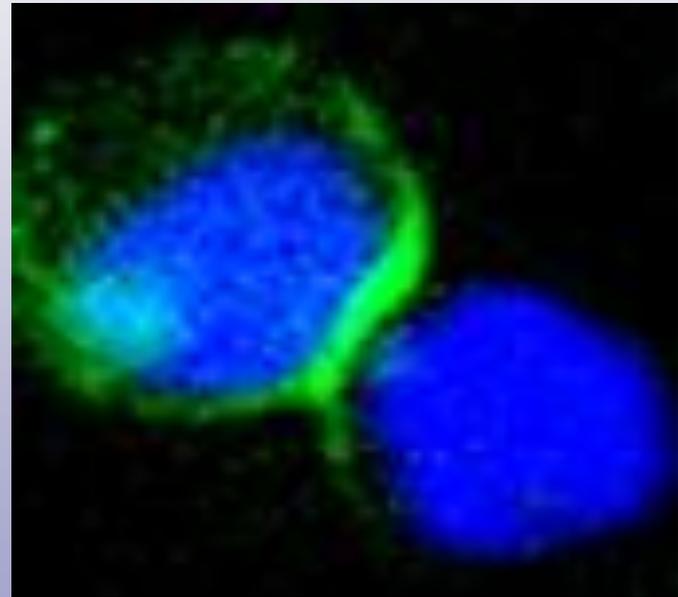
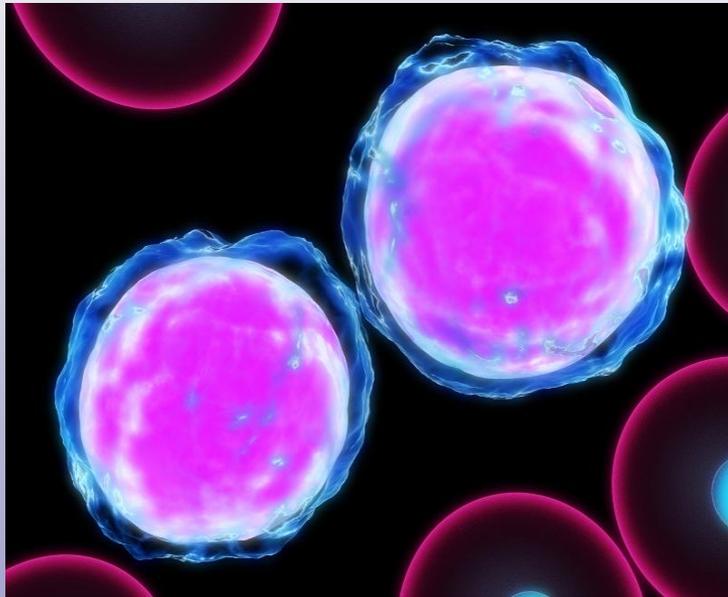


# Improving Graft-versus-Tumor: Strategies to Enhance T Cell Function

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# Relapse after Allogeneic SCT

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- Relapse and disease progression are the leading causes of treatment failure for most hematologic malignancies treated with allogeneic SCT
- Prognosis for patients who relapse is overall poor with few effective treatment options (except for CML)

# Relapse after Allogeneic SCT

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- Enhance GVT activity of donor T cells:
  - Ex-vivo activation
  - Promote T cell activation in vivo (anti-CTLA4, IL15)
  - DLI with cytokine therapy (i.e. IFN)
  - Targeted T cell therapy
  - Promote T cell engagement with tumor (bispecific antibodies)

# T cell activation to treat relapse

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- Non-specific T cell activation
  - In-vivo
  - Ex-vivo
- Specific T cell activation and expansion ex-vivo

# Activated DLI: Rationale

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- Co-stimulation is needed for appropriate T cell activation without anergy.
- Immunotherapy may fail due to limited T cell activation.
- Many tumors have immune escape mechanisms:
  - Down-regulation of MHC
  - Low or absent co-stimulatory molecules
  - Secreted factors can are inhibit T cells
- Activation through ex-vivo co-stimulation may bypass in-vivo suppression.
  - Reverse functional defects in patients with lymphoma\*
  - Augment immune responsiveness after autologous SCT for myeloma\*\*

