

NK Cell Therapeutics for Cancer

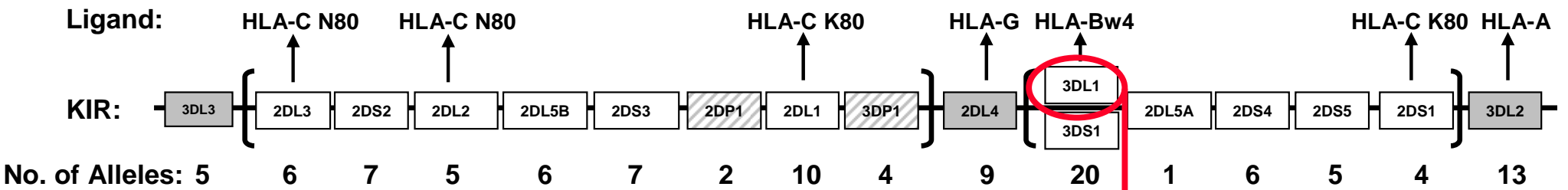
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Associate Director of Experimental Therapeutics
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10530**

**Survivor, one random FDA audit
Division of Heme/Onc/Transplant
Minneapolis, MN**



Chr. 19 determines the personality of NK cells: Killer-immunoglobulin receptor (KIR) gene locus

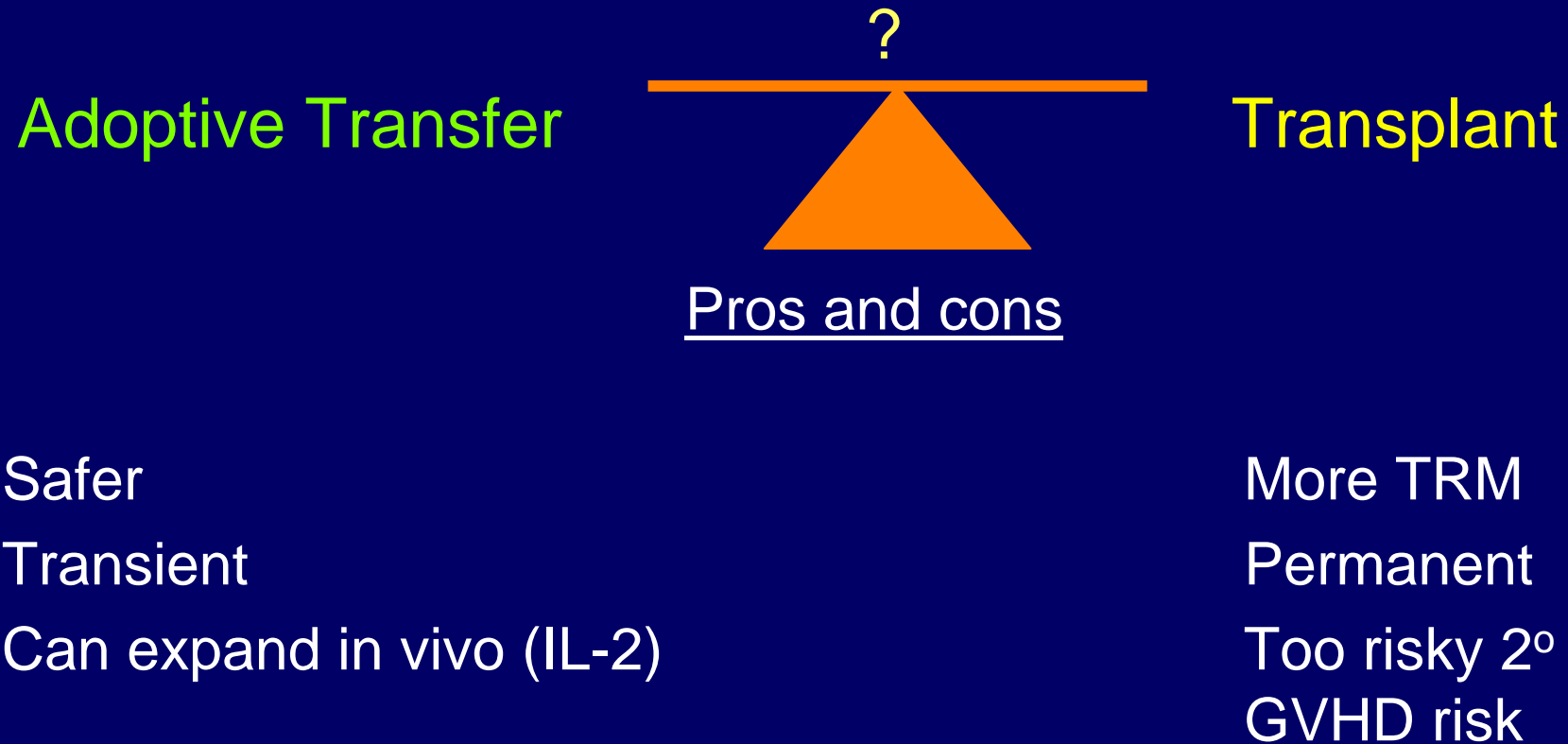


KIR3DL1*004 is not expressed at the surface

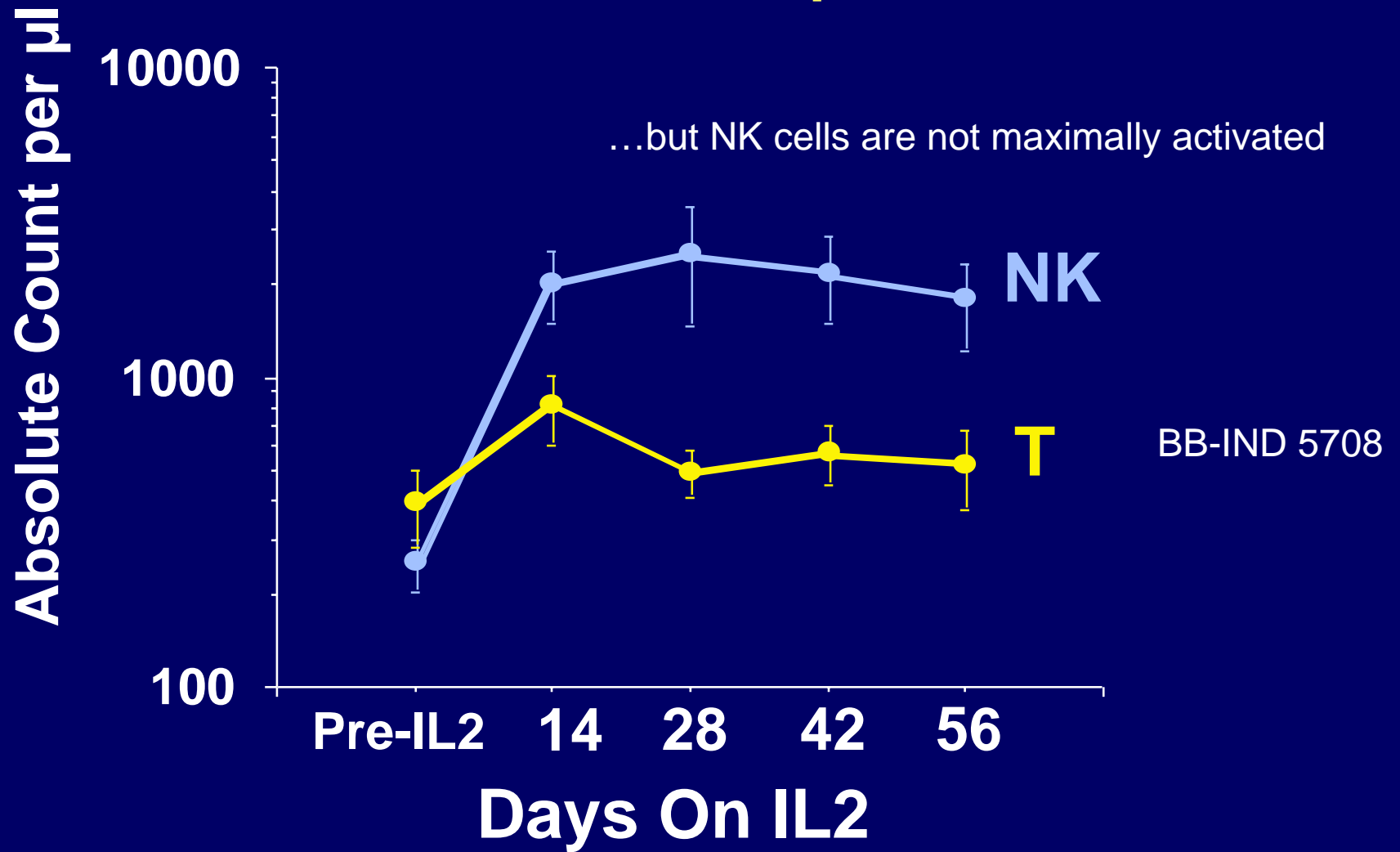
The interest in therapeutic uses of NK cells has been growing since in 2002

