AIBT Associazione Italiana di Immunogenetica e Biologia dei Trapianti
XXX Congresso Nazionale
Napoli, 10/12 ottobre 2024
"The programme of this event has been approved by the EFI Education Committee"

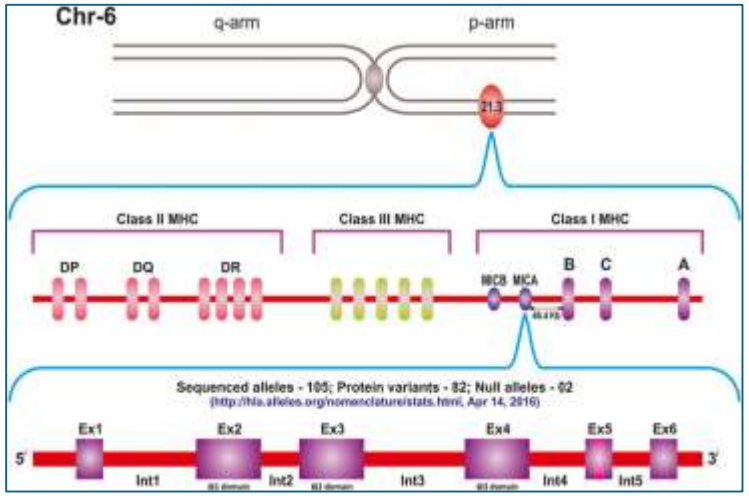
I polimorfismi dei geni *MICA* e *NKG2D* influenzano l'efficacia della terapia immunosoppressiva modificando il rischio di Rigetto Cronico Anticorpo-mediato nel Trapianto di Rene

Stefano Mocci
Università degli studi di Cagliari

MICA Gene - MHC Class I

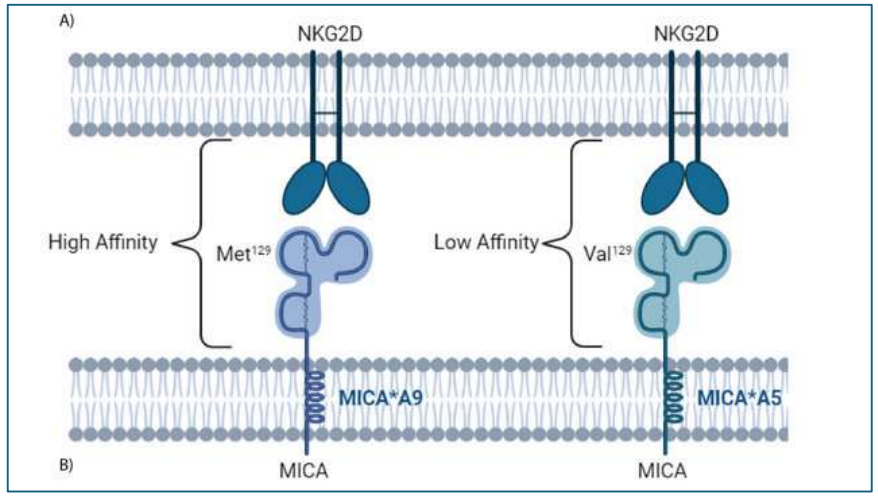
Receptor - NKG2D

MICA Location

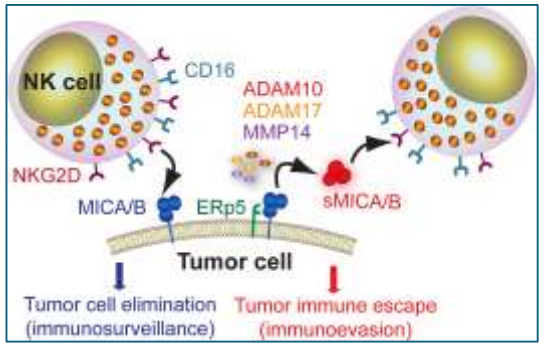


Baranwal AK, Mehra NK. Major Histocompatibility Complex Class I Chain-Related A (MICA) Molecules: Relevance in Solid Organ Transplantation. Front Immunol. 2017

MICA-129 MET/VAL Dimorphism



Major Histocompatibility Complex Class I Chain-Related α (MICA) STR Polymorphisms in COVID-19 Patients –Bautista et al.



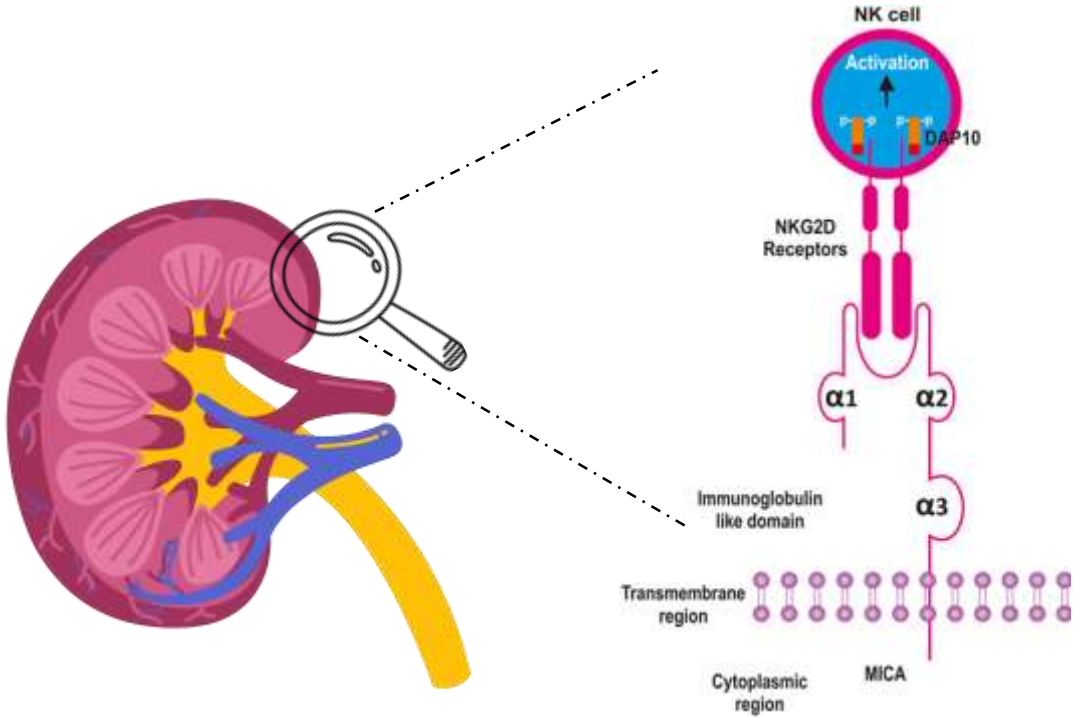
Leveraging NKG2D Ligands in Immuno-Oncology

