Bari 6-7 ottobre 2016

Il ruolo della target therapy nel linfoma mantellare

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Ematologia PISA

Mantle Cell Lymphoma

Cytology

Nodular / mantle

diffuse

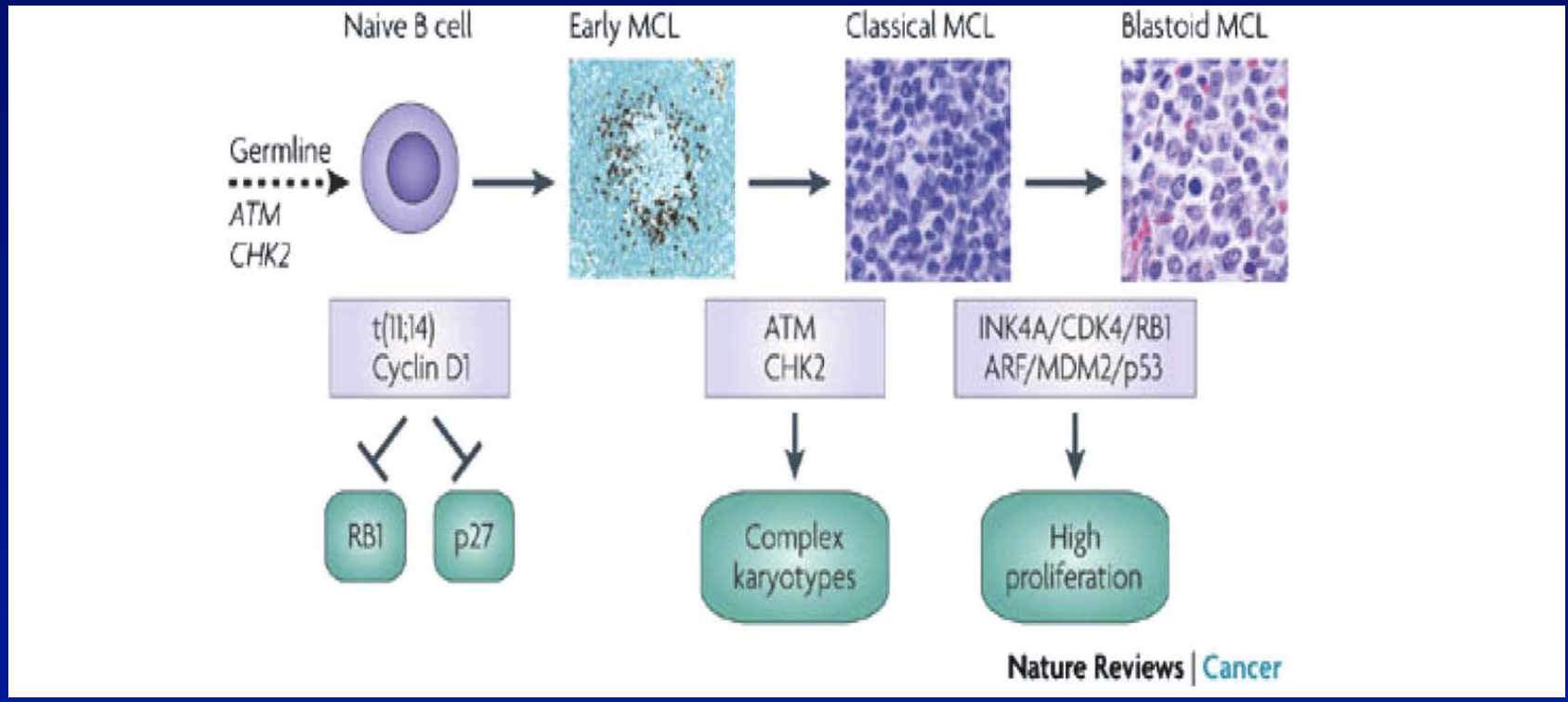
Typical (Classic)

Blastoid (Blastic)

small to medium-sized Ly with scanty cytoplasm, irregular nuclei, condensed chromatin. Rarely round nuclei (mimicking CLL), or abundant pale cytoplasm (mimicking Marginal Zone Lymphoma)

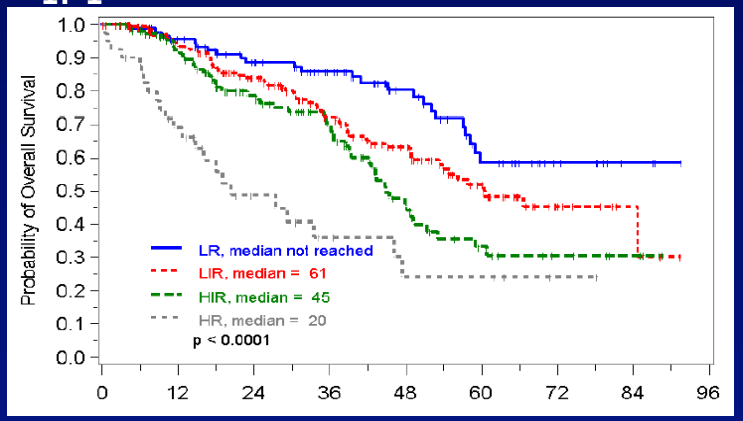
Classic Blastoid Variant: medium-sized Ly with scanty cytoplasm and round nuclei with finely dispersed chromatin and high mitotic index

Pleomorphic Blastoid Variant: heterogeneous large cells with irregular cleaved nuclei, finely dispersed chromatin, small distinct nucleoli

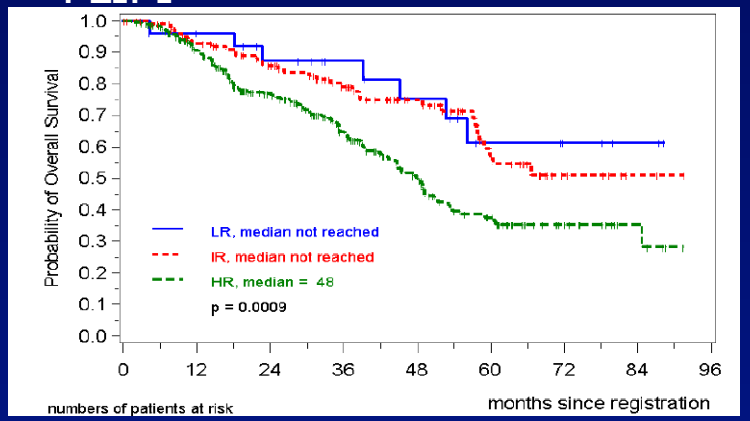

Naive B cell
Early MCL
Classical MCL
Blastoid MCL
Germline
ATM
CHK2
t(11;14)
Cyclin D1
ATM
CHK2
INK4A/CDK4/RB1
ARF/MDM2/p53
RB1
p27
Complex
karyotypes
High
proliferation
Nature Reviews | Cancer

A New Prognostic Index (MIPI) for Patients with AdvancedStage Mantle Cell Lymphoma

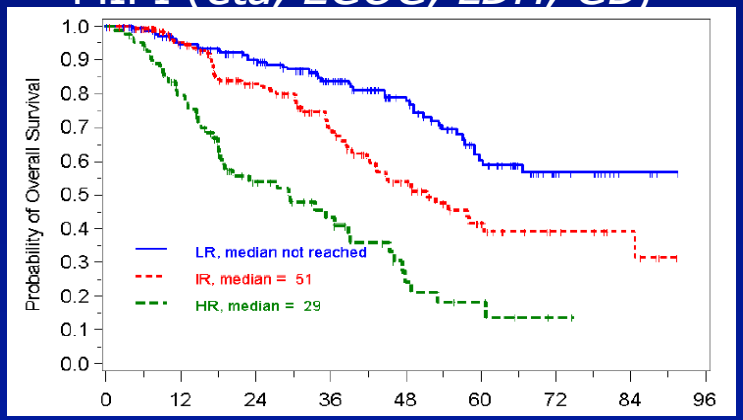
IPI



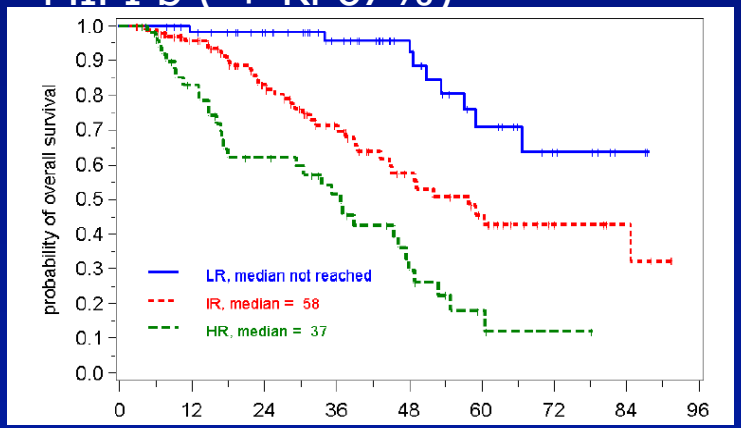
FLIPI



MIPI (*età, EGOG, LDH, GB*)



