



Novel treatment options in Waldenström macroglobulinaemia

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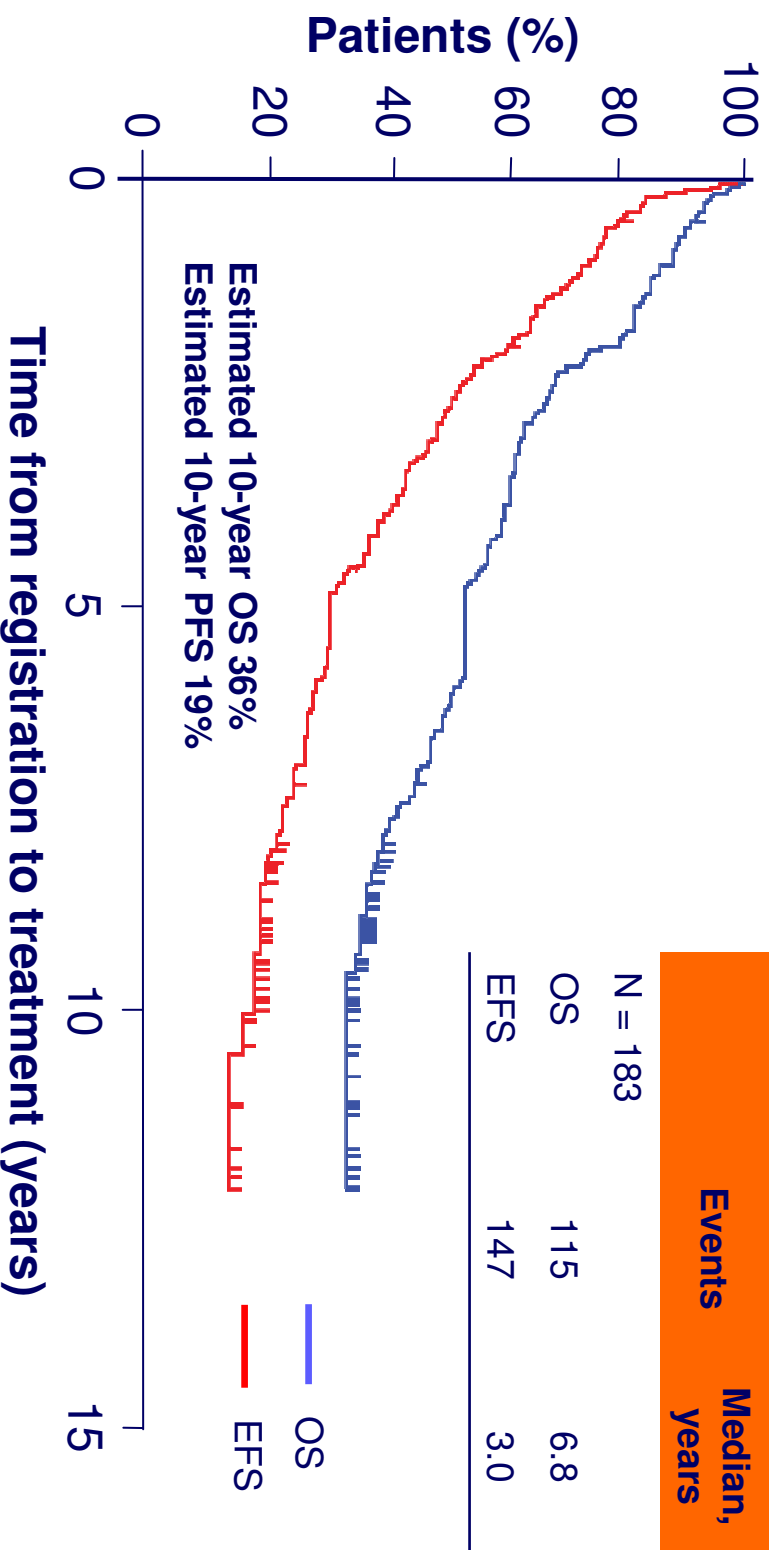
Major Stock Shareholder: No

Single-agent primary treatment of Waldenström macroglobulinaemia

	Chlorambucil	Nucleoside analogues	Rituximab
Response rate, %	50	70–80	40
Time to response, months	6–12	1.5–5	3–5
Duration of treatment, months	12–24	2–6	1
Cost	Low	Average	High
Myelosuppression	Moderate	Significant	None
Opportunistic infections	No	Yes	No
Stem cell toxicity	Yes	Yes	No
Miscellaneous	Secondary leukaemia	Secondary leukaemia transformation	IgM "flare"

Long-term survival after fludarabine in WM: 10-year follow-up of SWOG S9003 trial

Patients received fludarabine i.v. 30 mg/m² daily for 5 days



EFS = event-free survival;

