Supplementary Table 2: Most striking clinical studies focusing on KIR-mediated NK alloreactivity in aHSCT.

Hypotheses: aKIR: activating KIR, iKIR: inhibitory KIR, CR: complete remission

Population: AML: acute myeloid leukemia, AMLL: acute myelomonocytic leukaemia, ALL: acute lymphoid leukemia, CLL: chronic lymphoid leukemia ,CML: chronic myeloid leukemia, CMML: chronic myelomonocytic leukemia, CR: complete remission, HL: Hodgkin lymphoma, MDS: myelodysplastic syndroms, MM: multiple myeloma, MPN: myeloproliferative neoplasia, NHL: non-Hodgkin lymphoma

Graft's characteristics: ATG: anti-thymoglobulin, BM: bone marrow, CsA: ciclosporin-A, G-CSF: granulocyte colony stimuling factor, mAbs: monoclonal antibodies, MAC: myeloablative conditioning, MTX: methotrexate, MSD: matched sibling donor, MUD: matched related donor, MMUD: matched unrelated donor, NMAC: non-myeloablative conditioning, NMDP: national marrow donor program, PBSC: peripheral blood stem cell, PT-Cy: post-transplant cyclophosphamid, RIC: reduced intensity conditioning, TCD: T-cell deplete, TCR: T-cell replete

HLA and KIR assessments: PCR: polymerase chain reaction, -SBT: sequence based typing, -SSO: sequence specific oligonucleotide, -SSP: sequence specific primer, RT-PCR: reverse transcriptase PCR SNP: single nucleotid polymorphism

Clinical outcomes: #y: # years, DFS: disease free survival, EFS: event free survival, HR: hazard ratio, NRM: non-relapse mortality, OR: odds ratio, OS: overall survival, p: p-value, PFS: progression free survival, TRM: transplant related mortality

Study **EFFECT** **Hypotheses**	**Population**	**Graft's characteristics**	**Study design**	**HLA and KIR assessments**	**Main results**
Ligand/ligand model					
2002 (3) **POSITIVE EFFECT** **Ligand/ligand model**	Included pairs, n = 92 *Ages not reported* AML, n=57 ALL, n=35	Haploidentical donors Platform TCD	**Clinical study** *Details not reported* + **biological proof of concept** measurement of NK cell alloreactivity by screening of NK clones	**HLA, donors and recipients** *Not reported* **No KIR typing**	**Clinical results** • **Among the whole cohort** If absence of ligand-ligand incompatibility vs presence, respectively: - Rejection 15.5% vs 0% - Grade II-IV aGVHD 13.7% vs 0 % • **For AML recipients only:** - **ligand-ligand incompatibility in the GVHD direction is the only independent predictor of survival**. If absence of ligand-ligand incompatibility vs presence, respectively: - 5y EFS 5% vs 60% - 5y probability of relapse 75% vs 0% - **absence of ligand-ligand incompatibility in the GVHD direction is the only independent factor for poor outcome** (HR = 0.33) • **in ALL: no effect**

					<u>Biological conclusions ⇔ proof of concept</u> In humans, ligand-ligand model closely correlates with NK clones killing recipient's targets. In murine model, alloreactive NK cells increase engraftment, graft-versus-tumor effect and survival while decrease relapse and prevent GVHD by elimination of recipient APCs
2007 (4) **NEGATIVE EFFECT** **Ligand-ligand model**	Included pairs, n=116 *Ages not reported* AML, n=34 MDS, n=5 ALL, n=40 CML, n=35 AMLL, n=2	Haploidentical donors <u>Platform</u> TCR with ATG <u>Graft source</u> PBSC with G-CSF mobilized BM <u>Conditioning regimen</u> Only MAC	Retrospective Between November 2002 and October 2005 Monocentric, Peking University Institute of Hematology (China)	**<u>HLA, recipients and donors</u>** HLA-A, -B, -C and -DRB1 at allele-level molecular typing **<u>No KIR typing</u>**	**Ligand-ligand mismatch:** • **Considering aGVHD** - **independent risk factor for aGVHD** (HR=2.48, p=0.01) **- increase of aGVHD incidence in the standard-risk group** (87.5 vs 34.3%, p=0.001) compared to patients without ligand-ligand mismatch • **Considering TRM, OS and relapse** - **independent risk factor for OS** (HR=2.23, p=0.049) and **relapse** (HR=4.77, p= 0.017) - **higher cumulative relapse rate** (27.1 vs 0%, p=0.007 for AML / 53.7 vs 6.7%, p=0.003 for ALL) - **inferior OS rate** (50 vs 81.9%, p=0.040 for AML / 35 vs 74.8%, p=0.044 for ALL)

