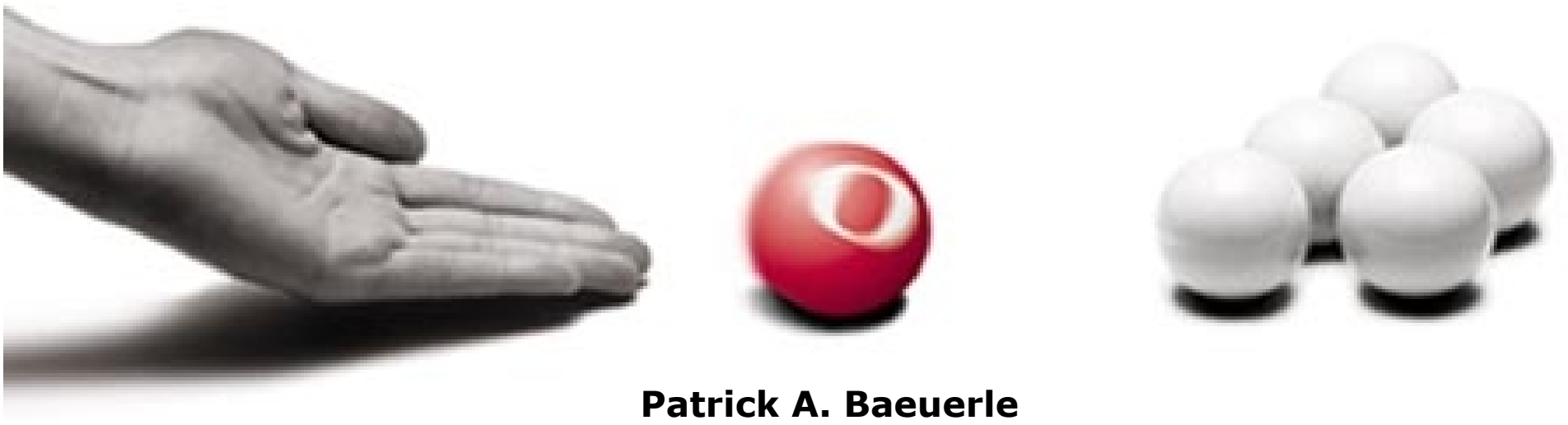
T Cell-engaging Antibodies for Cancer Therapy

iSBTc Workshop on Monoclonal Antibodies in Cancer

Washington DC, October 1, 2010



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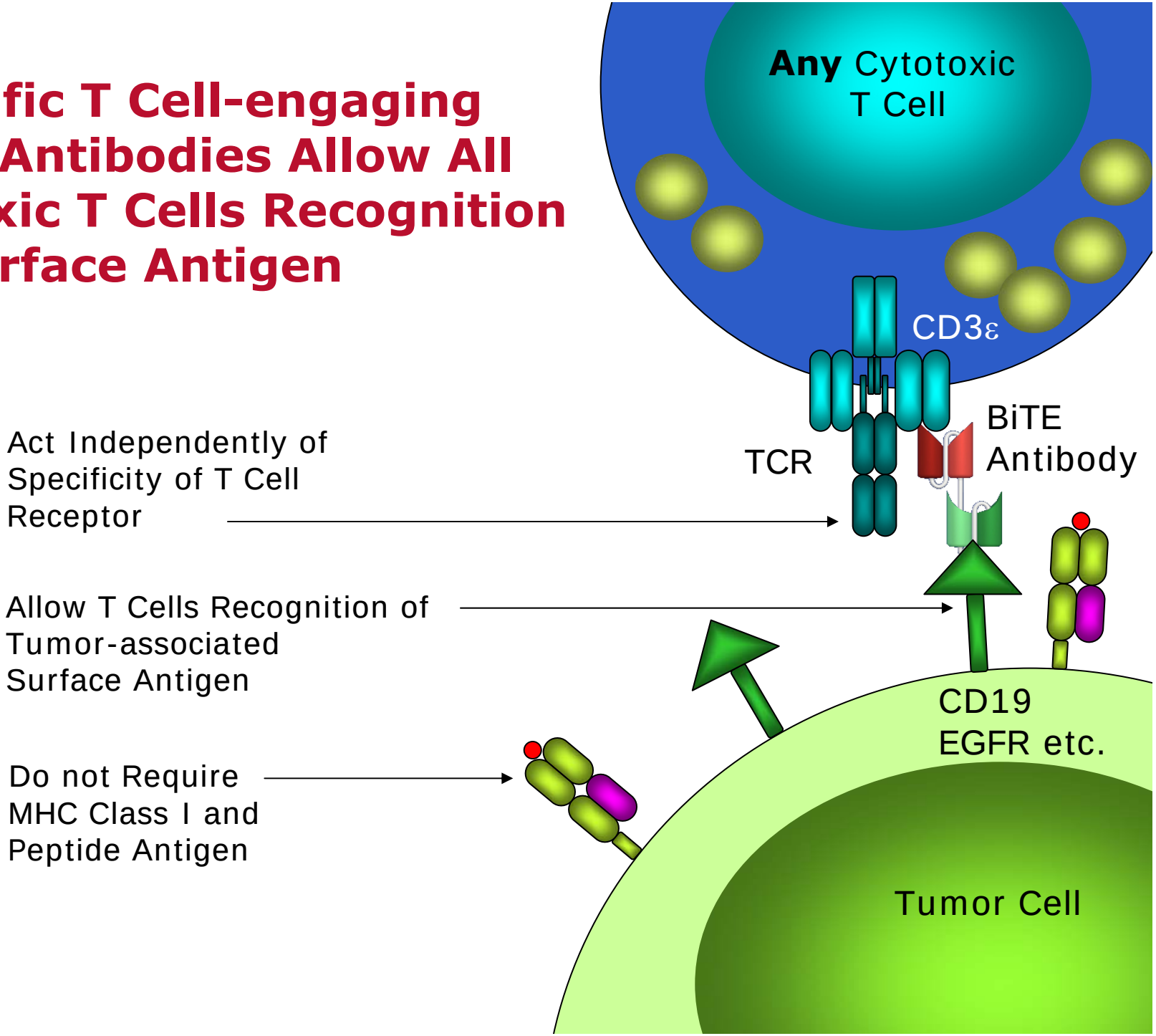
Bispecific T Cell-engaging (BiTE) Antibodies Allow All Cytotoxic T Cells Recognition of a Surface Antigen

