NUOVE FRONTIERE NELLA TERAPIA DELLE MALATTIE ONCOLOGICHE ED ONCOEMATOLOGICHE

Treviso
21 Novembre 2015

Cellule Natural Killer: alloreattività NK come piattaforma di immunoterapia della Malattia Minima Residua

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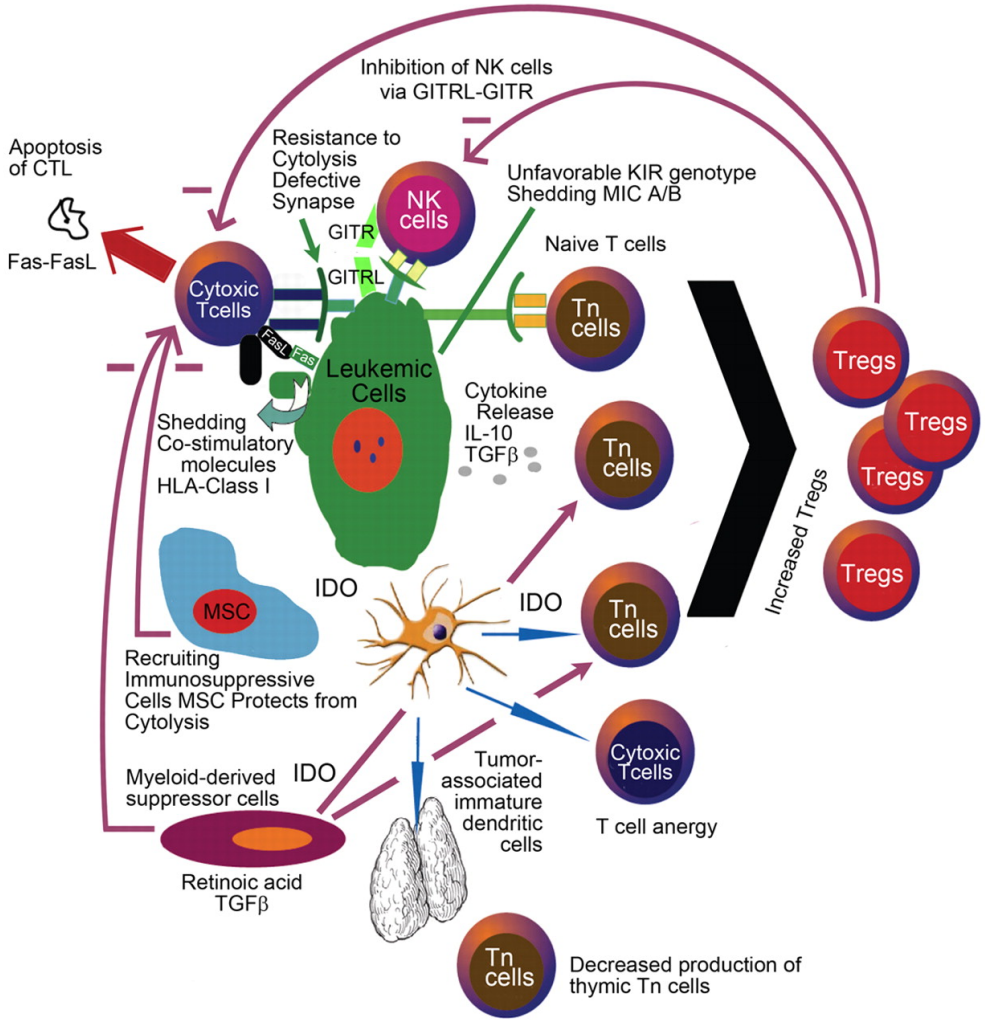
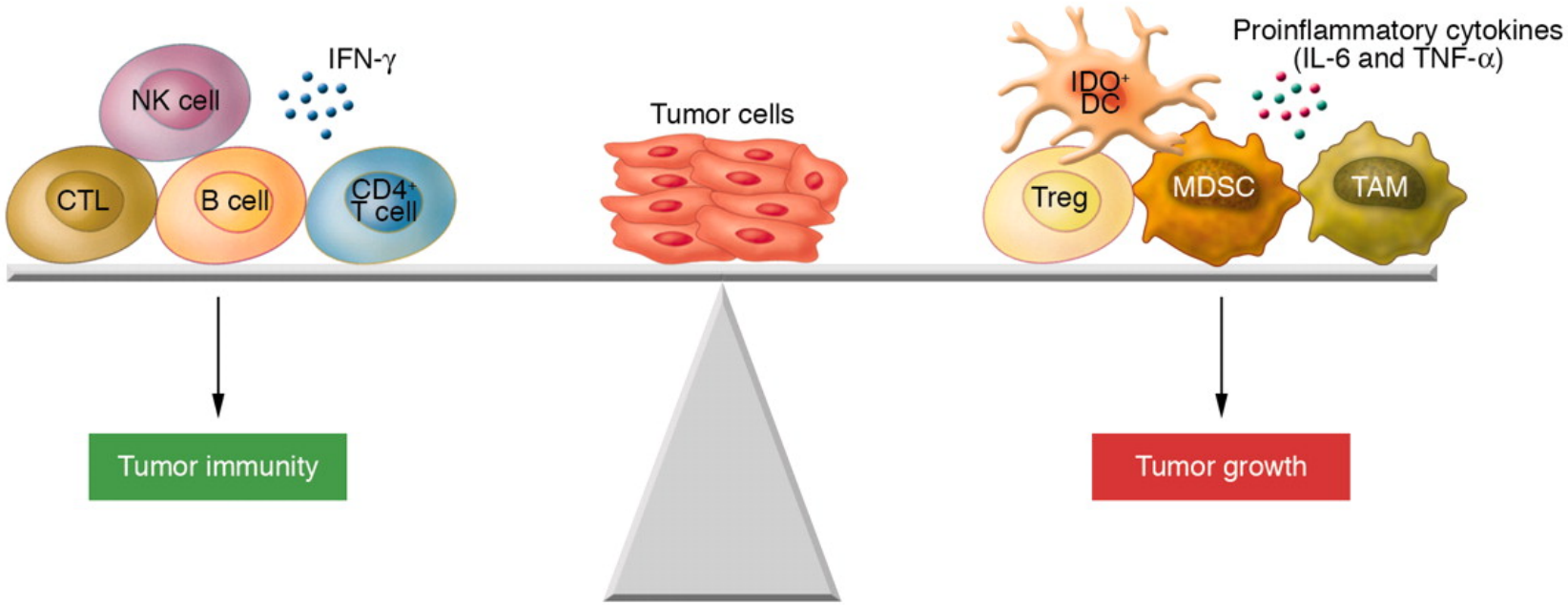
Azienda ospedaliero-universitaria Policlinico S.Orsola-Malpighi
Università degli Studi di Bologna

AML leukemic cells can inhibit immune effector cells by contact-dependent or -independent means.

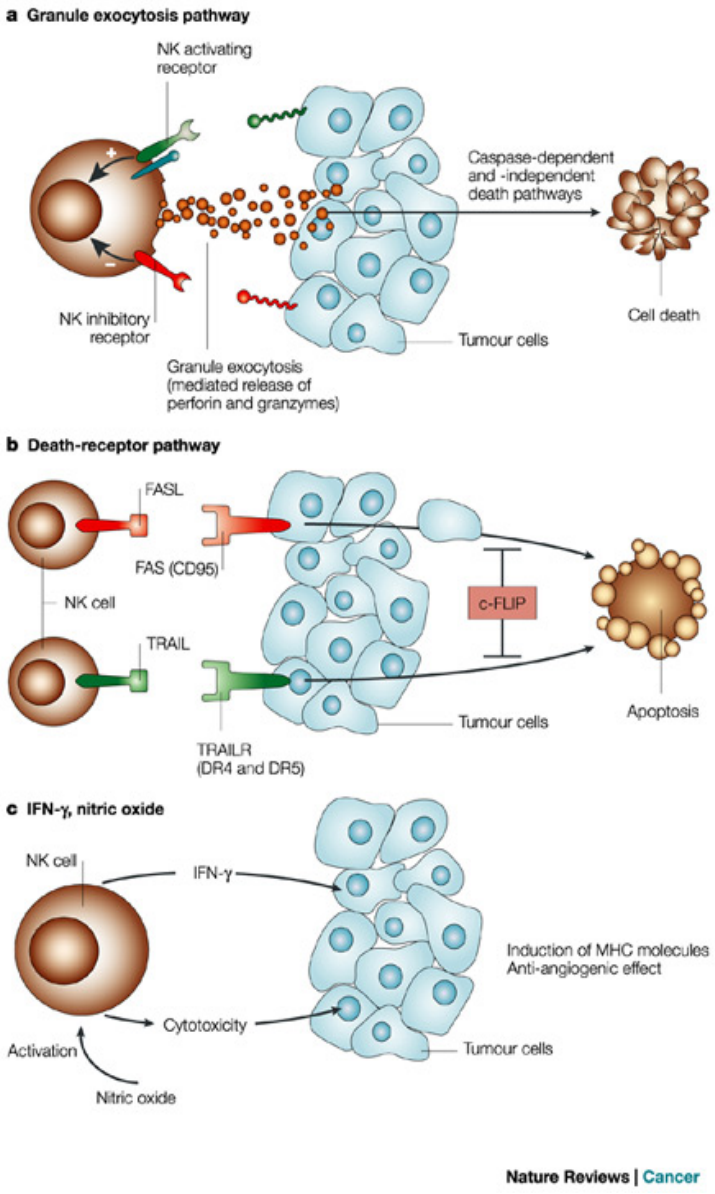


Ustun C et al. Blood 2011;118:5084-5095

Harnessing the immune system to treat cancer



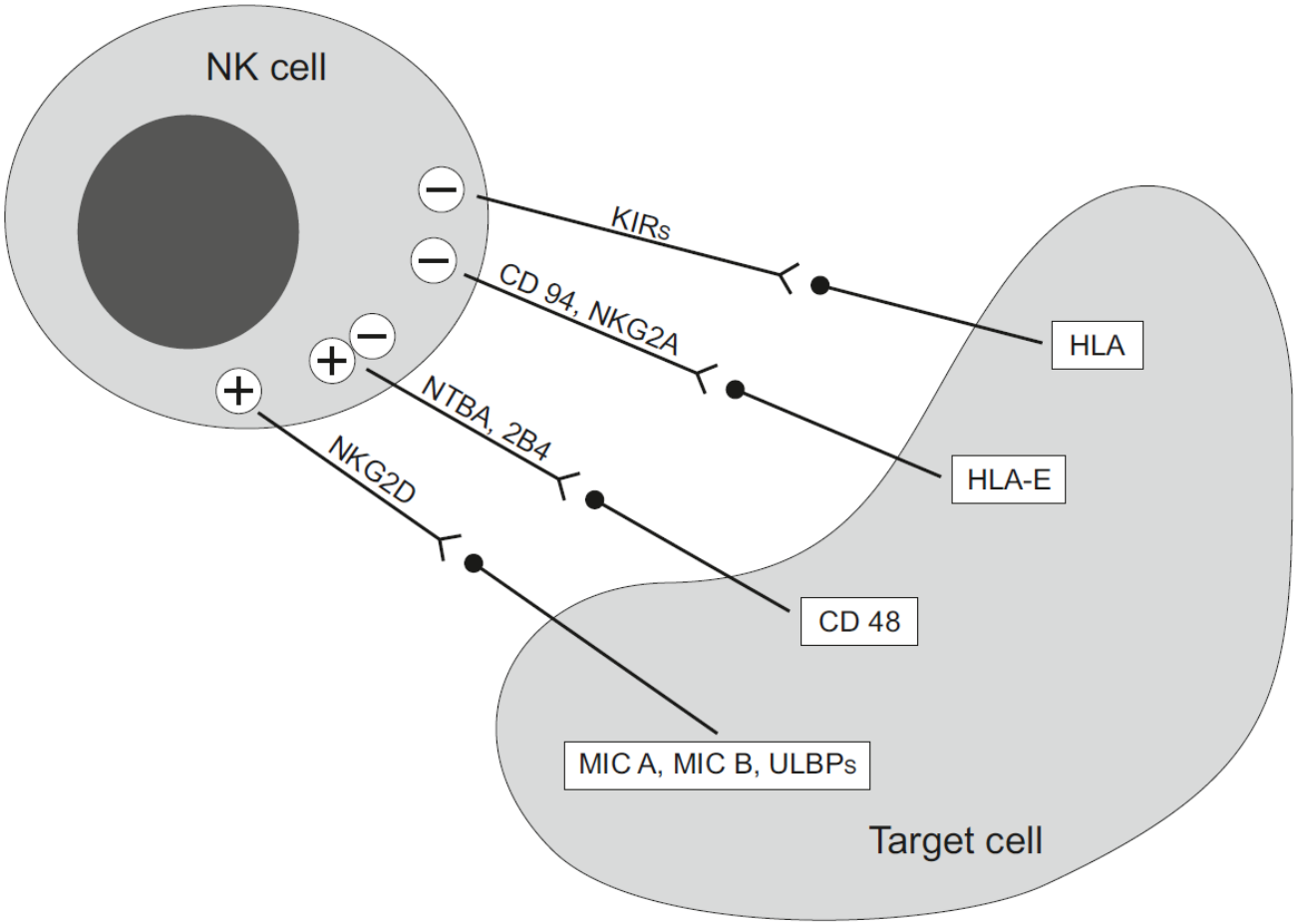
J. Clin. Invest. 117:1130-1136 (2007)



Cytotoxicity effects of NK cells on tumor cells

- Granule exocytosis via activating and inhibitory receptors (perforin and granzyme)
- Death receptor pathways (FAS-FASL; TRAIL-TRAILR)
- Soluble factors and small molecules (cytokines and NO)

Several pathways are involved in target cell-recognition by NK cells



Ruggeri & Curti, Front Immunol. 2015

Killer Immunoglobulin like Receptors (KIR)

- Transmembrane proteins belonging to the Ig-SF with 2 or 3 extracellular Ig-like domains

- Specific for different alleles of MHC class I molecules (HLA-A, -B ,-C)