2018 (5) **POSITIVE EFFECT** **Ligand-ligand model** *Focused on effectiveness considering disease status (remission or not)*	Included pairs, n=144 Adults only <u>Myeloid (n=51)</u> AML, n=32 MDS, n=15 MPN, n=4 <u>Lymphoid (n=93)</u> NHL, n=38 HL, n=34 MM, n=9 ALL, n=7 CLL, n=5 <u>Remission</u> CR, n=81 No CR, n=63	Haploidentical donor <u>Platform</u> TCR with PT-Cy <u>Graft sources</u> BM, n= 53 PBSC, n= 91 <u>Conditioning regimen</u> MAC, n=19 RIC, n=31 NMAC, n=94	Retrospective Between December 2009 and December 2014 <u>2 centers:</u> Institut Paoli Calmettes, Marseille, France Humanitas Cancer Center, Rozzano, Italy	**<u>HLA, donors and recipients</u>** DNA high-level typing **<u>No KIR typing</u>**	• **<u>If absence of CR</u>** **Ligand-ligand mismatch correlates with** **- Lower 2y relapse incidence**: 18% vs. 42%, p=0.068 (multivariate analysis: HR= 0.21, p=0.013) **- Better PFS**: 50% vs. 21%, p = 0.037 (multivariate analysis: HR = 0.42, p = 0.028) **- Trend for improved OS**: 50% vs 28%, p=0.141 when compared to patients without ligand-ligand mismatch, respectively. **Same rates of aGVHD** (18% vs. 17%, p = 0.892) **and cGVHD** (18% vs. 7%, p = 0.197) irrespective of the ligand-ligand mismatch. • **<u>If recipient in CR</u>** No significant effect of ligand-ligand mismatch
2019 (6)	Included pairs, n=444	Haploidentical donor <u>Platform</u>	Retrospective	**<u>HLA, donors and recipients</u>**	**Ligand-ligand mismatch** when compared with no ligand-ligand mismatch

NEGATIVE EFFECT **Ligand-ligand model** + "Host missing ligands", irrespective of the expression in donor. = missing ligand theory → no correlation with transplantation outcomes → is not discussed in the paper	Adults only <u>Acute leukemia only</u> AML, n=327 ALL, n=117 <u>Remission status</u> CR1 = 39% CR2= 26% No CR = 35%	TCR with PT-Cy <u>Graft sources</u> BM (54%) PBSC (46%) <u>Conditioning regimen</u> MAC (54%) RIC (46%)	Between 2009 and 2015 Multicentric Acute Leukemia Working Party of the EBMT, 500 centers worldwide	DNA high-resolution typing of class I and II HLA antigens **<u>No KIR typing</u>**	- **decreases 2y OS :** 46.8% vs 53.1%, p=0.11 (multivariate analysis: HR 1.4, p=0.03) - **strives for higher relapse:** HR 1.36, p=0.09, especially in patients with AML (HR 1.48, p=0.07) **Those effects on OS and relapse are stronger** - when using PBSC (compared to BM) - for AML recipients (compared to ALL) **No effect on aGVHD, cGVHD, engraftment or NRM**
Receptor/ligand model					
2005 (7) **POSITIVE EFFECT** **Receptor-ligand model**	Included pairs, n=178 Paediatric + adult <u>Myeloid (n=133)</u> AML, n=57	Matched sibling donor <u>Platform</u> *Ex-vivo* TCD (mAbs) <u>Graft source</u>	Retrospective Between 1981 and 1998 Single-center study in New-York, USA	**<u>HLA, donors and recipients</u>** Class I and II intermediate resolution (serology, PCR-SSP, or -SSO), and high resolution (-SBT) if needed to confirm HLA identity **<u>HLA, only for recipients</u>**	**<u>Missing ligand effect</u>** • <u>In AML and MDS</u> Compared with patients exhibiting all class I ligands for donor KIR, missing ligand effect: **- increases DFS** (HR=0.53, p=0.014) **- increases OS** (HR=0.53, p=0.03) **- lower incidence of relapse** (HR=0.41, p=0.04), withstanding multivariate analysis