	Transplant	Graft	Outcome
Ruggeri <i>et al</i> Science 3/2002	Haploidentical KIR-L Mismatch	TCD	Benefit in AML
Davies <i>et al</i> Blood 11/2002	URD KIR-L Mismatch	UBM	No Benefit
Giebel <i>et al</i> Blood 8/2003	URD KIR-L Mismatch	<i>In Vivo</i> TCD	Benefit

How can we best exploit NK cells?

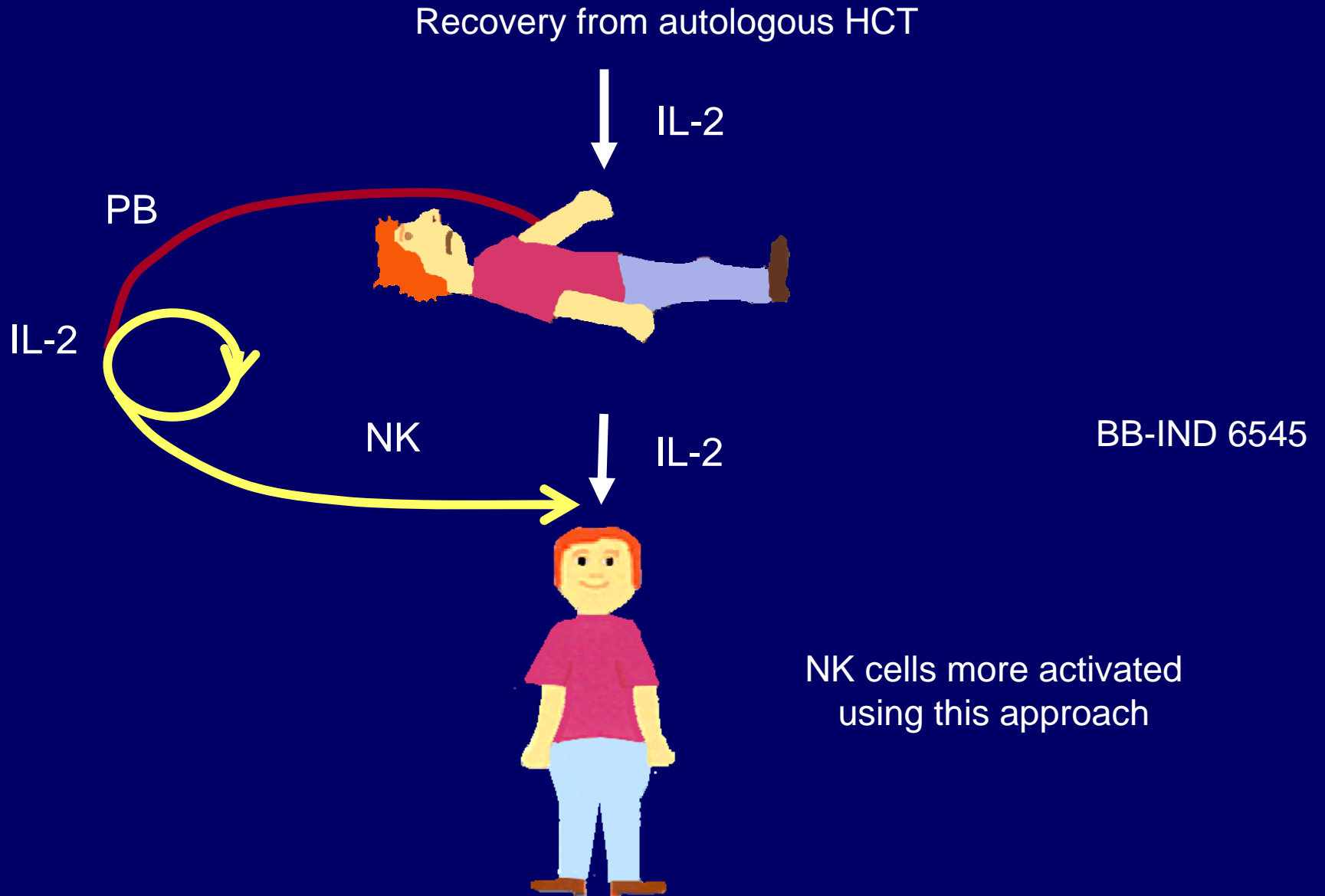


Outpatient Subcutaneous IL-2 Promotes In Vivo NK Cell Expansion



Miller et al, Biol Blood Marrow Transplant 3:34, 1997

837 IND #'s later: Autologous NK Administration in Cancer Patients



NK Cell-based Autologous Immunotherapy to Prevent Relapse (HD, NHL, BC)

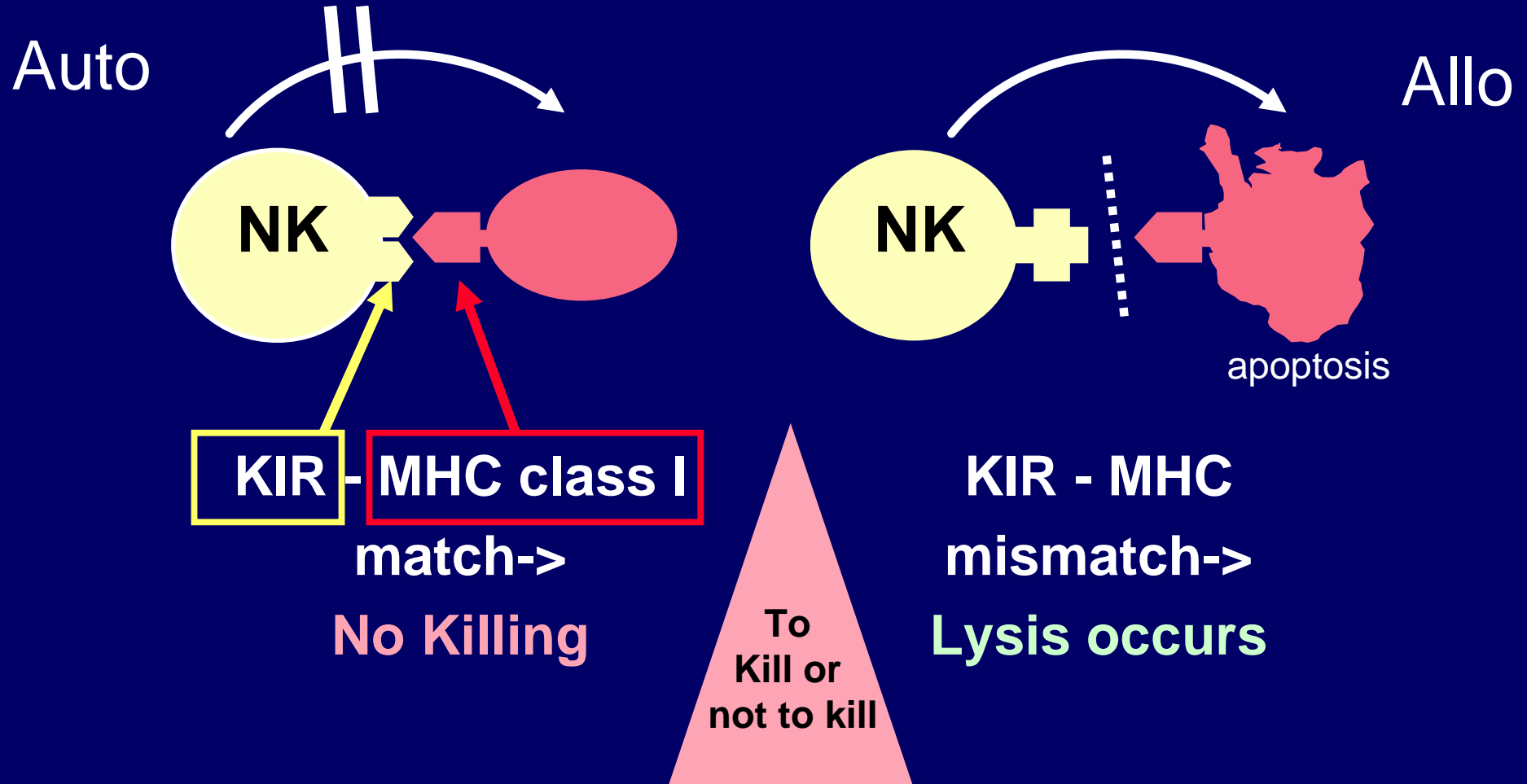
Burns et al, Bone Marrow Transplant, 32:177-186, 2003