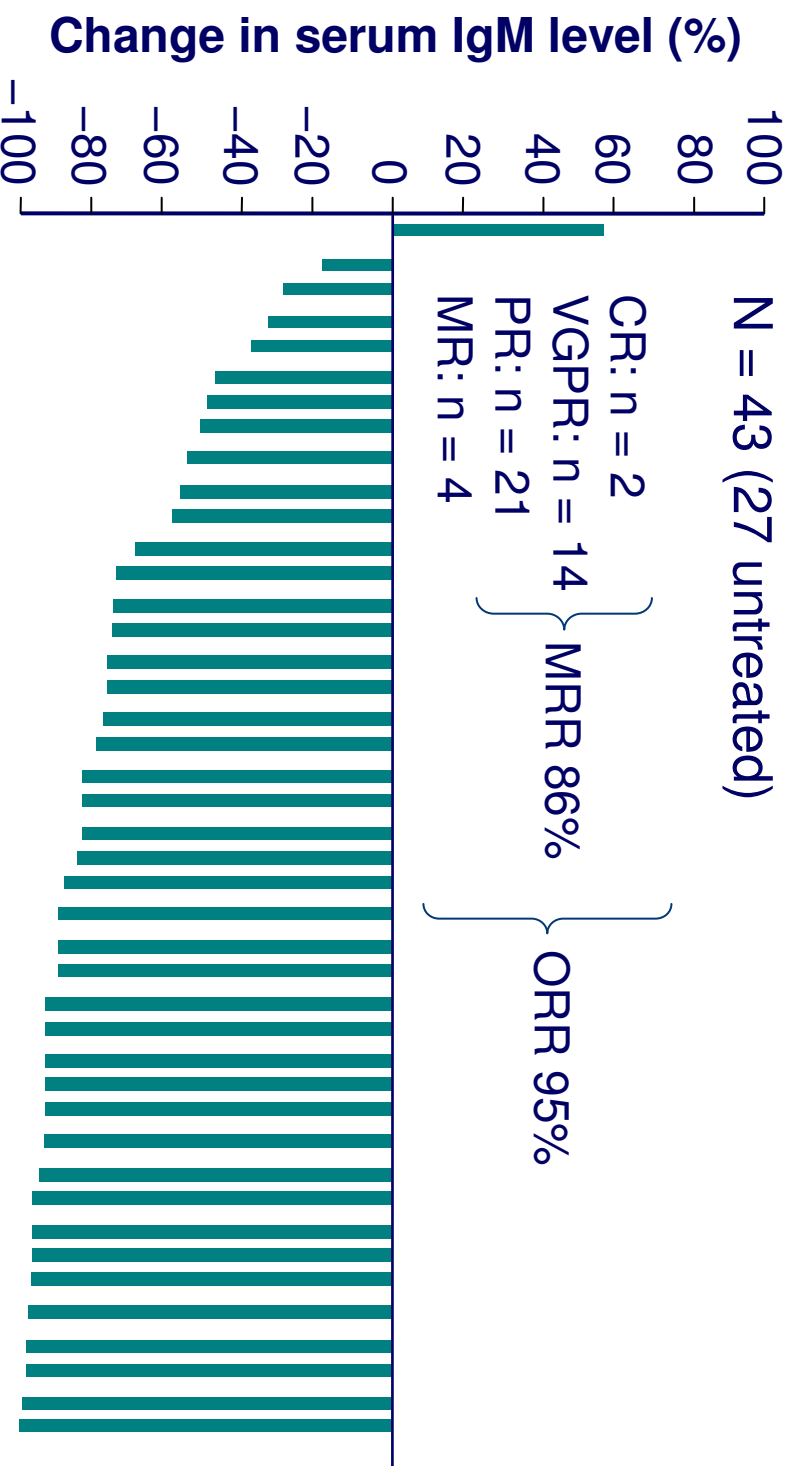
PFS = progression-free survival;

SWOG = Southwest Oncology Group.

Dhodapkar MV, et al. Blood. 2009;113:793-96.

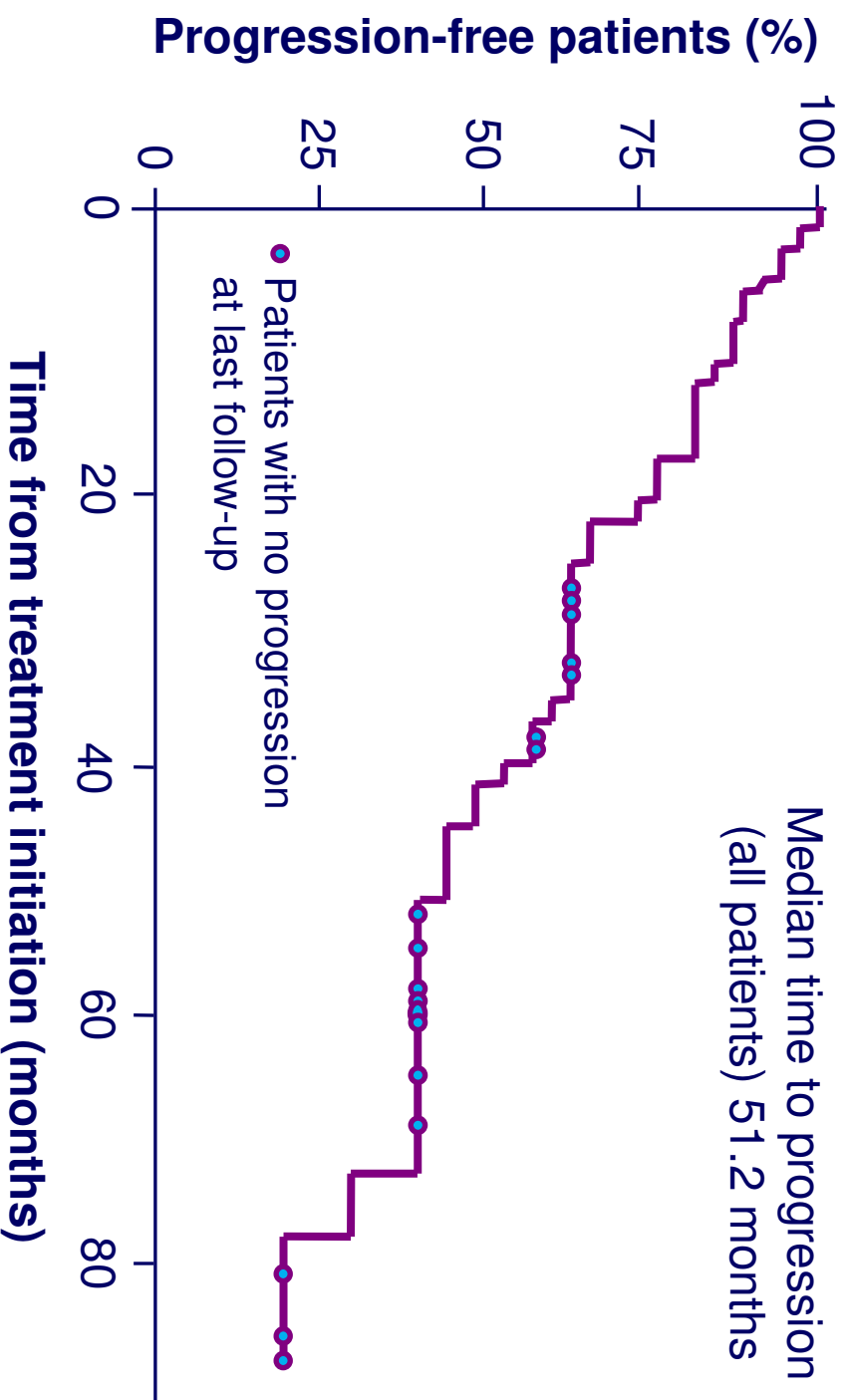
Long-term outcomes after fludarabine and rituximab in WM (1)

