

FOLLICULAR LYMPHOMA

Chemotherapy/Immunotherapy - single and combination therapy*

First-line Therapy^{c,d}

- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab (category 1)
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab (category 1) study¹
- Fludarabine + rituximab
- FND (fludarabine, mitoxantrone, dexamethasone) + rituximab
- Rituximab
- Radioimmunotherapy^{g,h} (category 2B) or CHOP followed by radioimmunotherapy^{g,h} (category 2B) [It is strongly recommended this treatment be on a prospective clinical study.]

First-line for Elderly or Infirm

- Rituximab, preferred
- Single agent alkylators (eg, chlorambucil or cyclophosphamide)

First-line Extended Dosing

Rituximab maintenance^{a,b,k} (category 2B) [It is strongly recommended this treatment be on a prospective clinical study.]

Second-line and Subsequent Therapy

- Bendamustine (category 2B) ± rituximab
- Chemo-immunotherapy (as in first-line therapy)
- High dose therapy with autologous stem cell rescue¹
- High dose therapy with allogeneic stem cell rescue, for highly selected patients¹
- Radioimmunotherapy^{g,h}
- See [Second-line Therapy for DLBCL \(BCEL-B 1 of 2\)](#)

Second-line Extended Dosing

Rituximab maintenance^k (category 1)

*For patients with locally bulky or symptomatic disease, consider IFRT 4-30 Gy ± additional systemic therapy.

Bendamustine + rituximab as second-line therapy in NHL (Rummel et al. 2005)

- Phase II study of bendamustine + rituximab in relapsed/refractory indolent and mantle cell lymphomas
- Treatment schedule:
 - Bendamustine 90 mg/m² on days 8 + 9, 36 + 37, 64 + 65, 92 + 93
 - Rituximab 375 mg/m² on days 1, 7, 35, 63, 91, 120
- Total of 63 patients, median age 64 years, 33% refractory to prior therapy
- Most had received one prior therapy (62%)

Rummel MJ et al. J Clin Oncol 2005;23:3383-9

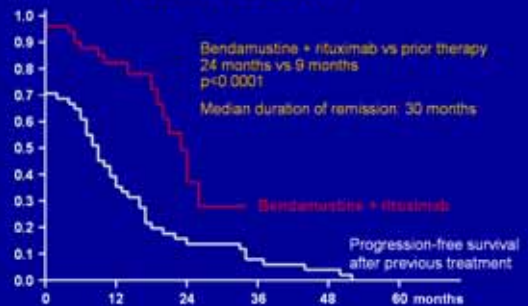
Bendamustine + rituximab as second-line therapy in NHL: response rates (Rummel et al. 2005)

	n	CR, %	PR, %	ORR, %
Follicular	24	71	25	96
Small lymphocytic	17	53	47	100
Mantle cell	16	50	25	75
Marginal zone	6	67	17	83
Total	63	60	30	90

CR, complete response; PR, partial response; ORR, overall response rate.

Rummel MJ et al. J Clin Oncol 2005;23:3383-9

Bendamustine + rituximab as second-line therapy in NHL: progression-free survival (Rummel et al. 2005)



Rummel MJ et al. J Clin Oncol 2005;23:3383-9

Bendamustine + rituximab as second-line therapy in NHL: toxicities (Rummel et al. 2005)

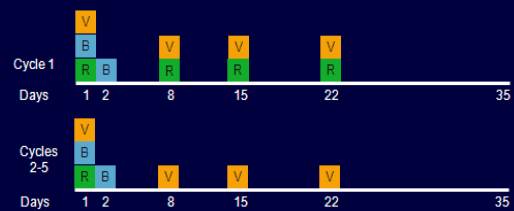
	WHO grade					
	0	1	2	3	4	3/4
Leukocytes	87	47	47	32	3	16%
Thrombocytes	173	19	15	6	1	3%
Anemia	169	23	5	2	-	1%
Nausea/vomiting	136	102	-	-	-	-
Allergic reaction	230	9	-	-	-	-
Cardiotoxicity	239	-	-	-	-	-
Neurotoxicity	239	-	-	-	-	-
Alopecia	235	4	-	-	-	-

All data are number of cycles, except where indicated.

Rummel MJ et al. J Clin Oncol 2005;23:3383-9

VERTICAL: Bortezomib, Bendamustine, and Rituximab (VBR) in Rel/Ref FL

- Phase 2 single-arm, open-label, multicenter trial; dose-escalation run-in
 - Bendamustine 50, 70, and 90 mg/m²/day
 - Bortezomib 1.6 mg/m²
 - Phase II: 90 mg/m²
 - Rituximab 375 mg/m²
- All patients given five 35-day cycles of therapy



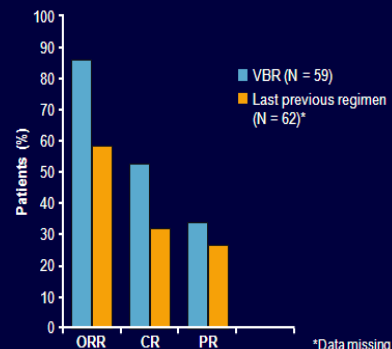
Fowler N, et al. ASH 2009. Abstract 933.

VERTICAL: Previous Regimens

Parameter	Patients (N = 63)
Previous regimens (median, n (range))	2 (1-11)
▪ Previous rituximab-containing regimen (median, n (%))	2 (1-6)
▪ ≥ 3 previous regimens, n (%)	29 (46)
Previous regimens, n (%)	
▪ 1	16 (25)
▪ 2	18 (29)
▪ 3	8 (13)
▪ 4	10 (16)
▪ 5	9 (14)
Time since last regimen, mos (range)	9 (0-76)
Refractory to last previous rituximab-containing regimen, n (%)	24 (39)
Refractory to last previous regimen, n (%)	30 (48)

Fowler N, et al. ASH 2009. Abstract 933.

VERTICAL: Results



Fowler N, et al. ASH 2009. Abstract 933.

