EARLE A. CHILES
RESEARCH INSTITUTE

Immunotherapy on the Horizon

Infinite universe, limited scope of comprehen-
sion, much too tight trousers

John Godwin, MD, MS

Program Leader Hematologic Malignancies

Robert W. Franz Cancer Research Center
Earle A Chiles Research Institute

EARLE A. CHILES RESEARCH INSTITUTE

Disclosures Relevant To Potential Commercial Bias

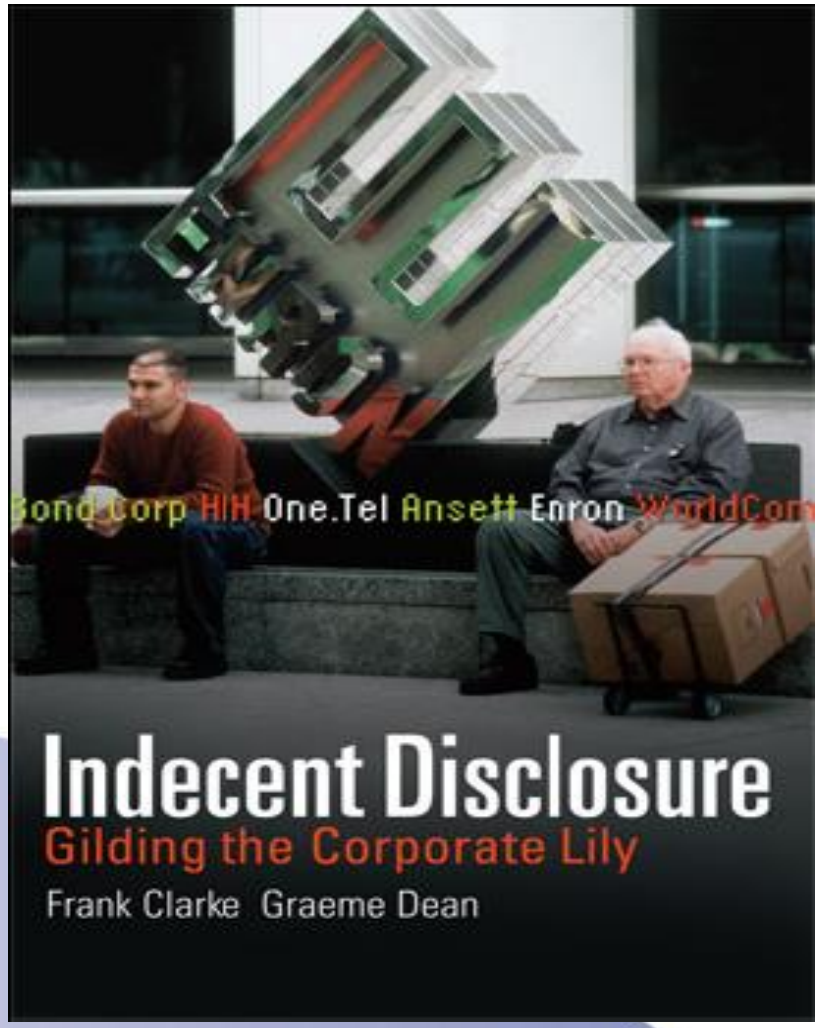
– John Godwin, MD, MS

- Speakers Bureau BMS,
- Local PI Phase I clinical trial – Macrogenics
- Local PI Phase III clinical trial – Amgen, Blinatumomab
- Institutional Grant Support - BMS

- There will be discussion about the use of products for non-FDA approved indications in this presentation.

•Rhetorical:

– Should I be an expert – if I have nothing to disclose?



EARLE A. CHILES RESEARCH INSTITUTE

Lecture Objectives

1. Describe New Immunotherapies Currently in Clinical Trial -Emphasis on Hematologic malignancies
2. Discuss Immunotherapy Cytokine Associated Toxicities
   a. Cytokine Release Syndrome (CRS)
3. T Cell Engager Therapies- Examples
   a. Blinatumomab in ALL. Cooperative Group Trial E1910
   b. First in man phase I clinical trial – MGD006 CD123 x CD3 DART

EARLE A. CHILES RESEARCH INSTITUTE

T Cell Cancer Immunotherapies- A Simple List

1. Cancer Vaccines (not further discussed)
2. mAbs that block T cell checkpoints
3. Bispecific mAbs that engage endogenous T cells
4. Adoptive T cell therapy
   a. Endogenous Tumor reactive T cells
   b. Gene modified TCRs
   c. Chimeric Antigen Receptors (CARs)

EARLE A. CHILES RESEARCH INSTITUTE

T Cell Cancer Therapies

- Check point inhibitors
- "Unleash" Immune response
- Immune reaction already present

- T Cell Engagers
- Create a Productive Immune Response

EARLE A. CHILES RESEARCH INSTITUTE

Bispecific Molecules

- Bispecific antibodies recruiting T cells have been under development for almost 20 years
- They hold the promise of mounting a polyclonal T-cell response against tumor cells by employing one of the immune system's most effective killer cell population-
- The T Cells engaged do not have T Cell Receptor specificity for the target

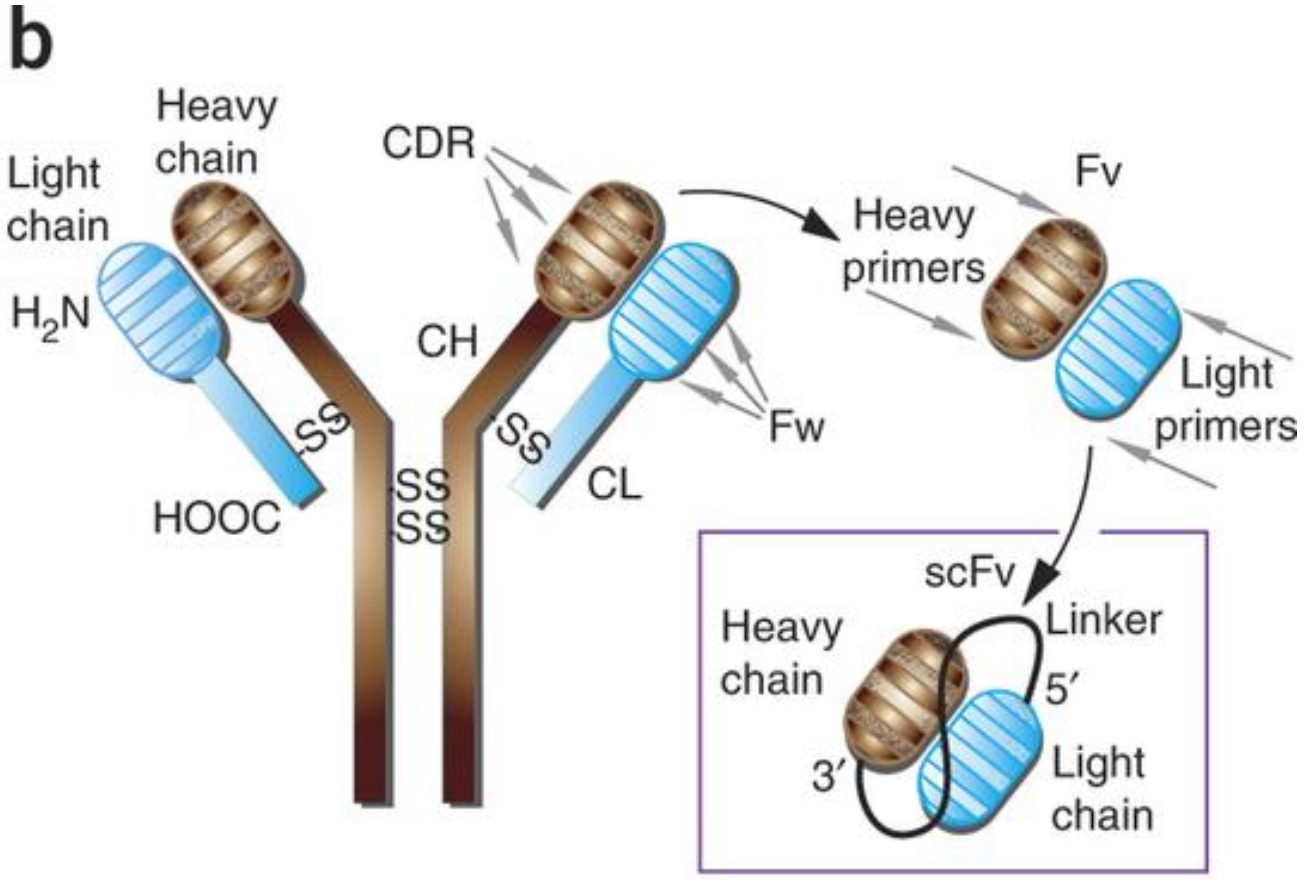
EARLE A. CHILES
RESEARCH INSTITUTE

ANTIBODY FRAGMENTS TO BISPECIFICS

EARLE A. CHILES RESEARCH INSTITUTE

scFv- Single Chain Variable Fragment

- Genetic engineering
- production of scFv- which are linked by a flexible pepetide with specific binding



Manipulation and length of the linker creates different scFV

EARLE A. CHILES RESEARCH INSTITUTE

Promise of Bispecifics in Cancer Treatment

- Activity NOT rely on Ag specific T-cell clones
- Immune escape mechanisms are less likely to impact the therapy
- Polyclonal: engages the large endogenous existing T-cell pool
- No need for MHC class I restriction, or antigen presentation
- Not only cytotoxic $CD8^+$ T -, but also $CD4^+$ T cells.