\* Laport, et al Blood 102:2004, 2003

\*\*Rapoport, et al Nature Medicine 11:1230, 2005

# aDLI: Patient Characteristics

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- N=18
  - Diagnosis:
    - AML 4; ALL 7 (Ph+, 2); HD 1; NHL 3;  
CLL 1; CML 1; MM 1;
  - Age: 45 (12-57)
  - Sex mismatch donor: 5
  - Months BMT to relapse: 5 (2-90)

# Activated DLI: Results

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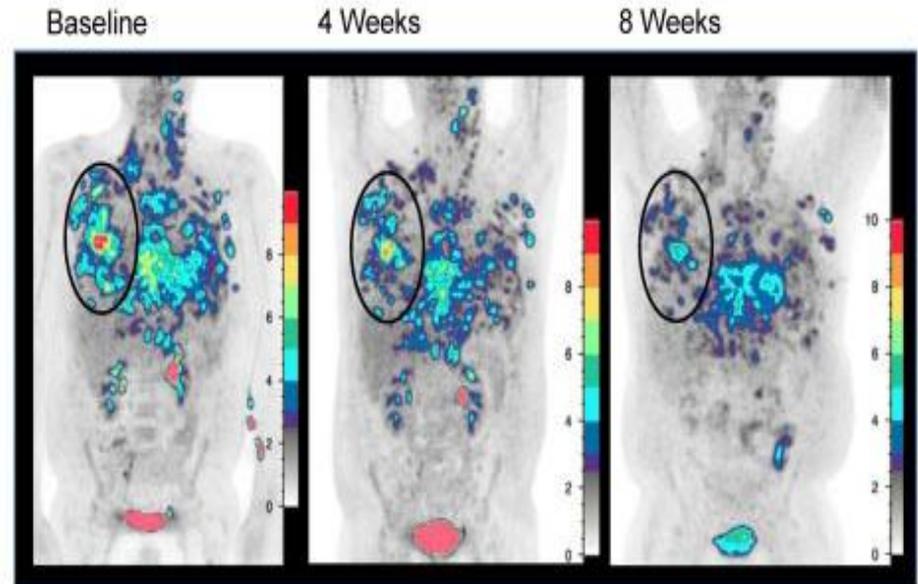
- Acute GVHD (17 evaluable patients)
  - Grade 0: 10
  - Grade I-II: 5 (skin only)
  - Grade III: 2
  - No patient died from complications related to GVHD.
- Response
  - CR: 8/17
    - CLL (1/1) 64+ mo
    - AML (2/4) 54+, 40 mo
    - NHL (1/3) 79+ mo
    - ALL (4/8) 8, 16, 22, 35, mo
  - PR: 1 (AML), 28 wk
  - NR/SD/NE: 9

# Activated DLI using expanded tumor-infiltrating lymphocytes

- Hypothesis that TILs preferentially contain anti-tumor effector T cells
- Ex-vivo co-stimulation and expansion could enhance anti-tumor activity
- 8 pts with B cell malignancies
  - Co-stimulate and expand T cells from tumor specimens with anti CD3/CD28 beads

# Activated DLI using expanded tumor-infiltrating lymphocytes

- No GVHD
- 4/8 with stable disease
  - 2 PET responses
  - 2 mixed responses
- Activated DLI using tumor-derived T cells is feasible and safe.
- Additional studies will determine activity of aDLI using TDL



- 36 yo male with primary refractory Hodgkin's Disease treated for relapse 28 months after allogeneic SCT
- Transient response
- Progressed at 4 mo

# CTLA4 Blockade with ipilimumab to treat relapse

*Bashey et al, Blood 113; 2009*

- CTLA4 blockade can augment anti-tumor immunity by inhibition of negative regulation of activation/co-stimulation.
- Ipilimumab is human IgG moAb against CTLA4
  - Tumor regression in murine models, augments antitumor vaccine activity, effective in some pts with melanoma.
- 29 pts with relapse >3 mo after MS (19) or URD (10) SCT treated with 4 dose levels
- No grade III/IV GVHD, 3 minor cGVHD.
- 2/14 pts with Hodgkin's disease had CR, 1 pt with MCL had PR.
  - NR in 6 MM, 2 AML/CML/CLL and 1 breast ca, 1 RCC.
- No DLT
- No response to subsequent DLI in any of 6 pts treated.
- Activity in a minority of pts with relapsed disease.

