Biomarcatori e fattori di rischio per pre-emptive therapy della GvHD acuta

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Bari 07.06.2017

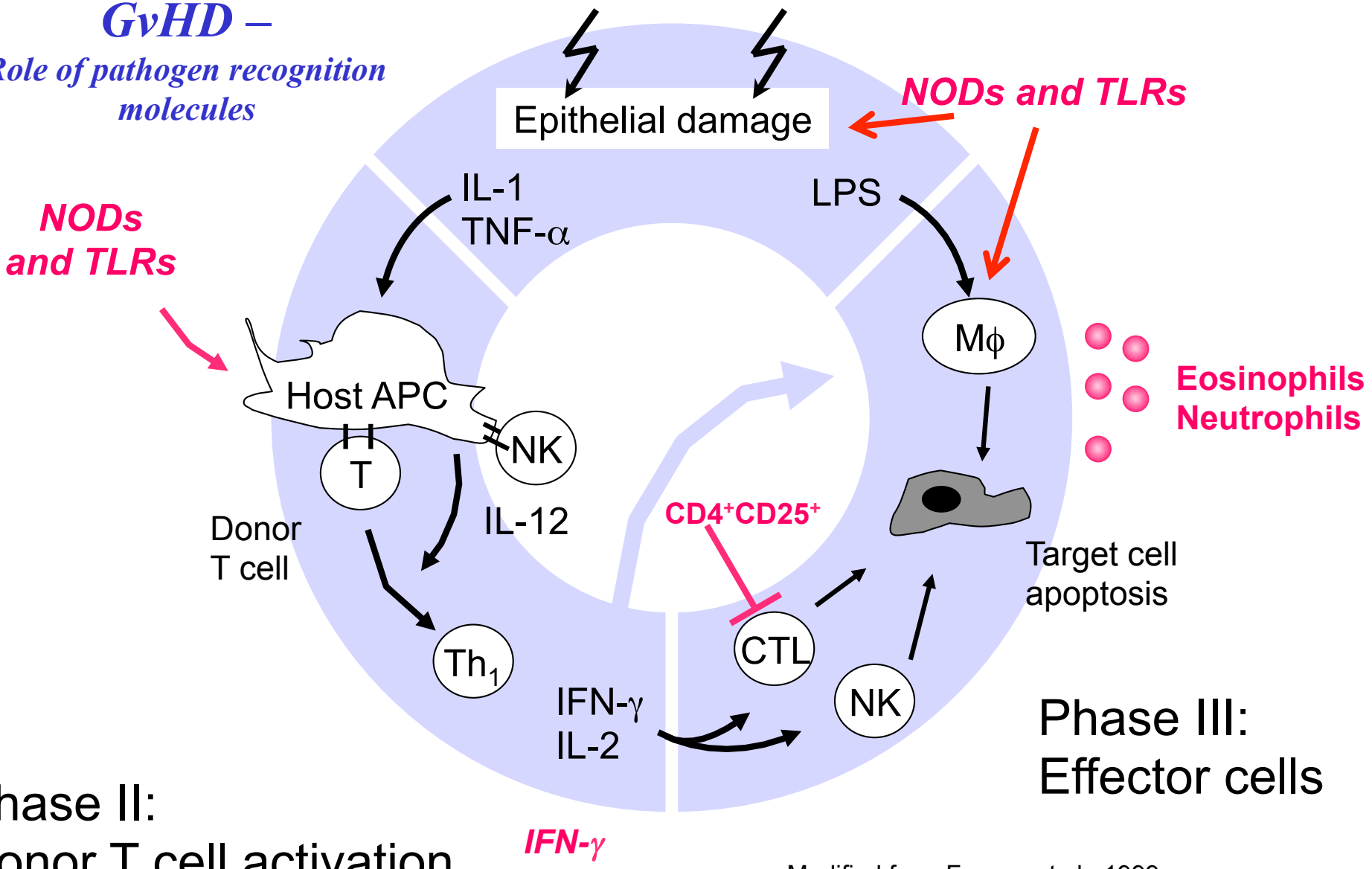
PROBLEMA

VORREI CONOSCERE QUALI SONO I PAZIENTI A RISCHIO DI GHVD

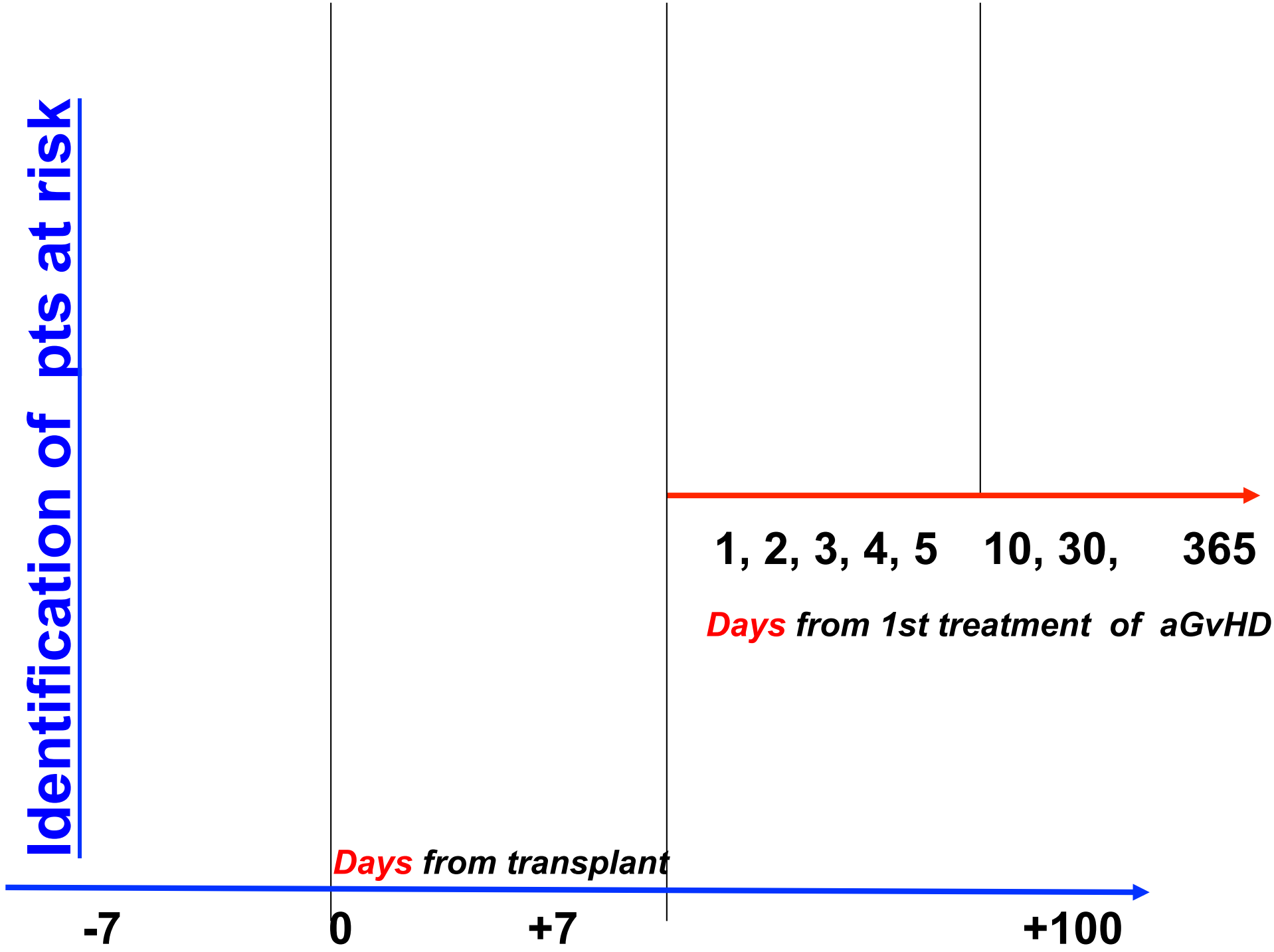
E , QUALORA LA SVILUPPINO, QUALI SONO QUELLI A RISCHIO DI COMPLICAZIONI LETALI

Activation of innate immunity triggers GvHD –

Role of pathogen recognition molecules



Modified from Ferrara et al., 1999
With modifications as added during GVHD course


Identification of pts at risk
Days from transplant
-7
0
+7
+100
1, 2, 3, 4, 5
10, 30,
365
Days from 1st treatment of aGvHD

What are the factors predicting acute GvHD ?

Patients studied = 1361

Unmanipulated, malignant, alive day +10

AML 390	**median age 35 (D and Ric)**
ALL 245	**median yy Tx 1997**
CML 378	**HLA= 959 Altern 402**
MDS 130	***ATG no 1046 yes 315***
Lymph 85	**BM 1201 PB 160**

GvHD II+

Variable		RR	P
Baseline	*Compared*		
ATG no	yes	.51	0.0000
YY<=97	YY >97	.58	0.0000
Don=	Alt don	2.0	0.0000
DA <=35	>35	1.2	0.02
CR1	CR>1	1.2	0.02
MA	RIC		
RA <=35	>35		
FD MR	other		

Worse outcomes with Any single locus mismatch

	n	RR (95% CI)	P-value
Survival	952	1.18 (1.07-1.30)	0.0009
DFS	945	1.16 (1.03-1.31)	0.004
TRM	945	1.34 (1.16-1.54)	<0.0001
Relapse	945	0.90 (0.81-1.00)	0.04
Engraftment	956	OR 0.90 (0.80-1.01)	0.06
Acute GVHD	957	1.38 (1.13-1.63)	0.0008
Chronic GVHD	910	0.96 (0.91-1.03)	0.25

- A single mismatch is associated with worse survival, DFS, TRM, acute GVHD

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Cytokine and Immune response gene SNPs and GvHD

Table 3. Non-human leucocyte antigen (HLA) gene polymorphisms associated with allo stem cell transplantation

Gene polymorphism	Association with HSCT if present in Recipient or Donor	Reference
TNFd3/d3	Recipient increased aGvHD/decreased survival	Middleton *et al.* (1998)
TNFd*4	Recipient or donor — increased aGvHD	Nordlander *et al.* (2002)
TNF-308*A	Donor — increased aGvHD	Takahashi *et al.* (2000)
	Donor — toxic complications	Wang *et al.* (2002)
		Bogunia-Kubik *et al.* (2003)
TNF-488*A	Recipient — increased aGvHD and cGvHD, early death	Mullighan *et al.* (2004)
TNFd*4 or 5	Recipient — decreased survival	Bettens *et al.* (2006)
TNFd*4	Recipient — increased aGvHD	Remberger *et al.* (2003)
TNFd*4 and TNFSF2-101x	Donor or recipient — decreased survival	Keen *et al.* (2004)
TNF-863, -857	Donor and/or recipient — increased GvHD & lower relapse	Ishikawa *et al.* (2002)
IL-10-1064 (11–15)	Recipient — increased GvHD	Cavet *et al.* (1999)
Lack of IFNγ allele2/2	Recipient — protective for GvHD	Mlynarczewska *et al.* (2004)
IL-6-174, IFNγ3/3	Recipient — increased a and cGvHD	Cavet *et al.* (2001)
IL-6-174	Recipient — increased cGvHD	Socié *et al.* (2001)
IL-10-5a2A/A	Recipient — decreased aGvHD	Lin *et al.* (2003)
IL-1-Ra VNTR (allele 2)	Donor — protection from aGvHD	Cullup *et al.* (2001)
TNF d3/d3; IL-10 (11–15)	(CBT) No association with aGvHD	Kogler *et al.* (2002)
VDR-intron 8	Recipient — increased aGvHD	Middleton *et al.* (2002)
	Donor — decreased TRM	
ER α intron 1	Recipient — occurrence GvHD	Middleton *et al.* (2003)
	Lower survival	
TNFRII 196R	Recipient — increased aGvHD	Stark *et al.* (2003)
	Donor — increased cGvHD	

Further genes: FAS, IL7R, IL4, IL23R

AM Dickinson,
Int J Immunogenetics

Conclusione 1:
pazienti a rischio pre condizionamento

fase >CR1 , donatore >35 anni

Rischio 1.2 (rilevante ?)