EARLE A. CHILES RESEARCH INSTITUTE

Barriers for BisAbs

- molecules are often unstable when stored or administered in vivo
- have proven difficult to produce to pharmaceutically acceptable standards
- Limited number of clinically useful targets – Tumor specific; safe

EARLE A. CHILES RESEARCH INSTITUTE

A Peak At The Plethora of BsAbs

- Many on the horizon -complex-

EARLE A. CHILES RESEARCH INSTITUTE

Table 1
Bispecific antibodies and other bispecific immunotherapeutics in clinical development.

BsAb (other names, sponsoring organizations)	BsAb format	Targets	Proposed mechanisms of action
Catumaxomab (Removab®, Fresenius Biotech, Trion Pharma, Neopharm)	BsIgG: Triomab	CD3, EpCAM	Retargeting of T cells to tumor, Fc mediated effector functions
Ertumaxomab (Neovii Biotech, Fresenius Biotech)	BsIgG: Triomab	CD3, HER2	Retargeting of T cells to tumor
Blinatumomab (Blincyto®, AMG 103, MT 103, MEDI 538, Amgen)	BiTE	CD3, CD19	Retargeting of T cells to tumor
Solitomab (AMG 110, MT110, Amgen)	BiTE	CD3, EpCAM	Retargeting of T cells to tumor
MEDI 565 (AMG 211, MedImmune, Amgen)	BiTE	CD3, CEA	Retargeting of T cells to tumor
BAY2010112 (AMG 212, Bayer; Amgen)	BiTE	CD3, PSMA	Retargeting of T cells to tumor
MGD006 (Macrogenics)	DART	CD3, CD123	Retargeting of T cells to tumor
MGD007 (Macrogenics)	DART	CD3, gpA33	Retargeting of T cells to tumor
AFM11 (Affimed Therapeutics)	TandAb	CD3, CD19	Retargeting of T cells to tumor
AFM13 (Affimed Therapeutics)	TandAb	CD30, CD16A	Retargeting of NK cells to tumor cells
GD2 (Barbara Ann Karmanos Cancer Institute)	T cells preloaded with BsAb	CD3, GD2	Retargeting of T cells to tumor
pGD2 (Barbara Ann Karmanos Cancer Institute)	T cells preloaded with BsAb	CD3, Her2	Retargeting of T cells to tumor
EGFRBi-armed autologous activated T cells (Roger Williams Medical Center)	T cells preloaded with BsAb	CD3, EGFR	Autologous activated T cells to EGFR-positive tumor
Anti-EGFR-armed activated T-cells (Barbara Ann Karmanos Cancer Institute)	T cells preloaded with BsAb	CD3, EGFR	Autologous activated T cells to EGFR-positive tumor
rM28 (University Hospital Tübingen)	Tandem scFv	CD28, MAPG	Retargeting of T cells to tumor
IMCgp100 (Immunocore)	ImmTAC	CD3, peptide MHC	Retargeting of T cells to tumor
DT2219ARL (NCI, University of Minnesota)	2 scFv linked to diphtheria toxin	CD19, CD22	Targeting of protein toxin to tumor
Duligotuzumab (MEHD7945A, Genentech, Roche)	DAF	EGFR, HER3	Blockade of 2 receptors, ADCC
LY3164530 (Eli Lily)	Not disclosed	EGFR, MET	Blockade of 2 receptors
MM-111 (Merrimack Pharmaceuticals)	HSA body	HER2, HER3	Blockade of 2 receptors
MM-141, (Merrimack Pharmaceuticals)	IgG-scFv	IGF-1R, HER3	Blockade of 2 receptors
RG7221 (RO5520985, Roche)	CrossMab	Ang2, VEGF A	Blockade of 2 proangiogenics
RG7716 (Roche)	CrossMab	Ang2, VEGF A	Blockade of 2 proangiogenics
TF2 (Immunomedics)	Dock and lock	CEA, HSG	Pretargeting tumor for PET or radioimaging
ABT-981 (AbbVie)	DVD-Ig	IL-1α, IL-1β	Blockade of 2 proinflammatory cytokines
ABT-122 (AbbVie)	DVD-Ig	TNF, IL-17A	Blockade of 2 proinflammatory cytokines
COVA322	IgG-fynomer	TNF, IL17A	Blockade of 2 proinflammatory cytokines

>30 BsAb in clinical development

Spies et. al. Alternative molecular formats and therapeutic applications for bispecific antibodies (Mol Immunol 2015)

EARLE A. CHILES RESEARCH INSTITUTE

Examples from Real World Use

Blinatumomab-CD19xCD3

First Bispecific antibody approved for Cancer Treatment

MGD006 – CD123xCD3

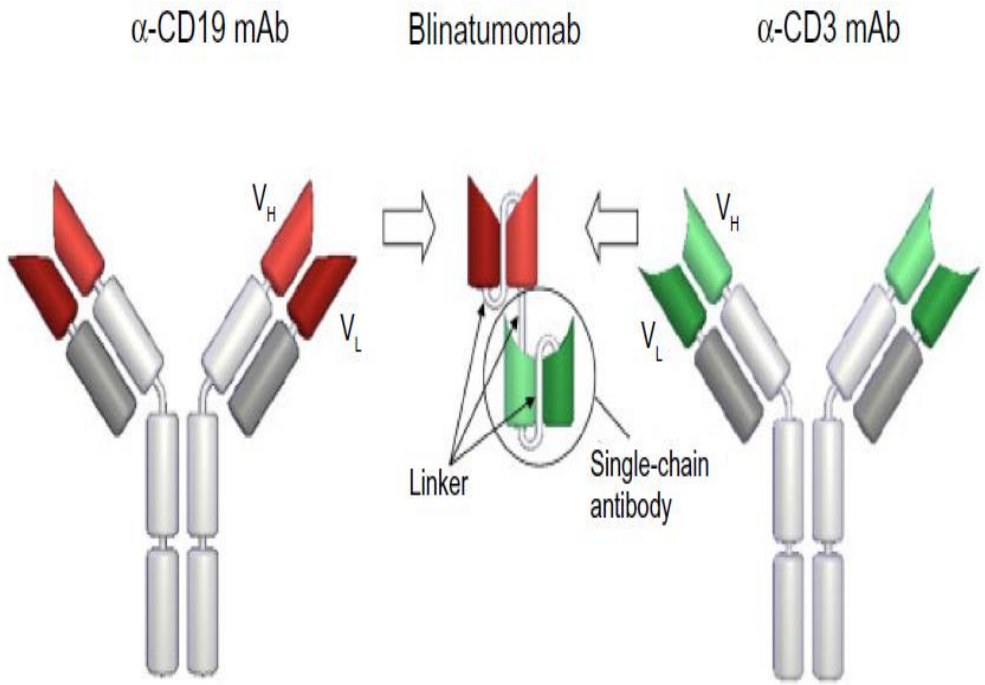
Dual Affinity Re-Targeting (DART) Bi-Specific

Antibody-Based Molecule

EARLE A. CHILES RESEARCH INSTITUTE

Blinatumomab CD19 X CD3 construct

- Blinatumomab is made of scFvs that form a 55 kDa fusion protein
- _Recombinant DNA corresponding VL and VH regions cloned into separate plasmid vectors as templates.
- VL_{CD19}-VH_{CD19}-VH_{CD3}-VL_{CD3}
- LINKER thought to give the two scFvs a significant degree of rotational ability to enhance binding of epitopes on separate cells



Pharmacology & Therapeutics 136 (2012) 334–342

EARLE A. CHILES RESEARCH INSTITUTE

Not T Cell Agonist In Isolation

- Blinatumomab alone does not activate T CELLS-
  - Purified T cells NOT activated in absence of CD19 expressing cells
- Conversely – Blin does not cause apoptosis of purified CD19 B cells
- All T-cell populations except naive T cells showed high-level redirected lysis.
- resting T cells – effective- no need for prior activation

Nagorsen et al. / Pharmacology & Therapeutics 136 (2012) 334–342

Potent

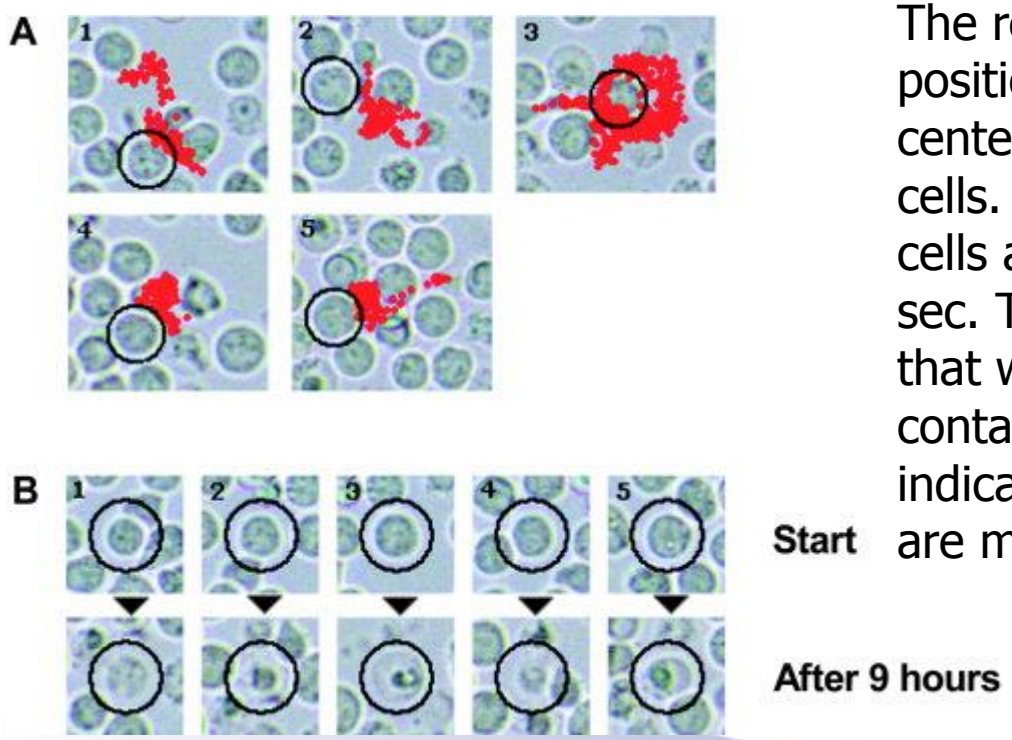
- Blinatumomab was found to be extremely potent,
  - Measured as half-maximum concentration for redirected lysis of CD19-positive target cells of 10–100 pg/mL using T cells from healthy donors
- The clinical target dose of 15µg/m2/day gives a steady state concentration of about 730 pg/ml

EARLE A. CHILES RESEARCH INSTITUTE

Serial killing of tumor cells by cytotoxic T cells redirected with a CD19-/CD3-bispecific single-chain antibody construct

BsCD19xCD3 alters the behaviour of T cells

Prolonged contacts of 1 individual T cell with 5 different NALM-6 B lymphoma cells during a 9 hr incubation.



