



First analysis of HOVON-65/GMMG-HD4 randomized phase III trial comparing Bortezomib, Adriamycine, Dexamethasone (PAD) vs VAD as induction treatment prior to High Dose Melphalan (HDM) in patients with multiple myeloma (MM).

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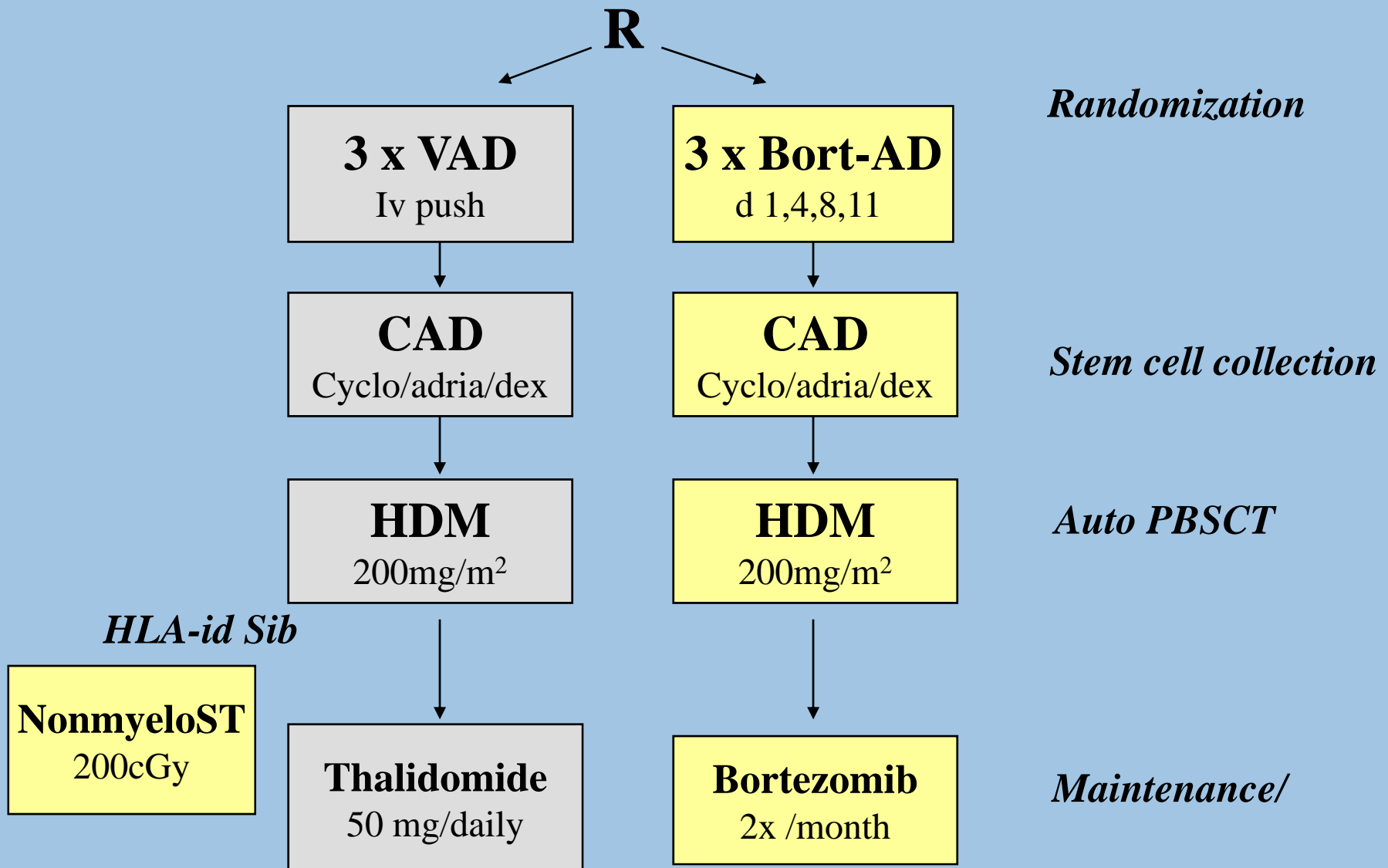
Disclosures