Individual changes in serum IgM concentration after treatment with fludarabine and rituximab (best response)

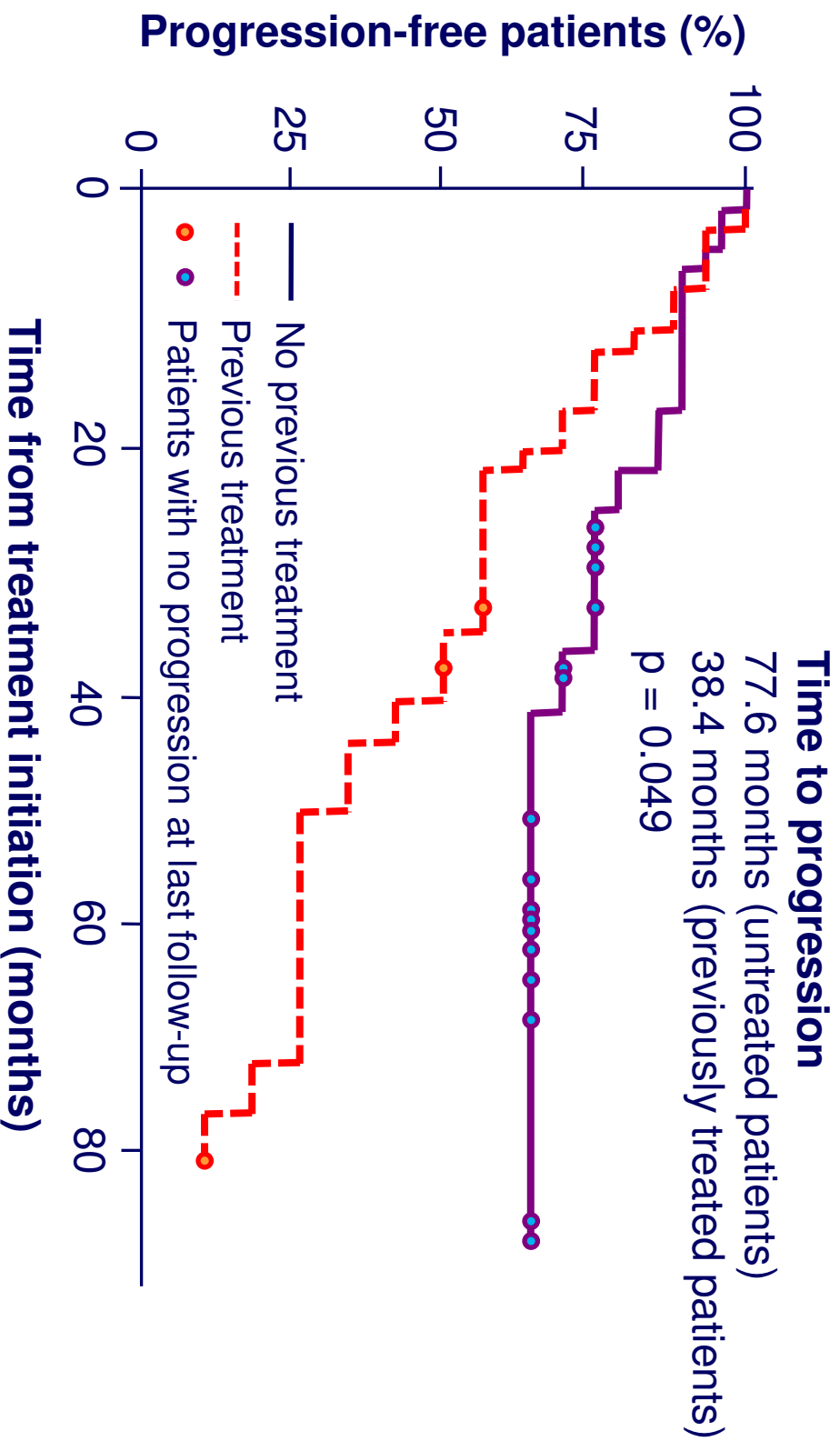


CR = complete response; MR = minor response; MRR = major response rate; ORR = overall response rate; PR = partial response; VGPR = very good partial response.

