Ruolo dell' allotrapianto

nel mieloma

nell'era dei nuovi farmaci

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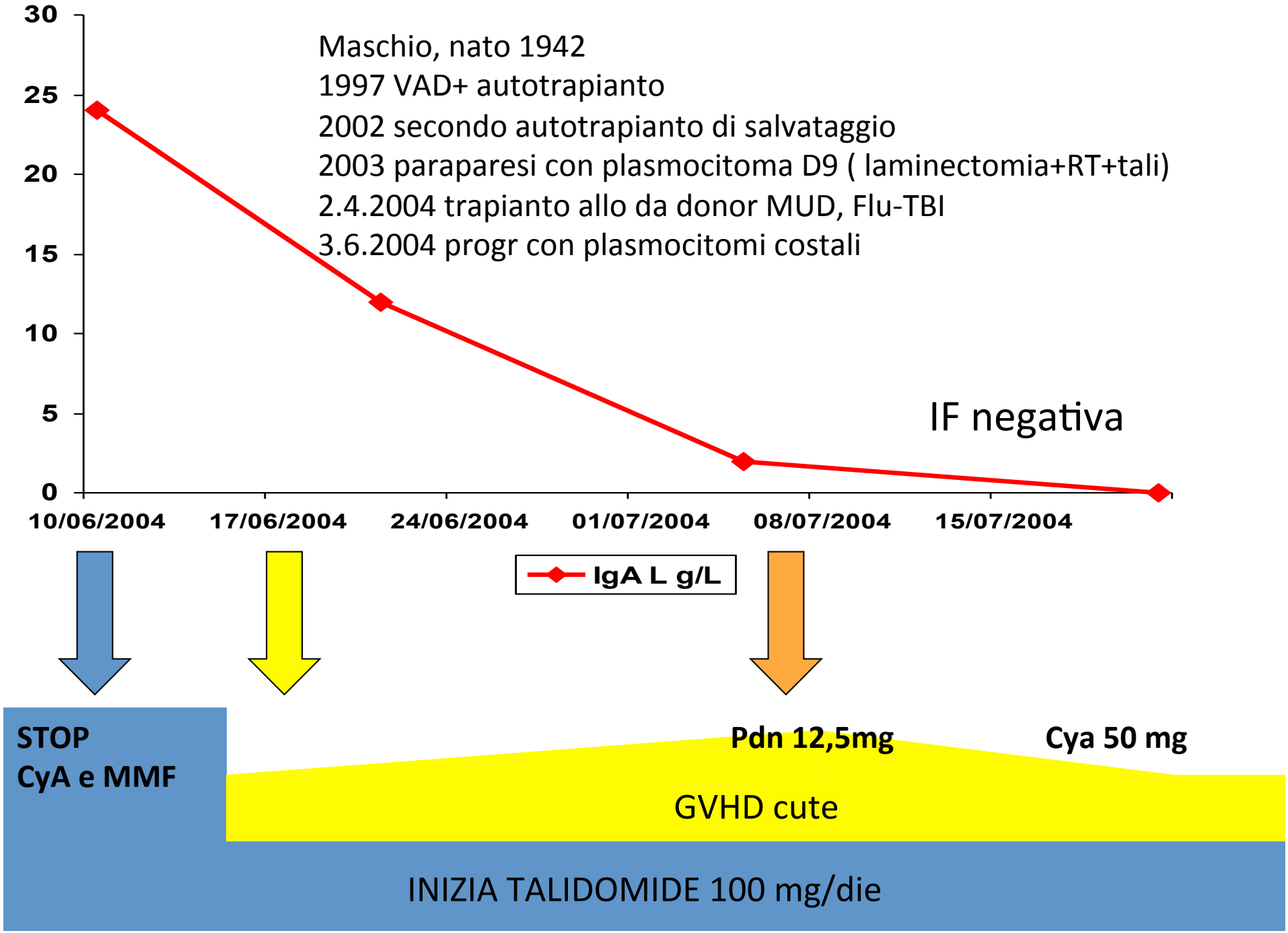
Outline

- **Evidenza graft-versus-myeloma**
- **Risultati degli studi nel MM alla diagnosi e alla ricaduta**
- **Attività EBMT**
- **Raccomandazioni degli esperti**
- **What's next?**

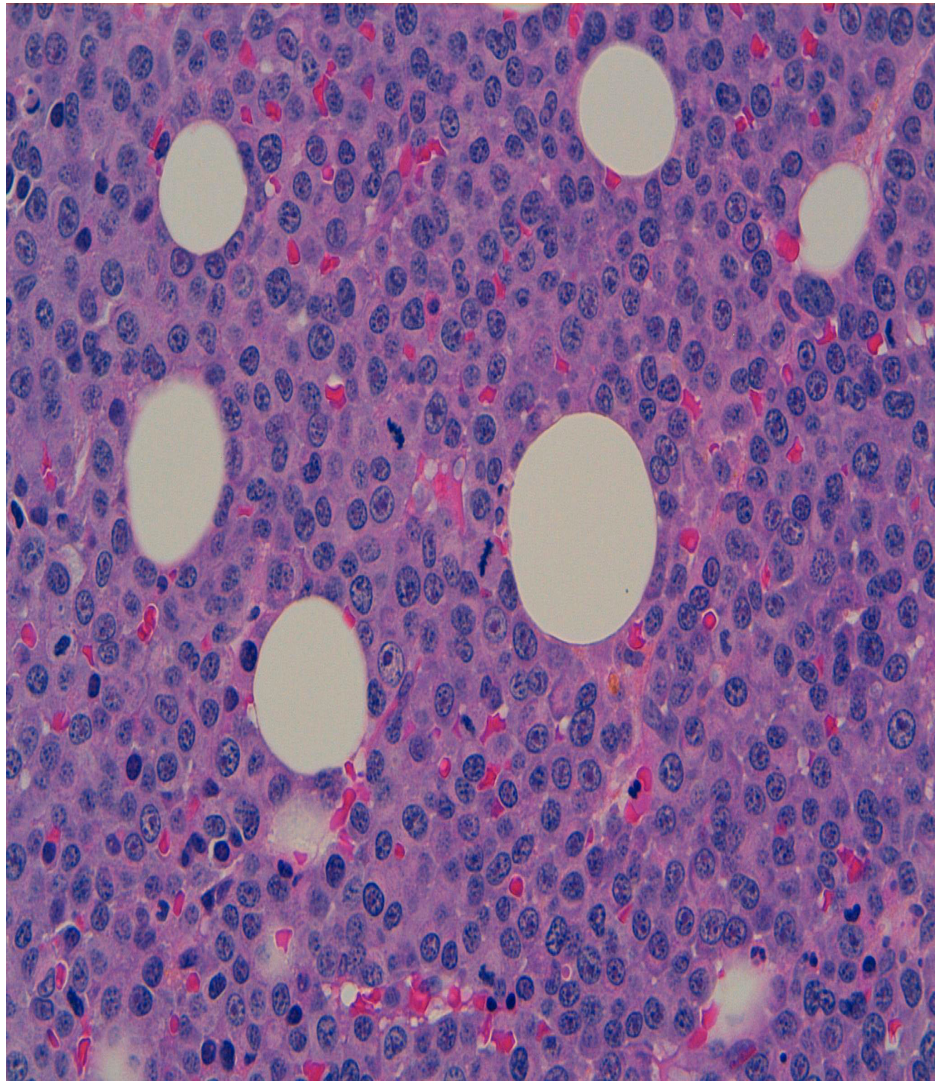
GRAFT-VERSUS-MYELOMA
historical evidences

- **Outcome comparison between autologous and allogeneic myeloablative transplant**
- **“long-term CR" after allogeneic transplant**
- **Higher quality of complete response after allogeneic transplant in comparison with autologous transplant**
- **Clinical activity of donor lymphocyte infusions or immusuppressant withdrawal in relapses after allo-SCT**

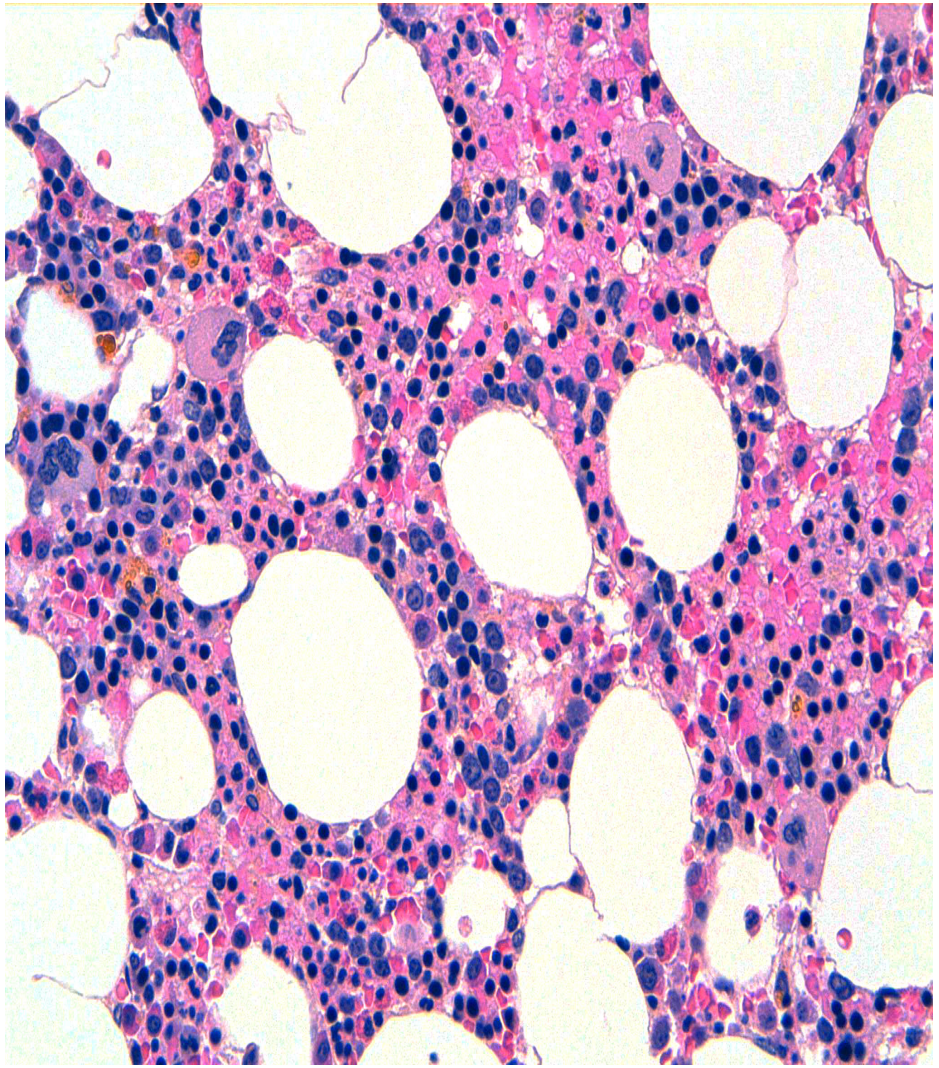

Maschio, nato 1942
1997 VAD+ autotrapianto
2002 secondo autotrapianto di salvataggio
2003 paraparesi con plasmocitoma D9 (laminectomia+RT+tali)
2.4.2004 trapianto allo da donor MUD, Flu-TBI
3.6.2004 progr con plasmocitomi costali
IF negativa
30
25
20
15
10
5
0
10/06/2004
17/06/2004
24/06/2004
01/07/2004
08/07/2004
15/07/2004
IgA L g/L
STOP
CyA e MMF
Pdn 12,5mg
Cya 50 mg
GVHD cute
INIZIA TALIDOMIDE 100 mg/die