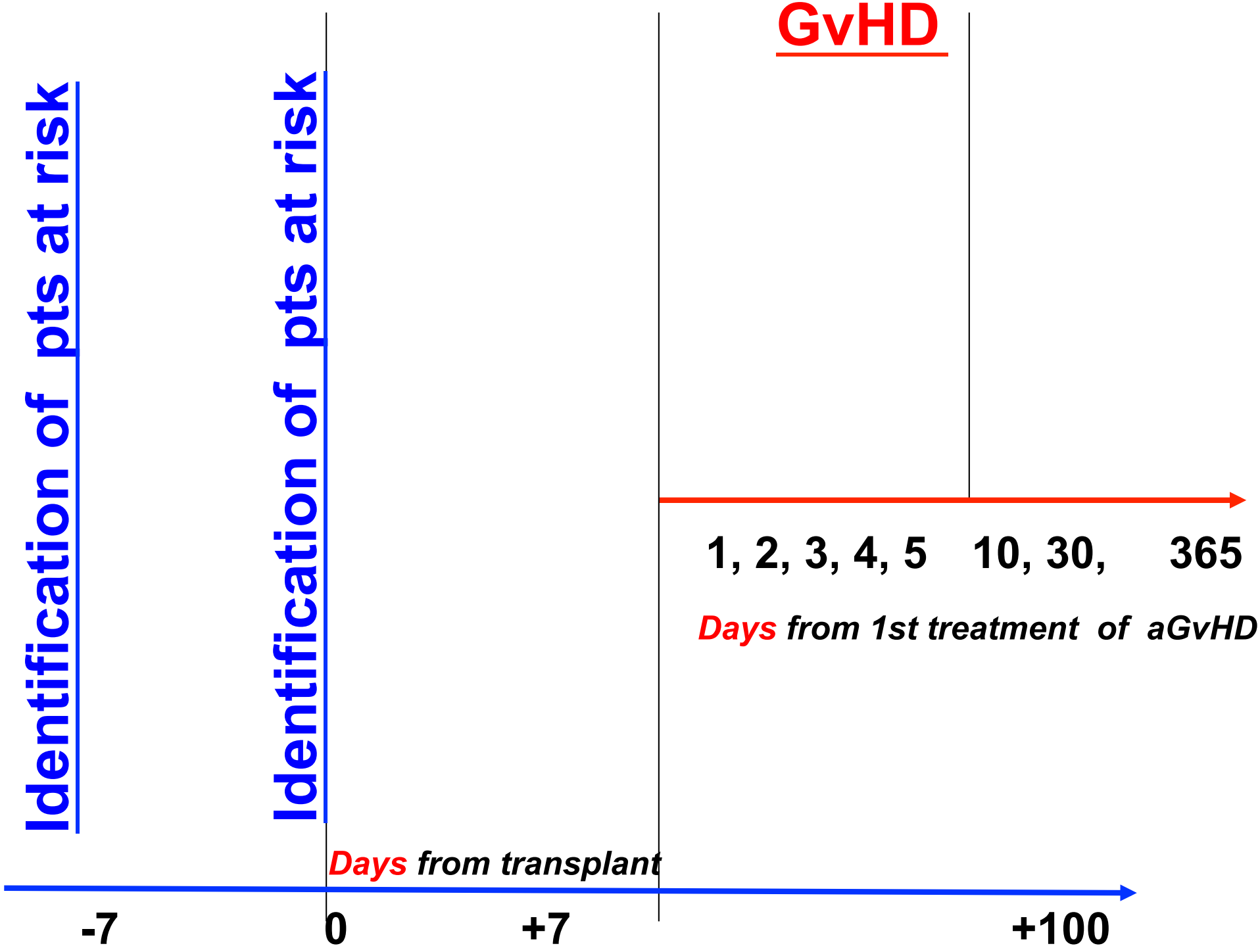
polimorfismo citochine

Controverso ancora non standardizz

 # Tipo di donatore, HLA=, e tipo di profilassi (per es ATG) , con anno di trapianto

Rischio 2 (clinicamente rilevante)

Non ci sono studi di terapia pre-emptive in base a questi fattori di rischio


GvHD
Identification of pts at risk
Identification of pts at risk
1, 2, 3, 4, 5
10, 30,
365
Days from 1st treatment of aGvHD
Days from transplant
-7
0
+7
+100

CD3$^+$/Tregs Ratio in Donor Grafts Is Linked to Acute Graft-versus-Host Disease and Immunologic Recovery after Allogeneic Peripheral Blood Stem Cell Transplantation

Domenico Pastore, Mario Delia,* Anna Mestice, Paola Carluccio, Tommasina Perrone, Francesco Gaudio, Paola Curci, Antonella Russo Rossi, Alessandra Ricco, Giorgina Specchia*

Biol Blood Marrow Transplant 18: 887-893 (2012)

CD3 /Treg ratio		GvHD II-IV	CMV CTL	CMV inf
Low Risk	<36	20%	15	15%
High risk	≥36	84%	3	69%
		.001	.001	.001

Table 4. Univariate Analysis of Potential Factors Affecting Grade II-IV aGVHD and CMV Infection/Disease

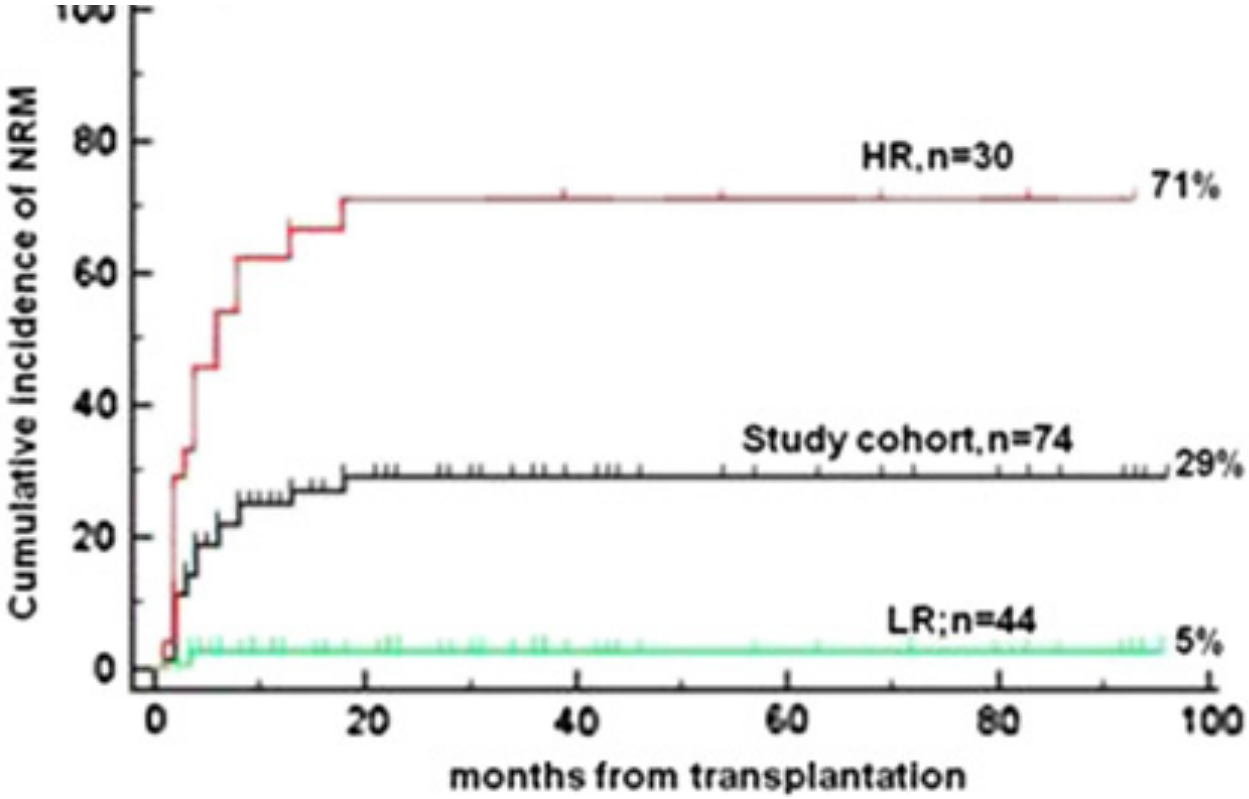
Factor	Grade II-IV aGVHD, *P* value	CMV Infection/Disease, *P* value
HLA mismatch, yes/no	.02	NS
ATG use, yes/no	NS	NS
gCD3/Tregs R, H/L	<.001	<.001
Donor type, MUD/sibling	NS	NS
Donor age	NS	—
Donor CMV serology, high risk/not high risk	—	<.001
aGVHD (grade II-IV), yes/no	—	<.001

Conditioning regimen intensity: 100% full ablative; transplantation source: 100% PBSC.