- MICA*008: rilascio esosomi
- MICA*002: taglio proteolitico
- MICA*009: taglio proteolitico
- MICA*010:01: non espresso

Aploblocco -1			Aploblocco -2		
		Attività citotossica			Attività citotossica
dbSNP	Alta	Bassa	dbSNP	Alta	Bassa
rs1049174	G	C	rs2255336	A	G

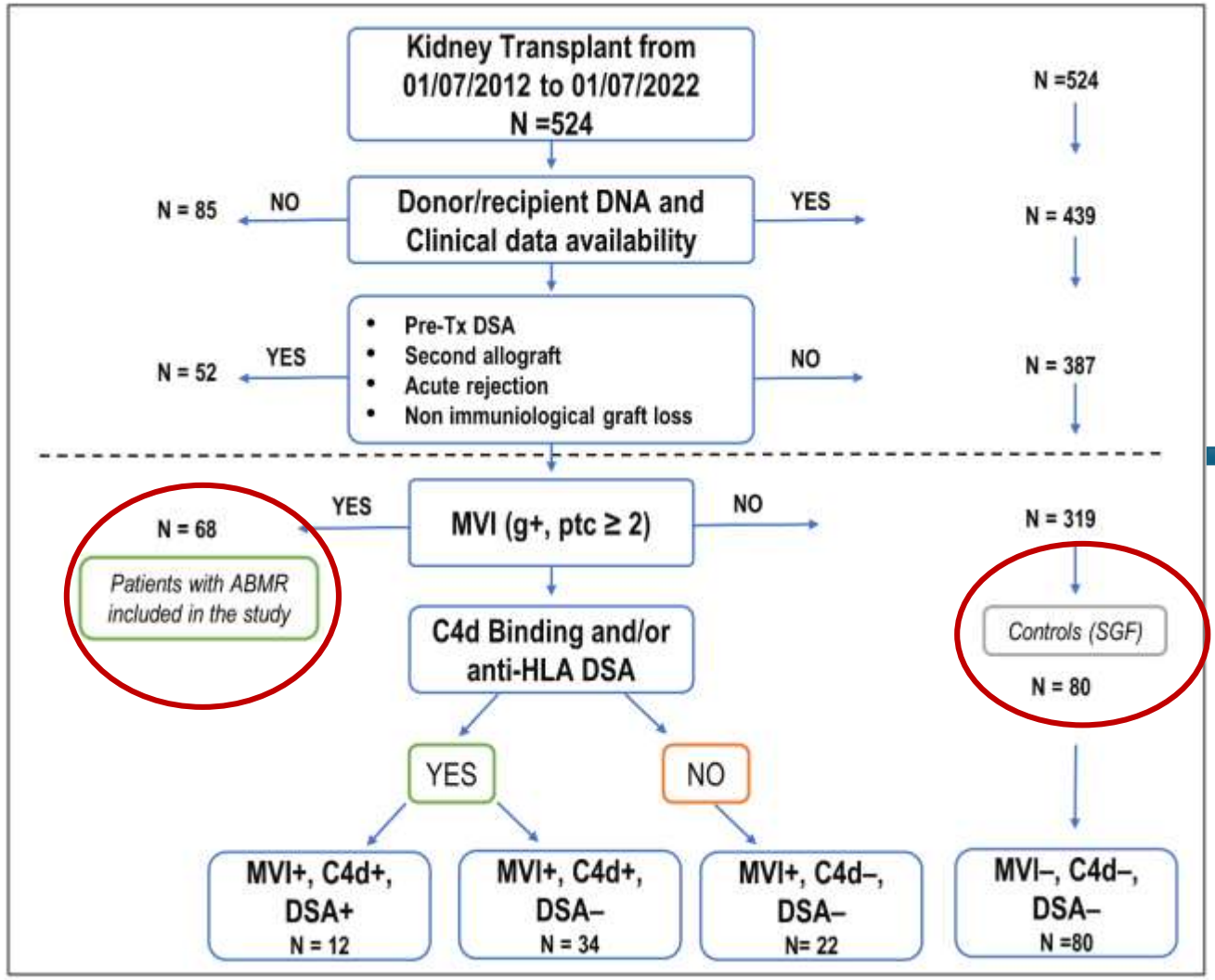
SCOPO DEL LAVORO

Indagare la correlazione tra la compatibilità allelica ***MICA*** tra ricevente e donatore e il genotipo NKG2D (***KLRK1***) con il rischio di AMR (rigetto anticorpo-mediato) e i loro potenziali effetti clinici e implicazioni per la terapia di mantenimento dell'organo.



Baranwal AK, Mehra NK. Major Histocompatibility Complex Class I Chain-Related A (MICA) Molecules: Relevance in Solid Organ Transplantation. Front Immunol. 2017