The red dots indicate the positions of the mass center of individual T cells. The positions of T cells are shown every 18 sec. Those target cells that were in longest contact with the T cell, as indicated by trajectories, are marked by a circle.

International Journal of Cancer
Volume 115, Issue 1, pages 98-104, 1 FEB 2005 DOI: 10.1002/ijc.20908
http://onlinelibrary.wiley.com/doi/10.1002/ijc.20908/full#fig2

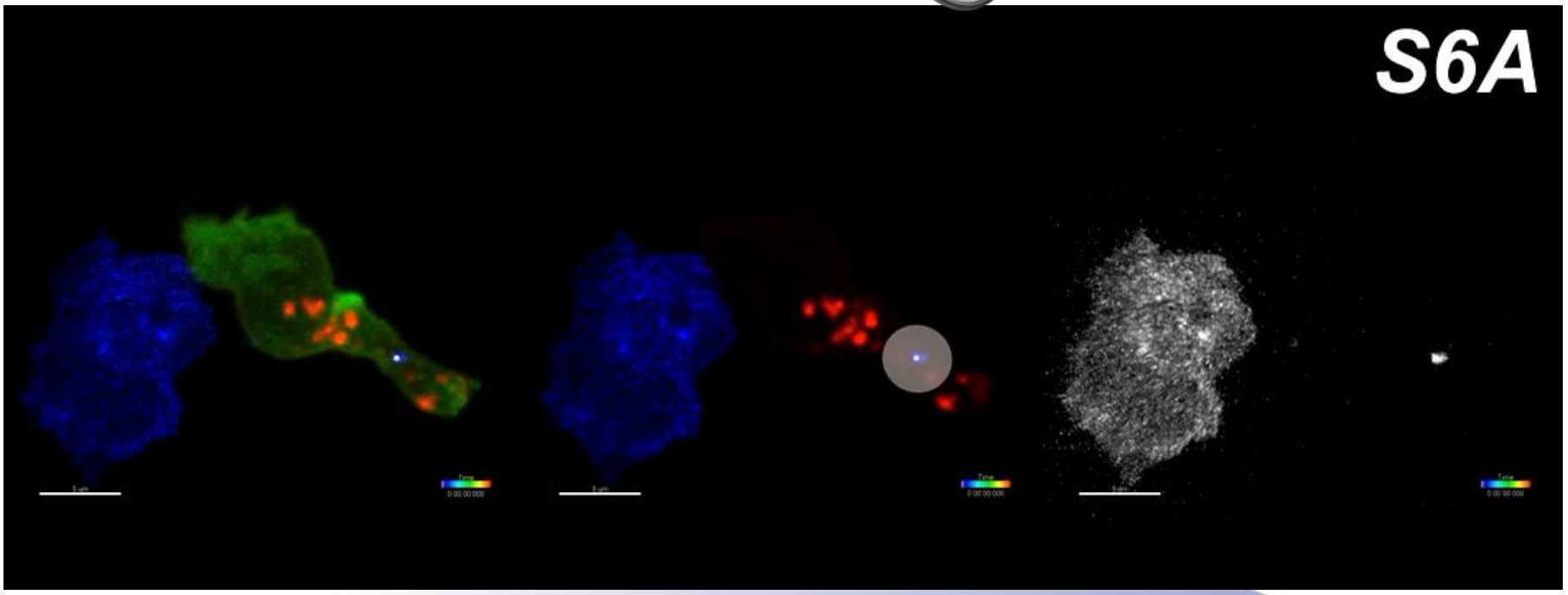
EARLE A. CHILES RESEARCH INSTITUTE

T-cell “Serial Killer”

- BiTE-activated T cells were shown to kill cancer cells by membrane perforation using perforin, granzymes
- At high effector Target ratios- killing is rapid
- Both CD8 and CD4 cells kill targets
- Serial lysis was observed by video microscopy- a single Tcell can latch on to kill and disengage over 30-200min

EARLE A. CHILES
RESEARCH INSTITUTE

4D Dynamics of Cytolytic Granules in Relation to Cytoskeletal Elements
(A) Time-lapse maximum intensity projection images of confocal sections taken through a CTL expressing Lifeact-EGFP, CD63-mCherry, and PACT-TagBFP as it interacts with an EL4-blue target cell



Killer T-Cell ;Credit: Gillian Griffiths/Jonny Settle

EARLE A. CHILES RESEARCH INSTITUTE

Phase I Blinatumomab

- First in Man Phase I studies- began in 2001
- Pts w relapsed / refractory NHL
- doses ranging from 0.75–13 μg/m^2 administered once, twice, or three times weekly as 2- or 4-hour intravenous infusions.
- Adverse events included fever, rigors, and fatigue. **Significant neurologic** events included aphasia, ataxia, disorientation, and seizures and led to discontinuation of therapy in 6 of 22 patients. Cytokine release syndrome and infections were also observed

D. Nagorsen et al. / Pharmacology & Therapeutics 136 (2012) 334–342

EARLE A. CHILES RESEARCH INSTITUTE

Phase I Blinatumomab

1. Following initiation of Blinatumomab infusion, T cells transiently disappeared from the circulation
2. Then re-appeared with activated phenotype, including expression of CD25 and CD69
3. For many pts T Cell counts expanded both CD4 and CD8, with the phenotype of effector memory cells

Ther Adv Hematol
2016, Vol. 7(3) 142–156

EARLE A. CHILES RESEARCH INSTITUTE

Change to CIV Infusion

- Based the short serum half-life of blinatumomab in humans of ~2 h
- And mechanism of action relying on a continued search-and-destroy mode of BiTE®-antibody-engaged T cells
- Changed to CIV dosing-
- This has become the standard for all treatments

EARLE A. CHILES RESEARCH INSTITUTE

Dose in ALL vs NHL

1. The MTD in NHL was 60µg/m2/day
2. Doses as low as 15µg/m2/day were effective in bone marrow involvement
3. In ALL the optimal dose was found to be 5 µg/m2/day – with a step up
4. stepped up to 15µg/m2/day
5. There was no additional benefit for higher doses in ALL

Ther Adv Hematol
2016, Vol. 7(3) 142–156

EARLE A. CHILES RESEARCH INSTITUTE

Topp, et. al. ALL Phase II

1. 189 PH1 neg ALL patients 2012-2013, enrolled and treated with Blinatumomab .
2. Primary refractory or relapsed within 12 mo of remission or relapse p AlloHSCT
3. After two cycles, 81 (43%, 95% CI 36–50) patients had achieved a CR or CRh: 63 (33%) patients had a CR and 18 (10%) patients had a CRh

