

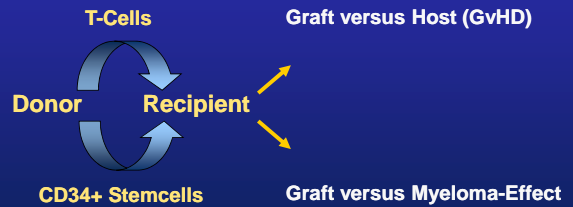


Universitätsklinikum  
Hamburg-Eppendorf

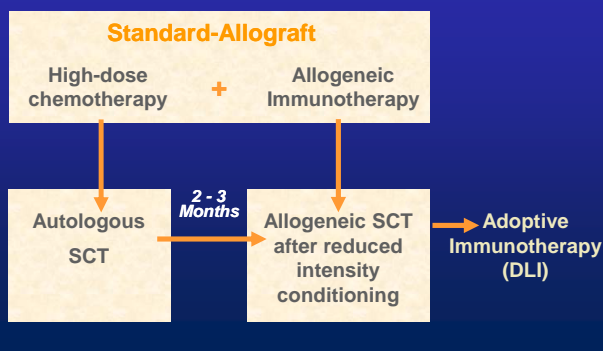
## Novel Agents and Allogeneic Stem Cell Transplantation in Multiple Myeloma

Nicolaus Kröger  
Dept. of Stem Cell Transplantation, University Hospital Hamburg  
Hamburg, Germany

## Allogeneic Stem Cell Transplantation



## Reduction of treatment related mortality from allogeneic SCT



## Rate of Complete Remission

Double HD-therapy		Auto-allo Tandem	
IFM 94	50%	Kröger	55%
MAG95	37%	Maloney	52%
Bologna	43%	Bruno	53%
Hovon	28%	Carella	62%
		Seok	83%
		Rotta	63%

## Rate of molecular remission based on rearranged immunoglobulin heavy chain genes

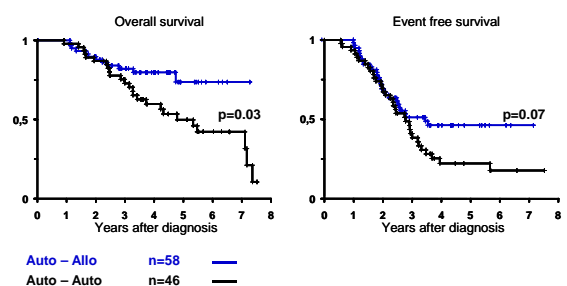
In CR: after allograft: 50% molecular CR  
after autograft: 7% molecular CR

*Corradini et al., JCO 1999*

In CR: after allograft: 50% molecular CR  
after autograft: 16% molecular CR

*Martinelli et al., JCO 2000*

## Outcome according to completed treatment (n=104) CR: 55% vs 26% p= 0.004



*Bruno et al., NEJM 2007*

## Improving Outcome with Novel Agents

### Aims

1. Increasing the numbers of CR
2. Improving depths of complete remission

## Improving Remission Status and Target Molecular Remission

Induction with new agents

↓  
autologous SCT

if no mCR

↓

## Improving Remission Status and Target Molecular Remission

Induction with new agents

↓  
autologous SCT

↓

RIC allograft or 2. auto?

## Spanish PETHEMA/GEM-2000 Trial

VBMCP/VBAD

↓  
Bu-MEL or MEL-200 / SCT

CR or nCR

↓  
IFN/PRED

PR or MR

↓  
CVB\* or MEL-200 /SCT  
or "allo-RIC\*\*"

↓  
IFN/PRED

\*Cyclophosphamide, Etoposide, BCNU  
\*\* Fludarabine/Melphalan-140

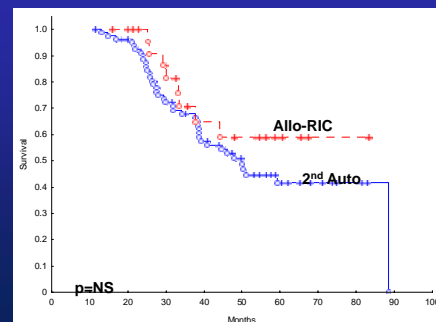
Rosñol, Blood 2008

## Response Up-grading with Second HDT "Auto" vs. "Allo-RIC"

Response	2 <sup>nd</sup> Auto (n=85)	Allo-RIC (n=26)
Non-evaluable	1 (1%)	-
CR (IF-) <sup>#</sup>	9 (10%)*	9 (35%)*
n-CR (EP-) <sup>†</sup>	7 (8%)	-
PR	8 (9%)	2 (8%)
MR	9 (10%)	2 (8%)
No change	45 (53%)	9 (35%)
Progressive disease	2 (2%)	-
TRM	4 (5%)**	4 (15%)**