*Data missing for 1 patient.

VERTICAL: Adverse Events

- Treatment-related adverse events: 100%
 - ≥ grade 3: 60%
 - Neutropenia: 27%
 - Thrombocytopenia: 6%
 - Anemia: 3%
 - Peripheral neuropathy, ≥ grade 3: 10%
 - Death: 2%
- Serious adverse events: 32%
 - Peripheral neuropathy resulting in discontinuation of therapy: 3%
- No observed cumulative hematologic toxicity

Fowler N, et al. ASH 2009. Abstract 933.

VERTICAL: Conclusions

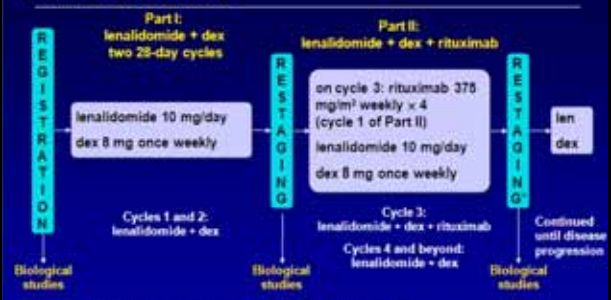
- VBR is active in patients with relapsed/refractory FL
 - VBR improved response rates and elicited higher CR rates
- VBR was generally well tolerated
 - Treatment-related AEs were mostly grade 1/2
- Follow-up is ongoing to evaluate PFS and OS

Fowler N, et al. ASH 2009. Abstract 933.

Lenalidomide – Rituximab ("R2") data in FL

		Patient population	N	ORR (%)	CR (%)
Lenalidomide monotherapy	Witzig et al, JCO 2009	relapsed/refractory FL	22	6 (27%)	2 (9%)
	Fowler et al, ASH 09 #1714	1st line FL	17	16 (94%)	16 (94%)
Lenalidomide-rituximab combination	Dutt et al, ASH 09 #1679	rituximab-refractory FL	13	11 (85%)	5 (38%)
	Ahmad et al, ASH 09 #1700	relapsed/refractory FL + MCL	15	8 (53%)	5 (33%)

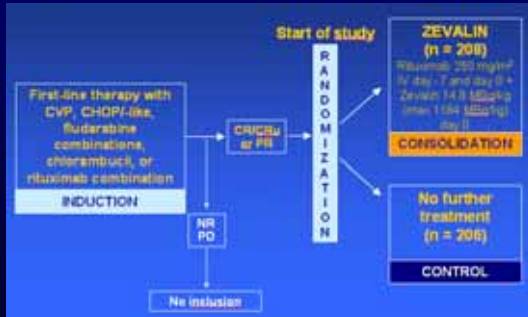
Lenalidomide + Rituximab + Dex in Rel/Ref Indolent NHL: Trial Schema



*Patients with SD or better after part II, continue on lenalidomide + dex until disease progression or development of clinically unacceptable toxicity

* Three months after first dose of rituximab
Ahmad et al. Abstract and poster presented at: 51st Annual ASH Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 1700.

1st line Follicular Lymphoma Schering-sponsored study (304820): FIT Study Scheme



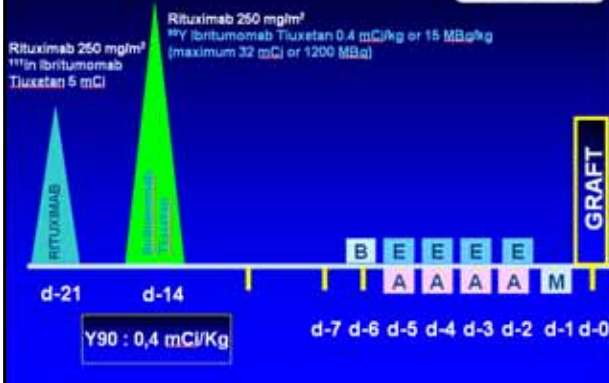
Hagenbeek A et al., Blood 2007; 110:643

FIT-TTNT in FL



ESO-d, St. Gallen, 23.02.2008. Medical Update Hämatonkologie, Int. Zeitschrift für ärztliche Fortbildung, Nr. 18, Juli 2009, I. Virgolini

Z BEAM



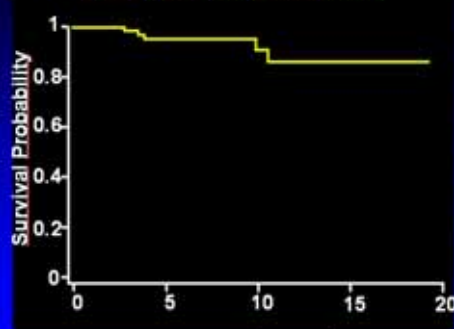
Patients Characteristics

Response	1 st -line (n=77)	2 nd -Line (n=27)	Salvage Before ASCT (n=77)	Post ASCT (n=75)
CR	24 (31%)	11 (41%)	33 (43%)	48 (64%)
CRu	17 (22%)	4 (15%)	26 (34%)	18 (24%)
PR	25 (32)	5 (19%)	17 (22%)	5 (7%)
Stable	5 (6%)	5 (19%)	1 (1%)	-
Progressive	5 (6%)	1 (4%)	-	-

Median delay (months) 1st line and transplantation (n=73): 31 m (7-332)
Median delay last salvage treatment and transplantation (n=75): 4.4 m (3-10)

Grossnerth C. et al. Blood 2007;110 (suppl:abstract 22)

Z-BEAM – PROGRESSION FREE SURVIVAL FROM TRANSPLANTATION



Nb	Event	Censored	Median Survival (95% CL)
75	7% (5)	93% (70)	NA (NA NA)