Lancet Oncol 16: 57–66.
Jan 2015

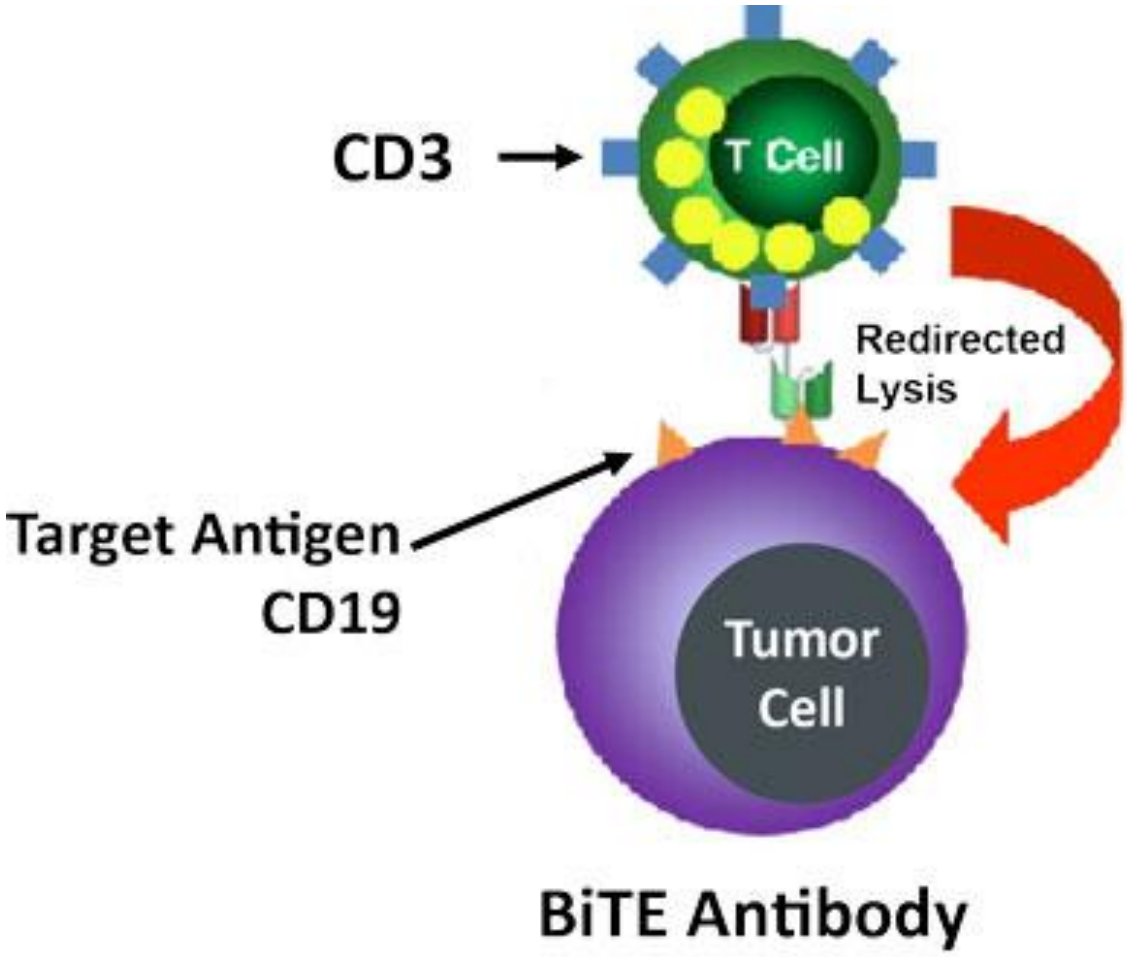
EARLE A. CHILES RESEARCH INSTITUTE

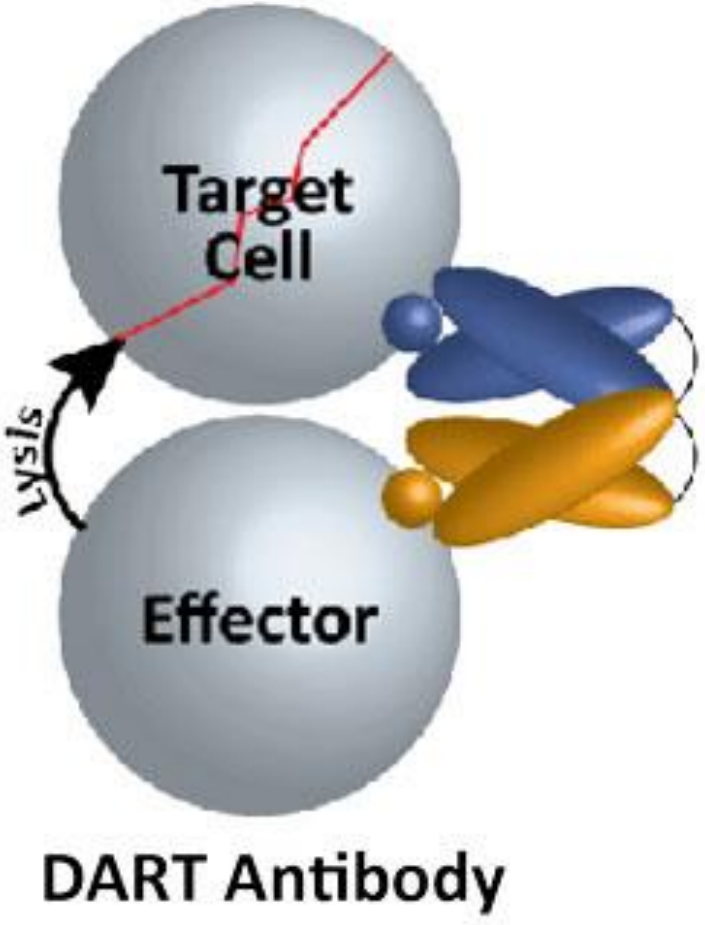
Topp, et. al. ALL Phase II

1. Study required pre-treatment w dexamethasone 10-24 mg /m2 per day up to 5 days for those with blasts >50% in marrow, or PB blasts >#15,000
2. Dex stopped 3 days before Blin
3. 9 µg/day for 1 week, then 28 µg/day for
4. 3 weeks to reduce risk of cytokine release syndrome.
5. required dexamethasone (20 mg) premedication within 1 h before treatment initiation in each cycle

Lancet Oncol 16: 57–66.
Jan 2015

DART v BiTE





bispecific T-cell engager

Dual affinity re-targeting

EARLE A. CHILES RESEARCH INSTITUTE

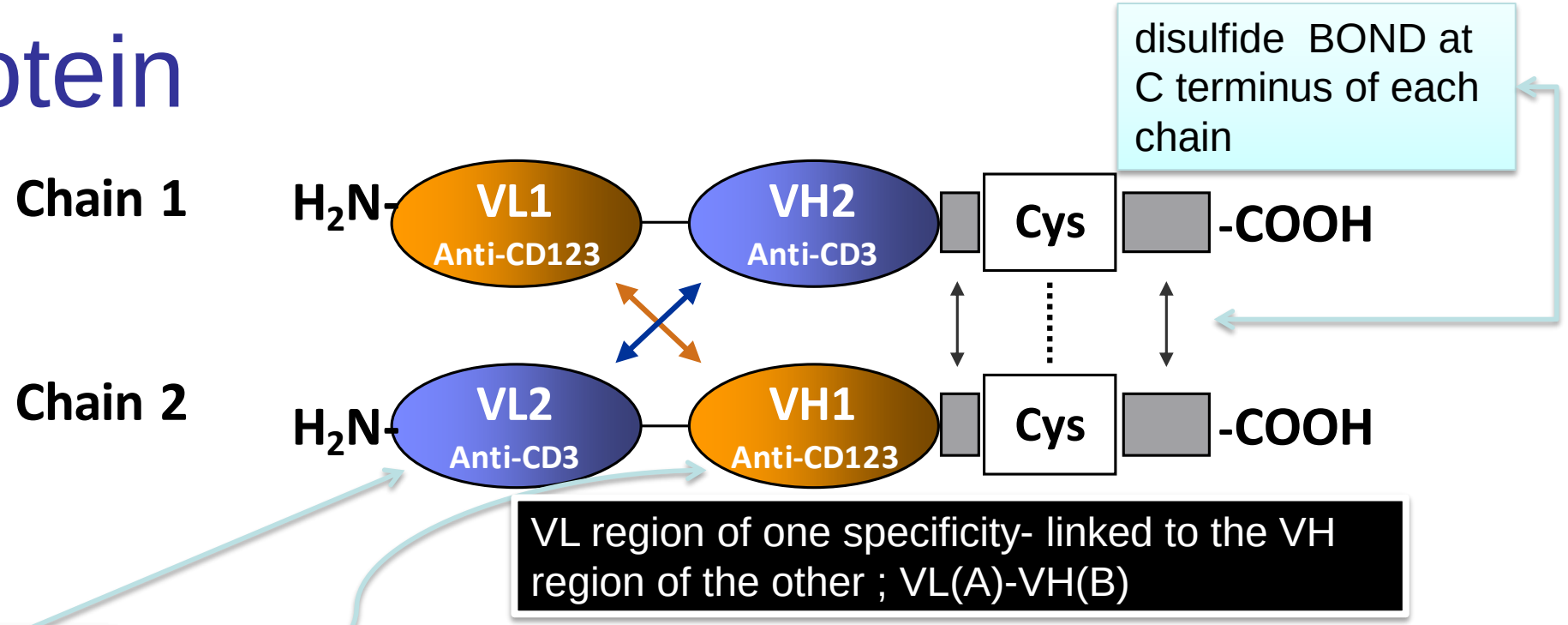
BiTE vs DART

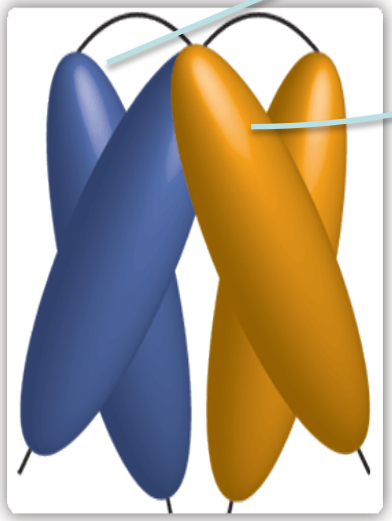
1. DART architecture is well suited for maintaining cell-to-cell contact,
2. apparently contributing to the high level of target cell killing.
3. CD19 x TCR and CD19 x CD3 DARTs have demonstrated in vitro killing of B-cell lymphomas by human T cells or peripheral blood mononuclear cells (PBMCs) that exceeds the killing with a similar bispecific antibody construct, BiTE

Application of dual affinity retargeting molecules to achieve optimal redirected T-cell killing of B-cell lymphoma. Blood 2011 Apr 28;117(17):4542-51.

