LENALIDOMIDE NEL LINFOMA MANTELLARE: DATI DELLA REAL LIFE

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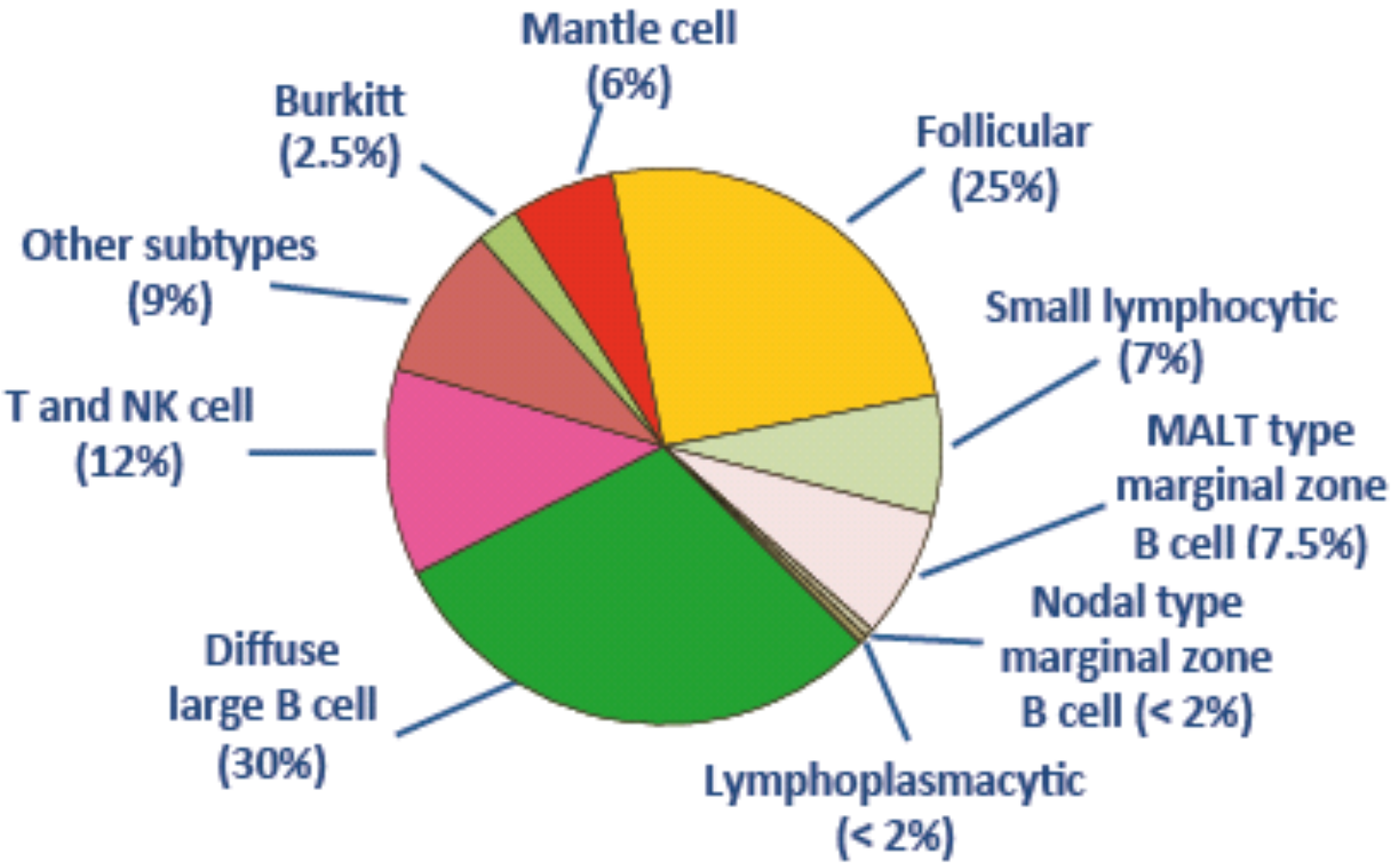
ROMA || UNAHOTELS DECÒ

