Chimeric Antibodies in AML: Hope or Reality

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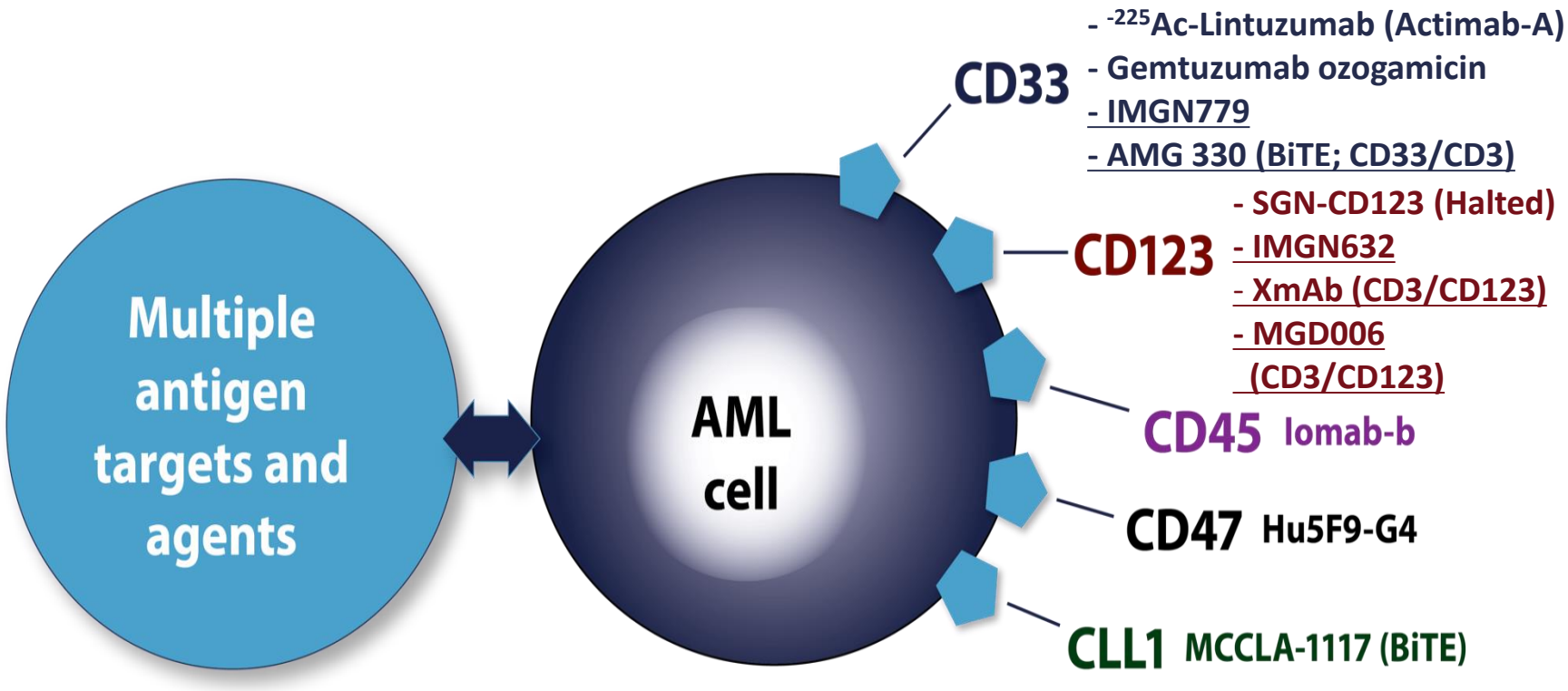
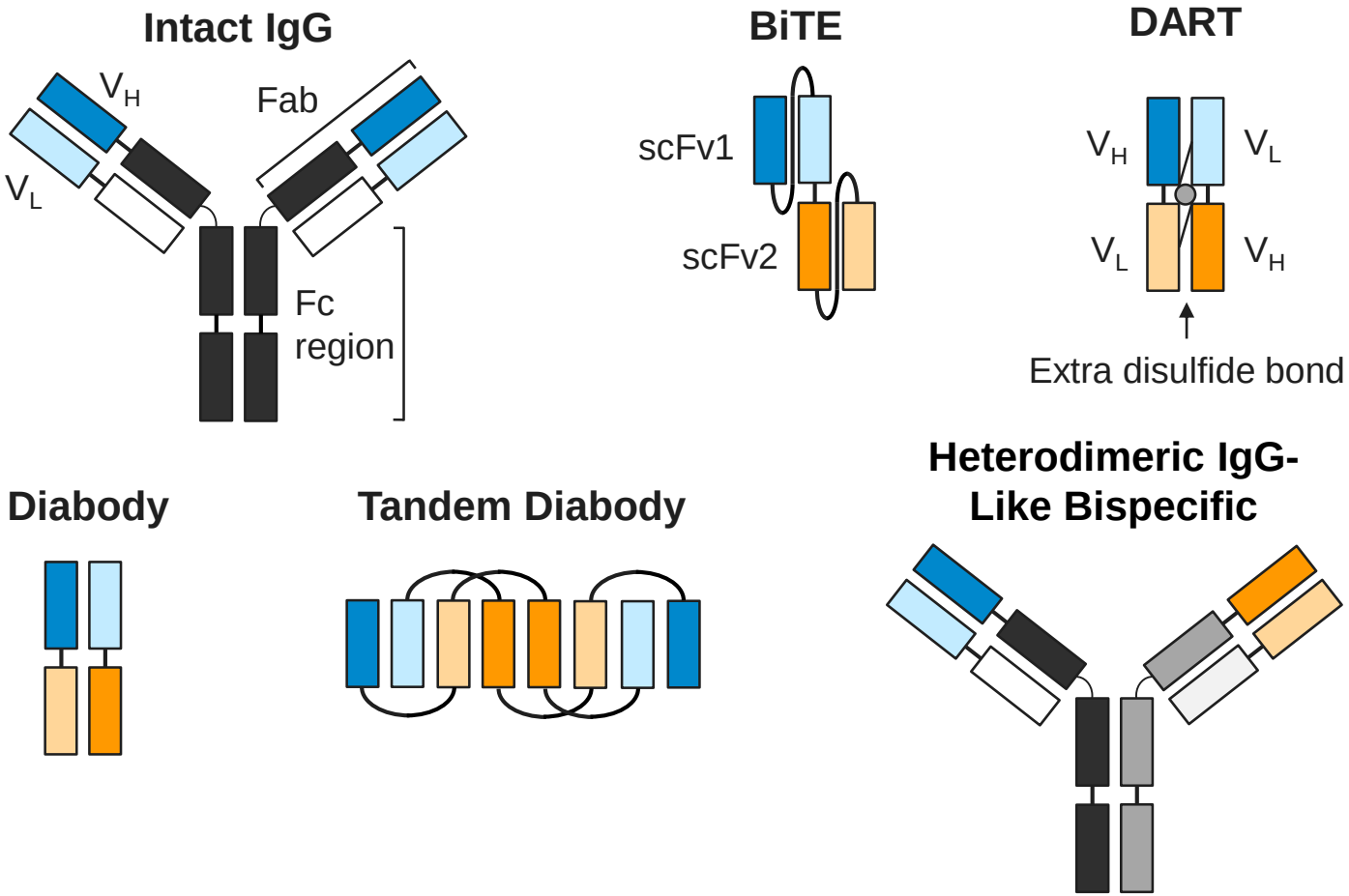
Target Antigens and Novel Antibodies in AML



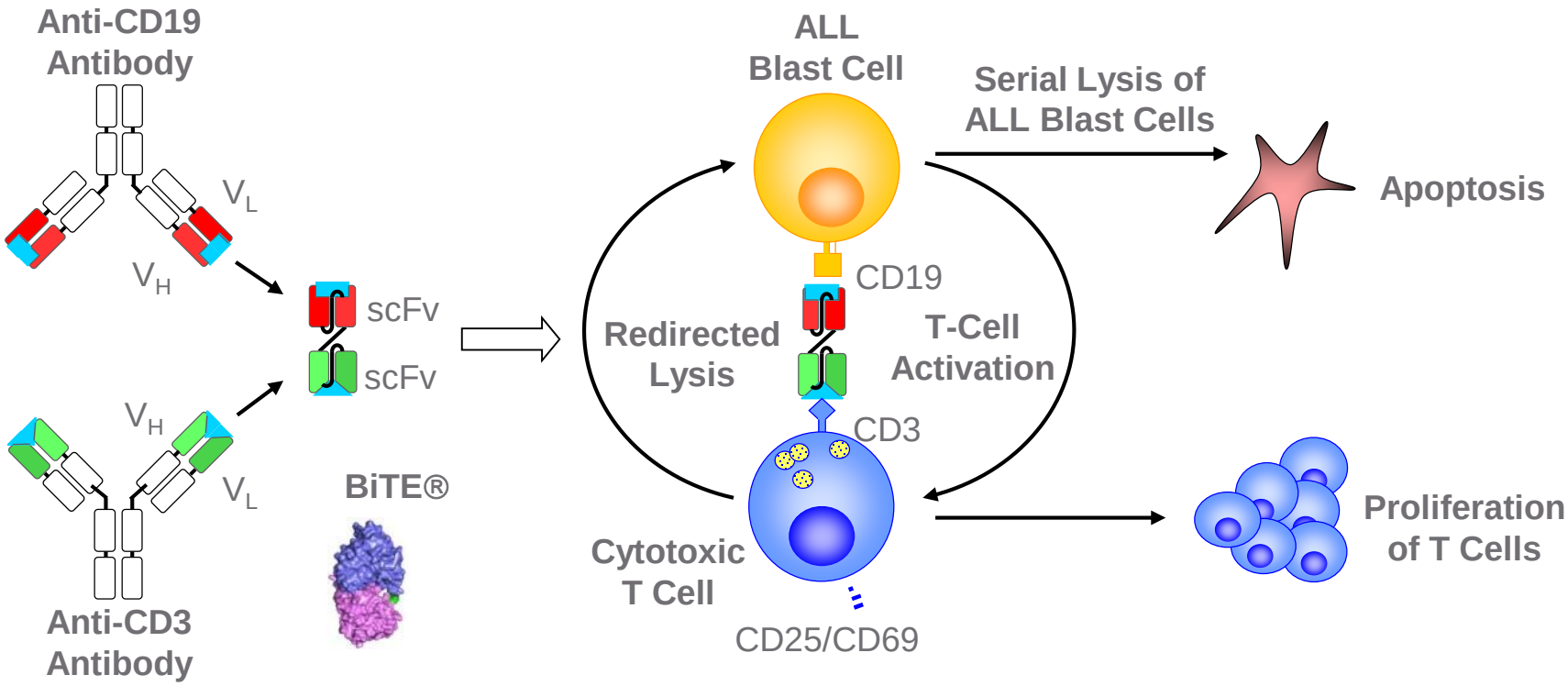
Selected Bispecific Antibody Formats



V_L, variable light chain; V_H, variable heavy chain; Fab, antigen-binding fragment; Fc, constant fragment; scFv, single-chain variable fragment; IgG, immunoglobulin G; BiTE, bispecific T-cell engager; DART, dual affinity retargeting molecule.

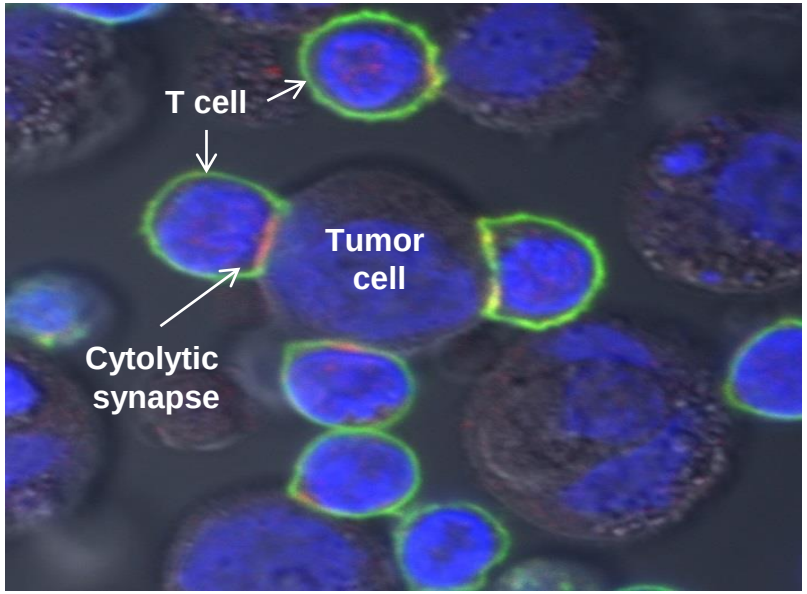
Garber K. *Nat Rev Drug Discov* 2014; 13:799-801.