Long-term outcomes after fludarabine and rituximab in WM (2)



Long-term outcomes after fludarabine and rituximab in WM (3)



Rituximab in combination with nucleoside analogues (1)

- Rituximab with cladribine plus cyclophosphamide¹
 - 18 previously untreated patients
 - ORR 94%; CR in 17% of patients
 - median time to response 2.4 months
 - median duration of response 58.6 months
- Rituximab with subcutaneous cladribine²
 - 29 patients (16 previously untreated)
 - ORR 59%; MR in 24% of patients

1. Thomas SK, et al. Haematologica. 2007;92:[abstract 1227].

2. Laszlo D, et al. Blood. 2007;110:[abstract 1357].

Rituximab in combination with nucleoside analogues (2)

- Rituximab with fludarabine plus cyclophosphamide (RFC)¹
 - 19 patients (5 previously untreated)
 - \geq PR in 79% of patients
 - no patients developed IgM “flare”
 - delayed response in 10 patients
- RFC (oral fludarabine and cyclophosphamide)²
 - 25 patients (mainly pretreated)
 - ORR 90%, VGPR in 35% of patients
 - median duration of response 8 months

1. Tedeschi A, et al. Blood. 2007;110:[abstract 1290].

2. Vargatig J, et al. Haematologica. 2007;92:[abstract 1226].

DRC regimen



D Dexamethasone 20 mg i.v.

R Rituximab 375 mg/m² i.v.

Cyclophosphamide 100 mg/m² p.o. b.i.d. (total 1,000 mg/m²)

DRC course repeated every 21 days × 6

Response, %

ORR	83
CR	7
PR	67
MR	9
SD	8
PD	8

N = 72

Median time to 50% IgM reduction

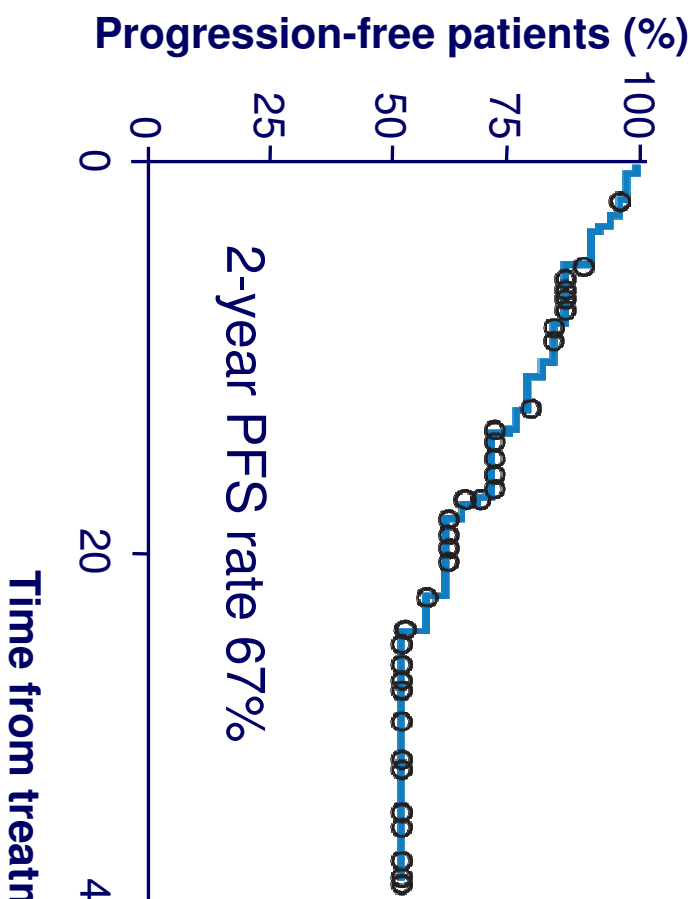
4.1 (range 0.7–14) months

IgM "flare" in 32%

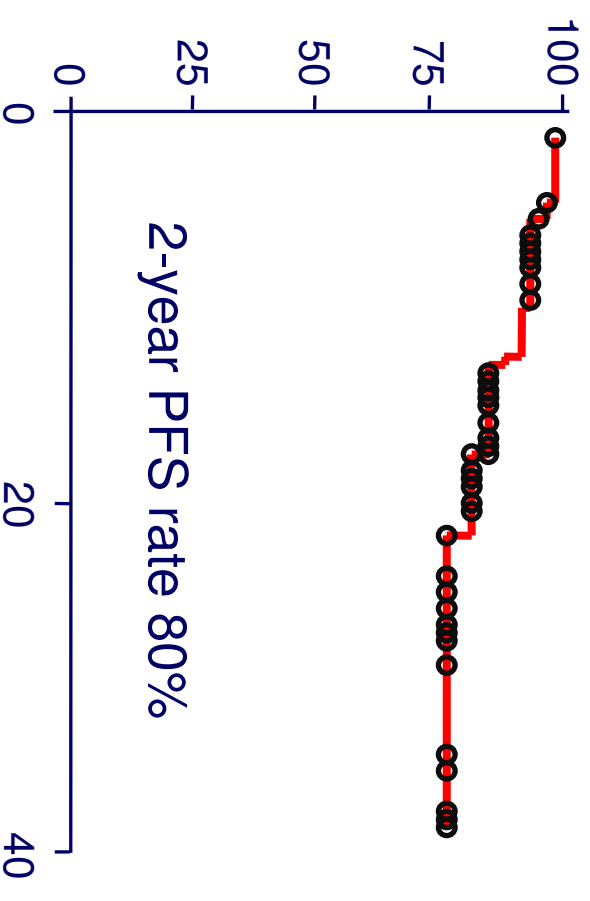
≥ 25% IgM increase in 11%

DRC regimen: time to progression

All patients



Patients with a response



Without additional treatment, 2-year survival rate 78%
2-Year overall survival rate 81%