Biopsia ostemidollari Em&Eos

3/6/2004,



16/9/2004,

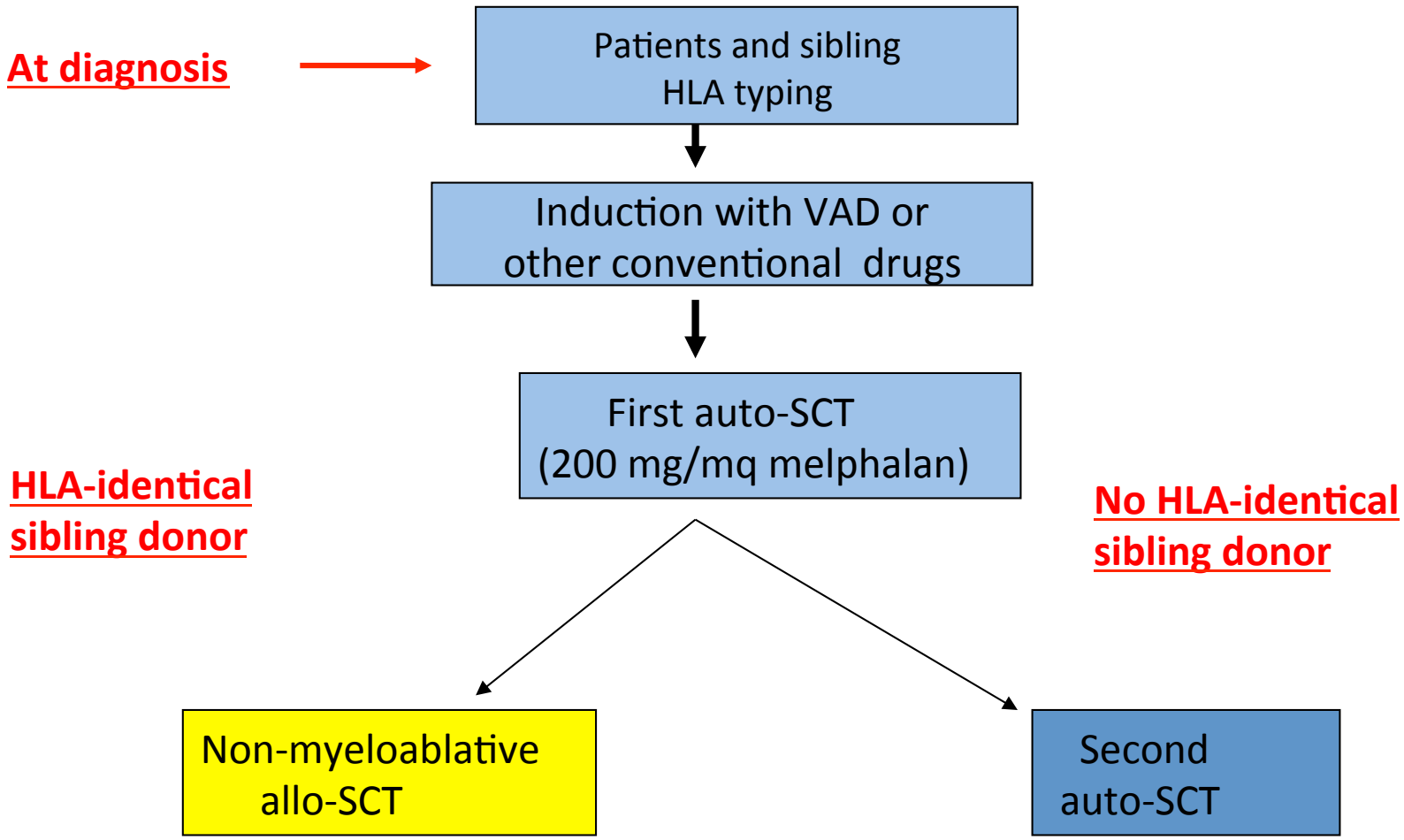


Vivo in RC a 13 anni dal trapianto con GVHD cronica cutanea di tipo lieve

TIMING OF ALLO-SCT IN MM

- **At diagnosis in newly diagnosed MM after auto-SCT**

- **At relapse**


At diagnosis
Patients and sibling
HLA typing
Induction with VAD or
other conventional drugs
First auto-SCT
(200 mg/mq melphalan)
HLA-identical
sibling donor
No HLA-identical
sibling donor
Non-myeloablative
allo-SCT
Second
auto-SCT

RANDOMIZED STUDIES OF AUTOLOGOUS PLUS MINI-ALLOGENEIC TRANSPLANT AT DIAGNOSIS
characteristics of the studies

Author	publication	Induction + ASCT	Conditioning before allogeneic SCT	N° pts with sibling donor HLA-id vs pts without donor	Criteria for selection
Garban-IFM	Blood 2006	VAD + mel 200	Bu 4, Flu 125, ATG-G 12,5	65 vs 219	Del 13 e ß 2>3
Bruno-GITMO	NEJM 2007	VAD + mel 200	TBI 2 Gy	80 vs 82	All patients
Bjorkstrand - EBMT	JCO 2011	VAD + mel 200	Flu 90 + TBI 2 Gy	108 vs 249	All patients
Rosinol-PETHEMA	Blood 2008	VBMCP-VBAD + mel 200	Flu 125 + melphalan 70 mg/ mq	25 vs 85	No CR o nCR after auto-SCT
Krishnam-CNT	Lancet Oncology 2011	Free induction + mel 200	TBI 2 Gy	226 vs 484	All patients

RANDOMIZED STUDIES OF AUTOLOGOUS PLUS MINI-ALLOGENEIC TRANSPLANT AT DIAGNOSIS

Clinical results

Autore-gruppo	N° pts with sibling donor HLA-id vs pts without donor	PFS	p	OS	p
Garban-IFM	65 vs 219	25 vs 30 (median, months)	NS	35 vs 41 (median, months)	NS
Bruno-GITMO	80 vs 82	2,8 vs 2,4 (median, years)	S	NR vs 4,2 (median, years)	S
Bjorkstrand - EBMT	108 vs 249	35% vs 18% (5-year PFS)	S	65% vs 68% (5-year PFS)	S
Rosinol-PETHEMA	25 vs 85	NR vs 31 (median, months)	NS	NR vs 58 (median, months)	NS
Krishnam-CNT	226 vs 484	43% vs 46% (3-year PFS)	NS	55% vs 58% (3-year PFS)	NS

AUTOLOGOUS PLUS NMI-ALLOGENEIC TRANSPLANT AT DIAGNOSIS

- **Feasible procedure with 1- year NRM 10-12%, but survival advantage only in 2 out 5 studies**
- **Reduction of quality of life due to chronic GvHD studies**

- **However, results from available studies are little informative for now-days clinical practice because:**

- **Unclear effect in pts with high-risk MM**
- **Studies without novel agents farmaci**

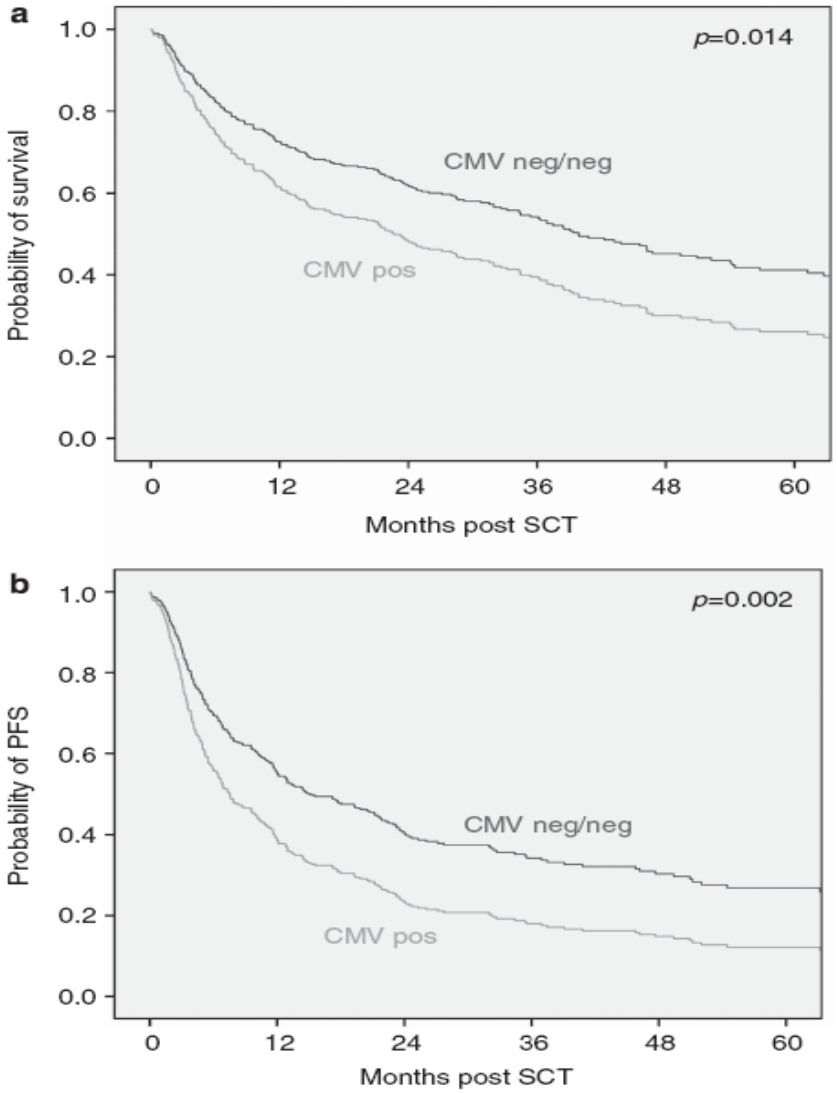
ALLO-SCT for relapsed MM

	Crawley, 2005-EBMT retrospective	Osman 2010	Kroger, 2010-EBMT prospective	Efebera, 2010	Auner, 2013-EBMT retrospective
N° pts	229 (168 relapsed)	20	49	51	413
Median age	52 (32-66)	52 (37-68)	50 (34-64)	51 (32-65)	54 (27-69)
Conditioning	Flu-TBI or Flu-chemo	Flu-TBI	Flu-melphalan	Flu-melphalan	Flu-TBI or Flu-alkylators
Donor: rel/unrel	192/37	14/6	0/49	40/11	237/172
NRM at 1 y	22%	25%	25%	25%	21%
Relapse at 2 y	41%	35%	55%	49%	/
PFS	21% (3y)	24% (3y)	20% (5y)	19% (2y)	Median 9,6 mo
OS	41% (3y)	24% (3y)	26% (5y)	32% (2y)	Median 24,7 mo