# Will IFN- $\alpha$ enhance GVT activity of DLI?

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- Rationale:
  - Increase cytotoxic activity of T cells
  - Increase HLA class II expression
  - Increase expression of adhesion molecules that augment immunogenicity of leukemia cells.
  - In mice, CD-8 dependent GVHD and GVL effects are enhanced by IFN signaling (*Robb, et al, Blood 2011*)
    - sensitize the leukemia cells to killing
    - augment donor CTL function.
- For CML, IFN- $\alpha$  does not add to DLI
- IFN- $\alpha$   $\pm$  GM-CSF has induced responses in leukemia (*Copper et al, BJH, 2001*)
- IFN- $\alpha$  may induce GVHD (*Grigg, et al, Int J Med 2011*)

# IFN-a and DLI

*Tang et al, Abst 658, ASH 2011, Abst 47, BMT tandem 2012*

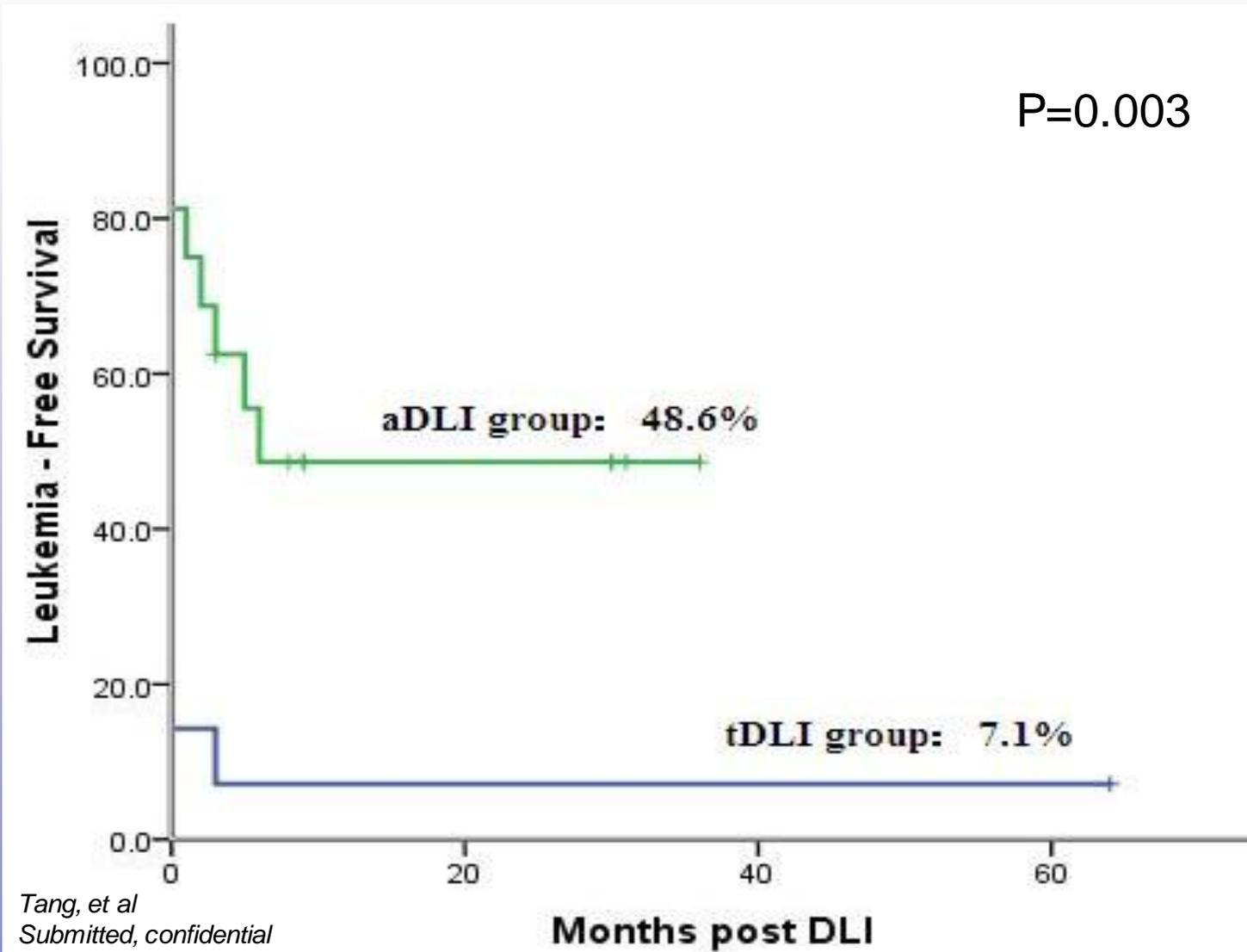
- IFN-a 3 MU/day SQ x 5 days and continued until CR, toxicity or relapse (median duration 16 days, range 5-50)
- G-CSF mobilized DLI (median  $9 \times 10^7$  CD3 cells/kg, range 2-20)
- Relapsed ALL (9) or AML (7)
  - Median time to relapse 5.5 mo (1-25 mo)
  - Salvage chemotherapy for 7 pt with 3 CR
- CR 75% (12/16)
  - CR for I-DLI only 67% (6/9) (no chemotherapy)
  - Median time to CR 7 days (6-14)
- Median f/u 5.5 mo(1-34)
- 7/16 alive in CR
- 2 yr LFT 50%