P. Sonneveld	Advisory Board Jansen-Cilag
H. Goldschmidt	Advisory Board Jansen-Cilag
H. van de Velde	Employee Jansen-Cilag

Study objectives

- The HOVON65 GMMG-HD4 randomised phase III trial was designed to assess the efficacy (CR+VGPR) of Bortezomib as **induction** treatment prior to high-dose therapy *and*
- To investigate the efficacy of Bortezomib as during **maintenance** treatment compared to Thalidomide
- Correlative studies were planned to investigate the relevance of prognostic subgroups in patients treated with Bortezomib
- **Here we present the first i.t.t. interim analysis on the response data for the initial 300 out of 825 registered patients.**

HOVON 65/GMMG-HD4



Schedule of PAD (3 cycles)

	Dose/day	Route	Days
Bortezomib	1.3 mg/m ²	i.v. rapid infusion	all cycles: Days 1,4,8,11
Doxorubicin	9 mg/m ²	i.v. rapid infusion	all cycles: 1, 2, 3, 4
Dexamethasone	40 mg	p.o.	all cycles: 1- 4, 9- 12, 17- 20

Study Endpoints

Primary endpoints

- **Progression-free survival**

Secondary endpoints

- **Response after Induction, HDM and overall (CR, VGPR, PR)**
- **OS from registration**
- **Toxicity**
- **PFS from HDM**

Response criteria

- **EBMT criteria as per protocol (start 2005)**
- **CR as in EBMT**
- **CR(u) : CR, immunofixation not done**
- **VGPR as in IMWG criteria**

Inclusion/exclusion criteria

Inclusion criteria

- **Multiple Myeloma stage II/III, A+B, all ISS stages**
- **Age 18-65 yr**
- **WHO performance 0 – 3**
- **Newly diagnosed**

Exclusion criteria

- **AL Amyloidosis**
- **Non-secretory MM**
- **Neuropathy CTC grade 2-4**
- **Severe concomittant disease**