Principles of BiTE Mode of action

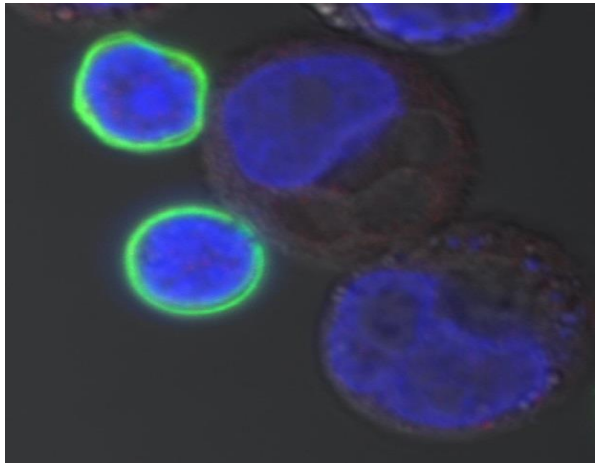


BiTE Mediates Formation of a Cytolytic Synapse Between T Cells and Tumor Cells

Target-expressing tumor cells +
Target antigen-BiTE



human pan-T cells
Control BiTE



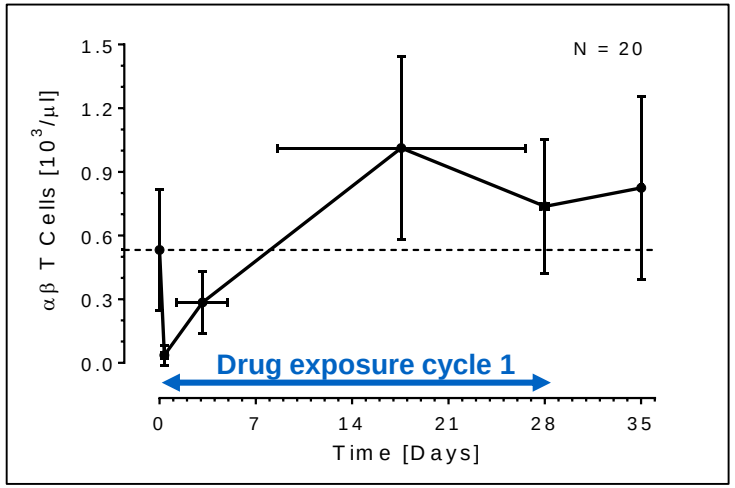
DAPI: Cell nuclei
CD45: T cell marker
PKC-theta: Activated T cell marker

Key aspects of the BiTE Mode of Action

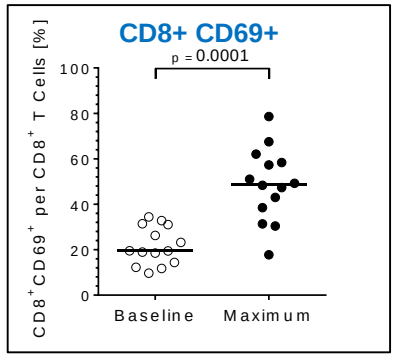
- Strictly target cell-dependent activation of resting T cells by BiTE® antibody construct
- Highly potent and complete lysis of target cell by BiTE® -activated T cells
- Lysis of dividing as well as non-dividing target cells
- Serial lysis by BiTE®-activated T cells
- Sustained proliferation of BiTE®-activated T cells
- Does not require MHC Class I and peptide antigen for recognition by T cell
- Does not require T cell clone with specific T cell receptor

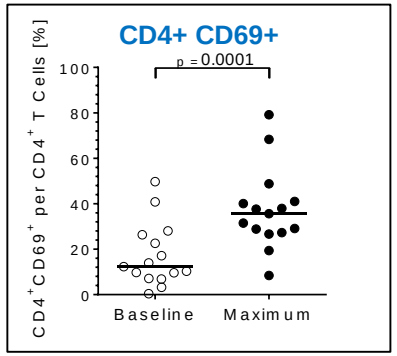
BiTE activates T cells and induces cytokine production

Initial T cell redistribution (>90%) followed by recovery to baseline and expansion

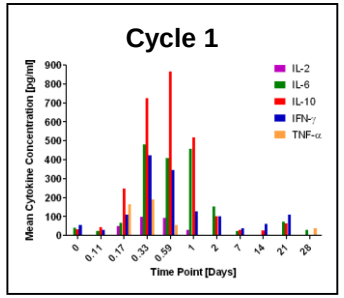


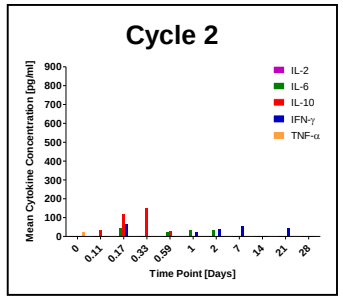
Maximal T cell activation within 2 days



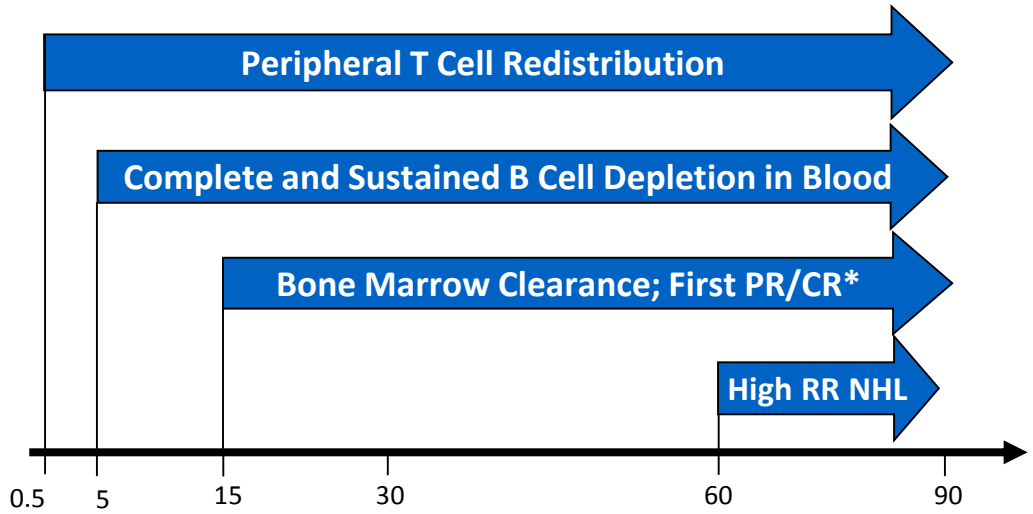


Transient cytokine release primarily in the first treatment cycle



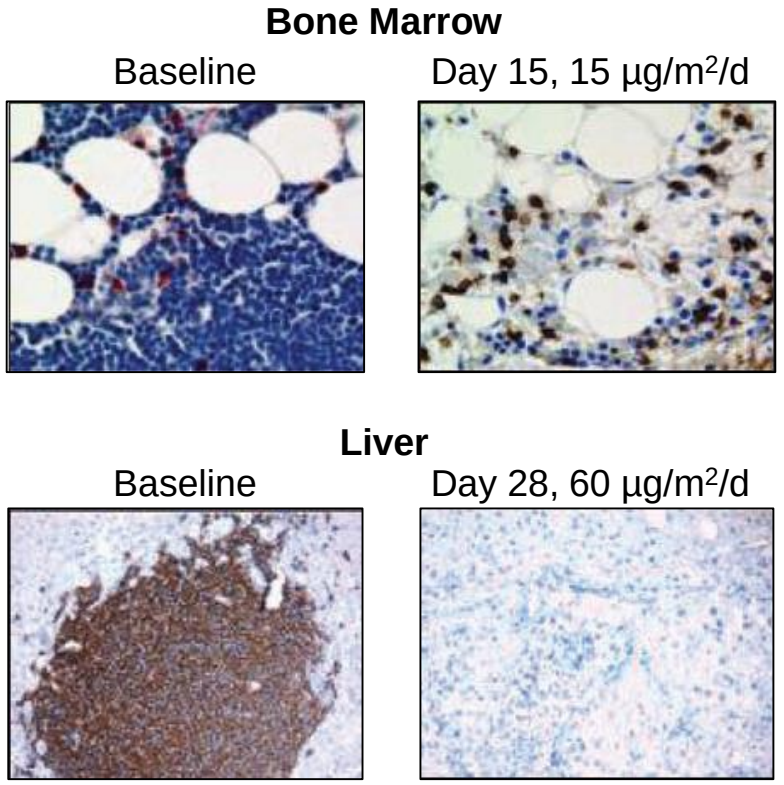


BiTE can deplete target cells in peripheral blood and also in tissues



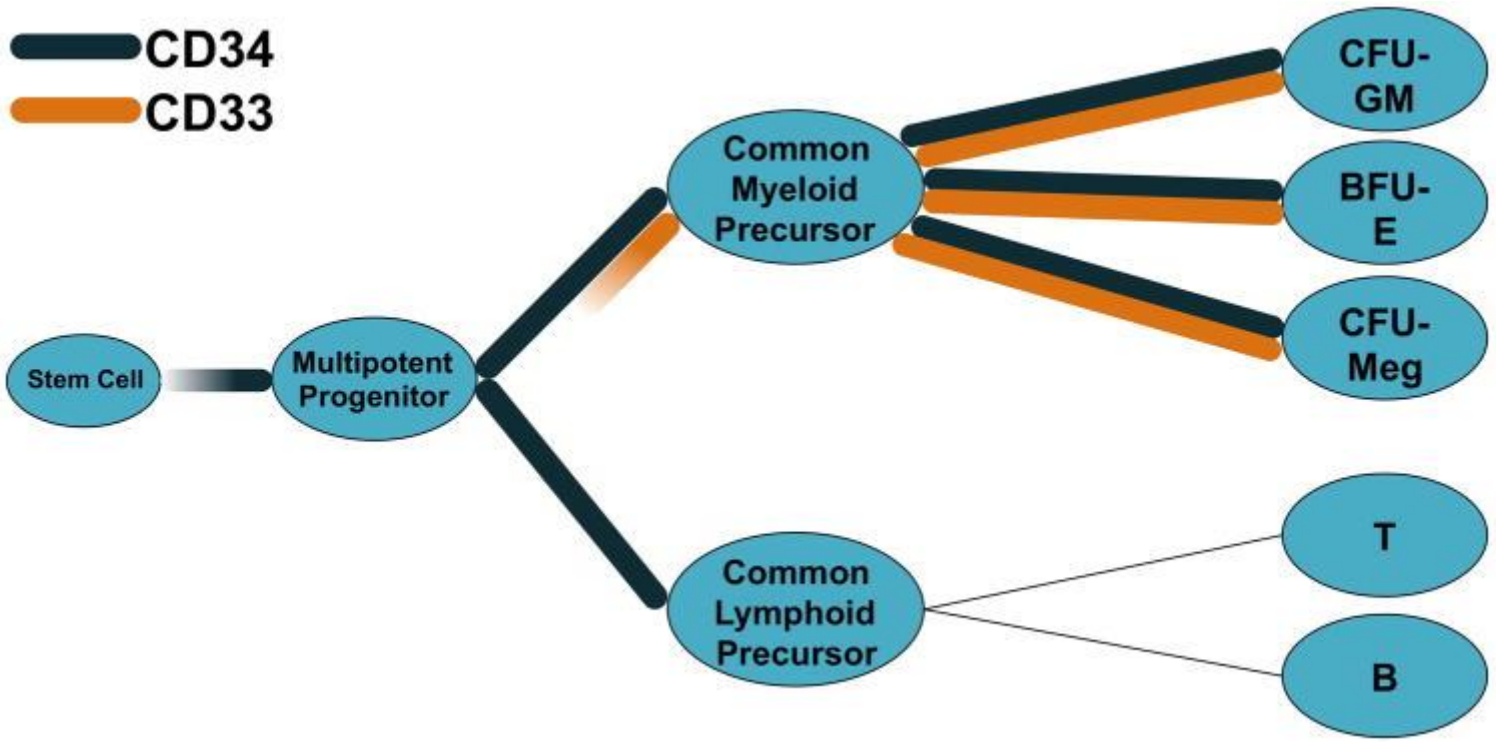
Blinatumomab Dose Levels Tested [µg/m²/Day]