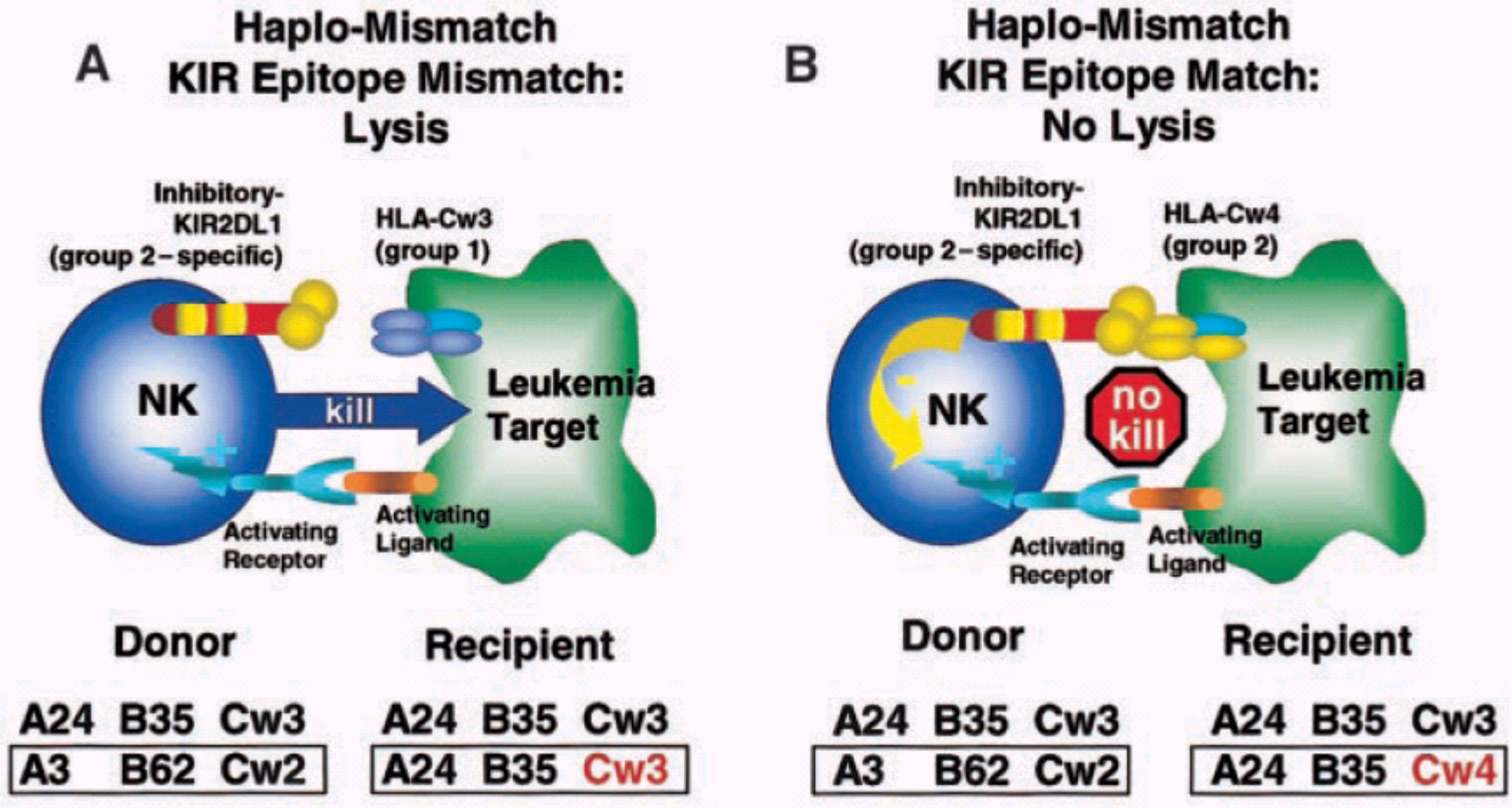
- Inhibitory KIR-receptors:

  KIR2DL1 (97%) : receptor for HLA-C group 2

  KIR2DL2/3 (100%): receptors for HLA-C group 1

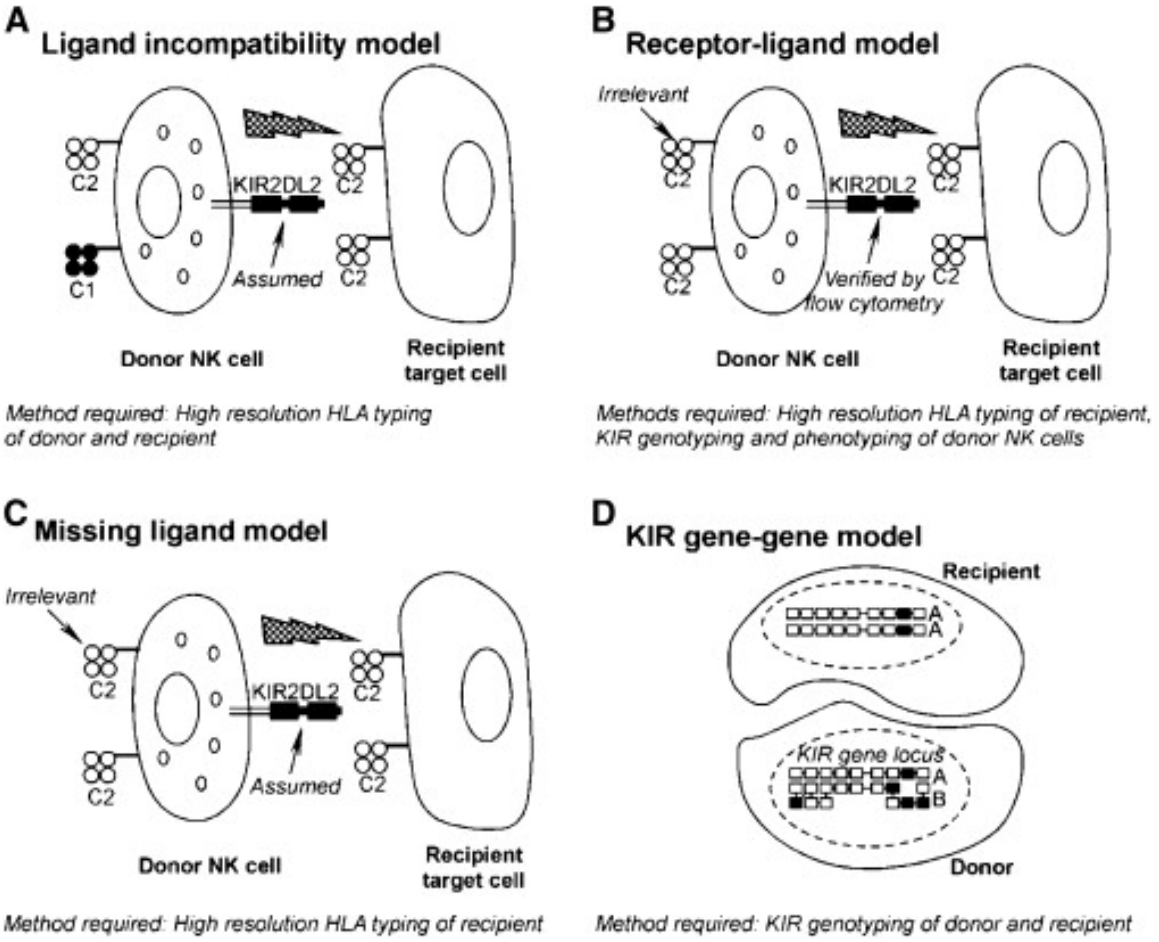
  KIR3DL1 (90%): receptor for HLA-Bw4

KIR-epitope mismatch in haploidentical SCT



Farag S et al, Blood 2004

Models of NK cell alloreactivity after allogeneic cell transplantation

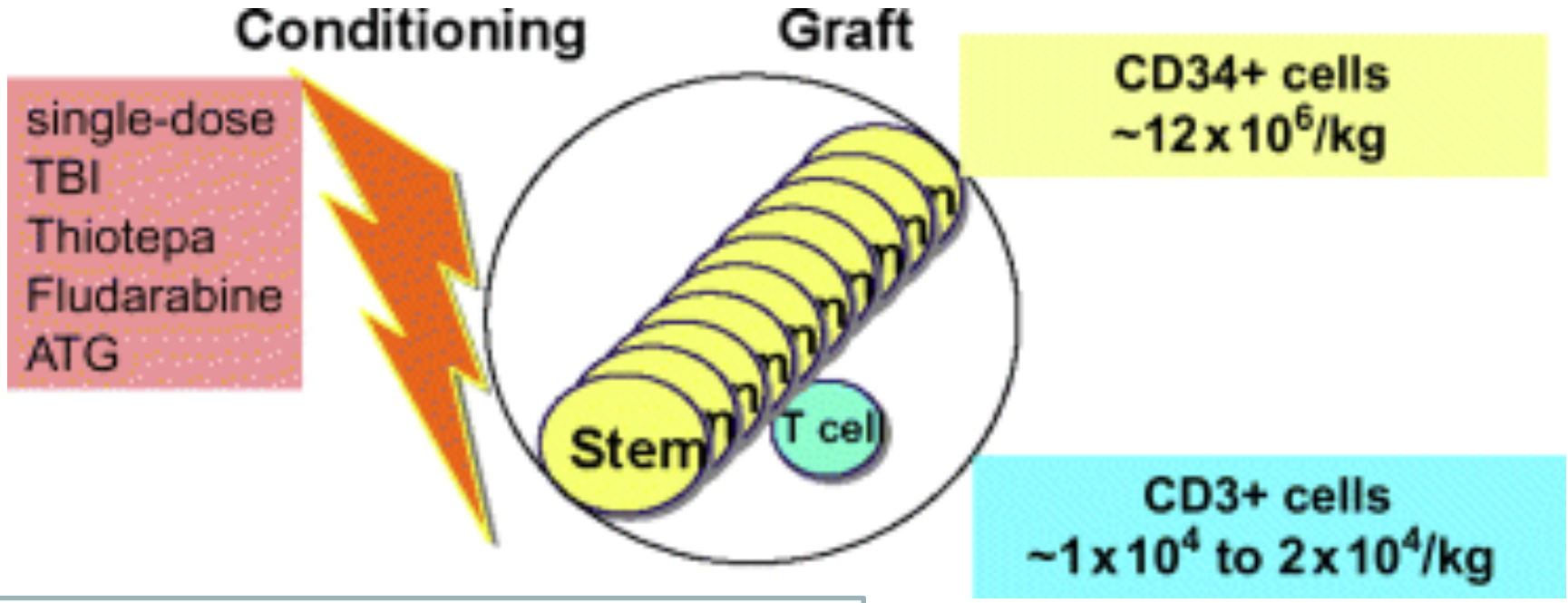


Heather J. Symons, BBMT, 2009

Donor–recipient HLA group combinations predicting NK cell alloreactivity

NK alloreactive donor	Recipient
None	Group 1 HLA-C, Group 2 HLA-C, HLA-Bw4
HLA-Bw4	Group 1 HLA-C, Group 2 HLA-C
Group 2 HLA-C	Group 1 HLA-C, HLA-Bw4
Group 1 HLA-C	Group 2 HLA-C, HLA-Bw4
Group 2 HLA-C or HLA-Bw4	Group 1 HLA-C
Group 1 HLA-C or HLA-Bw4	Group 2 HLA-C

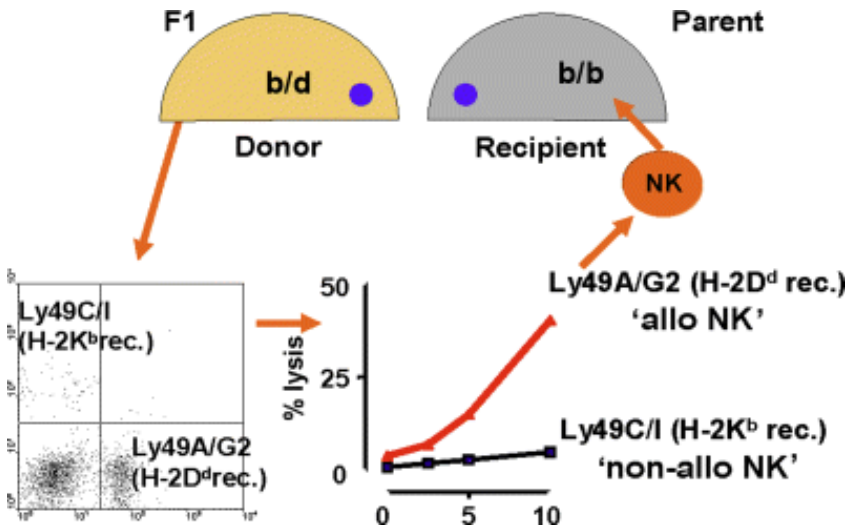
Allogeneic SCT and NK cell recognition of missing self: the model of haploidentical SCT

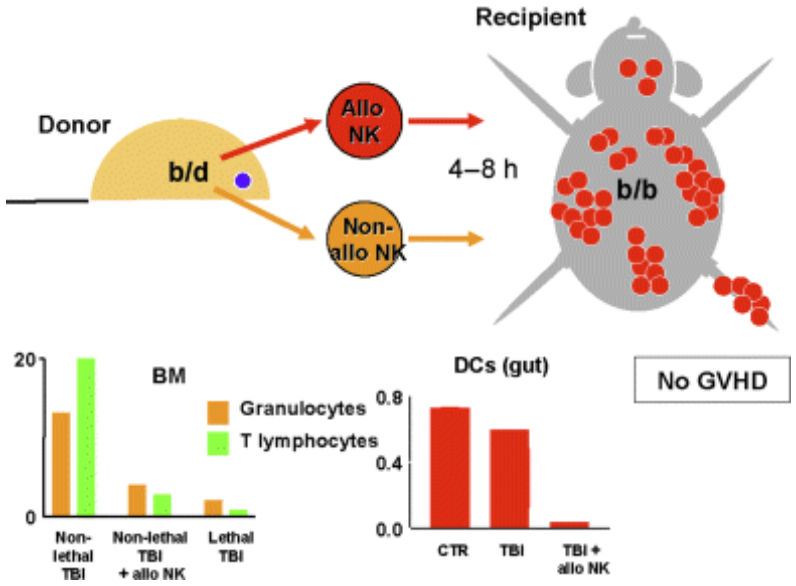


Highly immune suppressive and myeloablative conditioning regimens and infusion of extensively T-cell-depleted 'megadoses' of G-CSF-mobilized peripheral blood stem cells allow transplantation across the HLA barrier with >90% engraftment and <10% acute GVHD.