METODI



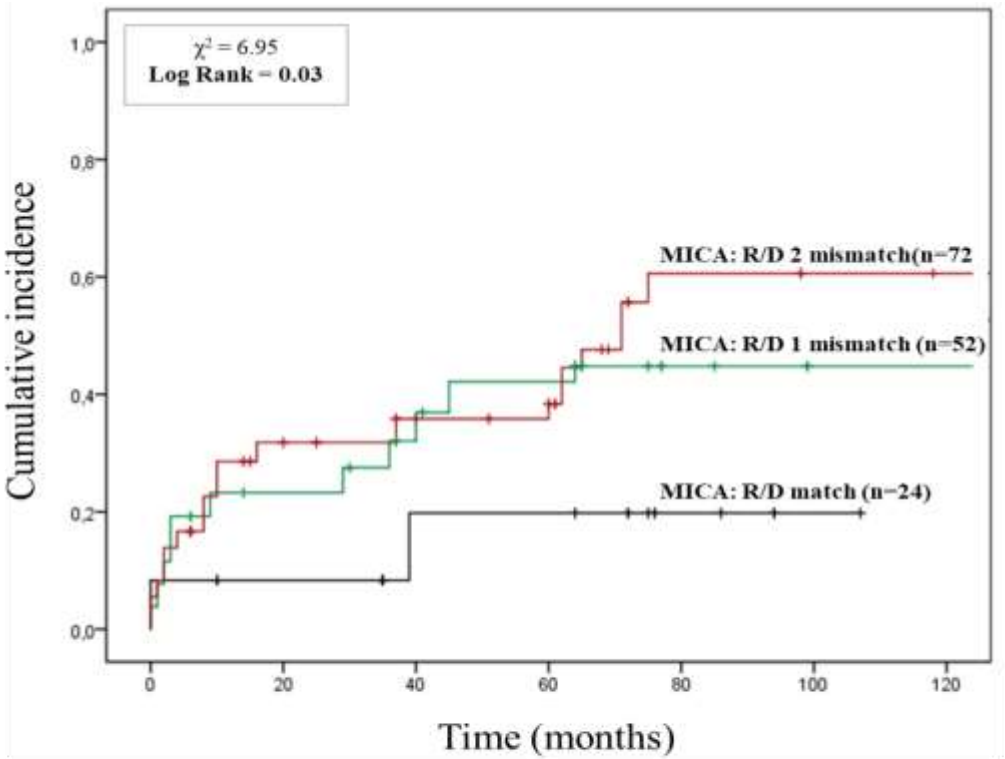
Dati clinici (e.g. Glomerular filtration, Serum creatinine levels, maintenance therapy..)

Analisi Genetica

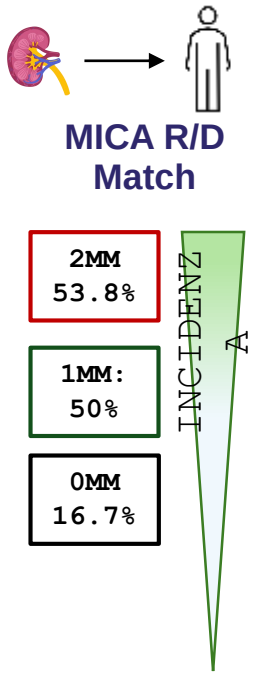
***1. HLA* loci**:
HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, HLA-G, HLA-H, HLA-DRB1, HLA-DRB3, HLA-DRB4, HLA-DRB5, HLA-DQA1, HLA-DQB1, HLA-DPA1, HLA-DPB1, ***MICA****, and MICB.*

2.* NKG2D Ricevente *(KLRK1): rs1049174, rs2255336 (Aplotipo-1 e 2)

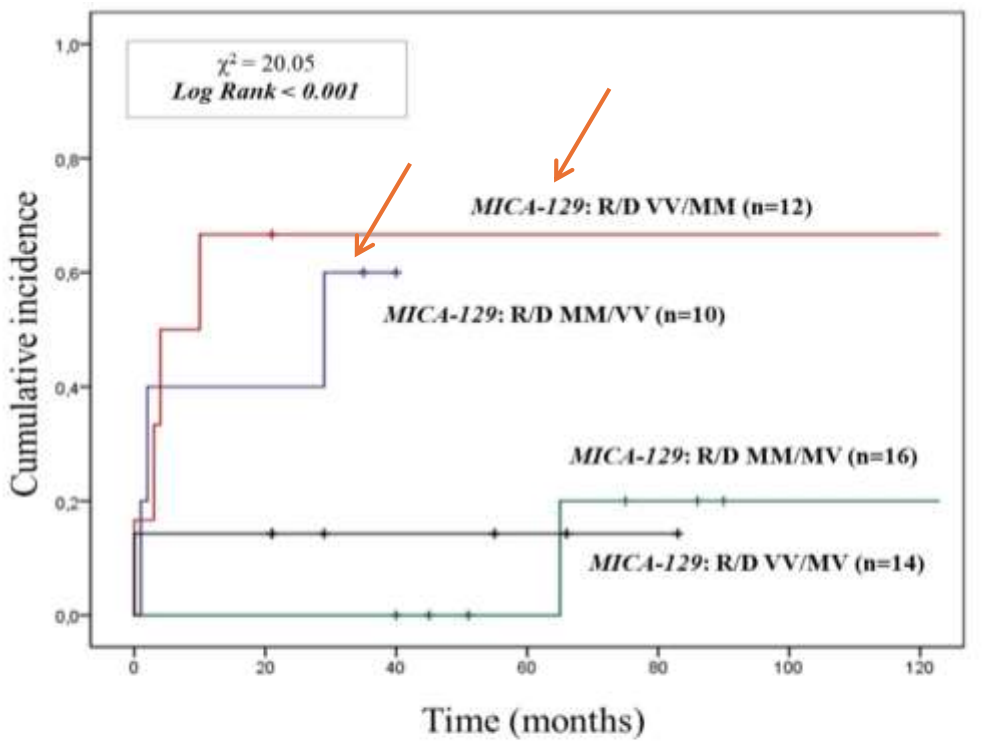
MICA R/D Mismatch



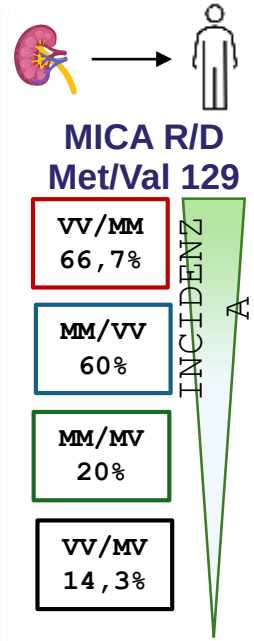
Time (Months)	0	20	40	60	80	100	120	
MICA 2 MM	72	40	27	22	8	6	5	Number at risk
MICA 1 MM	52	36	26	22	11	7	7	
MICA 0 MM	24	20	14	14	6	2	0	