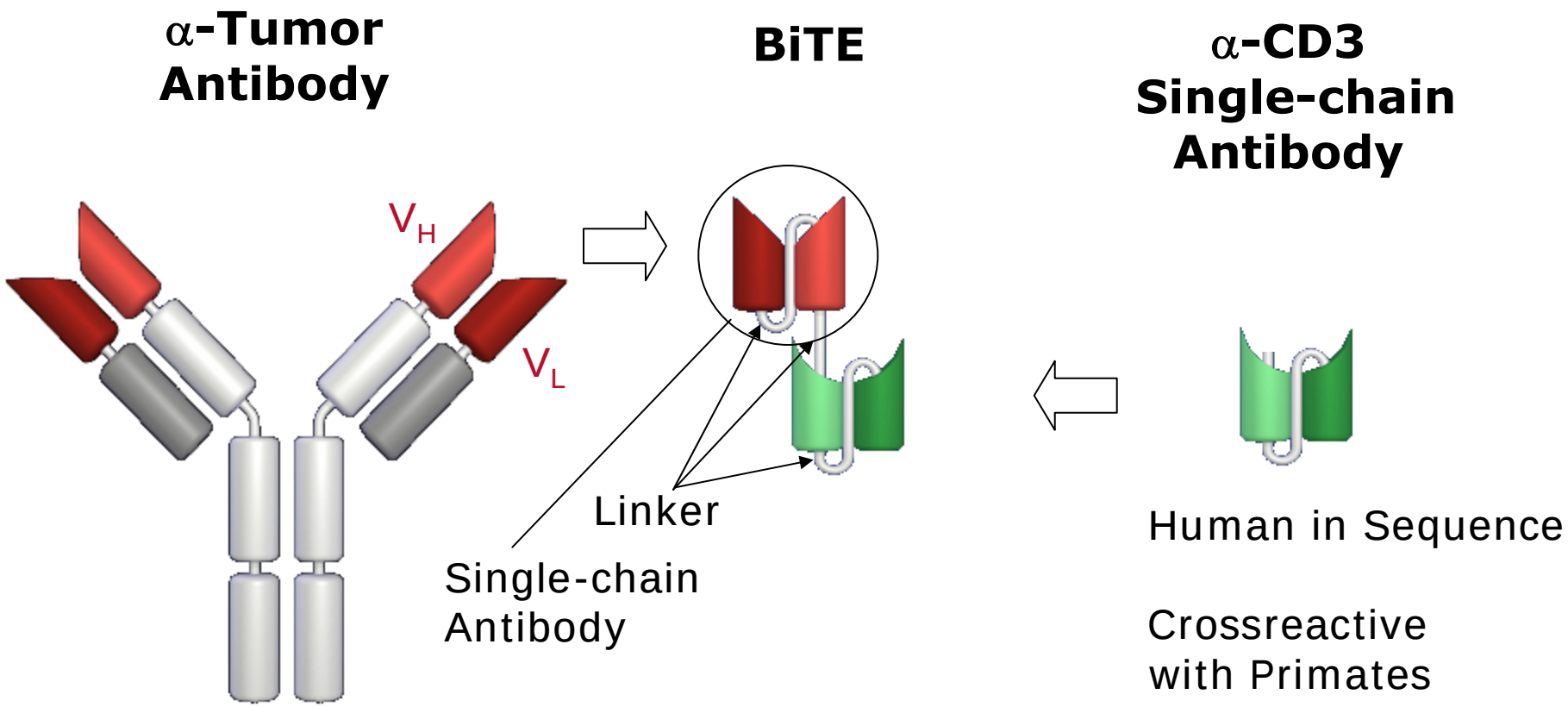


Act Independently of Specificity of T Cell Receptor

Allow T Cells Recognition of Tumor-associated Surface Antigen

Do not Require MHC Class I and Peptide Antigen

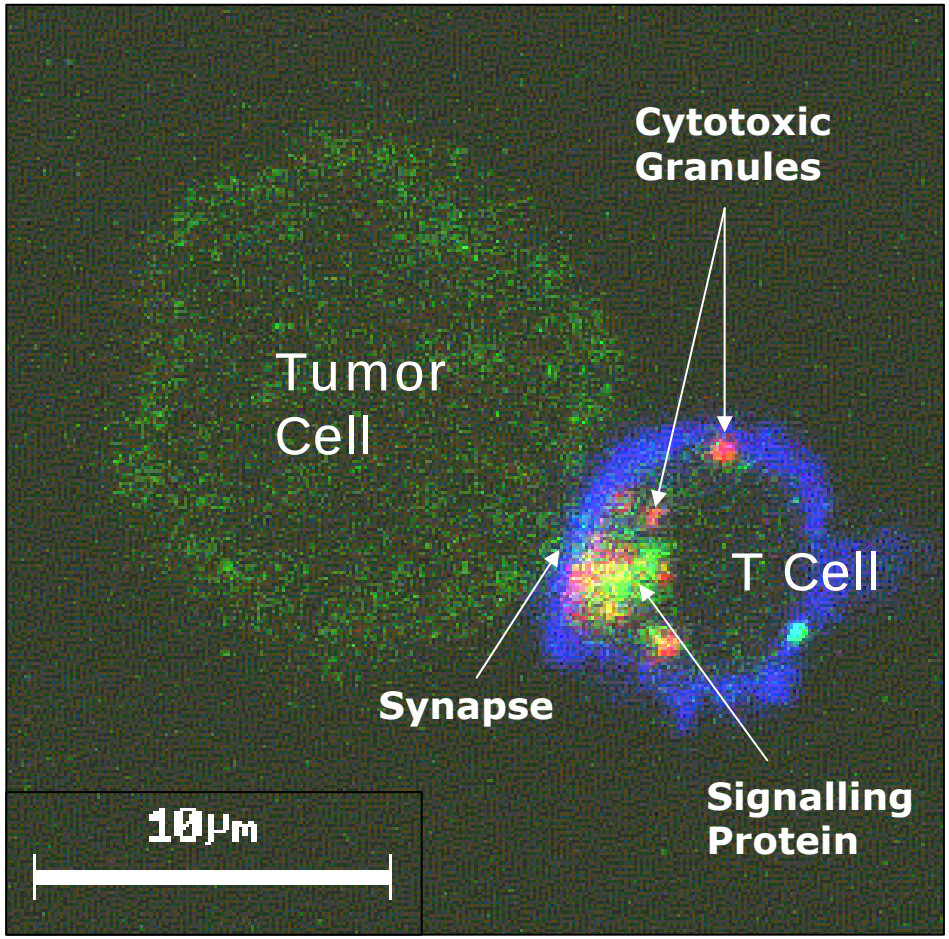
BiTE Technology Teaches Antibodies to Engage T Cells



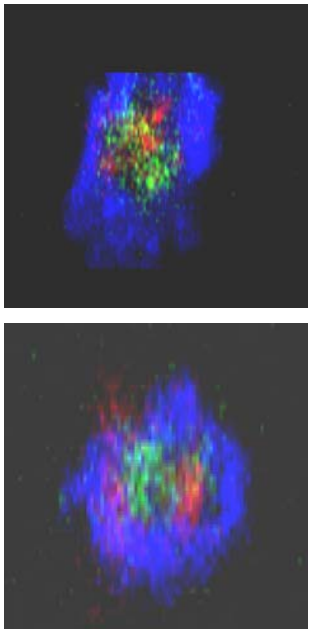
BiTE-engaged T Cells Form Cytolytic Synapses

Offner, S. et al. *Mol. Immunol.* **43**: 763-771 (2006)

Confocal Microscopy



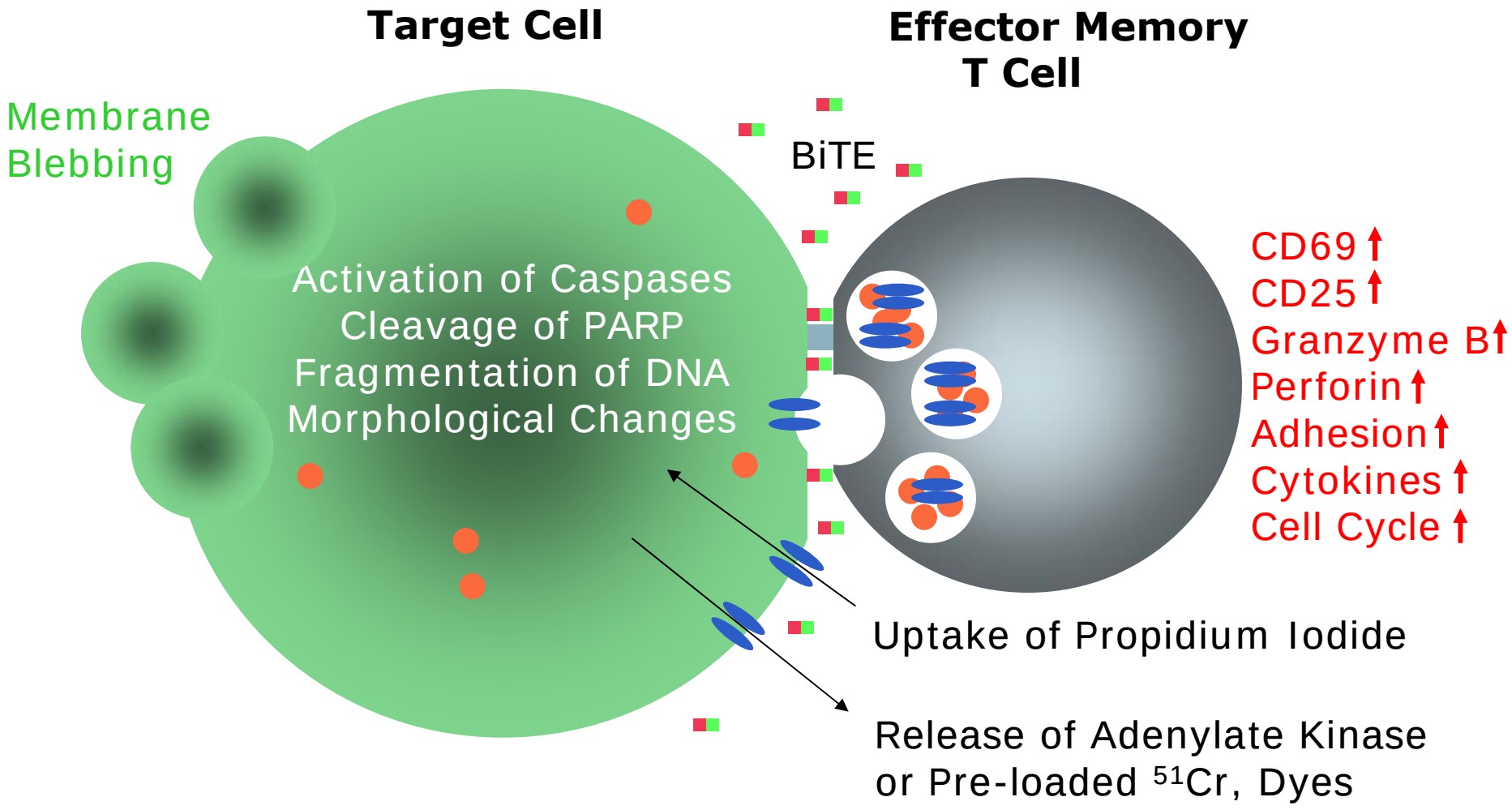
Synapses



Stainings:
Perforin
Lck
LFA-1 (CD11a)

BiTE Mode of Action

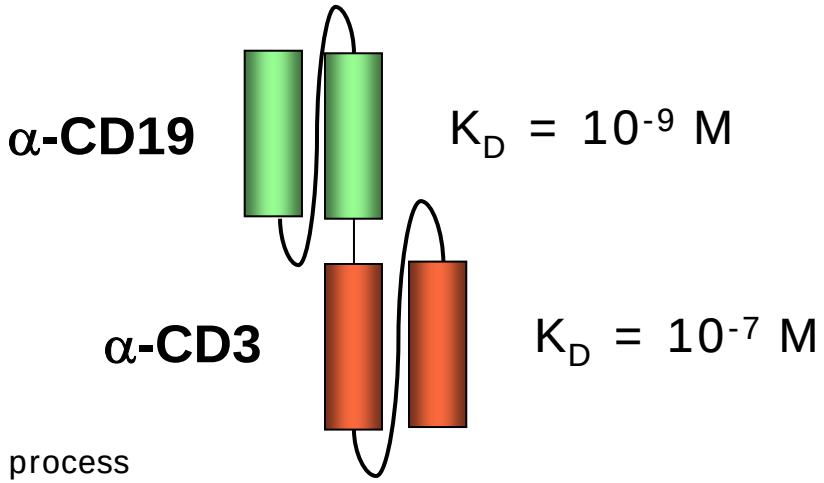
Haas, C. et al. *Immunobiol.* **214**: 441-453 (2009)



Clinical Proof of Concept with CD19/CD3-bispecific BiTE Antibody Blinatumomab (MT103)