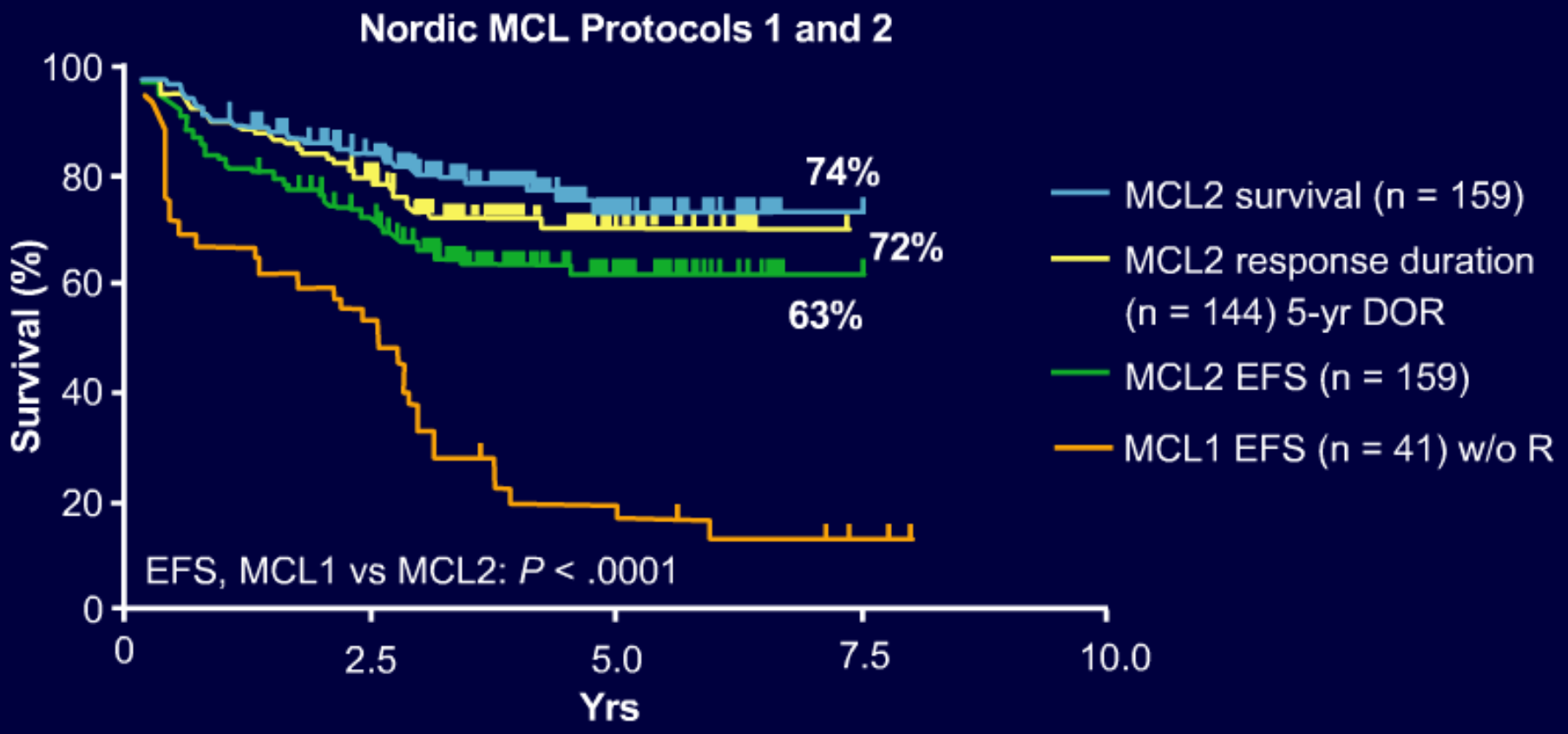
MIPI b (+ Ki 67%)



Based on data of 455 patients with advanced stage MCL from three randomized trials

Hoster E, GLSG & *European MCL Network.***Blood First Edition Paper, prepublished online October 25, 2007**

Intensive Chemotherapy Plus ASCT in MCL (Nordic MCL2 Study): Efficacy



- 6 (3.8%) treatment-related deaths

Geisler CH, et al. Blood. 2008;112:2687-2693.

- Nonostante buoni od ottimi risultati raggiunti con i trattamenti aggressivi incluso auto o allotrapianto nel 2016 non si è ancora raggiunto un plateau nella curva di sopravvivenza che continua a cadere anche opo dieci anni dalla remissione

Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG)

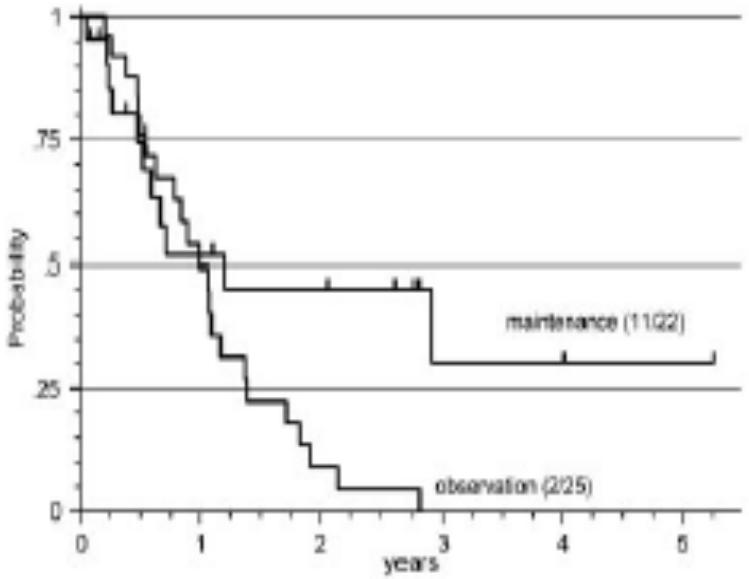
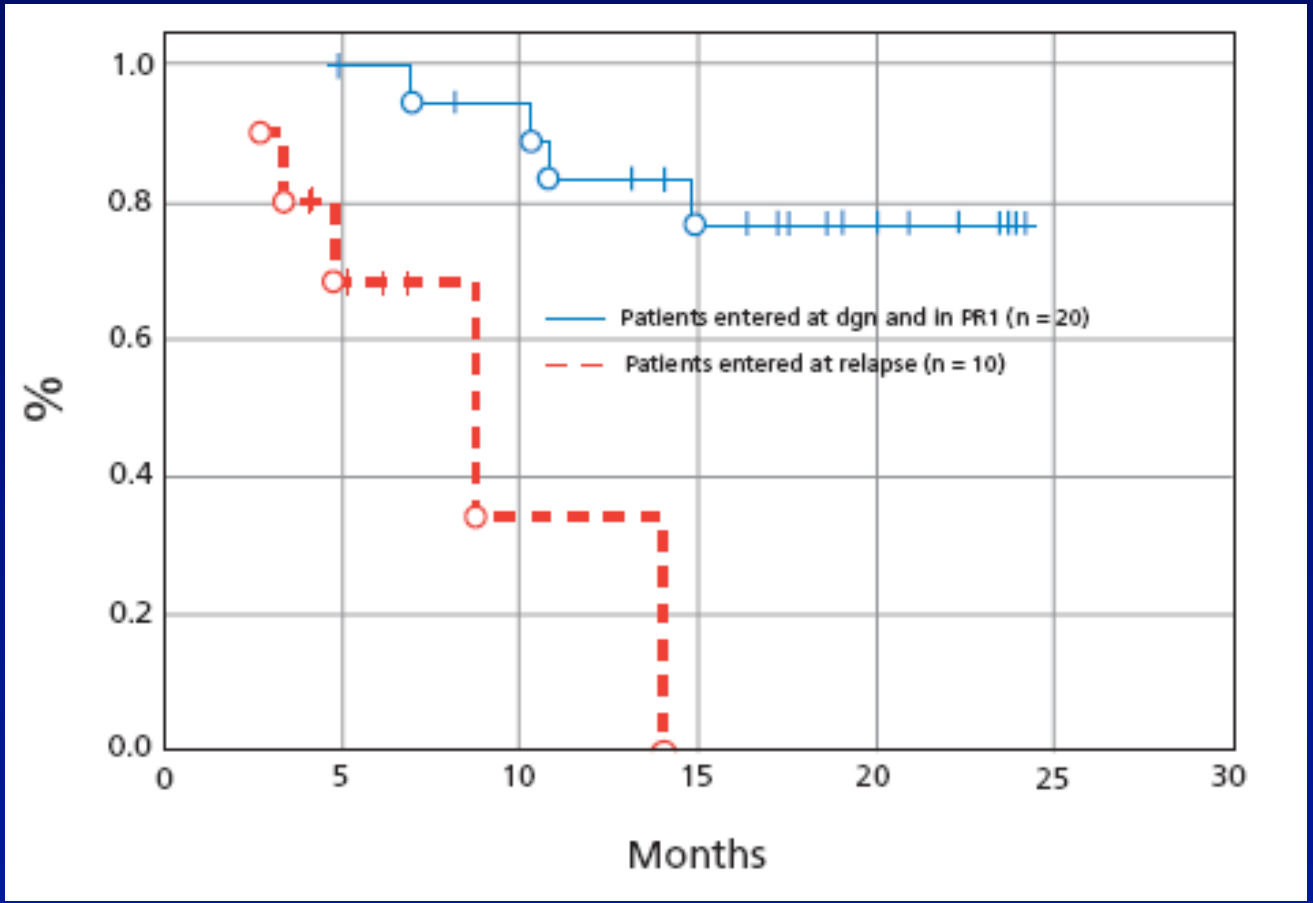


Figure 3. Response duration after R-FCM in patients with MCL. A significant prolongation of response duration by R-maintenance compared with observation only was observed ($P = .049$), with median response durations of 14 months versus 12 months but a higher proportion of ongoing remissions beyond 2 years of 45% versus 9%.