MICA R/D Mismatch Met/Val 129

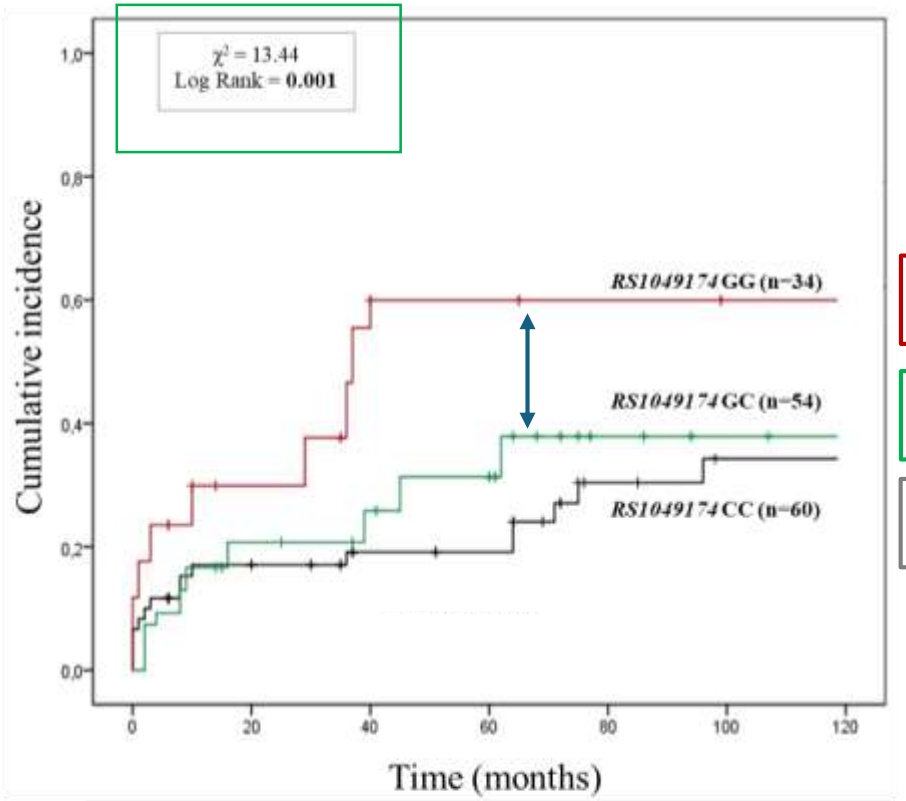


Time (Months)	0	20	40	60	80	100	120	
MICA-129: R/D VV/MM	12	4	3	3	3	3	1	Number at risk
MICA-129: R/D MM/VV	10	6	2	-	-	-	-	
MICA-129: R/D MM/MV	16	16	14	10	6	2	2	
MICA-129: R/D VV/MV	14	12	6	6	2	-	-	



rs1049174	C	G
rs2255336	G	A
	Low	High

Recipient *rs1049174 NKG2D (Aplotipo-1)*



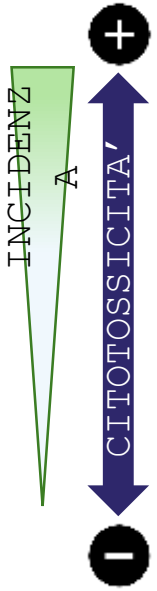
Time (Months)	0	20	40	60	80	100	120	
NKG2D [CC]	60	46	35	33	19	16	16	Number at risk
NKG2D [GC]	54	39	29	25	9	5	3	
NKG2D [GG]	34	18	10	7	5	3	3	

rs1049174 NKG2D

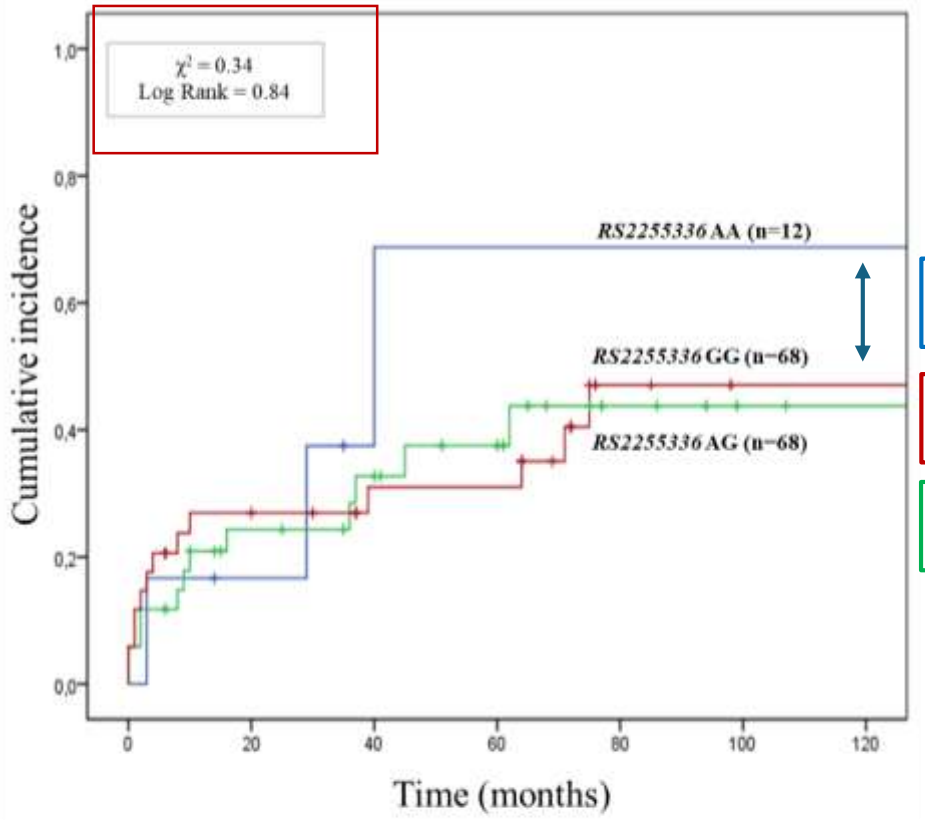
GG: 58.8%

GC 46,6%

CC 37%



Recipient *rs2255336* NKG2D *(Aplotipo-2)*



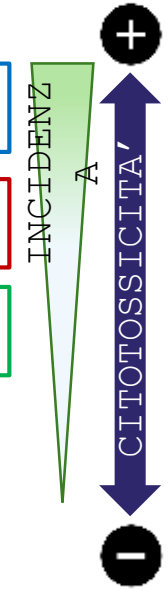
Time (Months)	0	20	40	60	80	
NKG2D [AA]	12	8	4	2	2	Number at risk
NKG2D [AG]	68	44	32	24	10	
NKG2D [GG]	68	46	34	34	12	