Standard R-CHOP in untreated WM

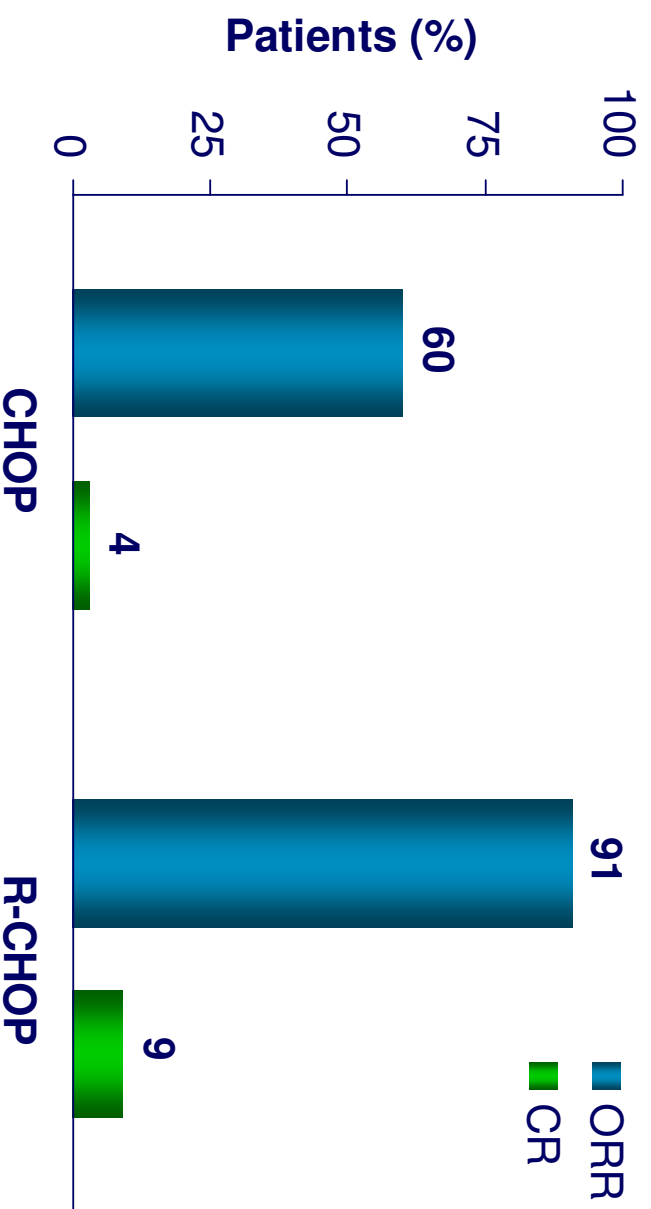
- 16 patients
 - median age 60 (range 44–79) years
 - median β_2 -microglobulin 3 (range 2.1–7.6) $\mu\text{g/mL}$
 - median haemoglobin 9 (range 7.7–10.9) g/dL
 - median IgM 6,389 (range 3,229–13,300) mg/dL
- Objective response 91%
 - 1 patient had an MR
- Median time to response 1.6 months
- Median time to maximum response 2.1 months
- The main adverse event was myelosuppression

CHOP = cyclophosphamide, hydroxydaunorubicin, Oncovin[®] (vincristine), prednisone; R-CHOP = CHOP and rituximab.

Abonour A, et al. Blood. 2007;110:[abstract 3616].

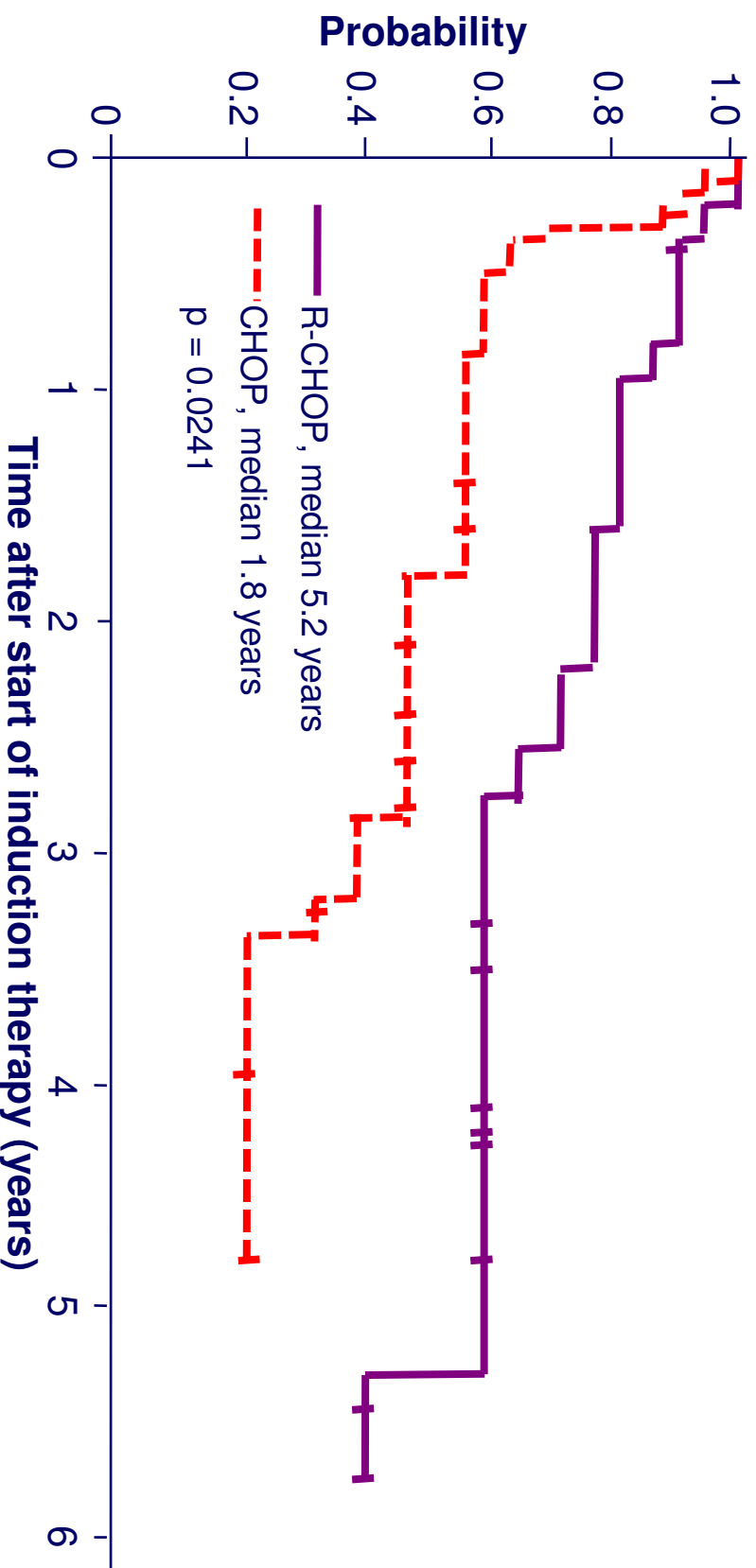
CHOP versus R-CHOP in WM (1)