Blinatumomab: First BiTE to Enter Clinical Trials

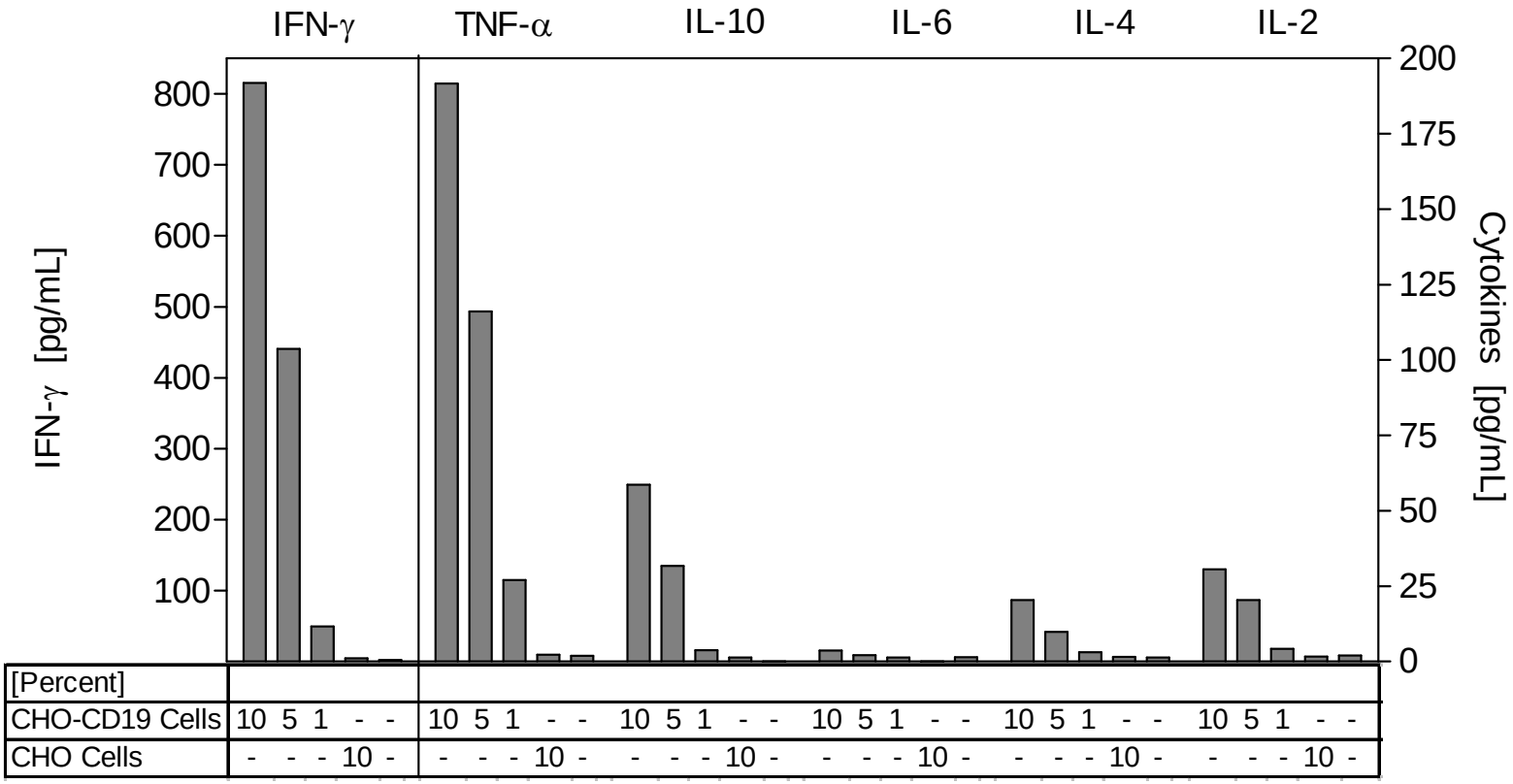
- **Bispecific for CD19 and CD3**
- **CD19 is pan-B cell antigen absent from stem cells and plasma cells but present on most human B cell malignancies**
- **Ongoing phase 1 trial in patients with refractory/relapsed non-Hodgkin's lymphoma (NHL)**
- **Completed phase 2 study in patients with minimal residual B-precursor acute lymphocytic leukemia (B-ALL)**
- **Initiated pivotal study in minimal residual B-ALL, and phase 2 study in relapsed/refractory ALL of adults**



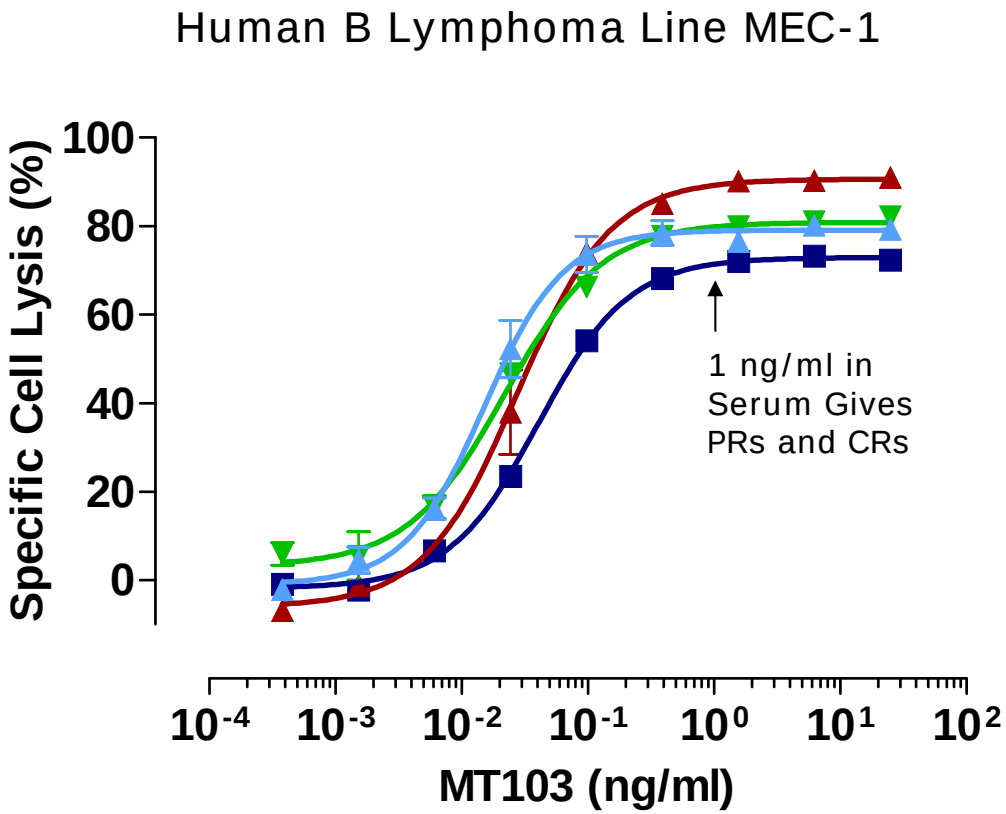
Mol. Wt.: 55 kDa
T1/2 β: ca. 2 h
Produced by CHO cell-based process

Cytokine Release from T Cells by Blinatumomab Is Dependent on CD19-expressing Target Cells

Brischwein K. et al., *J. Immunother*. **30**:798 (2007)



Blinatumomab Triggers Potent Lysis of Lymphoma Cells by Previously Unstimulated Human T Cells



4 Human T Cell Donors Tested

- PBMC 381
- PBMC 511
- PBMC 515
- ABi 014

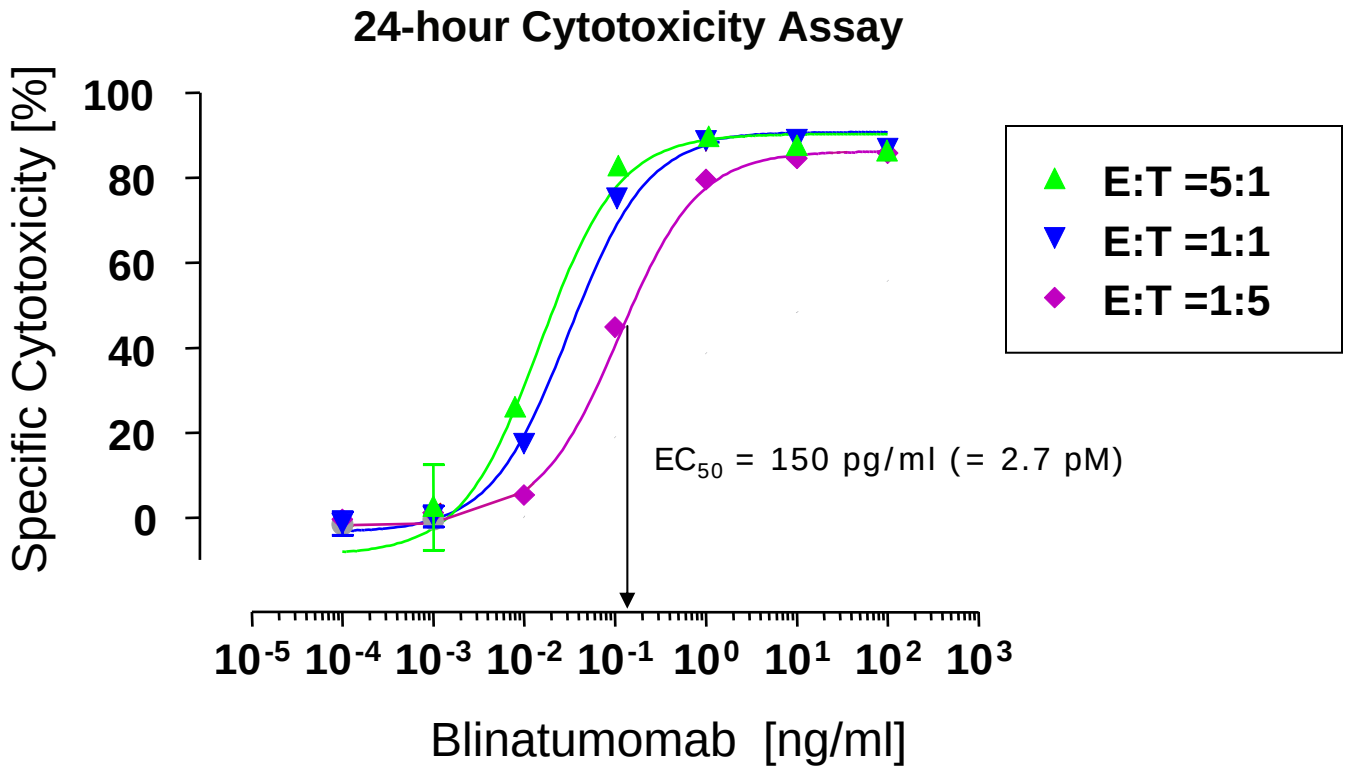
E:T ratio = 10:1
Assay time: 24 Hour s
Target: Cells: MEC-1 labelled with PKH-26