***PR = Partial Response; CR = Complete Response**

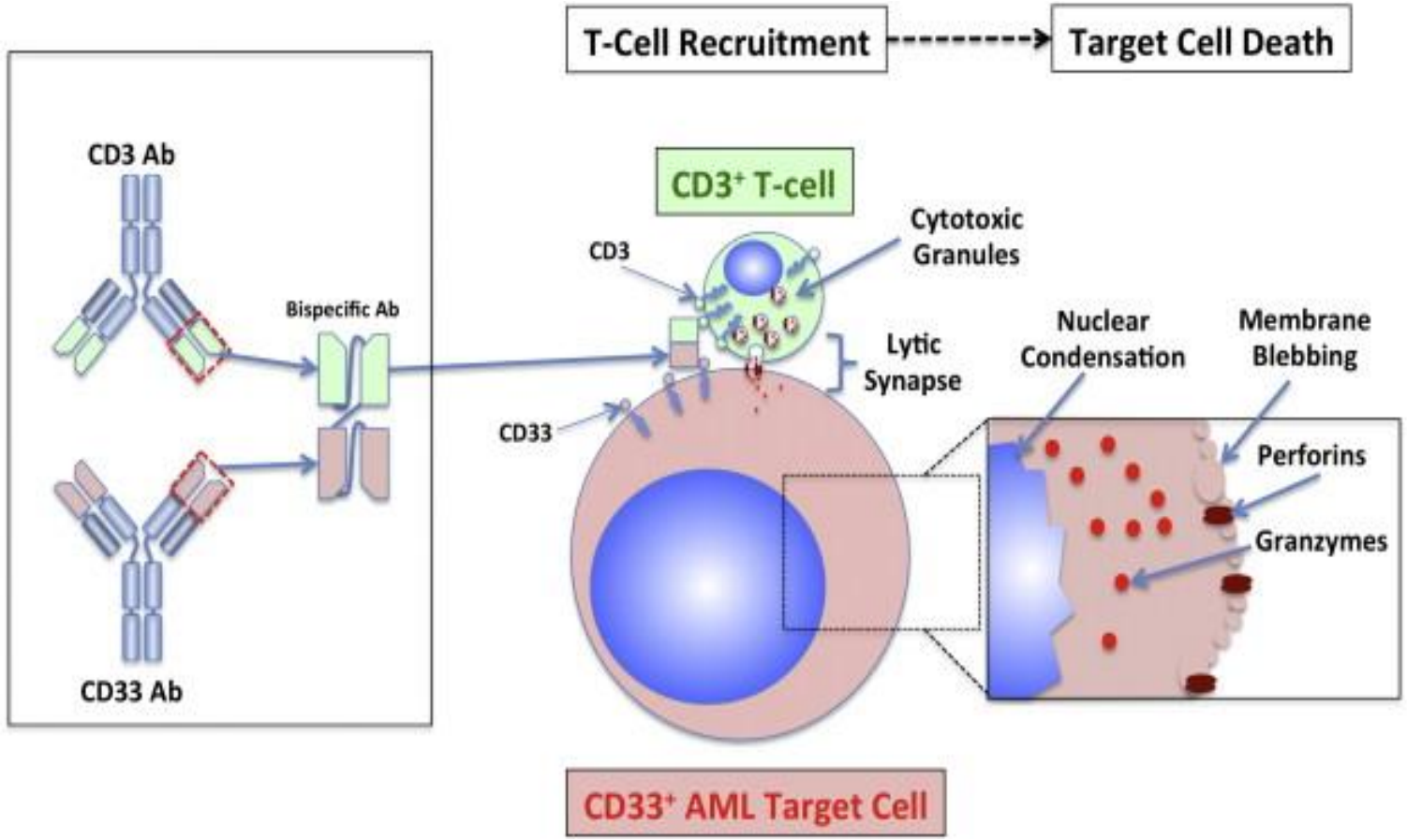


Bargou R et al. *Science* 321:974-78 (2008)
Bargou R et al ASH 2007
Viardot A et al. *Blood* 118:1637 (2011)

Why CD33?

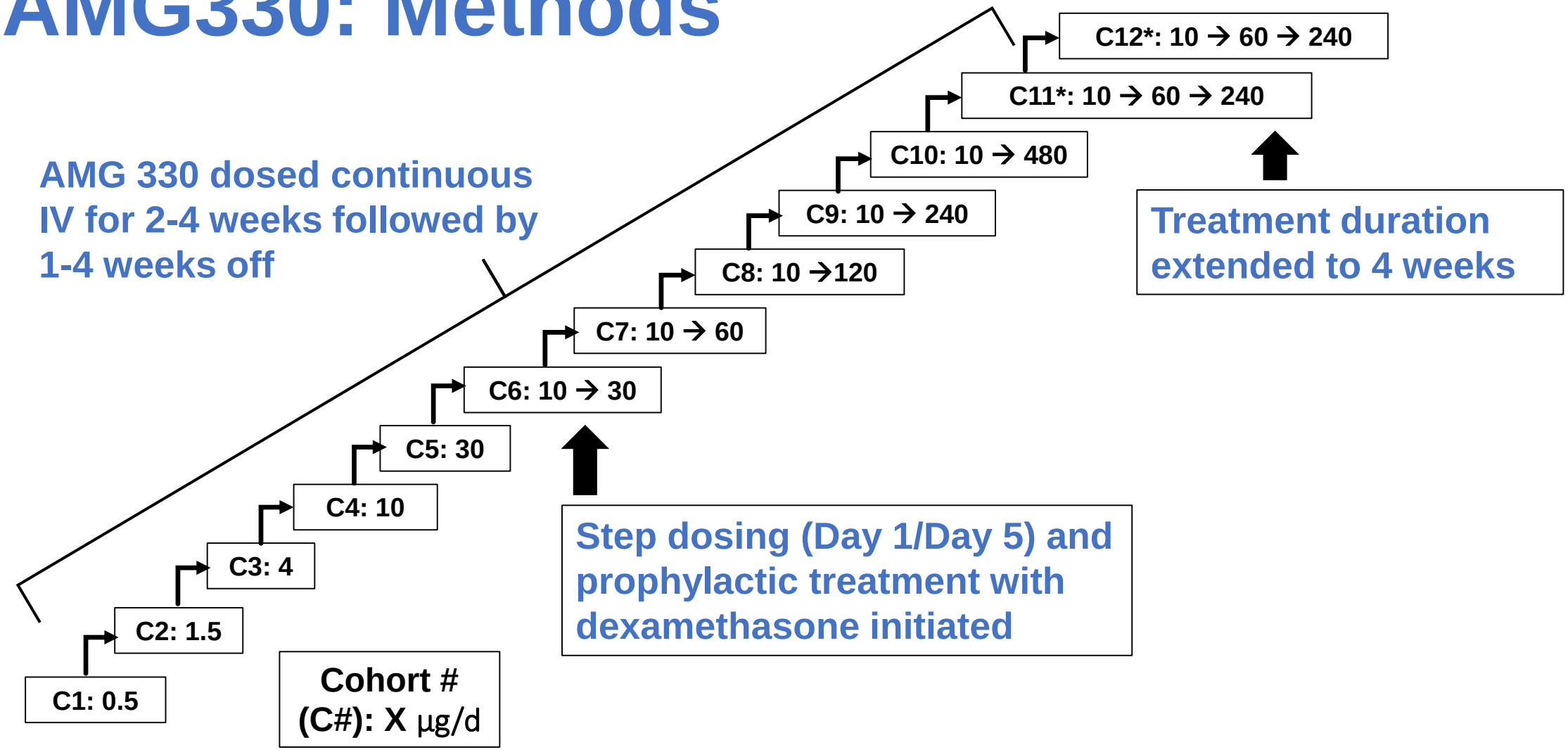

CD34
CD33
Stem Cell
Multipotent Progenitor
Common Myeloid Precursor
Common Lymphoid Precursor
CFU-GM
BFU-E
CFU-Meg
T
B

AMG-330: CD3-CD33



AMG330: Methods

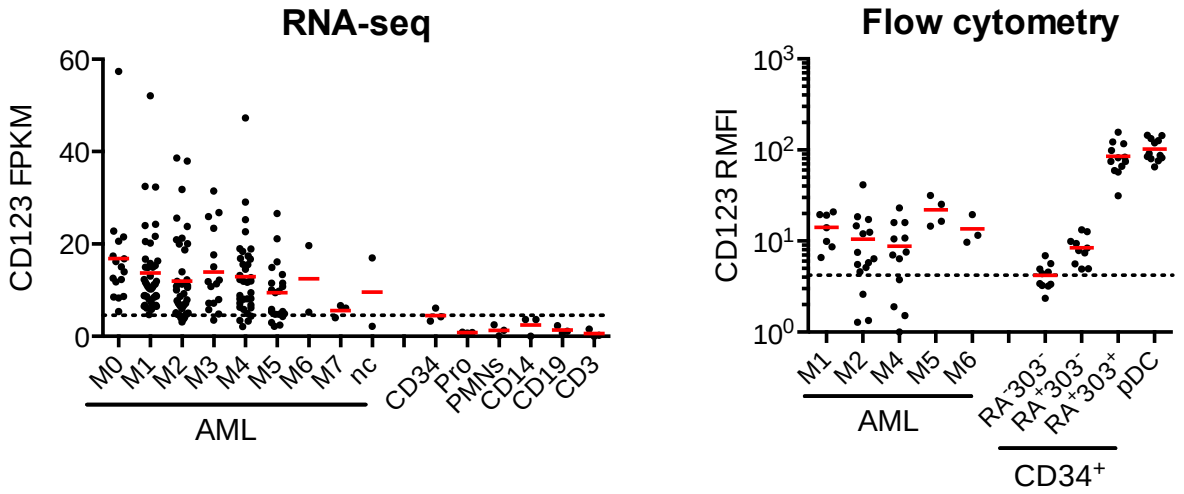
AMG 330 dosed continuous IV for 2-4 weeks followed by 1-4 weeks off



- The 1st dose step was after 3 days in both Cohorts 11 and 12;
- The 2nd dose step was after 4 days in Cohort 11 and after 2 days in Cohort 12.

IL-3 Receptor α (IL-3Rα): CD123

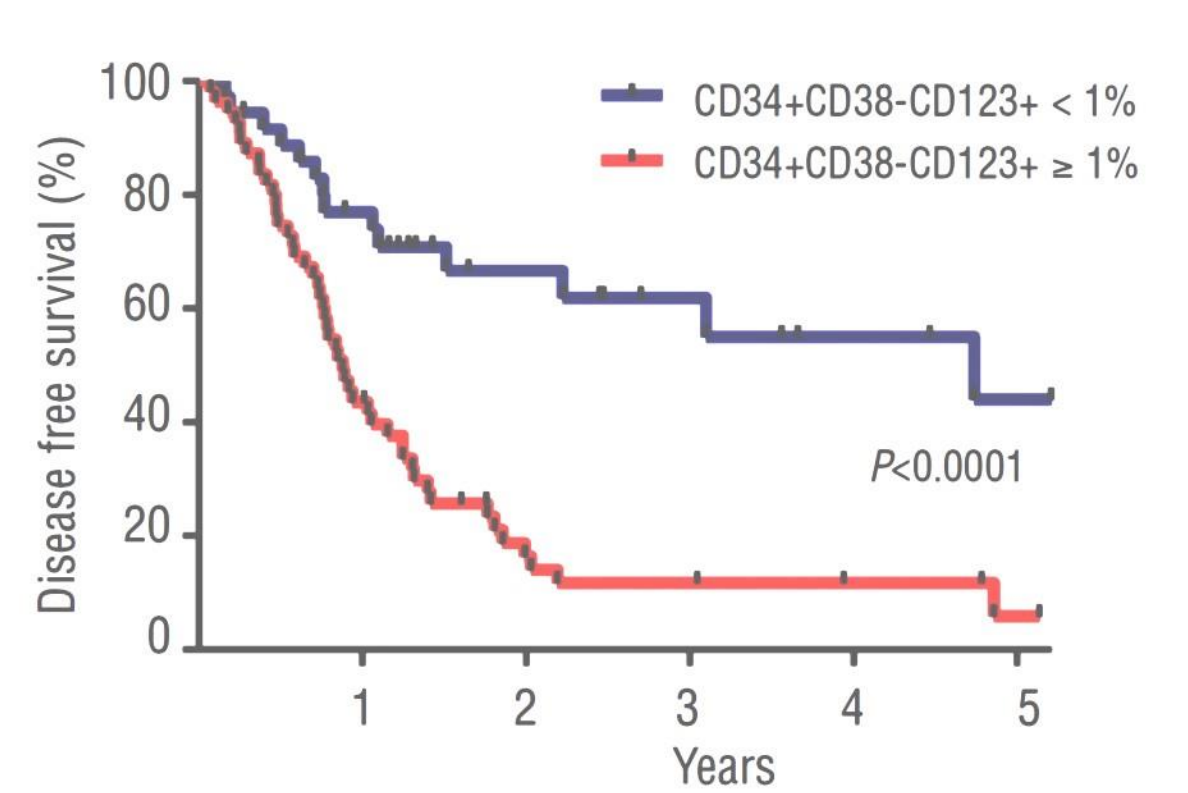
- Low affinity ligand binding subunit of IL-3R
- Binds IL-3 and heterodimerizes with common β subunit of GM-IL-5-IL-3 receptor complex to induce proliferative and anti-apoptotic signaling
- Differentially overexpressed in 93% of AML patients
- Correlation between CD123+ cells frequency and prognosis



Disease	CD123 Positivity
AML	93%
MDS	>50%
CML	>50 - 77.5%
B-cell ALL	80 - 99%
Classical Hodgkin's Lymphoma	50 - 60 %
Hairy Cell Leukemia	100%
CLL	10%
Systemic Mastocytosis	>50 - 100%
pDC Leukemia	100%

Jordan, et al. Leukemia. 2000 Oct; 14(10):1777-84; Jin, et al. Cell Stem Cell 2009 Jul 2;5(1):31-42; Munoz, et al. Haematologica 2001 Dec;86(12):1261-9; O'Brien and Rizzieri Cancer Invest 2013 May;31(4):215-20; Testa, et al. Blood. 2002 Oct 15; 100(8):2980-8; Tettamanti, et al. Br J Haematol 2013 May; 161(3):398-401; Vergez, et al. Haematologica 2011 Dec;96(12):1792-8