EARLE A. CHILES RESEARCH INSTITUTE

MGD006: CD123 x CD3 DART Protein





Equilibrium Dissociation Constants (K_D) for the Binding of MGD006 to Human and Cynomolgus Monkey CD3 and CD123

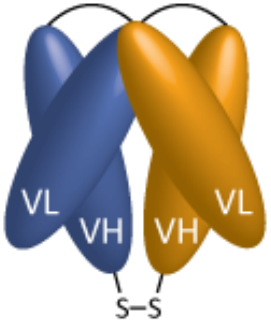
Antigens	k_a (± SD) ($M^{-1}s^{-1}$)	k_d (± SD) (s^{-1})	K_D (± SD) (nM)
Human CD3ε/δ	5.7 (± 0.6) x 10^5	5.0 (± 0.9) x 10^{-3}	9.0 ± 2.3
Cynomolgus CD3ε/δ	5.5 (± 0.5)x 10^5	5.0 (± 0.9) x 10^{-3}	9.2 ± 2.3
Human CD123-His	1.6 (± 0.4) x 10^6	1.9 (± 0.4) x 10^{-4}	0.13 ± 0.01
Cynomolgus CD123-His	1.5 (± 0.3)x 10^6	4.0 (± 0.7) x 10^{-4}	0.27 ± 0.02

The data are averages of 3 independent experiments each performed in duplicates.

Science Translational Medicine 27 May 2015: Vol. 7, Issue 289, pp. 289ra82

EARLE A. CHILES RESEARCH INSTITUTE

CD123= IL-3Rα



- CD123, the interleukin-3 receptor alpha chain (IL-3R α)
- CD123 is constitutively expressed on normal HSC.
- The majority of AML blasts express surface CD123.
- Leukemic Stem Cells (LSCs) are CD34+ CD38- **and express CD123** consistently at a higher density than observed for normal CD34 cells

- Redirected T-cell killing against targeted leukemia cells
  - –Selective elimination of leukemic stem cells
  - –Sparing of normal hematopoietic stem cells
- Anticipate very low dosing (ng/kg)

EARLE A. CHILES RESEARCH INSTITUTE

Toxicity of Cancer Immunotherapy

- **autoimmune toxicity** /
- Autoimmune toxicity, so-called “on target, off-tumor toxicity,” results from antigen-specific attack on host tissues that express the tumor target antigen
- Checkpoint inhibitors

- **cytokine-associated toxicity**.
- Cytokine-associated toxicity, also known as cytokine release syndrome (CRS), is a non–antigen specific toxicity that occurs as a result of high-level immune activation
- T Cell Engagers

EARLE A. CHILES RESEARCH INSTITUTE

CRS

- Cytokine-associated toxicity,
- cytokine release syndrome (CRS),
  - a **non–antigen-specific toxicity** that occurs as a result of intensive immune activation.

Lee et. al. Blood. 2014;124(2):188-195)

- CRS

Organ system	Symptoms
Constitutional	(BAD FLU LIKE) Fever, rigors,, fatigue, anorexia, **myalgias, arthalgias**, nausea, vomiting, headache
Gastrointestinal	Nausea, vomiting, diarrhea, Transaminitis, hyper bilirubinemia
Skin	rash
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, hypotension, increased cardiac output (early), diminished LVEF(late), QT prolongation, troponinemia
Coagulation Renal	Elevated D-dimer, hypofibrinogenemia ± bleeding AKI, TLS, hyponatremia, hyokalemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, altered gait, seizures

Lee et. al. Blood. 2014;124(2):188-195)

CRS Grading

EARLE A. CHILES RESEARCH INSTITUTE

Lee et al. Blood 2014		CTCAE 4.03	
Grade 1	Symptoms are not life threatening and require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgias, malaise)	Grade 1	Mild reaction; infusion interruption not indicated; intervention not indicated
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement <40% or hypotension responsive to fluids or low dose of one vasopressor or grade 2 organ toxicity	Grade 2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement ≥ 40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis	Grade 3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
Grade 4	Life-threatening symptoms Requirements for ventilator support or Grade 4 organ toxicity (excluding transaminitis)	Grade 4	Life-threatening consequences; pressor or ventilatory support indicated
Grade 5	Death	Grade 5	Death

Lee et. al. Blood. 2014;124(2):188-195)

CRS Management
Lee et al. Blood 2014

EARLE A. CHILES RESEARCH INSTITUTE

Cytokine Release Syndrome Grading assessment	Extensive co-morbidities or older age? No/Yes	Treatment
Grade 1: **•Fever (defined as ≥ 38.3** **•Constitutional symptoms**	N/A	• Vigilant supportive care • Assess for infection • Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed
Grade 2: **•Hypotension: responds to fluids or one low dose vasopressor** **•Hypoxia: responds to <40% O2** **•Organ toxicity: grade 2**	No	• Vigilant supportive care • As above for grade 1 • Monitor cardiac and other organ function closely
Grade 2: **•Hypotension: responds to fluids or one low dose vasopressor** **•Hypoxia: responds to <40% O2** **•Organ toxicity: grade 2**	Yes	• Vigilant supportive care • As above for grade 2 • Consider tocilizumab ± corticosteroids
Grade 3: **•Hypotension: requires multiple vasopressors or high dose vasopressors** **•Hypoxia: requires ≥ 40% O^2** **•Organ toxicity: grade 3, grade 4, transaminitis**	N/A	
Grade 4 **•Mechanical ventilation** **•Organ toxicity: grade 4 excluding transaminitis**	N/A	

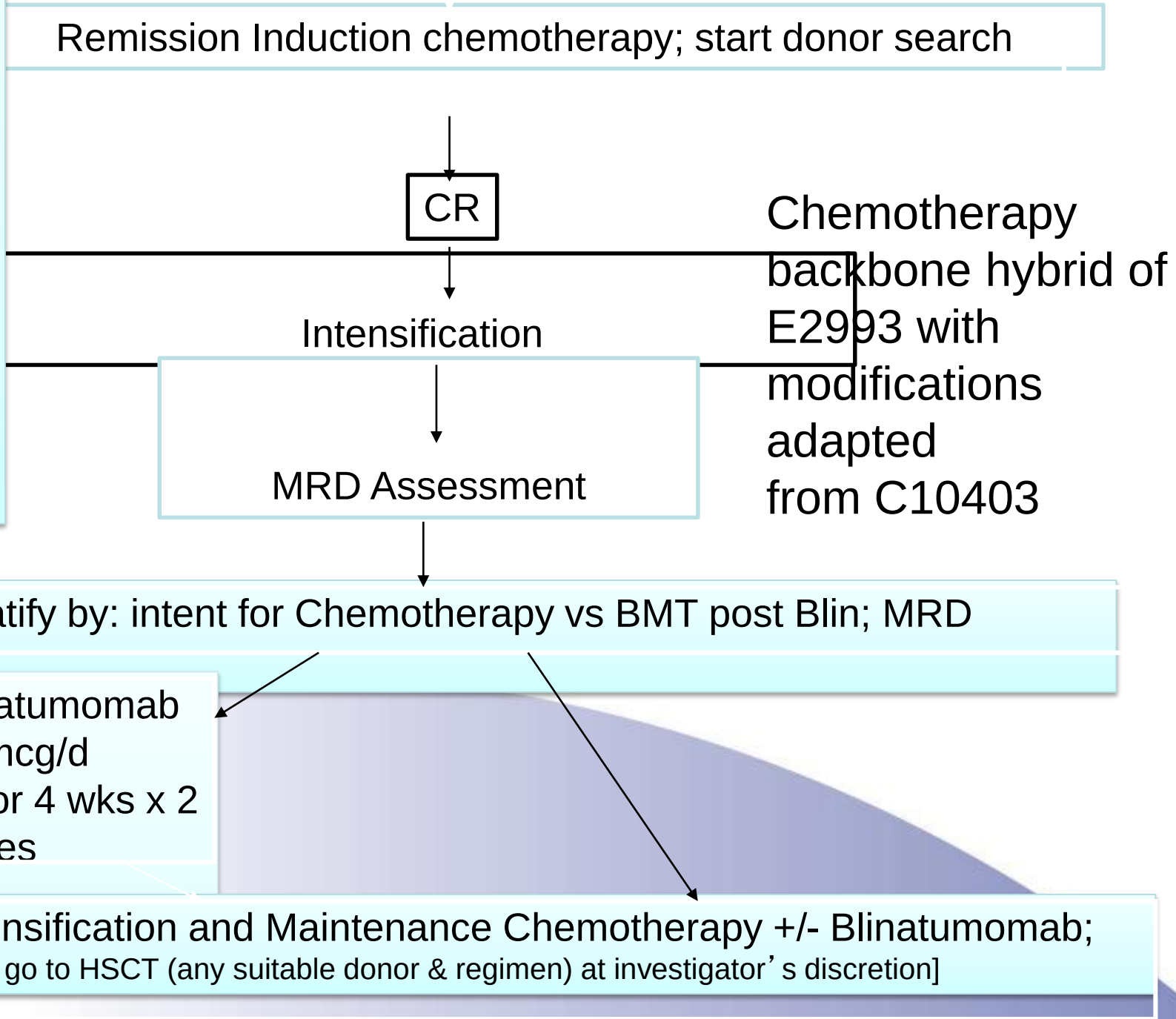
Lee et. al. Blood. 2014;124(2):188-195)

Newly diagnosed Ph neg B-ALL, age 40-70

EARLE A. CHILES RESEARCH INSTITUTE

E1910

A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed bcr-abl negative B ALL in Adults



