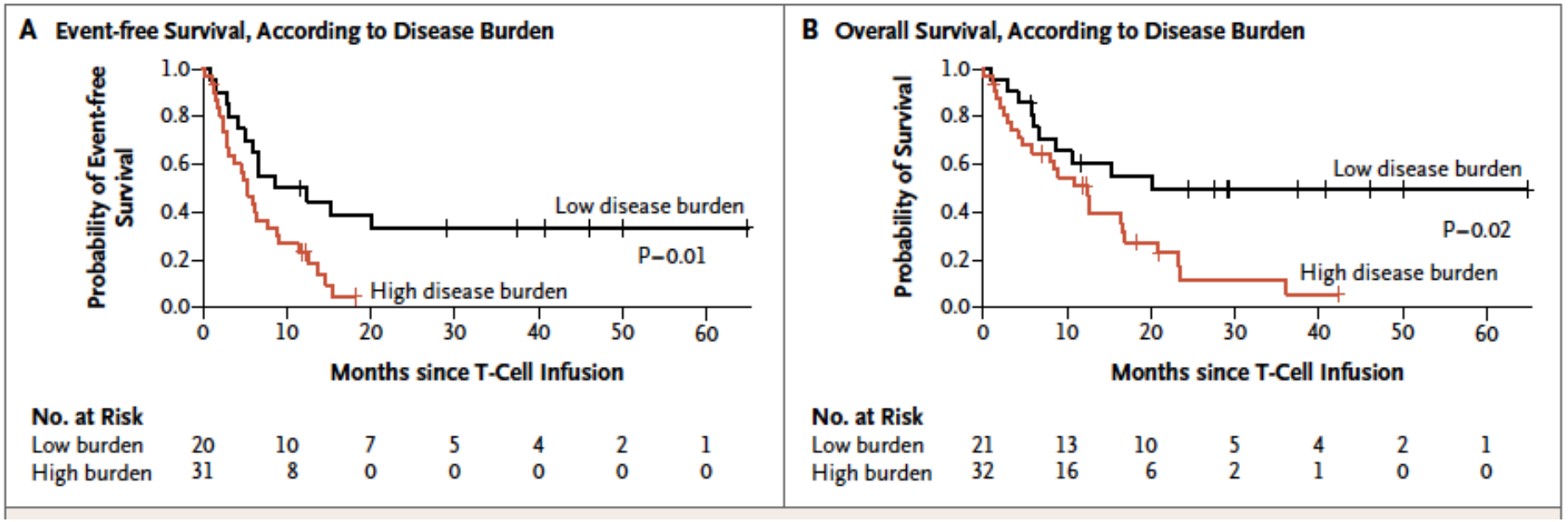
Topp et al. *Lancet Oncol.* 2015

Zugmaier et al. *Blood* 2015

Topp et al. *J Clin Oncol* 2014

Long-term survival of CD19 CAR T cell therapy in rr ALL: Results of a Phase I Trial

EFS and OS according to disease burden (high: > 5% blasts)