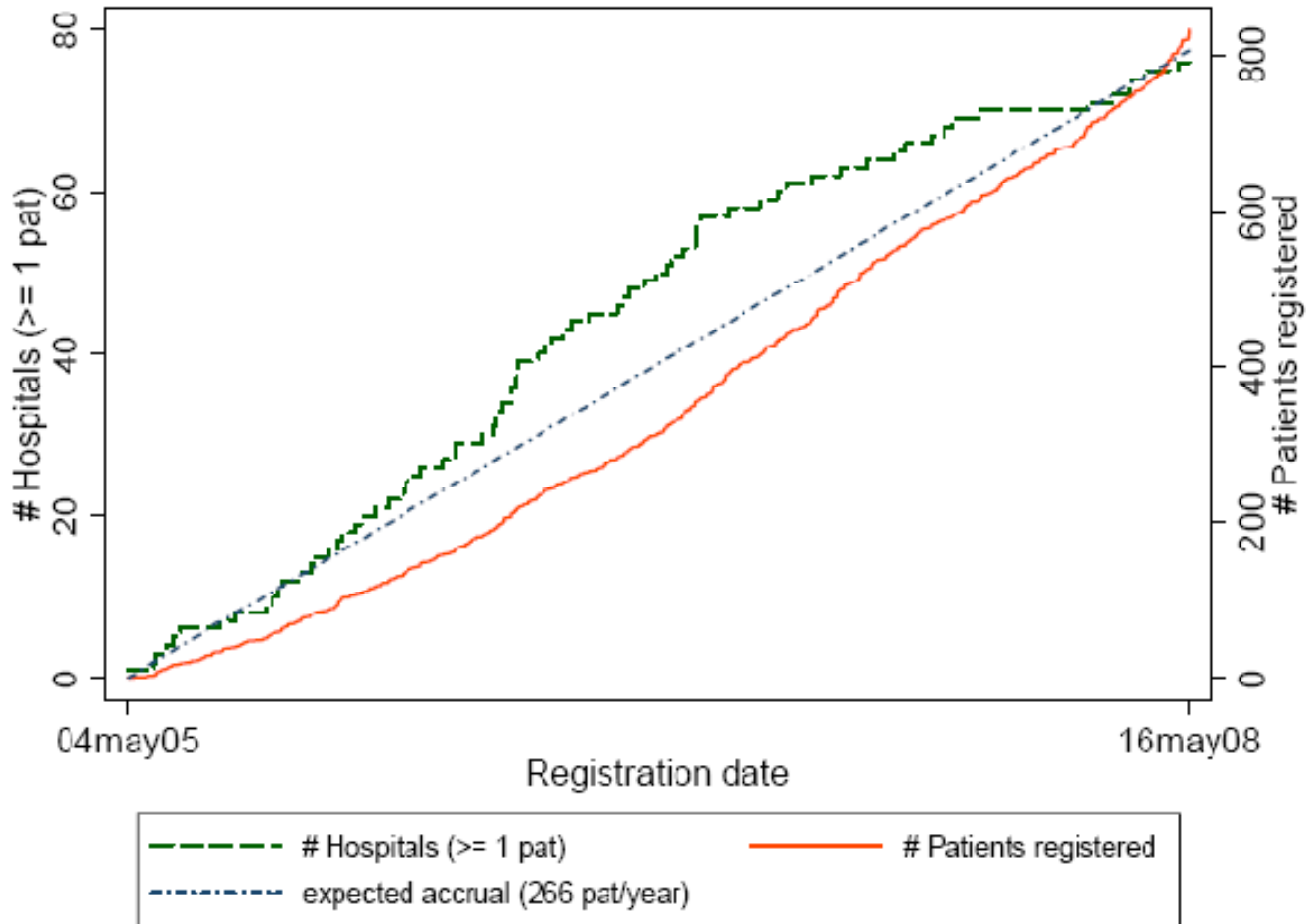
Response evaluation

- EBMT criteria as per protocol (start 2005)
- CR as in EBMT
- nCR: CR, immunofixation not done
- VGPR added as in IMWG criteria

Study conduct

- Cooperative trial by the Dutch-Belgium HOVON Myeloma Working Party & the German Multiple Myeloma Group GMMG based on a common protocol, study rules and data flow.
- The HOVON65 GMMG-HD4 randomised phase III trial was performed according to the newly defined European Law GCP regulations in 2005
- Including:
 - **HOVON initiated and sponsored the trial**
 - **On site center monitoring**
 - **European Good Clinical Practice regulations applied**
 - **Drug accountability program**
 - **Data Safety Monitoring Board**
 - **Timely data management for AE, SAE and SUSAR reporting**
 - **All data analysis and evaluation at HOVON DC for HOVON & GMMG**