# IFN-a and DLI vs Conventional DLI

Tang et al (China), Abst 658, ASH 2011, Abst 47, BMT tandem 2012

- Compared to 14 similar patients treated with DLI only (t-DLI):
- I-DLI resulted in:
  - Higher CR (75% vs 14%,  $p=0.001$ )
  - Better 2 yr LFS (50% vs 7%,  $p=0.05$ )
  - More aGVHD (56% vs 27%,  $p=0.05$ )
  - Similar TRM 18.8 vs 7% ( $p>0.05$ )

# IFN-a and DLI: 3 yr LFS



# Targeted cellular therapy for relapsed leukemia

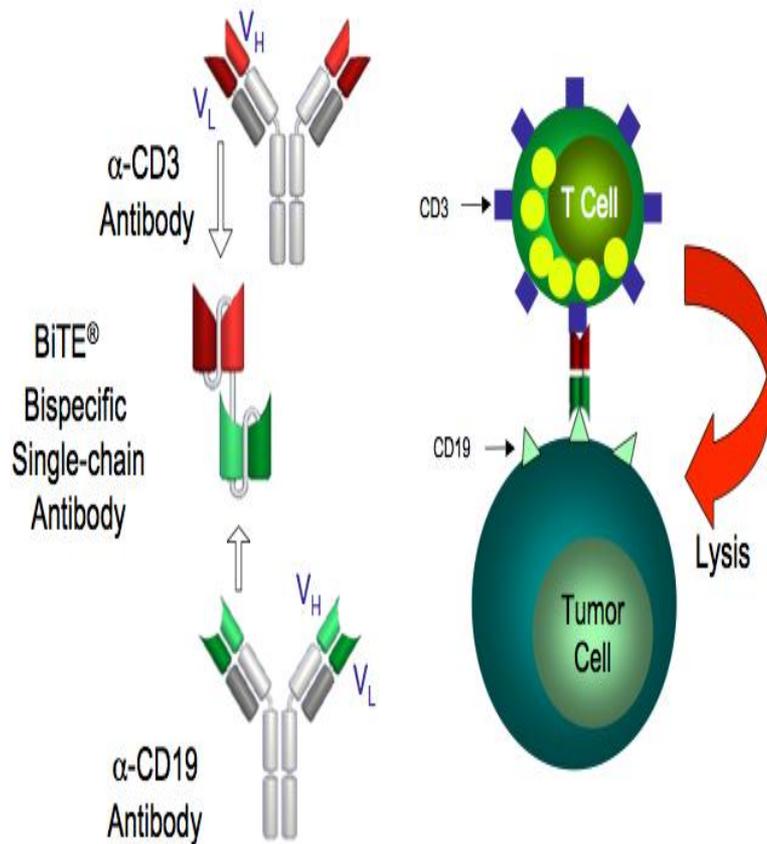
# Relapsed ALL

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- DLI may not be standard for ALL relapsing after SCT
- Novel therapies need to be investigated:
  - Selection and expansion of leukemia-specific CTLs
  - Monoclonal antibodies (unconjugated and conjugated (calicheamicin, pseudomonas immunotoxin
  - NK cell therapies
  - Vaccine therapies (likely best with MRD)
  - Activated DLI: ex-vivo activation through co-stimulation
  - T cells modified with chimeric antigen receptors to target tumor-specific antigens (i.e. CD19)
  - Bispecific antibodies (anti-CD19/anti-CD3 $\epsilon$ ; MT103, blinatumomab), anti-CD20/anti CD3

# Target Tumors with Bi-specific Antibodies

Mode of Action