Park et al. *NEJM* 2018

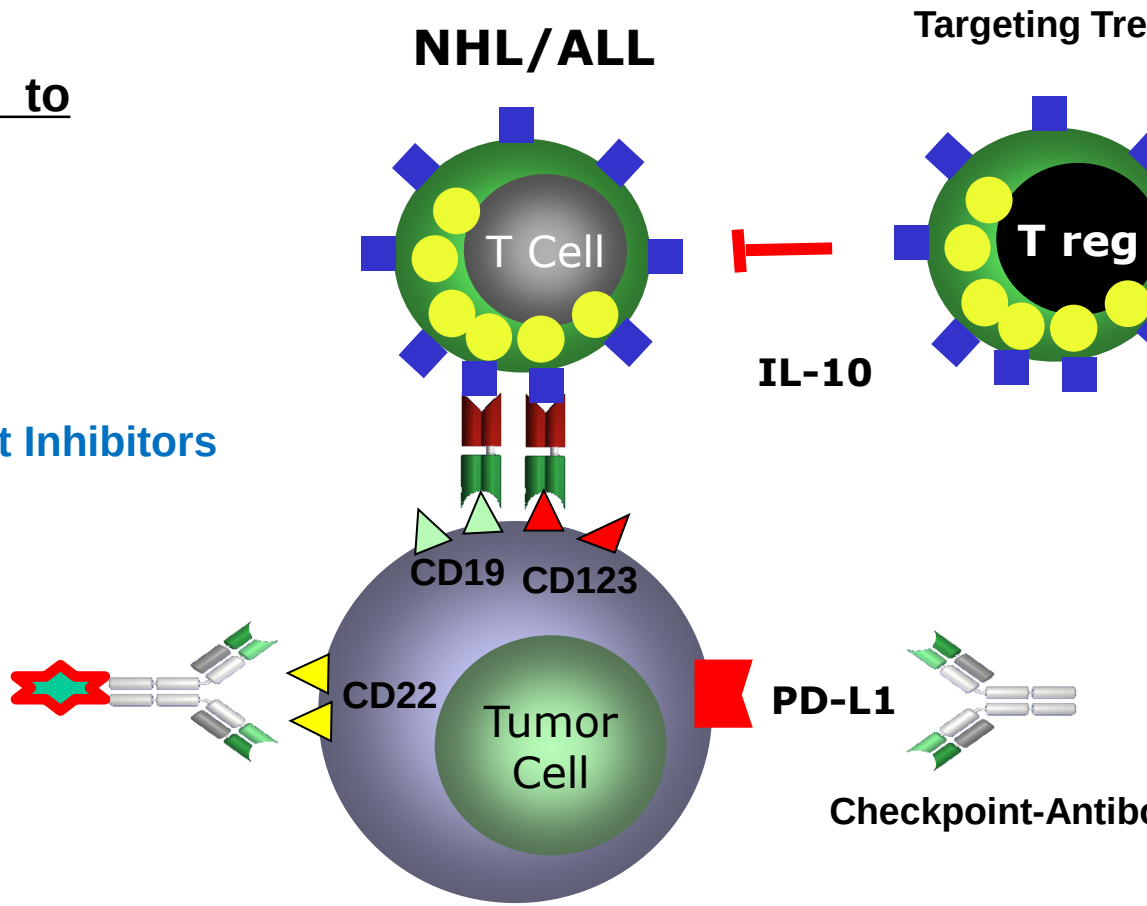
Multi-Targeting to overcome resistance

Immune escape/resistance to anti-CD19 BiTE

(1) Loss of target antigen

(2) Activation of T_{regs}

(3) Upregulation of Checkpoint Inhibitors