EC_{50} Range: 15–40 pg/ml = 0.27 - 7.2 pM

Serial Lysis by Blinatumomab-Engaged T Cells

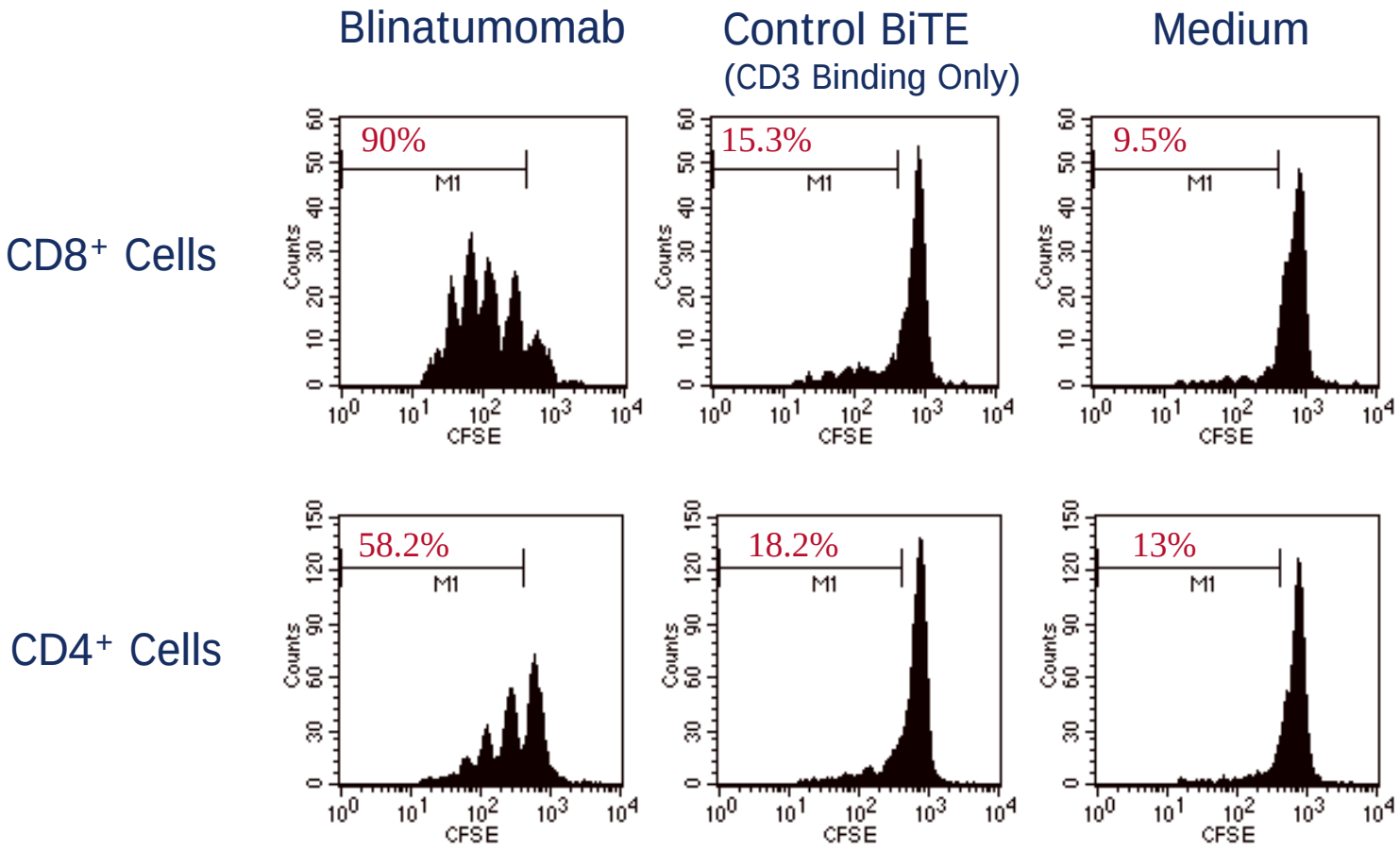
Hoffmann, P. et al., *Int. J. Cancer* (2005)

Effector (E) = Unstimulated human $CD8^+$ T Cells
Target (T) = Human Pre-B ALL Line NALM-6



Blinatumomab Induces T Cell Proliferation

Brandl et al., *Cancer Immunol. Immunother.* **56**:1551 (2007)



Key Hallmarks of Blinatumomab and Other BiTE Antibodies

- **Strictly target cell-dependent activation of resting T cells**
  - Monovalent binding of BiTE to CD3 does not activate TCR complex
- **Highly potent redirected lysis of target cell**
  - At femtomolar concentrations
  - $CD8^+$ $CD4^+$ and effector memory T cells contribute
  - Lysis of dividing and non-dividing target cells
- **Serial lysis by BiTE-activated T cells**
  - Activity at low E:T ratios <1
- **Proliferation of BiTE-activated T Cells**
  - Contribution to in-vivo efficacy
- **No internalization of target antigens or CD3**
  - Monovalent binding does not modulate surface expression

Ongoing Phase 1 Study in NHL Patients with Blinatumomab

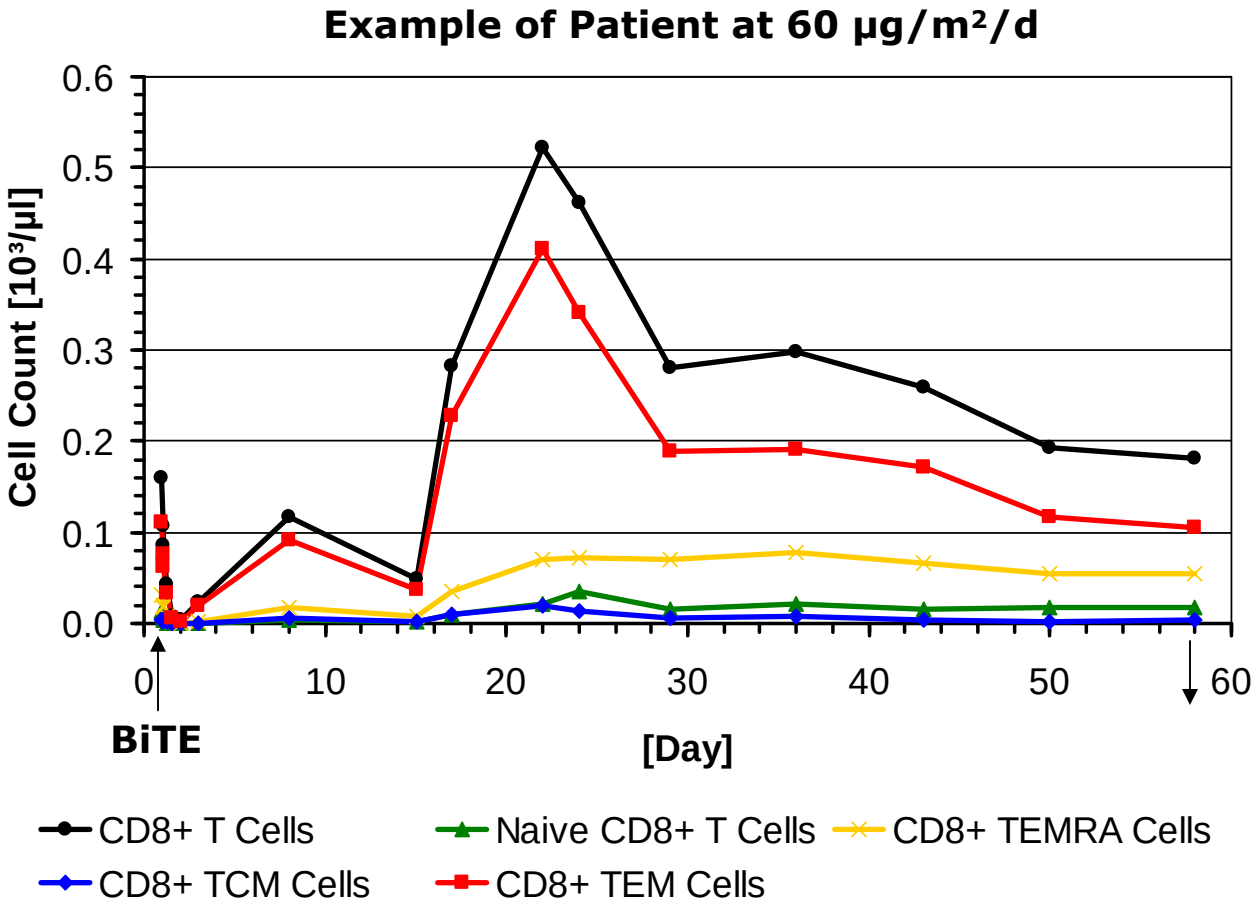
- **Study Population**
  - Relapsed/refractory NHL patients
  - Mostly follicular and mantle cell lymphoma
  - Median of 3 previous chemo/immunotherapies (some up to 12)
  - 86% pretreated with rituximab (up to 3 different rituximab-based single agent or combination regimens per patient)
- **Design**
  - 3+3 patient dose escalation
  - Thus far dose levels ranging from 0.0005 – 0.090 mg/m^2 per day
  - Continuous i.v. infusion via port with portable pump over 4-8 weeks (out-patient as of week 3)
  - Steroids at infusion start
  - Objectives: Safety and tolerability, PK, PD, anti-tumor activity