EBMT retrospective study

Table 4. Multivariate analysis of transplant-related outcomes

Variable	n	*RR*	*95% CI*	P-*value*
OS				
CMV serostatus				
Negative/negative	95	1		
Positive	271	1.51	(1.09–2.11)	**0.014**
Previous auto-SCTs				
1	199	1		
2–4	167	1.31	(1.01–1.71)	**0.047**
Age at RIC allo-SCT				
<54.1 Years	183	1		
⩾54.1 Years	183	1.3	(0.99–1.69)	0.053
PFS				
CMV serostatus				
Negative/negative	95	1		
Positive	268	1.59	(1.19–2.14)	**0.002**
Recipient/donor gender				
Male/male	142	1		
Male/female	95	0.63	(0.46–0.85)	**0.003**
Female/male	64	0.58	(0.40–0.83)	**0.003**
Female/female	62	0.75	(0.53–1.05)	0.09
NRM				
CMV serostatus				
Negative/negative	95	1		
Positive	271	1.79	(1.07–2.97)	**0.025**
Time first auto to RIC allo-SCT				
<2.6 Years	181	1		
⩾2.6 Years	185	2.08	(1.39–3.1)	<**0.001**



Auner HW , Bone Marrow Transplantation 2013

ALLO-SCT for relapsed MM

- Higher NRM that could be managed by donor choice

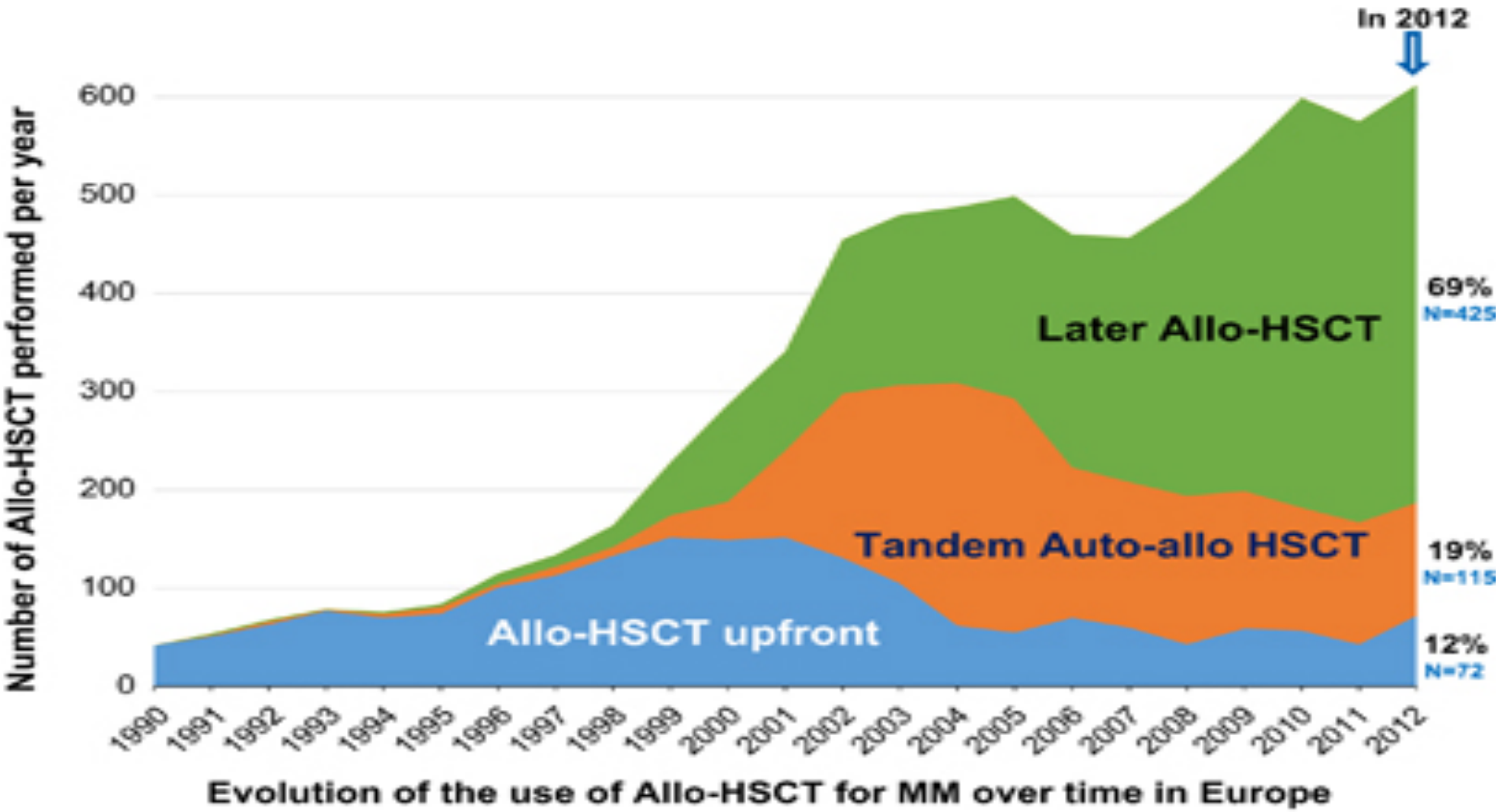
- Higher incidence of relapse (the most important issue)

- However, results from available studies are little informative for now-days clinical practice because:

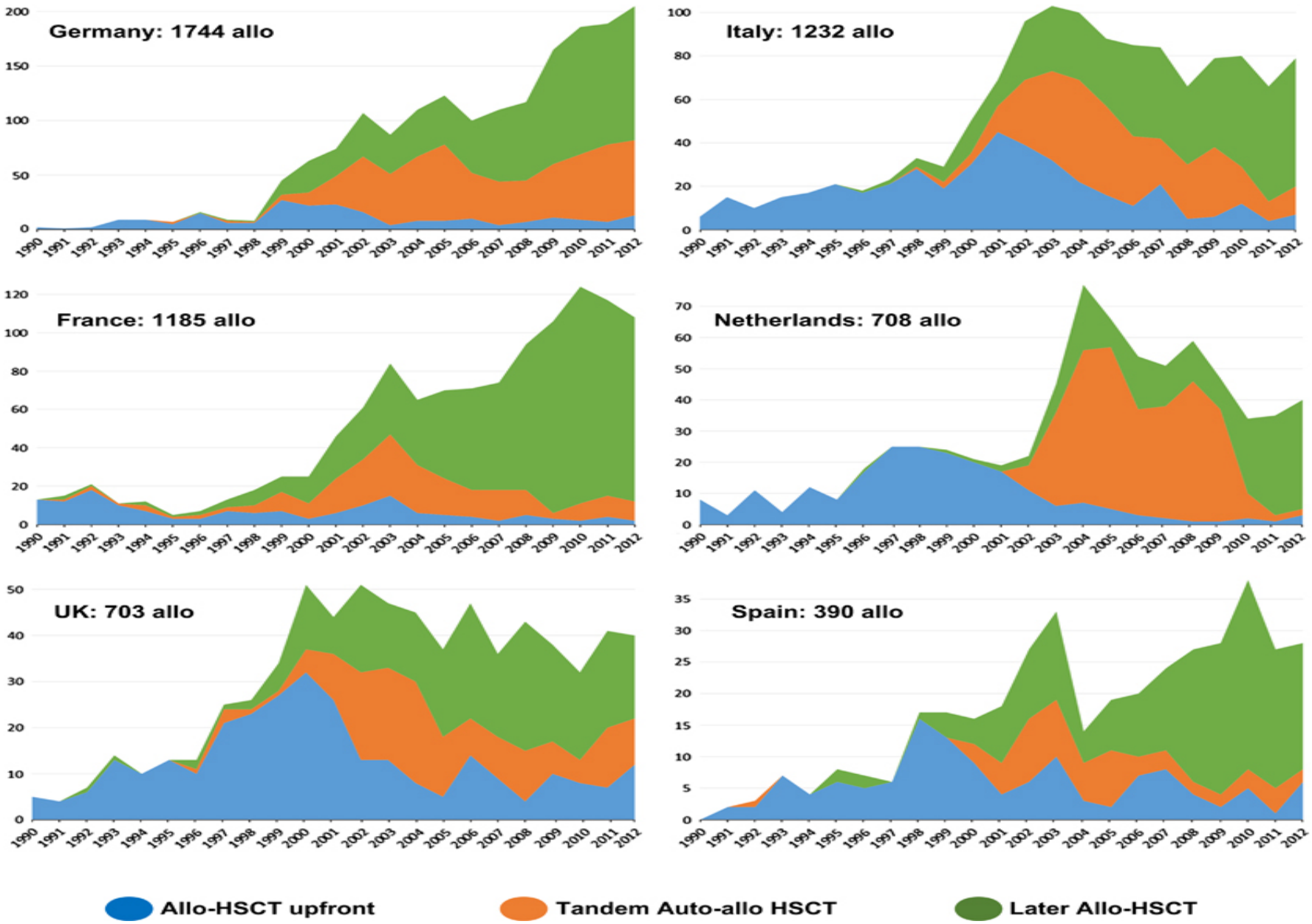
-Retrospectives studies with heterogeuos populations including haevily pretreated patients

-no informations about integration with immunomodulatory agents (Imids and bortezomib)

Activity in the EBMT registry



Sobh M et al, Leukemia 2016



Sobh M et al, Lekemia 2016

Recommendations for newly diagnosed pts

Table 3. Risk stratification and possible therapeutic questions within each risk categories

	High-risk	*Standard-risk*	*Low-risk*
Parameters	ISS II/III and t(4;14)[a] or 17p13 del	Others	ISS I/II and absence of t(4;14), 17p13 del and +1q21 and age <55 years
Median OS	2 years	7 years	>10 years
% Patients	20%	60%	20%
Therapeutic questions	There is a need for novel therapeutic approaches e.g. Allogeneic stem cell transplant or immune therapy approaches		Do these patients benefit from maintenance therapy? Is VGPR a good enough response in these patients, as they may revert to an MGUS state

Abbreviations: ISS, International staging system; MGUS, monoclonal gammopathy of undetermined significance; OS, overall survivalVGPR, very good partial response. [a]Survival of t(4;14) patients is improved with the use of velcade-based therapy.