Outcome of Allogeneic Peripheral Blood Stem Cell Transplantation by Donor Graft $CD3^+$/Tregs Ratio: A Single-Center Experience

Mario Delia*, Domenico Pastore, Anna Mestice, Paola Carluccio, Tommasina Perrone, Francesco Gaudio, Alessandra Ricco, Nicola Sgherza, Francesco Albano, Giorgina Specchia

M. Delia et al. / Biol Blood Marrow Transplant 19 (2013) 492–503

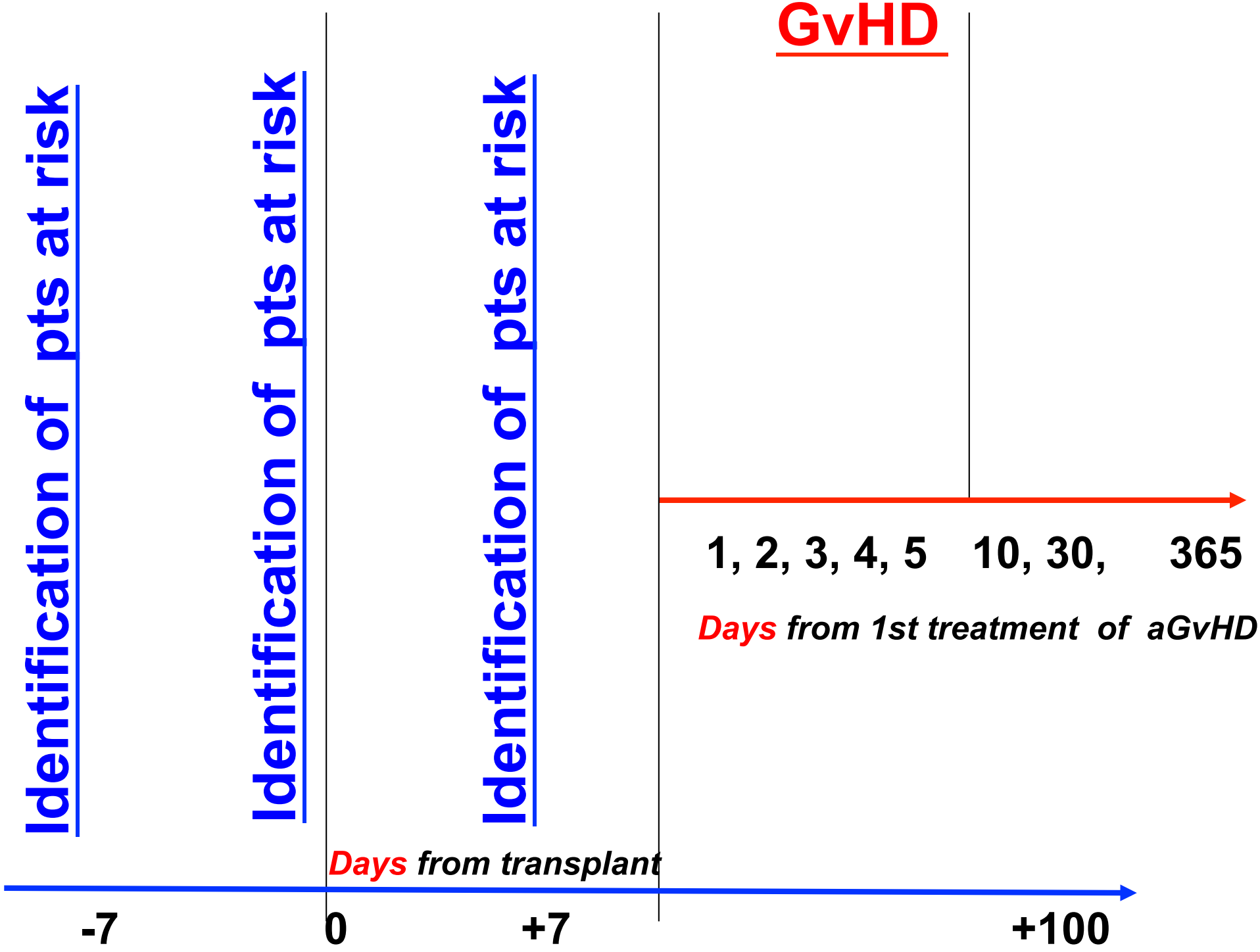


Conclusione 2:
pazienti a rischio giorno 0

rapporto CD3/Treg predice GvHD , CMV e NRM

In corso studio prospettico

Non ci sono studi di terapia pre-emptive in base a questo fattore di rischio


GvHD
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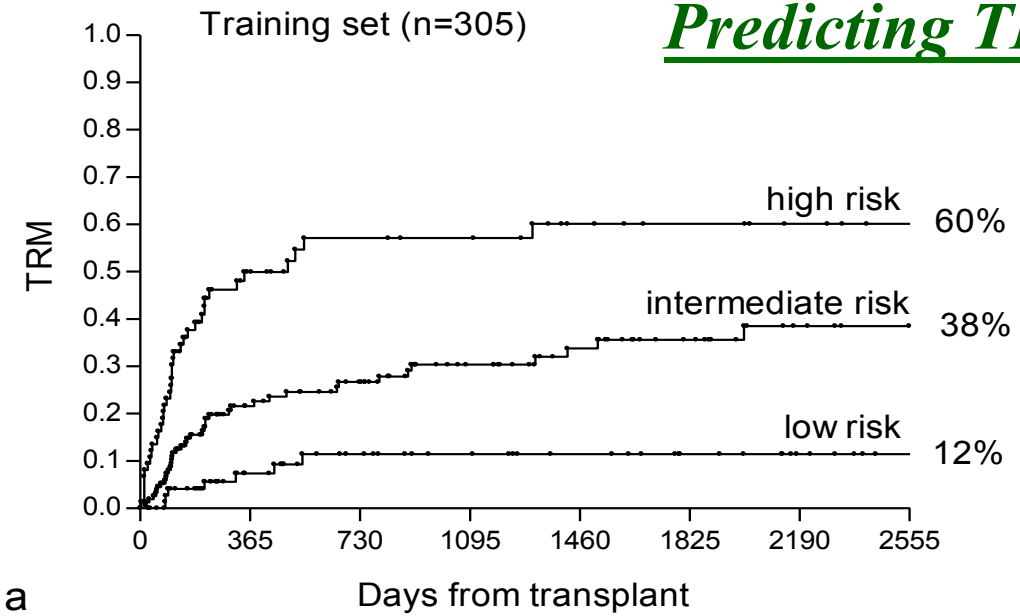
+100

Variables selected on DAY +7 by the COX model
as predictive of TRM

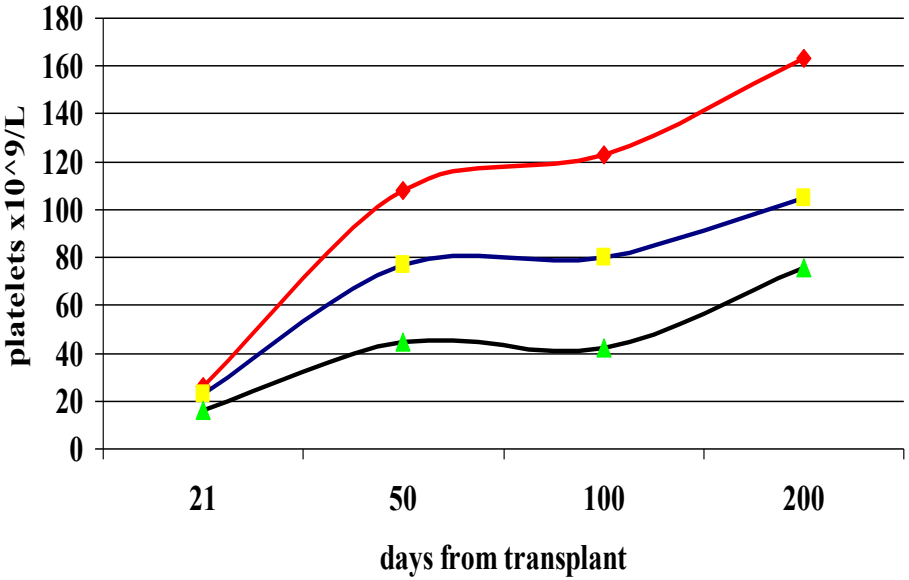
Variables	*P value*	
Cholinesterase	0.01	
Tot serum proteins	0.08	
BUN		0.0025
γGT		0.003
Donor type		0.001
Cell dose	0.04	

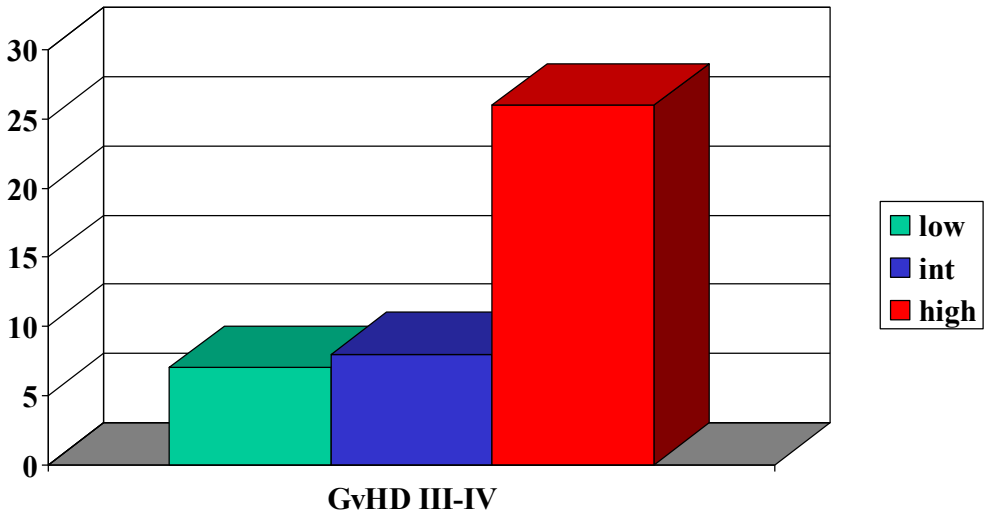
(Sormani et al Bone Marrow Transplant 2003; 32: 205)

Predicting TRM on day +7 after Tx

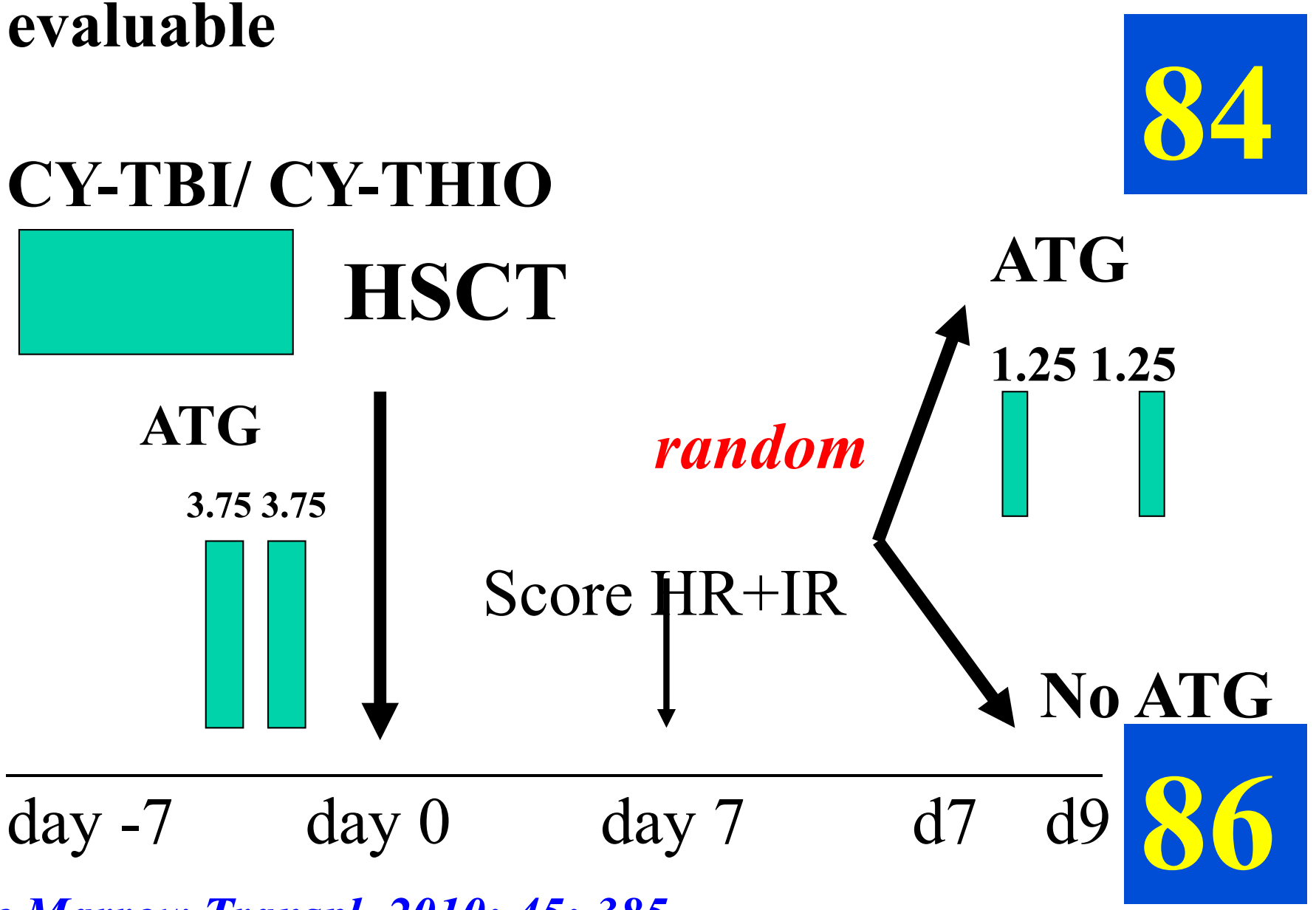


(Sormani et al. Bone Marrow Transpl. 2003: 32: 205).