Ruggeri et al, Immunological Reviews, 2006

Infusion of alloreactive NK cells results in ablation of lymphohematopoietic cells, such as granulocytes, T cells and DCs

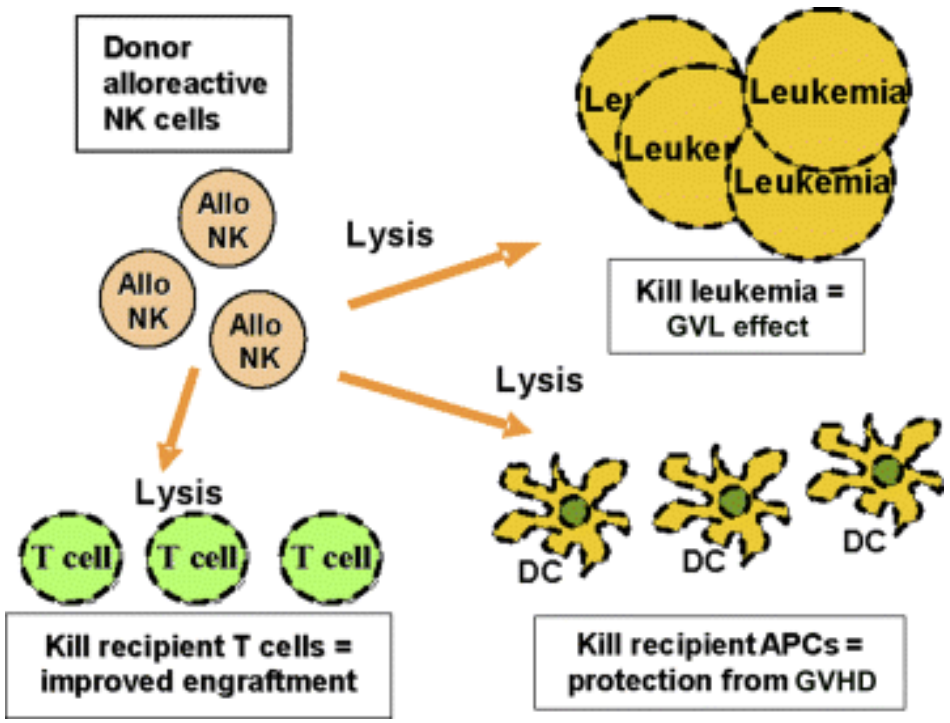




A mouse model of haploidentical transplantation with donor-versus-recipient NK alloreactivity

Ruggeri et al, Immunological Reviews, 2006

Allogeneic hematopoietic transplantation and natural killer cell recognition of missing self



Pretransplant infusion of donor alloreactive NK cells results in:

- Prevention of rejection of MHC-mismatched SCT transplants through ablation of recipient T lymphocytes (and other hematopoietic cells).
- Prevention of GVHD through killing of recipient DCs
- Eradication of AML cells

Ruggeri et al, Immunological Reviews, 2006

Science

AAAS

Effectiveness of Donor Natural Killer Cell Alloreactivity in Mismatched Hematopoietic Transplants

Loredana Ruggeri, *et al.*

Science **295**, 2097 (2002);

DOI: 10.1126/science.1068440

blood

2007 110: 433-440

Prepublished online Mar 19, 2007;

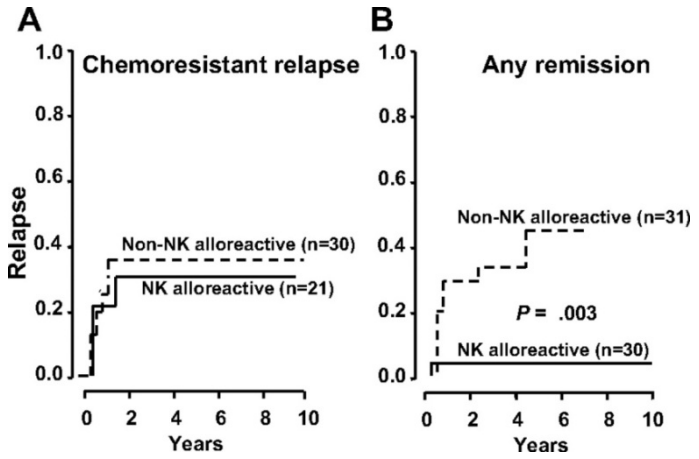
doi:10.1182/blood-2006-07-036687

Donor natural killer cell allorecognition of missing self in haploidentical hematopoietic transplantation for acute myeloid leukemia: challenging its predictive value.

Loredana Ruggeri, Antonella Mancusi, Marusca Capanni, Elena Urbani, Alessandra Carotti, Teresa Aloisi, Martin Stern, Daniela Pende, Katia Perruccio, Emanuela Burchielli, Fabiana Topini, Erika Bianchi, Franco Aversa, Massimo F. Martelli and Andrea Velardi

Data from haploidentical T-cell depleted transplantation suggested that KIR mismatch with tumor MHC may significantly impact on tumor cell killing, particularly in AML .

High risk AML patients receiving haploidentical T-cell depleted transplant with a KIR-ligand mismatch in the graft-versus-host (GVDH) direction had a relapse rate of 0% compared to KIR-ligand matched patients who had a relapse rate of 75%.

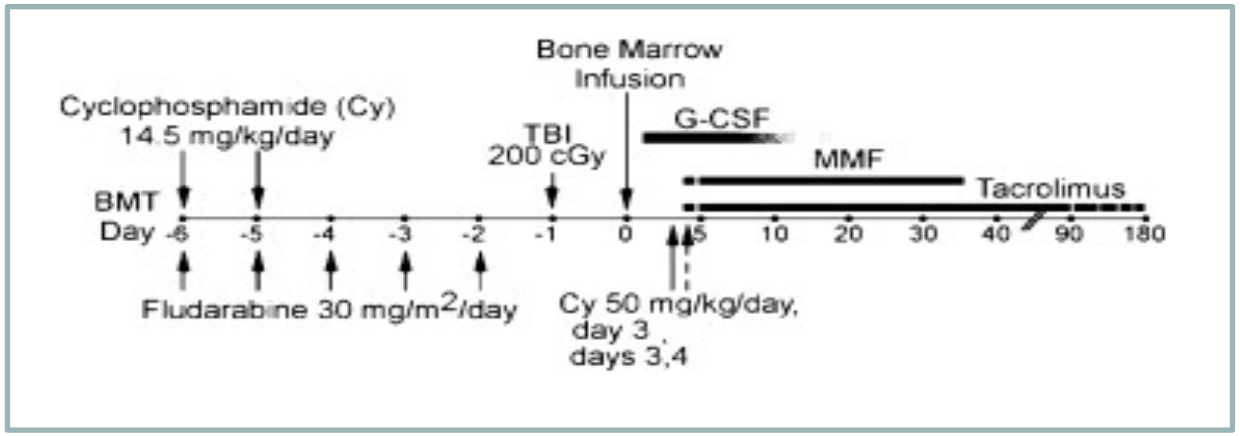


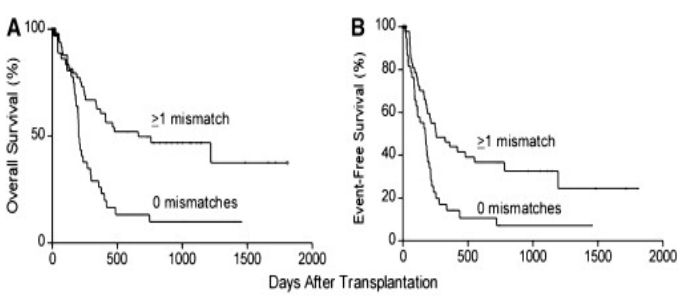
blood

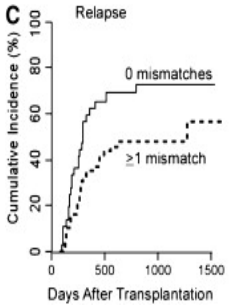
Anti-leukemia activity of alloreactive NK cells in KIR ligand-mismatched haploidentical HSCT for pediatric patients: evaluation of the functional role of activating KIR and redefinition of inhibitory KIR specificity

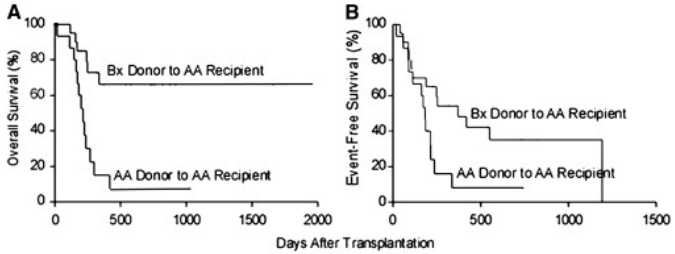
Pende D et al, Blood, 113; 3119-3129; 2009

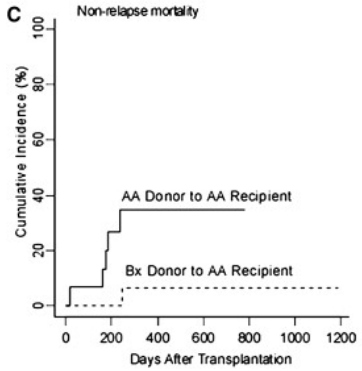
Improved Survival with Inhibitory Killer Immunoglobulin Receptor (KIR) Gene Mismatches and KIR Haplotype B Donors after Nonmyeloablative, HLA-Haploidentical Bone Marrow Transplantation











Heather J. Symons, BBMT, 2009

Genomic organization of the KIR locus.

		Centromeric Segment								Telomeric Segment								
KIR Haplotypes	Cen	3DL3	2DS2	2DL2/3	2DL5B	2DS3/5	2DP1	2DL1	3DP1	2DL4	3DL1/S1	2DL5A	2DS3/5	2DS1	2DS4	3DL2	Tel	KIR Haplotypes
A	A			2DL3			2DP1	2DL1			3DL1				2DS4		A	A
B	A			2DL3			2DP1	2DL1			3DS1	2DL5A	2DS3/5	2DS1			B	B
	B		2DS2	2DL2							3DL1				2DS4		A	
	B		2DS2	2DL2							3DS1	2DL5A	2DS3/5	2DS1			B	
	B		2DS2	2DL2	2DL5B	2DS3/5	2DP1	2DL1			3DL1				2DS4		A	
	B		2DS2	2DL2	2DL5B	2DS3/5	2DP1	2DL1			3DS1	2DL5A	2DS3/5	2DS1			B	

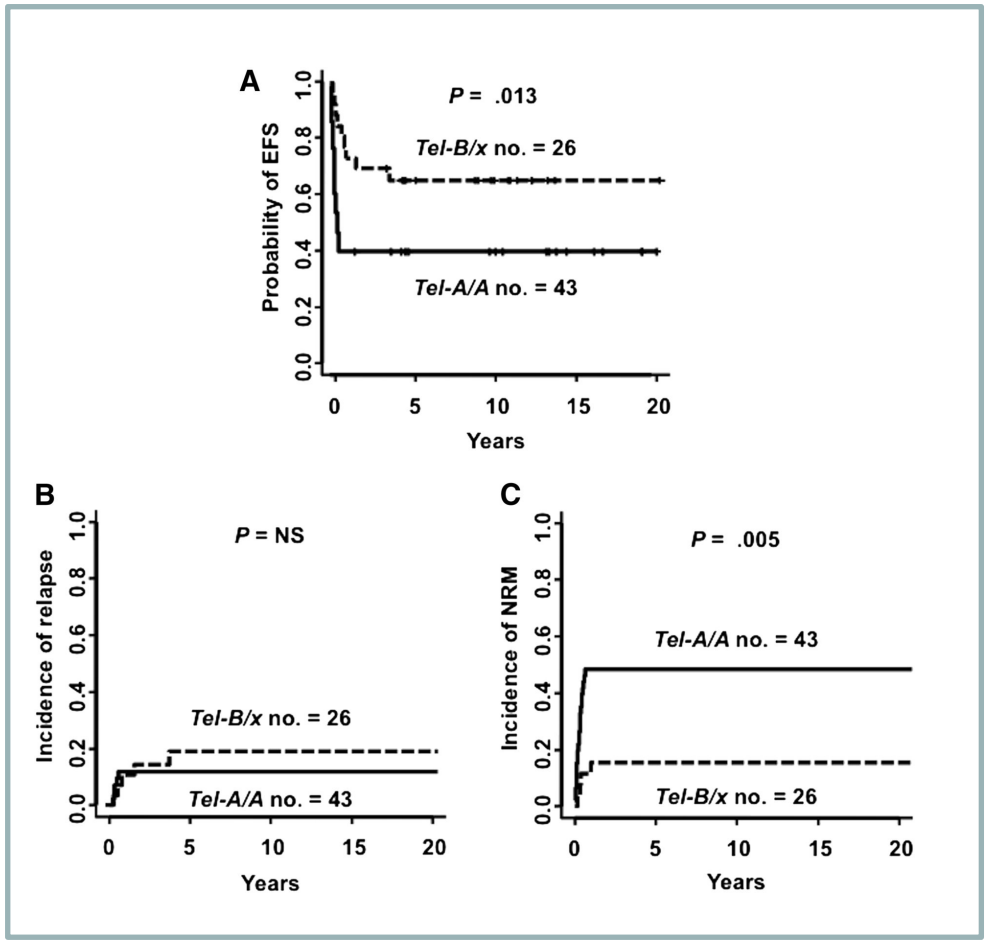
KIR genes segregate into groups *A* and *B* haplotypes. Framework genes located at the ends and in the central part of the locus (gray boxes) define 2 haplotype segments: the centromeric (Cen) and the telomeric (Tel).

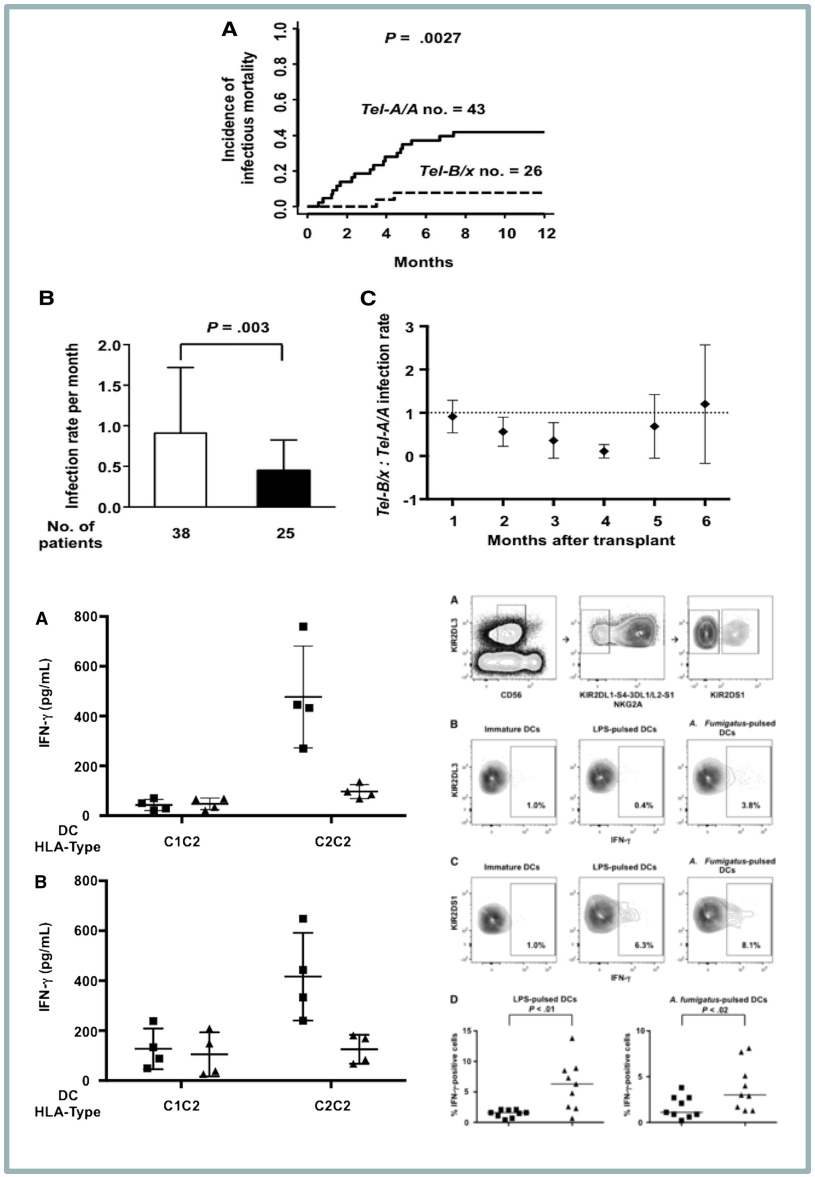
In the *A* haplotype, *KIR2DL1* and *KIR2DL3* are found in the centromeric segment and *KIR3DL1* and *KIR2DS4* in the telomeric. Combinations of *KIR2DL1/L2/L5/S2/S3/S5* are found in *B*-haplotype centromeric segments and combinations of *KIR2DL5/S1/S3/S5* and *KIR3DS1* in *B*-haplotype telomeric segments.