MCL epidemiologia

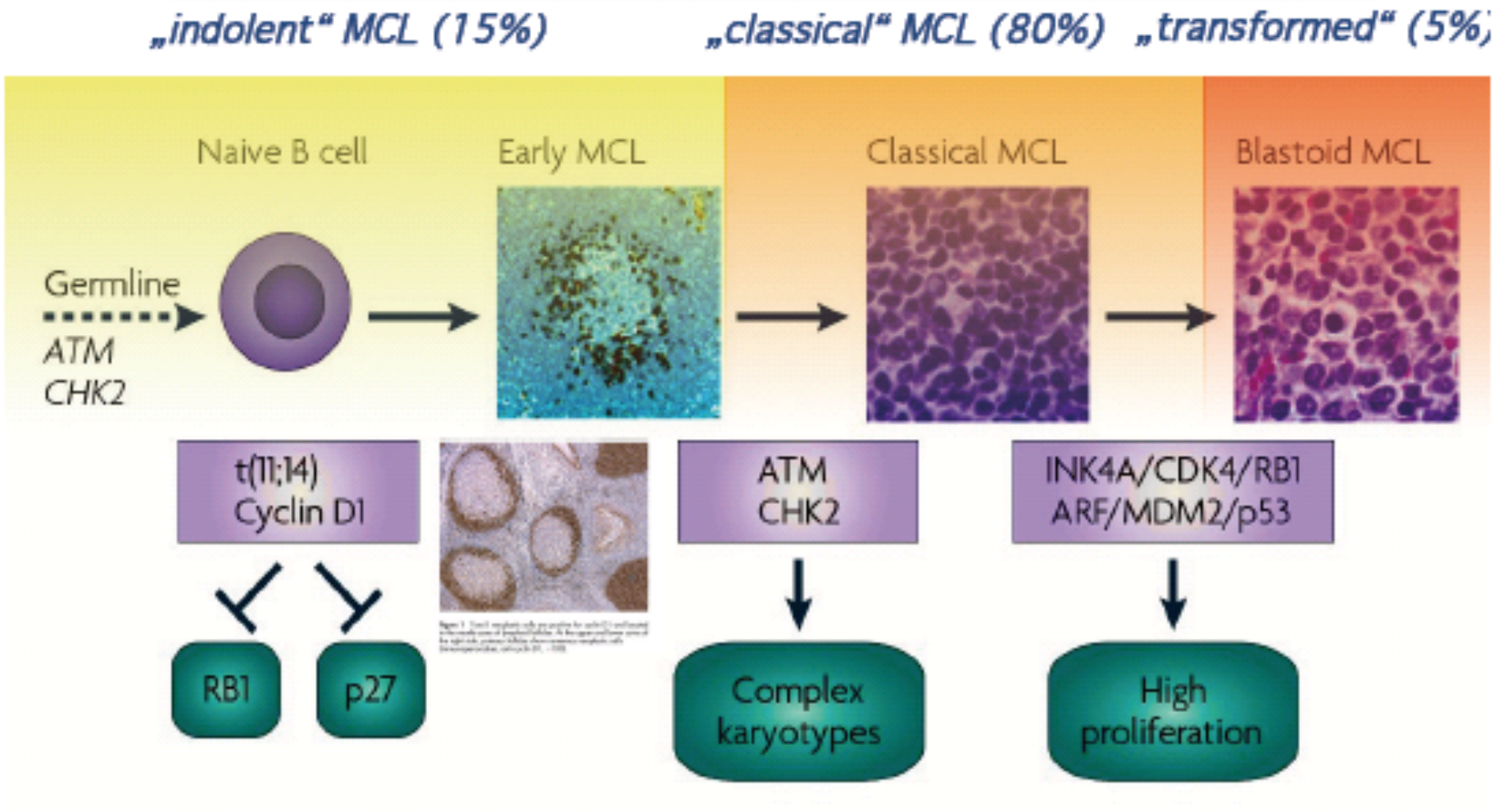


Lichtman. Williams Hematology, 7 edition. 2006.;1408.

MCL epidemiologia

- 74% maschi
- 0,5 nuovi casi/100,000 abit/ anno
- Età media: 63 anni
- Stadio: avanzato 70%
- Sintomi B : 50% circa
- Sedi coinvolte :
  - Linfonodi
  - Milza
  - Anello Waldeyer
  - Midollo osseo
  - Sangue
  - Sedi extranodali (gastrointestinale, SNC)