WJ Chng on behalf of IMWG, Leukemia 2014

ULTRA HIGH-RISK MM
(expected median OS < 2 years)

•presence of two or more adverse cytogenetic features

• one cytogenetic adverse feature plus either
- high LDH or
- ISS 3 or
- less then CR after induction or failure to eradicate residual disease after ASCT

• high number of circulating plasma cells

• less then PR after an optimized induction therapy

Usmani et al, Leukemia 2015

Recommendations for relapsed pts

Allogeneic HCT should be considered appropriate therapy for any eligible patient with early relapse (less than 24 months) after primary therapy that included an autologous HCT or with high-risk features (ie, cytogenetics, extramedullary disease, plasma cell leukemia, or high lactate dehydrogenase) provided that they responded favorably to salvage therapy before allogeneic HCT.

Giralt et al, ASBMT-EBMT-IMW consensus, BBMT 2015

Relapse and allogeneic transplantation

- We recommend consideration of an Allo-SCT largely in the context of clinical trials, particularly focusing on high-risk patients.
- Considering lack of consistent data indicating superiority of Allo-SCT over tandem auto SCT and concerns for treatment-related mortality despite RIC as well as rates of graft-versus-host disease in studies so far, consideration of an Allo-SCT within or outside a clinical trial should be with appropriate informed consent of the patient outlining the risks of treatment-related mortality and graft-versus-host disease.

Laubach J et al, IMW recommendations, Leukemia 2016

What's next?

- **Integrazione di allo-SCT e nuovi farmaci**
- **Identificazione di categorie ad alto rischio che potrebbero beneficiare di allo-SCT upfront**
- **Allo-SCT in prima recidiva ad alto rischio**

LENALIDOMIDE AFTER ALLO-SCT

Author	Trial type Purpose	N° pts	Lena daily dose	Days SCT-lena	OR (CR)	Acute GVHD	Discontinuation
Kneppers 2011	Phase II maintenance	30	10 mg	84	83% (33%)	37%	47%
Wolschlke 2013	Phase I/II maintenance	24	5 mg (MTD)	135	79% (43%)	38%	29%
Alsina 2014	Phase II maintenance	30	10 mg	96	/	27%	37%
El-Cheikh 2012	Retrospective, consolidation	12	15 + DLI	180	75% (33%)	8%	16%
Coman 2013	Retrospective, salvage	52	25 + dexa	720	83% (29%)	31%	Grade 3-4 tox 47%

Biol Blood Marrow Transplant 19 (2013) 424–428

Bortezomib Plus Dexamethasone Followed by Escalating Donor Lymphocyte Infusions for Patients with Multiple Myeloma Relapsing or Progressing after Allogeneic Stem Cell Transplantation

Vittorio Montefusco [1,*], Francesco Spina [1], Francesca Patriarca [2], Massimo Offidani [3], Benedetto Bruno [4], Mauro Montanari [3], Alberto Mussetti [1], Alessandra Sperotto [2], Ilaria Scortechini [3], Anna Dodero [1], Renato Fanin [2], Pinuccia Valagussa [5], Paolo Corradini [1,6]

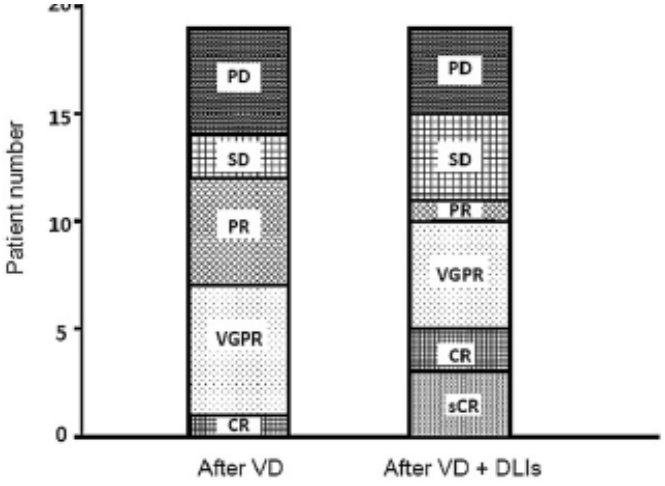


Figure 1. Upgrade of response between VD and DLI phases.

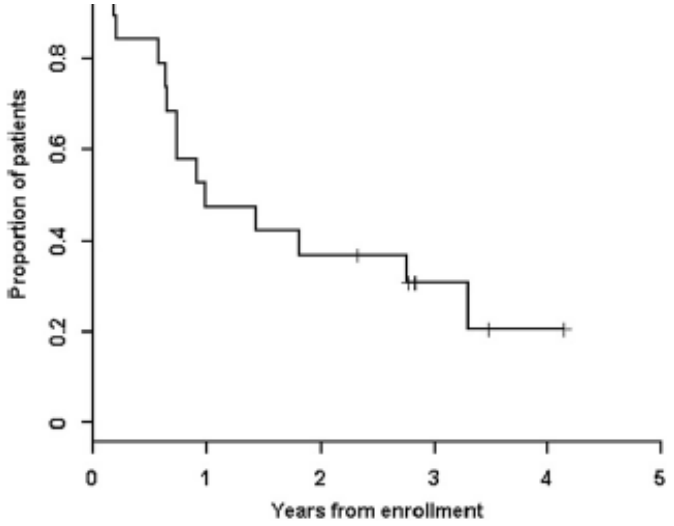


Figure 2. Progression-free survival curve.

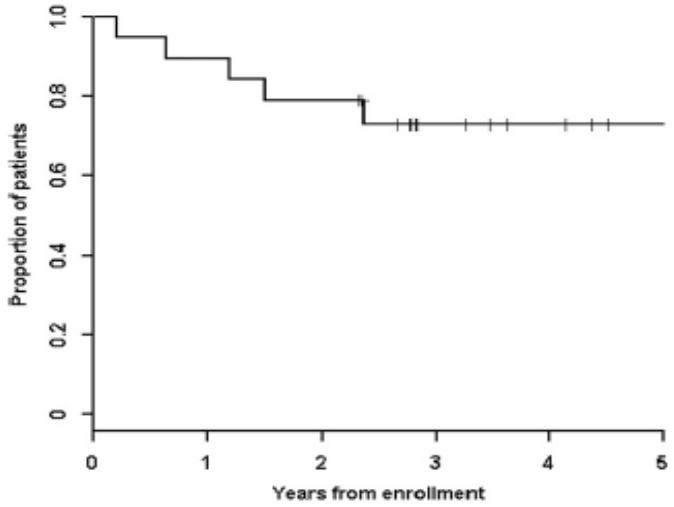


Figure 3. Overall survival curve.

Grade 3-4 toxicities:
1 pt thrombocytopenia
2 pts polineuropathy
1 pt astenia
1 pt infection
GVHD:
2 pts grade I-II acute GVHD
3 pts limited chronic GVHD

Imids and PI after allo-SCT

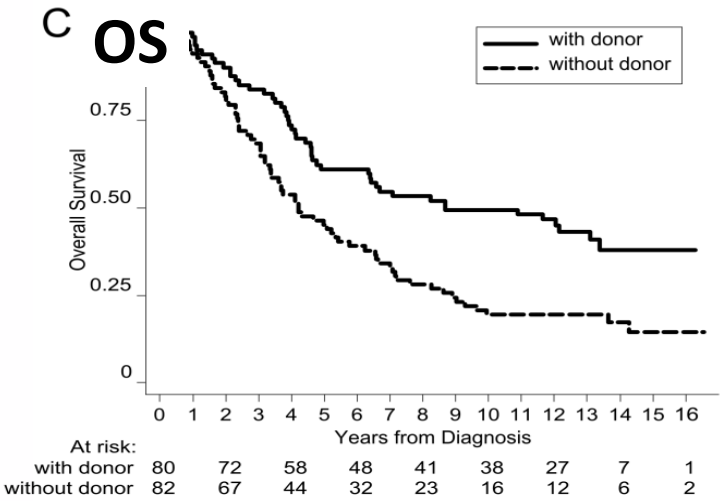
Lenalidomide

- May increase GVHD
- Clinical activity
- Low doses (5-10 mg/d) are suggested
- Start treatment after day +180

Bortezomib

- No increase of GVHD
- Clinical activity
- Use in combination with DLI

Long-term follow-up of Italian auto-allo approach in newly diagnosed MM
Overall Survival