Recipients lacks HLA ligand for at least one donor inhibitory KIR	CML, n=61 MDS, n=15 <u>Lymphoid</u> ALL, n=45	Bone-marrow derived graft <u>Conditioning regimen</u> Myeloablative conditioning		high-resolution for HLA-B and -C typing (alleles identification for epitope segregation) **<u>KIR, only for donors</u>** Gene detection of *KIR2DL1, KIR2DL2, KIR2DL3*, and *KIR3DL1* using PCR SSP	**If lacking 2 HLA ligands** for donor-inhibitory KIR, **even more higher DFS** (p=0.002) **and OS** (p=0.003). • **<u>In CML and ALL:</u>** No effect on DFS, OS or relapse Same risk for GVHD regardless the missing-ligand effect in any disease group
Educational model					
2014 (8) **NEGATIVE EFFECT** **Educational models based on iKIR**	Included pairs, n=283 Paediatric + adult AML, n=133 ALL, n=69 AL not specified, n=6	<u>Unrelated donors:</u> 10/10, n=193 9/10, n=72 8/10, n=17 7/10, n=1 <u>Platform</u> TCD, n=48	Retrospective Between 2002 and 2010 Multicentric study in Poland	**<u>HLA, donors and recipients</u>** Provided by each transplant center **<u>KIR, only for donors</u>** Gene detection of all KIR genes using PCR-SSP	**Comparing to recipients possessing HLA ligand cognate with the donor's NK cell licensing system, recipients lacking at least one HLA ligand have** - **decreased 4y OS** (death events 83.3% vs. 39.8%, p=0.001, HR=2.97, p=0.001) - **decreased 4y PFS** (91.6% vs. 47.7%, p=0.0001, HR=3.45, p=0.0001) - **decreased time to progression** (30.0% vs. 17.3%, p=0.013; HR=4.46, p=0.013)

	CL not specified, n=59 Lymphoma, n=9 MM, n=7	TCR, n=235 <u>Graft sources</u> BM, n=71 PBSC, n=201 <u>Conditioning regimen</u> MAC, n=174 RIC, n=96			**Those effects are not associated with aGVHD and independent from HLA-mismatch** Incidence of aGvHD comparable regardless of educational status groups (66.7% vs. 53.0%, OR=0.94, p=0.36)
Donor's haplotype based model					
2010 (9) **POSITIVE EFFECT** **KIR-B content score**	Included pairs, n=1409 Paediatric + adult AML, n=1086 ALL, n=323	<u>Unrelated donors:</u> 10/10, n=687 9/10, n=361 8/10, n=213 Less than 8/10, n=148 <u>Platform</u>	Retrospective Transplants facilitated by NMDP between 1988 and 2006 Multicentric study in USA	**<u>HLA, donors and recipients</u>** High-resolution HLA-A, -B, -C, -DRB1, and -DQB1 **<u>KIR, only for donors</u>** Gene detection of all genes using SNP based *KIR*/MALDI-	**<u>In AML, significant protective effect on relapse</u>** **- of donor *B/x* vs A/A genotype** (RR=0.72, p=0.003) - **of donor Cen-B/B vs Cen-A/A** (RR=0.34, p<.001) - **of donor with KIR B–content≥ 2 compared to < 2** - if HLA matched (RR=0.52, p<0.001) - and if HLA mismatched (RR=0.52, p<0.001) Same protective trends for donor Tel-B/B vs Tel-A/A (RR=0.52, p<0.07)