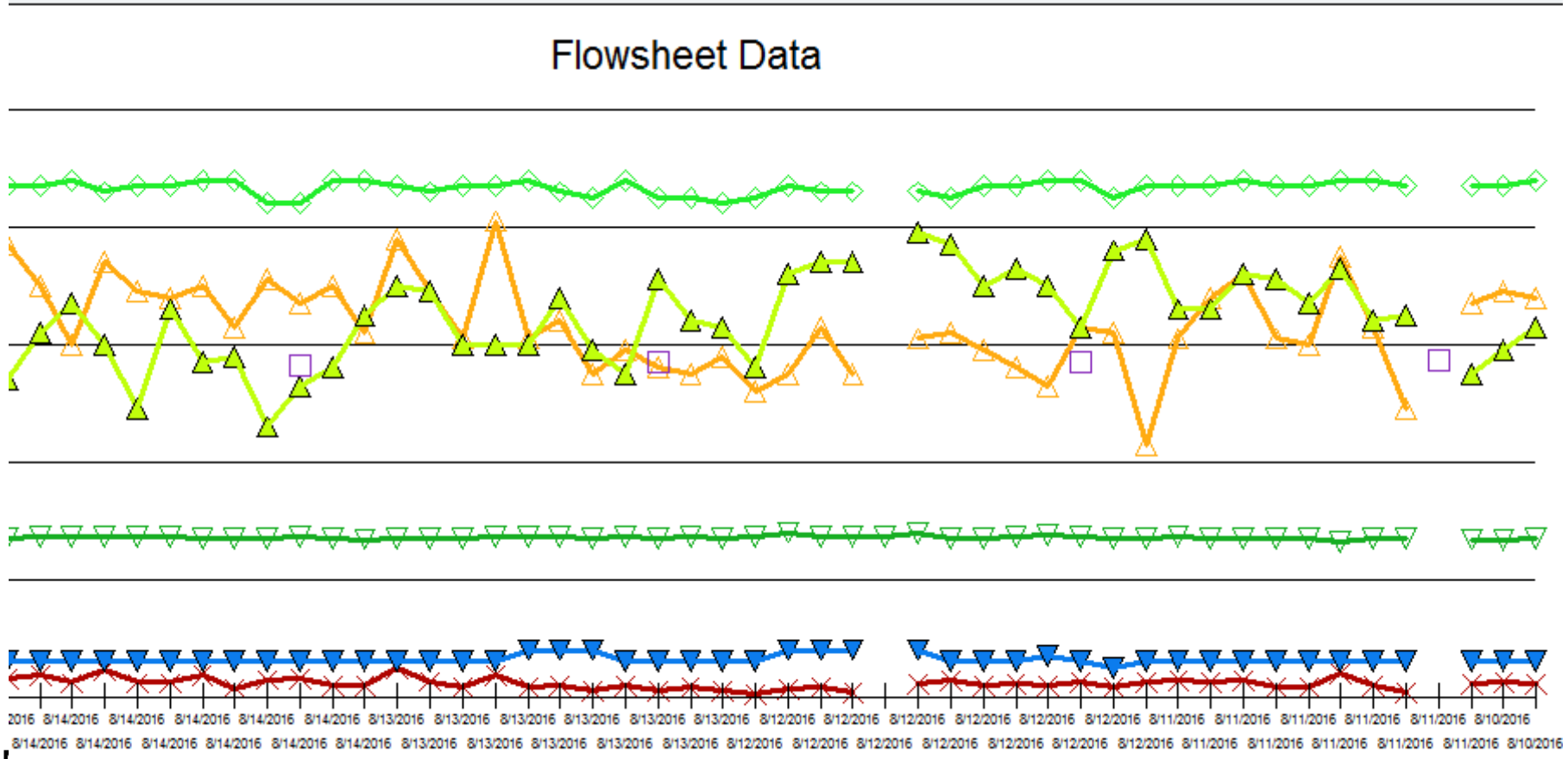
EARLE A. CHILES RESEARCH INSTITUTE

Pt R.M.

1. 32 yr male pre B ALL enrolled on E1910
2. Randomized to Blinatumomab
3. Admission on 8/10/16

R.M. week 1

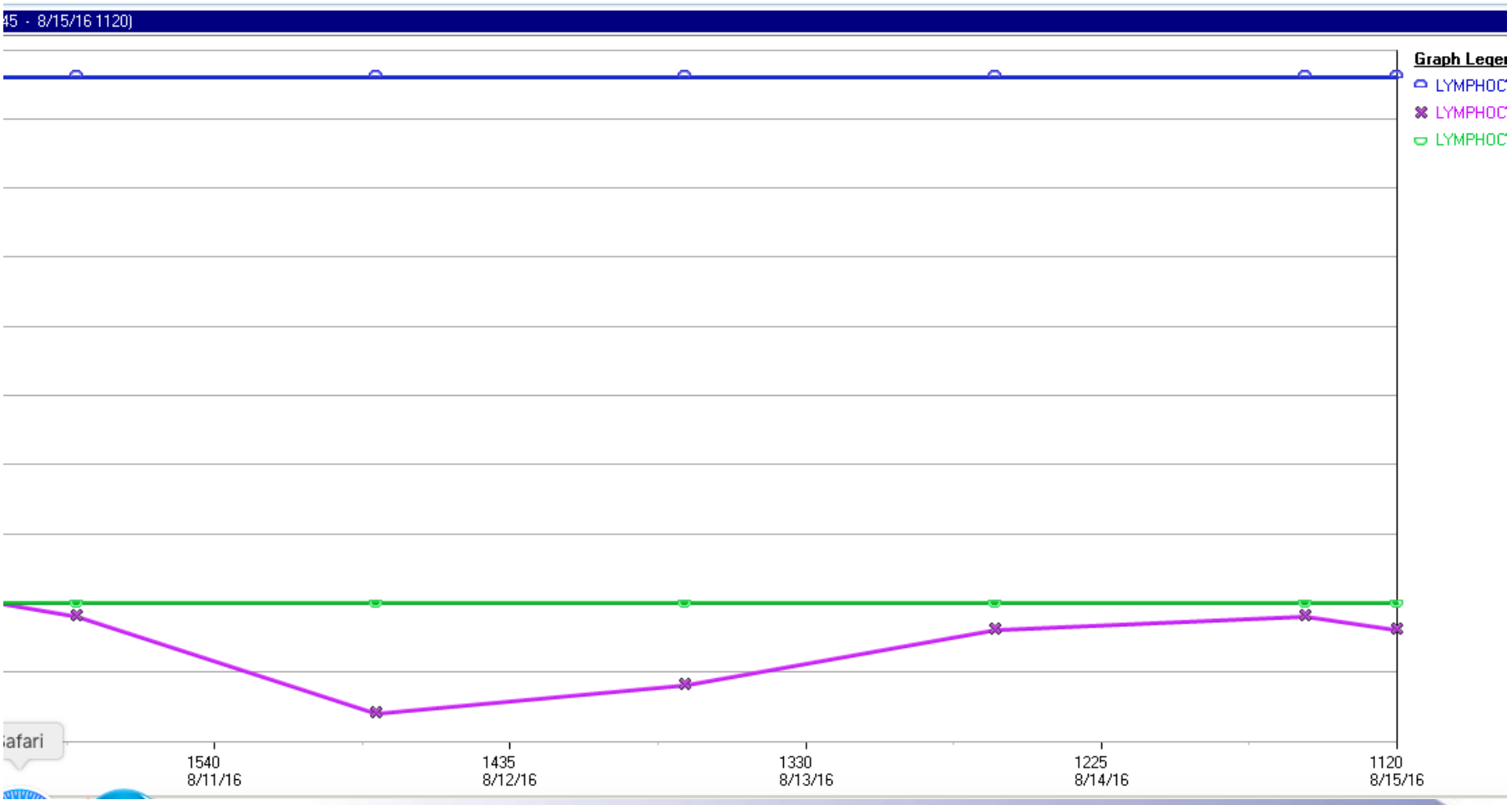
EARLE A. CHILES RESEARCH INSTITUTE



The graph shows the data in reverse-chronological order (8/15/2016 - 8/10/2016)

EARLE A. CHILES
RESEARCH INSTITUTE

R.M. Lymphocytes –



EARLE A. CHILES
RESEARCH INSTITUTE

A Phase 1, First-in-Human, Dose Escalation Study of MGD006,
a CD123 x CD3 Dual Affinity Re-Targeting (DART)
Bi-Specific Antibody-Based Molecule,
in Patients with Relapsed or Refractory Acute Myeloid Leukemia