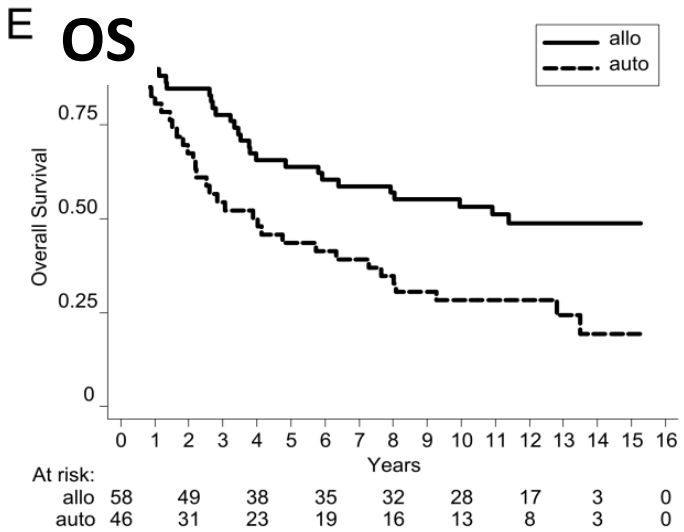
Intention to treat

median 8.7 years

median 4.2 years

p<0.001

Median follow-up 12.2 years



Protocol completed

median 11.4 years

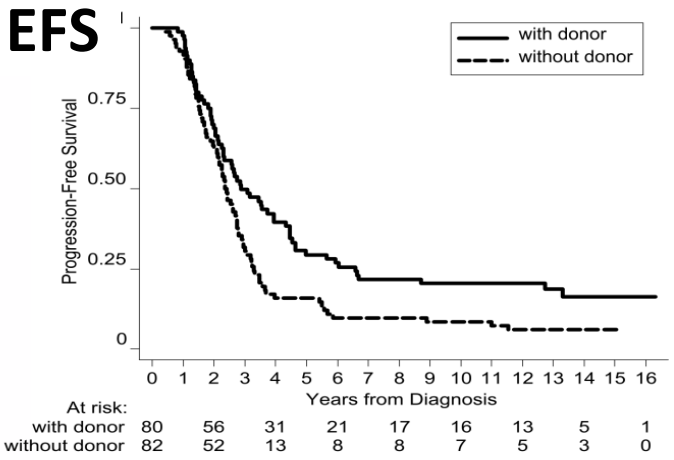
median 3.9 years

p=0.007

L.Giaccone, IMW 2017

Event-free Survival (follow-up 12.2 years)

Intention to treat

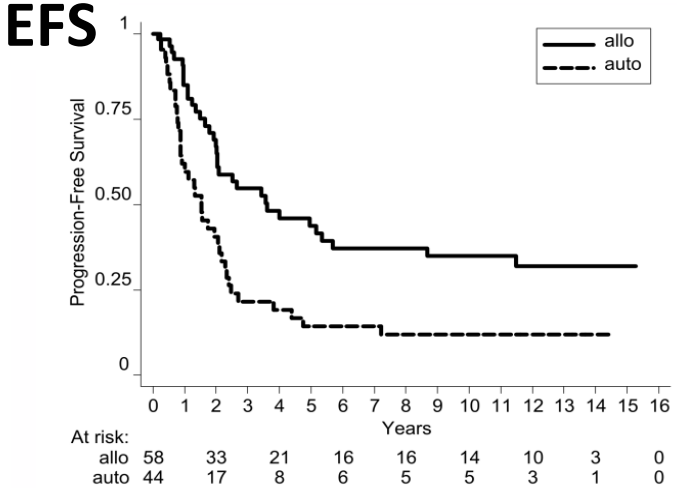


median 2.9 years

median 2.4 years

p=0.005

Protocol completed



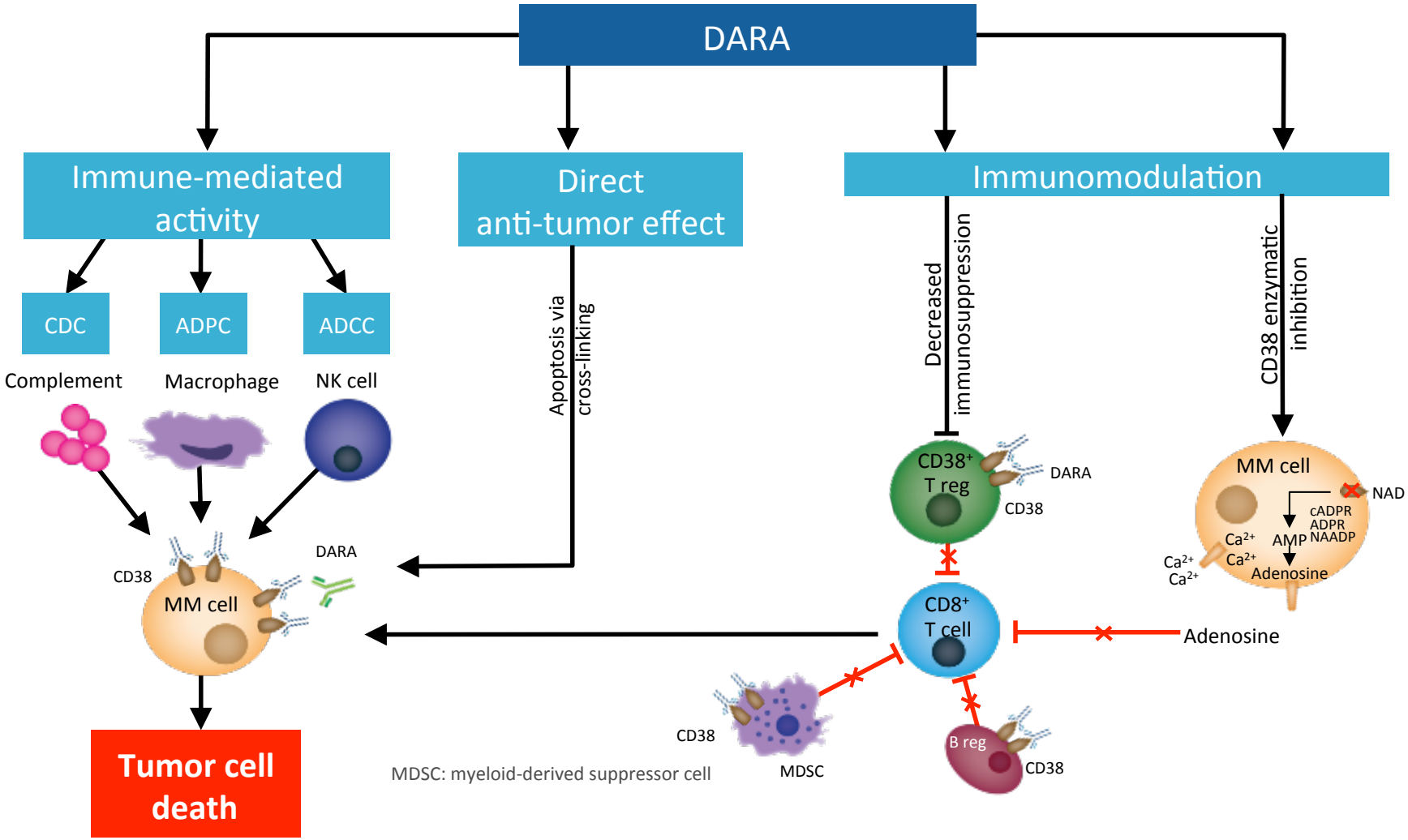
median 3.6 years

median 1.5 years

p<0.001

L.Giaccone, IMW 2017

Daratumumab: Mechanisms of Actions



T-127. Incidence and timing of graft versus host disease (GVHD) after daratumumab (Dara) anti-CD38 therapy post allogeneic transplant (alloHCT) for myeloma

RESULTS

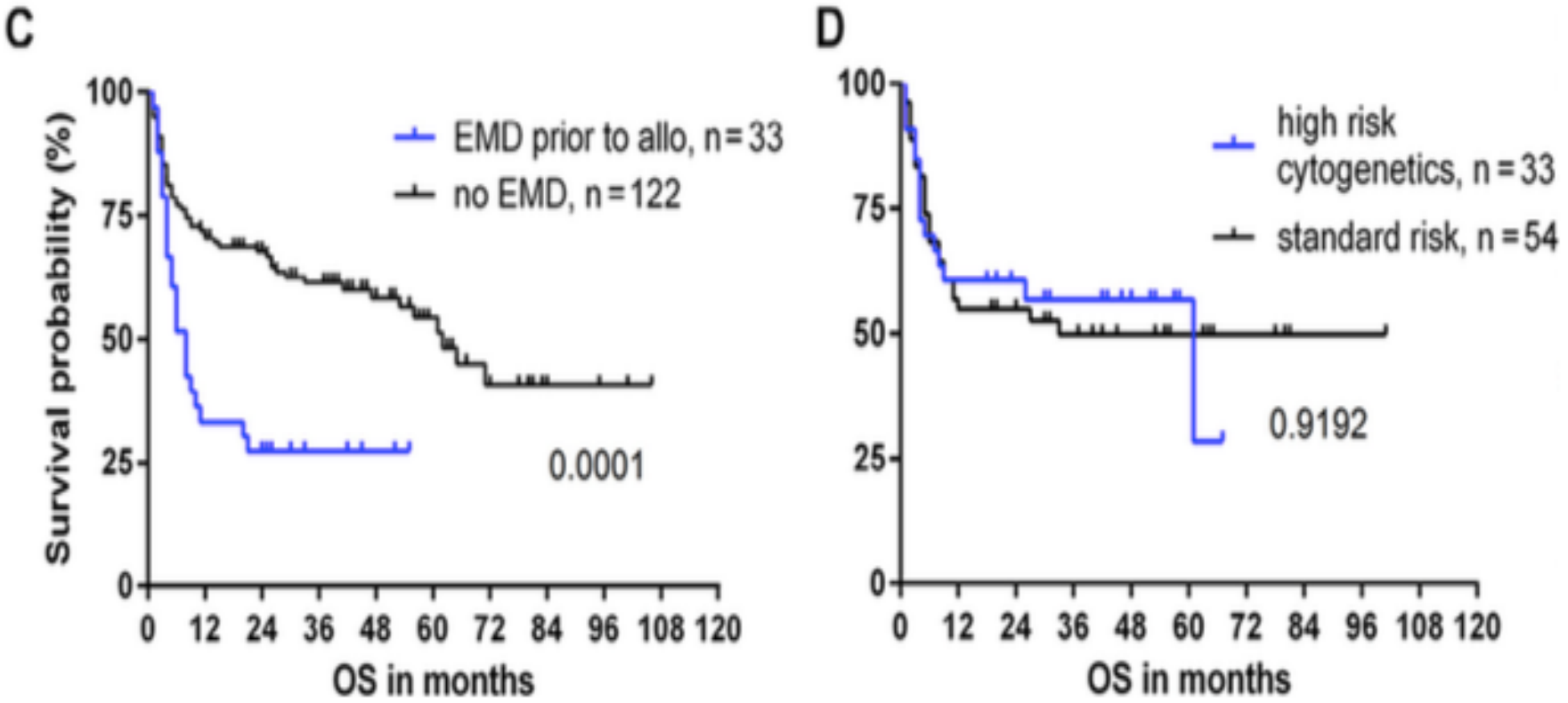
Variable (All: N=23)	Median (Range)or N (%)
Median follow up for surviving patients (months)	38.7
Time from alloHCT to first dose of Dara (years)	2.1 (0.25 – 15)
Number of Dara infusions	12 (1 – 19)
Patients developing GVHD after Dara	5 (22) 1 acute 4 chronic
Time to onset of GVHD from first dose of Dara (days)	207
Post-alloHCT regimen among patients with GVHD (N=5)	2 Dara alone 2 Dara + POM 1 Dara + LEN + BOR
Response to Dara CR VGPR PR MR SD PD	 1 (4) 1 (4) 6 (26) 2 (9) 8 (35) 3 (13)

Krishan et al, IMW 2017

What's next?

