

myelom & lymphom symposium

myelom lymphom NEU ÖSTERREICH

Me MYELOMA REGISTRY

NEUE MEDIKAMENTE IN DER BEHANDLUNG DES MULTIPLER MYELOMS UND MALIGNER LYMPHOME

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MM & NHL TAG 26.02.2010, INNSBRUCK NEW DRUGS

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NEUE MEDIKAMENTE IN DER BEHANDLUNG DES MULTIPLER MYELOMS

- Steigender Anteil älterer Menschen an der Bevölkerung
- steigende Inzidenz des MM
- effektivere Therapie (medianes Überleben x 4 / letzten 10 Jahren)
- -> deutlich steigende Prävalenz von MM Patienten mit Ihren typ. Problemen und Therapien

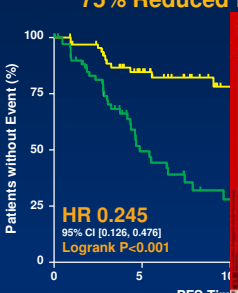


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MPR-R vs. MPR

Landmark PFS Analysis After Cycle 9

75% Reduced Risk in PFS



HR 0.245
95% CI [0.126, 0.476]
Logrank P<0.001



No. at Risk

MPR-R	75	40	17	3	1
MPR	81	21	8	1	1

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NEUE MEDIKAMENTE IN DER BEHANDLUNG DES MULTIPLER MYELOMS POLYNEUROPATHIE

Mileskin, L. et al. J Clin Oncol; 24:4507-4514 2006

Fortsetzung Thalidomid im Mittel für 19 Wochen
KEIN „DECKEL“

Dosisabhängigkeit

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Grad 1 Fortsetzung Therapie
Grad 2 Dosisreduktion 50%
Grad 3 Absetzen Thalidomid, Restart nur bei kompletter Rückbildung

Dosisreduktion oder Absetzen Thalidomid auch bei

- schmerzhafter** sensorischer Neuropathie
- motorischen** Defiziten

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MYELOMA ECOG E4A03 UPDATE & LANDMARK ANALYSIS



MEMO CLINIC ECOG

Primary Study Adverse Events

Randomized trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed myeloma (E4A03), a trial coordinated by the Eastern Cooperative Oncology Group: Analysis of response, survival, and outcome with primary therapy and with stem cell transplantation.

S. Vincent Rajkumar, Susanna Jacobus, Natalie Callander, Rafael Fonseca, David Vesole, Michael Williams, Rafat Abonour, David Siegel, Michael Katz, and Philip Greipp

Mayo Clinic, Rochester, MN; Dana Farber Cancer Institute, Boston, MA; University of Wisconsin, Madison, WI; Mayo Clinic Arizona, Scottsdale, AZ; St. Vincent's Hospital, New York, NY; University of Virginia, Charlottesville, VA; Indiana University, Indianapolis, IN; Hackensack University Medical Center, Hackensack, NJ and

MEMO CLINIC

Type (Grade 3+)	Toxicity*		Fisher's Exact p-value
	Rd (n=223)	Rd (n=220)	
DVT/PE	25%	11%	<0.001
Infection/Pneumonia	16%	8%	0.019
Cardiac ischemia	3%	0.5%	0.048
Neuropathy	2%	2%	0.999
Any non Hem toxicity (Grade ≥3)	56%	46%	<0.001
Toxicity of Any Type (Grade ≥4)	27%	17%	0.022
Early Death (≤4 months) All pts	5%	0.5%	0.003

*All pts who reported toxicity data

Primary Study Overall Response Rates

	Rd (n=214)	Rd (n=207)	Fisher's Exact p-value
Primary endpoint			
Overall response at 4 cycles	79%	69%	0.020
% successful mobilization (n=163)	96%	99%	
Overall survival			
1 year	89%	89%	0.005
2 year	78%	88%	0.007

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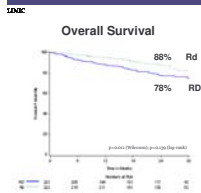
MYELOMA ECOG E4A03 UPDATE & LANDMARK ANALYSIS