N = 48
CHOP (n = 25)
R-CHOP (n = 23)



CHOP versus R-CHOP in WM (2)

Time to treatment failure after start of CHOP or R-CHOP therapy



Number of patients at risk

R-CHOP	23	18	16	9	7	3	0
CHOP	25	14	10	5	1	0	

Thalidomide and rituximab in WM: responses

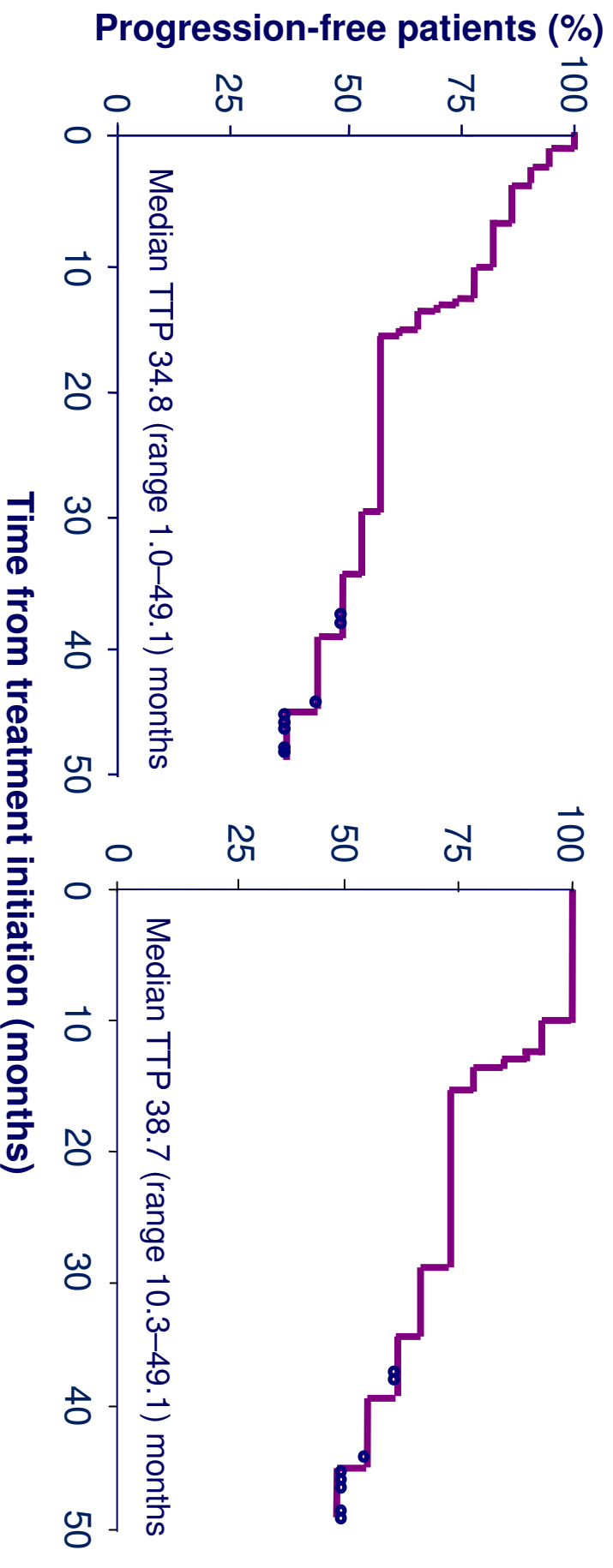
- 25 patients, 23 of whom received the intended therapy
- Responses in evaluable patients
 - CR in 1 (4%)
 - PR in 15 (60%)
 - MR in 2 (8%)
 - SD in 1 (4%)
- Median follow-up 42 months
 - median TTP 35 months for all patients
 - median TTP 38+ months for patients with a response

MR = major response.

Treon SP, et al. Blood. 2008;112:4452-7.