- Integrazione di allo-SCT e nuovi farmaci
- **Identificazione di categorie ad alto rischio che potrebbero beneficiare di allo-SCT upfront**
- Allo-SCT in prima recidiva ad alto rischio

Allo-SCT overcomes unfavourable cytogenetics



Rasche et al, BBMT 2016

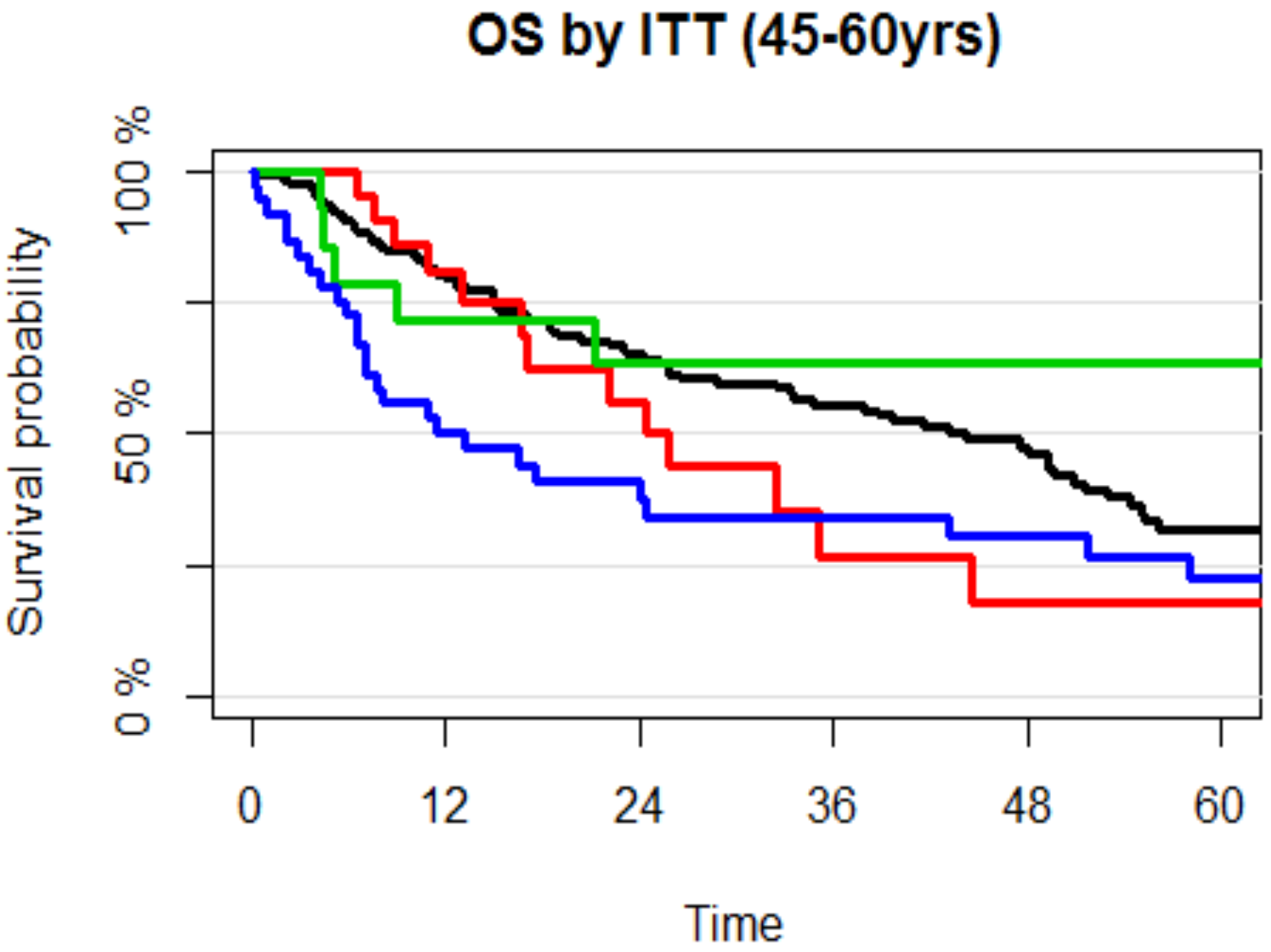
Outcome of 460 primary plasmacell leukemia pts between 1998-2012

Black
Single
Auto

Red
Double
Auto

Green
Auto-
Allo

Blue Allo
upfront



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- **Allo-SCT in prima recidiva ad alto rischio**

Allo-SCT AT FIRST RELAPSE

Allogeneic Stem Cell Transplantation in Multiple Myeloma Relapsed after Autograft: A Multicenter Retrospective Study Based on Donor Availability

Francesca Patriarca,[1] Hermann Einsele,[2] Francesco Spina,[3] Benedetto Bruno,[4] Miriam Isola,[5] Chiara Nozzoli,[6] Andrea Nozza,[7] Alessandra Sperotto,[1] Fortunato Morabito,[8] Gernot Stuhler,[2] Moreno Festuccia,[4] Alberto Bosi,[6] Renato Fanin,[1] Paolo Corradini[9]

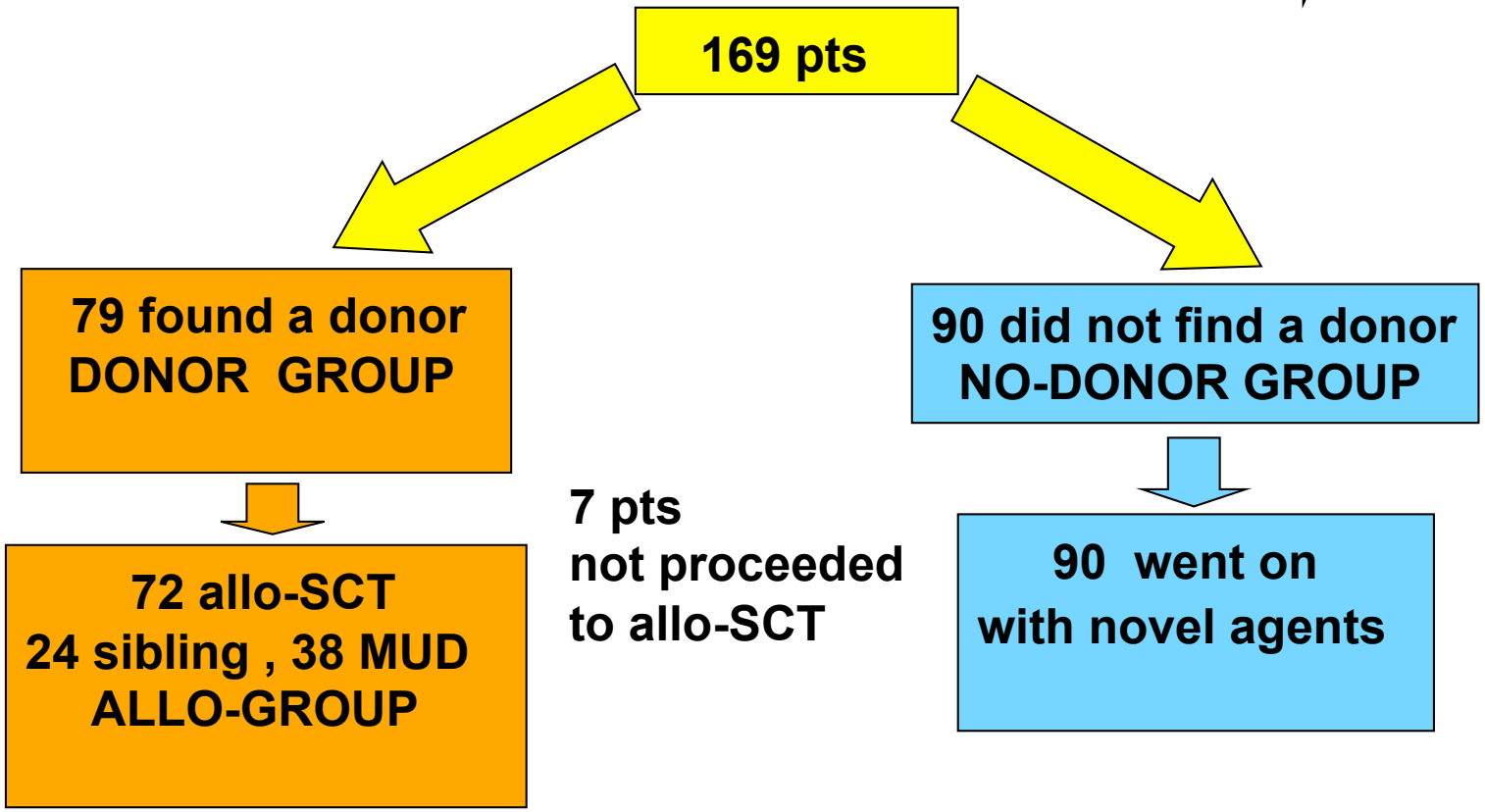
Biol Blood Marrow Transplant 18: 617-626 (2012)