Safety of Blinatumomab in NHL Patients

- To date, no cytokine storm, no autoimmunity, no lymphoproliferative disorder, no immune response to drug, no drug-related death
- Most frequent clinical adverse events (AEs) were flu-like: Pyrexia, chills, headache
- Most freqent laboratory AEs were as expected by mode of action: Lymphopenia and leukopenia
- Dose-dependency for certain AEs, e.g., pyrexia, chills, and CRP and D dimer increases
- 50% frequency of AEs during first three days, 50% during following 4-8 weeks (first dose phenomena)
- Most significant AEs leading to discontinuation were CNS-related AEs, such as aphasia, confusion, ataxia, seizure; occur shortly after treatment start; all fully reversible within days; no findings by MRI
- CNS events predominantly seen in patients with very low peripheral B cell counts (=> biomarker)
- CNS events can be mitigated by sneak-in dosing regimen

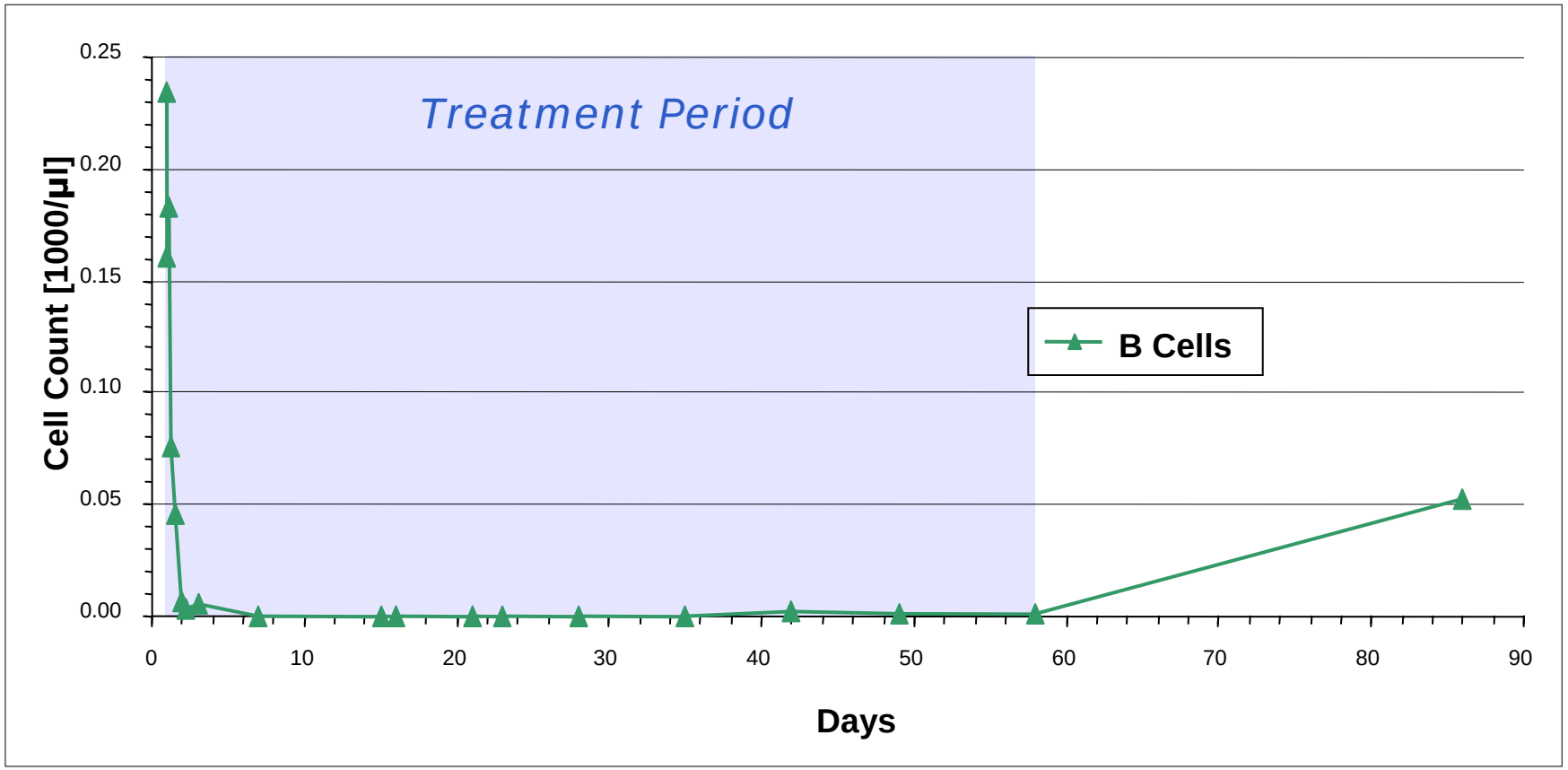
Activation and Selective Expansion of Effector Memory T Cells upon Start of BiTE Infusion

Bargou, R. et al. *Science* **321**: 974-977 (2008)

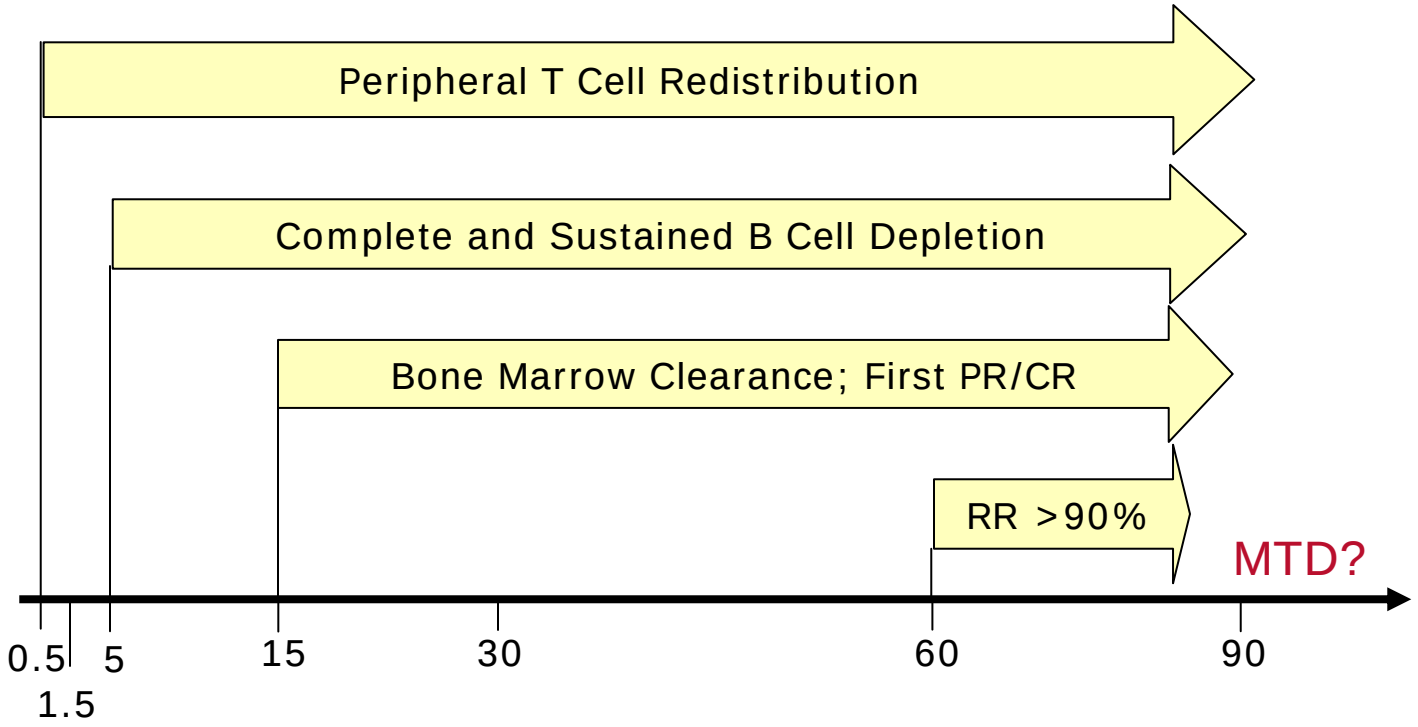


B Cell Depletion in Patient with Mantle Cell Lymphoma

Dose Level: 30 µg/m²/24 h



Dose-dependent Activity of Blinatumomab in NHL Patients



Dose-dependent Clinical Responses in NHL Patients in a Phase 1 Study (ASH Dec. 2009)