Conclusions

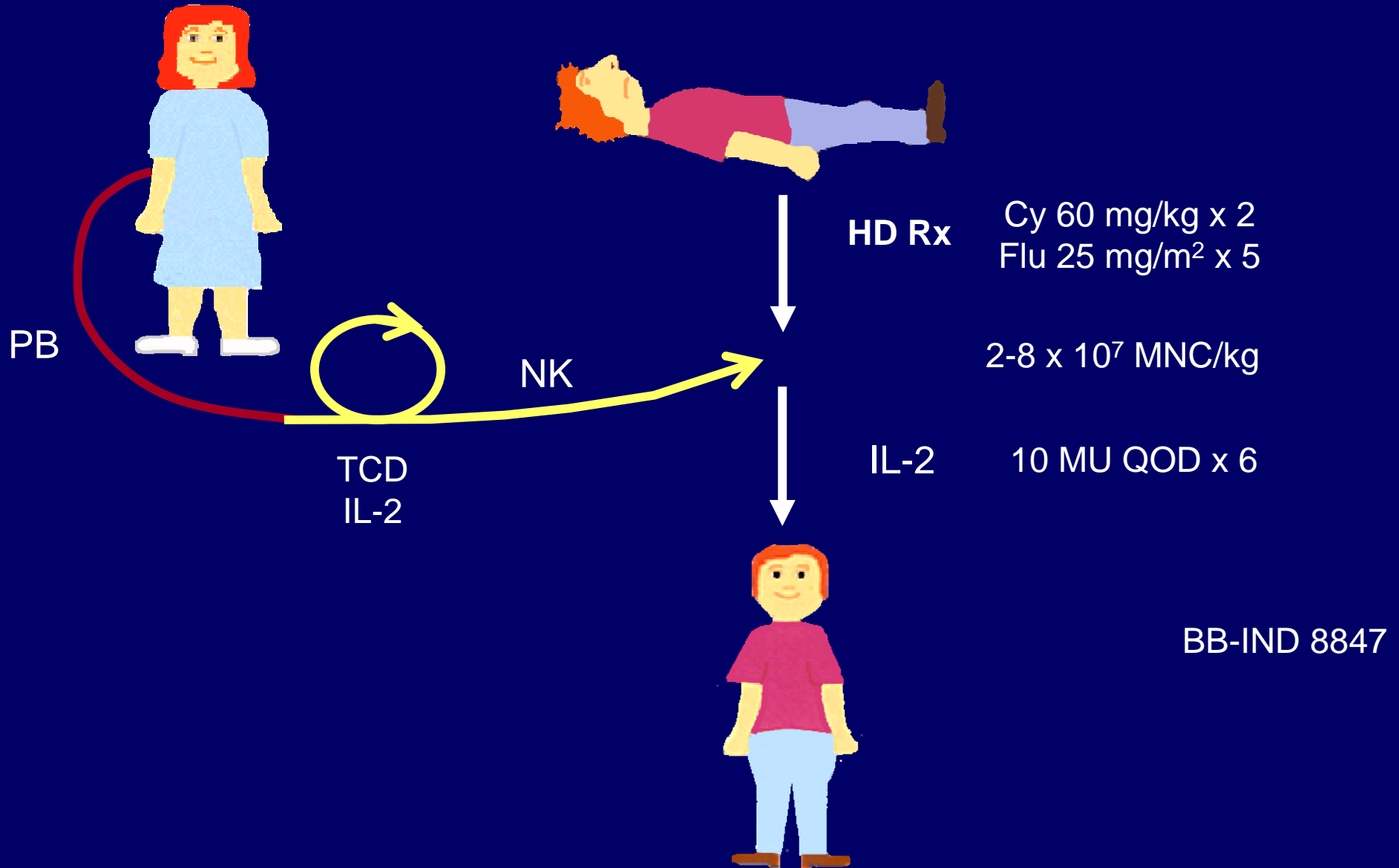
Enhanced activation of NK cells

A matched paired analysis with our data and data from the IBMTR showed no apparent efficacy (survival or time to disease progression)

Hypothesis: Autologous NK Cell Therapy Failed Due to Inhibitory Receptors that Recognize MHC



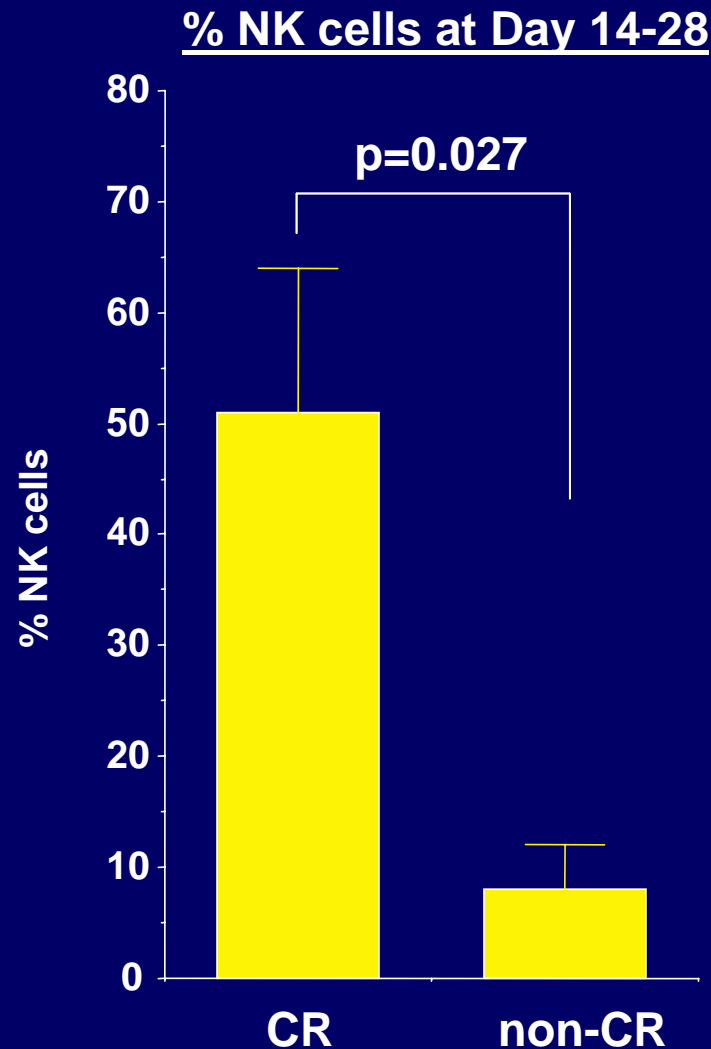
2302 IND #'s later: Related Donor Haploidentical NK Infusions After High Dose Chemotherapy