Scoring strategy reflecting the aKIR gene content		TCR <u>Graft source</u> BM, n=942 PBSC, n=467 <u>Conditioning regimen</u> Myeloablative conditioning		TOF + KIR-B content score	**<u>ALL: no effect</u>**
KIR matching model					
2010 (10) **POSITIVE EFFECT** **Inhibitory KIR gene mismatch**	Included pairs, n=86 Paediatric + adult AML, n=25 ALL, n=7 MDS, n=8	Haploidentical donors <u>Platform</u> TCR <u>Graft source</u> Bone-marrow derived graft	Retrospective Consecutive inclusion from 2 clinical trials, between 1999 and 2007 Single-center study in Baltimore, USA	**<u>HLA for recipients:</u>** PCR-SSOP + PCR-SBT **<u>HLA for donors:</u>** HLA-A at intermediate resolution	**Compared to recipients from donors with identical KIR gene content, recipients with inhibitory KIR (iKIR) gene-mismatched have** - **increased OS** (HR=0.37, p=0.0003) - **significant for lymphoid diseases** (HR=0.44, p=.03) - **as well as myeloid diseases** (HR=0.32, p=.004) - **improved EFS** (HR=0.51, p=0.01) - **lower relapse rate** (cause specific hazard ratio, SDHR=0.53, p=0.025).

	CML/CMML, n=11 CLL, n=8 Lymphoma, n=21 MM, n=6 High risk malignancies only	<u>Conditioning regimen</u> NMAC + PT-Cy		+ HLA-B, -C, -DRB1 and -DQB1 alleles at a high-resolution **<u>KIR, donors and recipients</u>** Gene detection of all KIR genes using PCR-SSP. Inheritance of B haplotype determined by the presence of specific aKIR and iKIR.	No significant difference in aGVHD, cGVHD, NRM or engraftment failure
Polymorphism					
2017 (11) **POSITIVE EFFECT** **KIR3DL1 level of expression:** Strength of 3DL1/Bw4 interaction correlates	Included pairs, n=1328 Paediatric + adult Only AML	<u>Unrelated donor</u> 10/10, n=716 9/10, n= 612 <u>Platform</u> TCD, n=112 <u>Graft sources</u>	Retrospective Between 1989 and 2008 Transplants facilited by NMDP	**<u>HLA, donors and recipients</u>** Provided by the Center for International Blood and Marrow Transplant Research **<u>KIR, for donors only</u>** * Gene detection for all KIR using PCR-SSO or –SSP	**KIR3DL1/HLA-B combinations with *in-vitro* weak or no inhibition** when compared to strong inhibition combinations, have - **lower relapse** (HR=0.72, p=0.004) - **lower overall mortality** (HR=0.84, p=0.03) **This effect is**

with NK alloreactivity **+ biological proof of concept** *In-vitro* testing of NK-cytotoxicity		BM, n=722 PBSC, n= 606 <u>Conditioning regimen</u> MAC, n=1123 RIC, n=186		* PCR-SBT or multiplex to classify *KIR3DL1* as *KIR3DS1,* high, low or null subtypes	- **greater in high-risk group** (relapse: HR=0.54, p<0.001 / mortality: HR=0.74, p<0.008). - **independent from the benefit of donor activating KIR2DS1** **<u>Biological conclusions</u>:** Correlation between predicted alloreactivity and alloreactivity measurements
2013 (12) **POSITIVE EFFECT** **KIR2DL1 dimorphism** 245C or 245R 245R is a more effective receptor than 245C	Included pairs, n=313 Paediatric only <u>Hematologic malignancies,</u> n=231 Lymphoid, n=116 Myeloid, n=115 <u>Solid tumors,</u> n=25 <u>Nonmalignant diseases,</u> n=57	MSD, n=86 MUD, n=98 Haploidentical donor, n=129 <u>Platform</u> TCD = 154 TCR = 159 <u>Conditioning regimen</u> MAC = 240 NMAC = 73	Retrospective Between January 2000 and January 2010. Monocentric, St Jude Children's Research (USA)	**<u>HLA, donors and recipients</u>** HLA-A, -B, -C, and -DRB1 using DNA methods **<u>KIR, for donors only</u>** Gene detection by PCR-SSP *KIR2DL1* functional allele typing using SNP assay	**KIR2DL1-R245 donor compared to 2DL1-C245 donor lead to** • **<u>increase survival</u>** **- Risk of death if RR donor compared with CC donor** : HR=0.4, p=0.0001 **- Risk of death if RC donor compared with CC donor**: HR, 0.42, p=0.0013 This effect : - withstands the multivariate analysis - is similar for patients with AML or ALL / in the subset of sibling, unrelated, or haploidentical donor / for T-cell depleted or replete grafts / in myeloablative or non-myeloablative settings as well - is higher when patients receive a 2DL1-R245+ positive graft with HLA-C receptor-ligand mismatch