170 patients were randomized and are evaluable



Bone Marrow Transpl. 2010; 45: 385

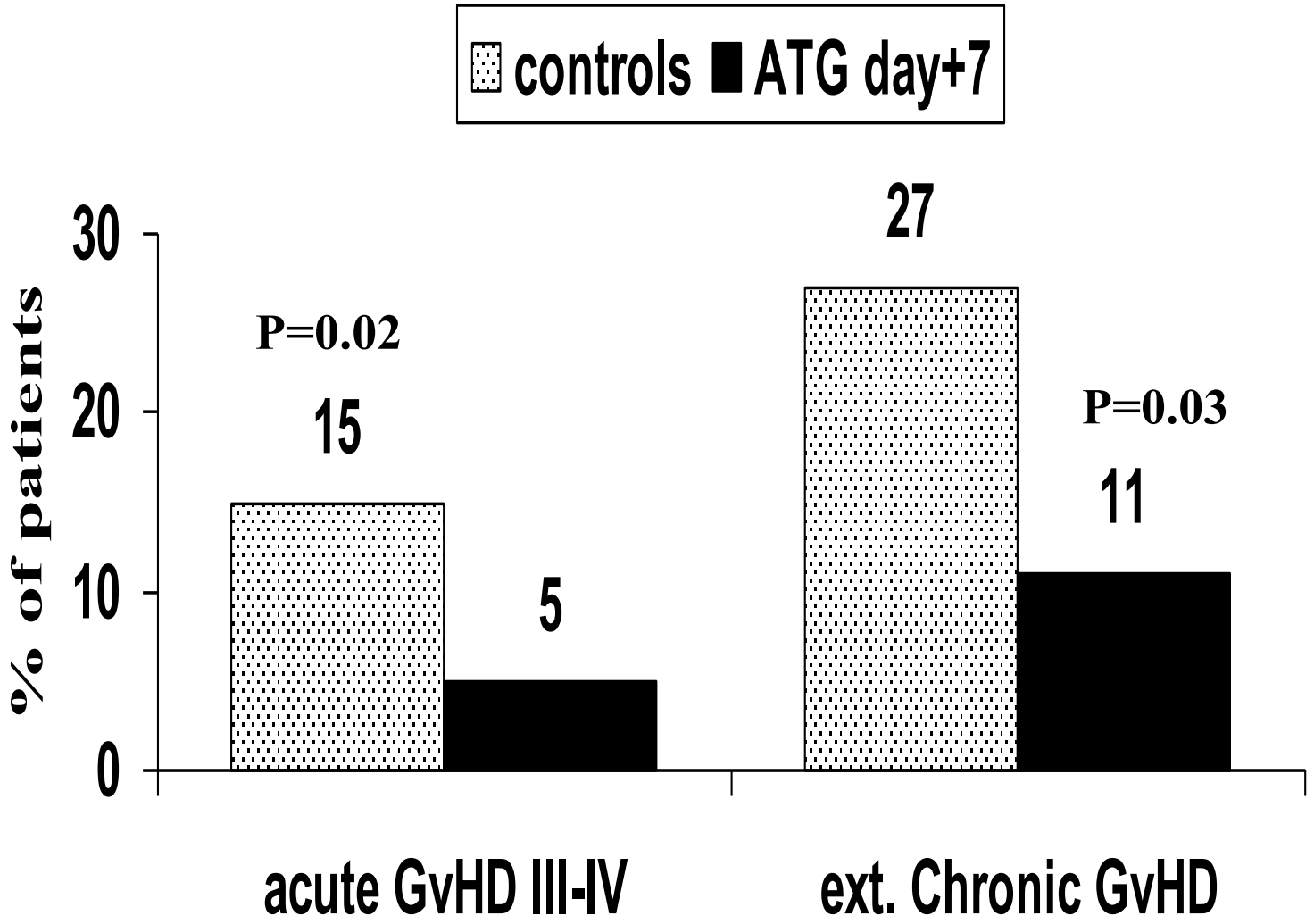
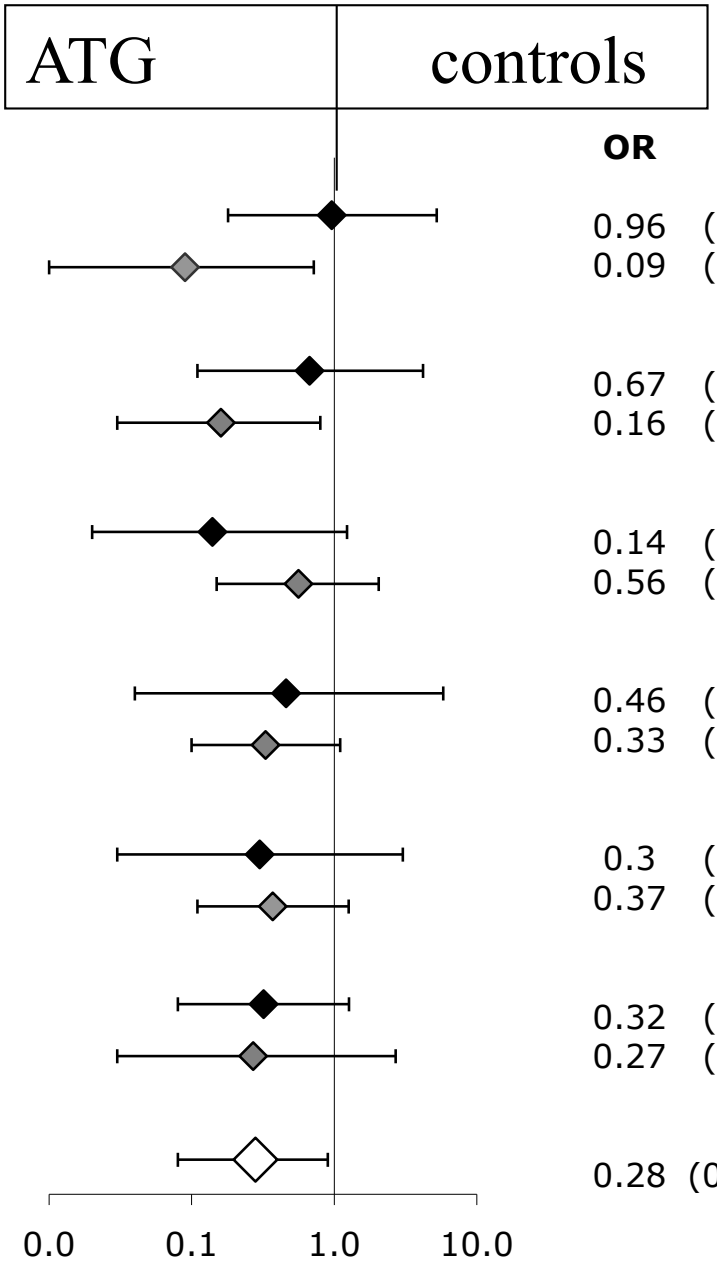


Fig.3

Bone Marrow Transpl. 2010; 45: 385

Bone Marrow Transpl. 2010; 45: 385 \

GvHD III-IV



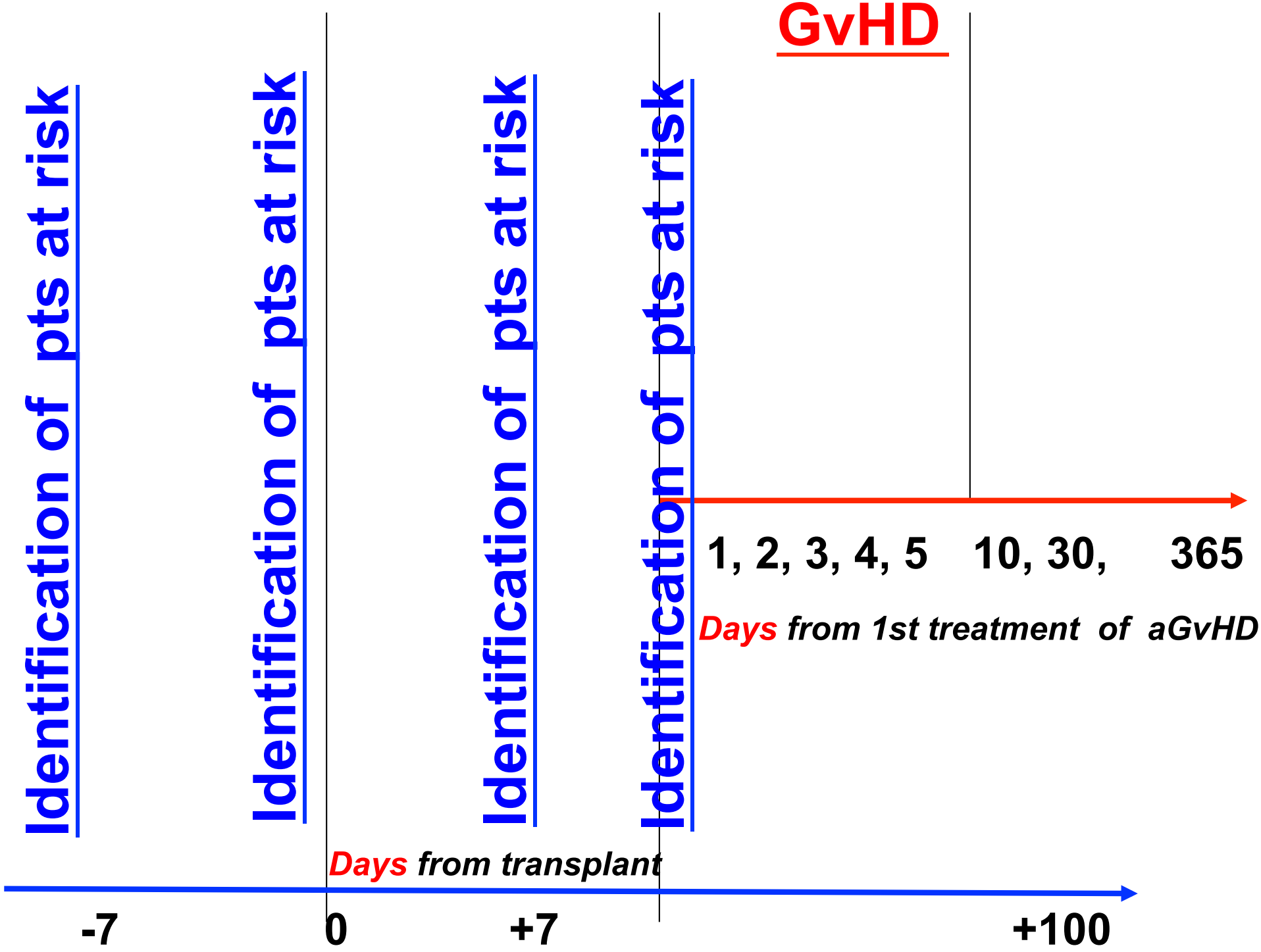
Variable	Group	OR	(95% CI)	p for interaction
Risk	medium	0.96	(0.18 to 5.23)	0.08
	high	0.09	(0.01 to 0.72)	
Phase	early	0.67	(0.11 to 4.20)	0.26
	advanced	0.16	(0.03 to 0.80)	
Age	<=35	0.14	(0.02 to 1.23)	0.28
	>35	0.56	(0.15 to 2.05)	
Donor	family	0.46	(0.04 to 5.80)	0.82
	unrelated	0.33	(0.10 to 1.10)	
HLA matching	matched	0.3	(0.03 to 3.03)	0.87
	mismatched	0.37	(0.11 to 1.26)	
F-Donor M-Recipient	no	0.32	(0.08 to 1.27)	0.89
	yes	0.27	(0.03 to 2.70)	
Overall		0.28	(0.08 to 0.90) p=0.03	