MEMO CLINIC

Results of Primary therapy beyond 4 cycles with Rd

	"Primary Rd" (n=142)
Best Response	%
Overall Response Rate	89%
CR ^b (IF ^c)	23%
CR + VGPR	56%
Duration of Response	25 Months
Grade 3 or more non heme toxicity	29%
2 yr-Survival	89%

*measured in serum or urine



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Best Response

Best Overall Response ^a	MPR-R N = 152	MPR N = 153	MP N = 154	P Value (MPR-R vs. MP)
ORR	77%	67%	49%	<0.001
CR ^b	18%	13%	5%	<0.001
≥ VGPR ^c	32%	33%	11%	<0.001
PR	45%	34%	37%	---
Progressive Disease	0%	1%	0%	---
Median time to first response, months	1.9	1.9	2.8	<0.001

a. As measured using EBMT criteria¹
 b. Immunofixation negative with or without bone marrow confirmation
 c. VGPR: >90% reduction in M-protein

1. Bladé J et al. *Br J Haematol*. 1998;102:1115-1123.

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7 Multiple Myelom & B-lymphom-symptom

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Revlimid klinische Probleme

- **Thromboseneigung**
- **Teratogenität** **SICHERHEITSMABNAHMEN**
- **Dosisanpassung bei Niereninsuffizienz**
- **Myelotoxizität**

- Thromboseprophylaxe effektiv
ASS/LMWH bei zusätzlichen RF)
Anamnestische T., Steroide, Immobilität,
- Keine Neurotoxizität

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Novel agents

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Carfilzomib

- Irreversible proteasome inhibitor
- Phase 2 study: single-agent CFZ in relapsed or refractory disease
 - 57 bortezomib-naïve patients
 - ORR 45%
 - Most common AEs: fatigue (59%), nausea (41%), dyspnea (36%), anemia (29%)
 - 35 bortezomib-treated patients (17% refractory to bortezomib, 26% had discontinued bortezomib due to toxicities
 - ORR 18%
 - Most common AEs: fatigue (57%), nausea (54%), vomiting (37%), dyspnea (34%), diarrhea (34%), anemia (31%), increased creatinine (31%), upper respiratory tract infection (31%)
 - PN infrequent, generally mild

Wang et al. ASH 2009 (abstract 302); oral presentation
Siegel et al. ASH 2009 (abstract 303); oral presentation
Vij et al. ASH 2009 (abstract 430); oral presentation

Pomalidomide (CC4047)

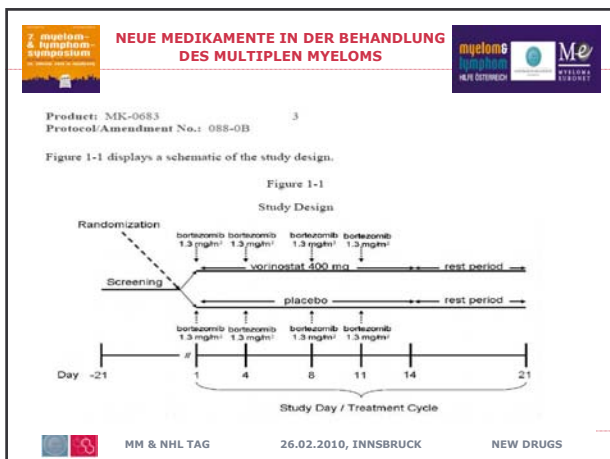
- Immunomodulatory (IMiD) agent
- Phase 1/2 dose escalation study
 - n=32 patients with relapsed/refractory disease
- Treatment: Pomalidomide +/- dex
- Results
 - Pomalidomide alone: ORR 38%, mean DOR 11.1 weeks, mean TTP 8.3 weeks
 - Pomalidomide + dex: ORR 38%, mean DOR 14.2 weeks, mean TTP of 20 weeks
 - Toxicity:
 - MTD not reached
 - Neutropenia and thrombocytopenia were the most common grade 3/4 toxicities

Richardson *et al.* ASH 2009 (abstract 301); oral presentation

Other novel agents

- HDACi:
 - Panobinostat
 - Vorinostat
- MoAbs
 - Anti-CSI
- HSP 90
 - Tanespimycin
- Aplidin
- Other proteasome/immunoproteasome inhibitors

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Figure 3. Plitidepsin-dexamethasone molecular model of apoptosis.