Mancusi et al. Blood 2015;125:3173-3182

blood

Haploidentical hematopoietic transplantation from KIR L–mismatched donors with activating KIRs reduces nonrelapse mortality and associates with reduced infectious rate

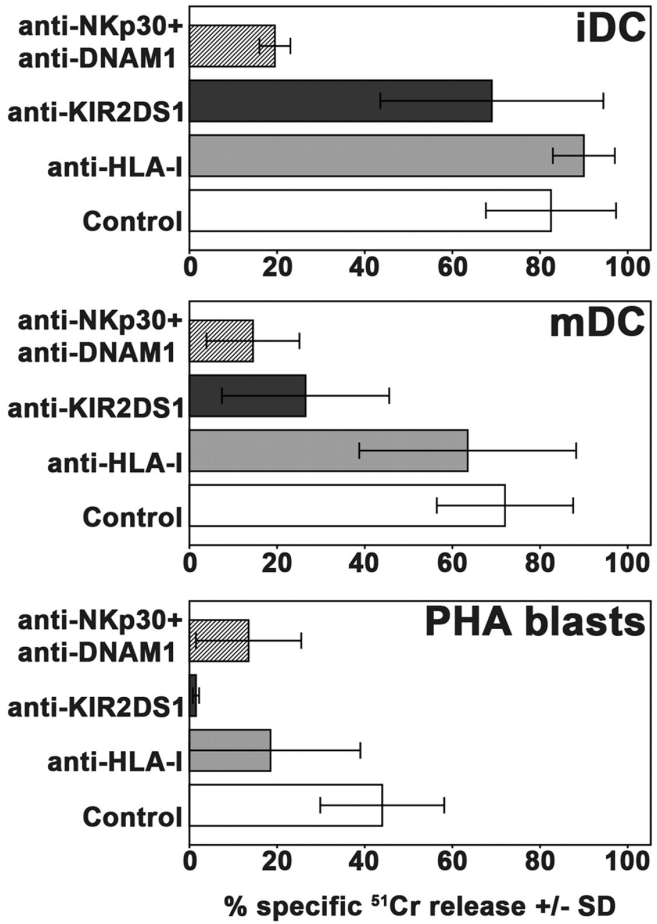




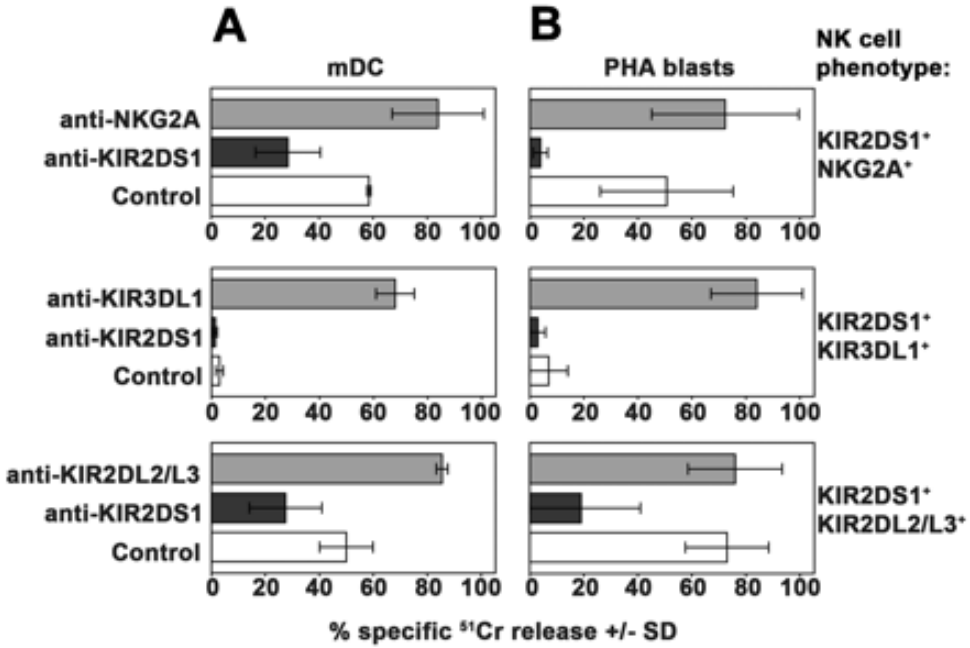
Mancusi et al. Blood 2015;125:3173-3182

blood

Natural killer cells expressing the KIR2DS1-activating receptor efficiently kill T-cell blasts and dendritic cells: implications in haploidentical HSCT



NK cells: donor P61 (C1/C1, Bw4/Bw4)
Target cells: donor RB (C2/C2, Bw4/Bw4)

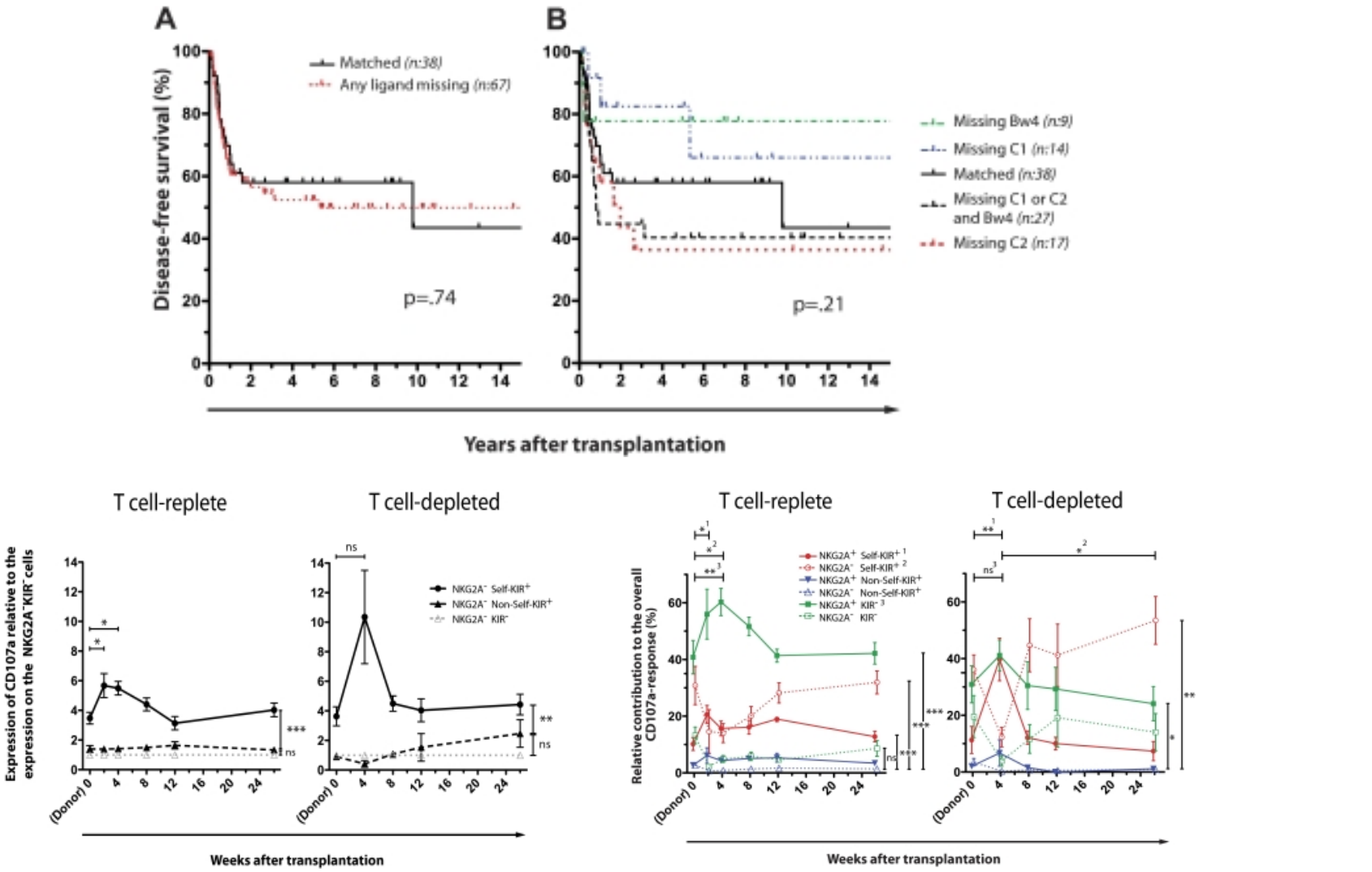


NK cells: donor P61 (C1/C1, Bw4/Bw4)
Target cells: donor RB (C2/C2, Bw4/Bw4)

Sivori et al. Blood 2011;117:4284-4292

blood

NK cells expressing inhibitory KIR for non-self-ligands remain tolerant in HLA-matched sibling SCT



T. Björklund et al. Blood 2010;115:2686-2694

blood

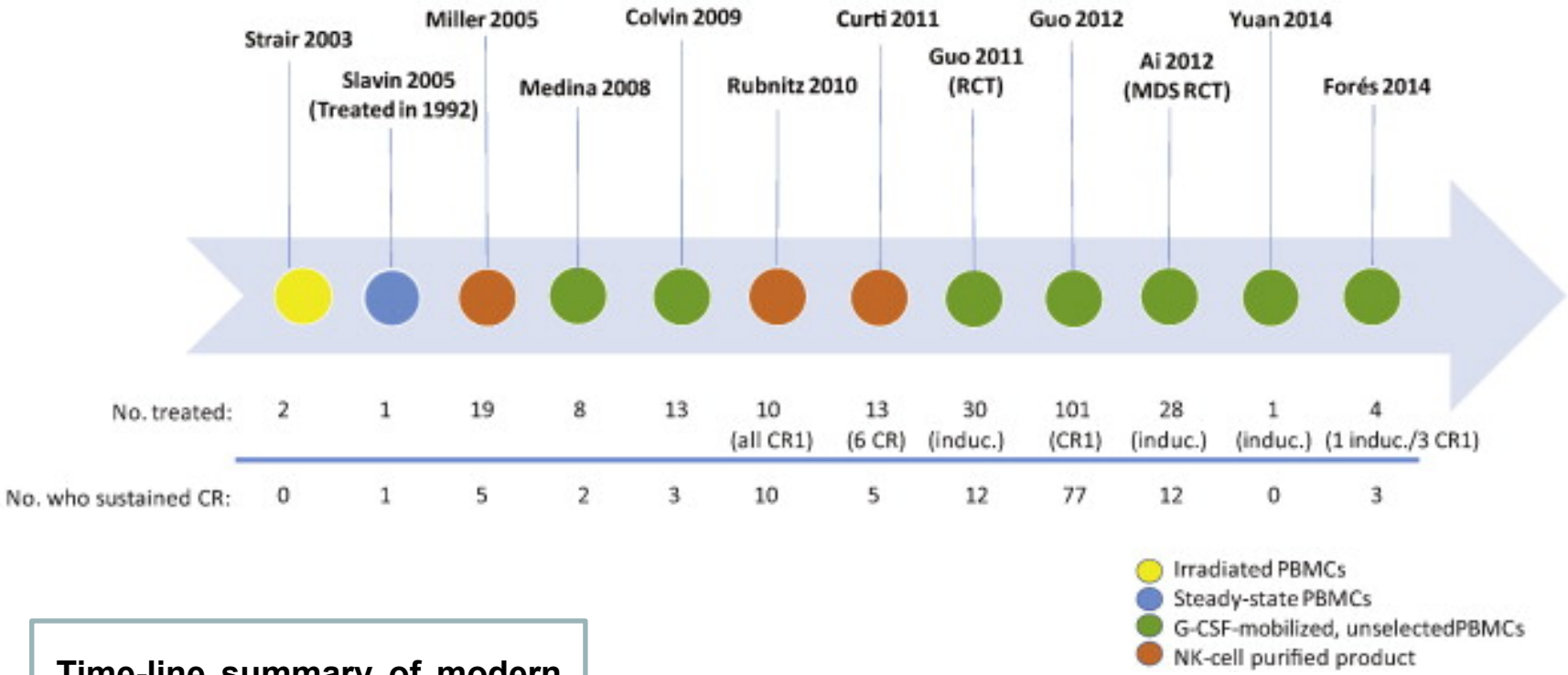
Impact of KIR-mismatch in unrelated SCT

Authors	Survival	TRM	Relapse	GVHD	ATG
Davies et al (2002)	↓	Not assessed	→	↑	No
Giebel et al (2003)	↑	↓	↓	↓	Yes
Bornhauser et al (2004)	→	→	↑	→	Yes
Schaffer et al (2005)	↓	↑	→	→	Yes

Question: Is there an impact of KIR-ligand incompatibilities on outcomes after unrelated stem cell transplantation?

Answer: the role NK cell alloreactivity in USCT is far from clear. It is too early to use a donor–recipient KIR(-ligand) algorithm for selection of a unrelated donor.

Harnessing the power of alloreactivity without triggering GvHD: how non-engrafting alloreactive cellular therapy might change the landscape of acute myeloid leukemia treatment



Time-line summary of modern clinical trials of non-engrafting alloreactive cell therapy for AML and MDS

Krakow et al, Blood Reviews, Volume 28, Issue 6, 2014, 249–261

blood

2005 105: 3051-3057
Prepublished online Jan 4, 2005;
doi:10.1182/blood-2004-07-2974

Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer

Jeffrey S. Miller, Yvette Soignier, Angela Panoskaltsis-Mortari, Sarah A. McNearney, Gong H. Yun, Susan K. Fautsch, David McKenna, Chap Le, Todd E. Defor, Linda J. Burns, Paul J. Orchard, Bruce R. Blazar, John E. Wagner, Arne Slungaard, Daniel J. Weisdorf, Ian J. Okazaki and Philip B. McGlave

Five/19 poor-prognosis patients with AML achieved complete remission after infusion of partially purified haploidentical NK cells.