Patients and Eligibility

- Poor prognosis AML
 - Primary refractory disease
 - Relapsed disease not in CR after 1 or more cycles of standard re-induction therapy
 - Secondary AML from MDS
 - Relapsed AML \geq 3 months after HCT.
- No active infections

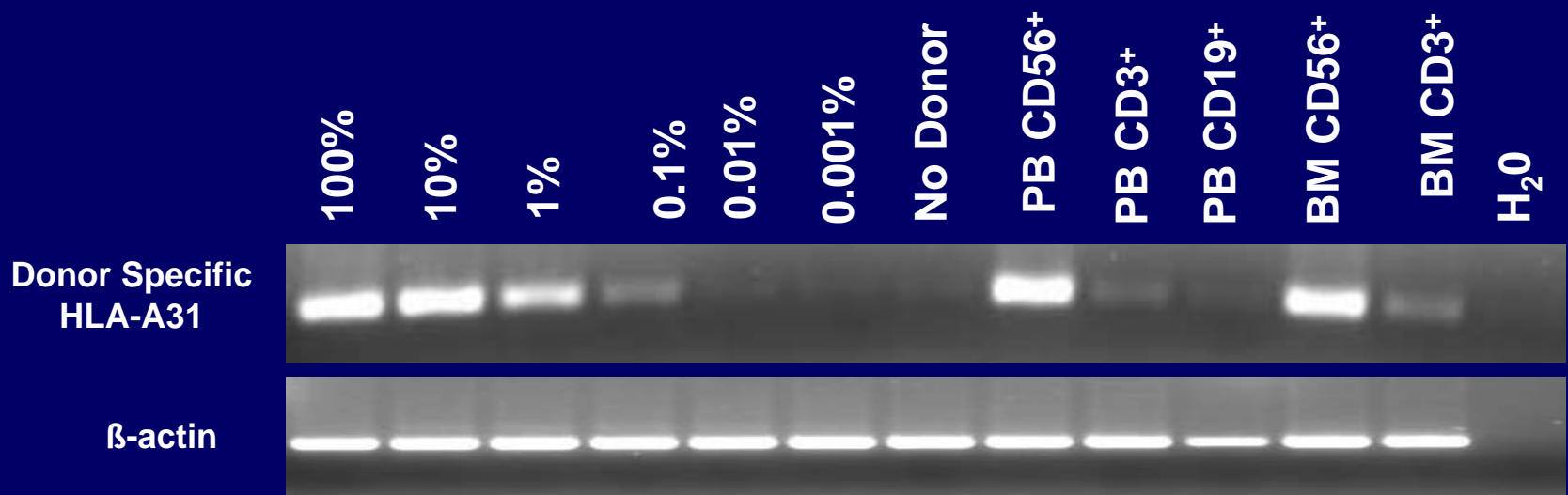
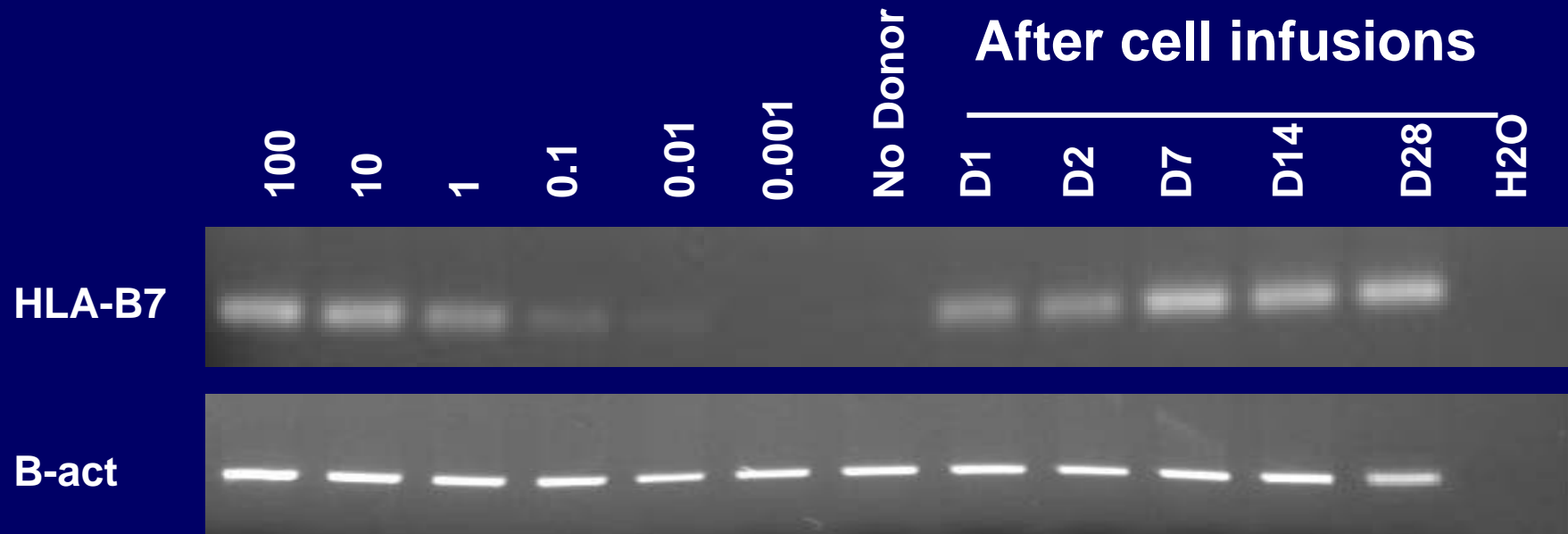
Higher Numbers of Functional NK Cells in Patients with CR After Adoptive Transfer



NK cells did not expand with lower dose preparative regimens

Correlates with an increase in IL-15 and IL-7

In vivo expansion of haploidentical NK cells in AML



Long-term Follow-up

- 10 of 32 (31%) remissions
- No correlation with KIR-L mismatch
- 3 of 10 total CRs went on to receive allo transplant (1 sib, 2 UCB) with DFS > 2.5 years
- 3 died of toxicity without relapse (1 meningitis, 1 CNS, 1 PTLD)
- 4 of 10 CRs lasted 4-11 months (probably not curative)

Hypothesis

The best strategy may be to combine adoptive transfer and in vivo expansion followed by HCT