Randomized, Multicenter, Open-label, Phase III Study of Plitidepsin in Combination with Dexamethasone vs. Dexamethasone Alone in Patients with Relapsed/Refractory Multiple Myeloma

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Figure 6. Overall survival.

Prognose des Patienten? International Prognostic Index (IPI)

Alter >60 Jahre
Stadium III/IV
>1 extranodaler Befall
schlechter Allgemeinzustand (WHO>1)
(=Karnofsky <80)
LDH > oberer Normwert

Parameter	Score	Points	Performance
Alter	≤60	0	87%
Alter	>60	1	79%
Stadium	I/II	0	87%
Stadium	III/IV	1	79%
WHO	0-1	0	87%
WHO	2-4	1	79%
LDH	≤ Normwert	0	87%
LDH	> Normwert	1	79%

Survival probability

Lagrange p<0.0001

Altersadaptierter IPI für Patienten <60 J.: LDH, WHO-Status >1, Stadium III/IV

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NEUE ANSÄTZE

Neue Antikörper GA 101, Ofatumomab,

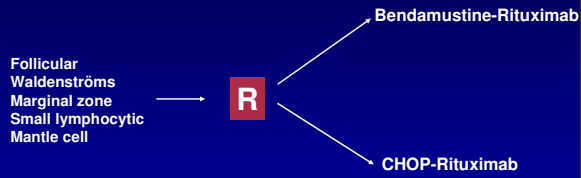
Neue Zytostatika Bendamustin

Novel Agents Bortezomib, Revlimid, Affinitor, .

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Bendamustine-Rituximab (B-R) vs CHOP-R

- StiL NHL 1-2003



Bendamustine 90 mg/m² day 1+2+R day 1, max. 6 cycles, q 4 wks

CHOP-R max. 6 cycles, q3 wks

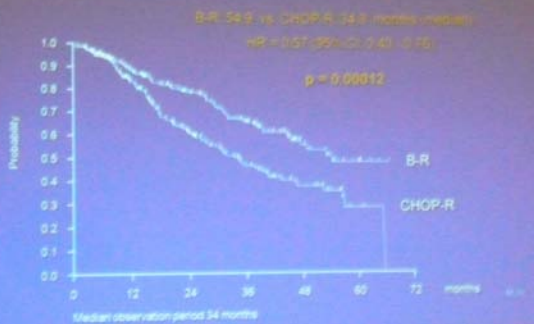
Rummel et al., Abstract 405, ASH 2009

B-R vs CHOP-R – Toxicities (all CTC - grades)

	B-R (n = 260) (no of pts)	CHOP-R (n = 253) (no of pts)	P value
Alopecia	-	+++	< 0,0001
Paresthesias	18	73	< 0,0001
Stomatitis	16	47	< 0,0001
Skin (erythema)	42	23	= 0,0122
Allergic reaction (skin)	40	15	= 0,0003
Infectious complications	96	127	= 0,0025
- Sepsis	1	8	= 0,0190

Rummel et al., Abstract 405, ASH 2009

Progression free survival



Rummel et al., Abstract 405, ASH 2009

POST ASH 2010 INNSBRUCK

Neue Studien in IBK

PILLAR-2: Study Design

DLBCL (IPI 3-5) $\xrightarrow{\text{R-CHOP (x 6-8)}}$ **CR** $\xrightarrow{\text{1:1}}$ **RAD001 (10 mg qd x 1yr)** or placebo $\xrightarrow{\text{1yr}}$ **DFS; OS; Safety**

* CR: No evidence of disease and disease related symptoms;
Definition of radiological CR: CT, PET; or CT+PET;
* assumptions: 2yr DFS: 65% (p) vs 74% (RAD); Cumulated Power: 90%;
HR=0.7

Key Inclusion Criteria

- Must have received all of the following agents:
 - Anthracycline or mitoxantrone
 - Cyclophosphamide
 - Rituximab
 - Bortezomib

CC-5013-MCL-001
EMERGE

Patients **MUST** have received ALL of these therapies in any order or combination

INNSBRUCK27.01.10POST ASH

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