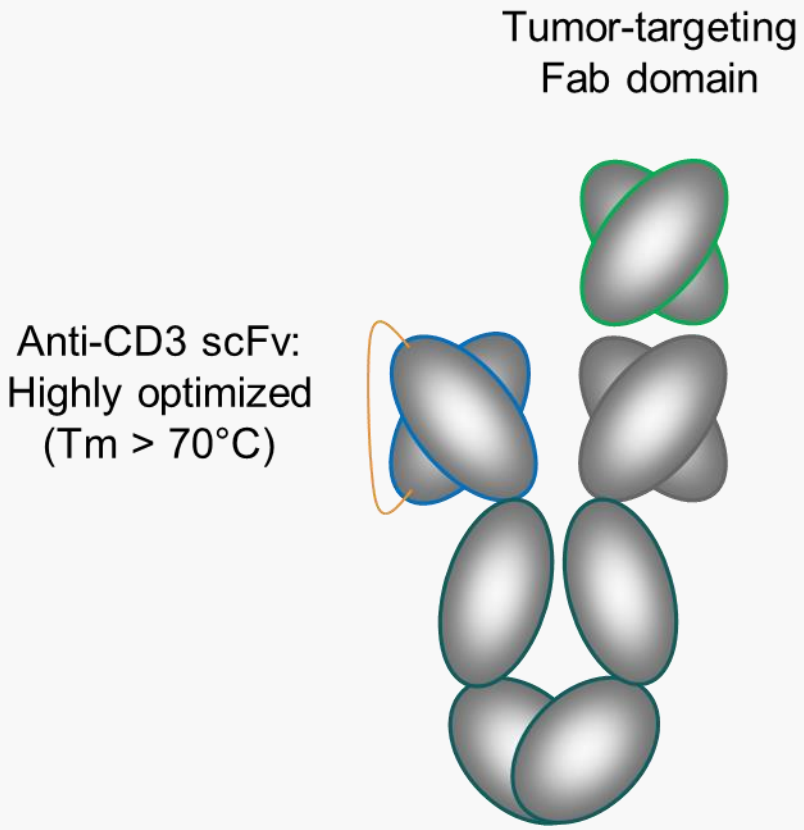
XmAb®14045: CD123 x CD3



Vergez F, Haematologica 2011

High expression on leukemia stem cells is associated with a poor prognosis

XmAb®14045: CD123 x CD3

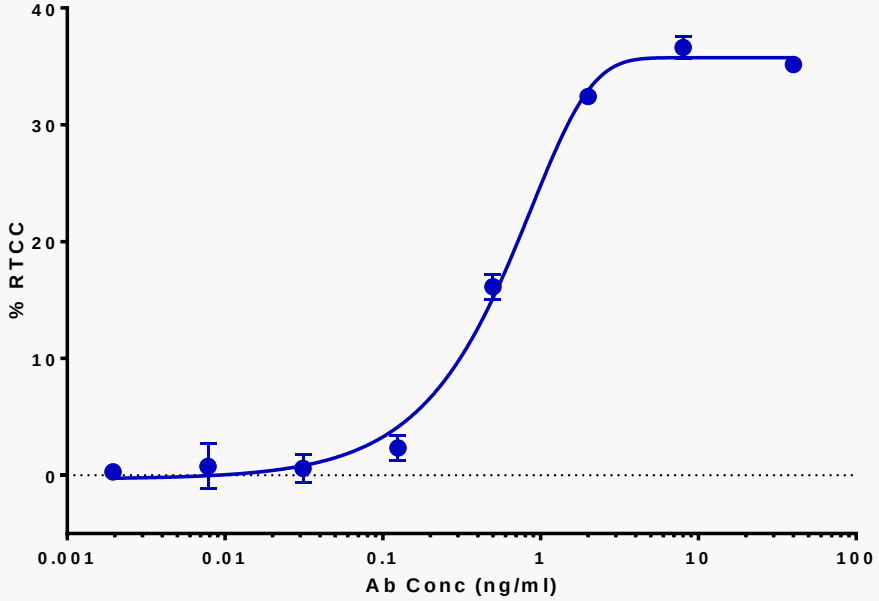


CD123 is frequently expressed on several hematologic malignancies, including

- Acute myelogenous leukemia (AML)
- B-cell acute lymphoblastic leukemia (B-ALL)
- Chronic myelogenous leukemia (CML)
- Hairy cell leukemia (HCL)
- Blastic plasmacytoid dendritic cell neoplasm (BPDCN)
- Any CD123-expressing tumor

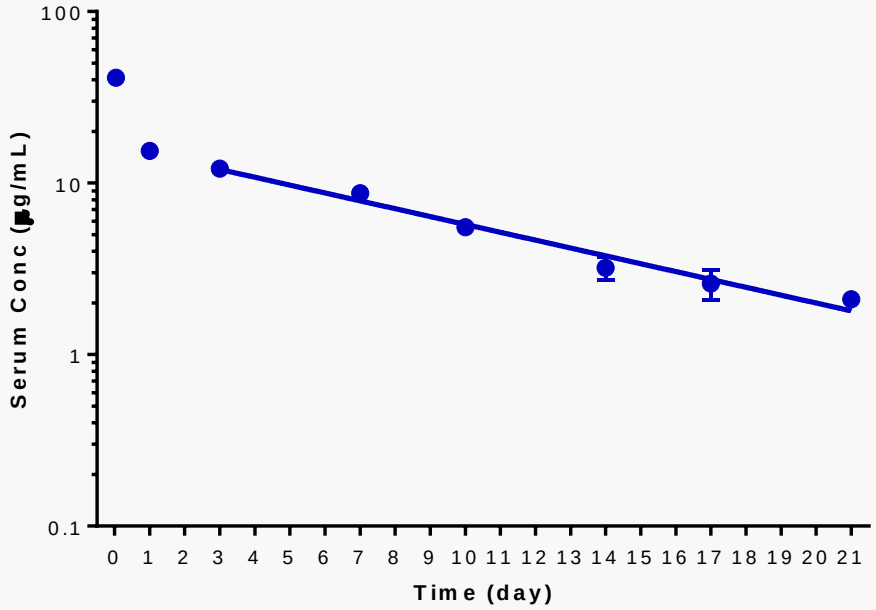
XmAb®14045: CD123 x CD3

Potent In Vitro Killing



Redirected human T-cell cytotoxicity against KG-1a AML cells (similar data using TF-1 cell line)

Antibody-like half-life in mice

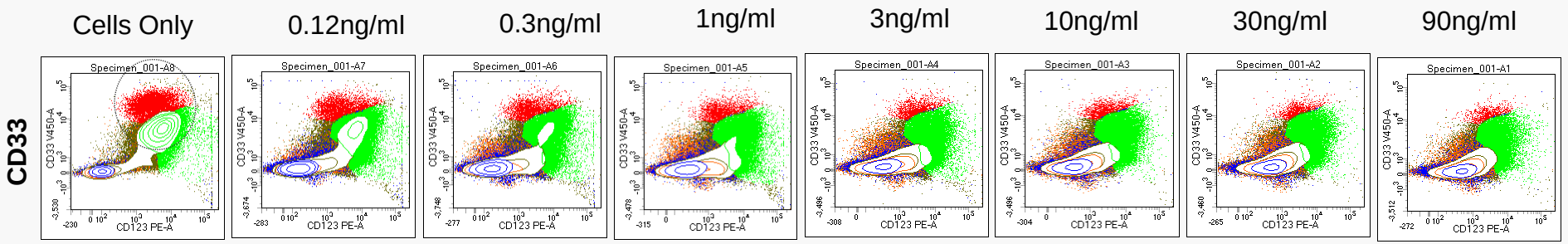


$T_{1/2}$ = 6.2±1.5 days

XmAb14045 kills primary CD123+ blasts and expands autologous T-cells in vitro

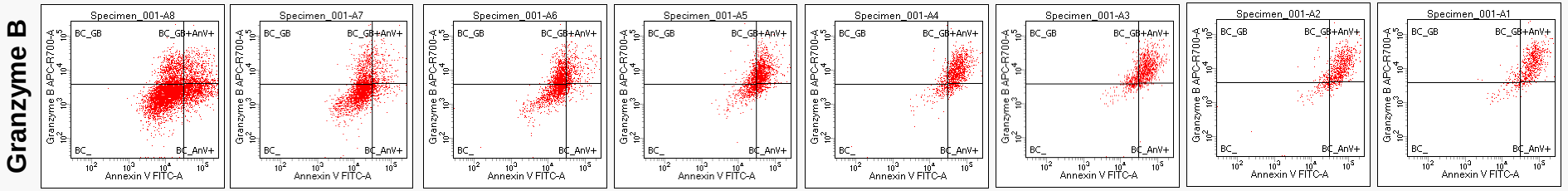
Experiment: 6 day incubation of XmAb14045 with AML patient-derived PBMC

CD123⁺ cells (red) decrease with increasing antibody dose

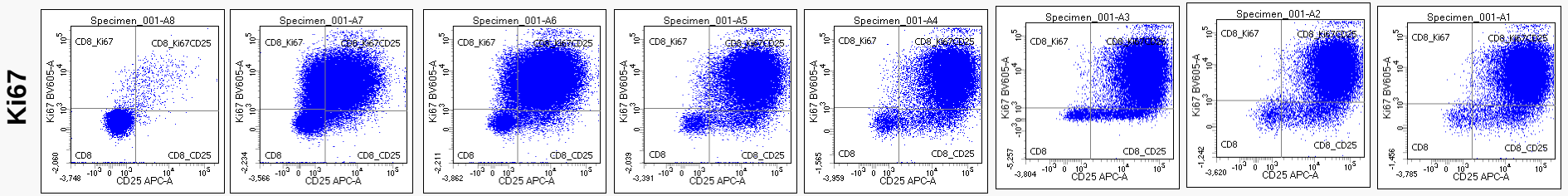


Red – Blast cells, Green – CD123+CD33mid, Blue – CD8+ T cells, Yellow – CD4+ T cells

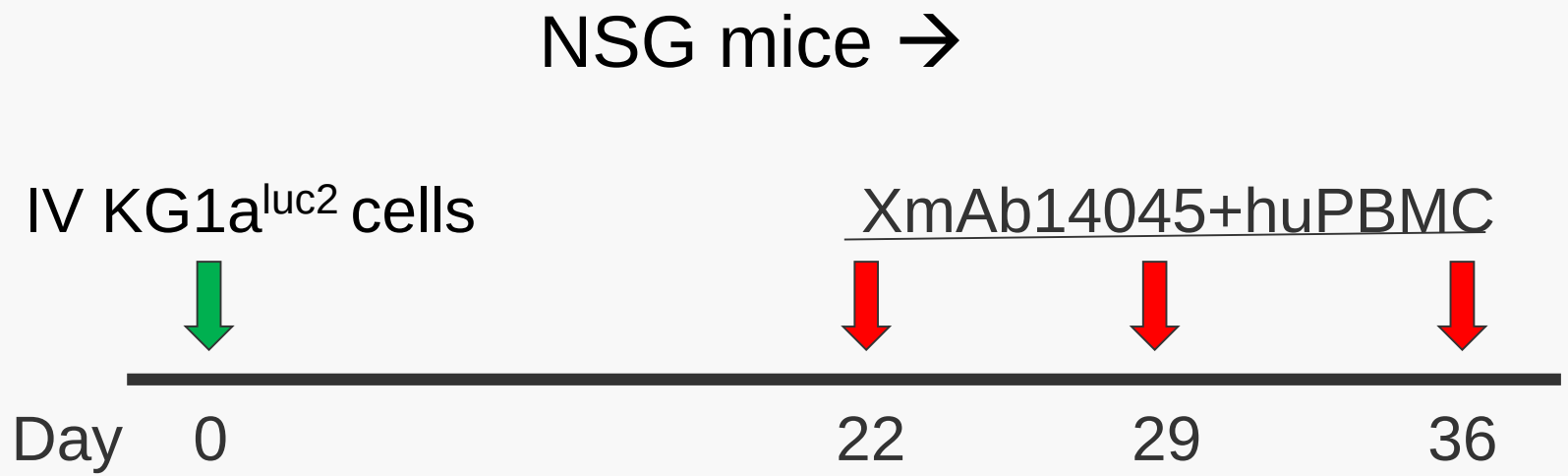
CD123⁺ cells become double positive for Annexin V and Granzyme B