Fig.4

Conclusione 2:
pazienti a rischio giorno +7

E’ possibile identificare pazienti a rischio di GvHD severa al giorno+7 dopo il trapianto

La terapia pre-emptive gg+7 , riduce significativamente la GvHD III-IV in pazienti ad alto rischio, ma non la TRM


GvHD
Identification of pts at risk
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Identification of pts at risk
1, 2, 3, 4, 5
10, 30,
365
Days from 1st treatment of aGvHD
Days from transplant
-7
0
+7
+100

A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study

Lancet Haematol 2015; 2: e21–29

John E Levine, Thomas M Braun, Andrew C Harris, Ernst Holler, Austin Taylor, Holly Miller, John Magenau, Daniel J Weisdorf, Vincent T Ho, Javier Bolaños-Meade, Amin M Alousi, James L M Ferrara, for the Blood and Marrow Transplant Clinical Trials Network

Biomarkers:

TNFR1: surrogate for TNFα, amplifies GI injury

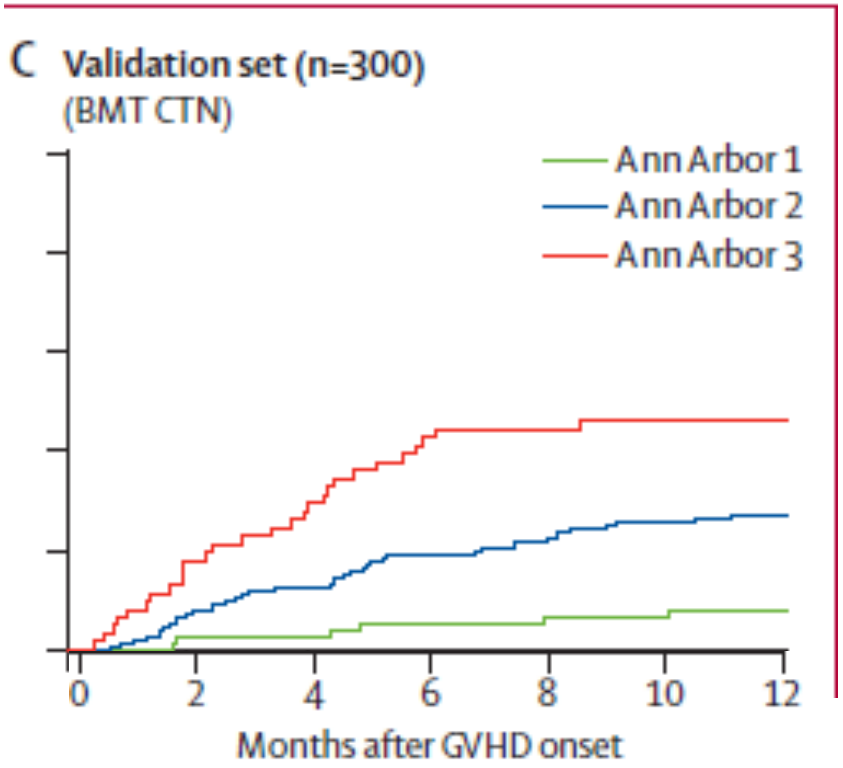
ST2 regulated by TNF + its ligand IL33 , affects inflamm.bowel disease

Reg3α: produced by Paneth cells, protects GI epithelium from infect.

Plasma samples taken 48 hours before/after initiation of glucocorticoid treatment of acute GvHD

damage.[35] The concentrations of these biomarkers at GVHD onset seem to reflect gastrointestinal tract disease activity that does not correlate with the severity of gastrointestinal symptoms at that time.

To our knowledge, this study is the first to use biomarkers to classify patients at onset GVHD of according to risk of treatment failure and non-relapse mortality outside of single centres. The biomarker algorithm was validated in patients from a wide range of centres with a large variety of personnel and biases and was superior to clinical grading for determining risk. This study suggests that GVHD biomarker algorithm scores might be useful to design risk-stratified trials of primary GVHD therapy.



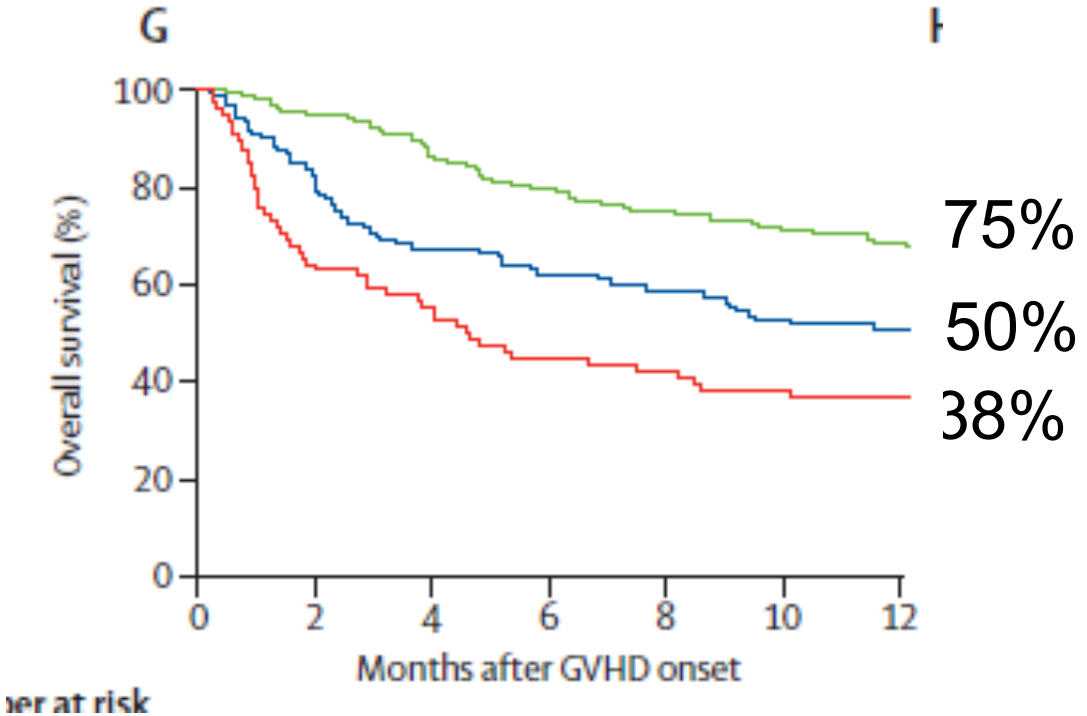
Non relapse mortality

46%

27%

8%

Survival



75%

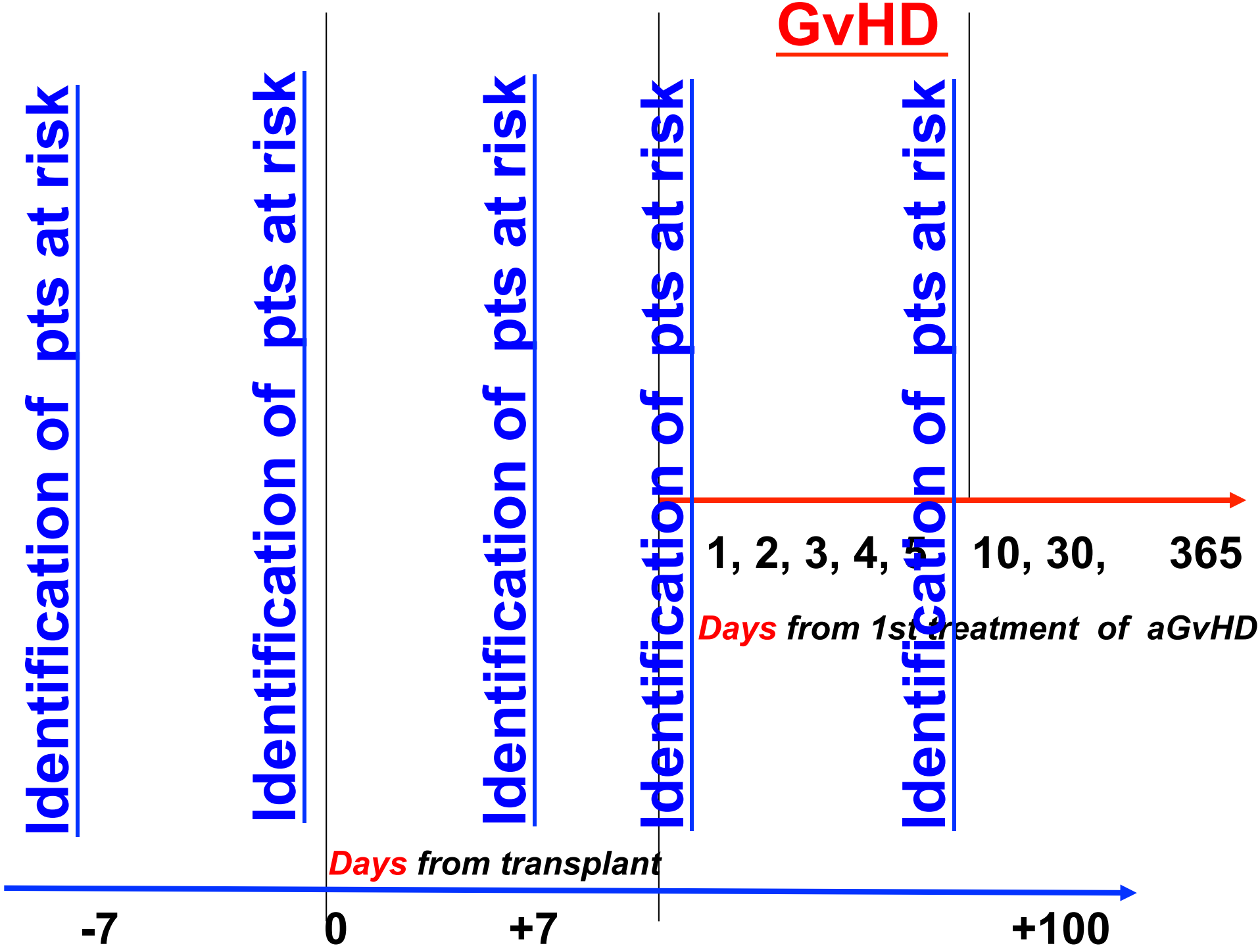
50%

38%

Conclusione 3:
pazienti a rischio alla DIAGNOSI di GvHD

E’ possibile identificare pazienti a rischio di GvHD severa – quindi TRM - alla diagnosi di GvHD, mediante 3 biomarkers