rs2255336 NKG2D

AA: 66.7%

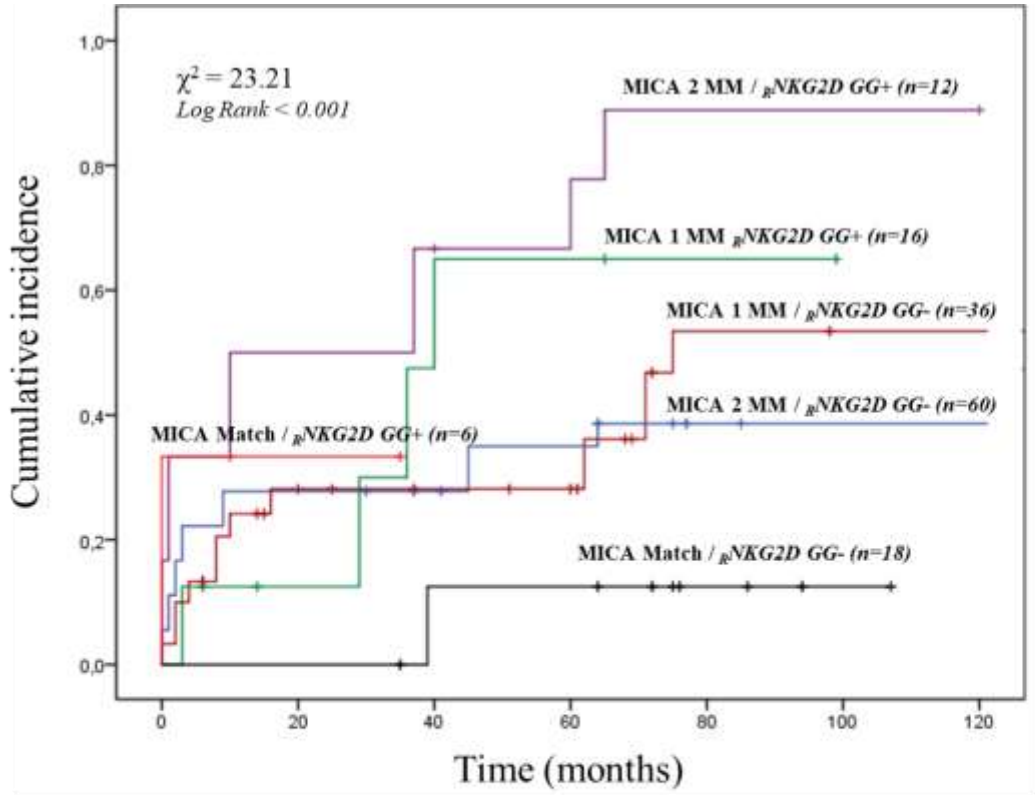
GG 50%

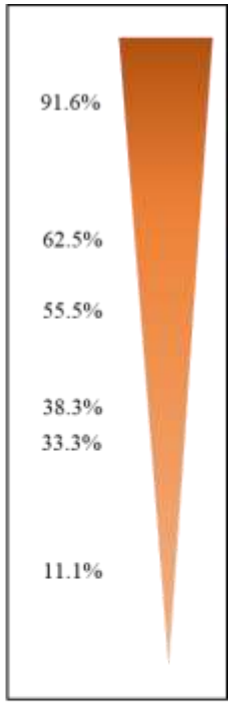
AG 38.2%



rs1049174	C	G
rs2255336	G	A
	Low	High

MICA mismatch + *rs1049174* NKG2D

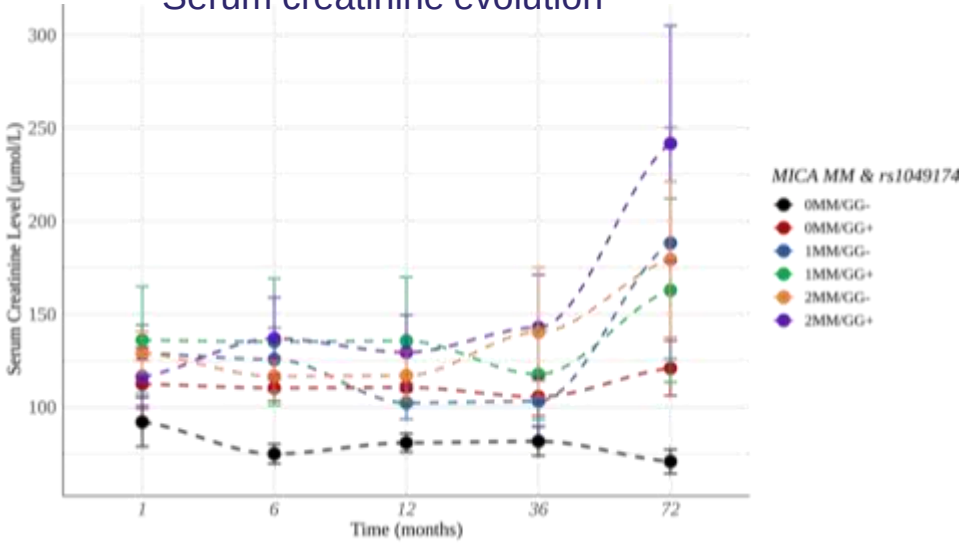




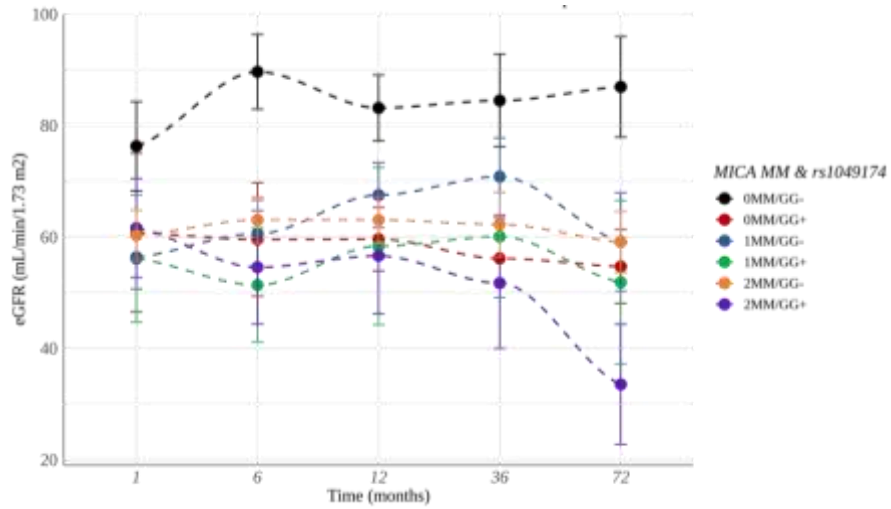
Time (Months)	0	20	40	60	80	100	120
2MM/GG+	12	6	4	2	0	0	0
1MM/GG+	16	10	6	4	2	0	0
1MM/GG-	36	26	22	18	9	7	7
2MM/GG-	60	36	24	22	7	5	5
0MM/GG+	6	4	2	0	0	0	0
0MM/GG-	18	18	14	14	12	3	0

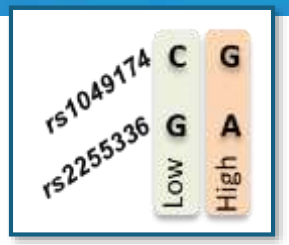
Number at risk

Serum creatinine evolution



Glomerular filtration evolution





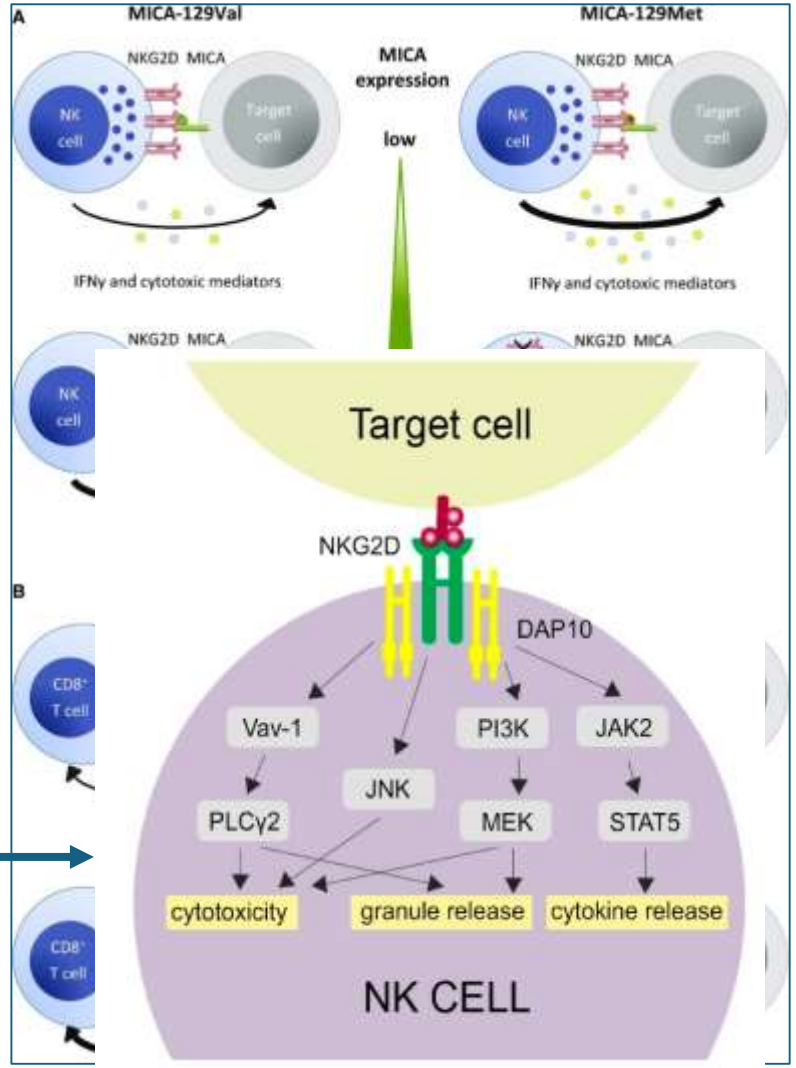
Correlation between maintenance therapy, antibody-mediated rejection and genetic profiles

Gene profiles of transplanted patients	Maintenance therapy	SGF (N = 80)	AMR (N = 68)	Comparisons of ABMR vs SGF		
				P value	OR	(95% CI)
***MICA* alleles 2MM**	Calcineurin inhibitors	18	14	0.477	1.6	(0.6 – 4.4)
	mTOR inhibitors	18	22			
Donor MICA Met129/ recipient G	Calcineurin inhibitors	12	2	**0.012**	0.139	(0.03 – 0.7)
	MTOR inhibitors	20	24			
rs1049174 GG	Calcineurin inhibitors	9	5	**0.015**	0.2	(0.0 – 1.0)
	mTOR inhibitors	5	15			
rs2255336 AA	Calcineurin inhibitors	4	0	**0.002**	0	(0.0 – 0.3)