Accrual



Patient characteristics

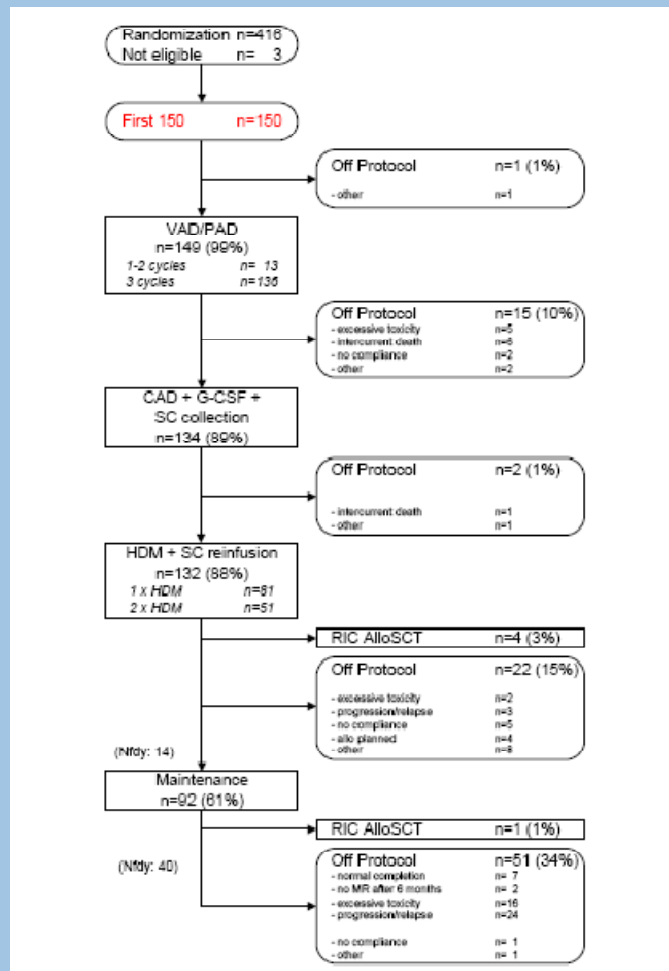
	VAD	PAD
Patients #	150	150
M/F	90/60	89/61
Median age yr	56	57
Stage II/III %	32/118	29/121
A/B %	128/22	136/14
ISS I/II/III %	54/19/28	59/22/19
IgA %	21	24
IgG %	60	62
LCD %	18	14

Patient characteristics

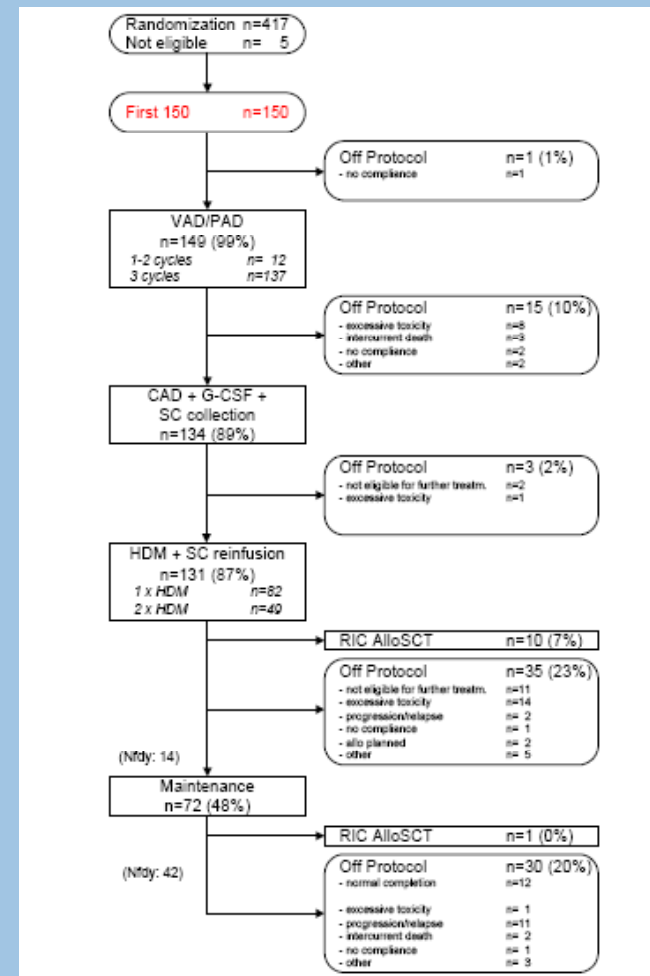
	VAD	PAD
Patients #	150	150
M/F	90/60	89/61
Well balanced for the stratification factors Beta-2-Microglobulin and Salmon-Durie stage and 1 HDM (NL) or 2 HDM (D)		
IgA %	21	24
IgG %	60	62
LCD %	18	14