\*p=0.01 \*\* p=0.08 #IF: immunofixation †: electrophoresis

## EFS 2nd Auto vs. Allo-RIC



Rosñol et al., Blood 2008

## Improving Remission Status and Target Molecular Remission

Induction with new agents  
 ↓  
 Cytoreduction (autologous SCT)  
 ↓  
 RIC allograft

### Platform for MRD-targeting Posttransplant strategies

↑	↑	↑
<b>Drug-based:</b> - Thalidomid - Bortezomib - Revlimid	<b>Adoptive Immunotherapy:</b> DLI: CD 8 depleted CD3+ cells Alloreactive NK-Cells Myeloma-specific CTL's	<b>Vaccination:</b> - mHag - Cancer testis antigen - Donor vaccination (idiotypic)

## Novel agents post allogeneic SCT

### Rationales

#### Bortezomib:

- highly active against myeloma cells
- in animal model: reduced GvHD but retain Graft versus leukemia effect (*Sun et al., PNAS 2004*) and lead to a decreased T-helper 1 response among alloreactive T-lymphocytes (*Blanco et al., Blood 2006*)

#### Lenalidomide and Thalidomide:

- activate T-cells and NK-cells which might augment the graft versus myeloma effect (*Lioznov et al., BMT 2009 in press*)
- low dose thalidomide more immunosuppressive properties (some activity in cGvHD)

## Bortezomib

- n = 23
- Relapse after allogeneic SCT
- 1.3 mg/m<sup>2</sup> day 1,4,8+ 11 with (61%) or without (39) dexamethasone
- Toxicity: Neuropathy: 52%  
Thrombocytopenia: 41%
- Overall response: 61%  
Complete remission: 22%

Bruno et al., Haematologica 2006

## Bortezomib as posttransplant strategy to enhance remission status

n= 18  
 1.3 mg/m<sup>2</sup> day 1,4,8 and 11 without dexamethasone  
 CR: 30 %  
 PR: 50 %  
 MR: 20 %

n = 1: skin aGvHD grade I to II  
 n = 1: skin aGvHD (< 25%)  
 n = 2: mild deterioration of pre-existing chronic skin GvHD

Kröger et al., Exp Hem 2006

## Toxicities according to NCI (CTC)

	Grade 0	Grade I	Grade II	Grade III	Grade IV
Leukocytes	11 ( 6 %)	1 ( 6 %)	3 (17 %)	1 ( 6 %)	2 (11 %)
Platelets	4 (22 %)	2 (11 %)	3 (17 %)	2 (11 %)	7 (39 %)
Neuropathy	3 (17 %)	6 (33 %)	6 (33 %)	2 (11 %)*	1 ( 6 %)*
Fatigue	3 (17 %)	14 (78 %)	1 ( 6 %)	–	–
Diarrhea	3 (17 %)	6 (33 %)	9 (50 %)	–	–
Nausea	8 (45 %)	9 (50 %)	1 ( 6 %)	–	–
Renal	16 (55 %)	–	2 (12 %)	–	–

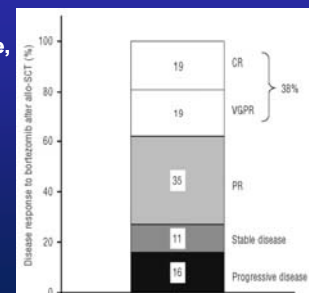
\*Neurotoxicity grade III/IV only in pat with ongoing CSA treatment

## Bortezomib after reduced intensity conditioning allo-SCT

- n = 37 after allogeneic SCT (87% for progressive disease, 14% residual disease)