	mTOR inhibitors	0	8			
MICA* 2MM + *rs1049174 GG	Calcineurin inhibitors	2	0	**0.025**	0	(0.0 – 0.7)
	mTOR inhibitors	0	10			

***Calcineurin inhibitors:** Cyclosporine, tacrolimus
***mTOR inhibitors:** Everolimus, Sirolimus

Take-home message

Mismatch R/D nel gene MICA	All'aumentare del numero di mismatches aumenta la probabilità di rigetto anticorpo mediato.
Dimorfismo Met/Val 129 MICA	La presenza di due mismatches influenza in modo comparabile il rischio di rigetto. **- Donor MetMet/RecipientValVal** **- Recipient MetMet/Donor ValVal**
Polimorfismi recettore NKG2D nel ricevente	**-Aplotipo-1: rs1049174** 3'UTR sito di legame del microRNA-1245 a regolazione negativa. La variante G maggiore espressione di NKG2D in vitro. **-Aplotipo-2: rs2255336** sostituzione amminoacidica vicino al sito di legame DAP10 maggiore affinità di legame.
Polimorfismo recettore NKG2D nel ricevente + il doppio mismatches R/D nel gene MICA	La presenza del polimorfismo rs1049174 [GG] nel ricevente e la presenza del doppio mismatches determinano il grado massimo di probabilità di rigetto.
Polimorfismi recettore NKG2D	In presenza del polimorfismo rs1049174 [GG], la risposta alla



Impact of t... and Disease Ri...