Forstpointner et Al BLOOD, 2006; 108: 4003

PLRG study: Zevalin consolidation of MCL 1st line therapy (II)
Event Free Survival



Jurczak W. et al., Haematologica 2006; 91: #0188
Updated Blood 2006;108:#2747

Lenalidomide

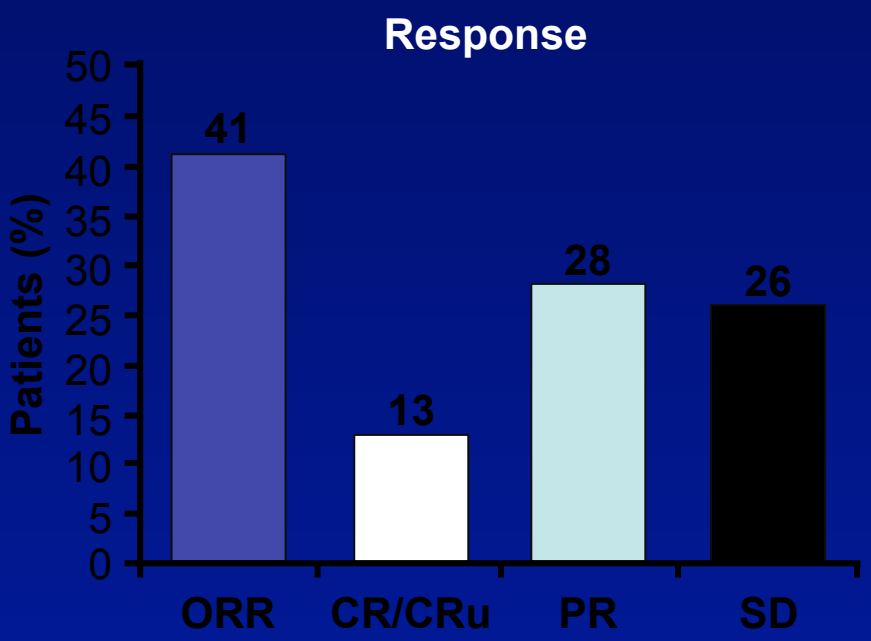
Histology	n	ORR, %	PFS, Mos
DLBCL	108	28	2.3
Mantle cell	57	42	5.7
Follicular (grade 3)	19	42	6.3
T-cell	33	45	4.6

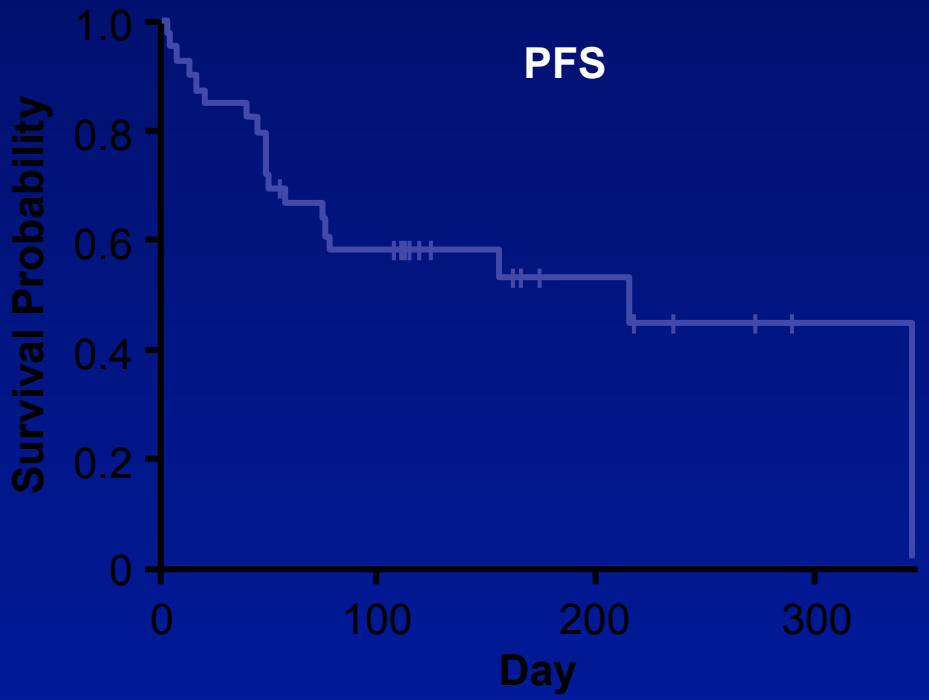
- ORR in patients with previous SCT: 37% (27/73)
- Grade 3/4 neutropenia: 41%; thrombocytopenia: 19%

Lenalidomide

- Treatment: lenalidomide 25 mg
  - PO QD on Days 1-21 every 28 days; continue for 52 wks
- Patients with relapsed/refractory MCL: N = 39
  - Median age: 66 yrs (range: 33-81)
  - Median number of previous therapies: 3 (range: 1-8)
    - 23% (9/39) had previous bortezomib therapy

Lenalidomide





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.

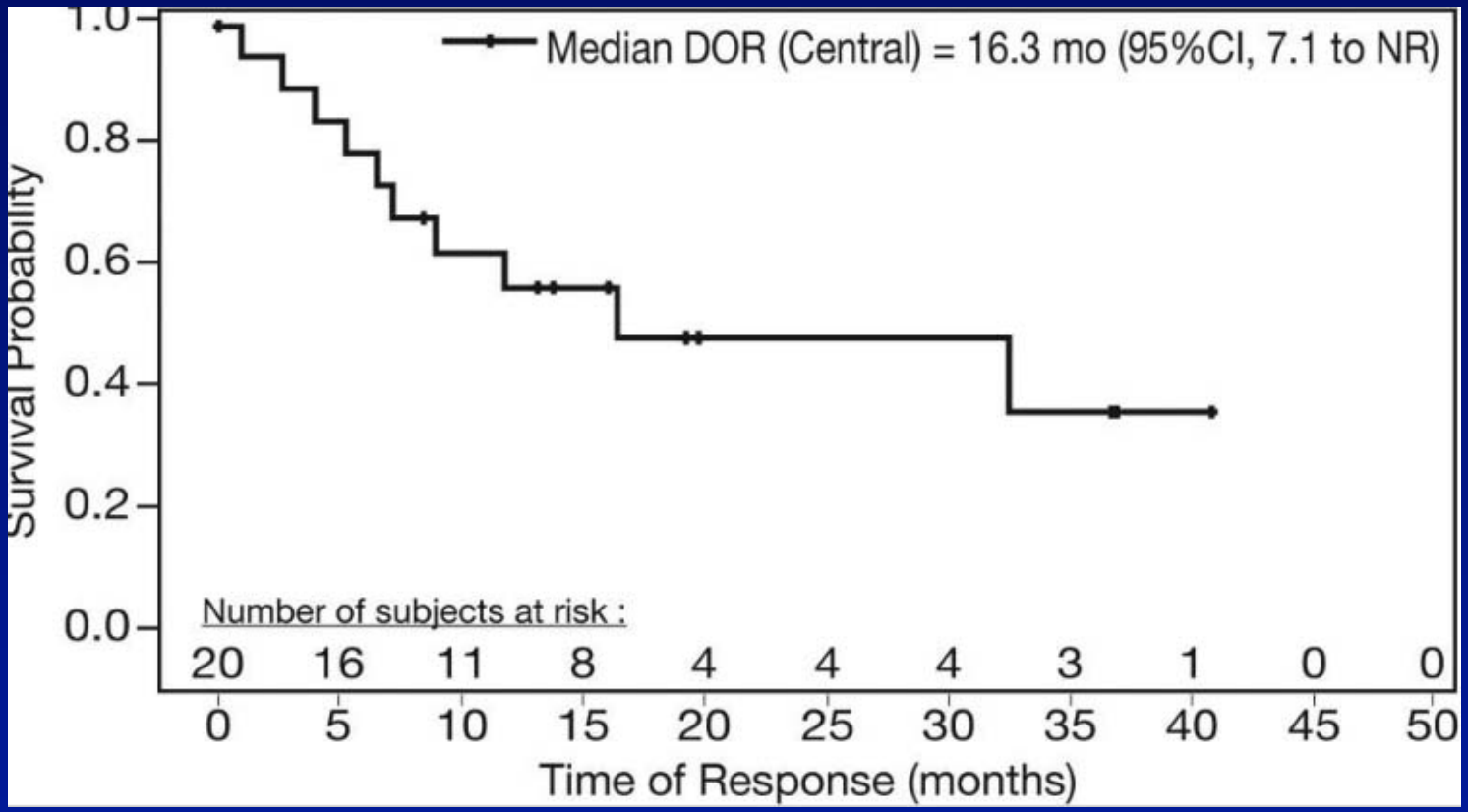
Lenalidomide in MCL Patients Previously Treated With Bortezomib

- 25 mg of lenalidomide PO QD on Days 1-21 of every 28-day cycle
- Median age: 66 yrs
- N = 14
- **ORR: 57%**
- **CR/CRu: 21%**
- **PR: 36%**
- **SD: 7%**

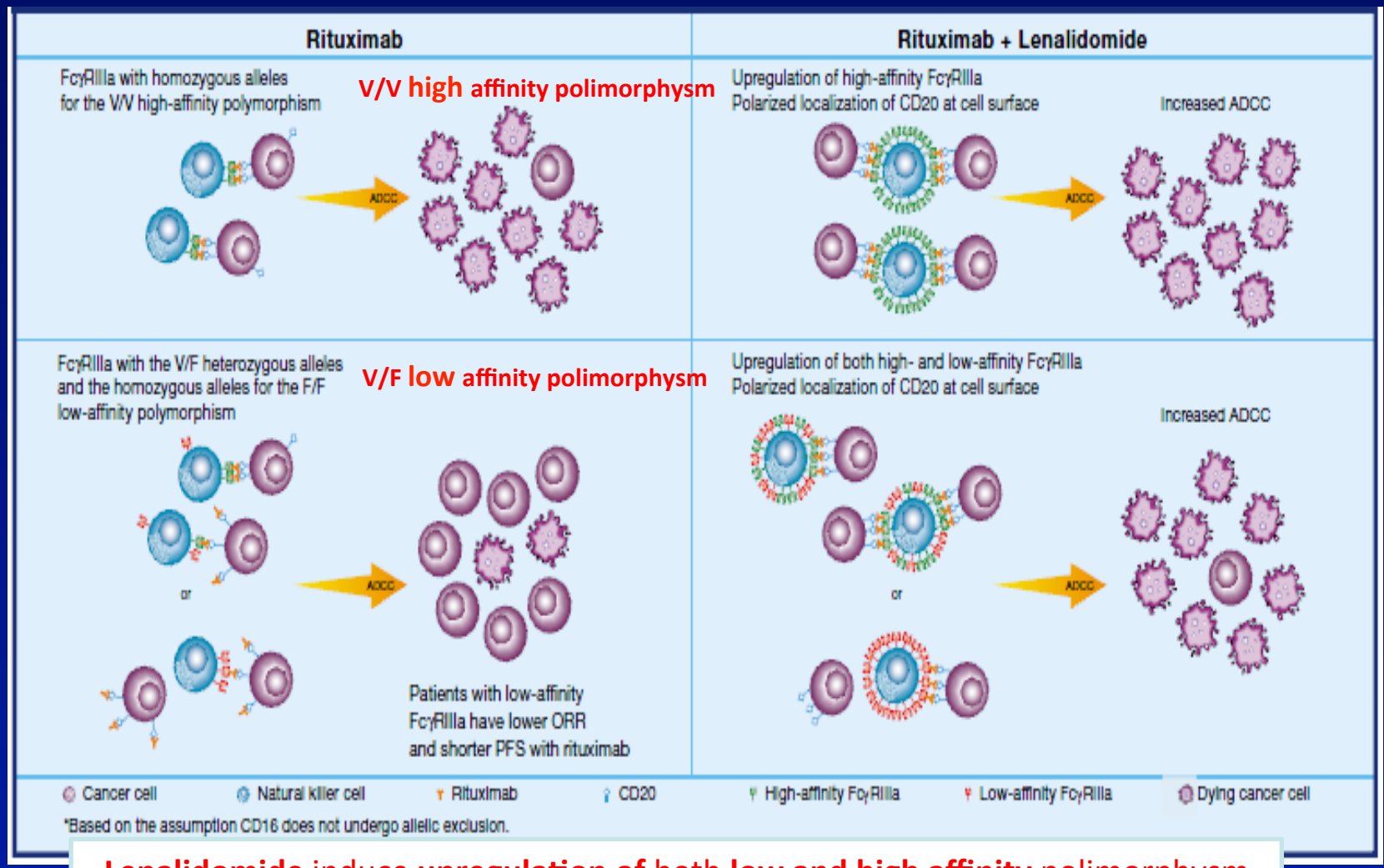
Grade 3/4 Adverse Events, %	
Neutropenia	50
Thrombocytopenia	43
Anemia	21
Fatigue	21
Leukopenia	21

Reeder CB, et al. ASH 2008. Abstract 1560.