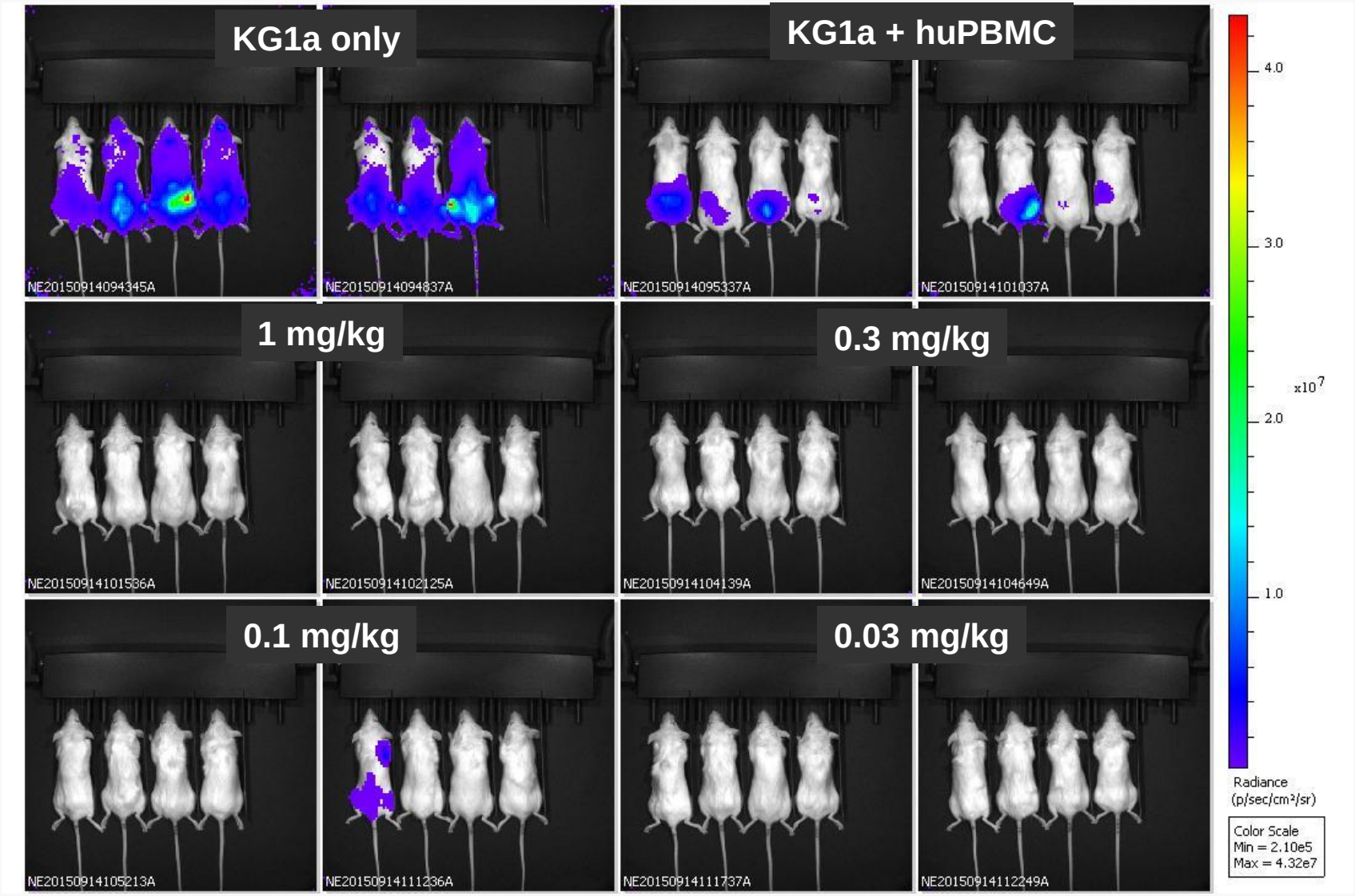
T cells activate and proliferate



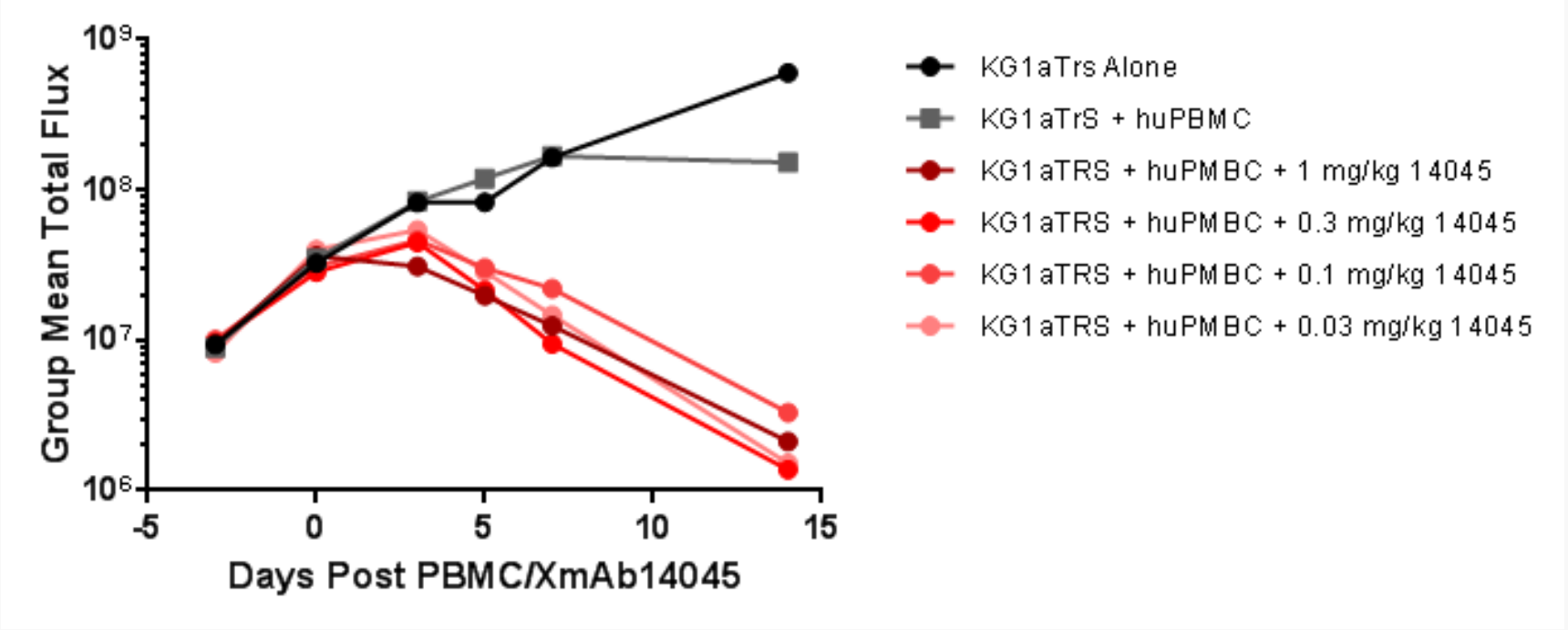
huPBMC-NSG mouse xenograft model



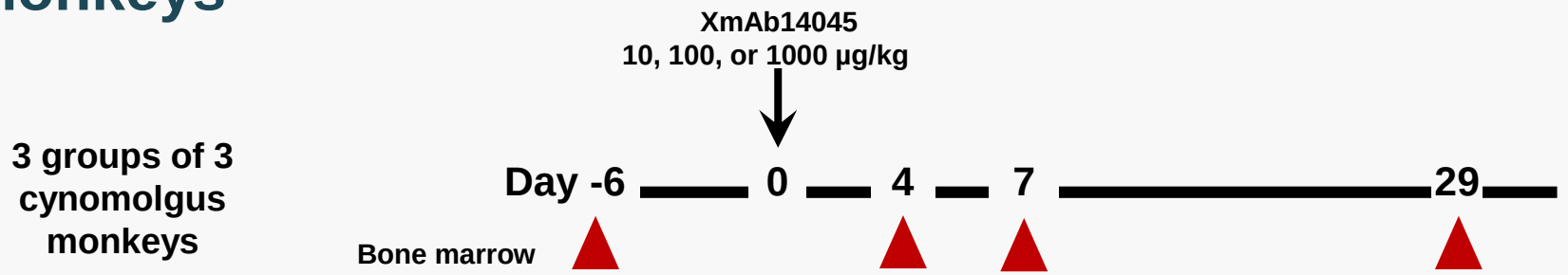
After weekly XmAb14045 doses x 3

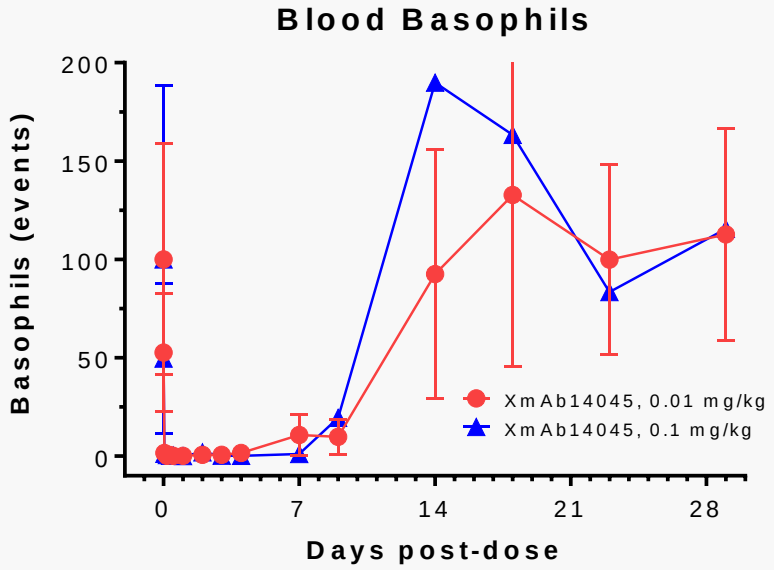


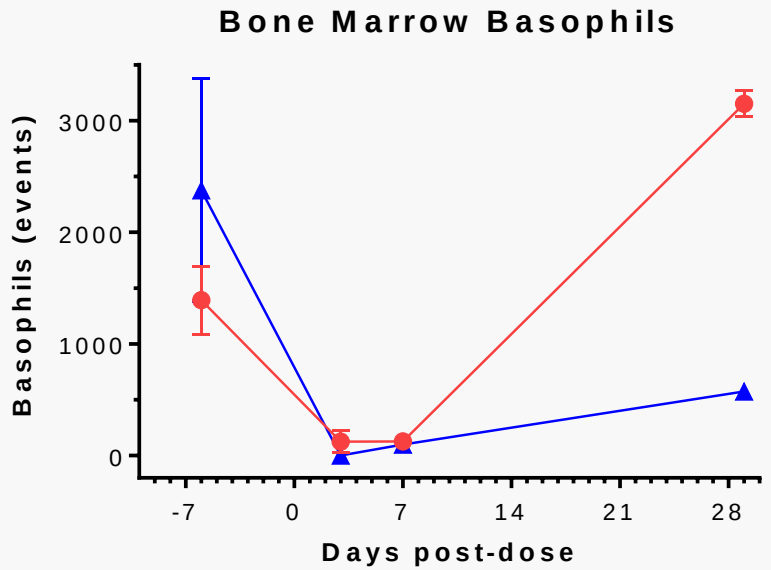
Tumor burden with XmAb14045 treatment



Single dose of XmAb14045 depletes CD123+ cells in monkeys

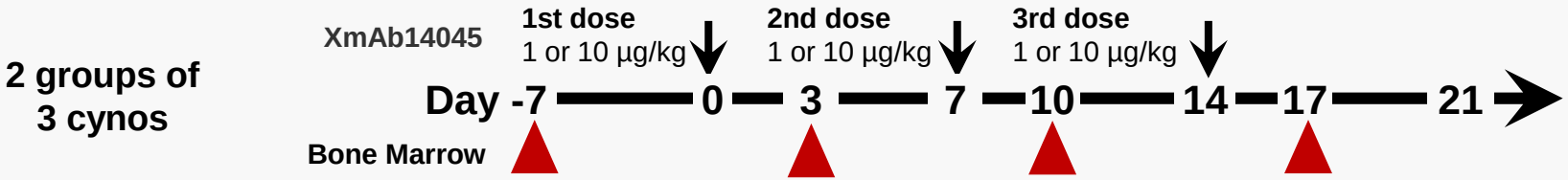


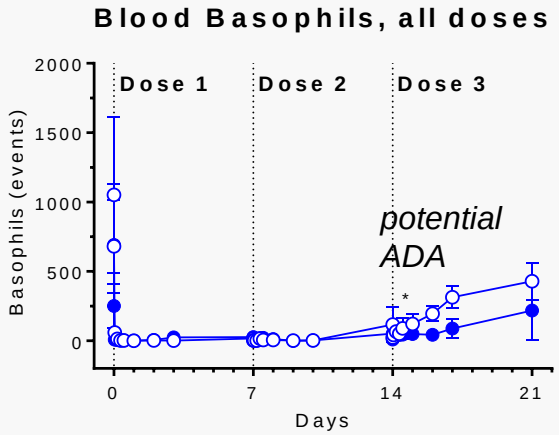


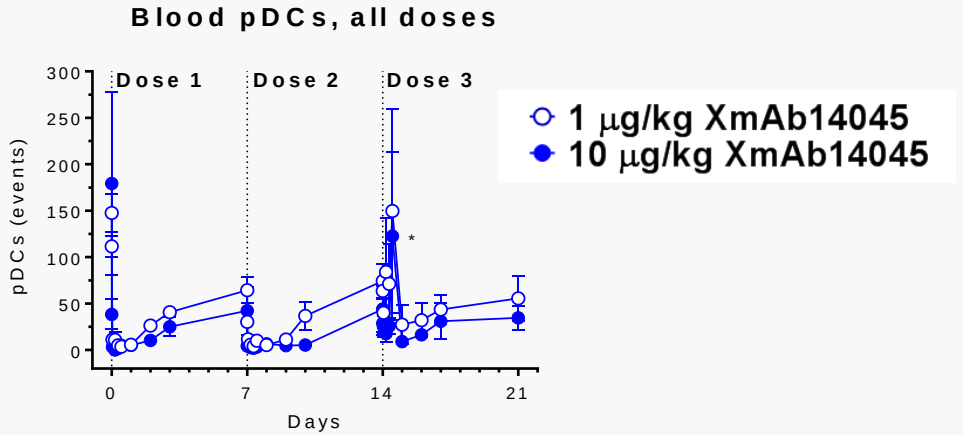


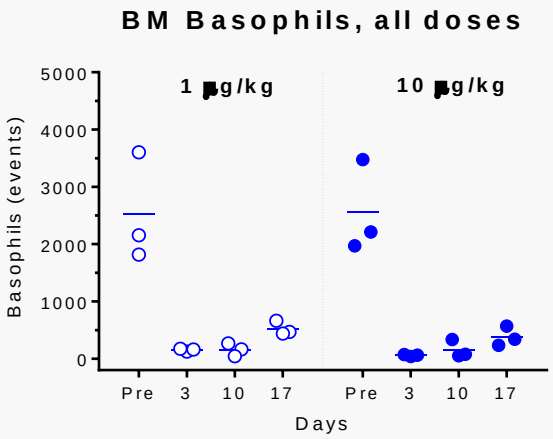
Basophil recovery supports weekly dosing