Patient flow

VAD



PAD



Pre & Post-ASCT Response with VAD vs Bortezomib-AD (PAD) induction

	VAD N=150	PAD N=150	P value
CR/nCR %	1	5	
≥ VGPR	15	42	< 0.000001
≥ PR	59	83	0.000014
	HDM-SCT	HDM-SCT	
CR/nCR %	9	23	0.0015
≥ VGPR	50	80	0.0019
≥ PR	80	93	0.0021

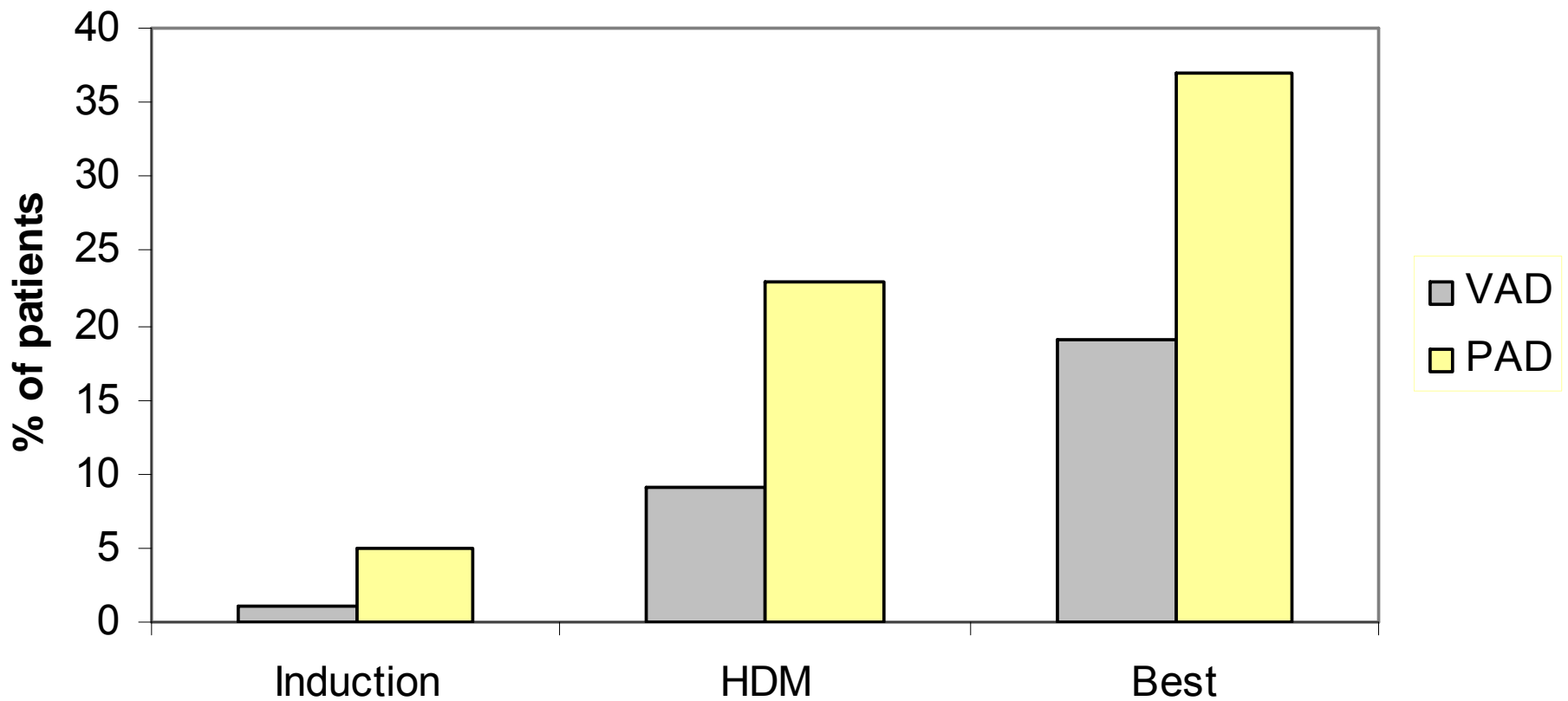
Impact of treatment arm on Post-Induction Responses