Non ci sono studi di terapia pre-emptive in base a questo modello Ann Arbor

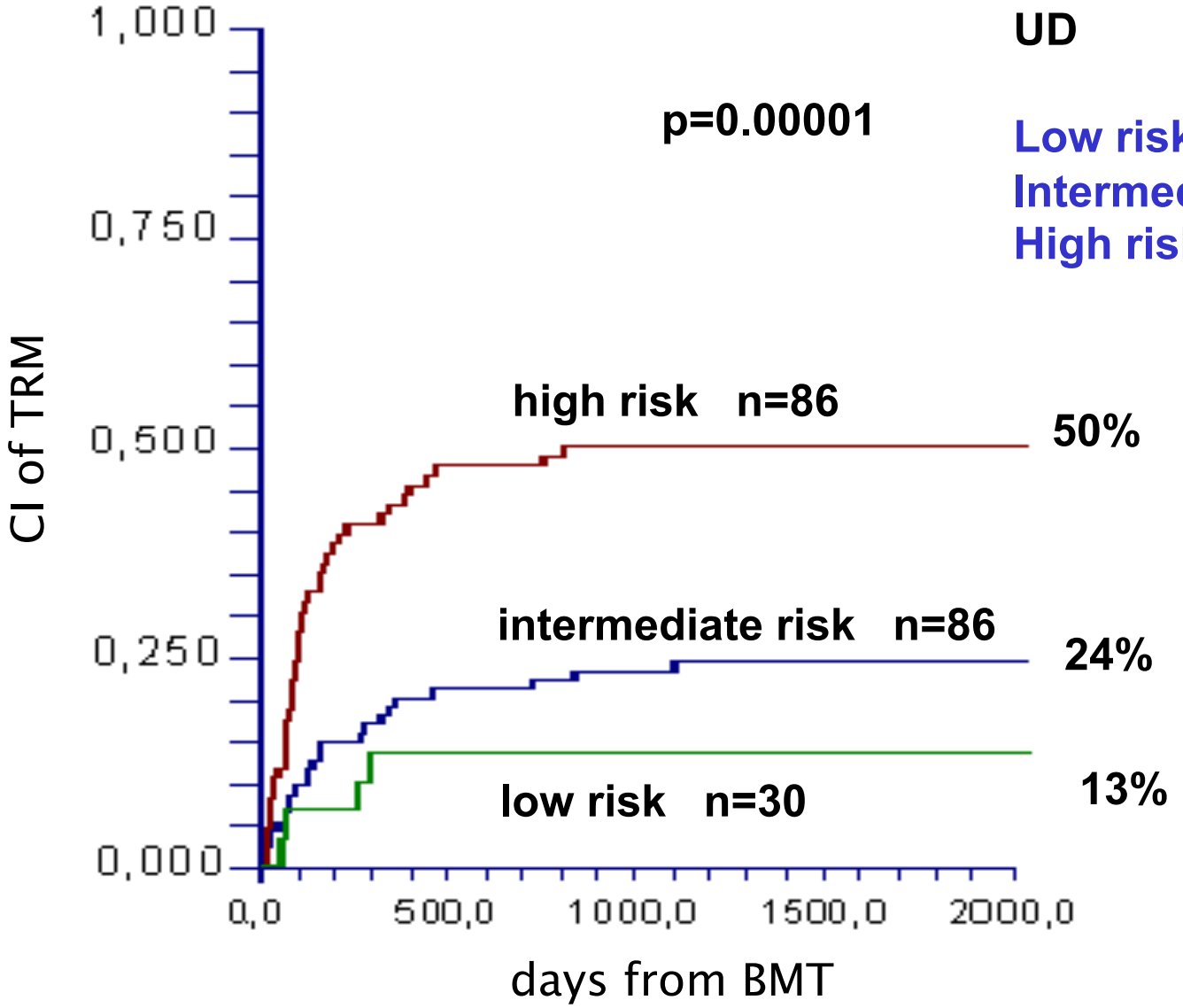

GvHD
Identification of pts at risk
Identification of pts at risk
Identification of pts at risk
Identification of pts at risk
Identification of pts at risk
1, 2, 3, 4, 5
10, 30,
365
Days from 1st treatment of aGvHD
Days from transplant
-7
0
+7
+100

Risk score DAY +5

aGvHD =>II
Response day 5
Age =>33
Disease phase =>CR1
UD

p=0.00001

Low risk = 0
Intermediate risk = 1
High risk >1



Blood. 2006 ;15:107:4177

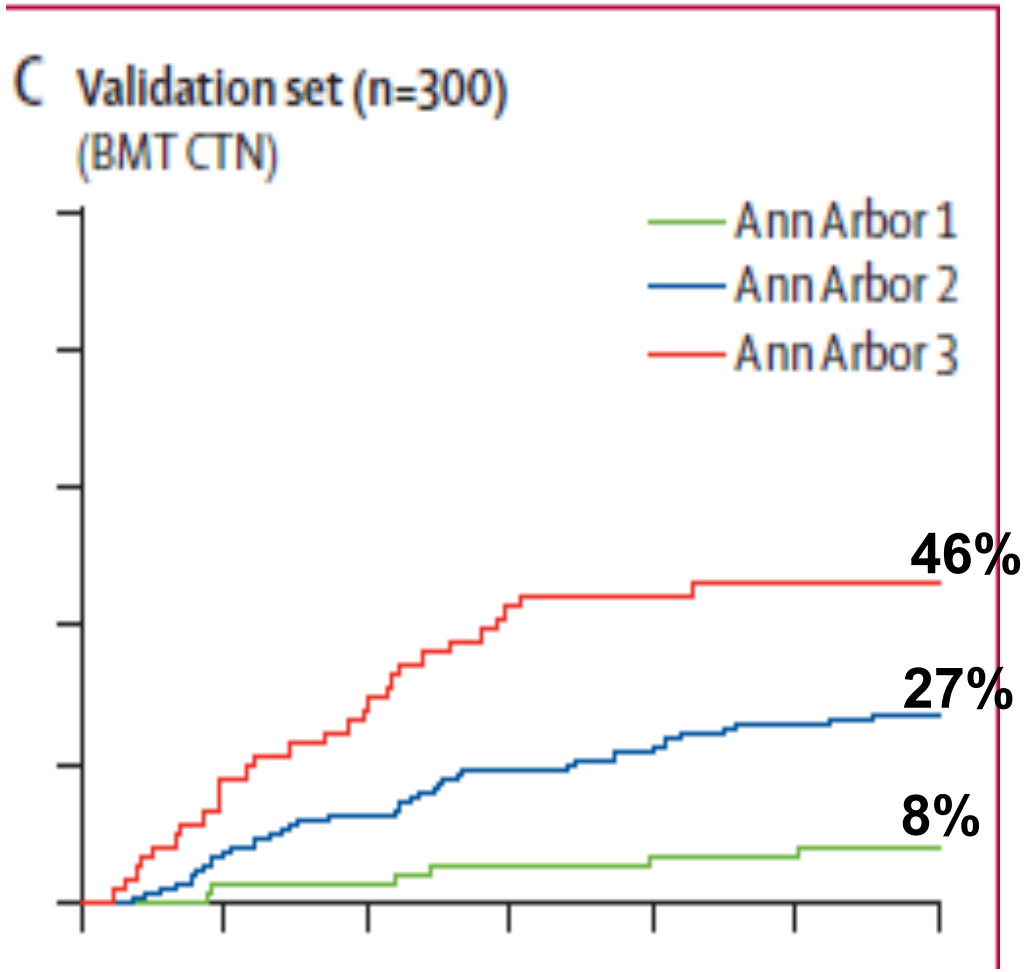
Conclusione 4:

pazienti a rischio dopo terapia di prima linea GvHD (gg +5 di terapia)

E' possibile indentificare pazienti ad alto rischio di TRM dopo 5 giorni di terapia della GvHD acuta

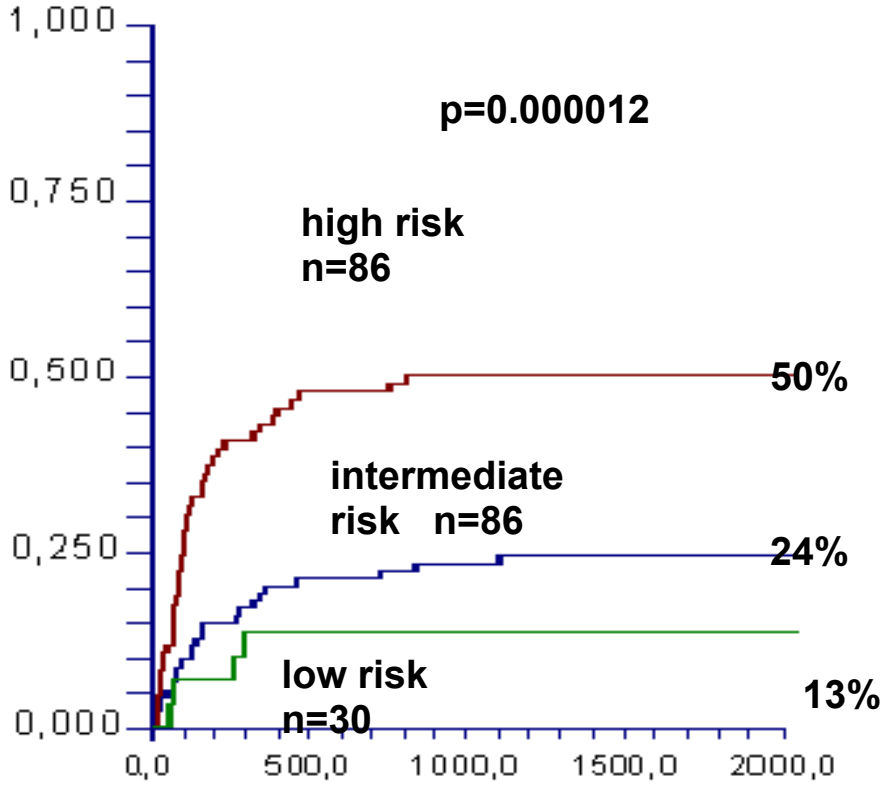
Non ci sono studi di terapia pre-emptive in base a score day+5