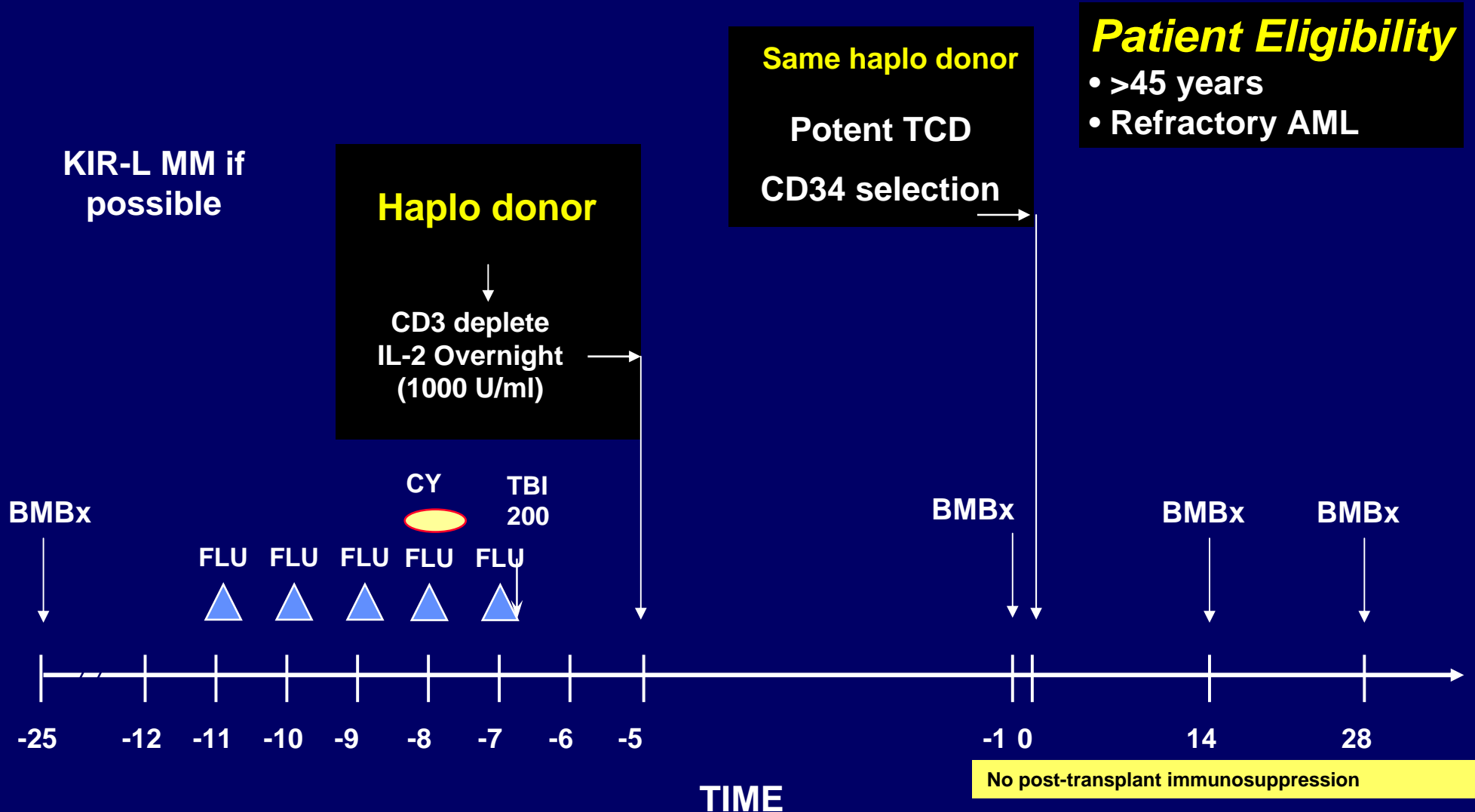
Adoptive Transfer

+

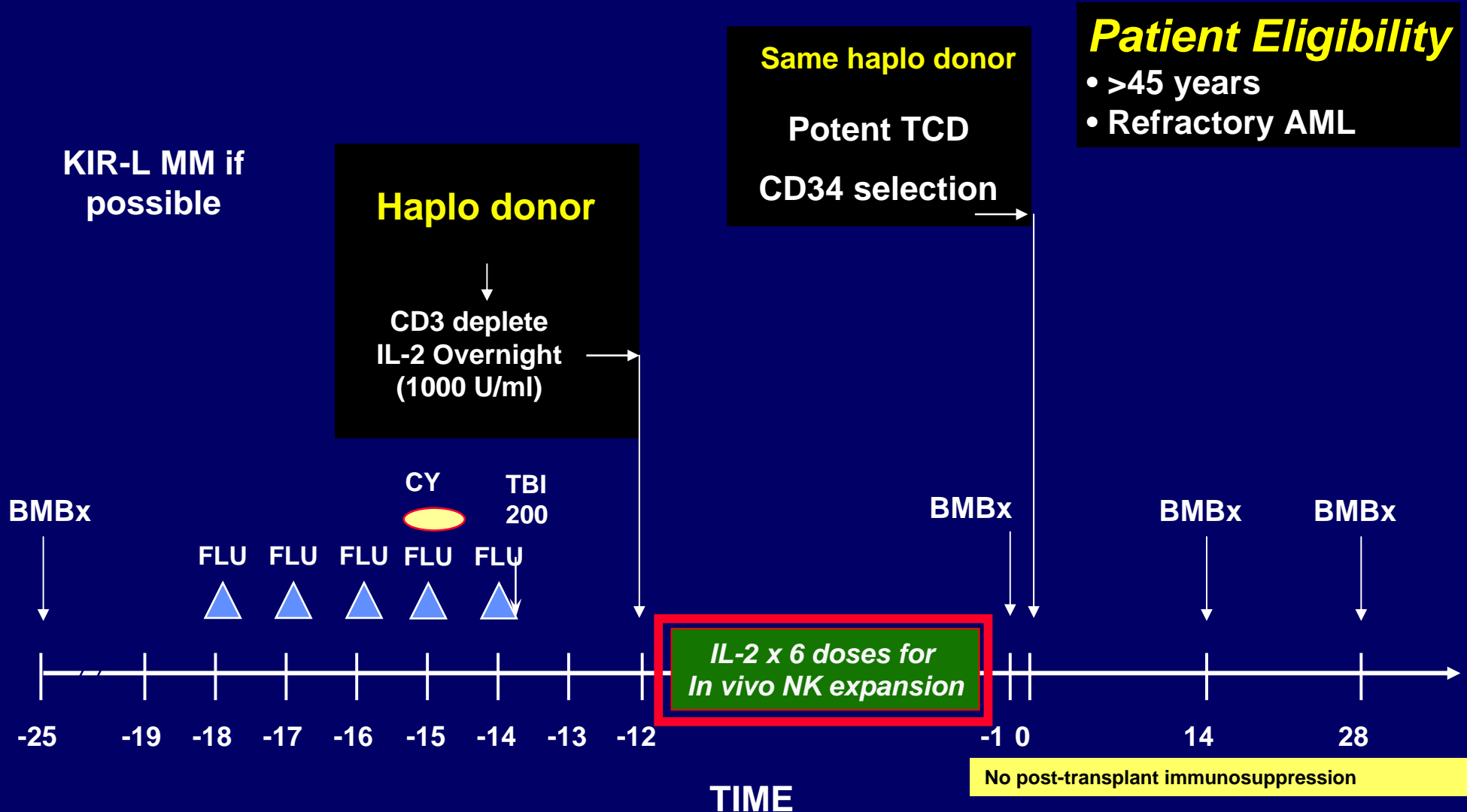
Transplant

The best of both worlds?