RATIONAL FOR STUDY UP-DATE

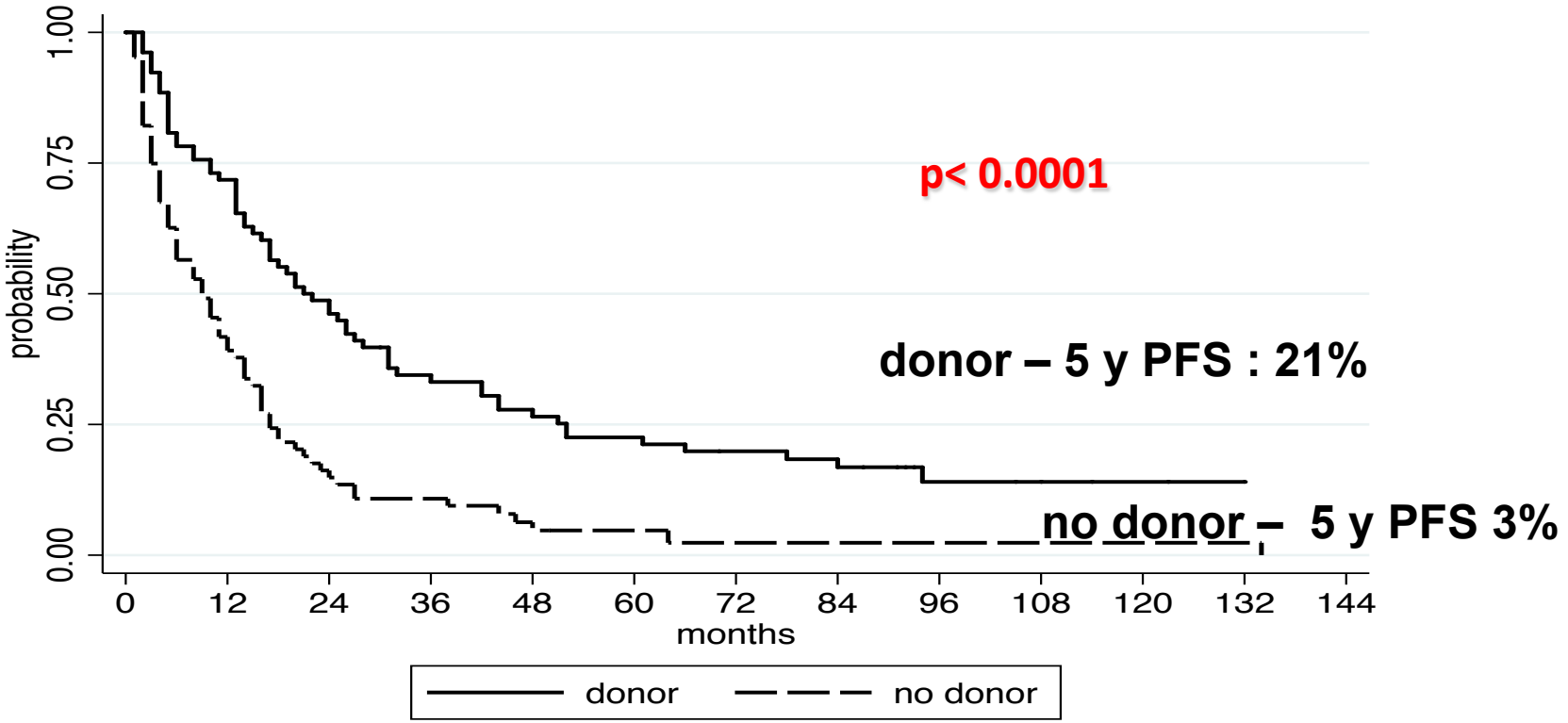
- There is still room for allo-SCT in high-risk MM patients.

- Follow up longer than 5 years is necessary for correct interpretation of the value of auto/RICallo in MM (Gahrton G, Blood 2013)

- Close-out date analysis BBMT study December 2010 ➡ February 2015

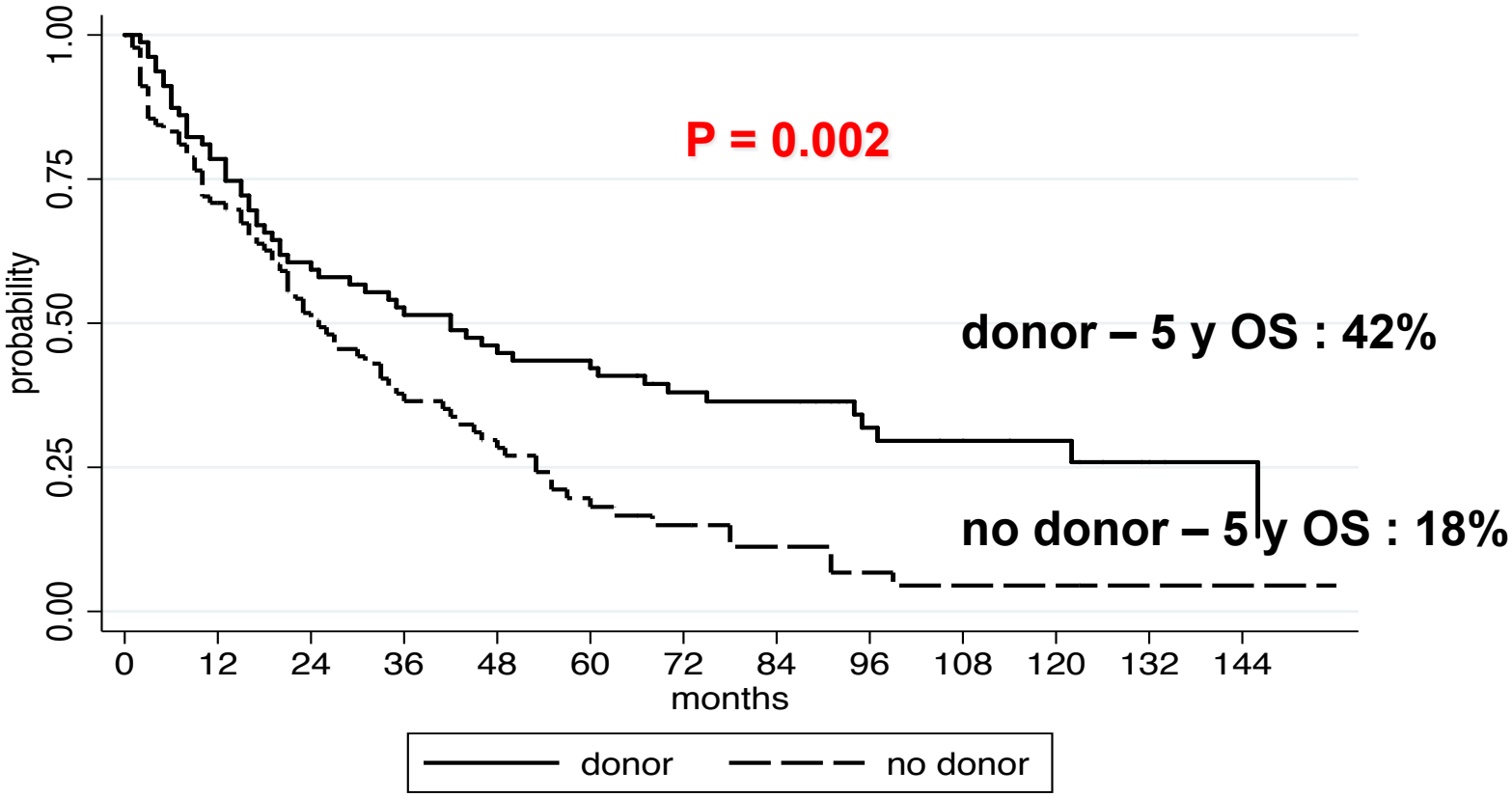


COMPARISON OF PROGRESSION-FREE-SURVIVAL BETWEEN DONOR AND NO-DONOR GROUP



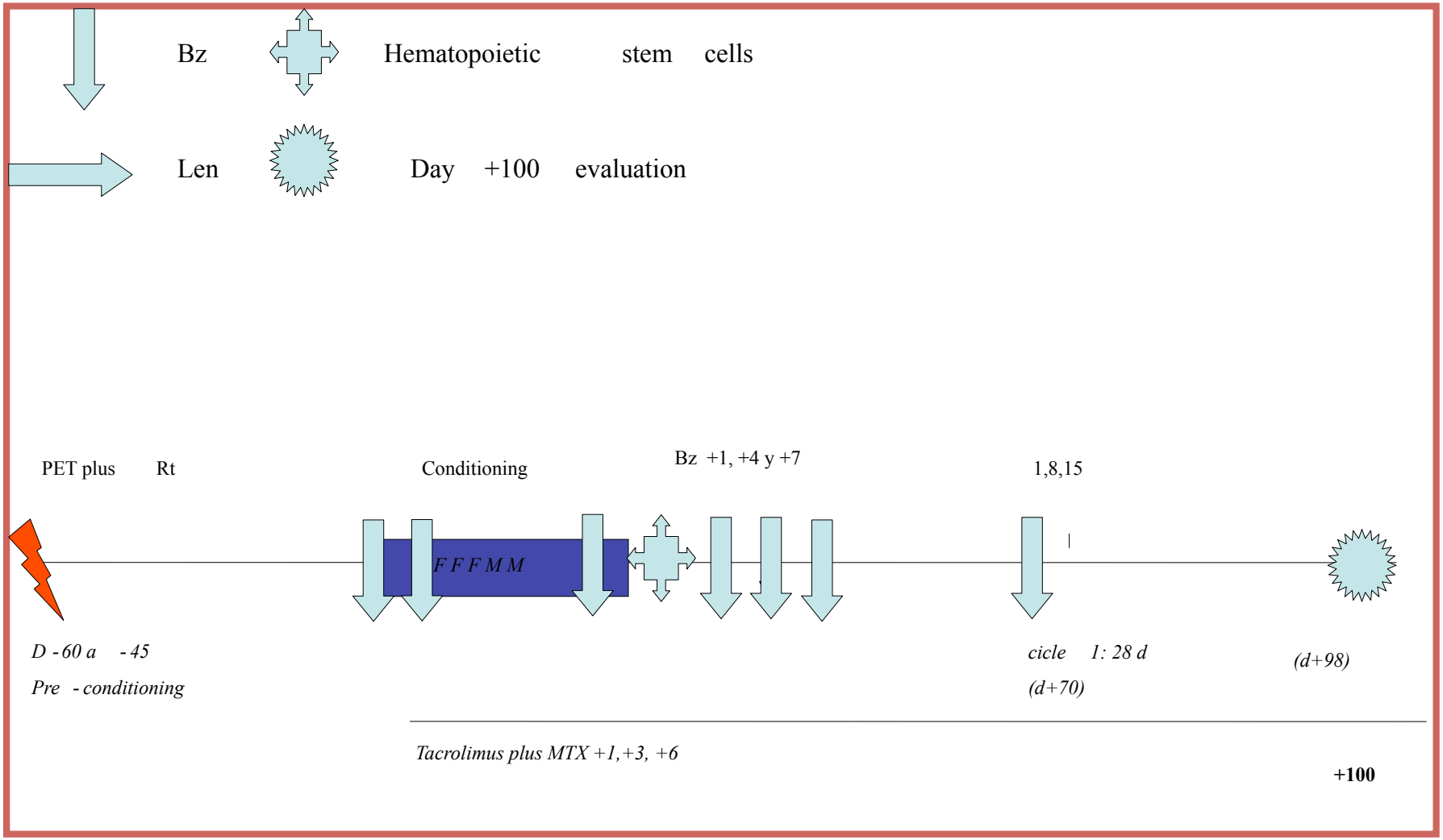
Median follow-up of patients: 87 months (11-156)