Day -2 +2 from PRED
ST2, TNFR1, Reg3α

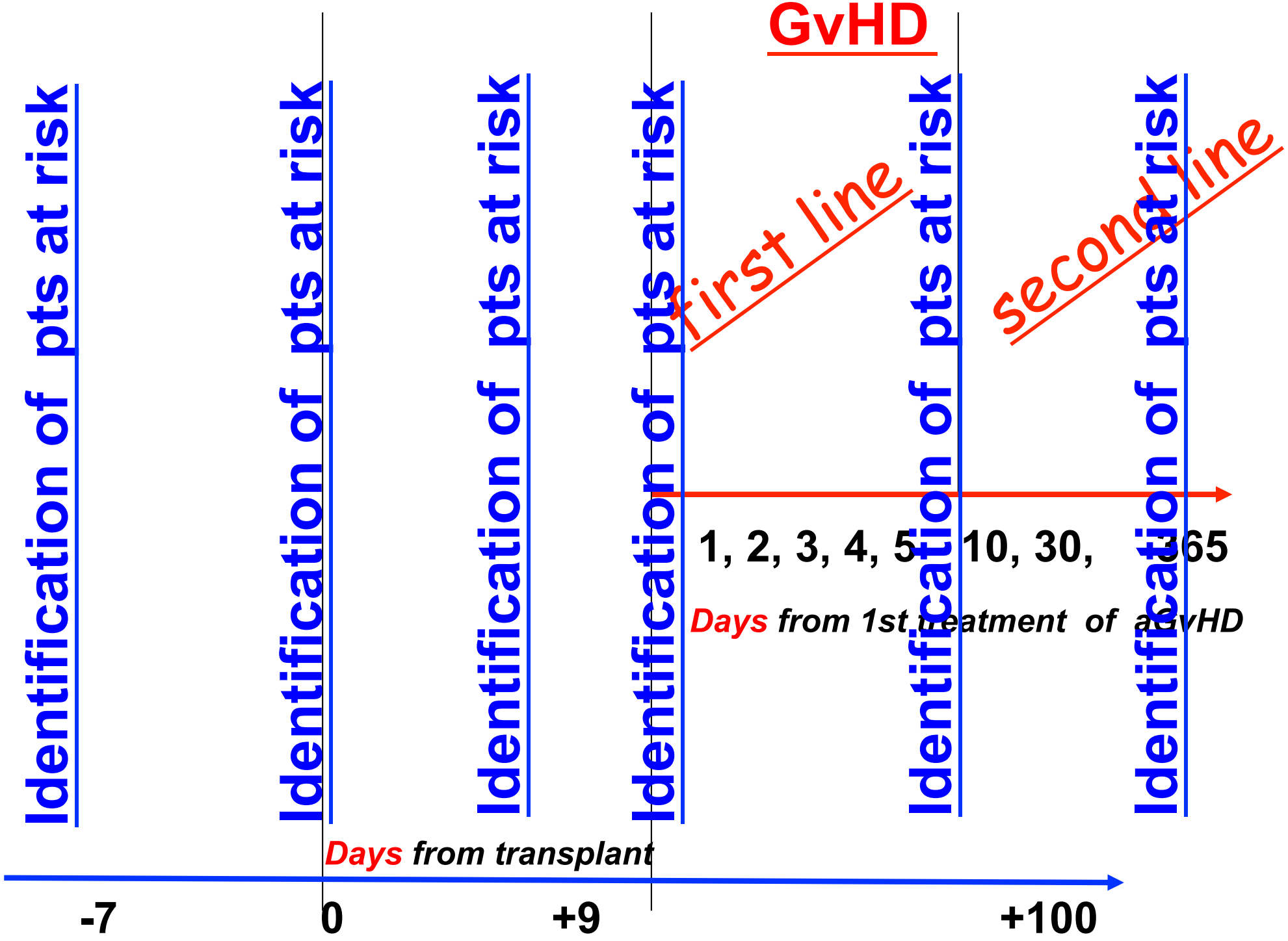


Lancet 2015; 2; e21

Day +5 from PRED
Resp/ GvHDII /age /don
Dis phase



Blood. 2006 ;15:107:4177


GvHD
Identification of pts at risk
Identification of pts at risk
Identification of pts at risk
Identification of pts at risk
Identification of pts at risk
Identification of pts at risk
first line
second line
1, 2, 3, 4, 5
10, 30,
365
Days from 1st treatment of aGvHD
Days from transplant
-7
0
+9
+100

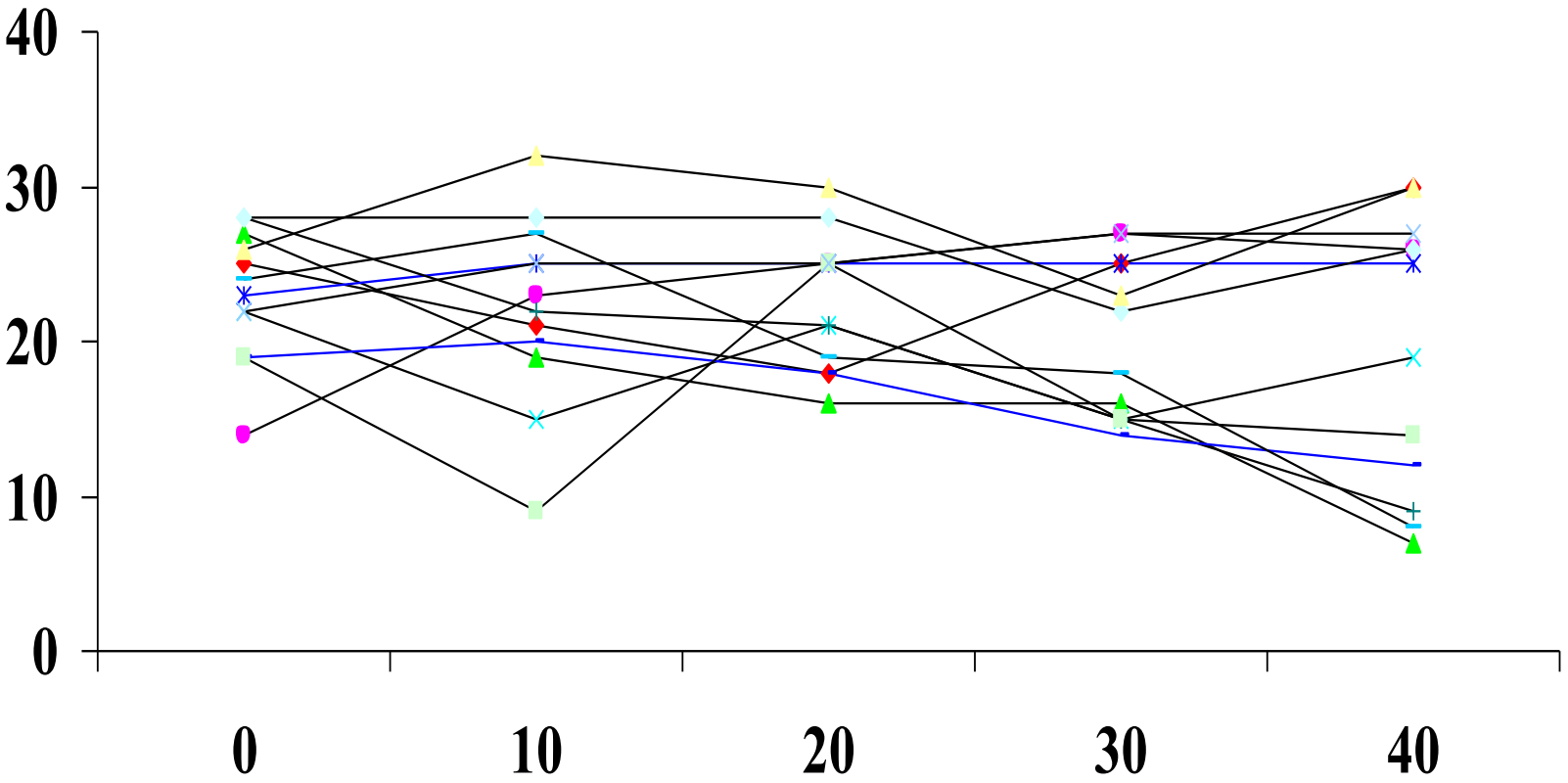
E la risposta?

E’ possibile valutare **rapidamente** se un paziente risponde ?

Score dinamico GvHD
24 variabili

GvHD (cute int feg globale)
Intestino (diarrea + vomito)
Infezioni (febbre, sepsi, batt fung vir)
Polmone (0/1)
Ematologia (piastrine 50)
Fegato ggT (40)
TAM LDH (300)
Nutrizionale CHE (2000,4000); TIBC (100,200); PT (5) ;
Nutrizionale parenterale (0/1)
Sicca sindr (0,1,2)
Dose di steroidi (0,<0.5,0.5-1,>1)
Ricovero (ambulatorio, DH, degente)
PF oggettiva (0,1,2)
PF soggettiva (0,1,2)

RISPOSTE DURANTE LA TERAPIA



Conclusione 5:

pazienti a rischio DURANTE la terapia della GvHD

monitorare i pazienti DURANTE il trattamento per GvHD ??