					• **<u>higher PFS</u>** - **RR donor compared with CC donor**: HR=0.42, p=0.0003 - **RC donor compared with CC donor**: HR=0.48, p=.0075 This effect: - withstands the multivariate analysis - is similar in patients with AML or ALL **No significant correlation with grade II-IV aGVHD**
Others					
2004 (13) Model predicting alloreactivity if donor has aKIR and recipient lacks the ligand for its inhibitory counterpart	Included pairs, n=220 Paediatric + adults <u>Myeloid (n=112)</u> AML n= 52, CML n=49, MDS n=11	Matched sibling donor <u>Conditioning regimen</u> NMAC = 58 MAC = 162	Retrospective Between January 1994 and April 2002 **2 centers in Birmingham, UK :** Children's Hospital and	**<u>HLA, donors and recipients</u>** - Class I: PCR-SSP + HLA-C with the adequate level to determine C1 or C2 groups - *Class II: not mentioned*	**<u>Results in myeloid malignancies</u>** 1/ Homozygous C2 recipients have decreased 4y OS compared to those carrying at least one C1 allele (31.6% vs 56.1%, p<0.005) 2/ In the subgroup of recipient C2-homozygoty: - the presence of *KIR2DS2* is significantly associated with decreased OS

Focused on association C1- recipients with 2DS2+ donors **NEGATIVE EFFECT**	<u>Lymphoid (n=108)</u> ALL n=54, NHL n=43, CLL n=11		Queen Elizabeth Hospital	**<u>KIR, only for donors</u>** Gene detection of all genes using PCR-SSP	- but if *KIR2DS2* is absent, OS is not significantly different from those recipients who possess C1 alleles 3/ No other significant difference between any of the other pairs analysed. 4/ No significant difference in the rates of aGVHD > grade II in any model **<u>No statistical results in lymphoid malignancies</u>**
2005 (14) **Descriptive statistics** Compare "relapse" group to "non-relapse" group and assess differences in KIR typing ⇔ Correlations between recipients' clinical outcomes and	Included pairs, n=65 Paediatric + adult AML, n= 22 ALL, n=16 CML, n= 27	Matched sibling donor <u>Platform</u> - TCR, n=31 - TCD, n=34 <u>Graft sources</u> BM = 47 PBSC = 18	Retrospective Between 1991 and 2002 Single center study in Brussel (academisch ziekenhuis–Vrije Universiteit Brussel)	**<u>HLA, donors and recipients</u>** molecular techniques for HLA-A, -B, -C, -DRB1, -DQB1 and -DPB1 **<u>KIR, donors and recipients</u>** Gene detection of *KIR2DL1-3, KIR3DL1-2, KIR2DS1-5* and *KIR3DS1* using PCR-SSP	**<u>General statistics</u>** - iKIR genes present in most of the donors. - Most variations between 2 groups observed in the number of aKIR - Higher frequencies of donor aKIR genes in the non-relapsing group compared to the relapsing group but no significant difference in the frequencies of individual KIR genes - No significant correlation between donors' total number of aKIR and relapse **<u>Donors 2DS1+/2DS2+</u>**

recipients' and donors' KIR typing **POSITIVE EFFECT**		<u>Conditioning regimen</u> Myeloablative conditioning			- **decrease relapse rate** compared other groups: OR=0.18, p=0.03. Effect withstanding the multivariate analysis. - **tend to increase 5y OS:** 59.2 and 35.5% in the 2DS1+2DS2+ and other donors, respectively, p=0.109) **<u>No statistical association between:</u>** - Relapse and recipient *HLA-C* groups only or in combination with the aKIR - Presence of a particular KIR gene or association and TRM, aGVHD or cGVHD
Models comparisons					
2004 (15) **Compare 3 models of alloreactivity prediction** - ligand-ligand model	Included pairs, n=36 Paediatric patients (<18 yo) Myeloid malignancy, n=17	Haploidentical <u>Platform</u> TCD <u>Graft source</u> Graft purification for CD34+ using mAbs	Retrospective **2 centers :** Memphis (USA) Tuebingen (Germany)	**<u>HLA, donors and recipients</u>** * Serology for HLA-A, -B, -DR specificities * Molecular biology for DRB1: PCR-SSO and -SSP * if serologically difficult to split and for oldest samples +	**<u>In order of efficience for relapse of primary disease prediction</u>** 1) Receptor-ligand model HR=5.3, p=0.0078 2) Ligand ligand model HR=2.1, p=0.47 3)Cytotoxicicty model HR=1.4, p=0.76 **<u>1) Receptor-ligand model</u>** **Absence of mismatch is associated to high risk of relapse in AML and ALL**