VOLUME 28 · NUMBER 6 · FEBRUARY 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

NKAML: A Pilot Study to Determine the Safety and Feasibility of Haploidentical Natural Killer Cell Transplantation in Childhood Acute Myeloid Leukemia

Jeffrey E. Rubnitz, Hiroto Inaba, Raul C. Ribeiro, Stanley Pounds, Barbara Rooney, Teresa Bell, Ching-Hon Pui, and Wing Leung

Ten AML patients (0.7 to 21 years old) in first CR received cyclophosphamide (60 mg/kg on day –7) and fludarabine (25 mg/m2/d on days –6 through –2), followed by KIR-L mismatched NK cells (median, 29 x 106/kg NK cells) and six doses of interleukin-2 (1 million U/m2). With a median follow-up time of 964 days (range, 569 to 1,162 days), all patients remain in remission. The 2-year event-free survival estimate was 100% (95% CI, 63.1% to 100%).

JOURNAL OF CLINICAL ONCOLOGY

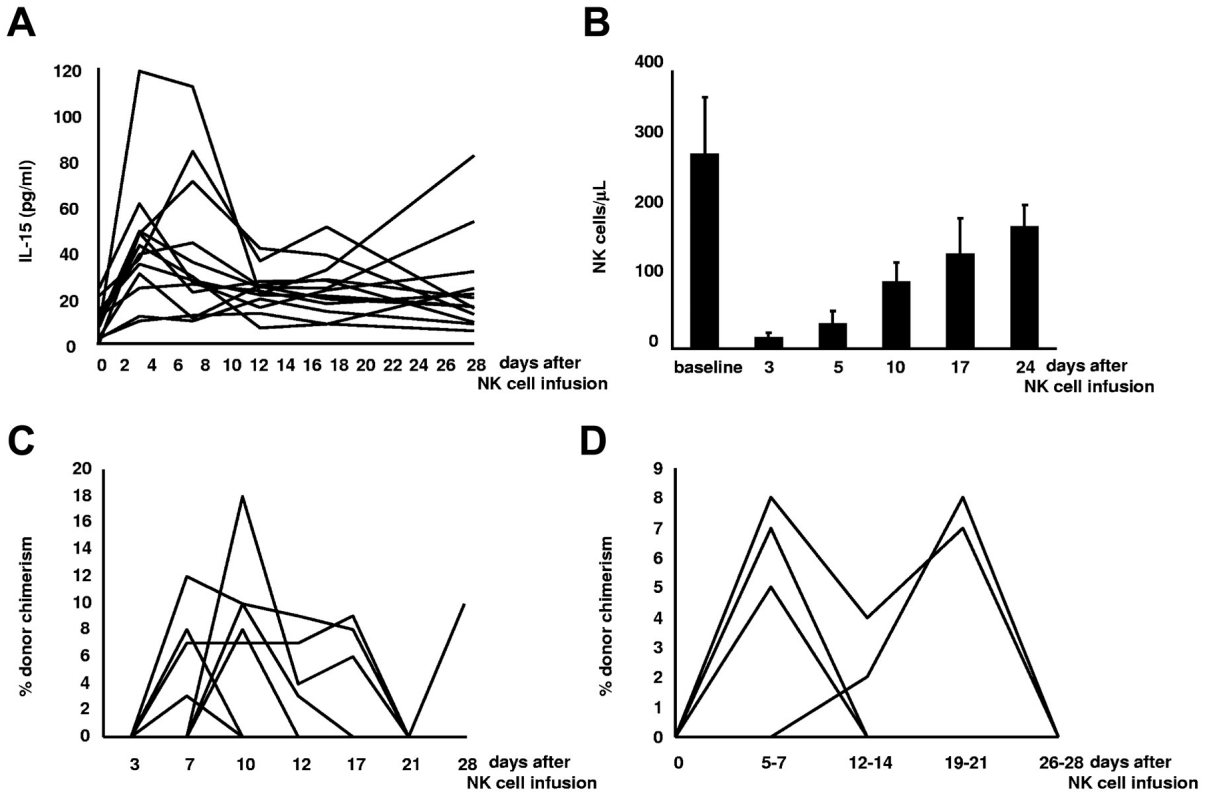
blood

BLOOD, 22 SEPTEMBER 2011 • VOLUME 118, NUMBER 12

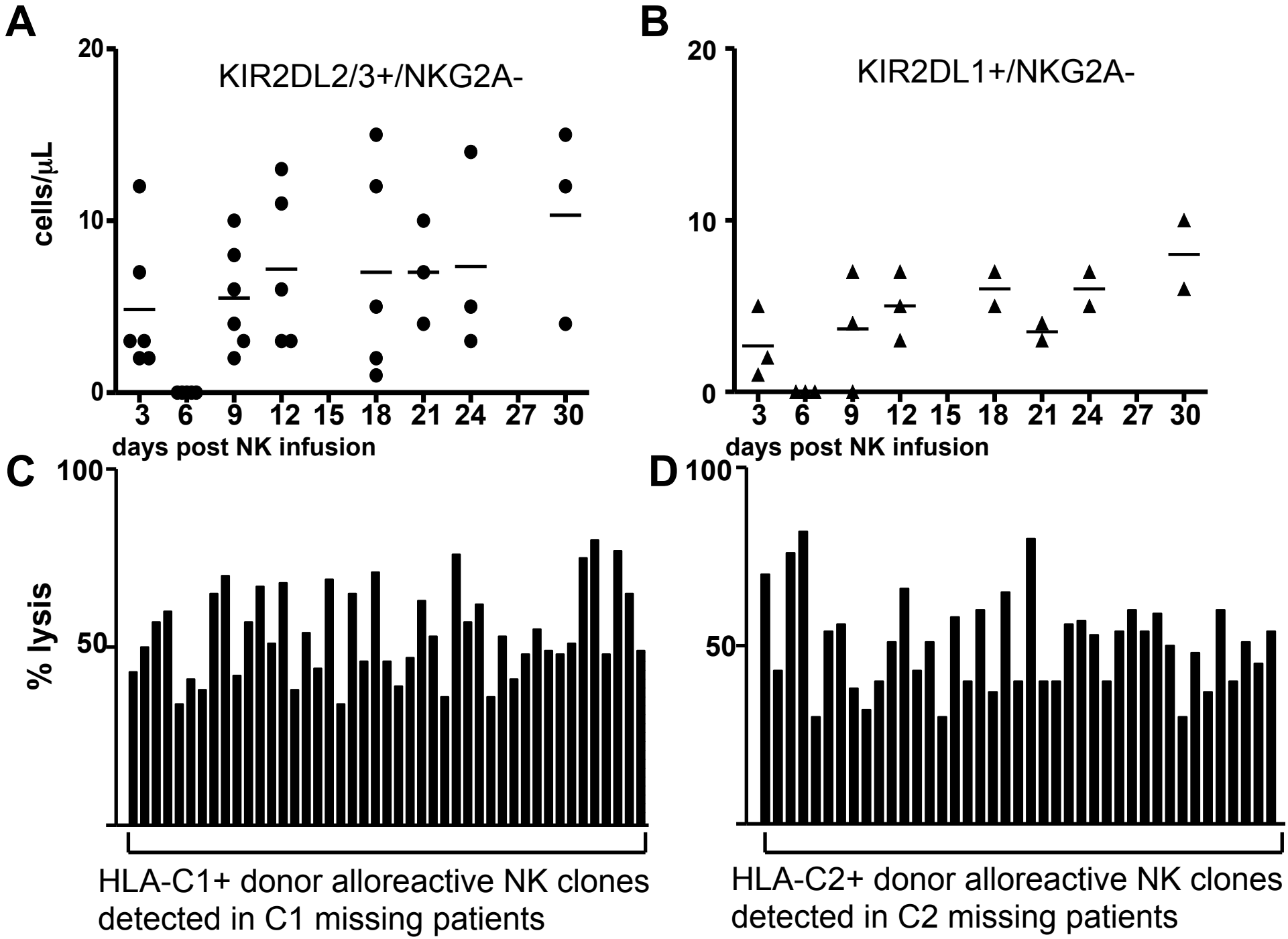
Successful transfer of alloreactive haploidentical KIR ligand-mismatched natural killer cells after infusion in elderly high risk acute myeloid leukemia patients

Antonio Curti,[1] Loredana Ruggeri,[2] Alessandra D'Addio,[3] Andrea Bontadini,[4] Elisa Dan,[1] Maria Rosa Motta,[1] Sara Trabanelli,[1] Valeria Giudice,[4] Elena Urbani,[2] Giovanni Martinelli,[1] Stefania Paolini,[1] Fiorenza Fruet,[4] Alessandro Isidori,[5] Sarah Parisi,[1] Giuseppe Bandini,[1] Michele Baccarani,[1] Andrea Velardi,[2] and Roberto M. Lemoli[1]

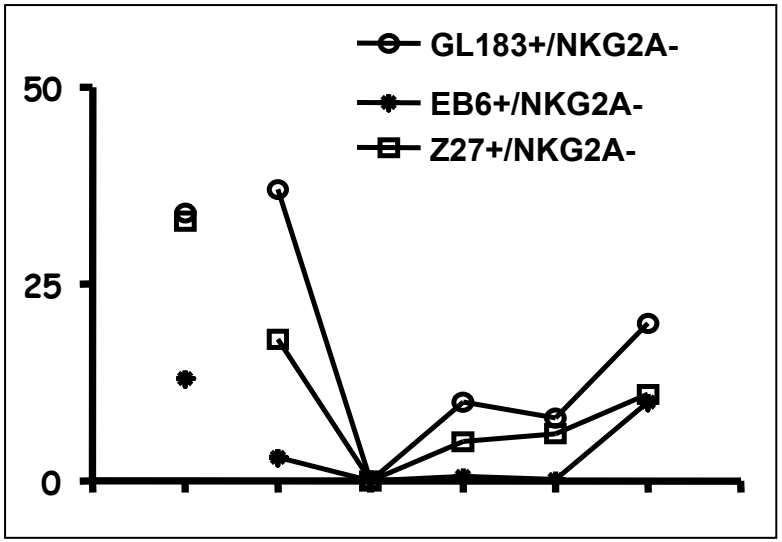
[1]Institute of Hematology, Department of Hematology and Oncological Sciences "L. and A. Seràgnoli," University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy; [2]Division of Hematology and Clinical Immunology, Department of Clinical and Experimental Medicine, University of Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy; [3]Azienda Istituti Ospitalieri, Hematology Unit, Cremona, Italy; [4]Immunohematology Service and Blood Bank, S. Orsola-Malpighi Hospital, Bologna, Italy; and [5]Hematology and Hematopoietic Stem Cell Transplant Centre, San Salvatore Hospital, Pesaro, Italy



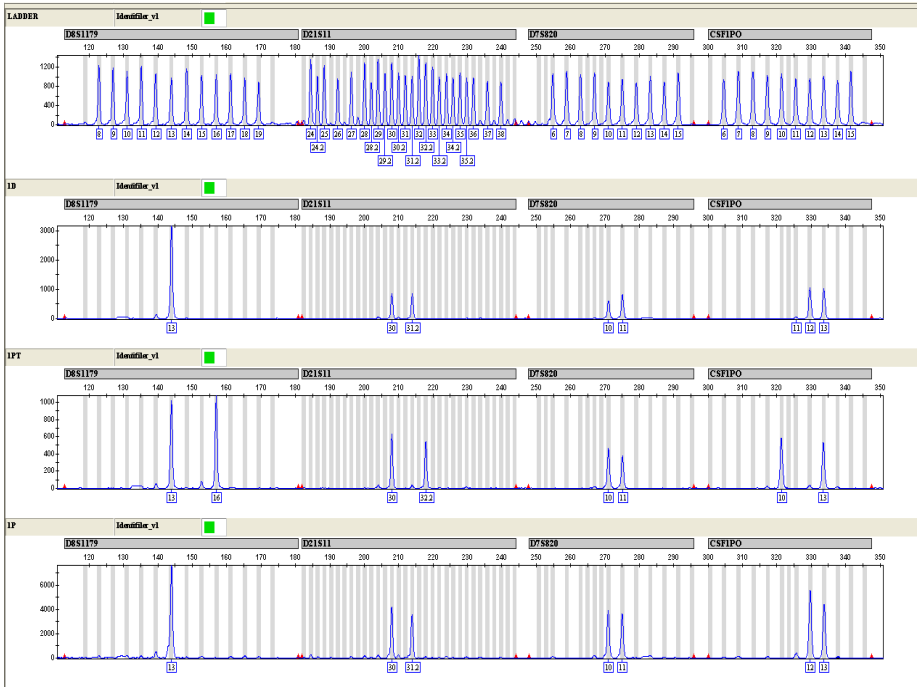
Curti et al. Blood 2011;118:3273-3279


A
KIR2DL2/3+/NKG2A-
cells/μL
20
10
0
3 6 9 12 15 18 21 24 27 30
days post NK infusion
B
KIR2DL1+/NKG2A-
20
10
0
3 6 9 12 15 18 21 24 27 30
days post NK infusion
C
% lysis
100
50
HLA-C1+ donor alloreactive NK clones
detected in C1 missing patients
D
100
50
HLA-C2+ donor alloreactive NK clones
detected in C2 missing patients

Detection of alloreactive KIR^{+}/NKG2A^{-} NK cells after haploidentical NK cell infusion