Siemaszko, J, NKG2D Natural Killer Cell Receptor—A Short Description and Potential Clinical Applications. *Cells* 2021

Grazie per l'attenzione

Università degli studi di Cagliari

Prof. Giglio Sabrina
Dr. Lorrai Michela
Dr. Mereu Caterina
Dr. Murgia Michela
Dr. Sanna Celeste

ASL Cagliari

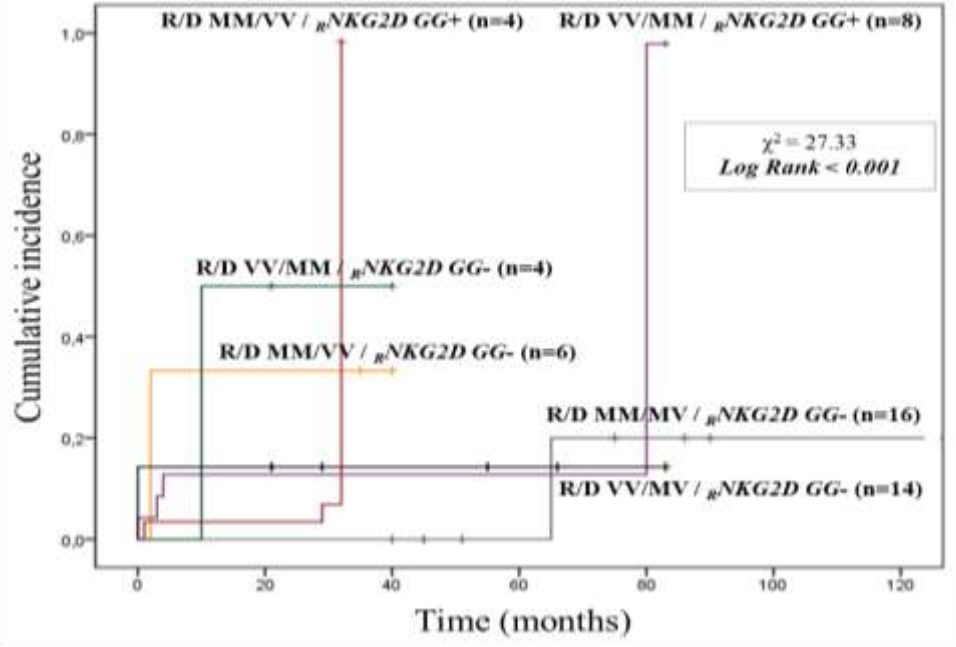
Dr. Giuressi Erika
Dr. Lai Sara
Dr. Littera Roberto
Dr. Rassu Stefania

ARNAS Brotzu

Prof. Pani Antonello
Dr. Argiolas Davide

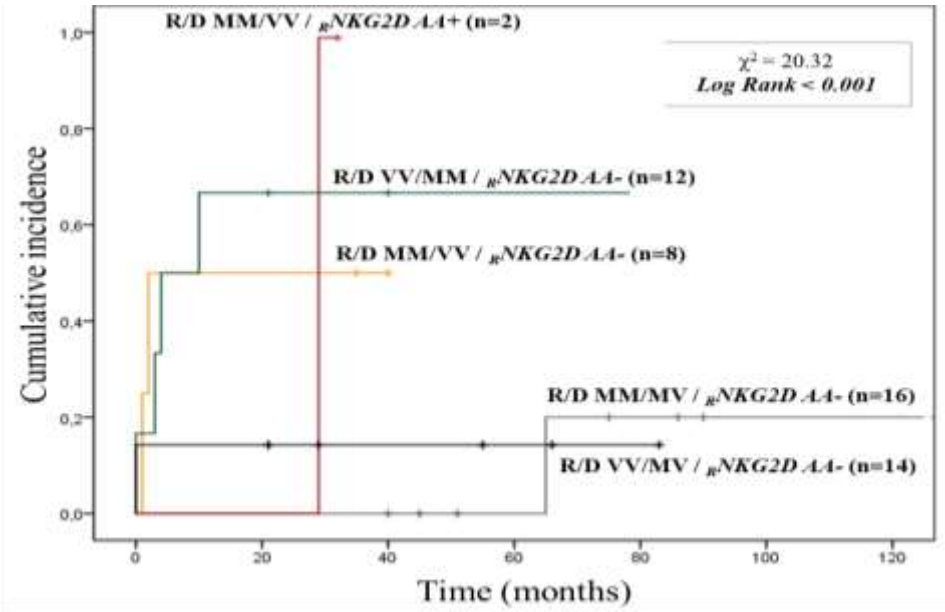
***Tutto il personale dell'Ospedale Binaghi**

MICA Met/Val 129 & *rs1049174* NKG2D

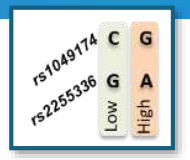


Time (Months)	0	20	40	60	80	100	120	Number at risk
R/D MM/VV / RNKG2D GG+	4	2	0	0	0	0	0	
R/D VV/MM / RNKG2D GG+	8	2	2	2	0	0	0	
R/D VV/MM / RNKG2D GG-	4	2	0	0	0	0	0	
R/D MM/VV / RNKG2D GG-	6	4	3	1	0	0	0	
R/D MM/MV / RNKG2D GG-	16	16	15	12	8	4	2	
R/D VV/MV / RNKG2D GG-	14	12	6	4	2	0	0	
R/D MM/MV / RNKG2D GG+	0	-	-	-	-	-	-	
R/D VV/MV / RNKG2D GG+	0	-	-	-	-	-	-	