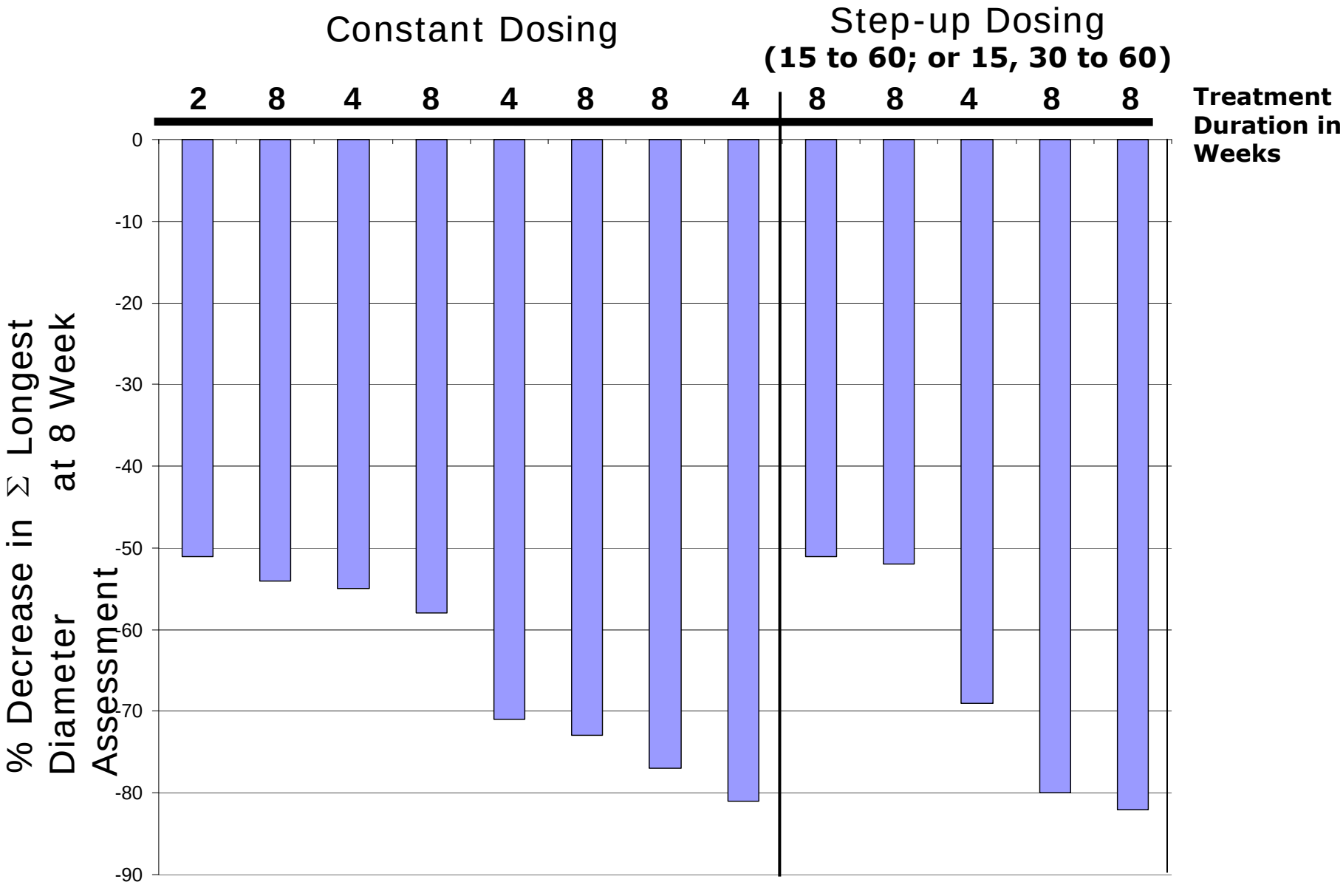
- By Cheson criteria and independent review of CT scans
- Mainly follicular and mantle cell lymphoma (MCL) patients

Dose Level	Patients (N = 50)	Complete Response	Partial Response	Overall Response Rate
0.5, 1.5 and 5 µg/m^2 per Day	13	0	0	0/13
15 and 30 µg/m^2 per Day	20	2	2	4/20
60 µg/m^2 per Day	13	5	7	12/13*
90 µg/m^2 per Day	4	1	1	2/4#

***One patient not evaluable due to treatment discontinuation after 2 days**
#Two patients not evaluable due to DLTs

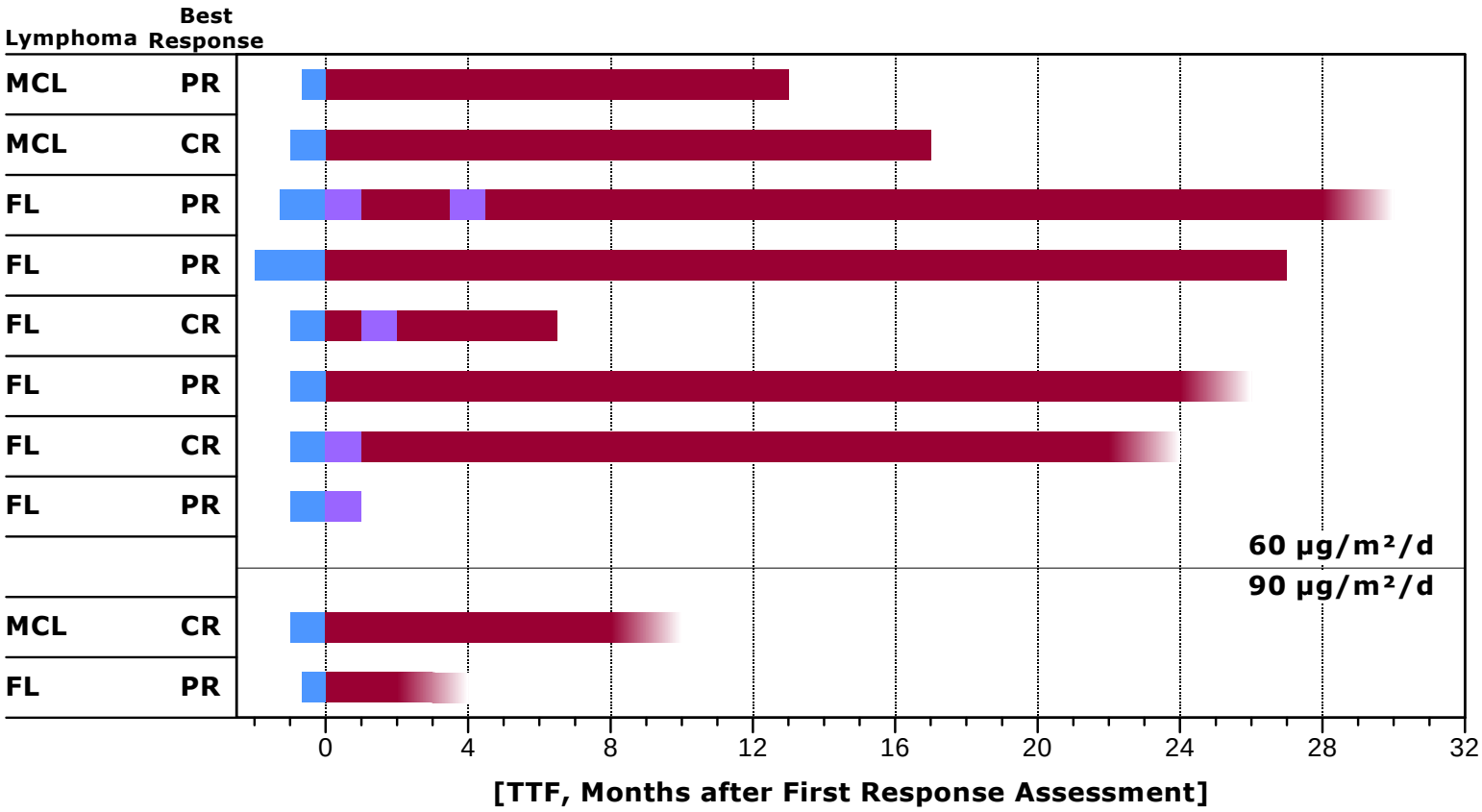
Response Assessment at 60 µg/m²/d

(EHA June 2010)



Durability of Responses in FL and MCL for Constant Dosing at 60 and 90 µg/m² per Day

EHA June 2010



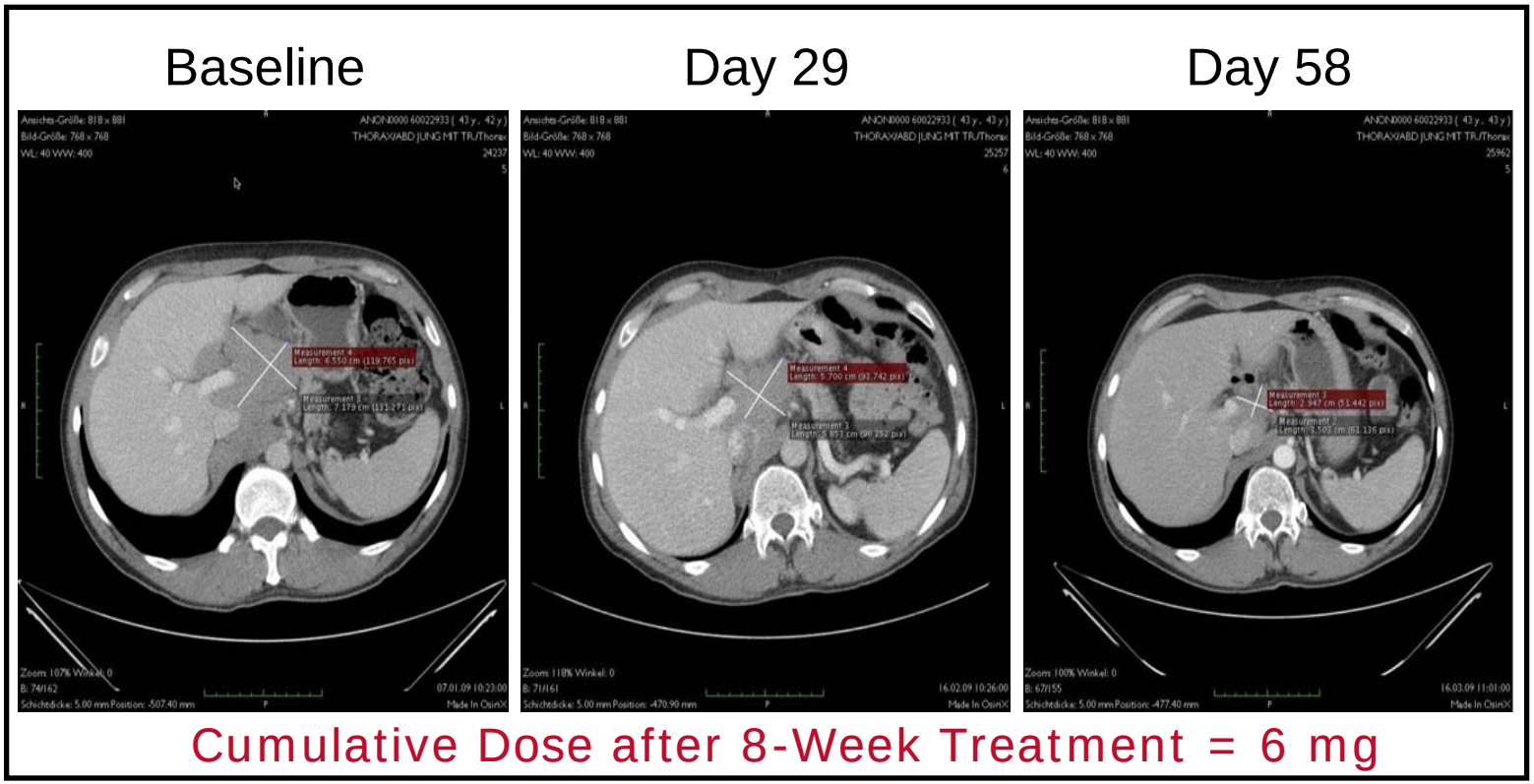
Responses at 60 µg:
- Median duration 21+ months
- Duration up to 30 months
- 4 patients = 2 years duration
- Three out of 8 ongoing