VNTR analysis



Curti et al., Blood, 2011

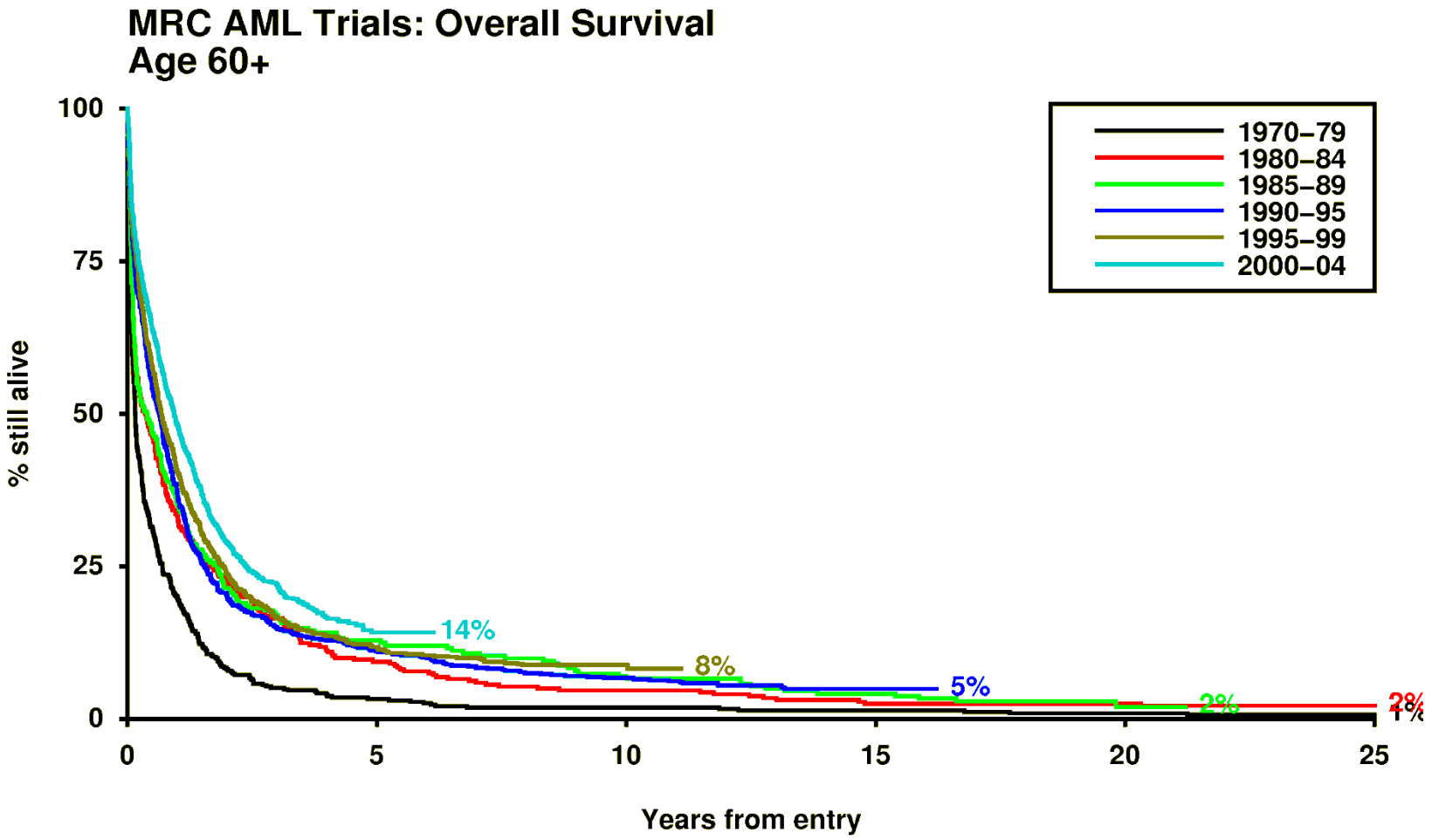
Study Design- Eligibility criteria

1) High risk AML patients with age greater than 18 years and in morphological (or better) CR after (re-) induction and consolidation chemotherapy, not eligible for stem cell transplantation

2) a suitable haploidentical KIR L-mismatched donor (HLA class I typing and KIR genotyping)

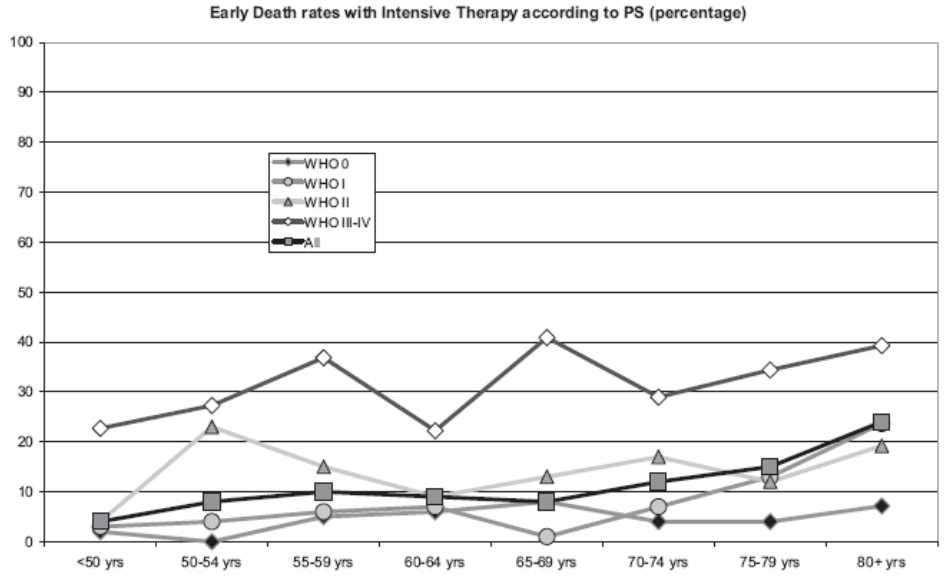
3) No major organ dysfunctions (“fit-to-chemo” patients)

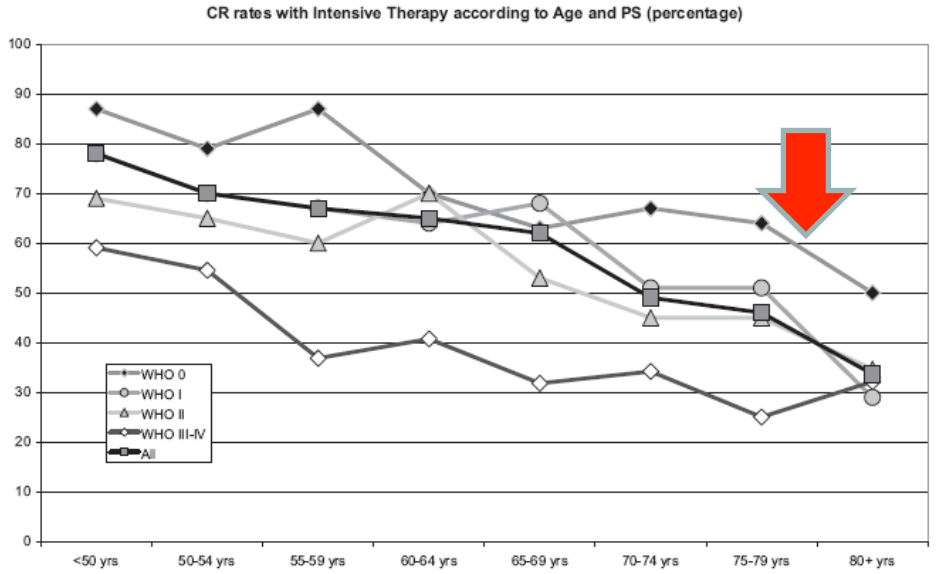
MRC Trials for Older Patients >60 years (n=3541)



Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry

Gunnar Juliusson,[1,9] Petar Antunovic,[2,9] Åsa Derolf,[3,9] Sören Lehmann,[4,9] Lars Möllgård,[4,9] Dick Stockelberg,[5,9] Ulf Tidefelt,[6,9] Anders Wahlin,[7,9] and Martin Höglund[8,9]





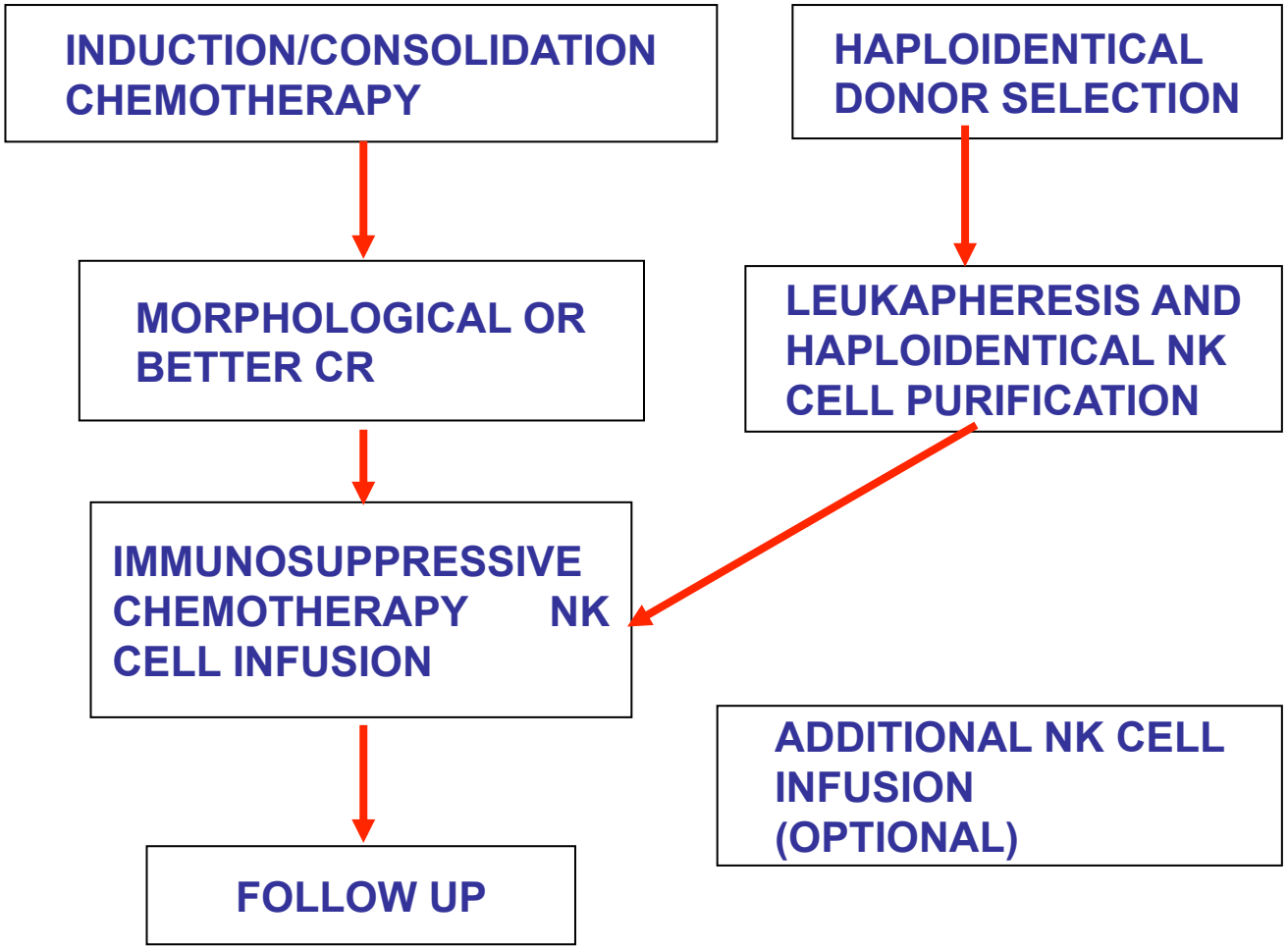
STUDY ENROLLMENT AND HAPLOIDENTICAL DONOR SELECTION

- 54 high risk AML patients were screened for the availability of one haploidentical KIR ligand mismatched donor
- 26 patients (48%) had one suitable donor.
- 21 patients (38%) infused so far. Among them, 17 patients infused in CR

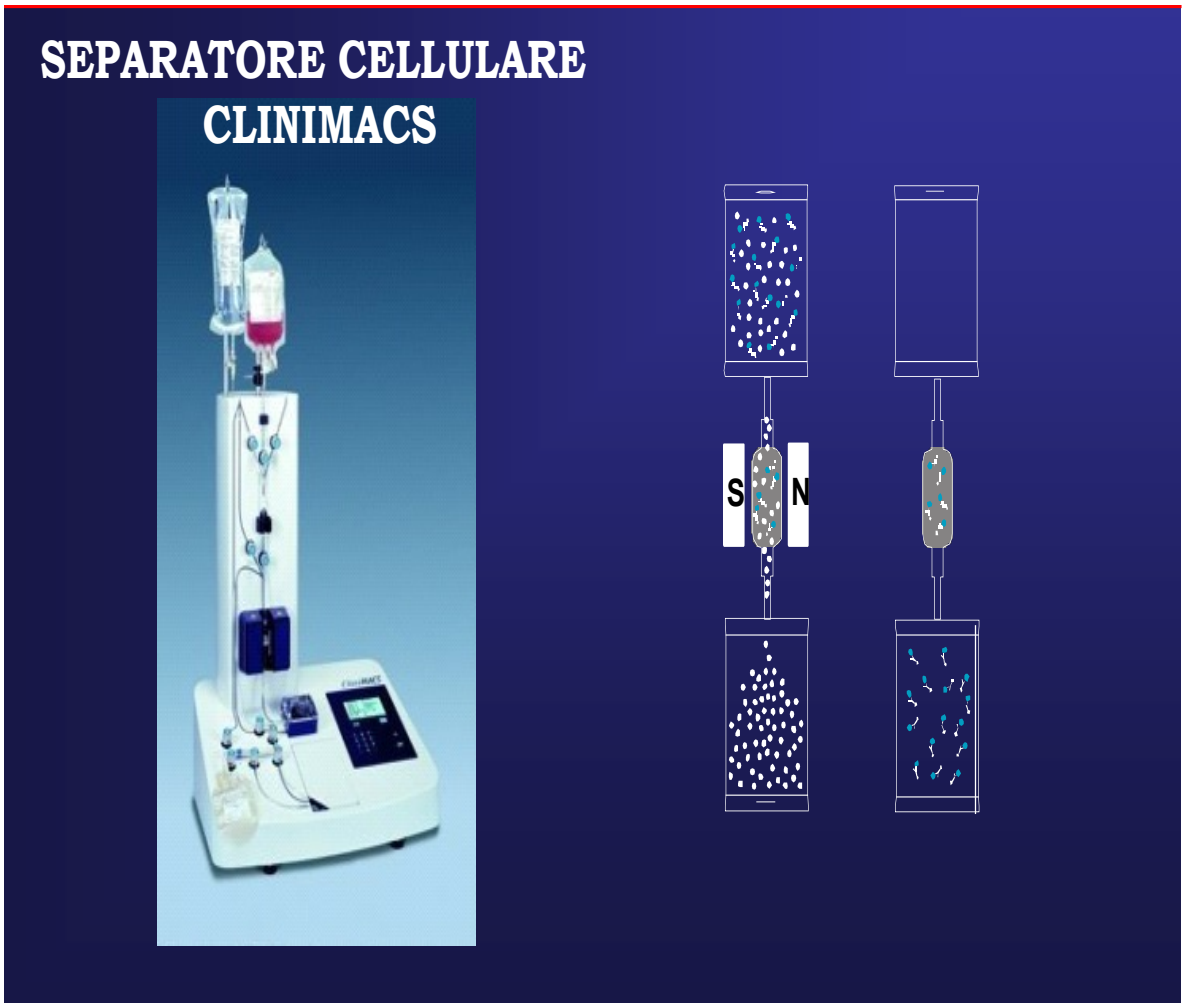
Donor and patient HLA typing identified the family member who did not express the class I group(s) expressed by the patient and had,therefore, the potential for NK alloreactivity. Donor KIR genotyping will then be performed to confirm that the donors possess the suitable KIR-mismatch.