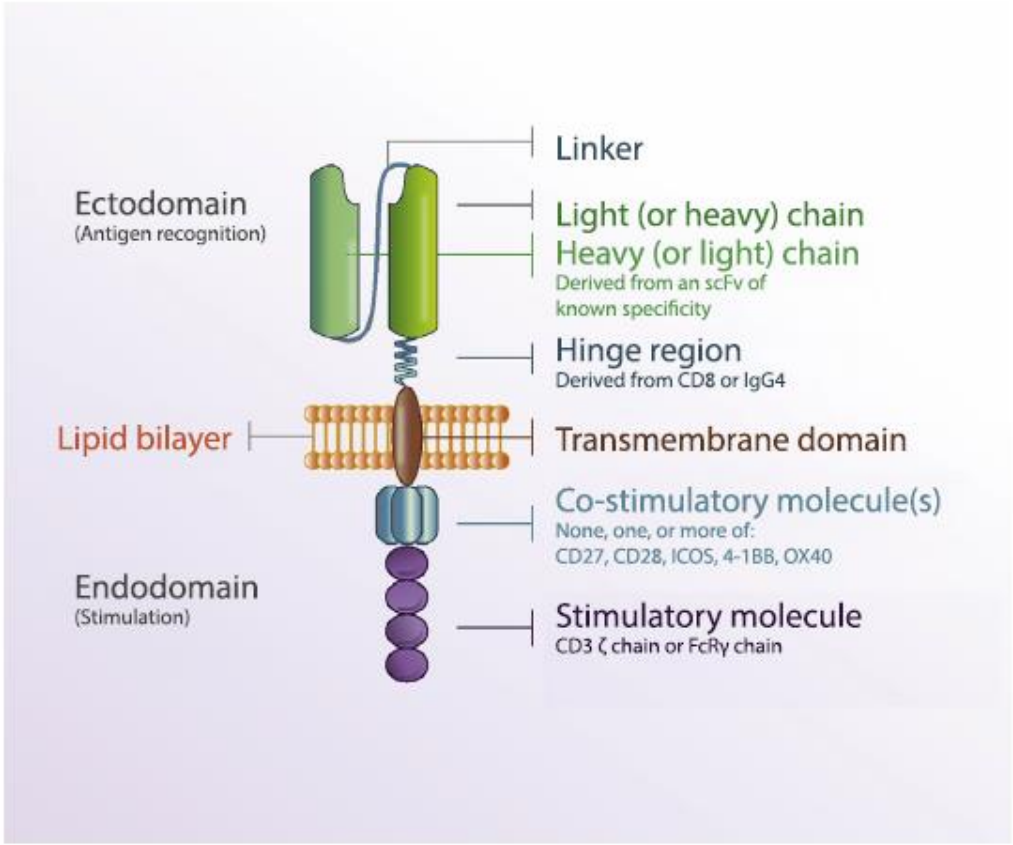
Braig Blood 2017
Duell Leukemia 2017
Topp Lancet Oncology 2015
Sotillo Cancer Discov. 2015
Köhnke Hematol. Oncol. 2015

Combinatorial Ph Ib Trials

e.g. BiTE + Checkpoint Ab

Does the CAR/BiTE approach work beyond CD19-positive diseases?