Responses at 90 µg:
- Two out of 2 ongoing

Treatment/Treatment in Response
Duration
Ongoing Response

Response in a Patient with Bulky Mantle Cell Lymphoma

- **Patient with MCL, stage IV A, 42 years, male**
- **Blinatumomab treatment at 60 µg/m²/d (monotherapy)**



Status of Phase 1 Study in NHL Patients

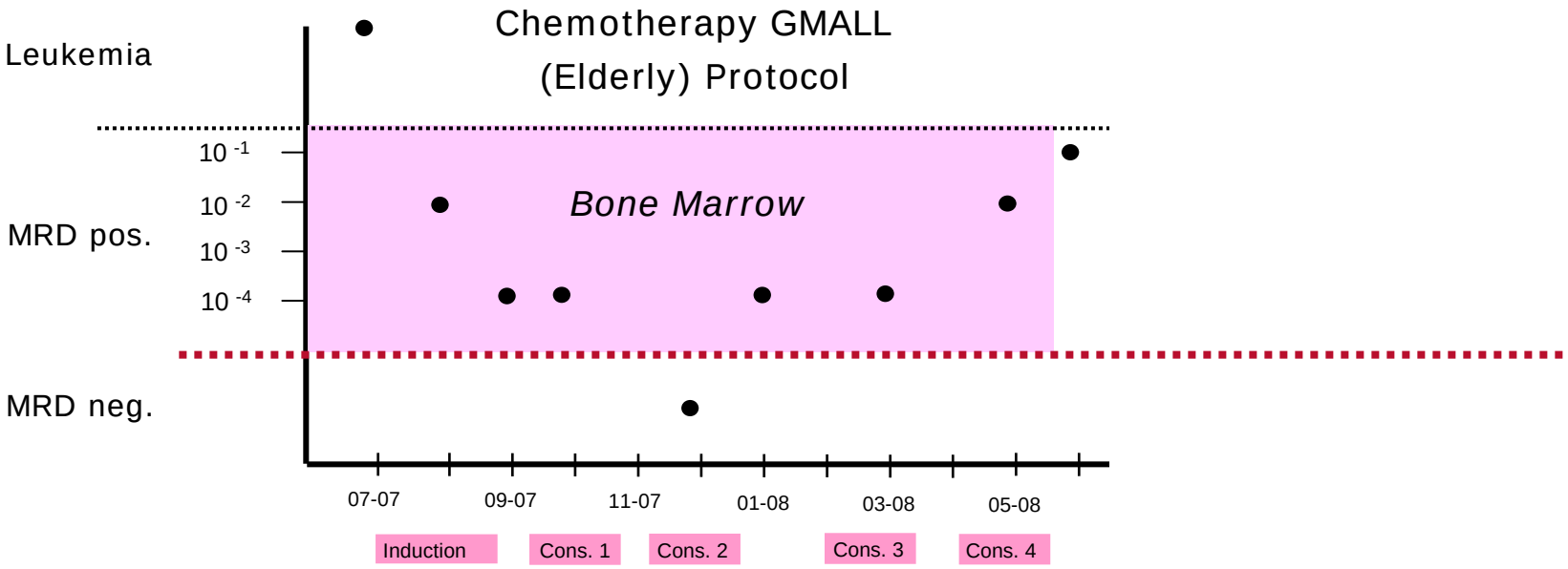
- **Favorable safety profile**
- **Very high response rate at dose levels ≥60 µg/m^2 per day**
- **Ongoing responses in half of the patients without further treatment or alternative therapies**
- **Study ongoing for optimization of dose and schedule and for exploration of other CD19$^+$ B cell malignancies**

Completed Phase 2 Study in Patients with B-lineage Leukemia (B-ALL)

- Patient population: B-ALL patients with high risk of relapse due to remaining bone marrow disease after standard therapy (= minimal residual disease; MRD); detectable by PCR
- Patients treated: 21, with the following MRD marker:
  - Bcr/abl neg. (individ. rearrangements) 14 patients
  - Bcr/abl neg., t(4;11) 2 patients
  - Bcr/abl pos. 5 patients
- Median age: 48 y (20-77); 12 female, 9 male patients
- Dosing: 15 μg blinatumomab/m²/day by repeated 4-week continuous infusions; at least 3 consolidation cycles *post* positive MRD response with 2-week intervals
- Prior treatment: At least induction/consolidation chemotherapy I (some up to consolidation V)
- 17 patients had never achieved MRD negativity on prior treatments

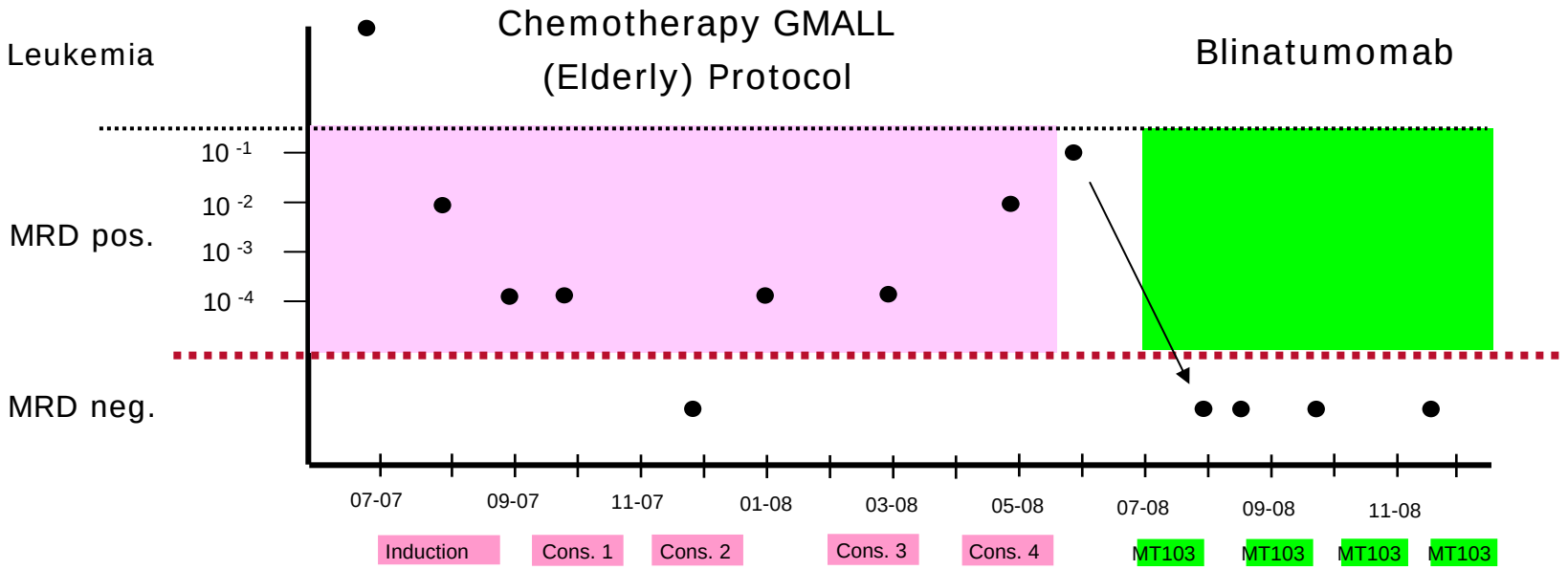
Course of Minimal Residual Disease During Frontline Consolidation Chemotherapy of ALL