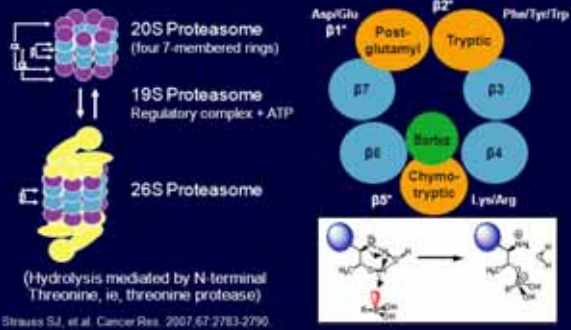
Relapsed/Refractory MCL: Approved and Investigational Agents

- Bortezomib
- Cytarabine
- Bendamustine
- Lenalidomide
- mTOR inhibitors
- Monoclonal antibodies
 - Anti-CD20 (rituximab, ofatumumab)
 - Radioimmunotherapy

Approved for R/R MCL

Off-label/investigational use in R/R MCL

Bortezomib and Proteasome Inhibition



Braunstein S, et al. Cancer Res. 2007;67:2783-2790.

Bortezomib Is Active in Relapsed MCL: Phase II Data

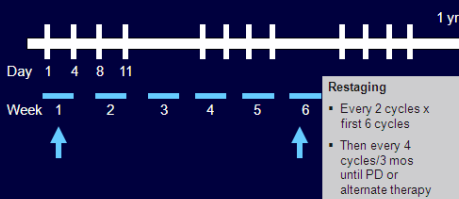
Reference	Patients, N	Regimen	ORR/CR	Outcomes, Mos	Median DOR
Goy A, et al. Ann Oncol. 2008; 20:520-525	168 MCL	B 1.3 mg/m ² on Days 1, 4, 8, 11 ≤ 21 days	32% ORR 8% CR/CRu	TTP 8.7 TTP/17.4 RFS 6.6	CR pts have not yet reached med DOR or med TTP, 9.2 mos in all responders
Fisher PL, et al. J Clin Oncol. 2006; 24:4897-4924	168 MCL	B 1.3 mg/m ² on Days 1, 4, 8, 11 ≤ 21 days	33% ORR 8% CR	TTP 8.2	8.2 mos
Giarembino J, et al. Br J Haematol. 2008;146:852-855	10 MCL 18 FL	B 1.3 mg/m ² on Days 1, 4, 8, 11 ≤ 21 days	13% ORR 0% CR	RFS 6.7	6.7 mos
O'Connor GA, et al. Br J Haematol. 2008;148:34-39	49 MCL	B 1.6 mg/m ² on Days 1, 4, 8, 11 ≤ 21 days	50% ORR 13% CR	RFS 6.3	7.8 mos
O'Connor GA, et al. J Clin Oncol. 2008; 23:879-884	11 MCL 3 SLL 2 MCL 10 FL	B 1.6 mg/m ² on Days 1, 4, 8, 11 ≤ 21 days	48% ORR 5/11 MCL pts with response (1 CR)	Survival HR	6-19+ mos
Borch A, et al. Ann Oncol. 2007; 18:116-121	29 MCL (13 Relapsed)	B 1.3 mg/m ² on Days 1, 4, 8, 11 ≤ 21 days	46% (1 CR)	TTP 12.8	10 mos
Braunstein S, et al. J Clin Oncol. 2008; 24:2106-2112	24 MCL 13 FL 14 other	B 1.3 mg/m ² on Days 1, 4, 8, 11 ≤ 21 days	22% ORR in MCL (1 CR)	Survival HR	102 patients had 1st comparative treatment

Updated Analyses of the PINNACLE Study: Bortezomib in Relapsed MCL

Key eligibility criteria

- MCL, cyclin D1+, or t(11,14)+
- PD
- ≤ 2 previous therapies
- Previous anthracycline and rituximab
- No > grade 2 toxicity from previous therapy

Bortezomib 1.3 mg/m² for 4 cycles beyond CR/CRu or, if no CR/CRu, up to 17 cycles until PD or toxicity



Goy A, et al. Ann Oncol. 2008;20:520-525.

Bortezomib in Relapsed/Refractory MCL: Efficacy

Patient Group	ORR, %	CR, %	Median DOR, Mos
Response evaluable (n = 141)	32	8	9.2
Refractory MCL (n = 58)	29	6	5.9
Previous high-intensity therapy (n = 58)	25	10	Not reached

Goy A, et al. Ann Oncol. 2008;20:520-525.

Bortezomib in Relapsed/Refractory MCL: Efficacy

TTP by treatment response, median mos

All patients	6.7
CR/CRu	NR
PR	9.1

OS (median): by treatment response

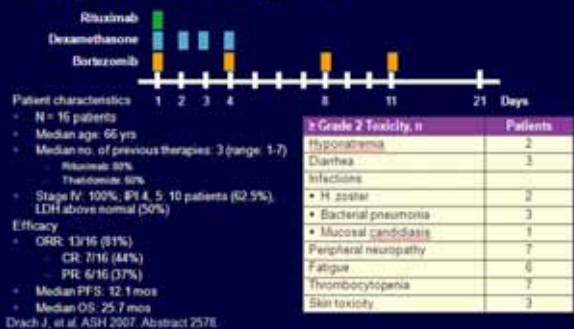
All patients	23.5 mos
Responders	35.4 mos
1-yr survival	
- All patients	69%
- Responders	91%

OS from initial diagnosis, mos

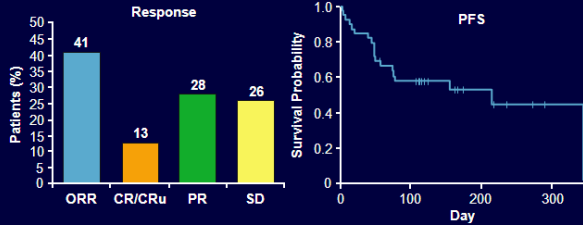
All patients	61.1
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Goy A, et al. Ann Oncol. 2008;20:520-525.