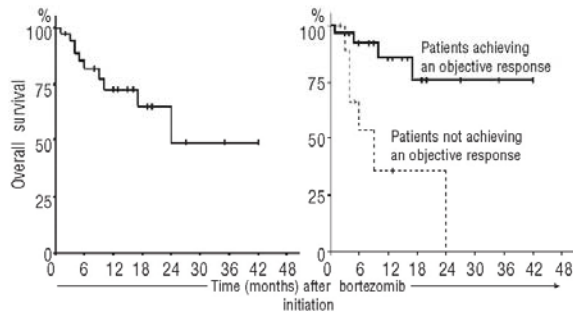
#### Toxicity

Neuropathy grade 1-2: 35%  
 Thrombocytopenia: 24%  
 Fatigue: 19%



El-Cheikh et al., Haematologica, 2008

### Overall survival after bortezomib salvage therapy initiation



El-Cheikh et al., Haematologica, 2008

### Thalidomide

#### IFM and SFGM

- Thalidomide (50 – 600 mg) in relapsed MM after allogeneic SCT
- n = 31
- 29% PR (6 PR, 3 VGPR)
- GvHD: n = 5
- 20% discontinue due to toxicity
- med PFS 12 months

Mohy et al., BMT 2005

### Thalidomide plus DLI

- Thalidomide (100 mg) plus DLI ( $1 \times 10^6 - 1 \times 10^7$  CD 3+ cells/kg)
- n = 18
- Toxicity:
  - Neutropenia grade 1+2: n = 5
  - Constipation grade 2: n = 2
  - Weakness grade 2: n = 1
- **Response**
  - ORR: 67%      2 yrs OS: 100%
  - CR: 33%      2 yrs PFS: 85%
  - PR: 22%
  - MR: 12%

Kröger et al., Blood 2004

### Low dose thalidomide (100 mg) and DLI

	after SCT	after DLI	after Thal/DLI
No. of patients	18	11	18
acute GvHD I-IV	10 (55%)	5 (46%)	2 (11%)
acute GvHD II-IV	4 (22%)	3 (27%)	0
chr.GvHD lim	4 (22%)	4 (36%)	7 (39%)
chr.GvHD ext	1 (6%)	0	0

Kröger et al., Blood 2004

### Lenalidomide

- n = 16; relapse after allogeneic SCT
- Prior relapse therapy:
  - DLI n = 11
  - thalidomide n = 14
  - bortezomib n = 11
- Dose: 25 mg for 21 days, (n = 8 with and without dexamethasone) n = 8
- Toxicity
  - grade 3/4 neutropenia n = 2
  - grade 3/4 thrombopenia n = 1
  - Thrombosis/PE n = 2
- ORR 87%
- CR 31%
- Increase of T-reg cells (FoxP3+ CD4 cells)

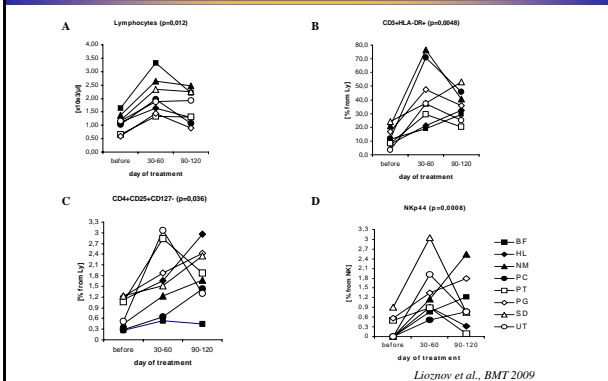
Minnema et al., Leukemia 2009

### Lenalidomide

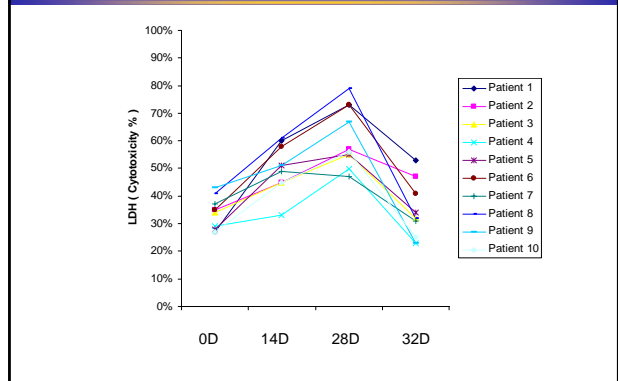
- Lenalidomide 15 – 25 mg with (n = 20) and without (n = 4) dexamethasone
- n = 24 as salvage therapy after allogeneic SCT
- median cycles: n = 5 (r, 2 – 17)
- Toxicity:
  - Neutropenia grade 3-4: 25%
  - Thrombocytopenia grade 3-4: 17%
  - Infections complications: 50%
- ORR: 66%      med. PFS: 9.7 months
- CR: 8%      med. OS: 19.9 months
- VGPR: 8%
- PR: 50%