Example of Patient #109-002



Effective Treatment of Minimal Residual Disease (MRD) with Blinatumomab

Patient #109-002



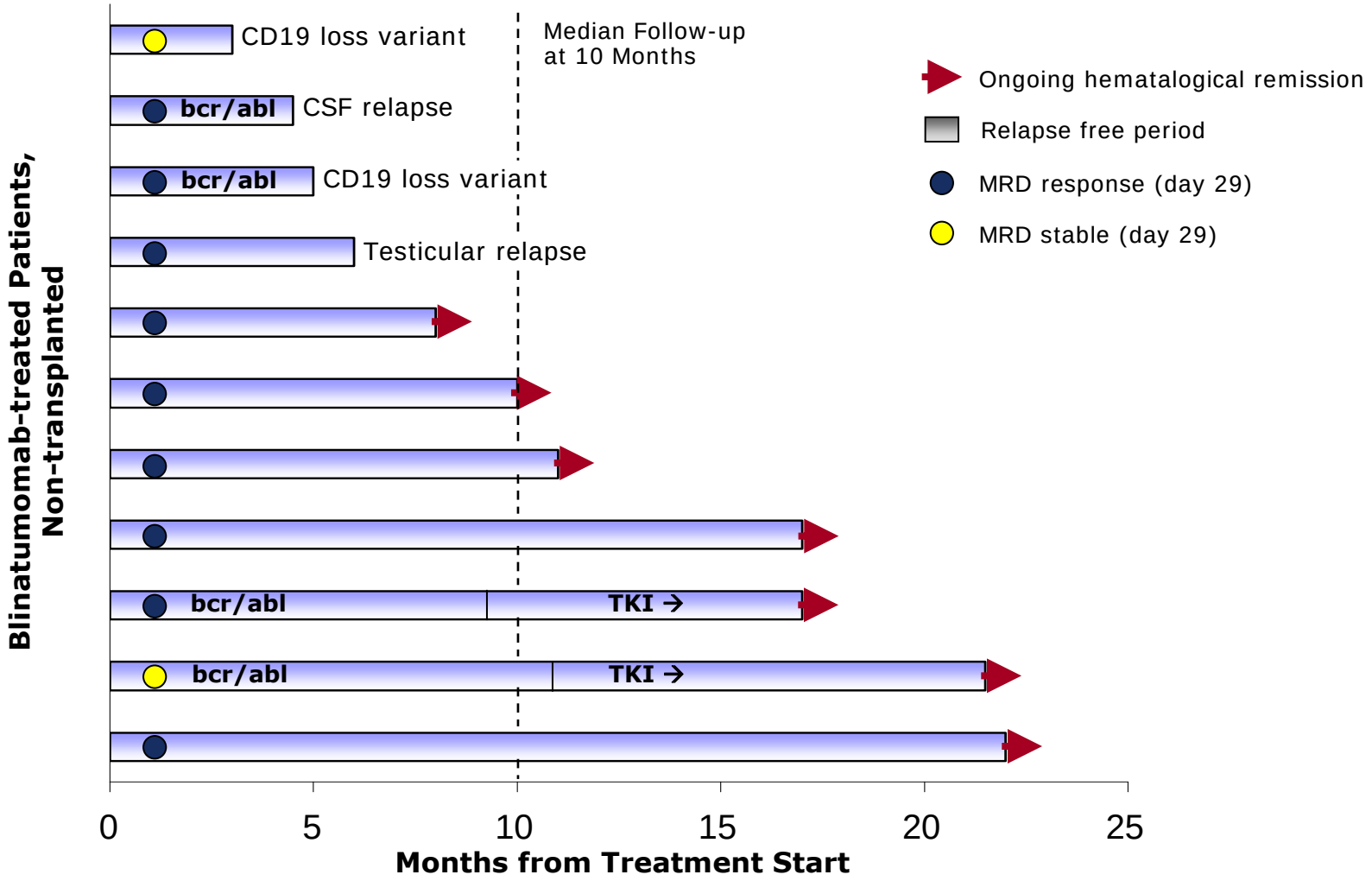
Response Data

Number of Patients Included in Study	Number of Patients Evaluable for Response Assessment	Number of Patients Reaching MRD Negativity	**MRD Response Rate**
21	20*	16	**80%**

*One patient not evaluable due to less than one treatment cycle and lack of response assessment

Hematological Relapse-Free Survival

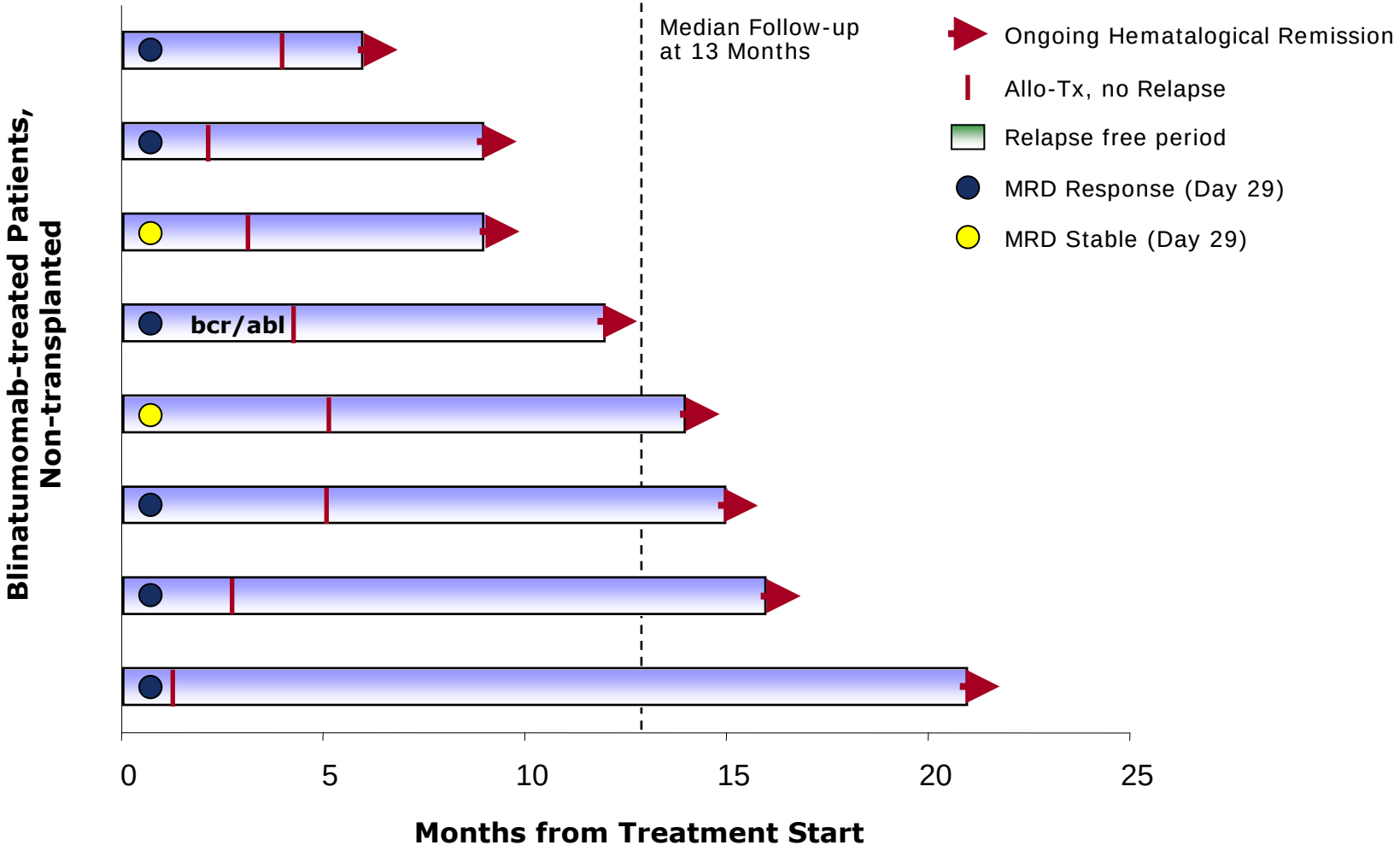
Non-transplanted Patients (EHA 2010)



- One patient was not evaluable due to early treatment stop (AE), one patient (who responded to treatment) withdrew consent
- TKI – tyrosine kinase inhibitor given at indicated time
- Current median relapse-free survival (RFS) is 10+ months

Hematological Relapse-Free Survival

Transplanted Patients (EHA 2010)



- Blinatumomab provides an active therapy that permits time to arrange for allogeneic transplant
- Patients receiving blinatumomab prior to transplant tolerate allogeneic transplant well
- Current median RFS is 13+ months; no clinical relapses encountered to date

Summary of Phase 2 Study in Patients with Minimal Residual B-lineage ALL (EHA 2010)

- **Complete molecular response in 80% (16 out of 20) of evaluable ALL patients**
- **Relapse free survival (RFS) so far up to 22 months, and ongoing; no median reached after 408 days; historical median RFS in this patient population is only 200 days**
- **Responses also observed in patients with tyrosine kinase inhibitor-refractory bcr/abl ($T_{315}I$), and with (4;11) translocation**
- **No mortality upon subsequent transplantation (N=8)**
- **Very favorable safety profile**

BiTE Antibodies Can Use Many Targets

BiTE Target (Development Partner)	Indication/Target Tissue	Developmental Status
CD19	**B cell malignancies and disorders**	**Pivotal**
EpCAM	**EpCAM$^+$ solid tumors**	**Phase 1**
CEA (MedImmune/AZ)	**CEA$^+$ solid tumors**	**Pre-clinical**
N.d. (Bayer Schering Pharma)	**Solid tumors**	**Pre-clinical**
N.d. (Sanofi-aventis)	**Solid tumors**	**Pre-clinical**
N.d. (Boehringer Ingelheim)	**Multiple myeloma**	**Pre-clinical**
EGFR	**EGFR$^+$ solid tumors**	**In-vivo PoC (monkey, mouse)**
CD33	**AML, CML, MDS**	**In-vivo PoC (monkey, mouse)**
MCSP	**Melanoma**	**In-vivo PoC (monkey, mouse)**
EphA2	**EphA2$^+$ solid tumors**	**In-vivo PoC (mouse)**
PSCA	**Prostate cancer**	**In-vitro activity shown**
FAP-alpha	**Sarcoma, stromal fibroblasts**	**In-vitro activity shown**
IGF-1R	**IGF-1R$^+$ solid tumors**	**In-vitro activity shown**
Her-2/neu	**Breast and gastric cancer**	**In-vitro activity shown**
Endosialin	**Neovasculature**	**In-vitro activity shown**
Carboanhydrase IX	**Renal cancer**	**In-vitro activity shown**
cMet	**cMet$^+$ solid tumors**	**In-vitro activity shown**

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