Thalidomide and rituximab in WM: time to progression

All evaluable patients



Median follow-up 47.1 months; progression in 10 of 18 patients with a response

For untreated patients, median TTP 36.04 (range 2.5-49.1) months

For pretreated patients, median TTP 15.25 (range 1.0-45.8) months ($p = 0.36$)

Bortezomib monotherapy in WM

Study	Patients, N	Median cycles, n	ORR, %	PR, %
WMCTG ¹	27	6	85	44
NCI-Canada ²	27	6	78	44
Dimopoulos ³	10	4	60	60

Grade \geq 3 sensory neuropathy, seen in 20–30% of patients, was reversible in most patients.

1. Treon SP, et al. Clin Cancer Res. 2007;13:3320-5.

2. Chen CI, et al. J Clin Oncol. 2007;25:1570-5.

3. Dimopoulos MA, et al. Haematologica. 2005;90:1655-8.

Twice-weekly BDR as primary treatment in WM

- 23 patients
- Median 7 (range 3–8) cycles

	Response	Patients, n (%)
CR or nCR		5 (22)
PR		14 (61)
MR		3 (13)
SD		1 (4)

83% (CR or nCR + PR)
96% (CR or nCR + PR + MR)

- Median time to $\geq 25\%$ decrease in IgM 1.1 months
- Median follow-up 22.8 (range 3.3–33.2) months
 - 18 (78%) of 23 patients remain progression free

BDR in WM: adverse events

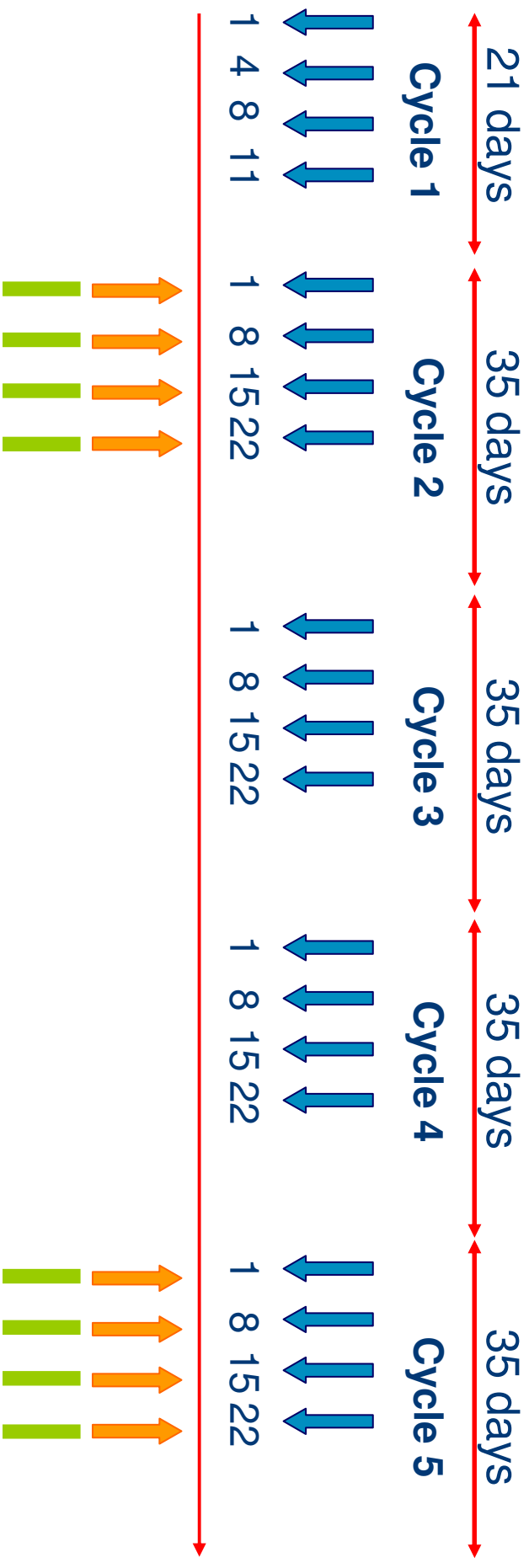
Adverse event*	Patients, %	
	Grade ≥ 2	Grade 3
Paraesthesia	69	30
Anaemia	83	4
Neutropenia	56	30 [‡]
Thrombocytopenia	43	9

* 13 (81%) of 16 resolved at a median of 6 months.

[‡] Or grade 4.

Of the first 7 patients on study, 4 had a herpes zoster infection necessitating treatment with valacyclovir 1 g/day p.o.

European Myeloma Network (EMN): BDR protocol as primary treatment



↓ **Bortezomib** { Cycle 1: bortezomib 1.3 mg/m²
Cycles 2–5: bortezomib 1.6 mg/m²

→ **Rituximab** (375 mg/m²)

■ **Dexamethasone** (40 mg)

EMN BDR protocol as primary treatment (Greece, Spain, France, Netherlands)

Preliminary results

- 30 patients accrued so far
- 25 patients are evaluable for a response (5 are early for evaluation)

Response	Patients, n
CR	1
PR	10
MR	4
SD	8
PD	2

Alemtuzumab in WM (1)

- 28 patients
 - 5 untreated
 - all previously treated patients had received rituximab
 - 25 patients evaluable

Response	Patients, %
ORR	76
PR	32
MR	44

Alemtuzumab in WM (2)

- Haematological adverse events
 - grade 3 events most common in previously treated patients (74% vs 20%; p = 0.041)

Haematological events (grade 3 and 4)	Patients, %
Neutropenia	39
Thrombocytopenia	18
Anaemia	7

Non-haematological events (grade 3 and 4)	Patients, %
Dermatitis	11
Fatigue	7
Infection	7

- After a median follow-up of 8.5+ months, 11 of 19 patients with a response remain free of progression

High-dose therapy for WM

Facts to consider

- Patients' advanced age, and therefore comorbidity
- Relatively benign clinical course of the disease
- Prior treatment with nucleoside analogues
- High risk of developing MDS or leukaemia

Autologous stem cell transplantation

Retrospective analyses

- EBM^T registry¹
 - 201 patients
 - at time of transplant, 86% of patients had chemosensitive disease and 14% had relapsed/refractory disease
 - transplant-related mortality rate 8%
 - 5-year PFS 33%; 5-year OS 61%
- French registry²
 - 32 patients
 - median EFS 32 (range 2–119) months
 - 5-year OS 58%

EBMT = European Group for Blood and Marrow Transplantation.