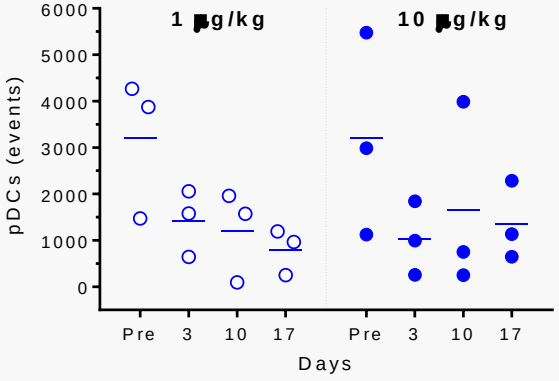
Repeat low dose of XmAb14045 depletes CD123+ cells in monkeys





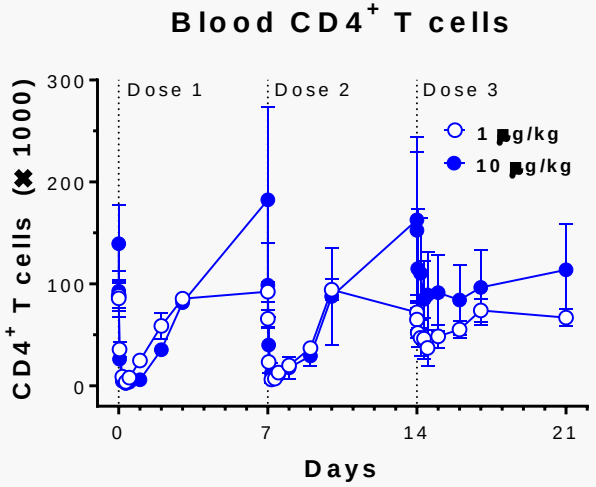


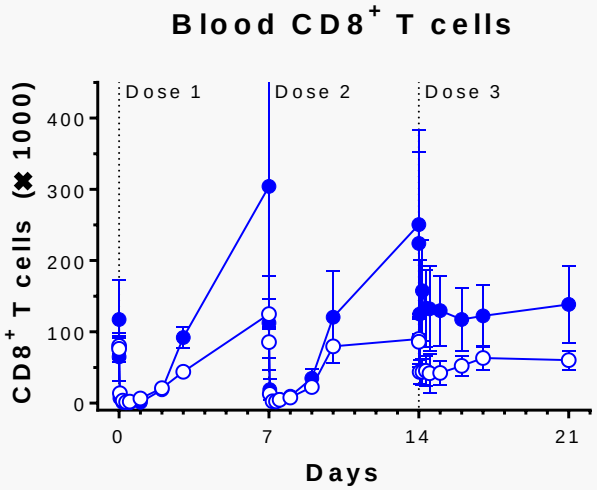




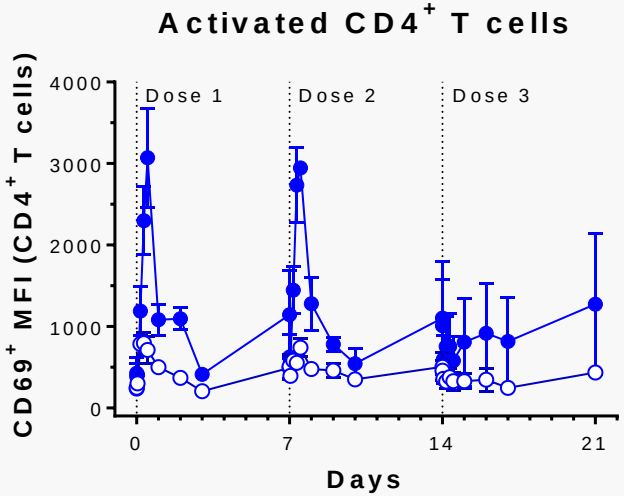
CD123+ cell depletion correlates with T cell redistribution & activation

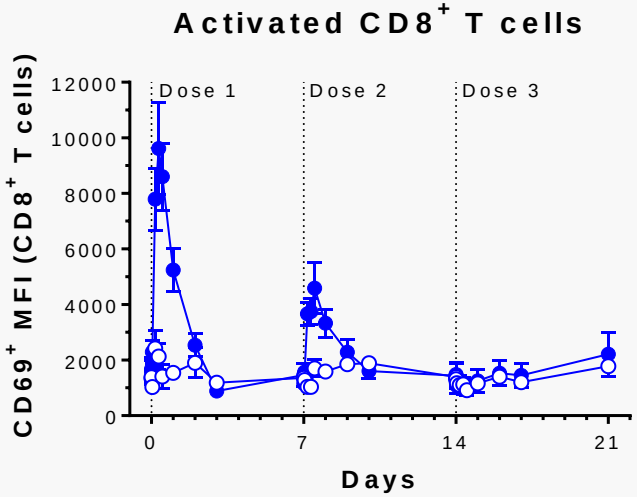
T cell redistribution



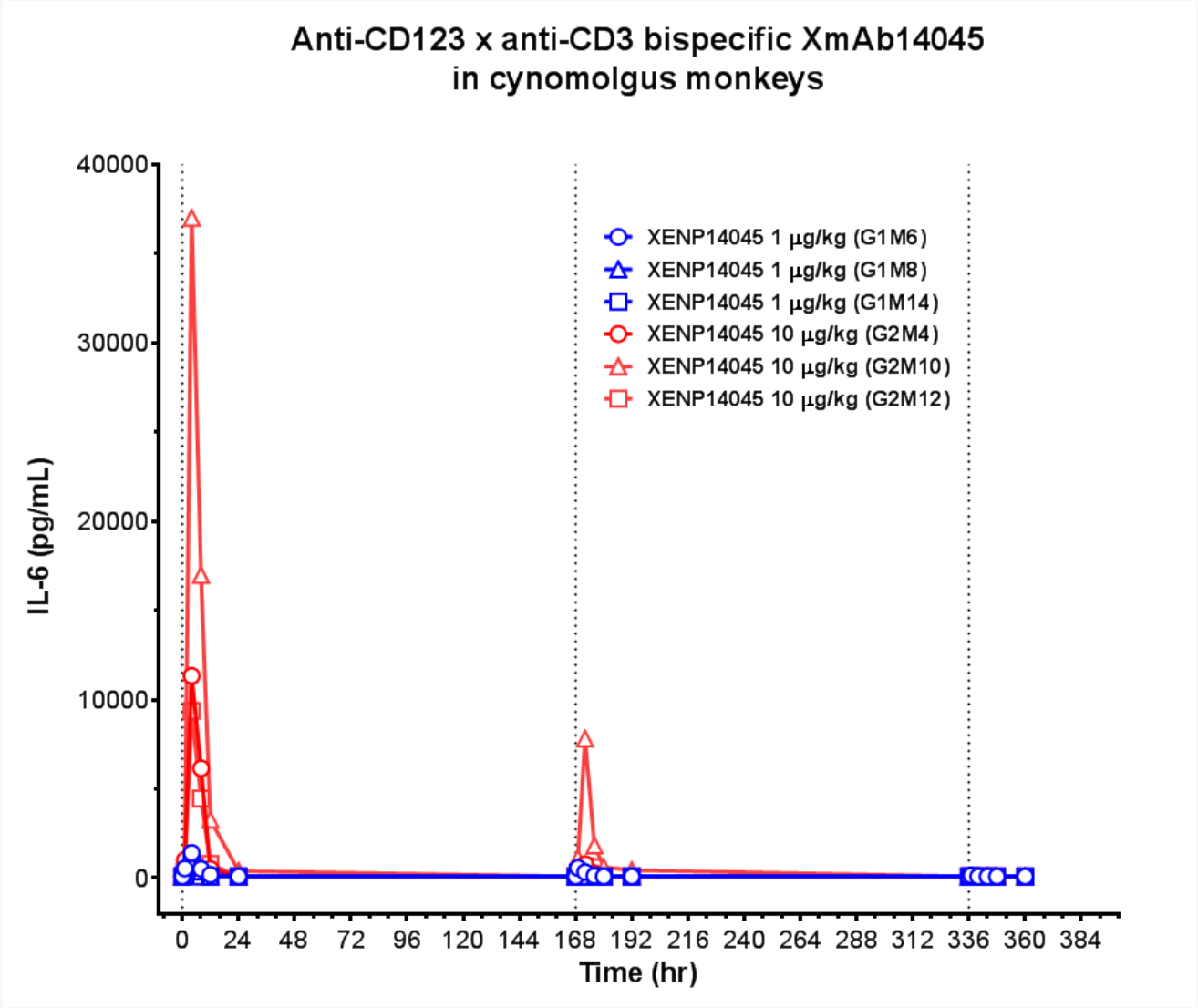


T cell activation





Cytokines levels decrease markedly after the first dose of XmAb



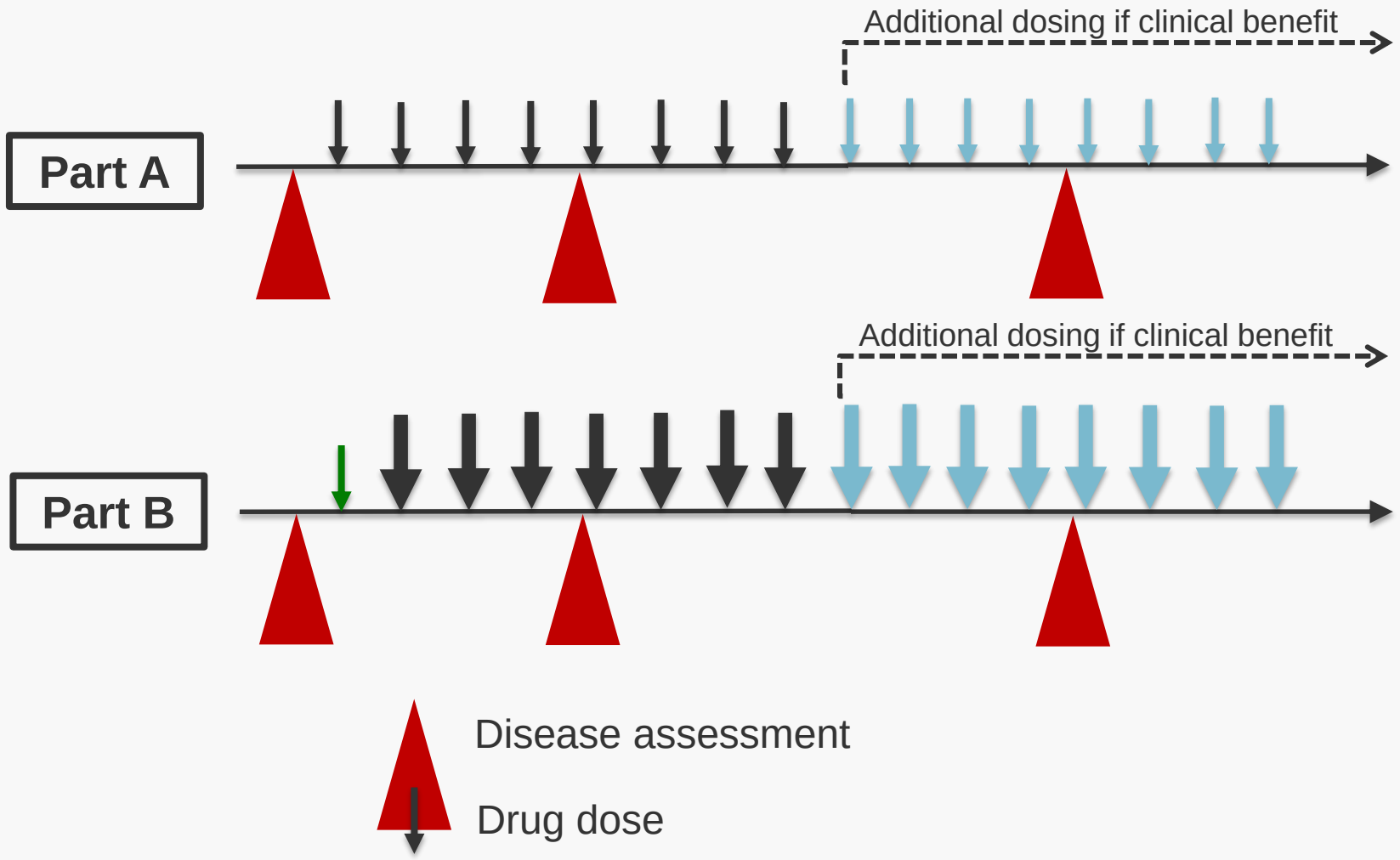
Average IL6 drop by dose

1 µg/kg	**3.6-fold**
10 ug/kg	**11-fold**

Average TNF drop by dose

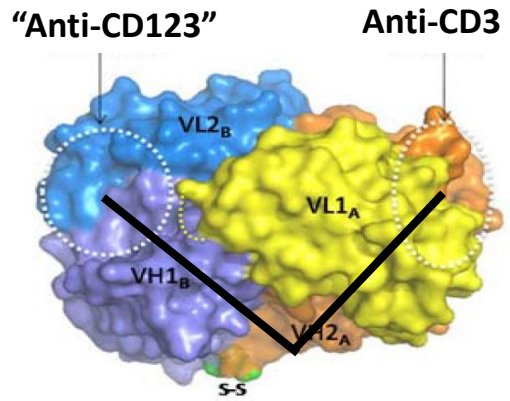
1 ug/kg	**1.7-fold**
10 ug/kg	**4.7-fold**