Long-term follow-up of lenalidomide in relapsed/refractory mantle cell lymphoma: subset analysis of the NHL-003 study P. L. Zinzani et Al Ann Oncol 2013



Proposed Mechanism for enhanced ADCC in pts with FL treated with R2, and the effect of FCgRIIIa polymorphism

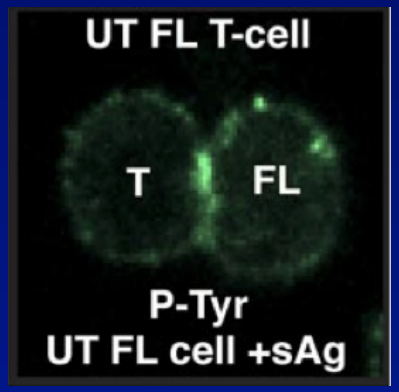


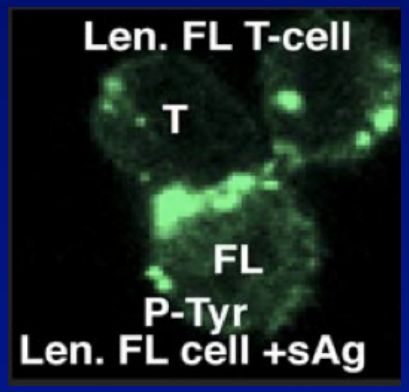
Lenalidomide induce **upregulation of** both **low and high affinity** polimorphysm **FcyRIIIa** + induce **CD20 polimerization** at cell surface

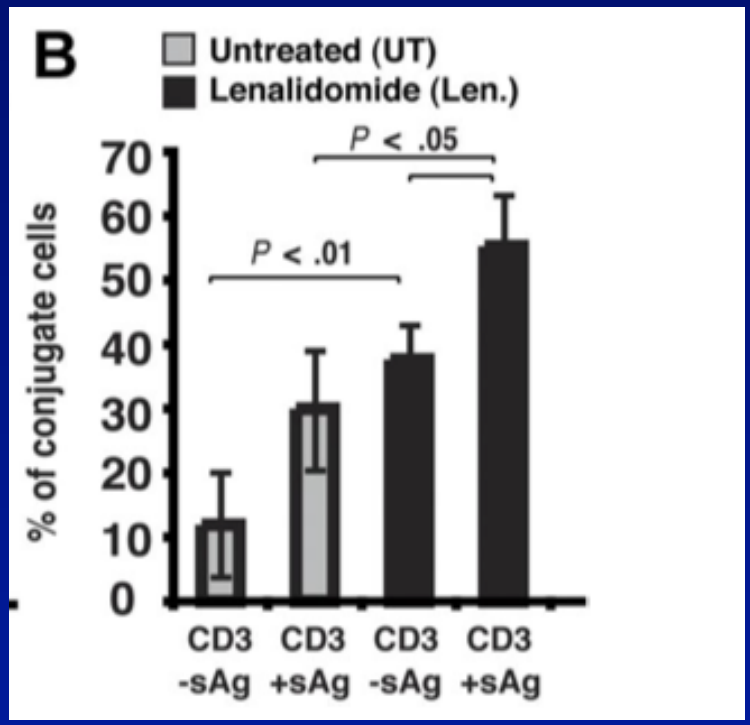
Dutia et al, ICML 2011; abstract 306

FL: sinapsi

Lenalidomide ripristina le sinapsi nel FL

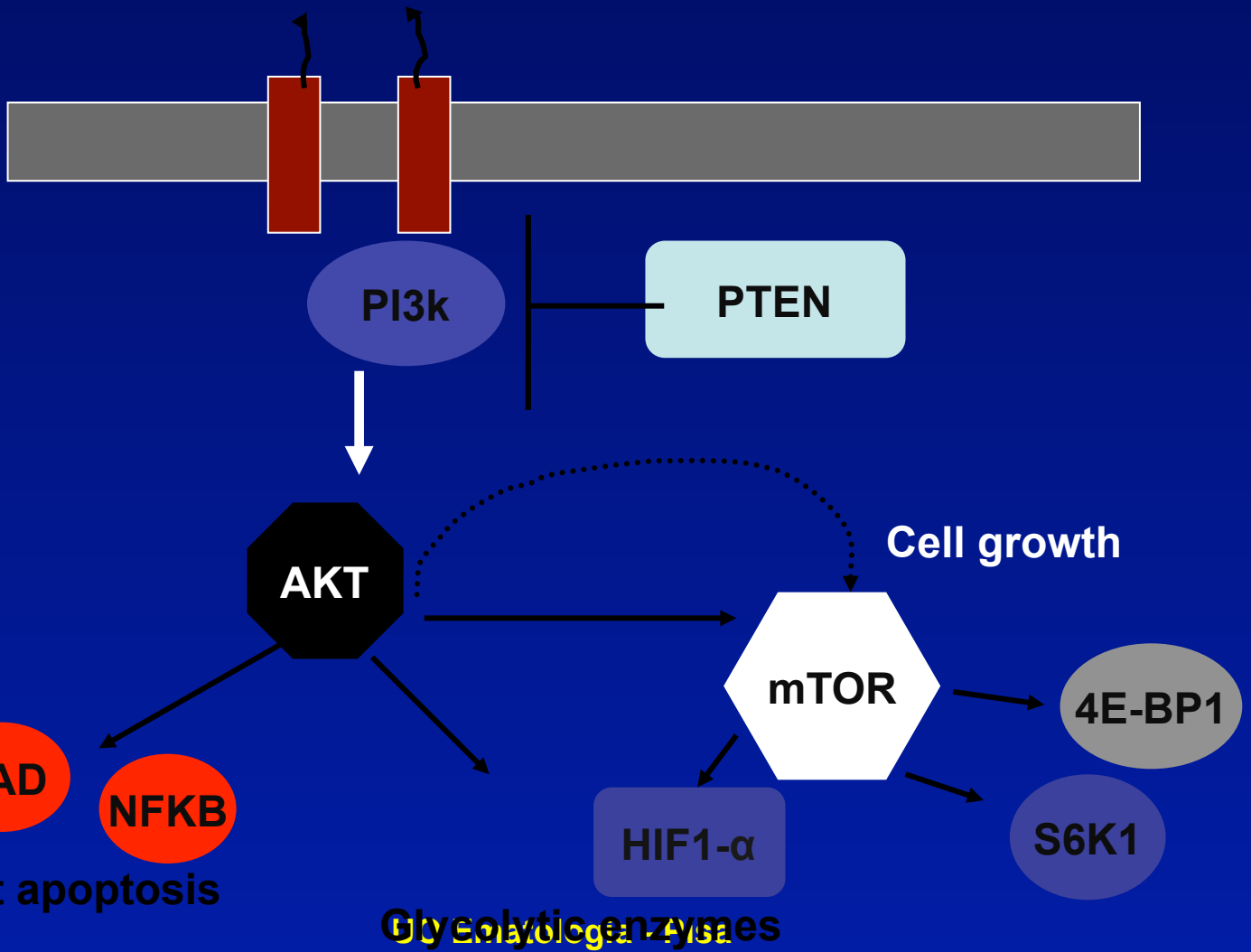






Ramsay, Blood 2009

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.

Phase III Trial in MCL: Temsirolimus vs Investigator's Choice

MCL confirmed locally
Relapsed/refractory to
2-7 previous therapies
Required:
Rituximab
Anthracycline
Alkylating agent

(N = 162)

→ **RANDOMIZE**

- **Temsirolimus 175 mg/wk x 3** then **75 mg/wk**
- **Temsirolimus 175 mg/wk x 3** then **25 mg/wk**
- **Investigator's choice** single agent

- Temsirolimus treatment to continue until progression, death, or unacceptable toxicity
- Primary endpoint: PFS

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

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 (0.25-0.78)	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 (5.8-15.1)
▪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	.0019	.6179	
Most common grade 3/4 adverse events, %			
▪Thrombocytopenia	59	52	36
▪Anemia	20	11	17
▪Neutropenia	15	22	26
▪Asthenia	13	19	8

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

Bortezomib for the treatment of mantle cell lymphoma: an update
Bryan Hambley *Ther Adv Hematol 2016*

Table 3. Bortezomib: relapsed or refractory regimens.