- receptor-ligand model - "cytotoxicity model": NK cell cytotoxicity against K562 cells lower than the median 1mo after transplantation should be predictive for high risk of relapse **UNDETERMINED EFFECT**	Lymphoid malignancy, n=19	No GVHD prophylaxis (all grafts contain less than 3.10^4 CD3 cells/kg)		PCR-SSP for class I of unrelated donors **<u>KIR, donors and recipients</u>** Surface expression of KIR molecules using flow cytometry and RT-PCR if KIR expression was difficult to define KIR genotyping : PCR-SSP	**<u>2) Ligand–ligand model</u>** **-** absence of mismatch is associated to high risk of relapse for AML only - the model misses some high-risk in AML - fails to classify ALL **<u>3)"Cytotoxicity model"</u>** The worst model in this serie

2010 (10)
 	
Compare 3 models of alloreactivity prediction
 	
- Ligand-ligand model
 	
- Haplotypes
	Included pairs, n=86
	
	AML, n=25
	
	ALL, n=7
	
	MDS, n=8
	
	CML/CMML, n=11
	
	CLL, n=8
	
	Lymphoma, n=21
		Haploidentical donors
		
		<u>Platform</u>
		
		TCR
		
		<u>Graft source</u>
		
		Bone-marrow derived graft
			Retrospective
			
			Consecutive inclusion from 2 clinical trials, between 1999 and 2007
			
			Single-center study in Baltimore, USA
				<u>HLA for recipients:</u>
				
				PCR-SSOP + PCR-SBT
				
				<u>HLA for donors:</u>
				
				HLA-A at intermediate resolution
				
				+ HLA-B, -C, -DRB1 and -DQB1 alleles at a high-resolution
				
				<u>KIR, donors and recipients</u>
					<u>iKIR mismatch</u>
					
					Compared to recipients from donors with identical KIR gene content, recipients of inhibitory KIR (iKIR) gene-mismatched have
					
					- **improved OS** (HR=0.37, p=0.0003)
					  - **significant for lymphoid diseases** (HR=0.44, p=0.03)
					  - **as well as myeloid diseases** (HR=0.32, p=0.004)
					
					- **improved EFS** (HR=0.51, p=0.01)
					
					- **lower relapse rate** (cause specific hazard ratio, SDHR=0.53, p=0.025).

- Gene-gene model for aKIR and iKIR **POSITIVE EFFECT**	MM, n=6 High risk malignancies only	<u>Conditioning regimen</u> NMAC + PT-Cy		Gene detection of all KIR using PCR-SSP. Inheritance of B haplotype determined by the presence of specific aKIR and iKIR.	No significant difference in aGVHD, cGVHD, NRM, or engraftment **<u>Haplotype mismatch</u>** **AA recipient transplanted with Bx donor compared to AA donor have:** - **improved OS** (HR=0.30, p=0.01) - **improved EFS** (HR=0.47, p=0.05) - **lower NRM** (HR=0.13, p=0.046) No significant effect on relapse, engraftment failure, aGVHD or cGVHD No significant correlation when recipient is Bx **<u>No significant difference with other models</u>**
2014 (16) **Compare 2 models of alloreactivity prediction**	Included pairs, n=57	Haploidentical donor <u>Platform</u>	Prospective Between 2004 and 2009	**<u>HLA, donors and recipients</u>** already known	**<u>KIR haplotypes</u>, <u>regardless of the pathology</u>** **decrease relapse for recipients of Bx donors compared to AA donors** (p=0.001). This effect