MCL uno spettro di malattie



Dreyling, ASH Educational 2009

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2019
Mantle Cell Lymphoma

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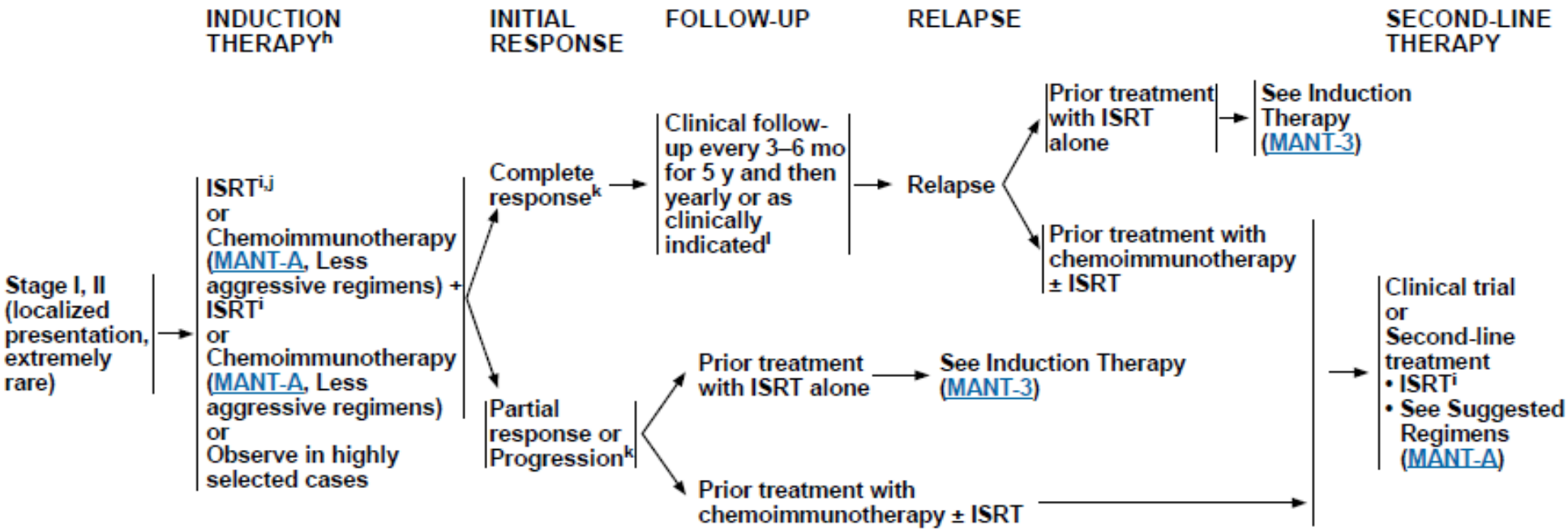

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

[h]Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.

[i]See Principles of Radiation Therapy (NHODG-D).

[j]Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited-stage mantle-cell lymphoma. Ann Oncol 2003;14:1555-1561.

[k]See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).

[l]Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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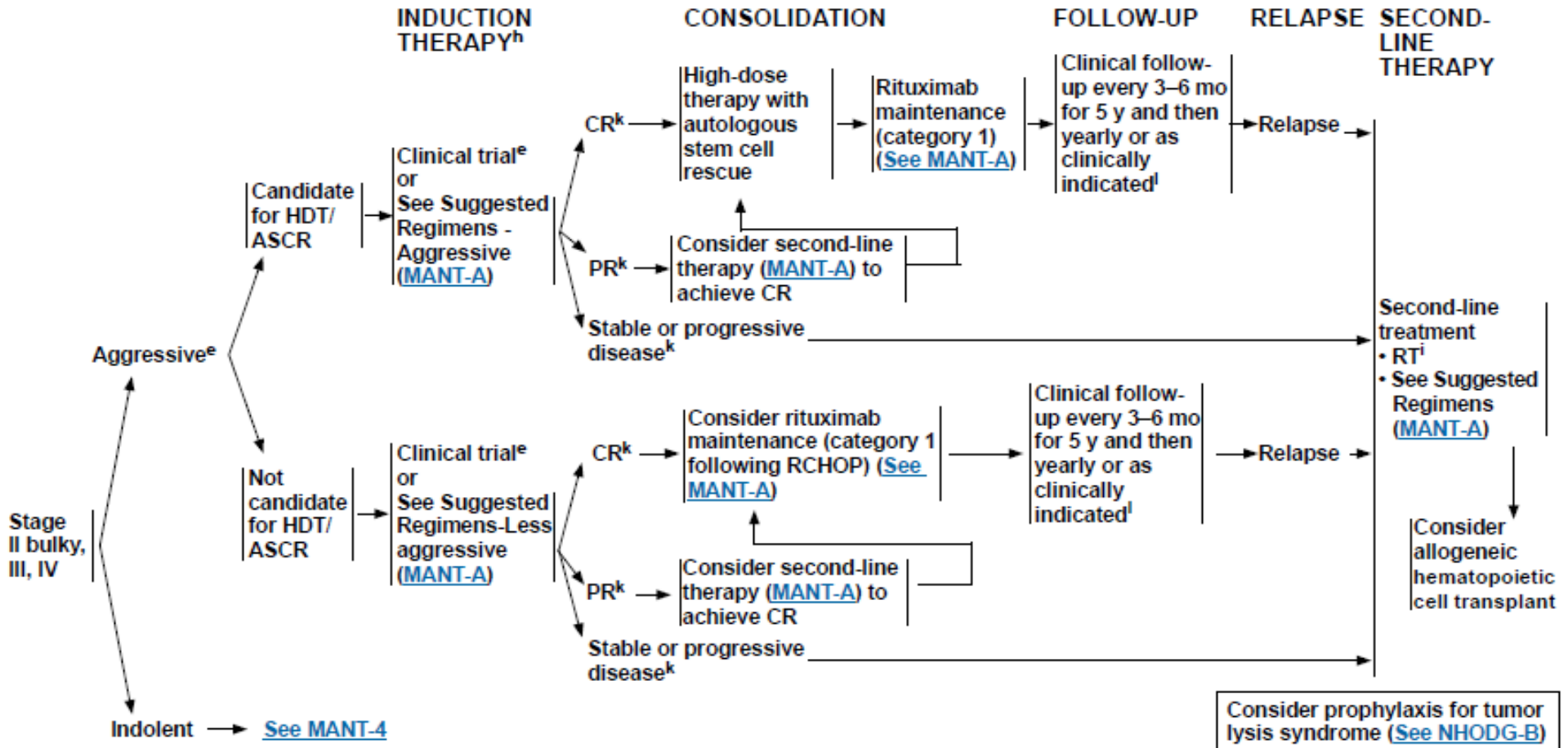