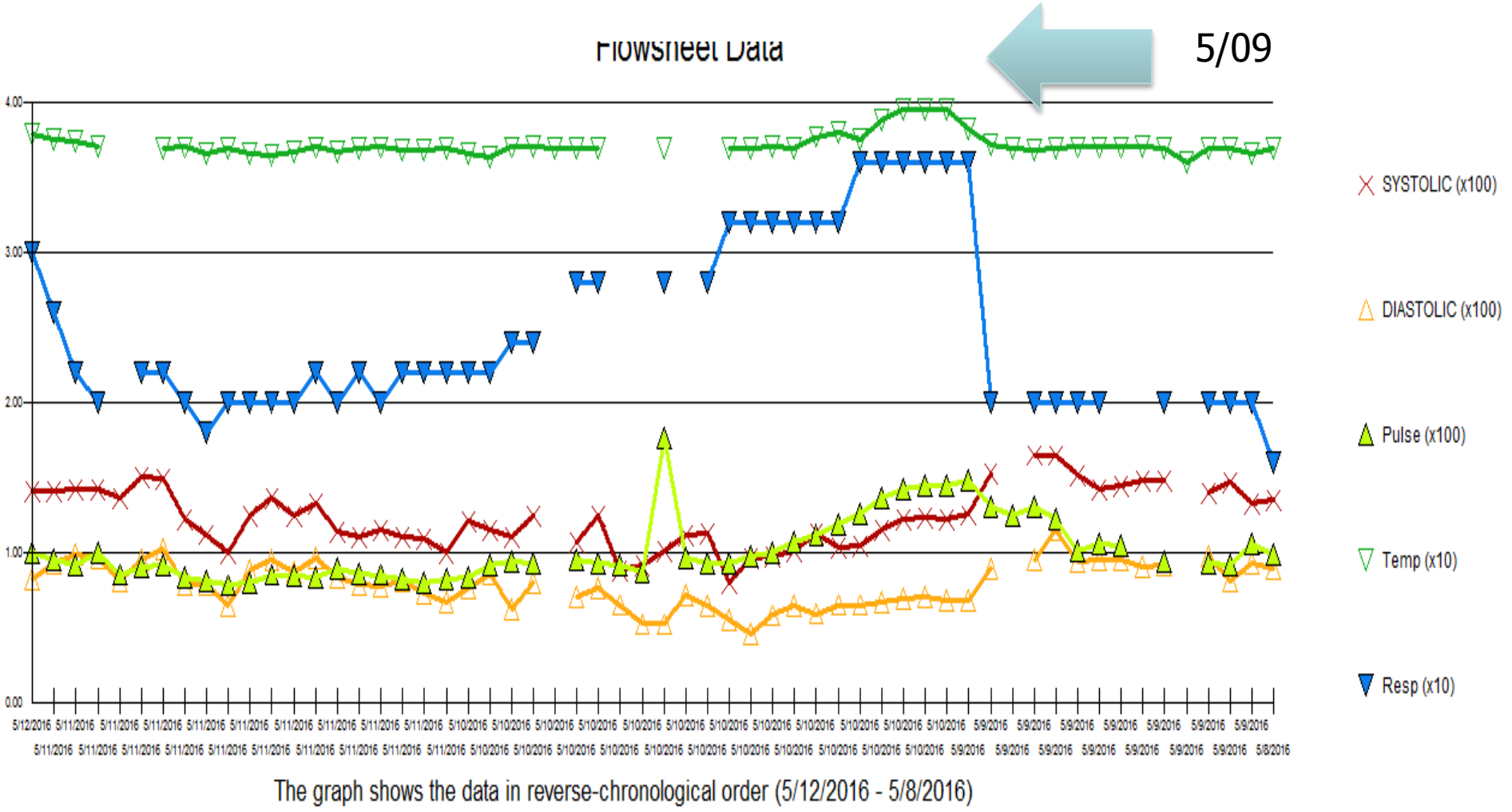
CP-MGD006-01

EARLE A. CHILES RESEARCH INSTITUTE

Patient- S.Q. MGD006

1. S.Q.: 54 yr old male, relapsed AML.
2. Dx 8/2012. induction x2, CR 11/2012. consolidation x3.
3. 1st Relapse 9/2013. 10/2013 second CR, no transplant. Vidaza 12/2013- 12/2015
4. 2nd Relapse 12/2015
   a. No CR despite 2 inductions
5. Admission 5/09/16 for study drug
6. Start time MGD-006 is 3:12pm- 5/09/16

EARLE A. CHILES RESEARCH INSTITUTE



The graph shows the data in reverse-chronological order (5/12/2016 - 5/8/2016)

5/9- 5/10: Grade 2 CRS as evidenced by grade 2 hypotension (BP min 80/55), grade 2 pyrexia (24hr tmax 39.5C), tachycardia and tachypnea. Tocilizumab administered at 0200; total of 2.5L NS boluses given. Infusion held per protocol. Once VSS, infusion resumed at 1334 on 5/10 at 30 ng/kg/hr.

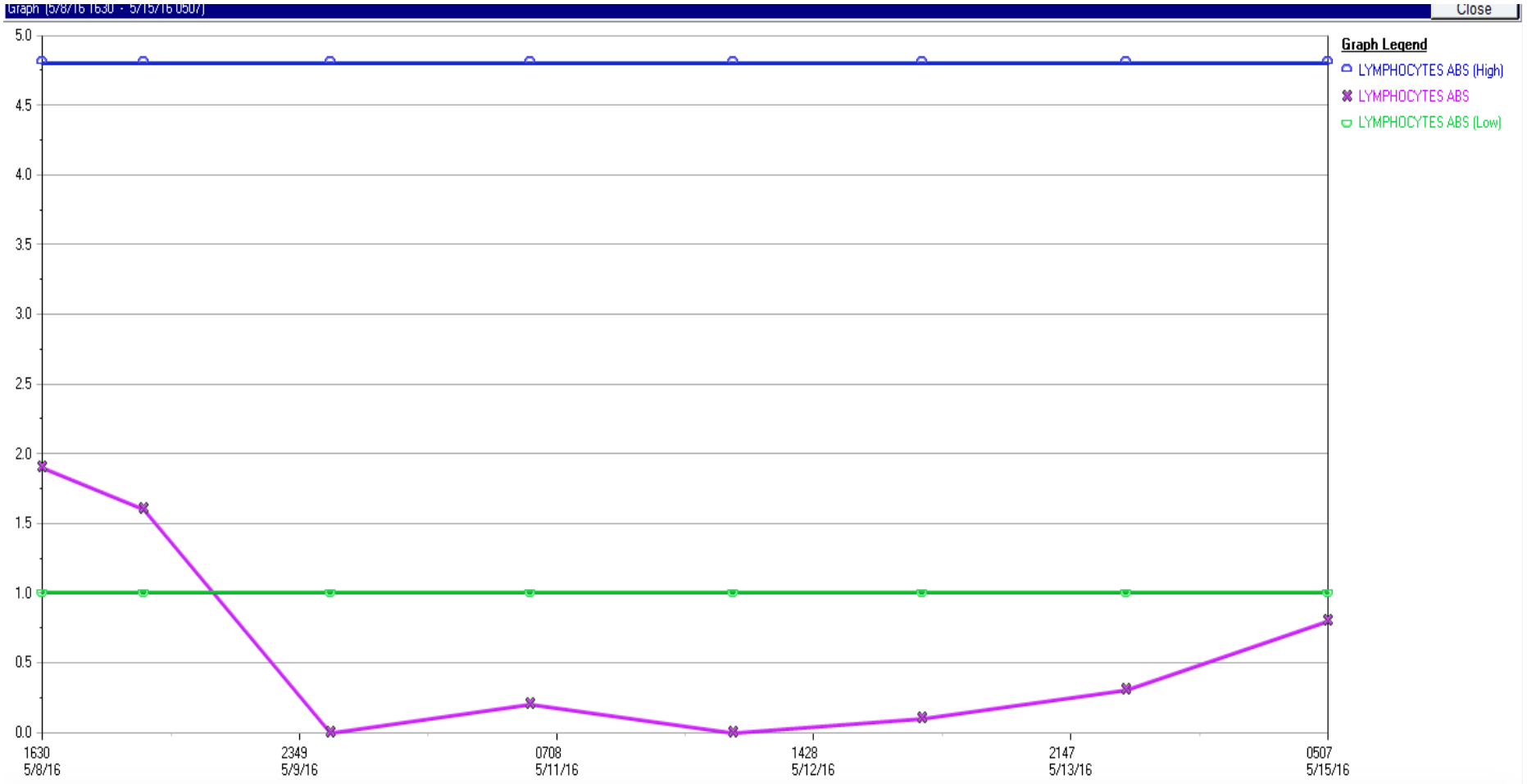
EARLE A. CHILES RESEARCH INSTITUTE

S.Q.- Subsequent Events

- **Week 2 infusion 5/16-5/17:** Grade 2 CRS
- Infusion held at 1500. Toci given at 1543.
- **5/17-5/18:** Grade 2 CRS
  - . Toci 4 mg/kg hung at 1600 and 500 NS bolus given. Patient febrile at completion of toci. MGD infusion stopped and held for 3 hours
- **5/18-5/19:** Tolerating infusion at goal rate of 500 ng/kg/hr.
  - New generalized erythema and joint aches (hands).
- **5/19-5/20**: CRS grade 1