Regimen/trial	Treatment scheme	Number of patients	Median age	Median follow-up (months)	Median number of prior lines	Prior ASCT	ORR	CR	PFS	OS	Reference
PINNACLE	Bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 in 21-day cycles (every 21 days until progression up to 17 cycles)	155	65	32	1	37%*	32%	8%	6.7 months	23.5 months	Fisher *et al.* [2006]; Goy *et al.* [2009]
BVR	Bendamustine 90 mg/m² IV on days 1 and 4 Bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11 Rituximab 375 mg/m² on day 1 (every 28 days up to six cycles)	30 (total) 7 (MCL)	64	24	4	20% (total)	82% (total) 71% (MCL)	51% (total)	47% (total) 2 years	UR	Friedberg *et al.* [2011]
CHOP *versus* V-CHOP	Cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, vincristine 1.4 mg/m² IV (to a maximum dose of 2 mg) and prednisolone 100 mg daily PO ×5 days on day 1 of each cycle with or without bortezomib 1.6 mg/m² on days 1 and 8 (every 21 days up to a maximum of eight cycles)	46	71 *versus* 69	34	1	None	48.8% *versus* 82.6%	21.7% *versus* 34.8%	8.1 *versus* 16.5 months	11.8 *versus* 35.6 months	Furtado *et al.* [2015]
CALGB-(Alliance) 50501	Bortezomib, 1.3 mg/m² IV on days 1, 4, 8, 11, and lenalidomide, 20 mg PO daily on days 1–14 (every 21 days up to a maximum of eight cycles)	53	67	46	1	40%	39.6%	15.1%	7 months	26 months	Morrison *et al.* [2015]
R-HAD + B	Bortezomib 1.5 mg/m² IV on days 1 and 4, cytarabine 2000 mg/m² (≤60 years) or 1000 mg/m² (>60 years) as a 3 h IVCI on days 2 and 3, and dexamethasone 40 mg PO daily on days 1–4 ± rituximab 375 mg/m² IV on day 0 (every 21 days given hematologic recovery)	8	65	UR	4	25%	50%	25%	5 months	15.5 months	Weigert *et al.* [2009]
NCIC IND 172	Gemcitabine 1000 mg/m² IV on days 1 and 8 and bortezomib 1.0 mg/m² IV on days 1, 4, 8, and 11 (every 21 days given hematologic recovery up to a maximum of four cycles)	26	62	15.9	1	15%	60%	8%	11.4 months	UR	Kouroukis *et al.* [2011]

ASCT, autologous stem cell transplantation; CALGB, Cancer and Leukemia Group B; CR, complete response rate; IV, intravenous; IVCI, intravenous continuous infusion; MCL, mantle cell lymphoma; NCIC, National Cancer Institute of Canada Clinical Trials Group; ORR, overall response rate; OS, overall survival; PO, orally; PFS, progression-free survival; UR, unreported.
*Including all 'high-intensity regimens' with or without ASCT (Hyper-CVAD, ICE, ESHAP, or DHAP, all with or without rituximab [Fisher *et al.* 2006]).

Bortezomib for the treatment of mantle cell lymphoma: an update

Bryan Hambley *Ther Adv Hematol 2016*

Bortezomib: upfront cytarabine-based, transplant, and maintenance post-transplant regimens.

Regimen/trial	Treatment scheme	Number of patients	Median age	Median follow-up	MIPI	ORR	CR	PFS	OS	Reference
V-BEAM	Carmustine (BCNU) 300 mg/m² IV on day −5 Etoposide 100 mg/m² IV twice daily on days −5 to −2 Cytarabine 100 mg/m² IV twice daily on days −5 to −2 Melphalan 140 mg/m² IV on day −1 Bortezomib in four dose cohorts: 0.8, 1, 1.3, and 1.5 mg/m² on days −11, −8, −5, and −2 (followed by ASCT on day = 0)	42 (total) 23 (MCL)	58	32 months	UR	95% (total) day +100	85%	32% (total) 57% (MCL) 5 years	67% (total) 72% (MCL) 5 years	William *et al.* [2014]
CALGB-(Alliance) 50403	Aggressive chemoimmunotherapy, followed by BEAM/ASCT, followed by: Bortezomib maintenance (BM): 1.6 mg/m² IV on days 1, 8, 15, and 22 once daily every 8 weeks for 10 cycles *versus* bortezomib consolidation (BC): 1.3 mg/m² IV on days 1, 4, 8, and 11 once daily every 3 weeks for four cycles starting at approximately day 90 after ASCT. Controls are from CALGB 59909 where no bortezomib was given (CON)	151 (total) 102 (randomized)	59	5.5 years	Low: 52% Int: 30% High: 17%	UR	UR	70% (BM) 69% (BC) 51.5% (CON) 5 years	UR	Kaplan *et al.* [2015]
HOVON 75 MCL	Three cycles of R-CHOP, followed by two cycles of cytarabine (2 g/m² twice daily for 4 days), followed by BEAM/ASCT, followed by randomization to bortezomib 1.3 mg/m² IV given once every 2 weeks (BM), for 2 years, starting between 6 and 12 weeks after ASCT *versus* no maintenance (CON)	140 (total) 62 (randomized)	56	50.9 months	Low: 57% Int: 32% High: 10%	100%	86%	61% (total) 71% (BM) 72% (CON) 4 year*	78% (total) 93% (BM) 90% (CON) 4 year	Doorduijn *et al.* [2015]
R-Hyper-CVAD	Cycle 1: Rituximab 375 mg/m², day 1 Cyclophosphamide 300 mg/m² IV over 3 h every 12 h × 6, days 2–4 Bortezomib 1.3 mg/m² after first dose of cyclophosphamide Doxorubicin 50 mg/m²/day IVPB, day 5 Vincristine 1.4 mg/m² IV (maximum 2 mg), day 5 after doxorubicin IV and day 12 (D12) Bortezomib 1.3 mg/m² day 5, immediately after vincristine Dexamethasone 40 mg IV or PO, days 2–6 and 12–16 Alternating with cycle 2: Rituximab 375 mg/m², day 1 Bortezomib 0.7/1/1.3 mg/m², day 1 after rituximab Methotrexate 200 mg/m² IV over 2 h, day 2 Methotrexate 800 mg/m² IVCI over 22 h, day 2 Cytarabine 3000 mg/m² IV over 2 h every 12 h × 4, days 3–4 (dose adjusted for age and serum creatinine) Bortezomib 0.7/1/1.3 mg/m², day 6 (every 21 days up to a maximum of eight cycles)	20	61	UR	Low: 40% Int: 40% High: 20%	100%	95%	UR	UR	Romaguera *et al.* [2010]
VcR-CVAD (ECOG-1405)	VcR-CVAD (every 21 days up to six cycles): Rituximab 375 mg/m² IV on day 1, bortezomib 1.3 mg/m² IV on days 1 and 4, cyclophosphamide 300 mg/m² IV every 12 h on days 1–3 (for a total of six doses), doxorubicin 50 mg/m² IVCI days 1 and 2 (total dose over 48 h = 50 mg/m²), vincristine 1 mg IV day 3, and dexamethasone 40 mg orally on days 1–4 Followed by rituximab maintenance: 375 mg/m² weekly ×4 every 6 months for 16 doses *or* optional ASCT	75	62	54	Low: 41% Int: 38% High: 22%	95%	68%	72% 3 years	88% 3 years	Chang *et al.* [2014]

Phase II study of VcR-CVAD with maintenance rituximab for untreated mantle cell lymphoma: an Eastern Cooperative Oncology Group Study Chang JE et AL Blood 2014

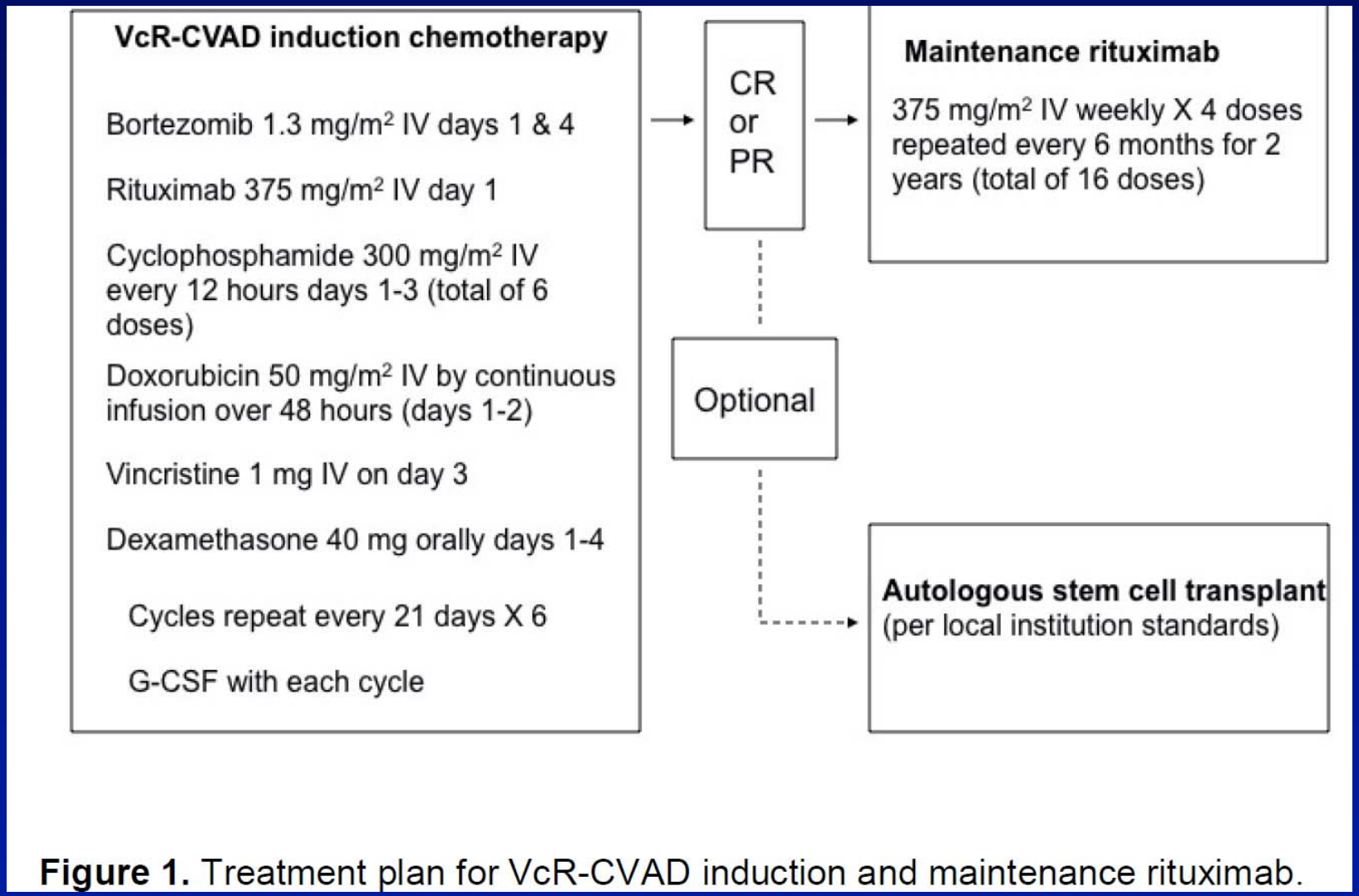


Figure 1. Treatment plan for VcR-CVAD induction and maintenance rituximab.