- 12/21 (57%) donor-recipient pairs were mismatched for HLA-C group 1
- 6/21 (28%) donor-recipient pairs were mismatched for HLA-C group 2
- 1/21 (5%) donor-recipient pairs were mismatched for HLA Bw4
- 1/21 (5%) donor-recipient pairs were mismatched for both HLA-C group 1 and Bw4
- 1/21 (5%) donor-recipient pairs were mismatched for both HLA-C group 2 and Bw4

Study Design- Flow chart



Immunomagnetic enrichment of NK cells



Two steps:

1) depletion of $CD3^+$ T cells
2) positive selection of $CD56^+$ NK cells.

Immunosuppressive Regimen

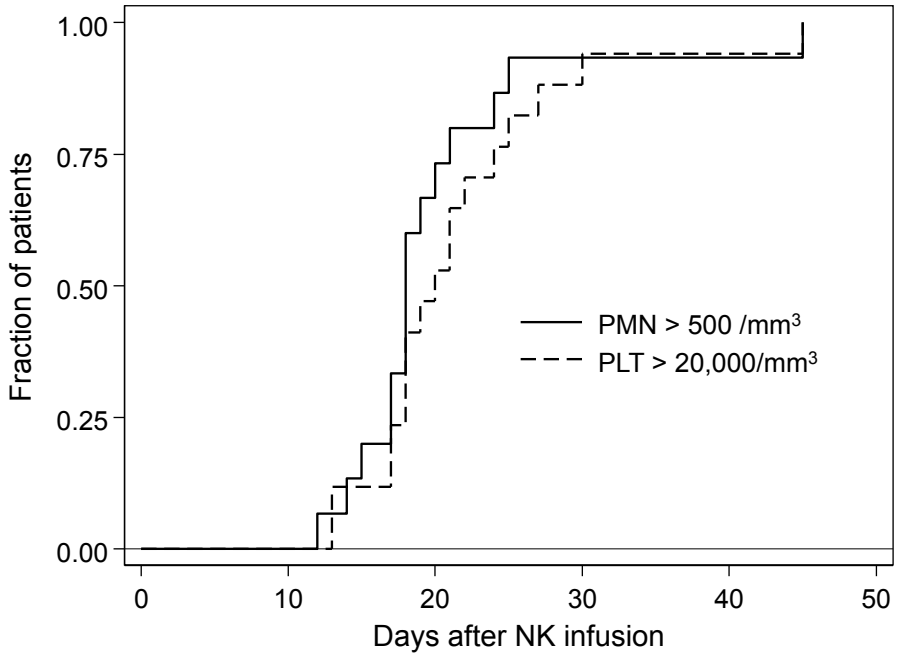
- **FLUDARABINE (Flu) 25 mg/m^2/day for 5 days (from day –7 to -3).**
- **CYCLOPHOSPHAMIDE (Cy) 4 g/m^2 (day -2).**

After 2 days from the administration of Cy, patients proceed to NK cell infusion (day 0). No GVHD prophylaxis is used as GVHD is not anticipated. IL-2 (10x10^6 IU/day, 3 times weekly) is administered sc for 2 weeks (6 doses total) after NK cell infusion.

Median time from CR to NK cell therapy = 5.5 months (range 4-9).

17 patients	Median
Age (yrs)	65 (51-73)
Sex (M/F)	9/8
WBC>30x10^9/L	6/17 (35%)
Secondary AML	3/17 (18%)
Cytogenetics:	
Favorable (t8;21;inv16)	2/17 (12%)
Intermediate (normal; -Y)	13/17 (76%)
Unfavorable (other than favorable and intermediate)	2/17 (12%)
Genotype:	
NPM+/FLT3-	1/17 (6%)
NPM+/FLT3+	0/17 (0%)
NPM-/FLT3-	13/17 (76%)
NPM-/FLT3+	3/17 (18%)

Hematological recovery



PMN mean 20.1 (16.1-24.0)
PLT mean 21.6 (18.1-25.2)

Curti et al, 2015, in press

Patients characteristics, response to NK cell infusion and follow-up

patient	age	sex	FAB	WBC	kariotype	AML type	disease status before NK infusion	response	folow-up (months)
1) D.E.R	63	M	M4	7.360	complex	de novo	morphological CR	CR	**CR(45)**
2) F.A	72	F	M1	1.170	+4;+8	de novo	morphological CR	CR	**CR(43)**
3) T.A	70	F	M5	58.600	XX	de novo	morphological CR	NE	dead(1)
4) D.F.S	73	M	M5	75.000	XY	de novo	morphological CR	CR	**CR(81)**
5) M.A	58	M	M4	74.800	XY	de novo	morphological CR	relapse(3)	dead (4)
6) V.V	58	F	M1	4.320	XX	de novo	morphological CR	CR	**CR(78)**
7) Z.G	64	M	M1	25.000	XY	de novo	morphological CR	relapse(5)	dead(6)
8) R.C.	53	F	M1	4.100	-7;+8	de novo	molecular relapse	CR	relapse(9)/ IICR(36)
9) P.R.	67	M	M0	2.700	XY	de novo	morphological CR	relapse(24)	dead (30)
10) D.P.C.	58	F	M1	5.800	inv16	de novo	persistent MRD+	CR	relapse(9)/II NK/ dead
11) D.D.	61	M	n.a.	2.900	XY	secondary	morphological CR	relapse (51)	CR (5-Aza)
12) V.A	72	M	n.a.	3.000	XY	secondary	morphological CR	CR	**CR(24)**
13) S.D	68	F	n.a.	59.000	XX	de novo	morphological CR	CR	**CR(23)**
14) C.A	61	M	n.a.	2.500	del(12)	secondary	morphological CR	Relapse (3)	Reinduction
15) V.L	62	F	M1	1.270	t(11)	de novo	morphological CR	CR	**CR(11)**
16) R.E.	64	F	M4	27.400	inv(16)	de novo	persistent MRD+	CR	**CR(9)**
17) N.A.	65	M	M0	189.500	XY	de novo	morphological CR	CR	**CR(6)**

Cell processing data according to clinical response

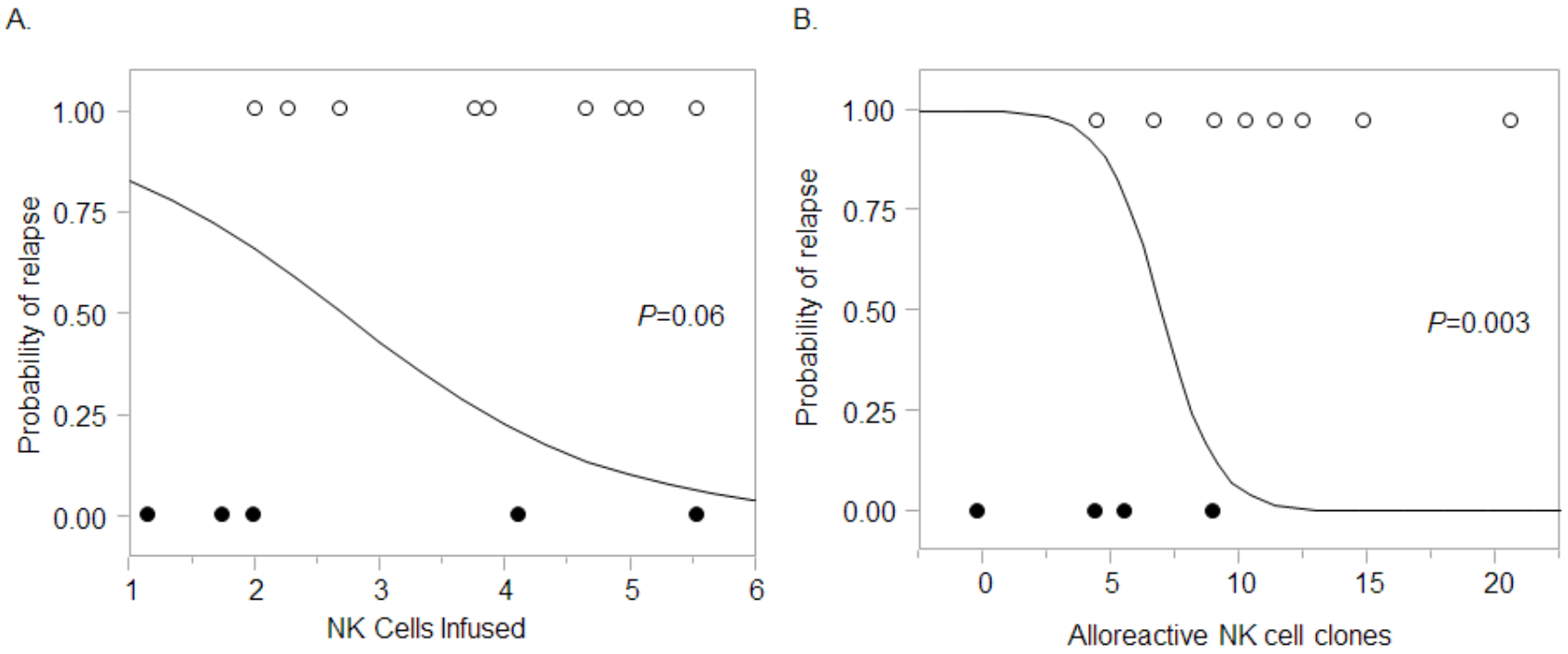
UPN	NK CELLS				T CELLS		
	PURITY	RECOVERY	COLLECTED (x 10^6/Kg)	INFUSED (x 10^6/Kg)	T-CELL LOG DEPLETION	COLLECTED (x 10^5/Kg)	INFUSED (x 10^5/Kg)
6	79,7	53,05	10,72	4,0	-3,04	1579	1
7	96,8	57,78	17,1	4,75	-3,11	1690	0,11
11	94,9	31,82	42,5	2,74	-2,53	1671,13	1
12	94,9	45,61	21,55	2,51	-2,6	1577,01	1
1	95,8	32,77	8,42	3,1	-2,84	580,27	1
2	92,8	56,48	28,29	4,14	-6,94	2167,93	3,1
4	95	54,97	24,29	5,53	-3,41	1266,23	1
15	99,2	42,84	10,64	5,1	-4,05	632,67	0,215
5	98,1	50,28	19,56	5	-3,67	1880,48	0,1
16	92,9	51,8	29,3	5	-2,33	1785,47	0,41
17	97,3	63,51	14,2	5	-3,07	1698,27	0,255
Median (range)	94,3 (79,7-99,2)	49,2 (31,82-63,51)	20,6 (8,42-42,5)	4,3 (2,51-5,53)	-3,4 (-6,94-2,33)	1503 (580,27-2167,93)	0,84 (0,1-3,1)

Responders

UPN	NK CELLS				T CELLS		
	PURITY	RECOVERY	COLLECTED (x 10^6/Kg)	INFUSED (x 10^6/Kg)	T-CELL LOG DEPLETION	COLLECTED (x 10^5Kg)	INFUSED (x 10^5/Kg)
8	92,4	65,4	3,8	1,81	-4,52	882,39	0,05
9	97,2	60,83	24,1	2,05	-2,71	1013,13	1
10	99,2	35,95	11,98	3,89	-4,3	1740,51	0,08
13	90,6	54,41	28,96	1,29	-2,15	1726,27	1
14	99,1	63,29	26,04	5	-6,86	1005,37	0,1
Median (range)	95,7 (90,6-99,2)	55,9 (35,95-65,4)	18,98 (3,8-28,96)	2,8 (1,29-5)	-4,1 (-6,86--2,15)	1273,53 (882,39-1740,51)	0,45 (0,05-1)