Bortezomib, Rituximab, Dexamethasone in Relapsed/Refractory MCL



Lenalidomide Monotherapy in Relapsed/Refractory MCL: Efficacy and Safety



Patients, n	Events, % (n)	Censored, % (n)	Median PFS Days (95% CI)
39	49 (19)	51 (20)	216 (75-344)

Zinzani PL, et al. ASH 2008. Abstract 262.

A Phase 1/2 Study of Lenalidomide in Combination With Rituximab in RR Mantle Cell Lymphoma

- Lenalidomide combined with rituximab has been shown to augment NK-mediated ADCC activity in preclinical studies
- Evaluate the safety and efficacy of lenalidomide + rituximab in patients with rel/ref MCL



Treatment continued until disease progression or major toxicity

Wang et al. Abstract and poster presented at: 51st ASH Annual Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 2719.

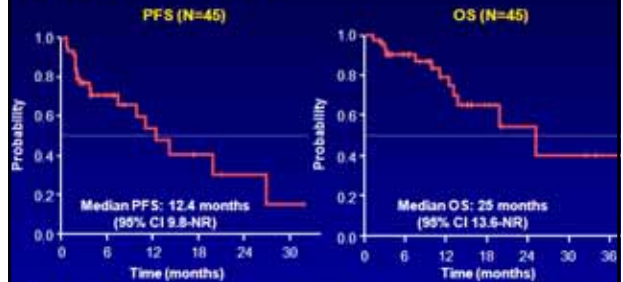
Phase 2 Outcomes: Efficacy of Rituximab + Lenalidomide at MTD in Rel/Ref MCL (N=45)

Best Response to Therapy	n (%)
CR, n (%)	13 (29)
PR, n (%)	11 (24)
ORR (CR + PR), n (%)	24 (53)
MR, n (%)	4 (9)
SD, n (%)	8 (18)
Clinical benefit (CR + PR + MR + SD)	36 (80)
Progressive disease, n (%)	9 (20)

MR=minor response.

Wang et al. Abstract and poster presented at: 51st ASH Annual Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 2719.

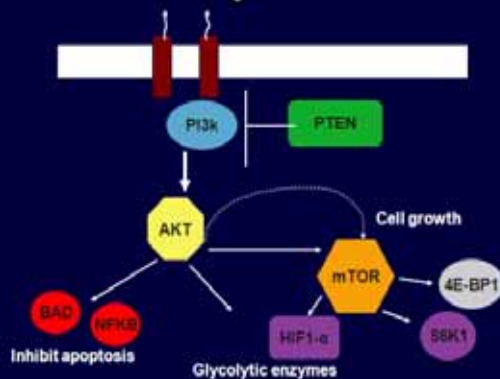
Lenalidomide + Rituximab in Rel/Ref MCL: Survival Outcomes



Median follow-up for censored observations was 9.4 months (range 2.1-38.9).

Wang et al. Abstract and poster presented at: 51st ASH Annual Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 2719.

mTOR/AKT Pathway



Temsirolimus: Single-Agent Activity in MCL

	n = 34	n = 27
	250 mg	25 mg
Patient characteristics		
• Median age, yrs (range)	70 (38-79)	68 (51-85)
• Previous treatments, n	3	
• ≥ 2 extranodal sites, %	69	
• Refractory disease, %	54	48
Results		
• ORR, % (n/N)	38 (13/34)	41 (11/27)
• CR, % (n/N)	3 (1/34)	4 (1/27)
• DR, mos	6.9	6.2
Toxicity		
• Dose reduction needed, % (n/N)	88 (30/34)	59 (16/27)

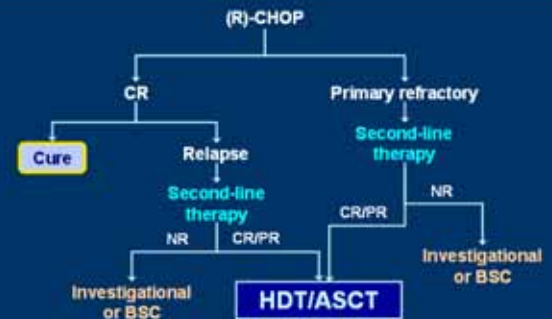
Witzig TE, et al. J Clin Oncol. 2005;23:5347-5356.

Treatment With Temsirolimus Compared With IC: Efficacy and Toxicity

	Temsirolimus 175/75 mg	Temsirolimus 175/25 mg	IC
PFS			
• Median, mos	4.8	3.4	1.9
• Increase in median PFS, %	153	79	
• HR (97.5% CI)	0.44 (0.25-0.76)	0.65 (0.39-1.10)	
• P value	0009	0618	
OS			
• Median, mos (95% CI)	12.8 (8.6-19.3)	10.0 (7.2-14.6)	9.7 (5.9-15.1)
• HR (95% CI)	0.80 (0.50-1.28)	0.96 (0.60-1.54)	
• P value	.3519	.8714	
ORR, % (95% CI)	22 (11-33)	6 (0-12)	
• P value	.0018	.6179	
Most common grade 3/4 adverse events, %			
• Thrombocytopenia	59	52	36
• Anemia	20	11	17
• Neutropenia	15	22	26
• Asthenia	13	19	9

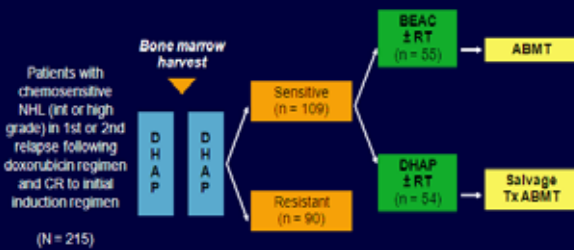
Hera G, et al. J Clin Oncol. 2009;27:3822-3829

Management of aggressive NHL



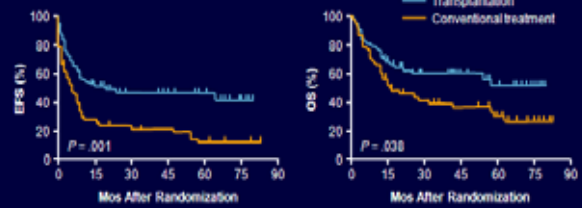
Salicrú A, et al. Ann Oncol 2003; 14:15-19

PARMA Study: ABMT vs Conventional Chemotherapy in Relapsed NHL



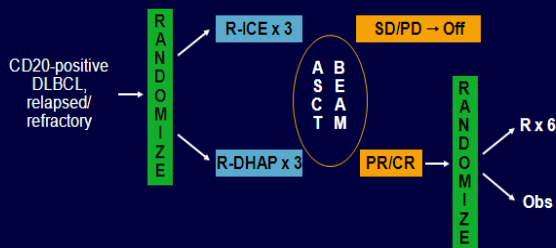
Philip T, et al. N Engl J Med. 1995;333:1540-1545.