Anti-BCMA CAR-T Cells: Phase I in rr Multiple Myeloma

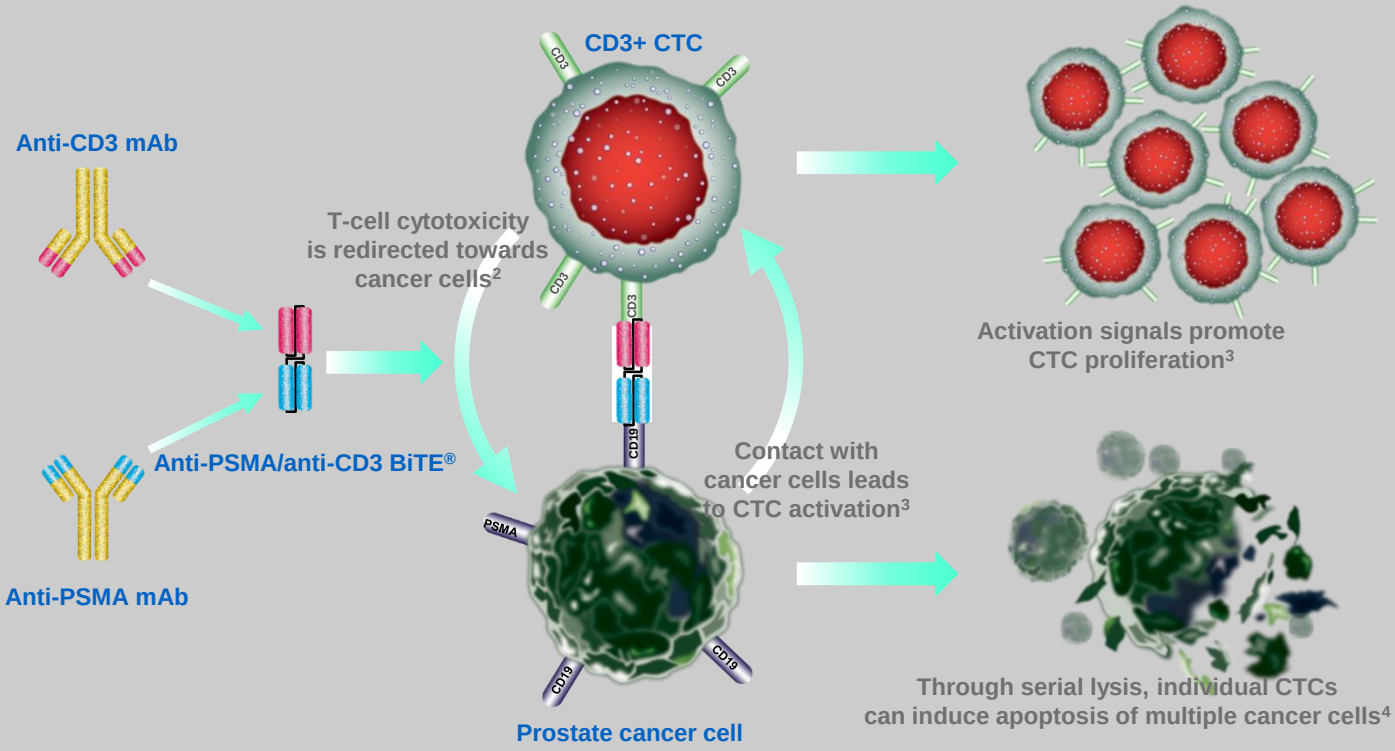


N=16: ORR 81%, 63% CR & VGPR

Brudno et al. *JCO* 2018

Efficacy in phase I for CARs/BiTEs also reported in AML (CD33, CD123)

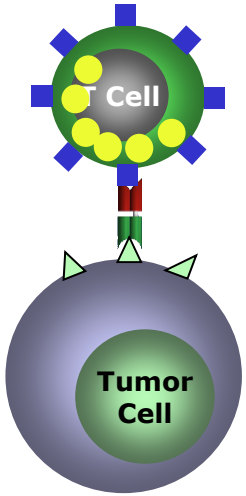
PSMA BiTE– First Results if a Phase I Trial in Patients with CR Prostate Cancer



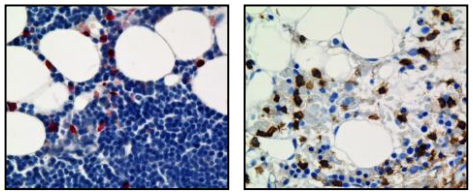
The BiTE Trial Program of the CCC Mainfranken

Genomic and immunological profiling

Preclinical Research	Phase-I and Phase II	Phase III, pivotal trials



NHL and ALL



Blinatumomab:

Approval for r/r ALL
2014- 2016 (FDA & EMA)

Approval for MRD ALL
2018 (FDA)

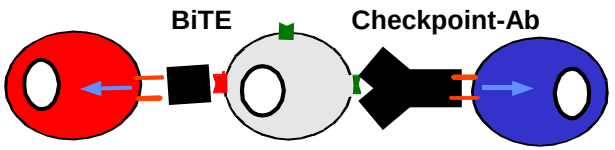
Phase I program:

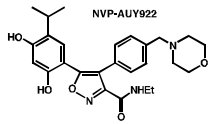
Prostate Cancer (PSMA)
CRC, Lung Cancer (EpCAM)
Lung Cancer (DLL-3)
Glioblastoma (EGFRvIII)
Her2-pos. Solid Tumors
Multiple Myeloma (BCMA)

GEMoaB Trials:

AML (CD33)

Combinatorial approaches





Small Molecules

New Developments in the Field - Future Directions

- Developing strategies mitigating neurotox -> higher dosing? -> improved efficacy? -> higher cure rates? - blinatumomab

- More convenient administration mode - e.g. half time extended BiTEs

- Combinatorial trials: targeting antigen escape and T cell exhaustion
  e.g. BiTEs + checkpoint antibodies, multi-targeting

- Targeted therapy of minimal residual disease beyond ALL
  (e.g. NHL, AML, localized HR Prostate Cancer)

- Efficacy & relevance of BiTEs &CARs in solid tumors - e.g. PSMA BiTE

Acknowledgements “Preclinical Work“

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Acknowledgements “NHL Trials“

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