[e] *TP53* mutation has been associated with poor prognosis in patients treated with conventional therapy, including transplant. Clinical trial is strongly suggested for these patients.
[h] Early referral for high-dose therapy with stem cell rescue is advisable for planning purposes.
[i] See Principles of Radiation Therapy (NHODG-D).
[k] See Lugano Response Criteria for Non-Hodgkin's Lymphoma (NHODG-C).
[l] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.

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SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

Induction Therapy

- Aggressive therapy
  - Preferred regimens
    - ◊ RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)
    - ◊ Alternating RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cytarabine, cisplatin)
    - ◊ NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone [maxi-CHOP]) alternating with rituximab + high-dose cytarabine)
    - ◊ HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab[c] (NOTE: There are conflicting data regarding the need for consolidation with HDT/ASCR.)
  - Other recommended regimen
    - ◊ Bendamustine + rituximab (category 2B)
- Less aggressive therapy
  - Preferred
    - ◊ Bendamustine + rituximab
    - ◊ VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
    - ◊ RCHOP[d]
    - ◊ Lenalidomide + rituximab
    - ◊ Modified rituximab-HyperCVAD in patients older than 65 y
  - Other recommended regimen
    - ◊ RBAC (rituximab, bendamustine, cytarabine) (category 2B)

Maintenance After Less Aggressive Therapy

- Rituximab every 8 weeks until progression or intolerance (category 1 following RCHOP; 2–5 y following modified rituximab-HyperCVAD)
  - Prospective trial data suggest no benefit after BR
  - Untested after VR-CAP, RBAC

See Second-line Therapy on MANT-A 2 of 4

Consolidation After Aggressive Therapy

- High-dose therapy followed by autologous stem cell rescue

Maintenance After HDT/ASCR

- Maintenance rituximab every 8 weeks x 3 y (category 1)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MANT-A 3 of 4 and MANT-A 4 of 4.
[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[c]Rituximab + ibrutinib can be used as a pre-treatment to limit the number of cycles of RHyperCVAD/rituximab maintenance. Wang ML, Lee H, Thirumurthi S, et al. Hematological Oncology 2017;35:142-143.
[d]There is a randomized trial that demonstrated that RCHOP was not superior to CHOP.