	P value	Odds Ratio	95% C.L.
\geq VGPR	0.000001	4.11	2.37-7.11
\geq PR	0.000014	3.26	1.91-5.57

Impact of treatment arm on Post-HDM Responses

	P value	Odds Ratio	95% C.L.
CR/nCR %	0.0015	3.59	1.63-7.91
≥ VGPR	0.0019	4.11	2.37-7.11
≥ PR	0.0021	3.15	1.51-6.57

CR/nCR on protocol



Stem Cell Collection ITT population

	VAD N = 150	PAD N = 150
Mobilization: Cyclo 4 g/m² + G-CSF		
Median No. CD34+ (x10⁶/kg)	9.26	10.48
Range	(4.10-37.60)	(4.00-37.00)
Median no. apheresis	1 (1-4)	1 (1-5)
Time to succesful apheresis (days)	110	111

H. Goldschmidt Abstract #3470

Monday, December 8, 2008

Poster Board III-552

Toxicities During Induction

	VAD N = 149	PAD N = 149
Any AE, n (%)	122 (82%)	129 (87%)
Grade \geq 3, n (%)	79 (53%)	88 (59%)
Grade \geq 4, n (%)	18 (12%)	32 (21%)
SAE, n (%)	52 (35%)	67 (45%)
AE leading to study drug discontinuation, n (%)	5 (3%)	9 (6%)
AE leading to death, n (%)	6 (4%)	3 (2%)