1. Kyriakou C, et al. Haematologica. 2007;92:[abstract 1228].
2. Dhedin M, et al. Haematologica. 2007;92:[abstract 1229].

Allogeneic stem cell transplantation (1)

- EBMT registry
 - 106 patients
 - at time of transplant, 70% had chemosensitive disease and 30% chemorefractory disease
 - conventional conditioning was administered to 41% of patients and RIC to 59%
 - 1-year non-relapse mortality rate 27%
 - 5-year PFS 48%; OS 63%

RIC = reduced intensity conditioning.

Kyriakou C, et al. Haematologica. 2007;92 Suppl 2:[abstract n. WM3.09].

Allogeneic stem cell transplantation (2)

- French registry
 - 22 patients; MA-allo in 11, RIC-allo in 11
 - transplant-related mortality rate
 - 36% in MA-allo group
 - 27% in RIC-allo group
 - median EFS
 - 36 months in MA-allo group
 - not reached in RIC-allo group
 - relapse rate
 - 36% in MA-allo group
 - no relapses in RIC-allo group

MA = myeloablative.

Dhedin M, et al. Haematologica. 2007;92:[abstract 1229].

Allogeneic stem cell transplantation (3)

- Seattle experience
 - 12 patients underwent RIC-allo-SCT
 - transplant-related mortality rate 17%
 - 10 of 11 evaluable patients had a response after the transplant (4 CR, 6 PR)
 - 5-year PFS rate 61%
 - median time to CR 12 months, thus supporting a graft-versus-tumour effect

SCT = stem cell transplantation.

Anderson LD, et al. Blood. 2006;108:[abstract 3034].

Recommendations for front-line treatment (1)

- Individual patient considerations in choosing a first-line treatment
 - presence of cytopenia
 - need for rapid disease control
 - age
 - comorbidity
 - candidacy for an autologous transplant

Recommendations for front-line treatment (2)

- Rituximab-based therapies may be the preferred initial treatment for most patients with WM
- When rapid disease control is needed, R-CHOP or NA-RC could be an appropriate choice
- Bortezomib-based combinations may emerge as a choice for patients with hyperviscosity in whom rapid reduction of the paraprotein is needed
- For patients who are, or may in the future be, candidates for ASCT, appropriate primary therapies include R-CHOP, DRC, and RT

DRC = dexamethasone, rituximab, and cyclophosphamide;

NA-RC = nucleoside analogues plus rituximib plus cyclophosphamide.

Dimopoulos MA, et al.

J Clin Oncol. 2009;27:120-6.

Recommendations for front-line treatment (3)

- DRC or RT may be preferable for patients with cytopenias, even for patients who are not candidates for ASCT
- Rituximab with a nucleoside analogue with or without cyclophosphamide may also be appropriate, especially in patients with features of advanced disease
- Some selected patients with low-risk disease may be appropriate candidates for single-agent rituximab or chlorambucil because of associated comorbid conditions

RT = rituximab and thalidomide.

Dimopoulos MA, et al. J Clin Oncol. 2009;27:120-6.

Recommendations for front-line treatment in transplant candidates

Clinical condition	Recommended treatment
Cytopenia	DRC Rituximab + thalidomide
High M-protein concentration	R-CHOP DRC

Recommendations for front-line treatment in non-transplant candidates

Clinical condition	Recommended treatment
Cytopenia	DRC Rituximab + thalidomide
High M-protein levels	Nucleoside analogues + rituximab Nucleoside analogues + rituximab + cyclophosphamide
Low M-protein level and cytopenia	Rituximab
Older age and slow progression	Chlorambucil

Recommendations for salvage treatment (1)

- The choice of salvage therapy depends on
 - front-line treatment
 - quality and duration of previous response
 - patient's age
 - tolerance of initial therapy
 - candidacy for SCT
- Re-use of a front-line single agent or combination is reasonable if a patient had an unmaintained response that lasted for at least 12 months

Recommendations for salvage treatment (2)

- For patients who have a short remission or resistance to a front-line regimen, second-line treatment may include agents of a different class, alone or combined
- RFC or RCC regimen may be appropriate, but should be avoided in younger patients and those who are eligible for ASCT
- Bortezomib-based therapy may be an appropriate second-line choice
- Alemtuzumab may represent a reasonable choice of third-line therapy

RCC = rituximab, cladribine, and cyclophosphamide;
RFC = rituximab, fludarabine, and cyclophosphamide.

Dimopoulos MA, et al. J Clin Oncol. 2009;27:120-6.

The role of high-dose therapy

- The place of autologous or allogeneic SCT requires further evaluation in the context of prospective trials
- According to the IPSSWM, one-third of patients belong to a high-risk group with a median survival of 3 years
- For younger patients with high-risk disease, prospective trials should be considered that incorporate high-dose therapy in the up-front treatment strategy
- All new randomized trials should stratify patients according to IPSSWM, and eventually specific treatments may be evaluated for the different IPSSWM risk groups