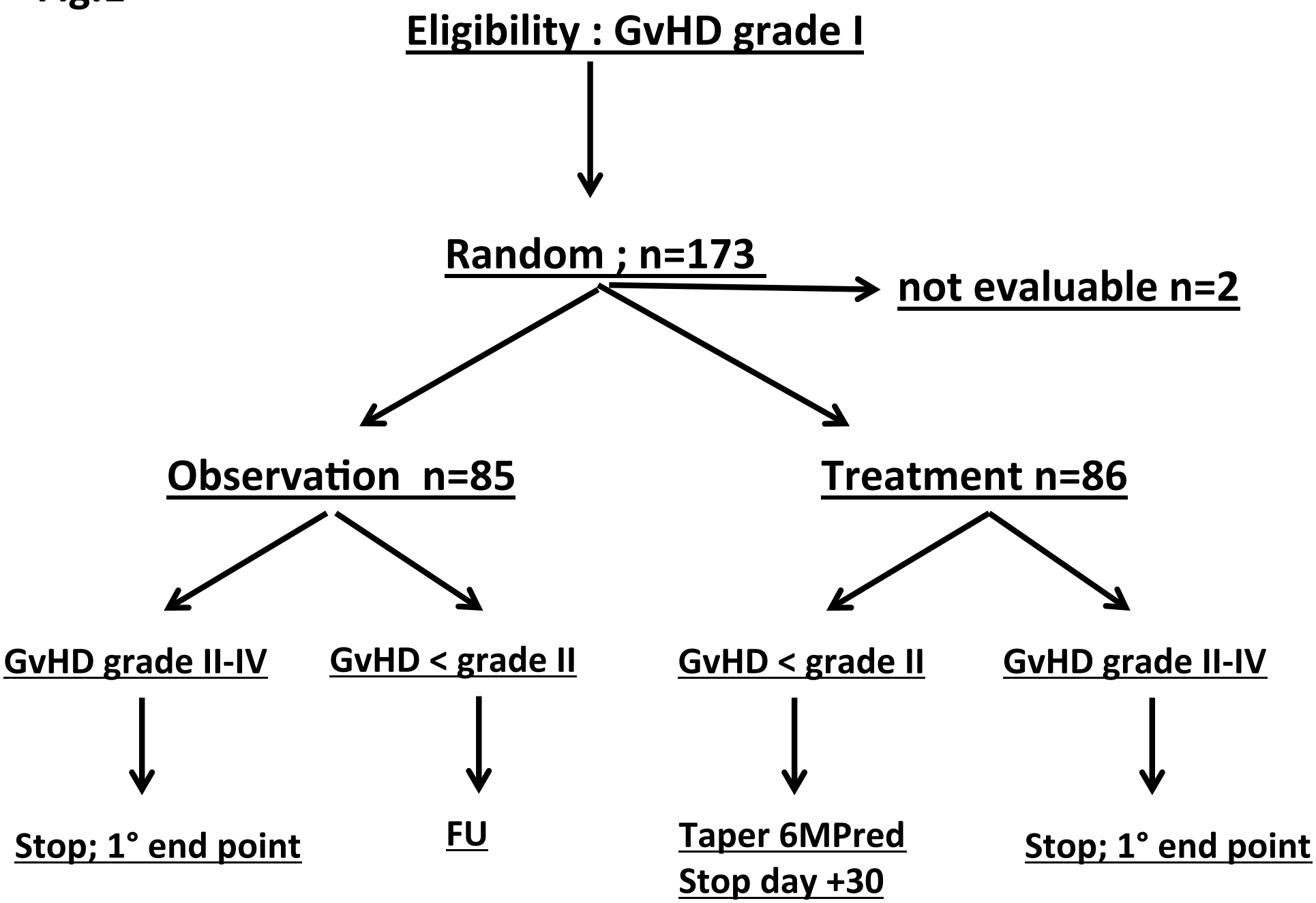
MA

Se trattassimo i pazienti MOLTO pecocemente

Per esempio GvHD grado I

Si potrebbe prevenire evoluzione in grado III-IV ????????

Fig.1


Eligibility : GvHD grade I
Random ; n=173
not evaluable n=2
Observation n=85
Treatment n=86
GvHD grade II-IV
GvHD < grade II
GvHD < grade II
GvHD grade II-IV
Stop; 1° end point
FU
Taper 6MPred
Stop day +30
Stop; 1° end point

RAMP: Cumulative incidence of acute GvHD grade III-IV

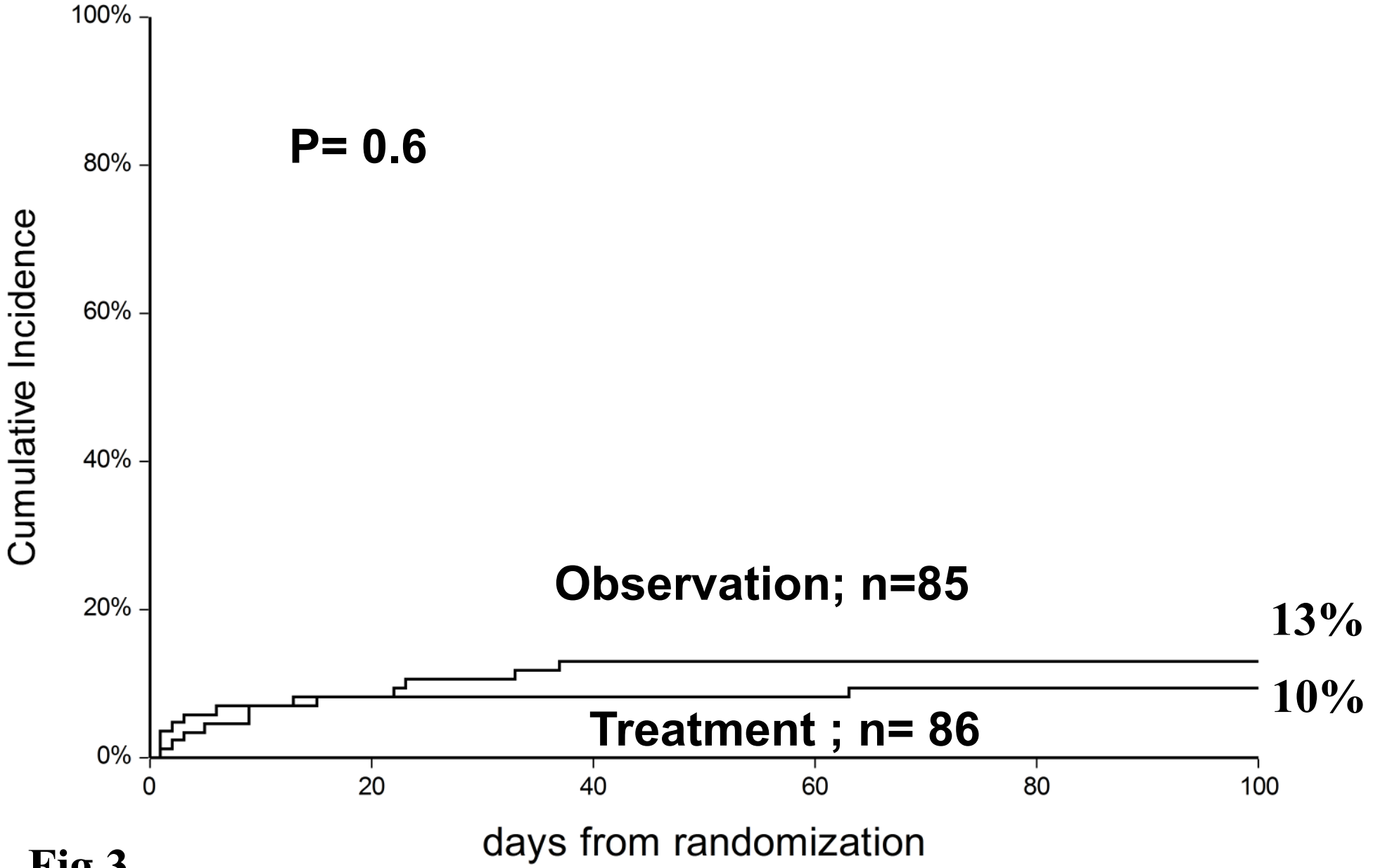


Fig.3

Conclusione 6:
Terapia molto precoce

NON modifica la storia naturale della malattia

PROBLEMA

VORREI CONOSCERE QUALI SONO I PAZIENTI A RISCHIO DI GHVD

E , QUALORA LA SVILUPPINO, QUALI SONO QUELLI A RISCHIO DI COMPLICAZIONI LETALI

Identificare i pazienti a rischio

 # prima del trapianto si’
 # giorno 0 si’
 # giorno +7 dal trapianto si’
 # alla diagnosi di GvHD si’
 # giorno +5 di terapia linea1 si’
 # durante terapia linea2 FORSE

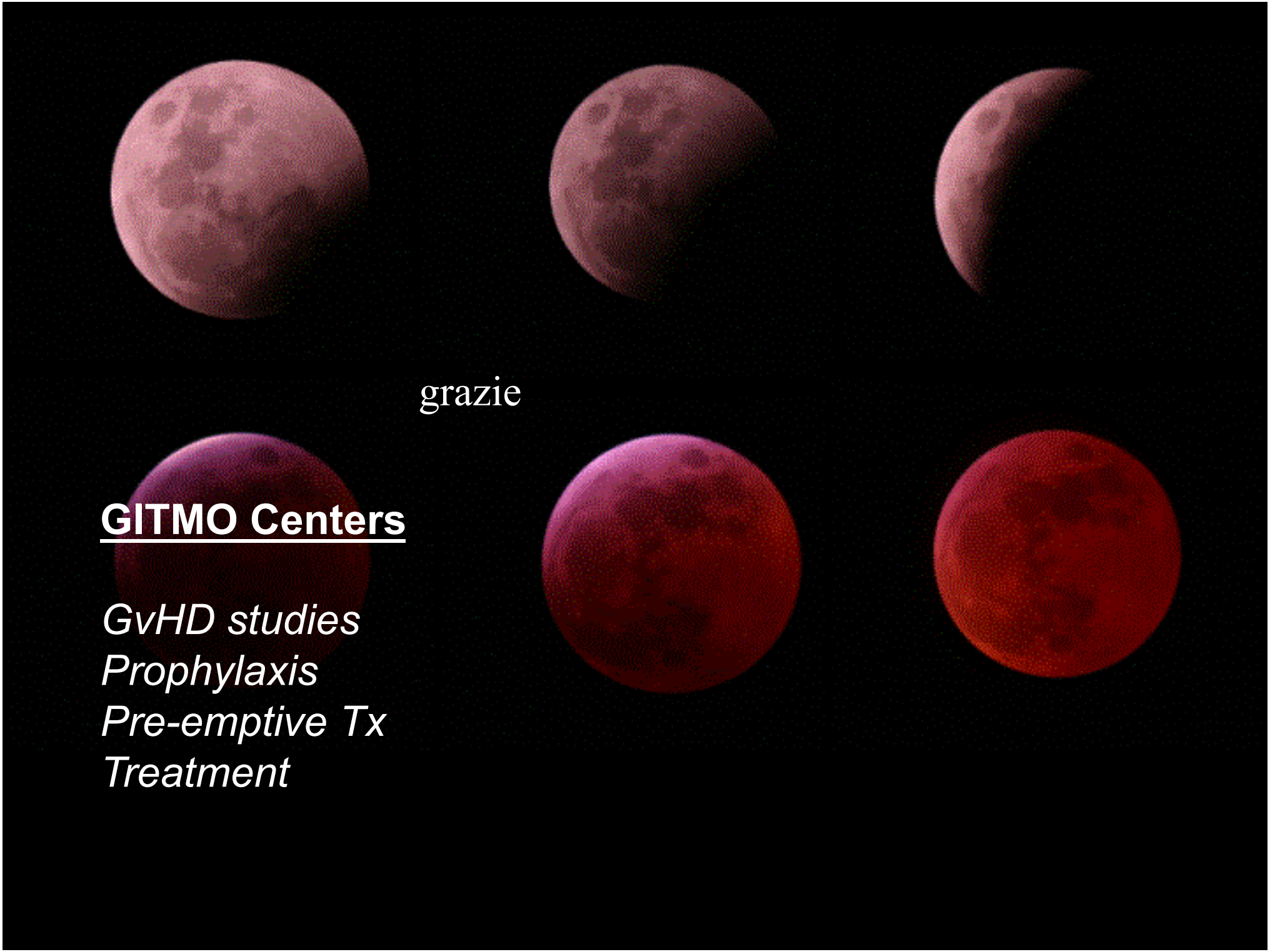
studio prospettico di terapia pre-emptive day+7: positivo

Pre-emptive day +7 : riduz GvHD III-IV

RAMP : steroidi alla diagnosi GvHD grado I, vs osservazione
= nessun effetto su GvHD III-IV

Profilassi / pre-emptive e' la risposta
Terapia ad oggi non modifica storia naturale della GvHD

Tutto quello che e' dopo il gg +7 serve?


grazie
GITMO Centers
GvHD studies
Prophylaxis
Pre-emptive Tx
Treatment