PARMA Study: Bone Marrow Transplantation vs Salvage Chemotherapy



Philip T, et al. N Engl J Med. 1995;333:1540-1545. Copyright © (1995) Massachusetts Medical Society. All rights reserved.

CORAL Trial: R-ICE vs R-DHAP in DLBCL



Gisselbrecht C, et al. ASCO 2009. Abstract 8509.

CORAL Study: Pts Included With Response After First-line Therapy

Response After First Line	R-ICE		R-DHAP		All	
	n	%	n	%	n	%
CR	108	54	101	52	209	53
CRu	23	11	24	12	47	12
PR	40	20	37	19	77	20
SD	6	3	10	5	16	4
PD	24	12	20	10	44	11
Not evaluated	0	0	1	1	1	0
Rituximab	122	60	122	63	244	62

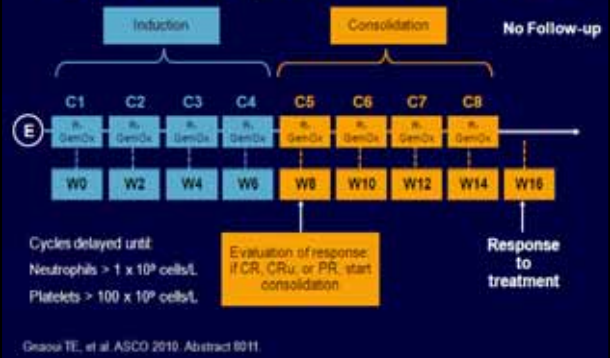
Gisselbrecht C, et al. ASCO 2009. Abstract 8509.

CORAL Study: OS and PFS

2-Year Outcome (Induction ITT), %	R-ICE	R-DHAP	P Value
OS	56	56	.4899
PFS	42	45	.4416

Gisselbrecht C, et al. ASCO 2009. Abstract 8509.

Prospective, Multicenter, Phase II Trial of R-GemOx in Relapsed/Refractory DLBCL



R-GemOx in Relapsed/Refractory DLBCL: Eligibility

- DLBCL diagnosis or Transformed CD20+ indolent lymphoma by World Health Organization classification at relapse
- 60 years of age or older or younger than 60 years of age (18 years or older) allowed if
 - Not eligible for high-dose chemotherapy or
 - Previous ASCT
- Measurable disease
- ECOG performance score 0-2
- Relapse after first or second response of PR or better
- Response less than PR following first-line treatment
- Previous treatment with ≥ 1 anthracycline-containing regimen

Gnaoui TE, et al. ASCO 2010. Abstract 8011.

R-GemOx in Relapsed/Refractory DLBCL: Response Data

Response, %	After 4 Cycles of R-GemOx (n = 48)	End of Treatment (n = 48)
ORR	60.4	45.8
▪ CR	23	23
▪ CRu	21	15
▪ PR	17	8
SD	4	8
PD	10	27
Death	8	17

Gnaoui TE, et al. ASCO 2010. Abstract 8011.

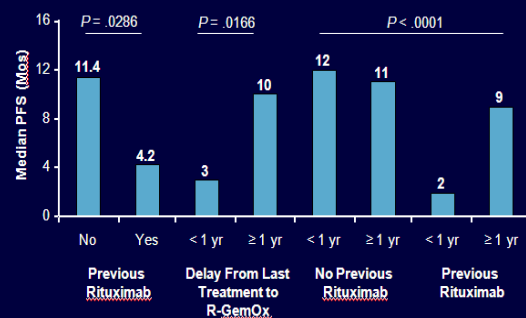
R-GemOx in Relapsed/Refractory DLBCL: Safety Analysis

Toxicities,* %	Safety Population (N = 48)	
	Grade 3	Grade 4
Hematologic		
▪ Thrombocytopenia	23	21
▪ Anemia	21	2
▪ Neutropenia	31	42
▪ Febrile neutropenia	4	0
Nonhematologic		
▪ Liver	15	0
▪ Neurologic	8	0
▪ Kidney	2	0

*Calculated using National Cancer Institute Common Toxicity Criteria (version 3.0).

Gnaoui TE, et al. ASCO 2010. Abstract 8011.

R-GemOx: PFS According to Delay From Last Treatment and Previous Rituximab



Gnaoui TE, et al. ASCO 2010. Abstract 8011.

R-GemOx in Relapsed/Refractory DLBCL: Conclusions

- R-GemOx as a salvage regimen demonstrated favorable safety profile and produced high ORR in patients with relapsed/refractory DLBCL who were unable to receive high-dose chemotherapy
 - ORR after 4 cycles: 60%
- Patients with early relapse (< 1 yr from last treatment) and previous rituximab treatment had shortest PFS duration with R-GemOx salvage therapy

Gnaoui TE, et al. ASCO 2010. Abstract 8011.

NHL-003 study design: Lenalidomide Monotherapy in Patients With Relapsed/Refractory Aggressive NHL

- Patients who had relapsed or were refractory to ≥ 1 prior treatment
- Therapy continued as tolerated or until disease progression
- Primary end point
 - ORR (pts with CR, CRu, or PR)
- Secondary end points
 - Response duration, PFS, Safety



Rel=relapsed/refractory, FL=follicular Grade 3 lymphoma, TL=transformed lymphoma.
Witzig et al. Abstract and poster presented at: 51st Annual ASH Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 1676.