Hematologic toxicity / Infections

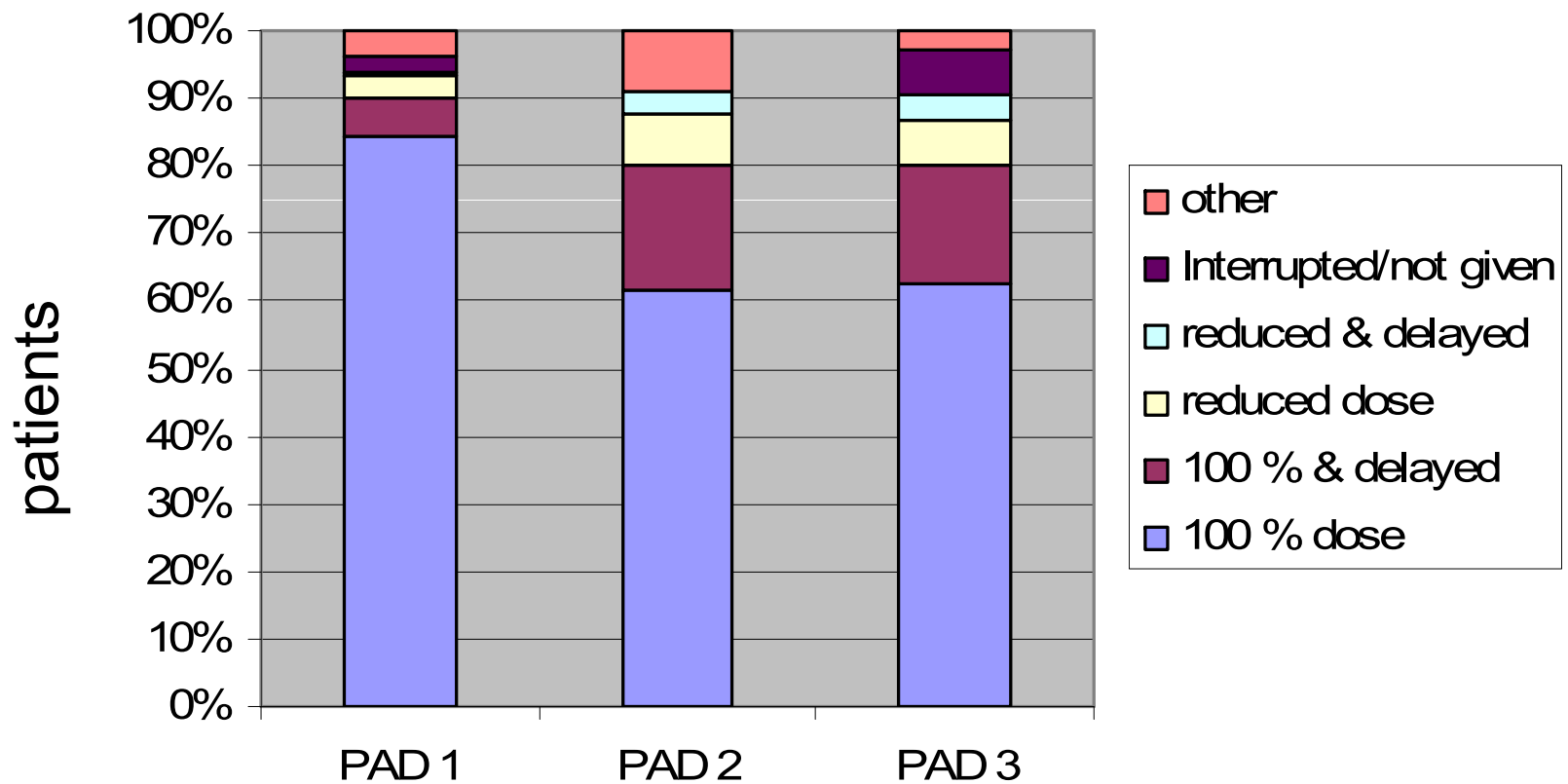
	VAD N = 149	PAD N = 149
Infections gr 2- 4		
any	42%	54%
pulmonary	17%	21%
ENT	6%	4%
GI	6%	7%
GU	5%	4%
FUO	4%	7%
Herpes Zoster	2%	3%

No difference in thrombocytopenia, anemia, leukocytopenia

Non Hematologic Toxicity grade 2-4

	VAD N = 149	PAD N = 149	P value
Fatigue	26%	29%	
Rash	11%	13%	
GI symptoms	30%	38%	
Peripheral Neuropathy			
Grade 2	17%	13%	
Grade 3,4	6%	16%	0.003
Cardiac Disorders	6%	6%	
Pneumonia	10%	11%	
DVT	3%	4%	

Dose adherence of Bortezomib



Reasons to go off protocol

	VAD	VAD/HDM	PAD	PAD/HDM
	%	%	%	%
Excessive toxicity	3	1	6	9
Not eligible FT	0	1	0	3
Progression/ Relapse	0	2	0	1
Intercurrent death	3		2	0
No compliance	2	2	1	1
Other	2	4	1	2
Allo		6		8
Cumulative	10	26	10	34

88 % of VAD and 87 % of PAD patients received HDM/ASCT

Impact of abnormal cytogenetics

	%	VAD		PAD	
		≥PR	≥VGPR	≥PR	≥VGPR
		%		%	
Del 13/13q <i>N=220</i>	Yes 46	85	48	96	64
	No 54	76	40	89	56
		<i>P < 0.01</i>			
t(4;14) <i>N=146</i>	Yes 20	76	29	96	52
	No 80	93	71	92	77
		<i>P < 0.001</i>		<i>P < 0.01</i>	