- Bi20 (FBTA05) (*Buhmann et al, BMT 43; 09*)
  - Anti CD20, anti CD3
  - Given with DLI to 6 pts with relapse after allo
  - 3/3 pts with CLL and 1/3 with NHL transient responses
- New antibodies with other targets
  - Anti-CD19 Bi-Specific T-Cell Engager (BiTE), *Blinatumomab*
    - 55 kD recombinant single chain variable fragments (scFv)
    - Anti-CD19 Fv (HD37)
    - Anti-CD3 $\epsilon$  Fv (L2K-07)
    - Gly/Ser linker

# Blinatumomab for Relapsed ALL after Allogeneic SCT

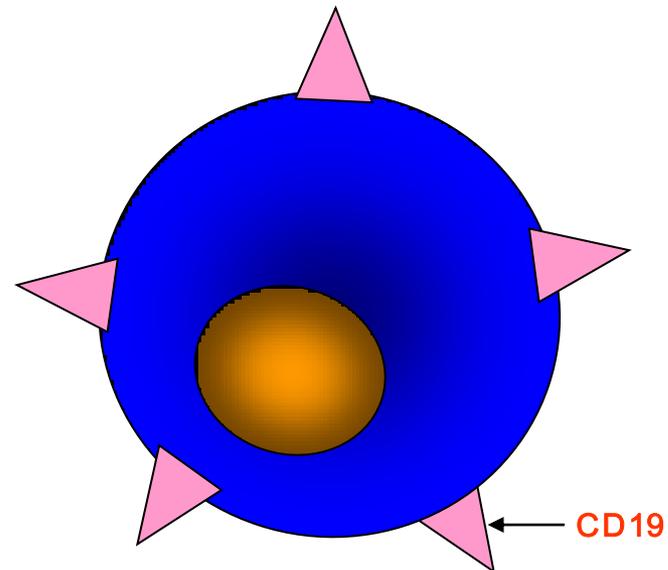
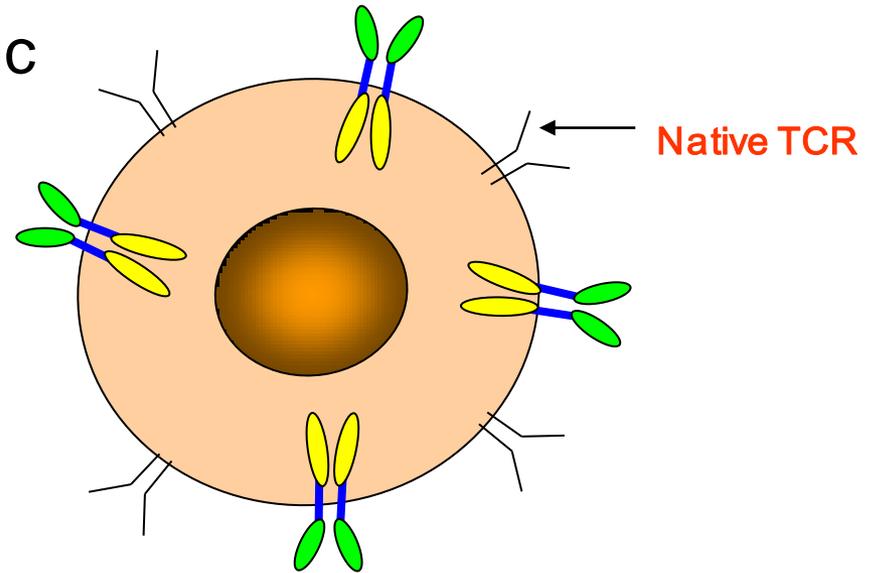
- 3 pts (age 7-15) with relapsed ALL after allogeneic SCT
  - 7 yo boy, relapsed 1 yr after allo, treated with MRD (3% blasts) to CR.
    - Followed by haplo SCT and 23+mo CR
  - 12 yo boy relapsed 21 mo after allo, treated with extensive disease.
    - Blasts cleared within 1 d, aplasia on d 15, and CR by d28
    - Relapsed 2 wks after stopping drug
  - 15 yo boy Ph+ ALL relapsed 1 yr after 3<sup>rd</sup> allo (haplo) SCT over 7 yrs
    - Treated with MRD to CR by 4 wk
    - Received 4 x 4 wk cycles, relapsed after cycle 4.
  - Expansion of donor derived T cells in all cases without GVHD