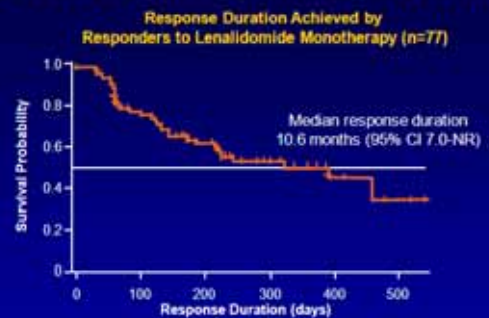
NHL-003: Baseline Patient Characteristics (N=217)

Baseline Patient Characteristics

Median age, years (range)	66 (21-87)
Men, n (%)	140 (64.5)
Median time from diagnosis, years (range)	2.7 (0.2-20.6)
Histology, n (%)	
DLBCL	108 (49.8)
MCL	57 (26.3)
TL	33 (15.2)
FL-III	19 (8.8)
IPi score, n (%)	
Low risk (0-1)	44 (20.3)
Intermediate risk (2-3)	136 (62.6)
High risk (4-5)	37 (17.1)

IPi=International Prognostic Index.
Witzig et al. Abstract and poster presented at: 51st Annual ASH Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 1676.

NHL-003: Response Duration of 10.6 months

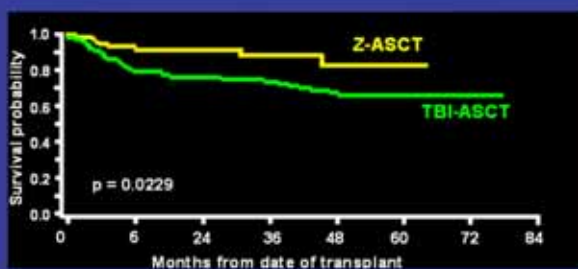


At a median follow-up of 9.2 months, median response duration was not reached among patients with a CR/CRu

Witzig et al. Abstract and poster presented at: 51st Annual ASH Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 1676.

Historical Comparison Escalated-Dose RIT with VP16 and Cyclophosphamide: Overall survival by treatment

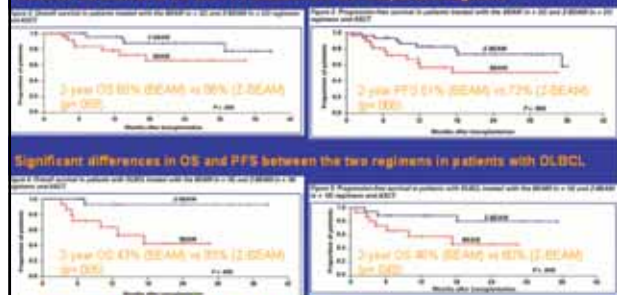
Z-ASCT (n = 62) versus TBI-ASCT (n = 126)



Nademanee A et al., Blood 2006;108:#327

Phase II HD-Chemotherapy with Zevalin and PBSCT in Pts. with rel./refr. DLBCL – Historical comparison with BEAM

Trend for differences in OS and PFS between the two comparative regimens



Median FU 19.5 mo (BEAM) vs. 20.3 mo (Z-BEAM)

Krishnan A, et al. Blood 2006;108:#3043

Enzastaurin: Efficacy in Relapsed/Refractory DLBCL

- PKC β -selective serine/threonine kinase inhibitor
- Phase II study of once-daily oral enzastaurin in 55 pts with relapsed/refractory DLBCL administered as continuous 28-day cycles until PD or toxicity
 - FFP for ≥ 2 cycles: 22%
 - 15% remained FFP for ≥ 4 cycles
 - 7% continue FFP 20-50 mos following study entry
 - Only 1 grade 4 adverse event: hypomagnesemia
 - Most frequent grade 3 adverse events: fatigue (n = 2), edema (n = 1), headache (n = 1), motor neuropathy (n = 1), thrombocytopenia (n = 1)
 - No deaths or treatment discontinuation caused by toxicity

Robertson MJ, et al. J Clin Oncol. 2007;13:1741-1746.

Enzastaurin: Ongoing Phase II and III Studies in DLBCL

- Phase II
 - Randomized trial of R-CHOP \pm enzastaurin for first-line treatment of int/high-risk DLBCL (active, not recruiting)^[1]
 - R-GEMOX plus enzastaurin for relapsed DLBCL (active, not recruiting)^[2]
- Phase III
 - Trial investigating maintenance enzastaurin for the prevention of relapse in DLBCL (recruiting)^[3]

1. ClinicalTrials.gov. NCT00451178. 2. ClinicalTrials.gov. NCT00436280. 3. ClinicalTrials.gov. NCT00332202.

Phase II: Fostamatinib Disodium

- 68 patients enrolled at 200 mg BID: relapsed and heavily treated refractory lymphoma
 - Group 1: DLBCL (n = 23)
 - ASCT: n = 12
 - ORR: 22%
 - 1 CR and 4 PR (5/23); also 4 SD
 - Group 2: FL (n = 21)
 - RIT: n = 9
 - ASCT: n = 5
 - Group 3: "Other" (n = 24)

Friedberg JW, et al. Blood. 2010;115:2578-2585.

Inotuzumab Ozogamicin + Rituximab in FL and DLBCL: Phase I/II Study

- CD22 expressed in > 90% of B-cell lymphomas
 - Represents novel therapeutic target in NHL
- Inotuzumab ozogamicin (CMC-544)
 - Cytotoxin calicheamicin conjugated to a humanized monoclonal IgG4 anti-CD22 antibody

Fayad L, et al. ASH 2008. Abstract 266.