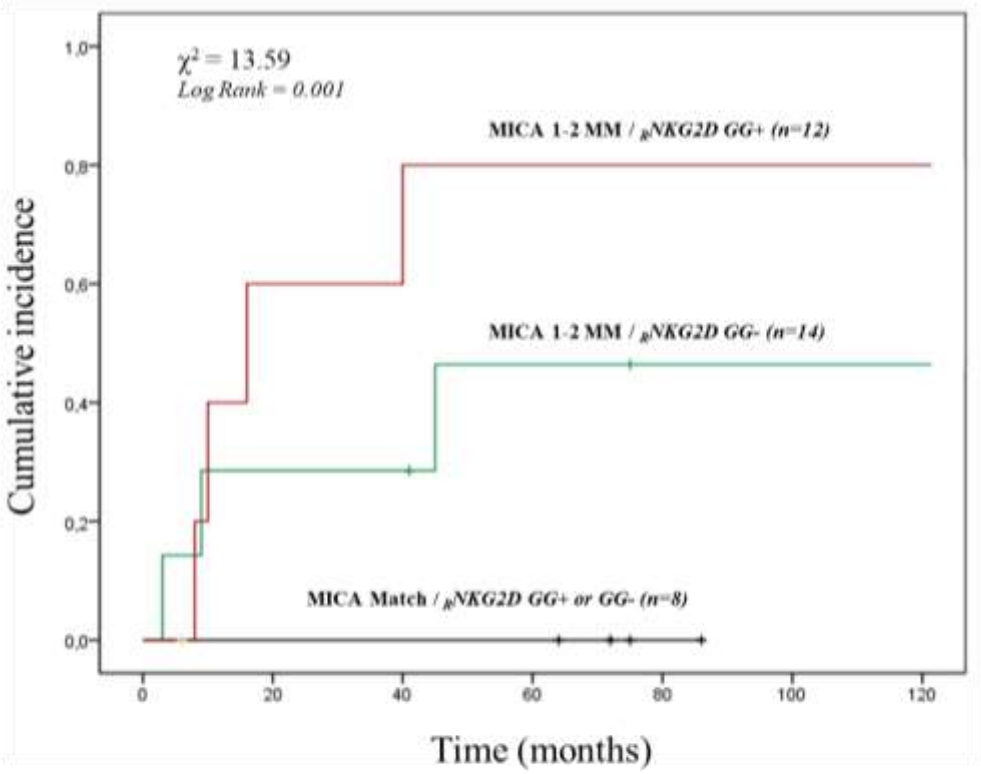
MICA Met/Val 129 & *rs2255336* NKG2D



Time (Months)	0	20	40	60	80	100	120	Number at risk
R/D MM/VV / RNKG2D AA+	2	2	0	0	0	0	0	
R/D VV/MM / RNKG2D AA-	12	4	1	1	1	1	0	
R/D MM/VV / RNKG2D AA-	8	4	1	0	0	0	0	
R/D MM/MV / RNKG2D AA-	16	16	14	10	6	2	2	
R/D VV/MV / RNKG2D AA-	14	12	6	4	2	0	0	
R/D VV/MM / RNKG2D AA+	0	-	-	-	-	-	-	
R/D MM/MV / RNKG2D AA+	0	-	-	-	-	-	-	
R/D VV/MV / RNKG2D AA+	0	-	-	-	-	-	-	

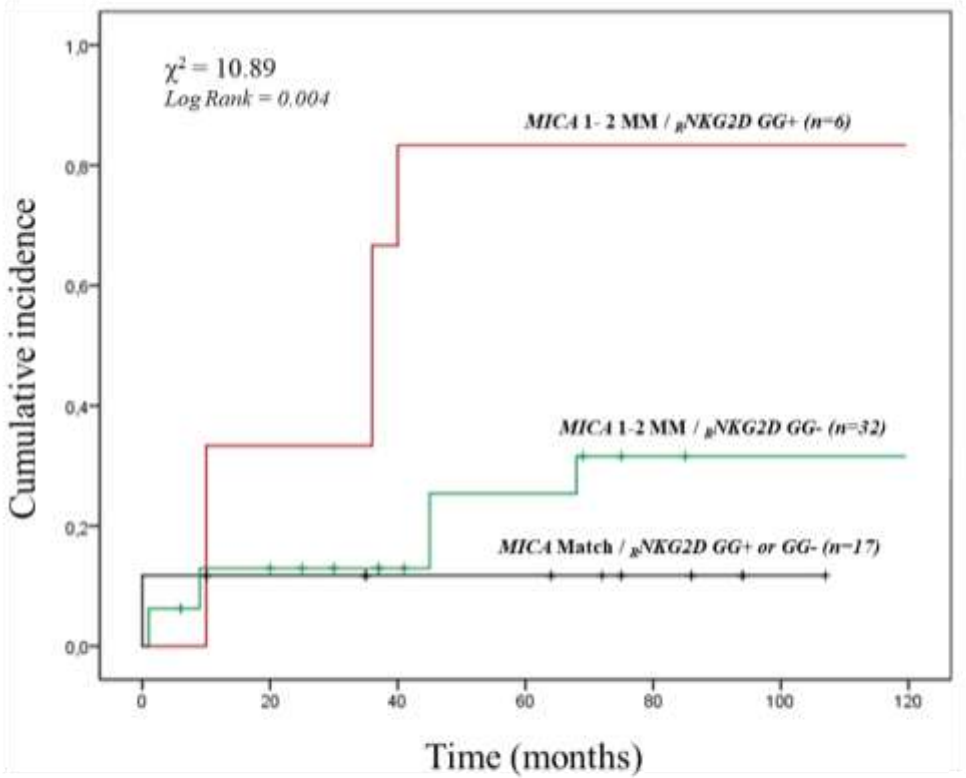


Kidney Antibody-mediated rejection: *R/D HLA-DRB1* match



Time (Months)	0	20	40	60	80	100	120	
MICA 1-2 MM / NKG2D GG+	12	5	5	1	1	1	1	Number at risk
MICA 1-2 MM / NKG2D GG-	14	10	10	6	5	5	5	
MICA Match / NKG2D GG+ or GG-	7	7	7	7	1	0	0	

Kidney Antibody-mediated rejection*:* R/D *HLA-A,-B,-C* ≤3 mismatches



Time (Months)	0	20	40	60	80	100	120	
MICA 1- 2 MM / NKG2D GG+	6	4	2	1	1	1	1	Number at risk
MICA 1-2 MM / NKG2D GG-	32	26	16	12	7	5	5	
MICA Match / NKG2D GG+ or GG-	17	13	10	10	5	1	0	