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SUGGESTED TREATMENT REGIMENS[a,b]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

Second-line Therapy

- Short response duration to prior chemoimmunotherapy (< expected median PFS)
  - Preferred regimens (in alphabetical order)
    - Acalabrutinib[e,f]
    - Ibrutinib[e] ± rituximab
    - Lenalidomide ± rituximab
    - Venetoclax
  - Other recommended regimens
    - Ibrutinib,[e] lenalidomide, rituximab (category 2B)
    - Venetoclax + ibrutinib (category 2B)

- Extended response duration to prior chemoimmunotherapy (> expected median PFS)
  - Preferred regimens (in alphabetical order)
    - Bendamustine ± rituximab (if not previously given)
    - Bortezomib ± rituximab
  - Other recommended regimens (in alphabetical order by category)
    - Small molecule inhibitors as above
    - Bendamustine, bortezomib, and rituximab (category 2B)
    - PEPC (prednisone, etoposide, procarbazine, cyclophosphamide) ± rituximab (category 2B)
    - RCHOP (if not previously given) (category 2B)
    - VRCAP (if not previously given) (category 2B)
    - See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability

Second-line Consolidation

- Allogeneic hematopoietic cell transplant (nonmyeloablative or myeloablative)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a]See references for regimens MANT-A 3 of 4 and MANT-A 4 of 4.
[b]Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.

[e]See Special Considerations for Use of Small-Molecule Inhibitors (NHODG-E).
[f]The phase 2 ACE-LY-004 study excluded patients treated with Bruton's tyrosine kinase (BTK) or BCL-2 inhibitor and concomitant warfarin or equivalent vitamin K antagonists.