Inotuzumab Ozogamicin + Rituximab in FL and DLBCL: Phase I/II Study

- Eligibility criteria
 - CD22+ B-cell NHL, with progression after 1-2 previous therapies
 - Rituximab-sensitive FL (n = 41) and DLBCL (n = 33)
- Dosing regimen (four 28-day cycles)
 - Day 1: rituximab 375 mg/m²
 - Day 2: inotuzumab ozogamicin 0.8, 1.3, or 1.8 mg/m²
 - Up to 8 cycles for patients with clinical benefit after 4 cycles
- Patients restaged after every 2 cycles

Fayad L, et al. ASH 2008. Abstract 266.

Inotuzumab Ozogamicin + Rituximab in NHL: Response Rates and Survival

- Inotuzumab ozogamicin at MTD equally effective in FL and DLBCL

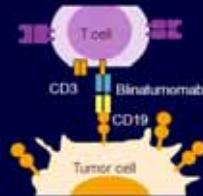
Response Rate, %	Inotuzumab Ozogamicin Dose			
	0.8 mg/m ² (n = 1)	1.3 mg/m ² (n = 2)	1.8 mg/m ² (n = 29)	All Doses (n = 32)
FL				
• OR	100	100	72	75
• CR/CR _i	100	50	45	47
• PR	0	50	27	28
DLBCL				
• OR	20	100	79	70
• CR/CR _i	20	0	37	33
• PR	0	100	42	37

- PFS rate at 6 months in ITT population receiving MTD
 - FL: 93% (80% CI: 83% to 97%)
 - DLBCL: 65% (80% CI: 48% to 78%)

Fayad L, et al. ASH 2008. Abstract 266.

Phase I: Blinatumomab in Relapsed NHL

- Blinatumomab is a bispecific T cell-engaging antibody
 - Targets CD19 antigen, stimulates T-cell lysis of tumor cells
- Blinatumomab mediated T cell-stimulated tumor cell lysis
 - Independent of antigen processing, peptide antigen presentation, MHC II, β_2 -microglobulin, or costimulatory molecules
- Active at low concentrations
- Short serum half-life: 2-3 hours



Bargou R, et al. ASH 2008. Abstract 267.

Phase I: Blinatumomab in Relapsed NHL

- Dose escalation of blinatumomab (0.0005-0.09 mg/m²/day) continuous intravenous infusion for 4-8 weeks
- Dose-limiting toxicity evaluated during initial 2-week inpatient treatment
- Most adverse events resolved to grade \leq 1 and did not require treatment discontinuation
 - Treatment permanently discontinued in 10 patients

Hematologic Adverse Events, NHL	Patients (N=38)
Neutropenia	31 (82)
Leukopenia	25 (67)
Thrombocytopenia	18 (47)
Lymphopenia	18 (47)
Anemia	15 (39)

Non-Hematologic Adverse Events, n (%)	Patients (N=38)
Fatigue	27 (71)
Elevated creatinine phosphatase	22 (57)
Headache	17 (44)
Fatigue Weight loss Diarrhea	15 (39)
Chills	14 (36)
Diarrhea	14 (36)
Weight gain	14 (36)
Elevated ALT	13 (33)
Elevated AST	13 (33)
Elevated gamma-GT	13 (33)
Fatigue	13 (33)
Weight loss	11 (28)
Weight gain	11 (28)
Elevated glucose	10 (26)
Low potassium	10 (26)
Trenchard edema	10 (26)

Bargou R, et al. ASH 2008. Abstract 267.

ENDE

NHL 003: Prior Treatment History (N=217)

Prior Treatment

Median prior treatment regimens, n (range)	3 (1-13)
Refractory to last therapy, n (%)	96 (44.2)
Refractory* to rituximab, n (%)	117 (53.9)
Type of prior treatment regimens, n (%)	
Rituximab + combination chemotherapy	192 (88.5)
Combination chemotherapy	135 (62.2)
Rituximab	205 (94.5)
Bortezomib	20 (9.2)
SCT	73 (33.6)

* Refractory= \leq 6 months response or no response.
SCT=stem cell transplantation.
Witzig et al. Abstract and poster presented at: 51st Annual ASH Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 1676.

Phase II Study of Lenalidomide + Rituximab in frontline Indolent NHL

- Patients with untreated stage III or IV indolent NHL
- Rituximab; 375 mg/m² i.v. Day 1
- Lenalidomide; 20 mg/day p.o. Days 1-21, q 28-days x 9 cycles

Tumor subtype	n	SD	PR	CR/CRu	ORR (CR/CRu)
FL	17	1	0	16	94% (94%)
SLL	3	0	2	1	100% (33%)
MZL	8	3	1	4	63% (50%)
Total	28	4	3	21	86% (75%)

- 28 patients received at least 1 post-baseline tumor assessment and were evaluable for response

CR=unconfirmed complete response.
Fowler et al. Abstract and poster presented at: 51st Annual ASH Meeting and Exhibition, December 5-8, 2009, New Orleans, LA. Abstract 1714.

Ergebnisse I - Ansprechraten

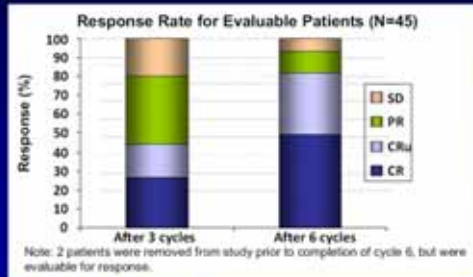
- Bislang 74 pts eingeschlossen, davon haben 48 pts mindestens 6 Zyklen erhalten

Histologie	N	NE	SD	PR	CR/CRu	% ORR (%CR/CRu)	
						Evil* (n=45)	ITT (n=48)
Follikulär	30	1	1	3	25	97 (86)	93 (83)
SLL	5	-	1	2	2	80 (40)	80 (40)
Marginal	13	2	3	2	6	73 (55)	62 (46)
Gesamt	48	3	5	7	33	89 (73)	83 (69)