Conclusions

- PAD is a safe and effective induction regimen
- 80 % of patients can complete 3 cycles without dose reduction
- 42 % of patients achieves at least VGPR after 3 PAD cycles
- 80 % of patients achieves at least VGPR after PAD followed by HDM+ASCT
- PAD improves CR & VGPR significantly compared with VAD after induction and after HDM+ASCT
- Stem cell apheresis is successful in all PAD treated patients
- 87 % of patients achieve HDM/ASCT



Acknowledgements



D-Heidelberg-Univ
NL-Rotterdam-EMC Centrum
NL-Amsterdam-VUMC
NL-Groningen-UMCG 1376
D-Hamburg-AK Altona
NL-Utrecht-UMCU
D-Berlin-Charité Ben. Frank.
D-Homburg-University
NL-Amsterdam-AMC
NL-Nijmegen-Radboud
NL-Heerlen-Atrium
D-Hagen-Krankenhaus Hagen
NL-Enschede-MS Twente
NL-Nieuwegein-Antonius Ng
NL-Amersfoort-Meander
D-Frankfurt am Main-Goethe
NL-Leiden-LUMC
NL-Zwolle-Sophia
NL-Den Haag-Leyenburg
NL-Utrecht-Diakonessen
NL-Gouda-Groene Hart
D-Ludwigshafen-Klin. der Stadt
D-Cottbus-Carl-Thiem-Klinikum
D-Stuttgart-Robert-Bosch
D-Essen-Univ
NL-Dordrec-Schweitzer-Dortwijk
D-Bochum-Bochum
D-Köln-Klinikum
D-Frankfurt-Städ Klin Frankfurt
NL-Den Haag-Brönovo
NL-Amsterdam-OLVG
NL-Rotterdam-Clara
NL-Winterswijk-Beatrix
NL-Leidschendam-Antoniushove
NL-Delft-RdeGraaf
D-Siegen-Marien Krankenhaus
D-Bielefeld-Staedt Klin
D-Bayreuth-Klin. Bayreuth
D-Hamm-Ev. Krankenhaus
D-Lemgo-Klin Lippe
D-Kaiserslauter-Westpfalz-Klin
D-Essen-Essen-Süd
NL-Drachten-Smellinghe
NL-Apeldoorn-Gelre, Lukas
NL-Den Bosch-Jeroen Bosch - GZG
NL-Roosendaal-Franciscus
NL-Breda-Amphia, Langendijk
NL-Den Haag-Westeinde
NL-Arnhem-Rijnstate

Prof. Dr. Hartmut Goldschmidt
Prof. Dr. P. Sonneveld
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Prof. Dr. E. Vellenga
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Dr. Martin Hoffmann
Dr. Norma Peter
Prof. Dr. Walter-Erich Aulitzky
Prof. Dr. Ulrich Dührsen
mw. H.W.A. Berenschot
Dr. med. Christian Teschendorf
PD Dr. Christof Scheid
Prof. Dr. med. H.G. Derigs
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dhr. Dr. O.C. Leeksa
mw. A.A. van Houten
mw. Dr. M.E.P. Smeets
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dhr. C.G. Schaar
dhr. Dr. H.A.M. Sinnige
dhr. Dr. J.Th.P. Janssen
dhr. O.J.L. Loosveld
mw. F.H. Heyning
mw. dr. E.J.M. Mattijssen

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K. Wheatley (Birmingham, UK)

Datamanagement: L. el Jarari, S.G.R. Verelst, J. Hoogendam, .

Statistician: B. van der Holt

CKTO: CKTO 2004-10
ISRCTN: ISRCTN6445289

Janssen-Cilag Orthobiotech

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Bortezomib feasibility

	IFM ASH 2008	H65 ASH 2008
	VD	PAD
n	239	150
SAE	34	41
PNP total	25	23
PNP 3+4	2	16
Discontinue V	6	10
(n)CR %	15	5
\geq VGPR	39	42