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LENALIDOMIDE

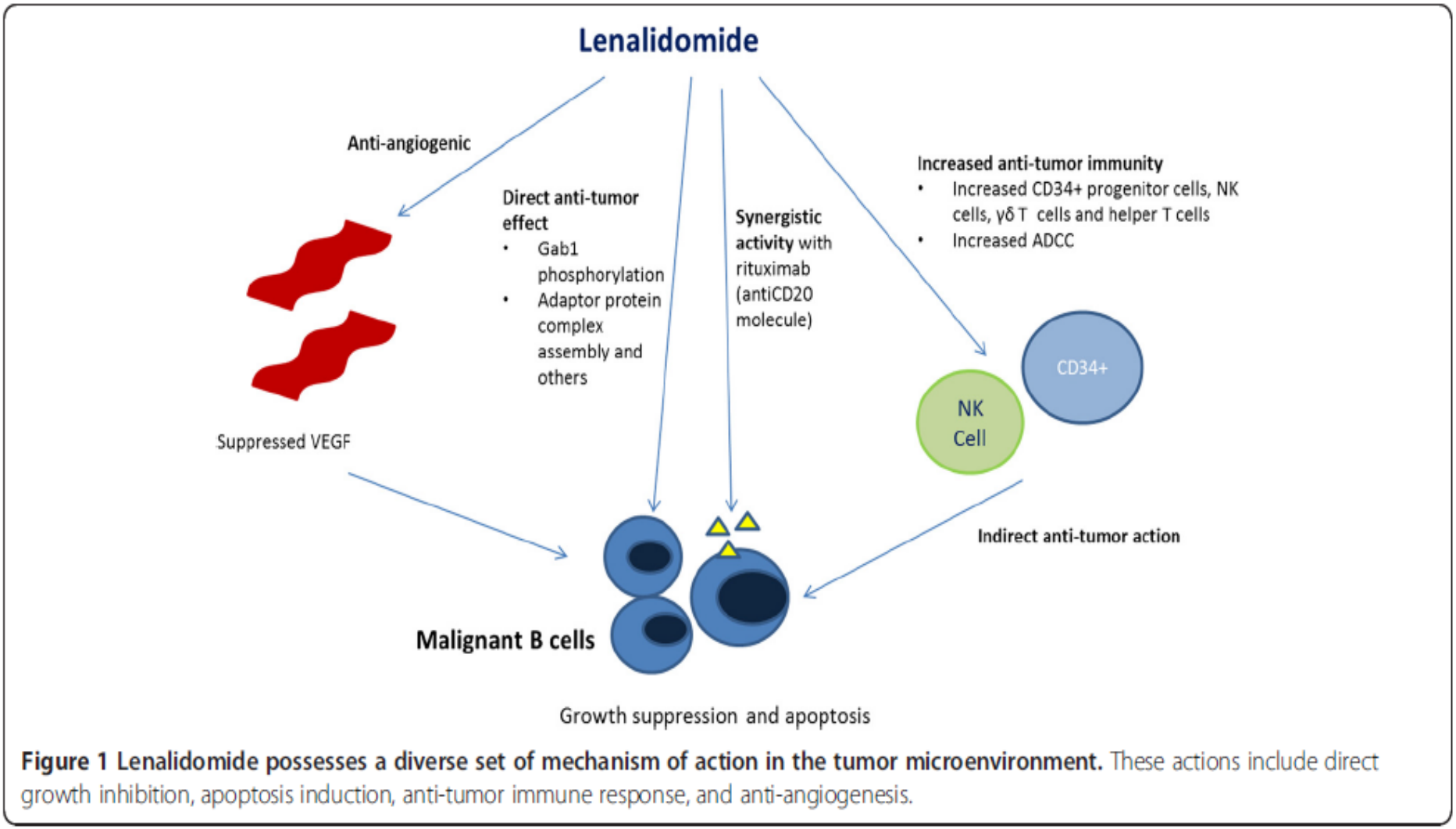

Figure 1 Lenalidomide possesses a diverse set of mechanism of action in the tumor microenvironment. These actions include direct growth inhibition, apoptosis induction, anti-tumor immune response, and anti-angiogenesis.

Desai *et al. Journal of Hematology & Oncology* 2013, **6**:55
http://www.jhoonline.org/content/6/1/55

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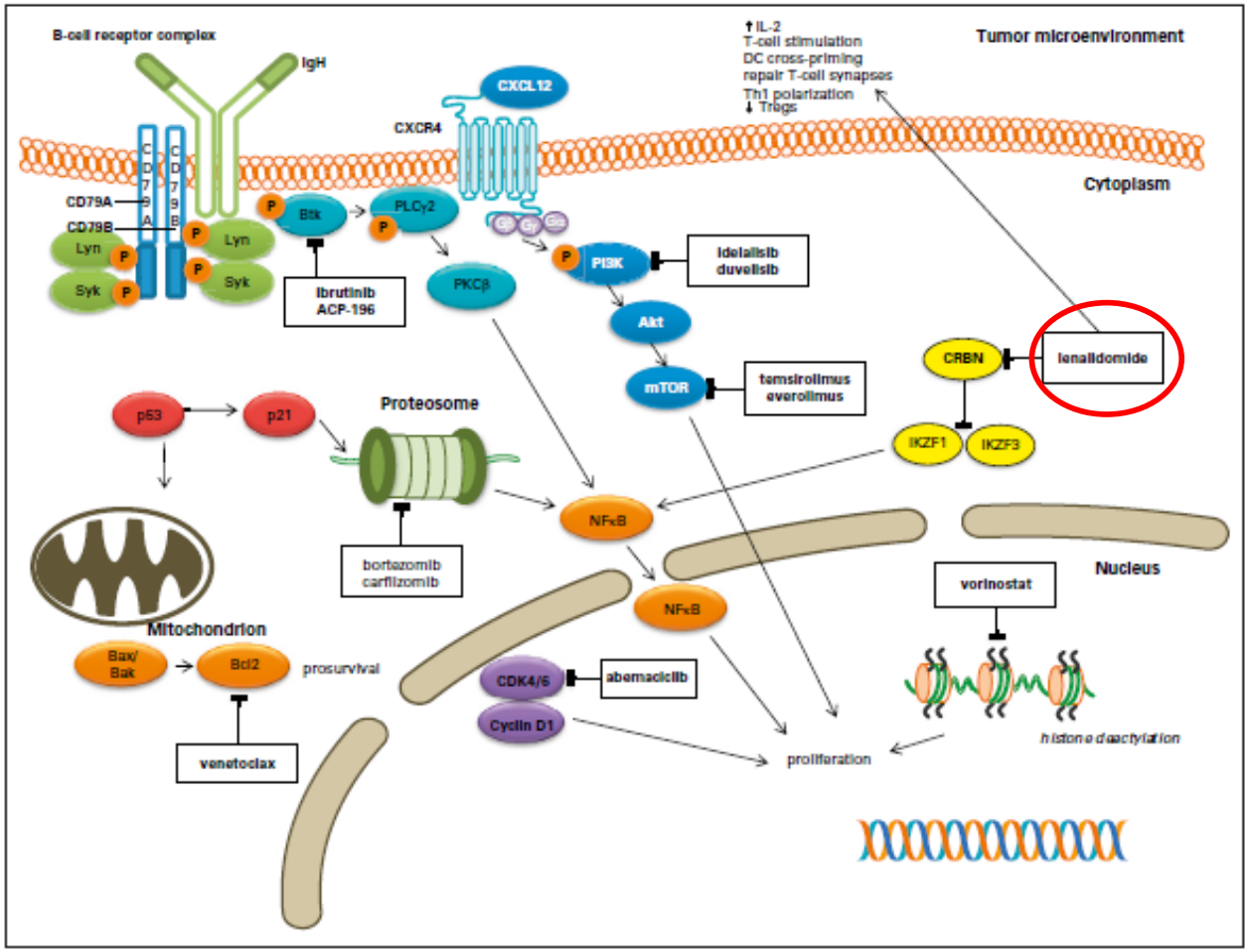
JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Mantle Cell Lymphoma