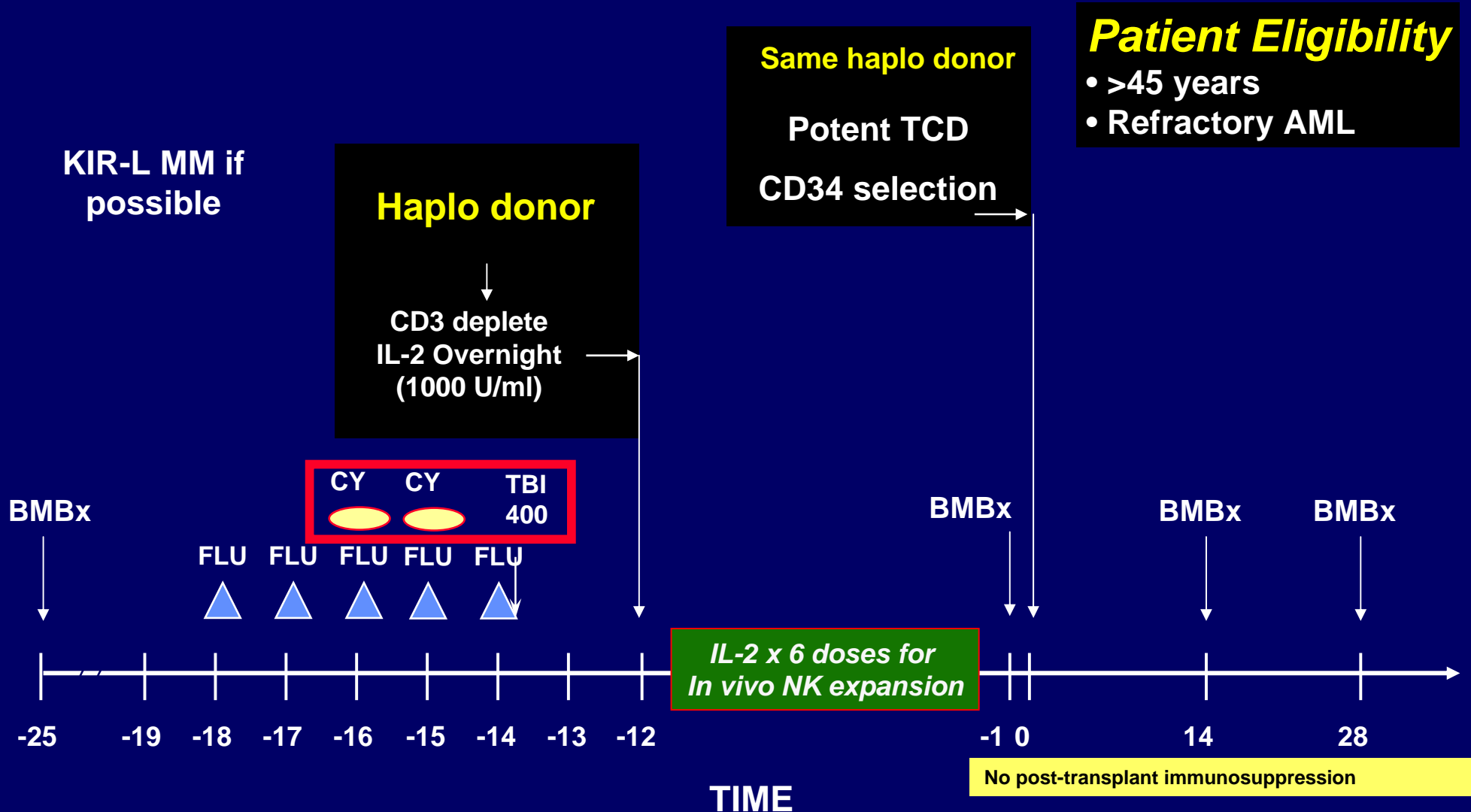
Haplo related donor RIC strategy to combine NK cells and HCT for patients with refractory AML



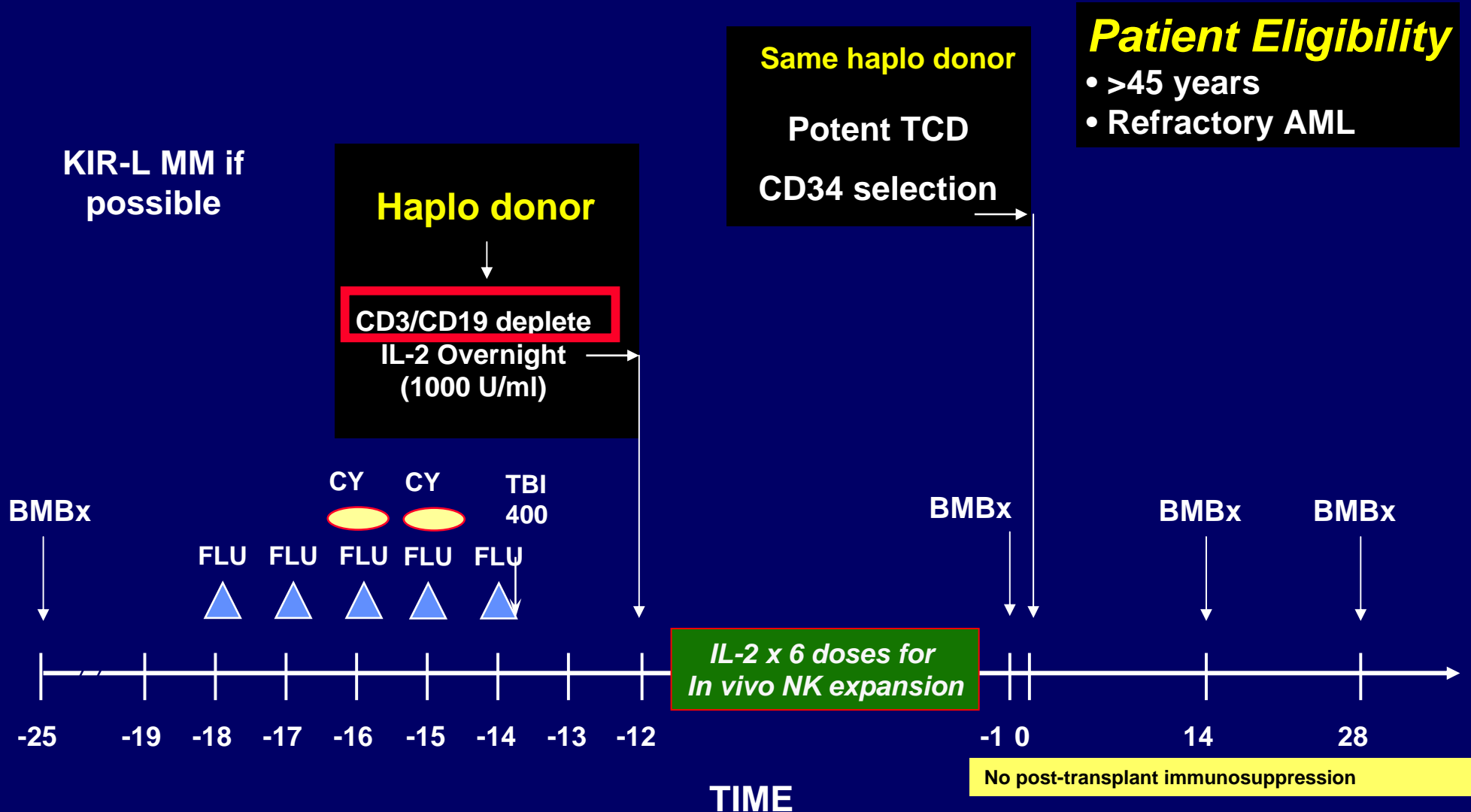
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Haplo related donor RIC strategy to combine NK cells and HCT for patients with refractory AML



Where do we go from here?

- Improve Donor choice
- Improve NK cell activation
 - Interrupt inhibitory receptor mechanisms
- Increase target sensitivity
 - Bortezomib

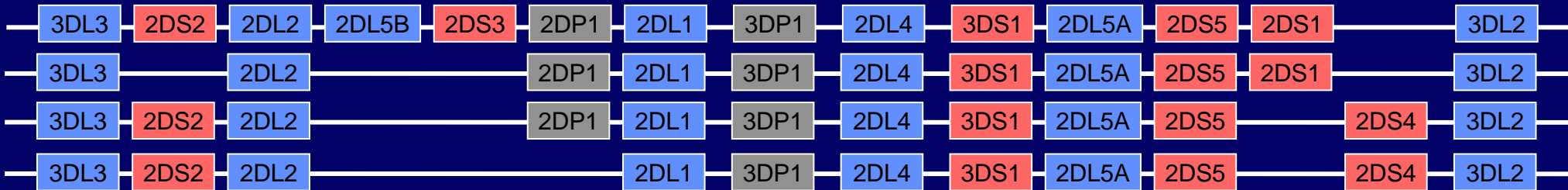
Killer-Immunoglobulin Receptor (KIR) Gene Locus

Group-A Haplotype:

Absence of 2DL5, 2DS2, 2DS1, 2DS3, 2DS5, 3DS1



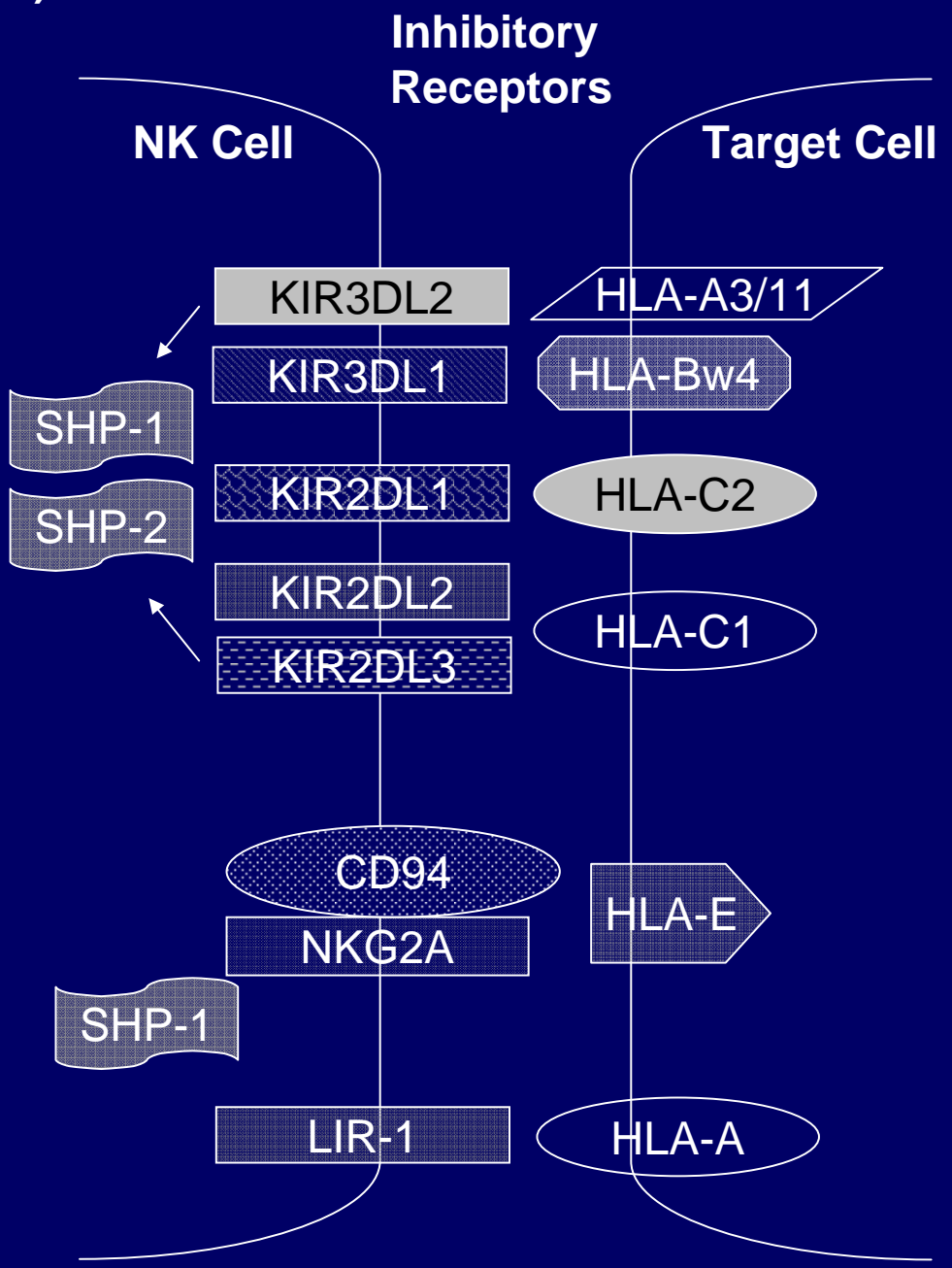
Group-B Haplotypes: Presence of at least one of above



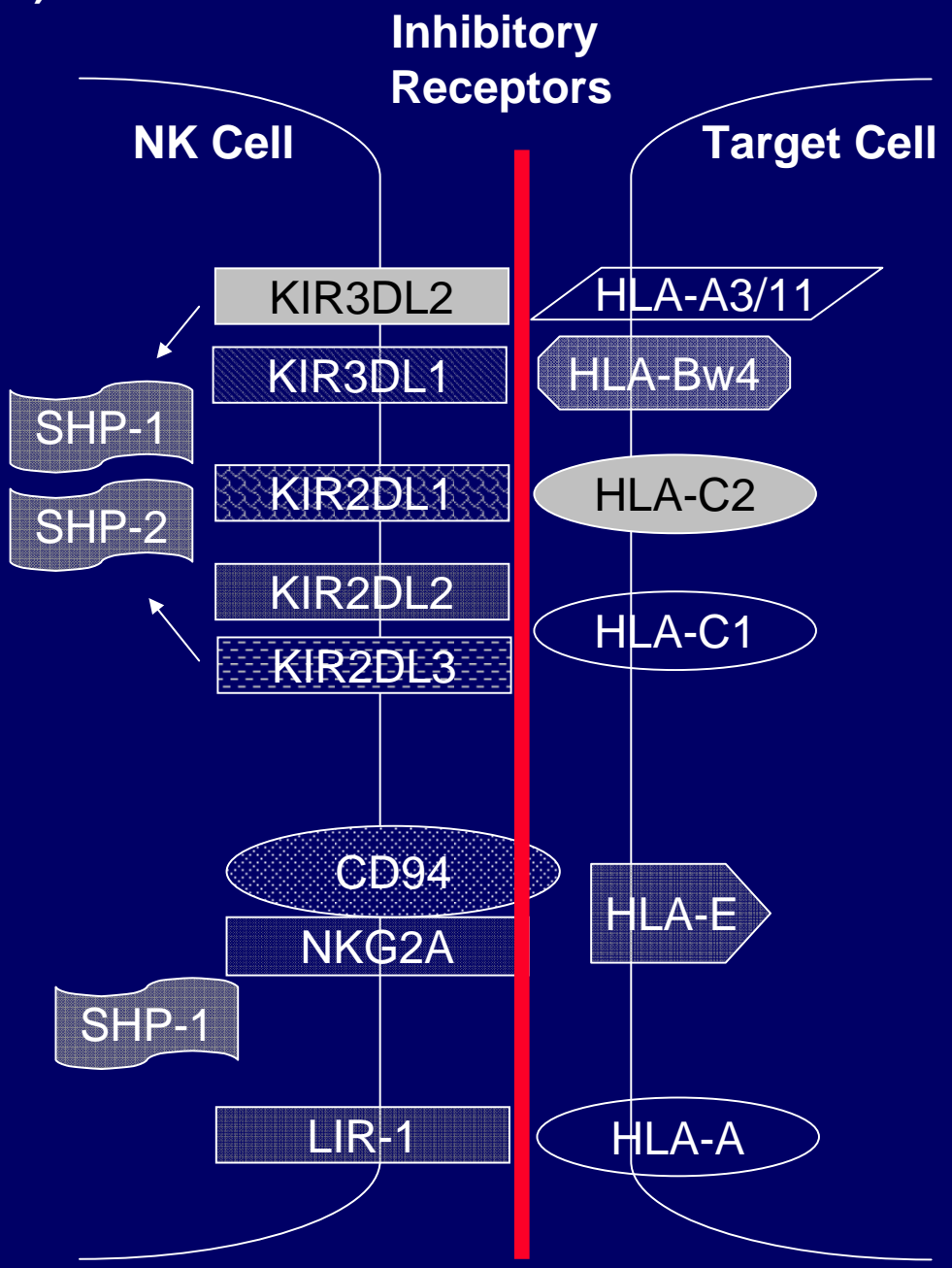
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A)