# Blinatumomab for Relapsed ALL after Allogeneic SCT

- Blinatumomab is tolerated after allogeneic SCT
- Expansion of donor derived T cells in all cases
- No GVHD
- May be useful as primary therapy
  - 2 of 3 pts relapsed quickly after stopping drug
- May be useful to induce MRD prior to alternative therapy

# Targeting Tumors with Chimeric Antigen Receptors

- CARs combine an Ag recognition domain of antibody with intracellular signaling domain into single chimeric protein.
- Gene transfer to stably express CAR on T cells confers novel Ag specificity.



# CART-19 Therapy For CLL

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- N=9
- Median age 65 (51-78)
- Prior regimens, median 5 (2-10)
- Median follow-up 6 mo (1-24 mo).
- Massive T cell expansion >3 logs
- In vivo persistence beyond 2 yrs
- 3 CR, 4 PR, 2 NR, (ORR 78%)

# Allogeneic CART-19 for Relapsed CLL

*Kochenderfer et al. ASBMT Feb 2011, Abst 21*

- 65 yo male with relapsed CLL after URD SCT
  - DLI x 4 with NR
  - Second SCT (same donor) with NR
- Allogeneic CAR-T 19 ( $1 \times 10^6/\text{kg}$ ) cells from his URD
  - Biochemical tumor lysis syndrome
  - Disappearance of peripheral B cells by d26
  - Bone marrow without CLL or B cells by d26
  - CT with >50% decrease
- Total of 4 pts treated, NR in next 3

# Treatment of Relapse

- Not discussed:
  - Disease specific issues
  - Multiple new therapies (later workshop session)
  - Other cellular therapies, i.e. NK cells (earlier NK session)
  - Impact of cell dose and dose escalation
  - Impact of pre-DLI chemotherapy (C Schmid)
  - Pre-emptive DLI (mixed chimerism, MRD, etc...)
- For additional state of the art information:
  - “Treatment of Relapse: Report from the NCI sponsored 1st International Workshop on the Biology, Prevention and Treatment of Relapse after Allogeneic SCT. *BBMT* 16: 1467, 2010.
  - Relapse Workshop 2012 manuscript

# Relapse Therapy, 2012

- Since first workshop in 2010, no major breakthroughs
- Many reasons to be optimistic about the future potential to treat relapsed disease.
- Several major advances:
  - New drugs
  - New targeted cell therapies
  - New antibody therapies
  - Momentum and interest in the community!



# Special Thanks

- Christoph Schmid
- Marcos de Lima
- David Avigan
- Alan Wayne
- Nancy Hardy
- Mino Battiwalla
- Michael Bishop
- Nicolaus Kroger
- Sergio Giralt

- Carl June
- Bruce Levine
- Michael Kalos
- Noelle Frey
- Alison Loren
- Ran Reshef
- Elizabeth Hexner
- Ed Stadtmauer
- Selina Luger
- Steven Schuster
- Jakub Svoboda
- Sunita Nasta

Many More