- ligand-ligand model - KIR haplotypes (⇔ KIR-B content score) **UNDETERMINED EFFECT**	Adults only, refractory diseases AML,n=36 ALL,n=8 NHL/ mantle cell lymphoma/ CLL, n=6 CML/ CMML/ SMD,n=3 MM, n=4 <u>Remission status</u> CR, n=29 PR, n=28	TCD (ex-vivo CD3/CD19 depletion) <u>Conditioning regimen</u> Reduced intensity conditioning	Multicenter phase I/II study, 7 centers in Germany	**<u>KIR, for donors only</u>** * Gene detection of all KIR genes using real time-PCR * Quality insurance through commercial typing kits	**- is greater if recipient is in partial remission** (p=0.008) compared to CR (p=0.297) **- is greater in AML recipients compared to ALL** recipients No effect on reconstitution of NK cells, no effect on NRM **<u>Ligand-ligand mismatch, for AML recipients only</u>** - reduces EFS compared to KIR matched pairs16.0 % vs 53.0 % respectively, HR=2.27, p=0.045
2017 (17) **Compare 3 models of alloreactivity prediction in**	Included pairs, n=106 Paediatric + adult	MSD, n=36 MUD, n=22 MMUD, n=35 Unknown, n=13	Retrospective Monocentric, Niigata University	**<u>HLA, recipients and donors</u>** Serologic typing at of HLA-A, -B, and -DRB1 until 2006 and by DNA typing of	**<u>Donor Bx haplotype compared to AA haplotype</u>** **- increases risk for grade III to IV aGVHD** A/A: 4.9% vs B/x: 20.0%; p= .02 **- especially if associated with receptor-ligand mismatch**

Japanese population Ligand-ligand model Receptor-ligand model Haplotype based models **NEGATIVE EFFECT**	AML, n=44 ALL, n=28 CML, n=14 MDS, n=9 NHL, n=11	<u>Platform</u> TCR without ATG <u>Graft sources</u> BM, n=86 PBSC, n=20 <u>Conditioning regimen</u> MAC, n=90 RIC, n=16	Medical Hospital (Japan) Between January 1989 and September 2011	HLA-A, -B, -C, and -DRB1 from 2007 HLA allele data were retrospectively retyped if possible **<u>KIR, for donors only</u>** Gene detection of all genes using PCR-SSO	no missing ligand: 7.7% vs 1 missing ligand and A/A: 5.3%, vs 1 missing ligand and B/x: 25.0; p=.047 **No difference in 5-year OS, relapse and NRM**
2018 (18) **Compare several models of alloreactivity prediction** - Haplotypes - Ligand-receptor	Included pairs, n=208 Adults only ALL, n=36 AML, n=71	Haploidentical donor <u>Platform</u> TCR platform with PT-Cy <u>Graft sources</u>	Retrospective Between October 2005 and December 2016 Single institution	**<u>HLA, donors and recipients</u>** High-resolution HLA-A, -B, -C, -DRB1, -DQB1, and -DPB1 using Sanger sequencing of at least exon 2 and 3 of class I loci and at least exon 2 of class II loci	**<u>KIR receptor-ligand mismatch for iKIR</u>** - **improves OS** (HR=0.63; p=0.050) - **improves DFS** (HR=0.57; p=0.012) - **decreases relapse/progression** (HR=0.41;p=0.001) **<u>When compared to donors with A/A haplotypes, donors KIR B/x with 2DS2</u>** - **improve OS** (HR=0.43; p=0.005) - **improve DFS** (HR=0.45; p=0.003)

- Ligand–ligand - KIR B content score - aKIR educational models - Effect of specific aKIR: *KIR2DS1* and *KIR2DS2* **POSITIVE EFFECT**	MDS/MPN/CML, n=42 NHL/HL/CLL, n=51 MM, n=5 Others, n=3	PBSC, n=137 BM, n=71 <u>Conditioning regimen</u> MAC, n=86 NMAC, n=122		**<u>KIR, donors and recipients</u>** Gene detection of all genes using PCR-SSP	- **decrease relapse/progression** (versus B/x without 2DS2 : HR= 0.43, p=0.024 / versus A/A haplotype: HR=0.58, p=0.187) - increase NRM (for A/A versus B/x with 2DS2: HR=5.74, p=0.001 / for B/x without 2DS2 versus B/x with 2DS2: HR=3.76, p=0.039) **No correlation for the other predictive models** **→ Design of an algorithm for donor selection taking NK alloreactivity into account**

<u>STUDIES</u>

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