* Evaluierbar sofern mindestens eine Nachuntersuchung vorlag
NE = nicht evaluierbar, IT = intent-to-treat

Fowler N et al # 8036, ASCO 2010

Ergebnisse II – Ansprechraten nach 3 und 6 Monaten



- Molekulares Ansprechen
10/11 pts wurden unter Therapie (6 Zyklen) BCL-2 negativ

Fowler, N et al # 8036, ASCO 2010

Ergebnisse III Progressionsfreies Überleben

- Mediane Nachbeobachtung 12 Monaten (Range 3-20)
- 1 Progress (FL)



Fowler, N et al # 8036, ASCO 2010

Ergebnisse IV - Nebenwirkungen

Grad 3 und 4 Adverse Events (n=45)	n (%)
Fatigue	1 (2)
Infection (Serious)	1 (2)
Linfopenie	1 (2)
Neuropathie	1 (2)
Neutropenie	10 (21)
Myelgie	4 (8)
Rash	4 (8)
Thrombozytose	2 (4)
Thrombocytopenie	4 (8)

- 3 Patienten wurden aufgrund von Tox aus der Studie genommen (1x schwere Reaktion auf Rituximab, 1x Rash Grad 3 - Diätose mit leukozytäretheliale Vasculitis, 1x schwere Thrombozytose)
- Rash bei 48% (22pts), alle Grade, kein Wiederauftreten bei Reexposition
- Kein Patient mit Toxicodermisyndrom

Fowler, N et al # 8036, ASCO 2010

VERTICAL: Study Objectives

- Primary objective
 - CR
- Secondary objectives
 - ORR (CR + PR)
 - PFS
 - Duration of response
 - Assessment of safety/tolerability of VBR regimen

Fowler, N, et al. ASH 2009, Abstract 933.

Phase 1/2 Study of Lenalidomide + Rituximab in Rel/Ref MCL: Baseline Patient Characteristics

	Phase 1 (n=15)	Phase 2 (n=45)
Median age, years (range)	73 (56-84)	66 (46-85)
Median time from diagnosis, months (range)	30 (15-88)	28 (1-96)
Men/women, n	13/2	41/4
Median prior lines of therapy, n (range)	2 (1-4)	2 (1-4)
No. of prior therapies, n		
1	4	20
2	4	13
3	2	6
4	5	6

Wang et al. Abstract and poster presented at: 51st ASH Annual Meeting and Exhibition, December 5-8, 2009, New Orleans, LA, Abstract 2719.

Guideline Recommendations for Treatment of Relapsed DLBCL

- Second-line therapy in candidates for high-dose therapy + ASCT
 - DHAP ± rituximab
 - ESHAP ± rituximab
 - GDP ± rituximab
 - GemOx ± rituximab
 - ICE ± rituximab
 - MINE ± rituximab
- Second-line therapy for patients who are not candidates for high-dose therapy
 - Clinical trial
 - Rituximab
 - CEPP ± rituximab
 - Lenalidomide
 - EPOCH ± rituximab

NCCN practice guidelines in oncology: non-Hodgkin's lymphomas V.1.2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf.

NHL-003: Safety Profile of active treatment

Most common* Gr. 3/4 adverse event	Grade 3, n (%)	Grade 4, n (%)
Neutropenia	52 (24.0)	37 (17.1)
Thrombocytopenia	29 (13.4)	13 (6.0)
Anemia	18 (8.3)	2 (0.9)
Leukopenia	12 (5.5)	4 (1.8)
Asthenia	9 (4.1)	3 (1.4)
Dyspnea	10 (4.6)	2 (0.9)
Back pain	9 (4.1)	1 (0.5)
Fatigue	10 (4.6)	0 (0.0)
Abdominal pain	8 (3.7)	0 (0.0)
Pain	8 (3.7)	0 (0.0)
Pneumonia	6 (2.8)	1 (0.5)
Dehydration	6 (2.8)	0 (0.0)
Pleural effusion	3 (1.4)	3 (1.4)

* Most common adverse event includes any Grade 3 or 4 event occurring in >5 Patients on study
 Weitz et al. Abstract and poster presented at: 51st Annual ASH Meeting and Exhibition, December 5-8, 2009.
 New Orleans, LA. Abstract 9276

Z-BEAM patients characteristics



Nb	n=77		
Median age	53 yr (31-64)		
Histology		Response after last salvage treatment: pre transplantation	
Follicular G1	41%	CR	27 (36%)
Follicular G2	27%	CRu	31 (41%)
Follicular G3	12%	PR	17 (22%)
Follicular	12%	STABLE	1 (1%)
Marginal Zone	6%		
Lymphocytic	1%		
FLIPI 0-2	74%		
3-5	26%		
BM positive	22%		
Delay (months)		Median	
1st line and transplantation (n =65)		31 m	(7-332)
Last salvage treatment and transplantation (n= 70)		4.4 m	(3-10)

VERTICAL: Patient Characteristics

Characteristic	Patients (N = 63)
Median age, yrs (range)	58 (42-83)
Male, n (%)	40 (63)
KPS ≤ 80%* n (%)	16 (25)
Median LDH, U/L (range)	186 (117-1132)
FLIPI risk groups, n (%)	
▪ Low	19 (30)
▪ Intermediate	21 (33)
▪ High	23 (37)
Extranodal or tumor mass > 7 cm, n (%)	13 (21)
Bone marrow involvement, n (%)	18 (29)
Median time from diagnosis, mos (range)	50 (7-273)

Fowler N, et al. ASH2009. Abstract 933.

CORAL Study: PFS

2-Year PFS According to Patient Subgroup (ITT)	Patients, %	P Value
Failure from diagnosis		< .0001
▪ ≥ 12 mos (n = 160)	64	
▪ < 12 mos (n = 228)	31	
Previous rituximab		< .0001
▪ No (n = 147)	62	
▪ Yes (n = 241)	30	

Gisselbrecht C, et al. ASCO 2009. Abstract 8509.