Phase II study of VcR-CVAD with maintenance rituximab for untreated mantle cell lymphoma: an Eastern Cooperative Oncology Group Study Chang JE et AL Blood 2014

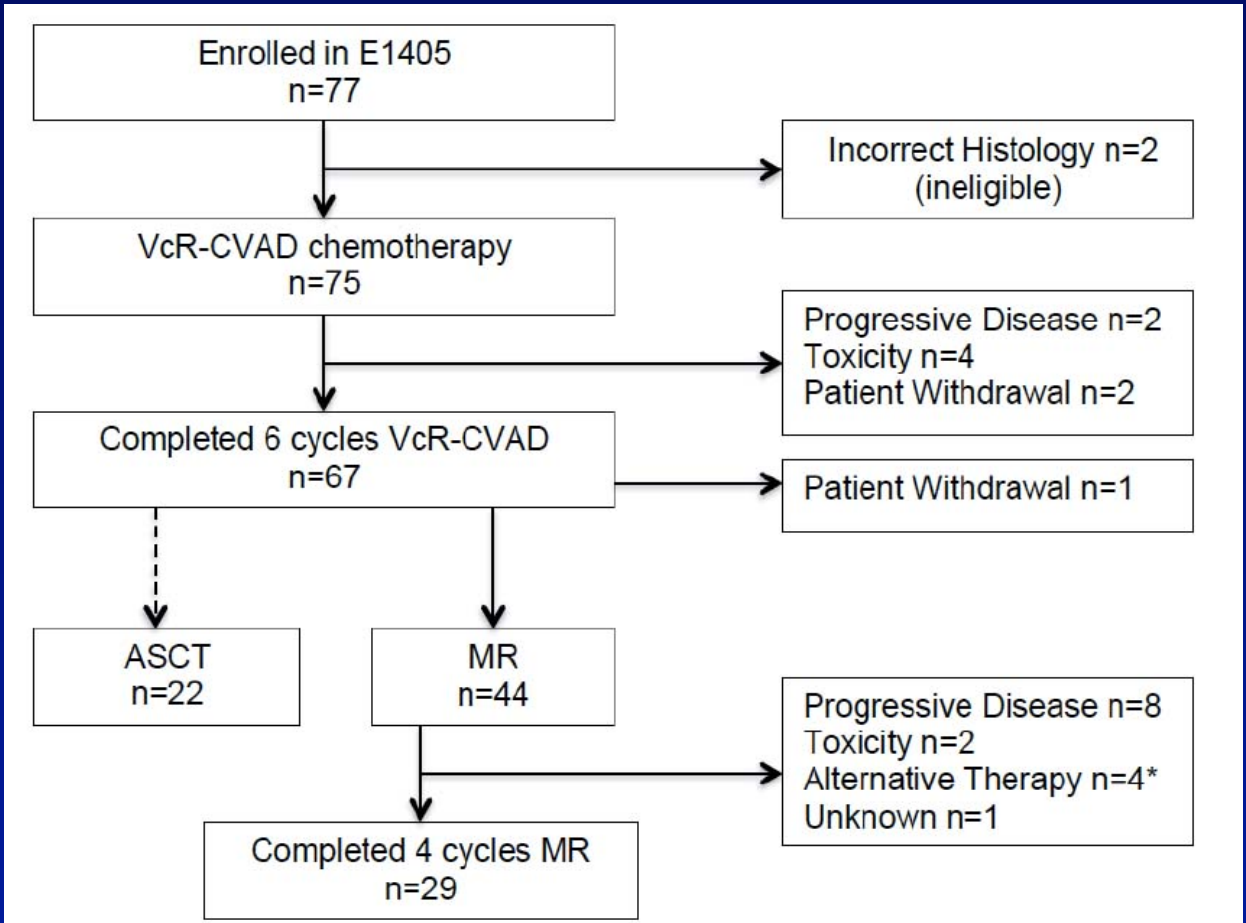
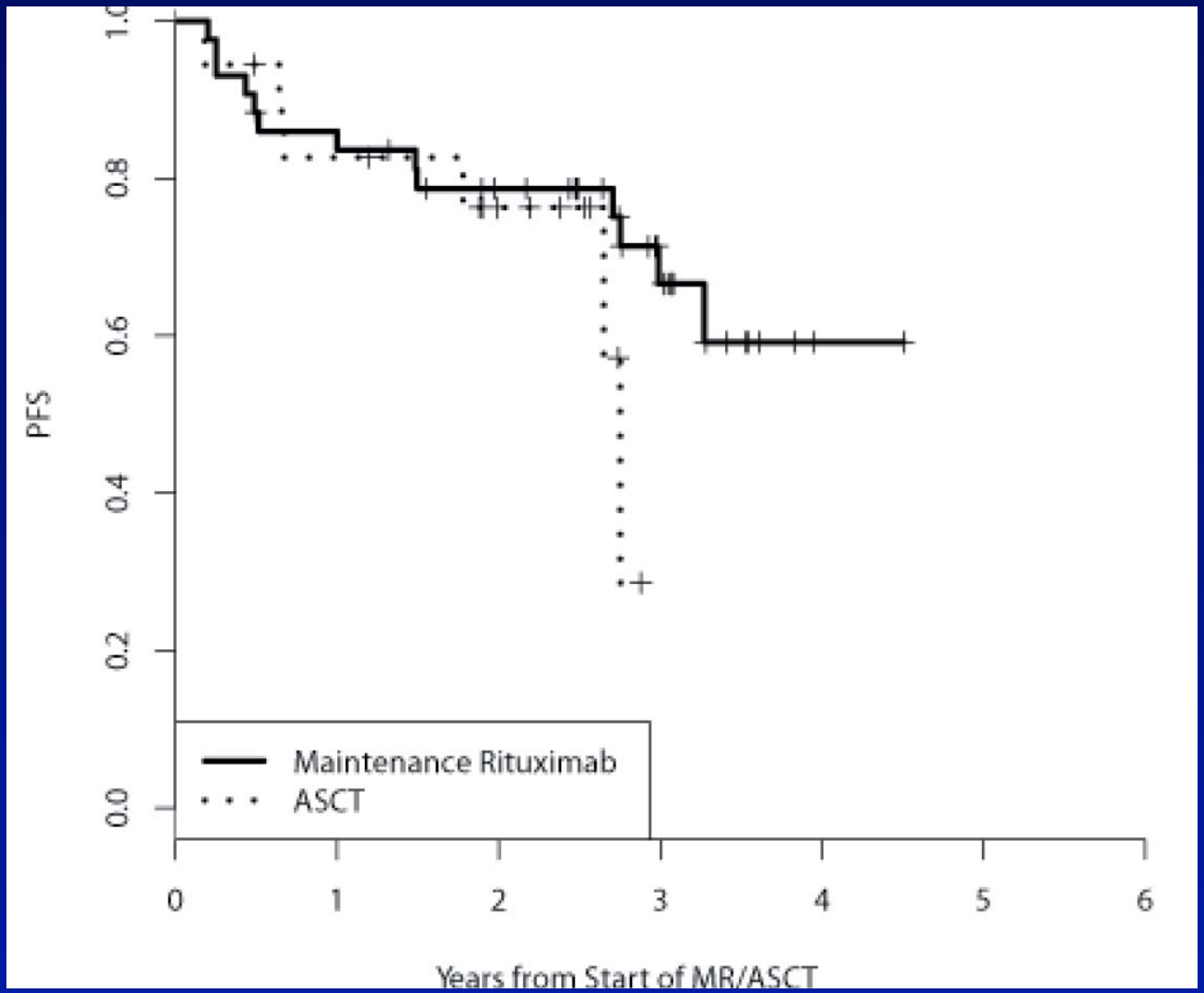


Figure 2. Throughput of patient enrolled on E1405. ASCT = autologous stem cell transplant. MR = maintenance rituximab. *Includes one patient who received ASCT after 1 cycle of MR.

Phase II study of VcR-CVAD with maintenance rituximab for untreated mantle cell lymphoma: an Eastern Cooperative Oncology Group Study Chang JE et AL Blood 2014