Chan Yoon Cheah, John F. Seymour, and Michael L. Wang



MANTLE CELL LYMPHOMA: RELAPSE

Lenalidomide monotherapy in MCL

Author	N.	ORR	CR/Cru	Median PFS (months)	Median DOR (months)
Wiernik 2008	15	53%	13%		
Haberman 2009	15	53%	20%	6	14
Eve 2012	26	31%	8%		
Wang 2012 (+ RTX)	44	57%	36%	11	19
Witzig 2011, Zinzani 2013	57	42%	12%	9	16
Goy ASH 2012 (Bortezomib R/R)	134	28%	8%	4	17
REVEAL 2013	66	39%	12%	12	

VOLUME 31 · NUMBER 29 · OCTOBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Single-Agent Lenalidomide in Patients With Mantle-Cell Lymphoma Who Relapsed or Progressed After or Were Refractory to Bortezomib: Phase II MCL-001 (EMERGE) Study

Andre Goy, Rajni Sinha, Michael E. Williams, Sevgi Kalayoglu Besisik, Johannes Drach, Radhakrishnan Ramchandren, Lei Zhang, Sherri Cicero, Tommy Fu, and Thomas E. Witzig

MCL-001: Patient Demographics and Baseline Characteristics

Characteristic (N = 134)	No. of Patients (%)
Median age, years (range)	67 (43-83)
Age ≥ 65 years	85 (63)
Males	108 (81)
Stage III-IV	124 (93)
ECOG PS	
0-1	116 (87)
2	18 (13)
Intermediate to high MIPI score	90 (67)
High tumor burden*	77 (58)
Bulky disease†	44 (33)

*High tumor burden: ie, at least 1 lesion ≥ 5 cm in diameter or at least 3 lesions ≥ 3 cm in diameter

†Bulky disease: at least 1 lesion ≥ 7 cm

} By central radiology review

MCL-001: Prior Treatment History at Baseline

Characteristic (N = 134) Characteristic (N=134)	No. of Patients (%)
≥ 3-year duration of MCL	82 (61)
Median no. of prior treatment regimens (range)	4 (2-10)
No. of prior systemic anti-lymphoma therapies 2 3 ≥ 4	 29 (22) 34 (25) 71 (53)
Refractory to prior bortezomib	81 (60)
Received prior high-dose or dose-intensive therapy*	44 (33)
Refractory to last therapy	74 (55)
Time from last prior systemic anti-lymphoma therapy < 6 months ≥ 6 months	 96 (72) 38 (28)

*Includes stem cell transplant, hyperCVAD, or R-hyperCVAD.