Lioznov et al., BMT 2009 (in press)

## Lenalidomide increases the frequency of activated T-, NK- and T-reg cells



## Cytotoxicity of NK cells before and after treatment with lenalidomide



## Study: Upgrade Remission by Post-allo Transplant Strategies

**Aim: Target CR (mCR)**

1. No CR on at least day +100 after allografting
2. Start DLI (1 x 10e6 CD3+ cells/kg) after withdrawal of immunosuppression and no GvHD alone
3. Escalating DLI (half log) not before 6 weeks if no complete remission and no GvHD
4. If no CR after DLI add new agents (thalidomide or bortezomib or lenalidomide)
5. If no CR change to another novel agent

Monitor CR by immunofixation and BM examination by flow cytometry and patient specific IgH PCR or highly sensitive quantitative plasma cell chimerism

## Target CR posttransplant

Patients with non-complete remission after allogeneic SCT (n = 32)  
(evaluable for response: according EBMT criteria: n = 32, FACS: n = 27, molecular methods: n = 30)

escalating DLI (n = 30), median: 2 DLIs  
Thalidomide (n = 1) Bortezomib (n = 1)  
(due to cGvH)

**CR**  
EBMT: n = 8 (27%)  
FACS: n = 7  
Molec.: n = 7

PD n = 2      non CR n = 24

plus one or two novel agent  
thalidomide / bortezomib or  
lenalidomide

**CR**  
EBMT: n = 11  
FACS: n = 10  
Molec.: n = 8

Overall: CR (EBMT): n=19 (59%); FACS: n=17 (63%); molecular: n= 15 (50%)

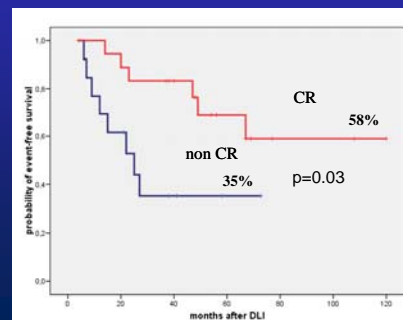
## DLI +/- new agents post allotransplant in non CR patients (PR/VGR)

Factors influencing achievement of CR:

MUD vs HLA-identical sibling:	n.s.
aGvHD vs no GvHD:	n.s.
cGvHD vs no cGvHD :	n.s.
del.13q vs no del.13q:	n.s
salvage vs upfront allo SCT:	n.s
<50y vs > 50 y:	62 vs 22%, p=0.02

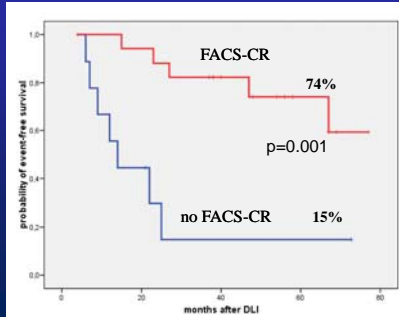
## DLI +/- new agents after allo-SCT for patients with PR/VGR

According EBMT criteria: 5 year PFS



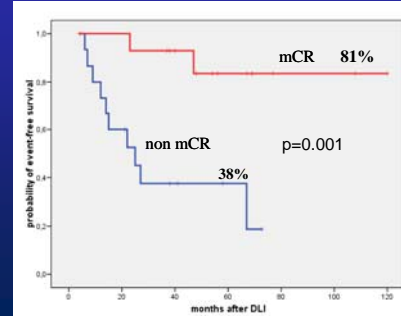
## DLI +/- new agents after allo-SCT for patients with PR/VGPR

According Flow cytometry (sensitivity:  $10^{-4}$ )



## DLI +/- new agents after allo-SCT for patients with PR/VGPR

According to molecular methods (sensitivity  $10^{-5}$  to  $10^{-6}$ )



*Kröger et al., Exp Hem 2009*

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