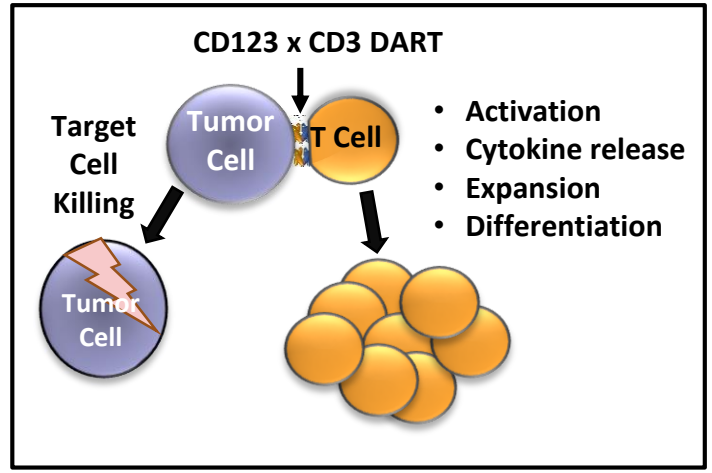
XmAb14045 Phase 1 Design



Flotetuzumab: CD123 x CD3 Bispecific DART Protein

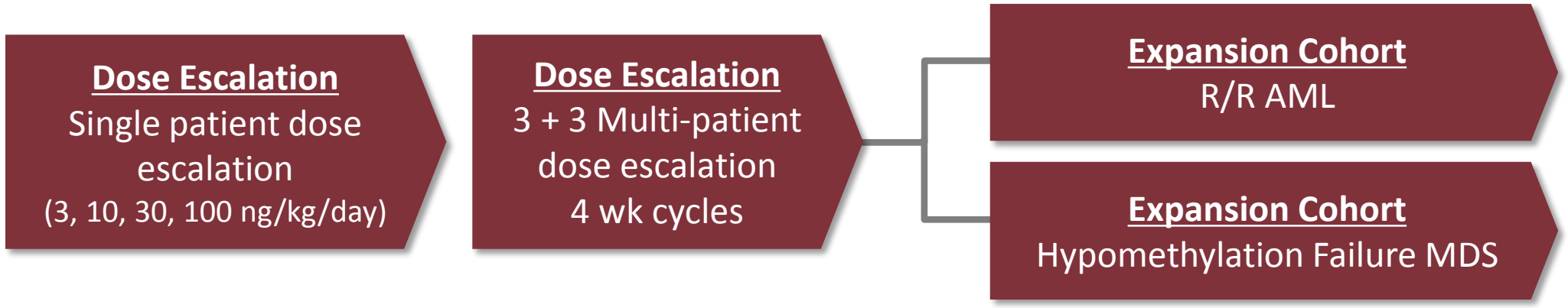
- DART bispecific platform
  - Multiple applications across different diseases
  - Predictable manufacturability
  - Long-term stability
  - Optimal variable light and heavy chain pairing allows for tighter conformation and closer proximity between effector (CD3+) cells and target (CD123+) cells
- Ability to tailor half-life and valency
- Flotetuzumab (MGD006/S80880) mode of action: redirected T-cell killing of CD123+ Cells





Root, et al. Antibodies 2016, 5, 6
Chichili, et al. Sci Transl Med. 2015 May 27;7(289)

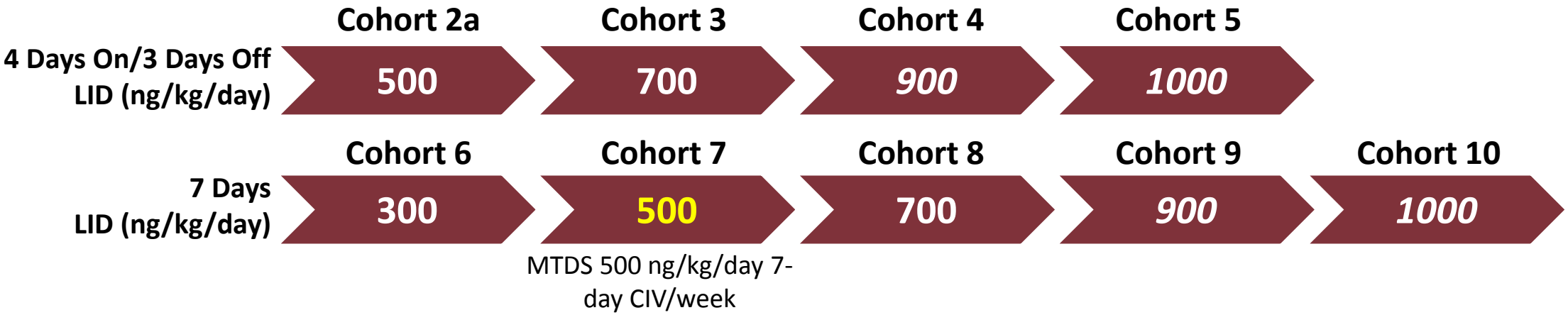
Flotetuzumab Phase 1 Study Design



(N=24 each cohort)

- Flotetuzumab Phase 1 key inclusion/exclusion criteria
  - Refractory AML unlikely to benefit from cytotoxic chemotherapy
  - Patients with MDS who have experienced treatment failure with induction therapy or hypomethylating therapy and have ≥10% marrow blasts
  - Prior history of allogeneic stem cell transplant is exclusionary
- Flotetuzumab Phase 1 study objectives
  - Safety and preliminary clinical activity
  - Optimize approach to delivery and supportive care (manage CRS while minimizing corticosteroid use)
  - Define PK, PD and PK/PD relationships

Dosing Scheme in Multi-Patient Dose Escalation



Lead-in Dose (LID)	•Week 1: 30 ng/kg/day x 3 days, 100 ng/kg/day x 4 days
Cycle 1 Weeks 2-4	•Arm A: (Cohorts 2-5): 4 days on, 3 days off schedule •Arm B: (Cohorts 6-10): 21 days continuous infusion
Cycle 2 and Beyond	•4 days on, 3 days off schedule

Flotetuzumab Phase 1 Patient Demographics†

Characteristic		All Patients (n=57)
Age	Mean ± SD	63.6 ± 14.28
	Median (Range)	67.0 (29.0, 84.0)
Gender [n(%)]	Female	25 (43.9)
Diagnosis [n (%)]	AML	52 (91.2)
	MDS	5 (8.8)
AML Subclassification	Relapse	10 (19.2)
	Refractory	**28 (53.8)**
	HMA Treatment failure (≥ 2 cycles)	14 (26.9)
AML Risk Stratification (ELN 2017)	Favorable	3 (5.8)
	Intermediate	18 (34.6)
	Adverse	**26 (50)**
	Unknown	5 (9.6)
MDS IPSS Risk Category	High	2 (40.0)
	Intermediate-1	1 (20.0)
	Intermediate-2	2 (40.0)

† Data cut-off November 30th , 2017

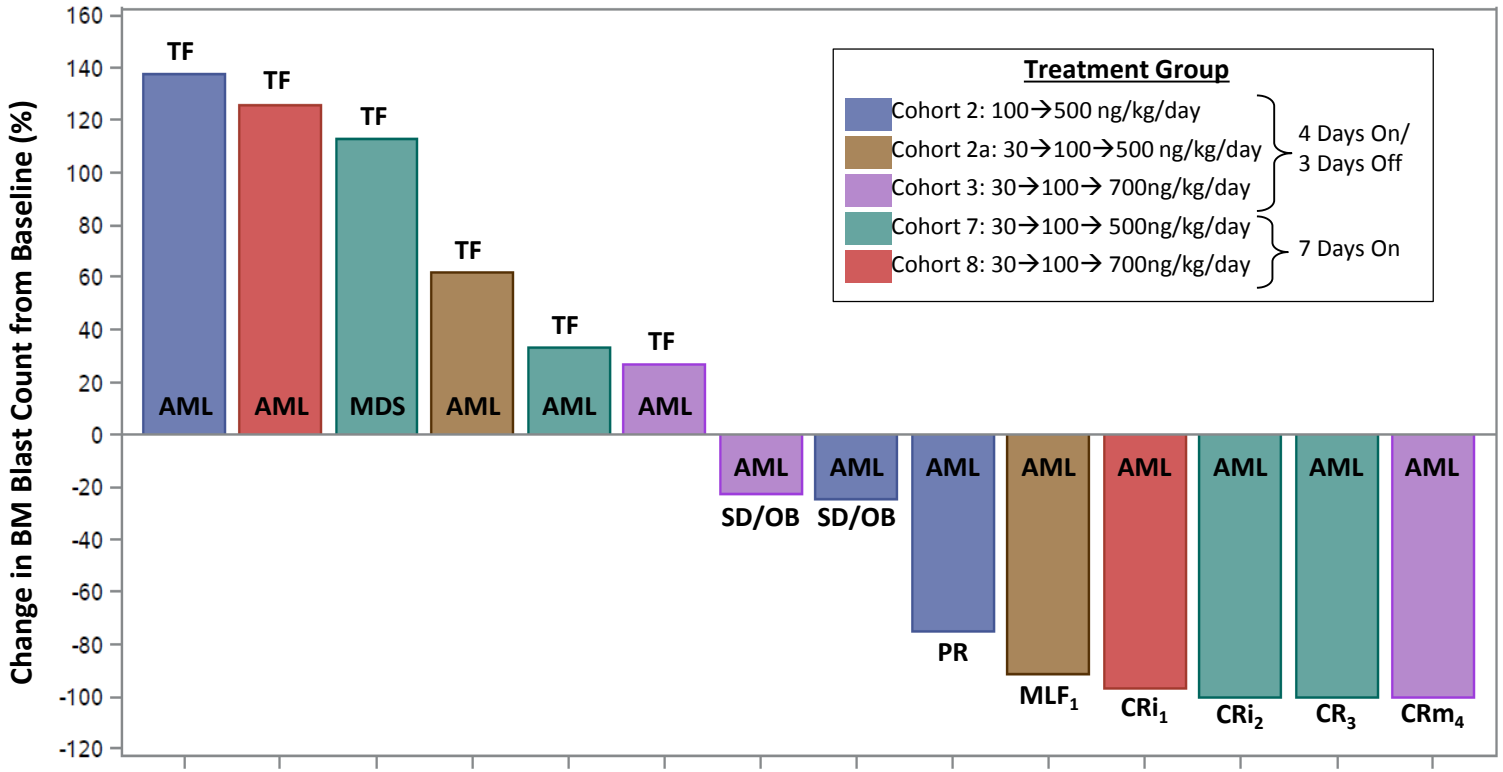
Flotetuzumab Phase 1 Study Safety: Overview*

Adverse Event	Related to Flotetuzumab	
	All (N=57)	≥ Gr 3
Infusion related reaction/Cytokine release syndrome	46 (80.7)	9 (15.8)
Pyrexia	14 (24.6)	2 (3.5)
Nausea	13 (22.8)	
Chills	8 (14.0)	
Platelet count decreased	8 (14.0)	7 (12.3)
Lymphocyte count decreased	8 (14.0)	8 (14.0)
White blood cell count decreased	7 (12.3)	6 (10.5)
Anemia	6 (10.5)	6 (10.5)
Fatigue	8 (14.0)	
Vomiting	8 (14.0)	
Diarrhea	7 (12.3)	1 (1.8)
Edema peripheral	6 (10.5)	
Hypocalcaemia	7 (12.3)	2 (3.5)
C-reactive protein increased	6 (10.5)	2 (3.5)
Alanine aminotransferase increased	6 (10.5)	1 (1.8)
Blood bilirubin increased	6 (10.5)	
Hypomagnesaemia	6 (10.5)	

**Cutoff date: November 30, 2017; Includes events occurring in ≥10% of the population.*

Anti-Leukemic Activity at Threshold Dose ≥ 500 ng/kg†

Of 14 patients treated with flotetuzumab in dose escalation phase at threshold dose ≥ 500 ng/kg/day who received ≥ one cycle of treatment and had post-treatment bone marrow biopsy