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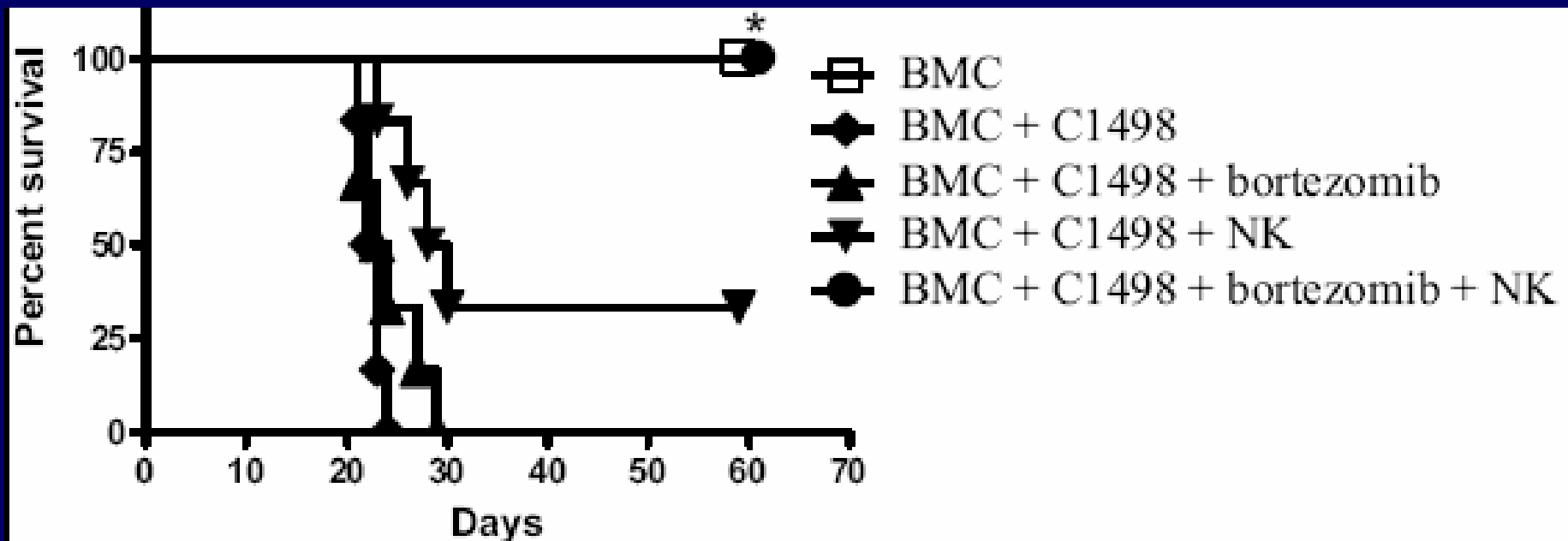
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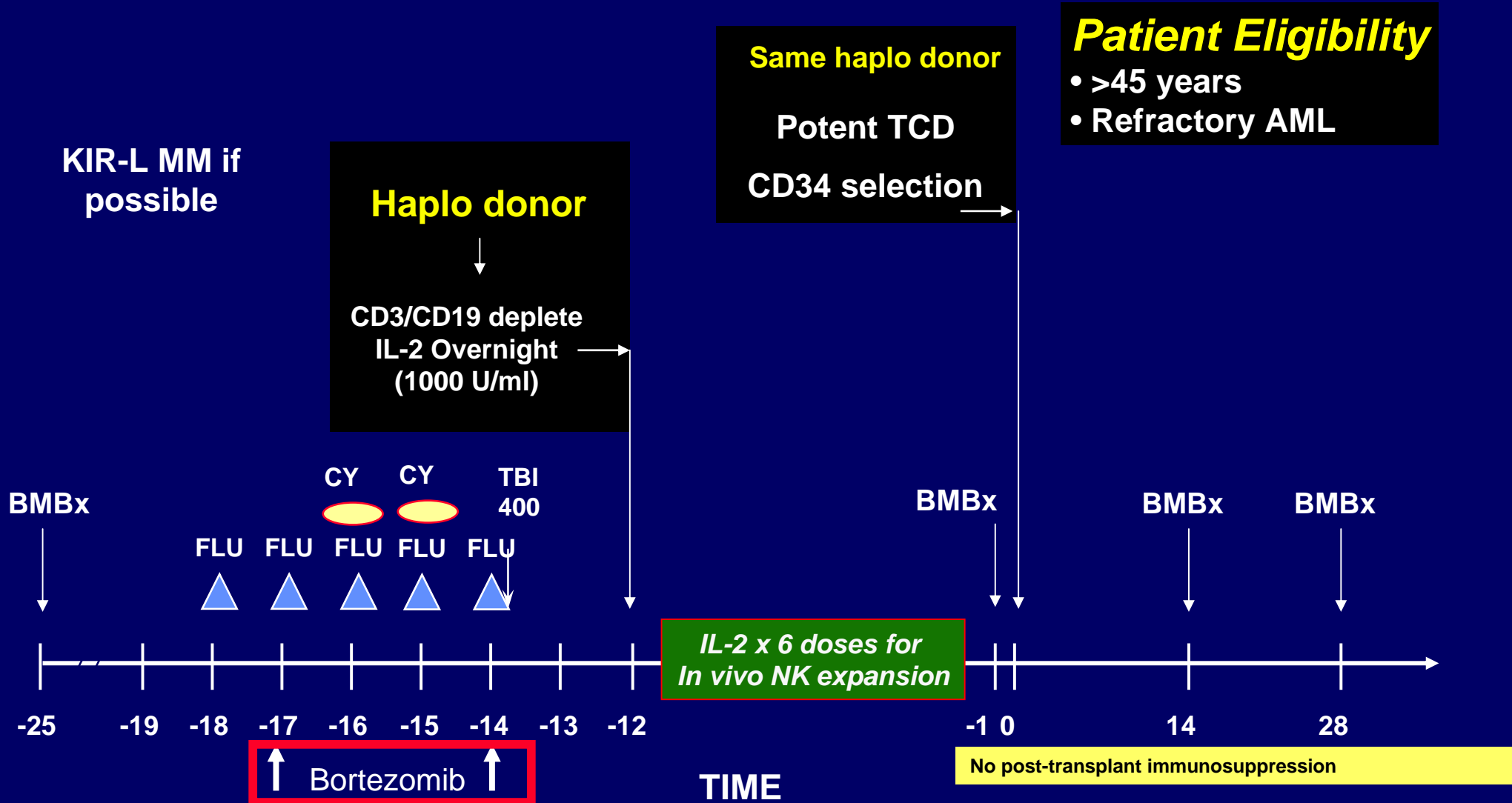
SENSITIZATION OF TUMOR CELLS TO NK CELL-MEDIATED KILLING BY PROTEASOME INHIBITION

RUNNING TITLE: BORTEZOMIB INCREASES NK CELL KILLING

William H.D. Hallett*, Erik Ames*, Milad Motarjemi*, Isabel Barao*, Anil Shanker†, David L. Tamang*, Thomas J. Sayers†, Dorothy Hudig* and William J. Murphy*



Haplo related donor RIC strategy to combine NK cells and HCT for patients with refractory AML



Lessons and Issues

- Important strategic decisions
 - Do the right thing, do not forget the patient
 - Well-intended improvements may lead to failures (pure NK cells not clinically active)
 - Put as few people at risk as possible
 - Minimize patients exposed to therapies that will not work
 - BE FLEXIBLE
 - Do not do it alone
- Regulatory authorities
 - Work with the FDA and they will work with you
 - Be concrete, realistic and logical about your goals
 - Do not do it alone
- Funding of the project:
 - Huge issue but if science is solid NIH/NCI still good investors
 - If tied to therapeutics, clinical partners must also be will willing to invest
- Lessons learned
 - The field is narrowing...decide your contribution and make sure it is realistic
 - Specialized ETU's needed for clinical implementation
 - Make sure you have lab endpoints to teach you something when your trial fails and most of them will
 - COMBINATIONS ARE THE KEY TO SUCCESS...this is a challenge!

P01 (PI: Jeffrey S. Miller)

“NK Cells and their receptors in unrelated donor transplantation”

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