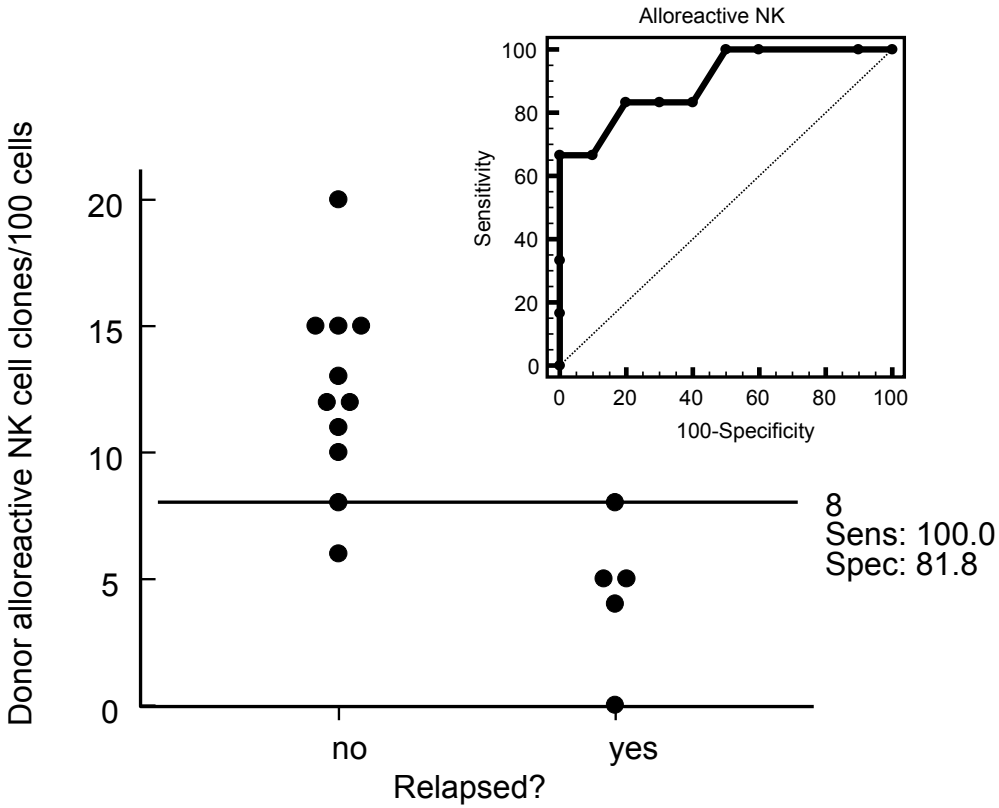
NON-responders

The percentage of donor alloreactive NK cells correlates with relapse rate



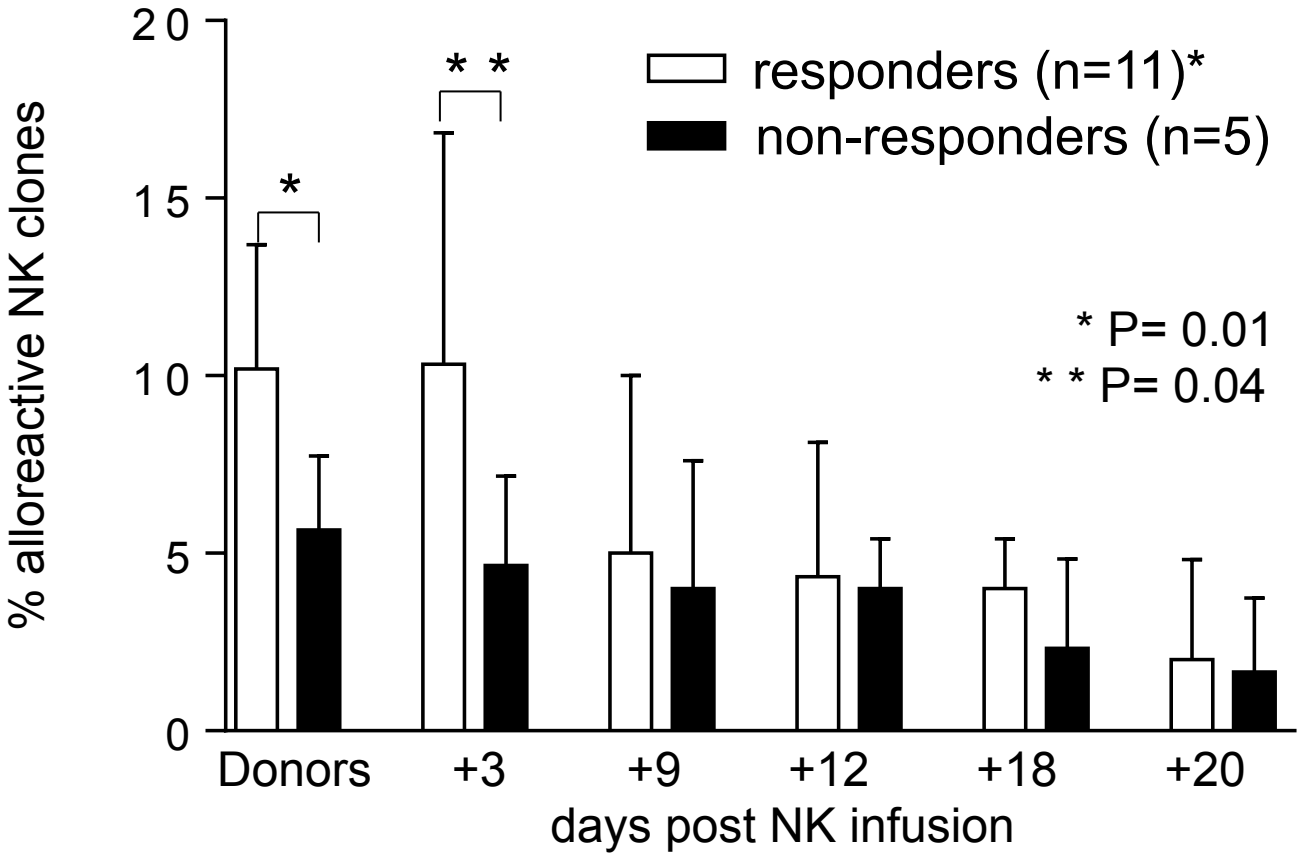
Curti et al, 2015, in press

Identification of a threshold of alloreactive NK cell clones predictive for clinical response



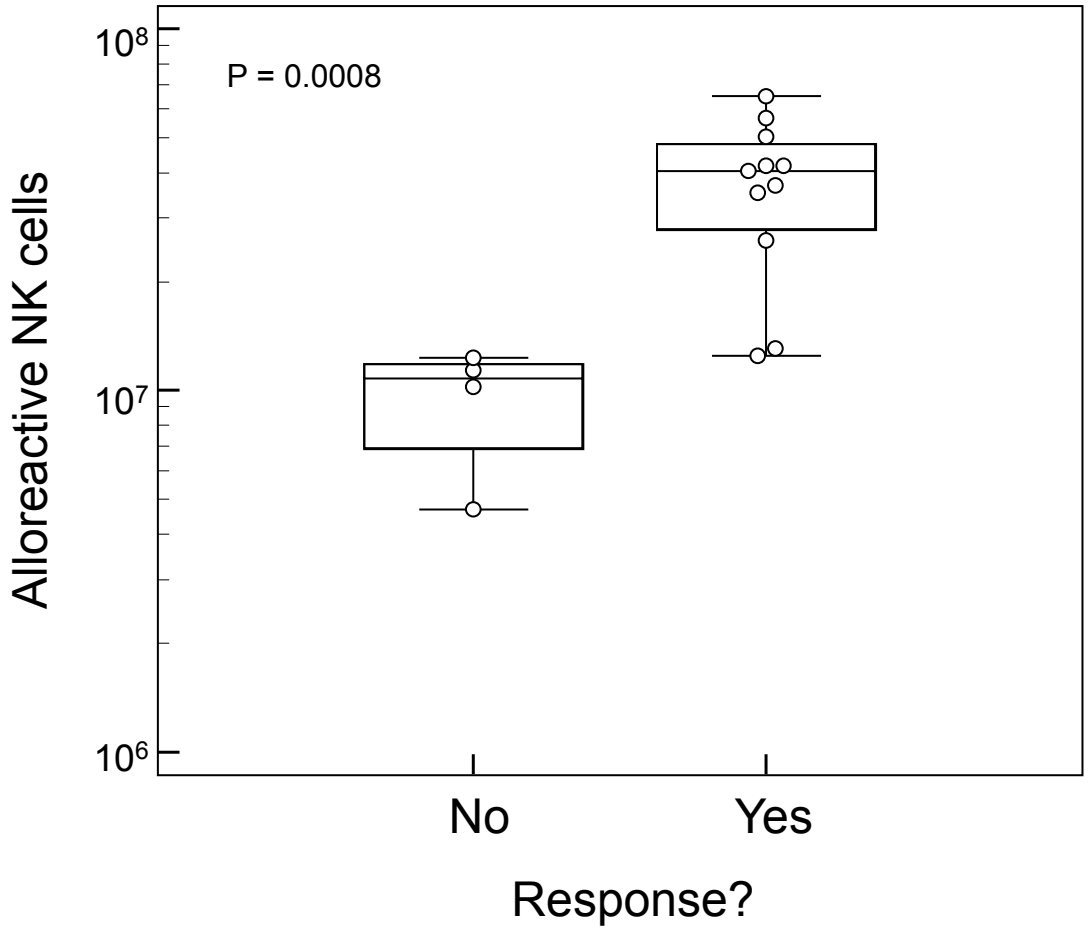
Curti et al, 2015, in press

Larger alloreactive NK cell repertoires are associated with reduced relapse rate



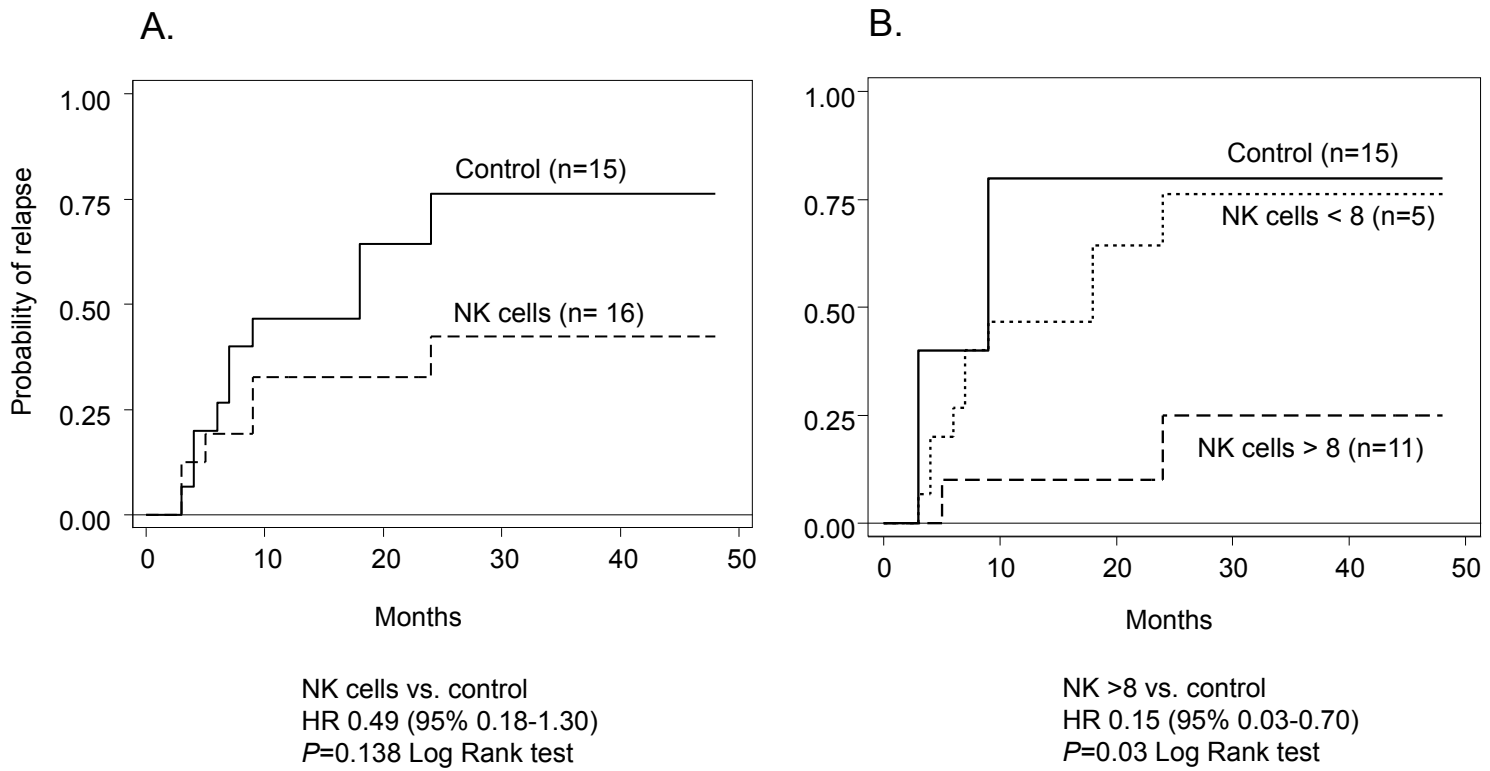
Curti et al, 2015, in press

Impact of the absolute number of infused alloreactive NK cells on clinical response



Curti et al, 2015, in press

Larger alloreactive NK cell repertoires are associated with reduced relapse rate

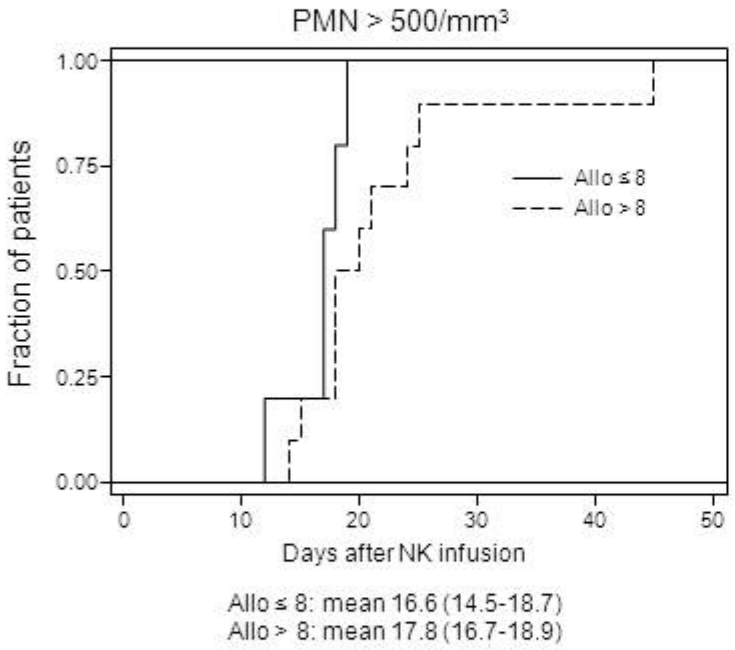


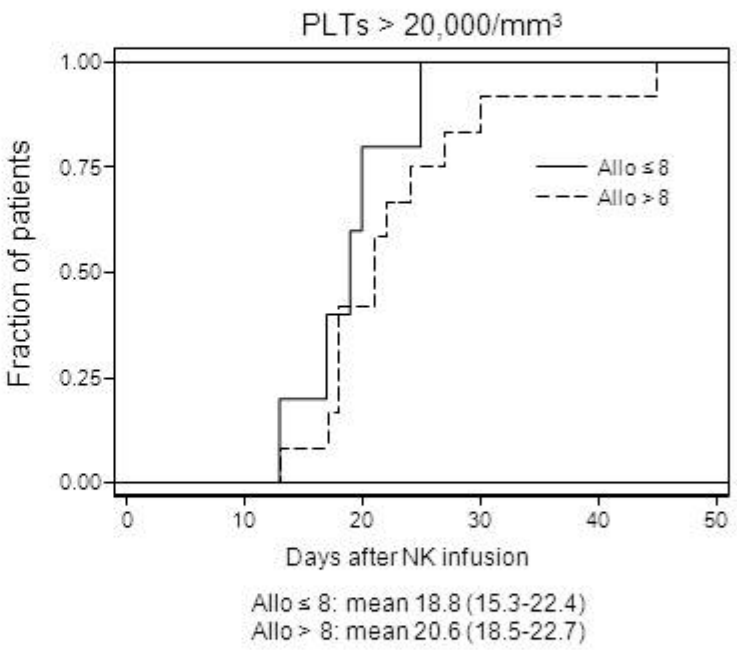
NK cells vs. control
HR 0.49 (95% 0.18-1.30)
P=0.138 Log Rank test

NK >8 vs. control
HR 0.15 (95% 0.03-0.70)
P=0.03 Log Rank test

Curti et al, 2015, in press

Hematological Recovery accordingly to donor alloreactivity





Curti et al, 2015, in press

Conclusions

- Infusion of purified NK cells is feasible in elderly AML patients as post-CR consolidation strategy

- At the clinical level, 9/16 CR patients are disease-free after a median follow-up of 27 months, without any additional treatment. Two of the relapsed patients had a prolonged CR phase without concomitant anti-leukemia treatment.

- The infusion of higher number of alloreactive NK cells is associated with prolonged disease-free survival. The number of donor alloreactive NK cell clones may be used as a predictive biomarker for better clinical outcome

MULTICENTER PHASE II CLINICAL STUDY OF ADOPTIVE IMMUNOTHERAPY WITH ALLOREACTIVE NK CELLS AS CONSOLIDATION STRATEGY FOR ELDERLY ACUTE MYELOID LEUKEMIA PATIENTS

TYPE OF STUDY: Phase IIb, multicentric

STUDY CENTERS:

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•Chair of Hematology, Department of Internal Medicine (DiMI), University of Genoa, IRCCS Azienda Ospedaliera Universitaria S. Martino-IST, Genoa, Italy.

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EXPECTED PROJECT DURATION 36 months

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