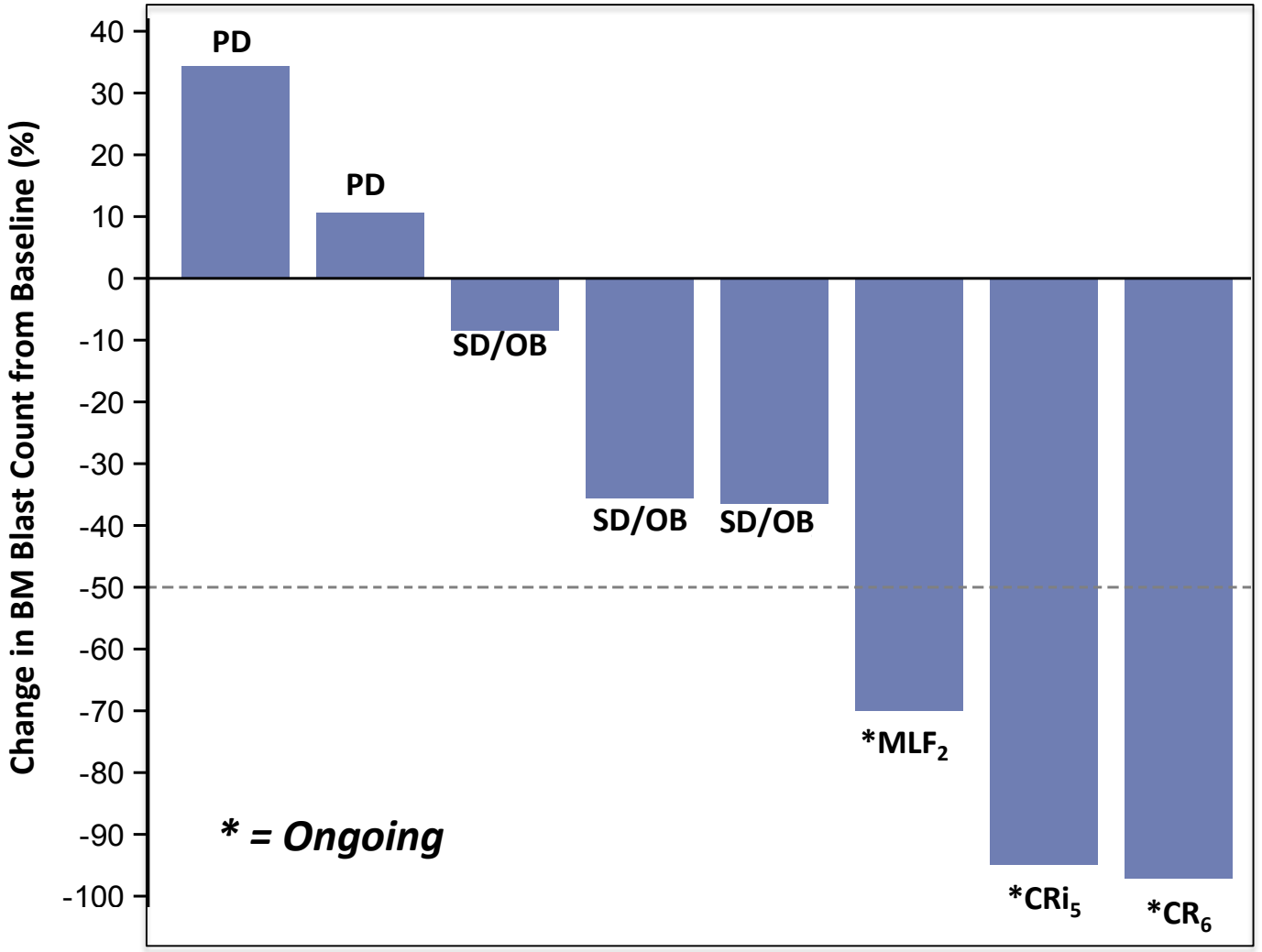
- Rapid responses after single cycle of therapy in majority of patients that respond (cycles ≤ 2)
- Anti-leukemic activity observed in 8/14 pts (57%)
- Objective resp. rate (CR/CRi/MLF/PR): 6/14 pts (43%)
- CR Rate: 4/14 (28%) (CR/CRi)

CR = Complete Response; CRm = molecular CR; CRi = Complete Response with incomplete hematological improvement; MLF = Morphologic Leukemia-free state; PR = Partial Response; SD/OB = Stable Disease/Other Anti-Leukemic Benefit; PD= Progressive Disease; (Modified ELN 2017 criteria)

† Data cut-off Aug. 1, 2017; presented at ESMO 2017

Expansion Cohort-Evaluable Population

- Cohort expansion at MTDS (500 ng/kg/day 7-day CIV) will enroll 24 AML and 24 MDS patients
- 11 AML patients dosed to date, with eight evaluable at data cutoff
- Six patients (75%) have evidence of anti-leukemic activity; three patients are still ongoing
- Expansion cohort open in 13 sites worldwide (7 US, 6 EU)

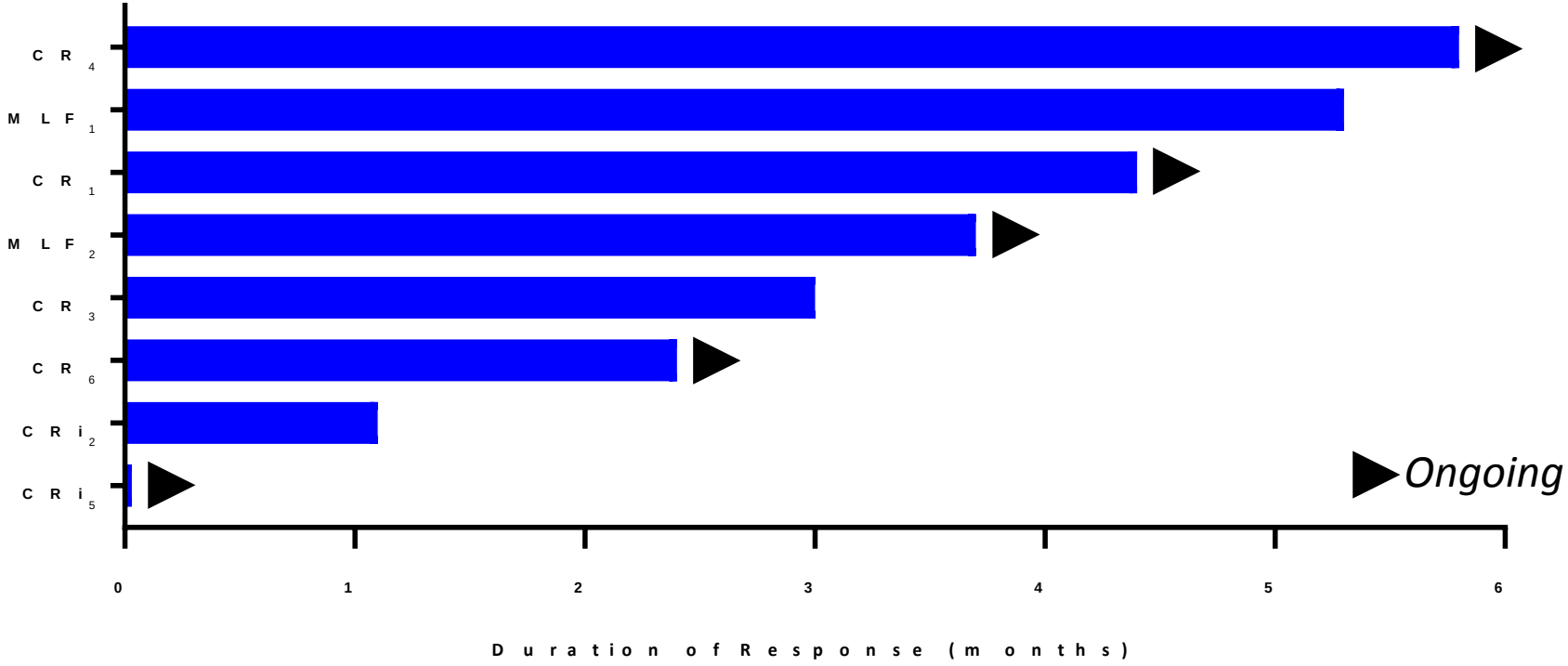


CR = Complete Response; CRm = molecular CR; CRi = Complete Response with incomplete hematological improvement; MLF = Morphologic Leukemia-free state; PR = Partial Response; SD/OB = Stable Disease/Other Anti-Leukemic Benefit; PD= Progressive Disease; (Modified ELN 2017 criteria)

† Data cut-off Dec. 4, 2017

Flotetuzumab Phase 1 Duration of Response†

- Durable responses in patients that achieve MLF, CRi, CR
- Duration of response ranges from 1.0 to 5.8 months, with 5 patients still ongoing



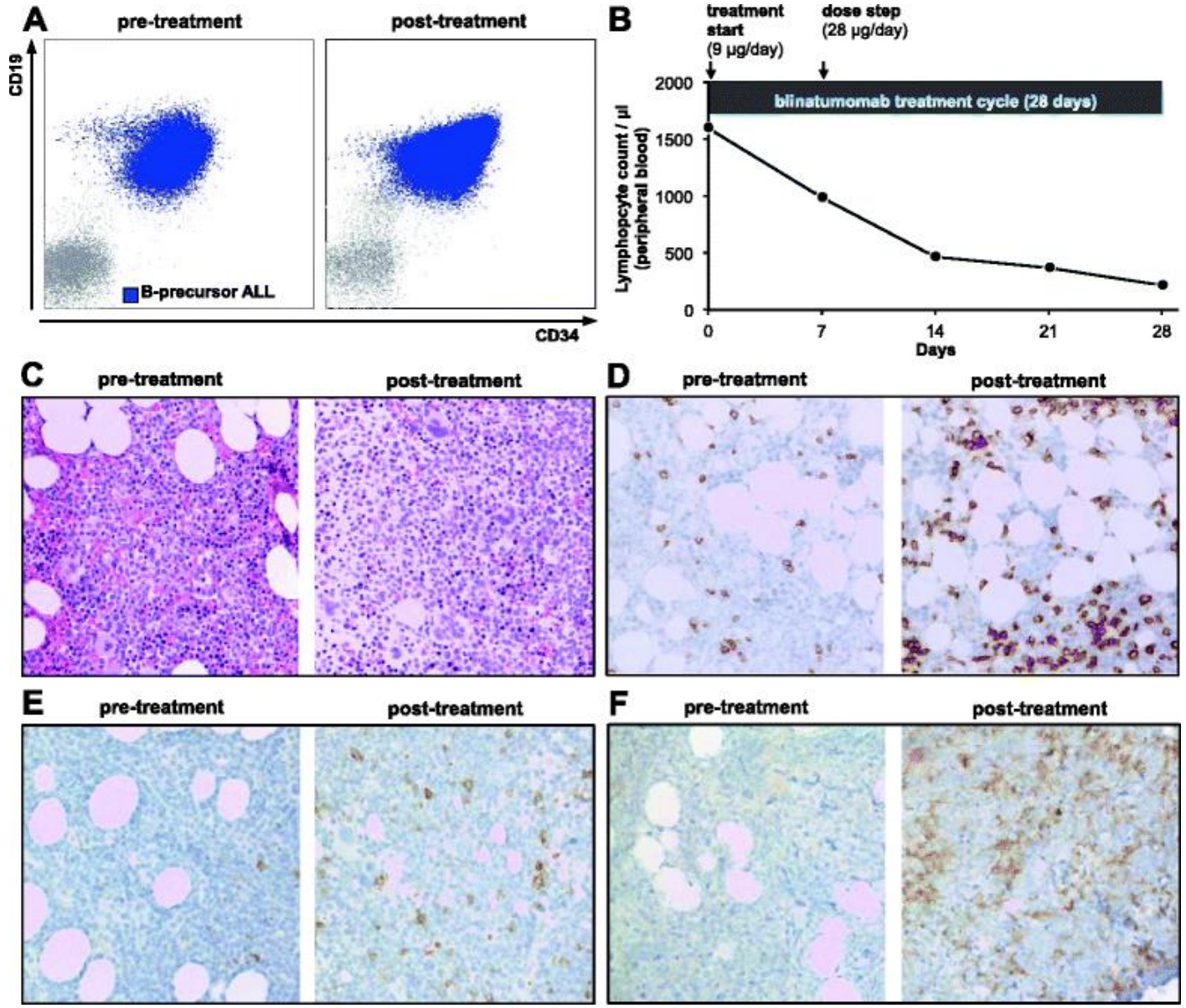
CR = Complete Response; CRm = molecular CR; CRi = Complete Response with incomplete hematological improvement; MLF = Morphologic Leukemia-free state; PR = Partial Response; SD/OB = Stable Disease/Other Anti-Leukemic Benefit; PD= Progressive Disease; (Modified ELN 2017 criteria).

† Data cut-off Nov. 30, 2017

Study Conclusions

- Flotetuzumab is a potent CD123 x CD3 bispecific DART molecule that redirects T-cells to kill CD123-positive AML blasts, in vitro and/or in vivo.
- In patients with AML, flotetuzumab has an acceptable safety profile to date.
- Encouraging initial anti-leukemic activity at ≥ 500 ng/kg/day (threshold dose) in AML pts.
- Anti-leukemic activity even in high risk patients (adverse cytogenetics).
- Cohort expansion now ongoing and enrolling at 13 sites in US and EU.

Increase of PD-L1 expressing B-precursor ALL cells in a patient resistant to the CD19/CD3-bispecific T cell engager antibody blinatumomab



Kohnke T, et al J Hematol Oncol, 2015

Conclusions

- Immunotherapy a new modality in AML
- Immunotoxins leading with GO already re-approved
- Bi-specific antibodies in early clinical trials showing activity
- Immune Checkpoint inhibitors in trials
- Potential role for these agents in MRD clearance