COMPARISON OF OVERALL SURVIVAL BETWEEN DONOR AND NO-DONOR GROUP



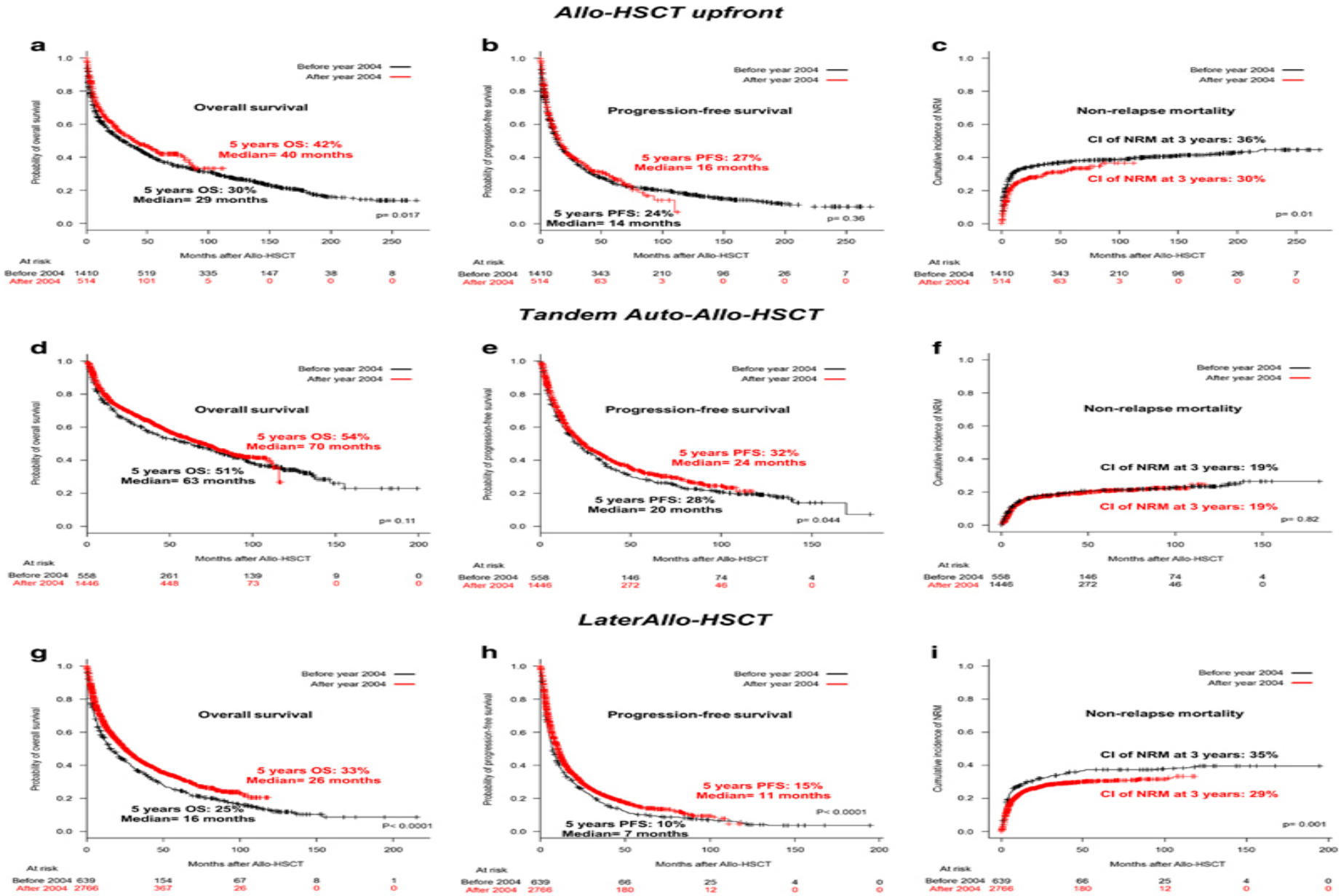
EMN-allo-RIC trial per mieloma in prima ricaduta ad alto rischio chemioresponsivo. PI: Perez-Simon (Spain)

Ricaduta ad alto rischio: < 24 mesi da un trapianto autologo, e/o senza aver mai ottenuto RC e/o con cariotipo sfavorevole



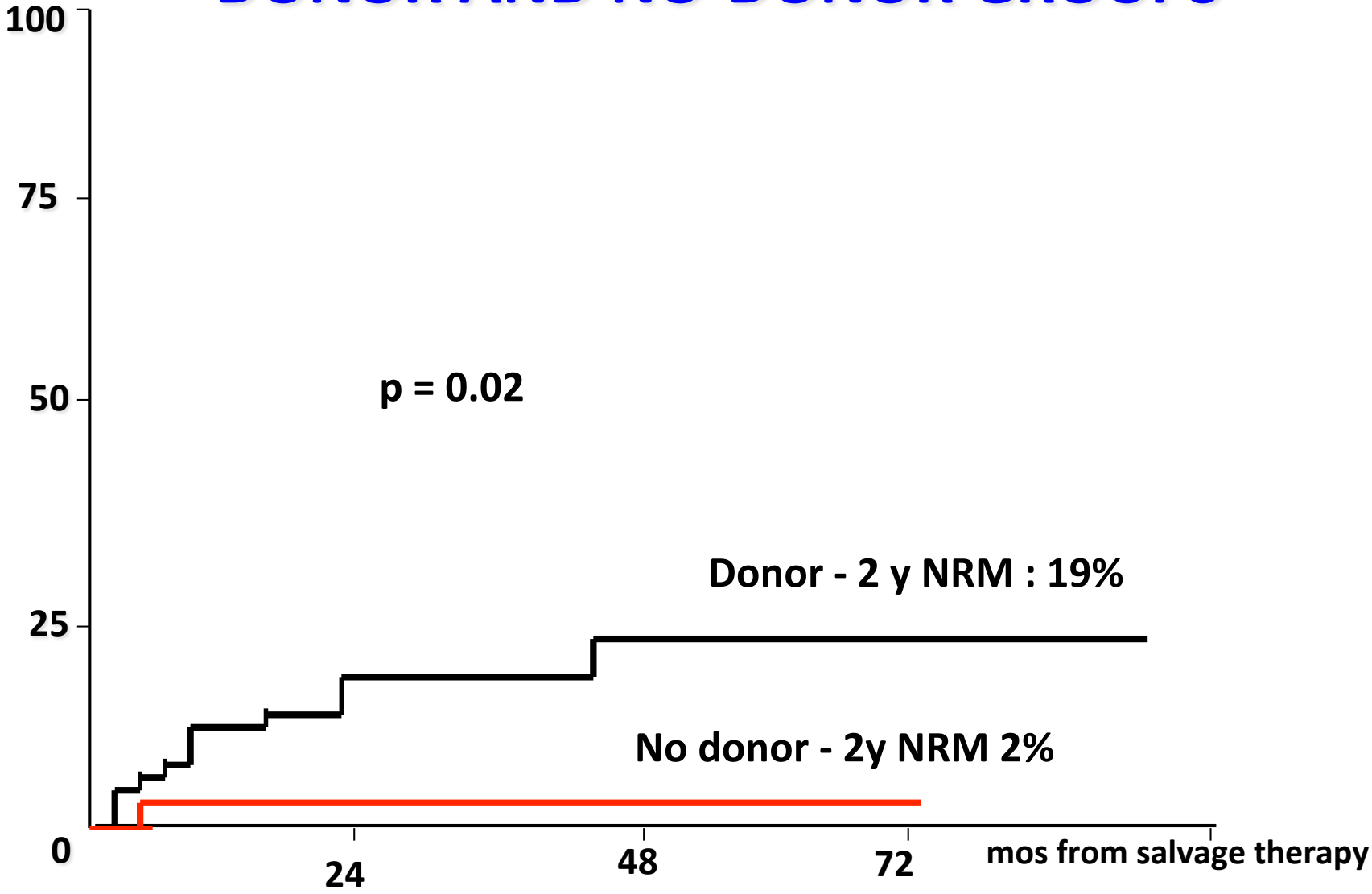
Conclusions

- **Integrazione di allo-SCT e nuovi farmaci : inibitori PI, Imids, Mo Ab anti CD38+**
- **Identificazione di categorie ad alto rischio che potrebbero beneficiare di allo-SCT upfront: leucemia plasmacellulare, FISH con delezione cromosoma 17**
- **Identificazione di categorie che potrebbero beneficiare di allo-SCT in ricaduta: prima recidiva ad alto rischio**



Sobh M et al, Leukemia 2016

NON-RELAPSE-MORTALITY OF THE DONOR AND NO-DONOR GROUPS



Donor group: 1 pt acute GVHD , 3 pts chronic GVHD, 4 pts infection

No-donor group: 1 pt second cancer

T-127. Incidence and timing of graft versus host disease (GVHD) after daratumumab (Dara) anti-CD38 therapy post allogeneic transplant (alloHCT) for myeloma

PATIENT CHARACTERISTICS

Variable (All: N=23)	Median (Range) or N (%)
Age at diagnosis (y)	48 (33-55)
Female/male	10 (43)/13 (57)
Race	
Caucasian	11 (58)
Hispanic	5 (26)
Asian	2 (11)
African American	1 (5)
Missing	4
Number of therapies pre-alloHCT	2 (1 - 9)
Conditioning regimen	
Cy/TBI	1 (4)
Flu/Cy	1 (4)
Flu/Cy/TBI	3 (13)
Flu/Mel	5 (22)
Flu/Mel/ATG	2 (9)
Flu/Mel/Bort	2 (9)
Flu/Mel/Bort +/- ATG	6 (26)
Flu/Mel/TBI	1 (4)
TBI	2 (9)
GVHD prophylaxis	
MMF/Cy	3 (13)
Tacro/MMF/Cy	4 (17)
Tacro/MTX	15 (65)
Tacro/Siro	1 (4)

Krishan et al, IMW 2017