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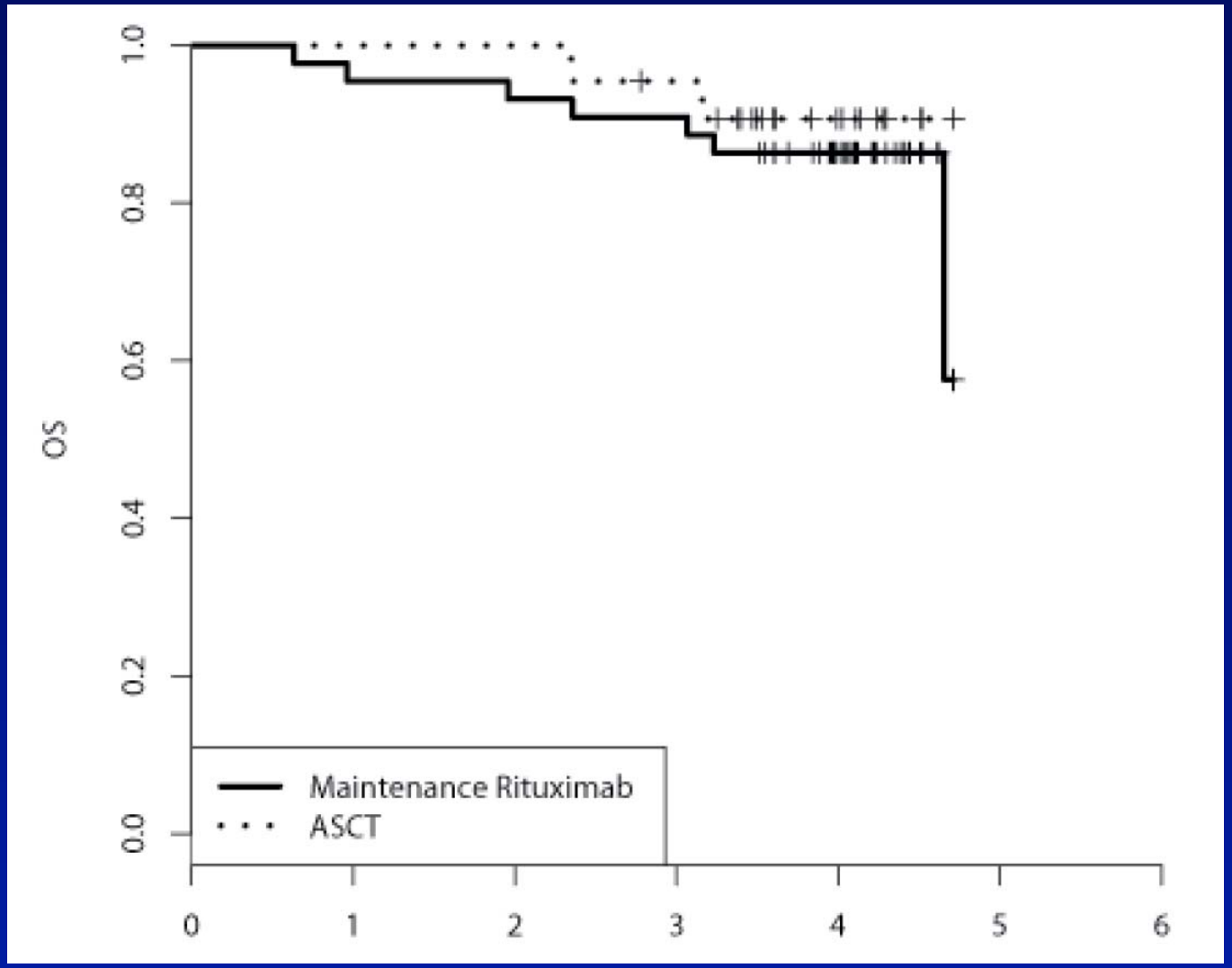
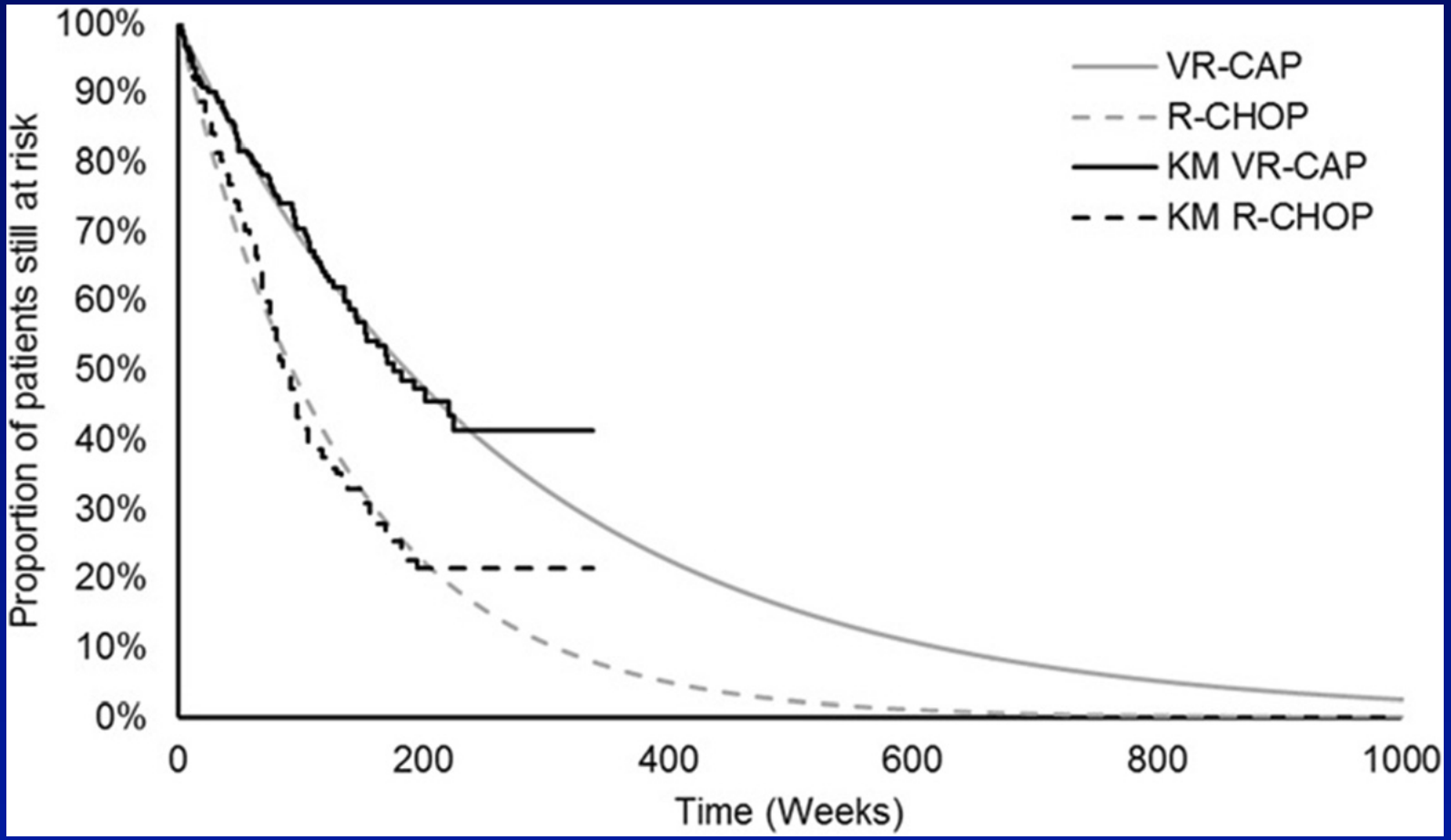
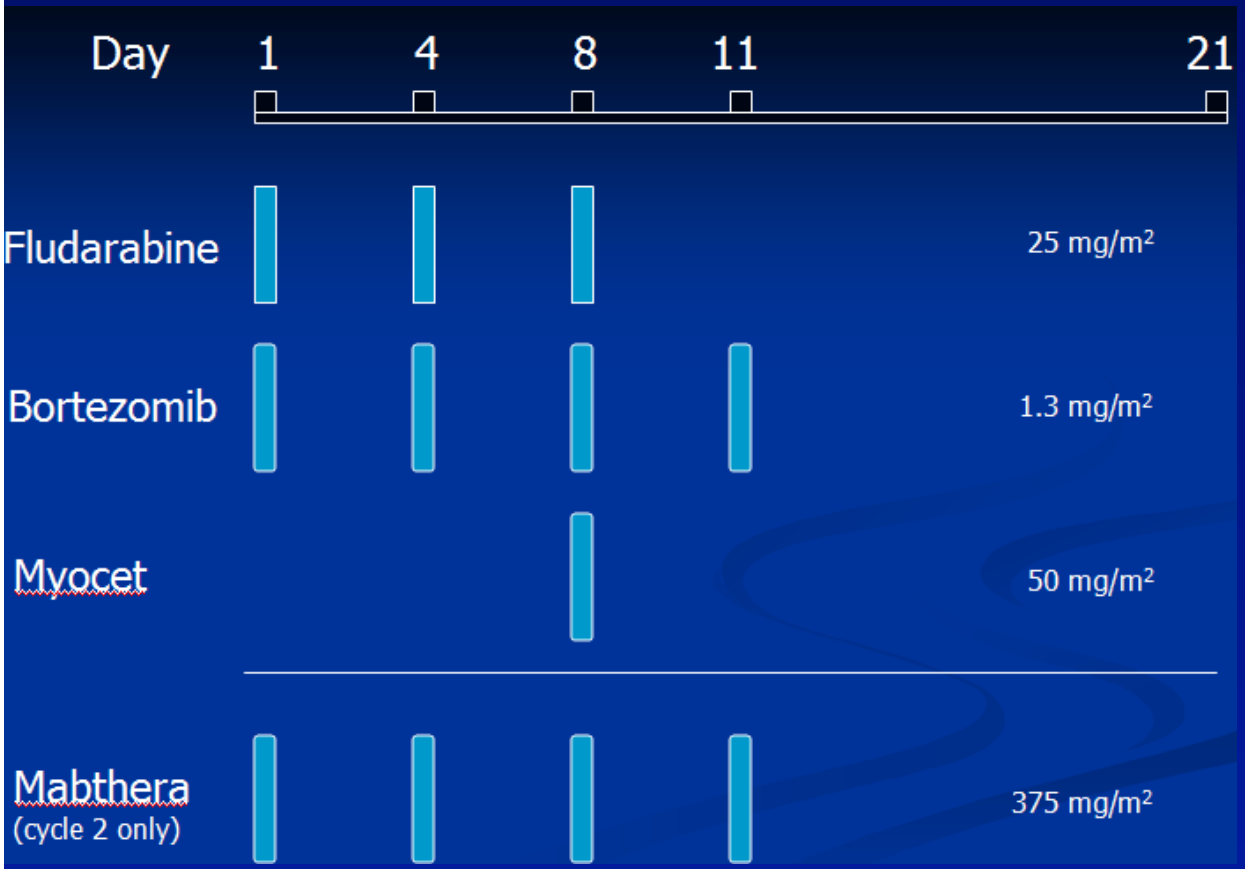


Cost-effectiveness analysis of bortezomibin combination with rituximab,cyclophosphamide, doxorubicin, vincristineand prednisone (VR-CAP) in patients with previously untreated mantle cell lymphoma Marjolijn van Keep BMC Cancer (2016)