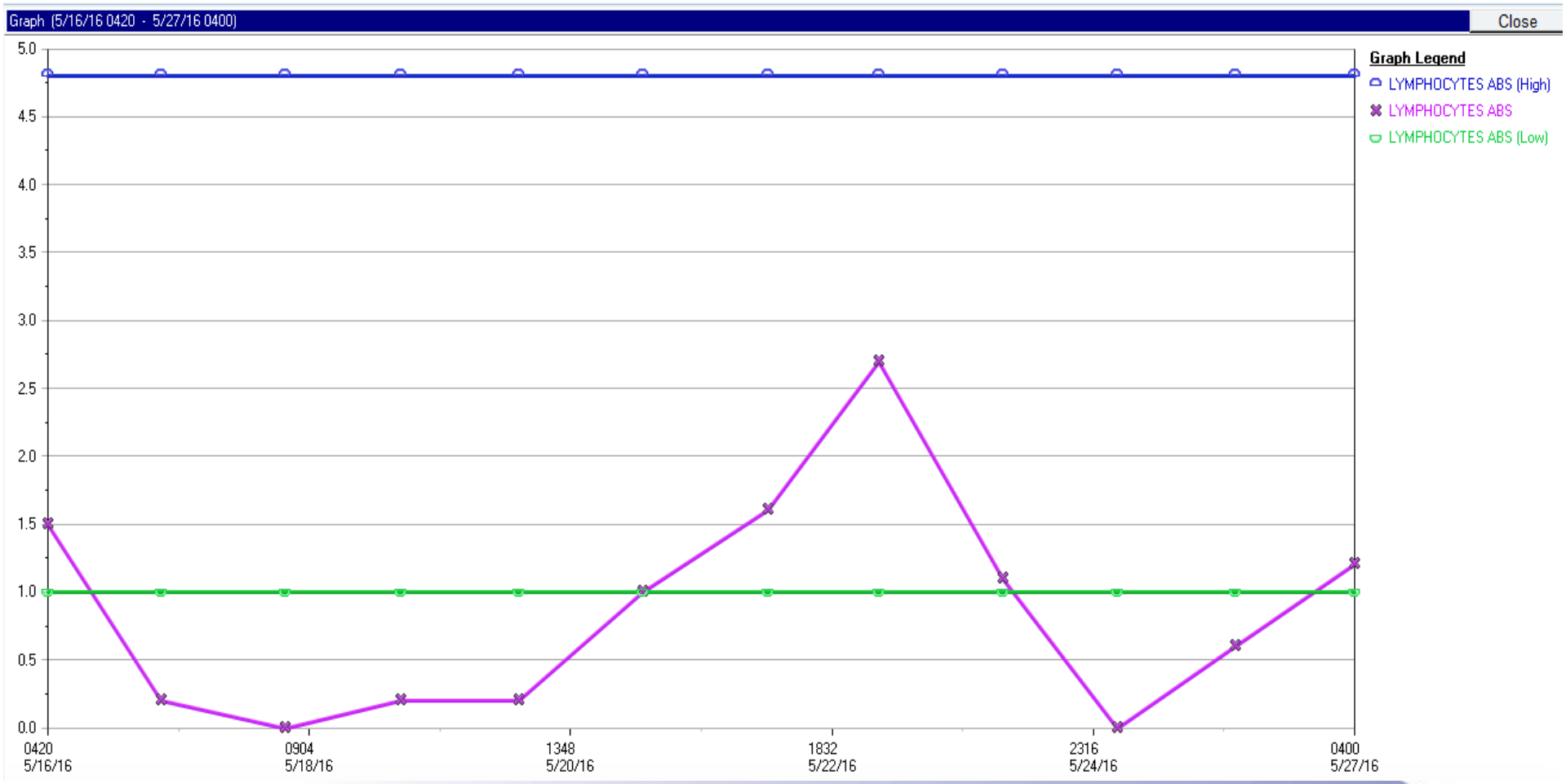
EARLE A. CHILES RESEARCH INSTITUTE

SQ lymphocytes Wk 1 Start



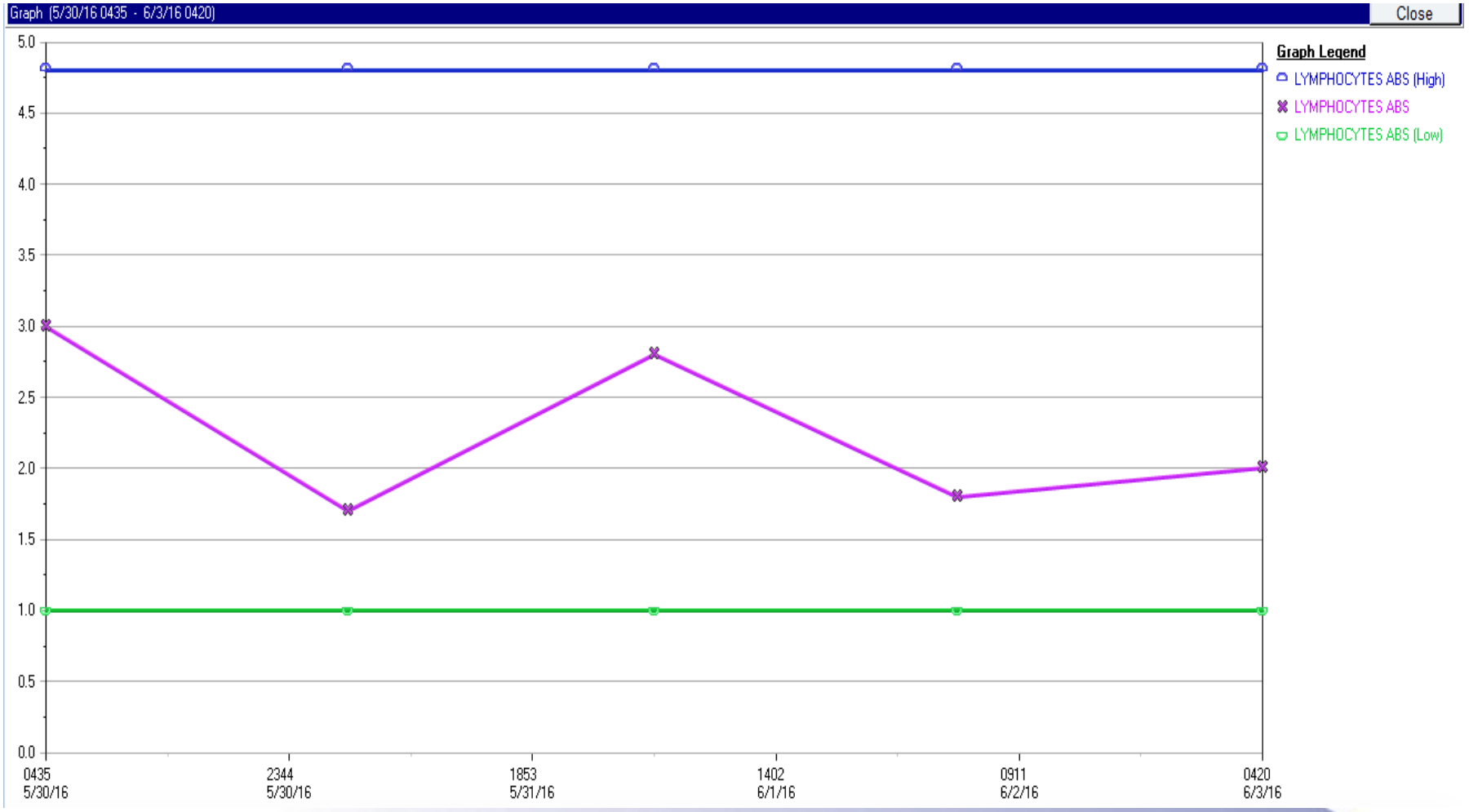
EARLE A. CHILES RESEARCH INSTITUTE

S.Q. –Lymphocytes wk2,3



EARLE A. CHILES RESEARCH INSTITUTE

S.Q. Wk 4



Week 4 infusion started 5/30 @ 0748. **5/30-5/31:** CRS Grade 1 as evidenced by hypotension (102/68) and pyrexia (38C). Hypotension resolved with MIVF rate increase and fever was responsive to tylenol. Infusion continues at goal rate.

EARLE A. CHILES RESEARCH INSTITUTE

Considerations

1. Different drugs
2. Different diseases
3. Markedly different CRS potential

EARLE A. CHILES RESEARCH INSTITUTE

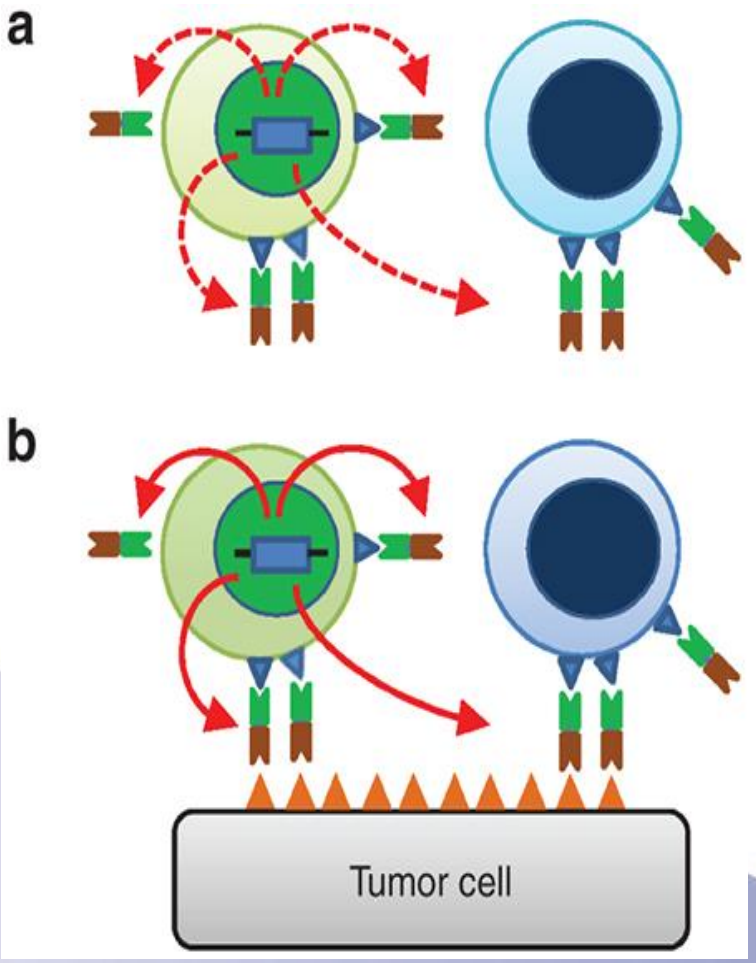
New Directions

- Engager T Cells: A New Class of Antigen-specific T Cells That Redirect Bystander T Cells
  - *Molecular Therapy* (2015); **23** 1, 171–178.
- report the generation of T cells that themselves secrete a bispecific T-cell engager (ENG T cells) specific both for CD3 and the tumor-associated antigen

EARLE A. CHILES RESEARCH INSTITUTE

Engager T Cell Secretion

Model of ENG T-cell mode of action. (**a**) ENG T cells (light green) express and secrete engager molecules
(**b**) Once engager bind antigen, ENG and bystander T cells are activated



Iwahori. *Molecular Therapy* (2015); **23** 1, 171–178.

EARLE A. CHILES
RESEARCH INSTITUTE

Discussion And Close