R-FVMy



CR / PR

ZEVALIN

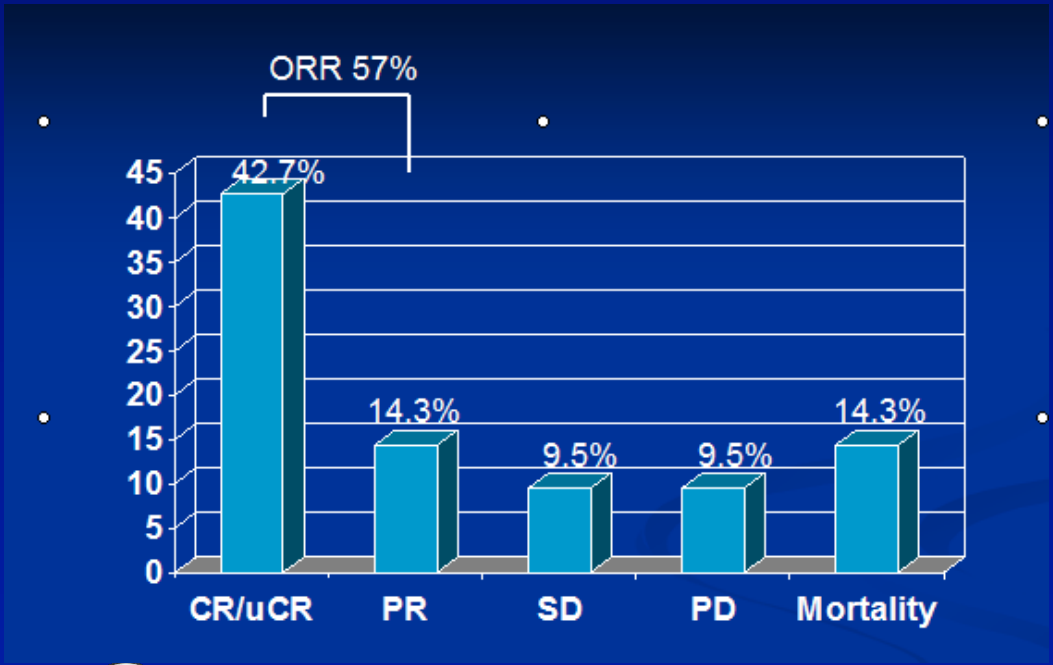
21 pts affetti da MCL

16 pretrattati

5 fragili

18 /21 (86%) hanno completato il trattamento

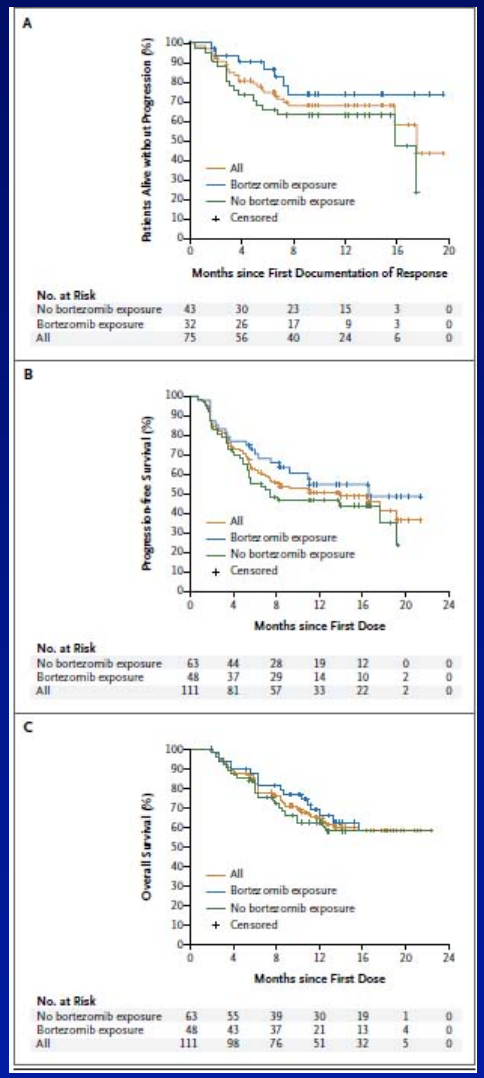
3 decessi : 2 x sepsi, 1 x insuff epatica (pz con cirrosi HCV+)



8/9 pts in CR

+ 1/3 PR consolidati con Zevalin

Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma *Wang ML et Al NEJM 2013*



BKT inhibitor is a highly active new agent showing durable singleagent activity in relapsed and refractory mantle cell lymphoma.

The favorable toxicity profile suggests that ibrutinib provides the opportunity for treatment with less intensive and more effective regimens than those currently available

Ibrutinib in mantle cell lymphoma patients: glass half full? Evidence and opinion

Deborah M. Stephens and Stephen E. Spurgeon *Ther Adv Hematol 2015*

able 1. Published combination studies with ibrutinib for patients with mantle cell lymphoma.

Agent combined with ibrutinib/MOA	Dose	Ibrutinib dose	Phase	Population (No. MCL)	ORR (CR)	PFS/OS	Reference
Rituximab (anti-CD20 mAb)	375 mg/m² intravenous weekly × 4, then monthly × 2 years	560 mg oral daily	II	R/R MCL (50)	87% (38)	NR/NA	(Wang *et al.* 2014a)
Ublituximab (glyco-engineered anti-CD20 mAb	900 mg intravenous, cycle 1: days 1, 8, 15; cycle 2–6: day 1	560 mg oral daily	II	R/R MCL (7)	83% (50)	NA/NA	(Sharman *et al.* 2014) (ClinicalTrials.gov identifier: NCT02013128)
BR (multiple)	R = 375 mg/m² intravenous, cycle 1–6: day 1 B = 90 mg/m², cycle 1–6: days 1–2	280 or 560 mg oral daily	I/Ib	R/R MCL (12) TN MCL (5)	94% (76)	NR/NA	(Maddocks *et al.* 2015)
R-CHOP (multiple)	R = 375 mg/m² intravenous, cycle 1–6: day 1 C = 750 mg/m² intravenous, cycle 1–6: day 1 H = 50 mg/m² intravenous, cycle 1–6: day 1 O* = 1.4 mg/m² cycle 1–6: day 1 P = 100 mg oral, cycle 1–6: days 1–5	280, 420, 560 mg oral daily	Ib	TN MCL (5)	NA	NA/NA	(Younes *et al.* 2014)
Lenalidomide (immuno-modulatory)	10 or 15 mg oral daily	280 or 320 mg oral daily	I	R/R MCL (2)	NA	NA/NA	(Christian *et al.* 2014) (ClinicalTrials.gov identifier: NCT0195549)

*Max = 2 mg.
B, bendamustine; C, cyclophosphamide; CR, complete response; H, doxorubicin; mAb, monoclonal antibody; MCL, mantle cell lymphoma; MOA, mechanism of action; NA, not available; NR, not reached; O, vincristine; ORR, overall response rate; OS, overall survival; P, prednisone; PFS, progression-free survival; R, rituximab; R/R, relapsed/refractory; TN, treatment naïve.

Ibrutinib in mantle cell lymphoma patients: glass half full? Evidence and opinion Deborah

M. Stephens and Stephen E. Spurgeon ***Ther Adv Hematol 2015***

Table 2. Combination therapies in clinical development with ibrutinib for patients with mantle cell lymphoma.

Drug	Mechanism of action	Preclinical data	Clinical investigation
ABT-199 (GDC-0199)	BH3 mimetic; inhibits BCL-2 pathway	Synergy with ibrutinib in apoptosis induction in MCL cell lines [Zhao *et al.* 2015]	Planned phase I combination study in R/R MCL
Bortezomib	Proteosome inhibitor	Synergy with ibrutinib in MCL cell lines [Dasmahapatra *et al.* 2013]	Combination phase I/II study in R/R CLL currently underway [ClinicalTrials.gov identifier: NCT0236458]
Palbociclib isethionate	Cyclin-dependent kinase 4 and 6 inhibitor	Palbociclib sensitizes resistant MCL cells to killing by ibrutinib [Chiron *et al.* 2014]	Phase I study in R/R MCL currently underway [ClinicalTrials.gov identifier: NCT02159755]
Selinexor (KPT-330)	Selective inhibitor of nuclear export	Synergy with ibrutinib (inhibition of BTK) in primary CLL cells [Hing *et al.* 2015]	Combination phase I study for R/R B-cell malignancies currently underway [ClinicalTrials.gov identifier: NCT02303392]

MCL, mantle cell lymphoma; R/R, relapsed/refractory.

Temsirolimus vs Ibrutinib relapsed / resistant MCL

ASCO 2016 Dreyling et al

- phase III randomized trial
- 280 patients in < 1 year
- response rate was 72% with ibrutinib vs 40% with temsirolimus
- median progression-free survival was 14.6 vs 6.2 months. Median duration of response was not yet reached for ibrutinib
- response of ≥ 18 months occurred in 58% of ibrutinib responders vs 20% of temsirolimus responders

Ibrutinib in Relapsed Mantle Cell Lymphoma Mitchell R. Smith 2016

- Ibrutinib is a marvelous addition to mantle cell lymphoma treatment options. There remains room for improvement, however, as mantle cell lymphoma in one of three patients does not respond to ibrutinib, and with median follow-up of 20 months fewer than 50% of patients remain on ibrutinib therapy.

Other Novel Agents in MCL

Drug	Mechanism/Rationale
Pan Bcl-2 inhibitors ABT-737, AT-101, GMX-15-070	Ongoing studies single agent and combination with rituximab / strong rationale for combination with bortezomib
HDAC inhibitors (SAHA, depsipetide)	SAHA showed activity in MCL in preclinical models
Anti-TRAIL antibodies (TRM-1)	Fully human Mab agonistic to the TRAIL receptor 1 Induction apoptosis/extrinsic pathway
HSP inhibitors HSP90 17AAG (geldamycin) HSP 27	Activity shown in MCL cell lines Study ongoing
IKK inhibitors	Stabilization of NFKB
Inhibitors of Raf/MEK signaling pathway	Sorafenib, orally administered Small-molecule signal transduction inhibitor
Farnesyl transferase inhibitors	Tipifarnib/ongoing
BL22 immunotoxin	Calicheamycin/CD22 (CMC-544) / others