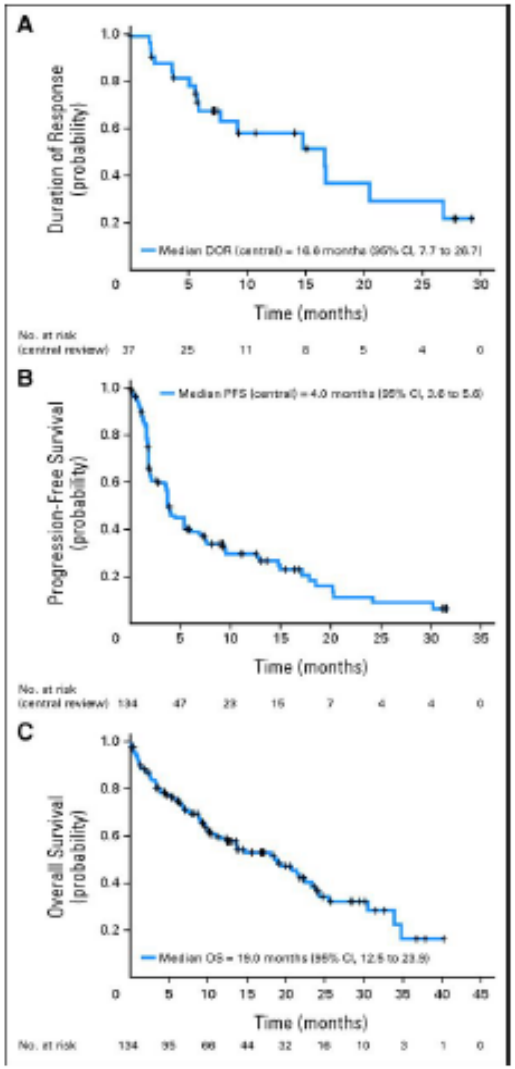
Andre Goy et al. JCO 2013;31:3688-3695

MCL-001: Efficacy of Lenalidomide

Efficacy Parameter (N = 134)	Central Review n (%)	Site Review n (%)
ORR*	37 (28)	43 (32)
CR/CRu	10 (8)	22 (16)
PR	27 (20)	21 (16)
SD	39 (29)	36 (27)
PD	35 (26)	43 (32)
Median DOR, months (95% CI)	16.6 (7.7-26.7)	18.5 (12.8-26.7)
Median DOR for CR/CRu, months (95% CI)	16.6 (16.6-NR)	26.7 (16.8-NR)

NR, not reached.
*No response assessments were available for 23 patients (central) and 12 patients (investigator).

Lenalidomide in relapsed/refractory mantle-cell lymphoma



Duration of Response

PFS

OS

Andre Goy et al. JCO 2013;31:3688-3695

Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

Marek Trněný, Thierry Lamy, Jan Walewski, David Belada, Jiri Mayer, John Radford, Wojciech Jurczak, Franck Morschhauser, Julia Alexeeva, Simon Rule, Boris Afanasyev, Kamil Kaplanov, Antoine Thyss, Alexej Kuzmin, Sergey Voloshin, Kazimierz Kuliczkowski, Agnieszka Giza, Noel Milpied, Caterina Stelitano, Reinhard Marks, Lorenz Trümper, Tsvetan Biyukov, Meera Patturajan, Marie-Laure Casadebaig Bravo, Luca Arcaini, on behalf of the SPRINT trial investigators and in collaboration with the European Mantle Cell Lymphoma Network

Lancet Oncol 2016; 17: 319-31

	Lenalidomide group (n=170)	Investigator's choice group (n=84)
Median age in years (range)	68·5 (44–88)	68·5 (49–87)
Age ≥65 years	115 (68%)	57 (68%)
Sex		
Male	123 (72%)	63 (75%)
Female	47 (28%)	21 (25%)
Mantle cell lymphoma stage at diagnosis		
I/II	13 (8%)	3 (4%)
III	30 (18%)	20 (24%)
IV	123 (72%)	59 (70%)
Missing	4 (2%)	2 (2%)
MIPI score at baseline		
Low	42 (25%)	21 (25%)
Intermediate	66 (39%)	37 (44%)
High	60 (35%)	25 (30%)
Missing	2 (1%)	1 (1%)
Ki-67 index >30%	31 (18%)	19 (23%)

	Lenalidomide group (n=170)	Investigator's choice group (n=84)
(Continued from previous column)		
Previous anti-lymphoma therapies		
Anthracyclines	157 (92%)	78 (93%)
Rituximab	156 (92%)	77 (92%)
Cytarabine	62 (36%)	32 (38%)
Bortezomib	21 (12%)	7 (8%)
Bendamustine	6 (4%)	6 (7%)
Temsirolimus	3 (2%)	1 (1%)
Best response to last previous systemic anti-lymphoma therapy		
Complete response and unconfirmed complete response	58 (34%)	29 (35%)
Partial response	42 (25%)	30 (36%)
Stable disease	31 (18%)	9 (11%)
Progressive disease	33 (19%)	10 (12%)
Unknown	6 (4%)	6 (7%)
Received previous autologous stem-cell transplantation	30 (18%)	18 (21%)

Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

Marek Trněný, Thierry Lamy, Jan Walewski, David Belada, Jiri Mayer, John Radford, Wojciech Jurczak, Franck Morschhauser, Julia Alexeeva, Simon Rule, Boris Afanasyev, Kamil Kaplanov, Antoine Thyss, Alexej Kuzmin, Sergey Voloshin, Kazimierz Kuliczkowski, Agnieszka Giza, Noel Milpied, Caterina Stelitano, Reinhard Marks, Lorenz Trümper, Tsvetan Biyukov, Meera Patturajan, Marie-Laure Casadebaig Bravo, Luca Arcaini, on behalf of the SPRINT trial investigators and in collaboration with the European Mantle Cell Lymphoma Network

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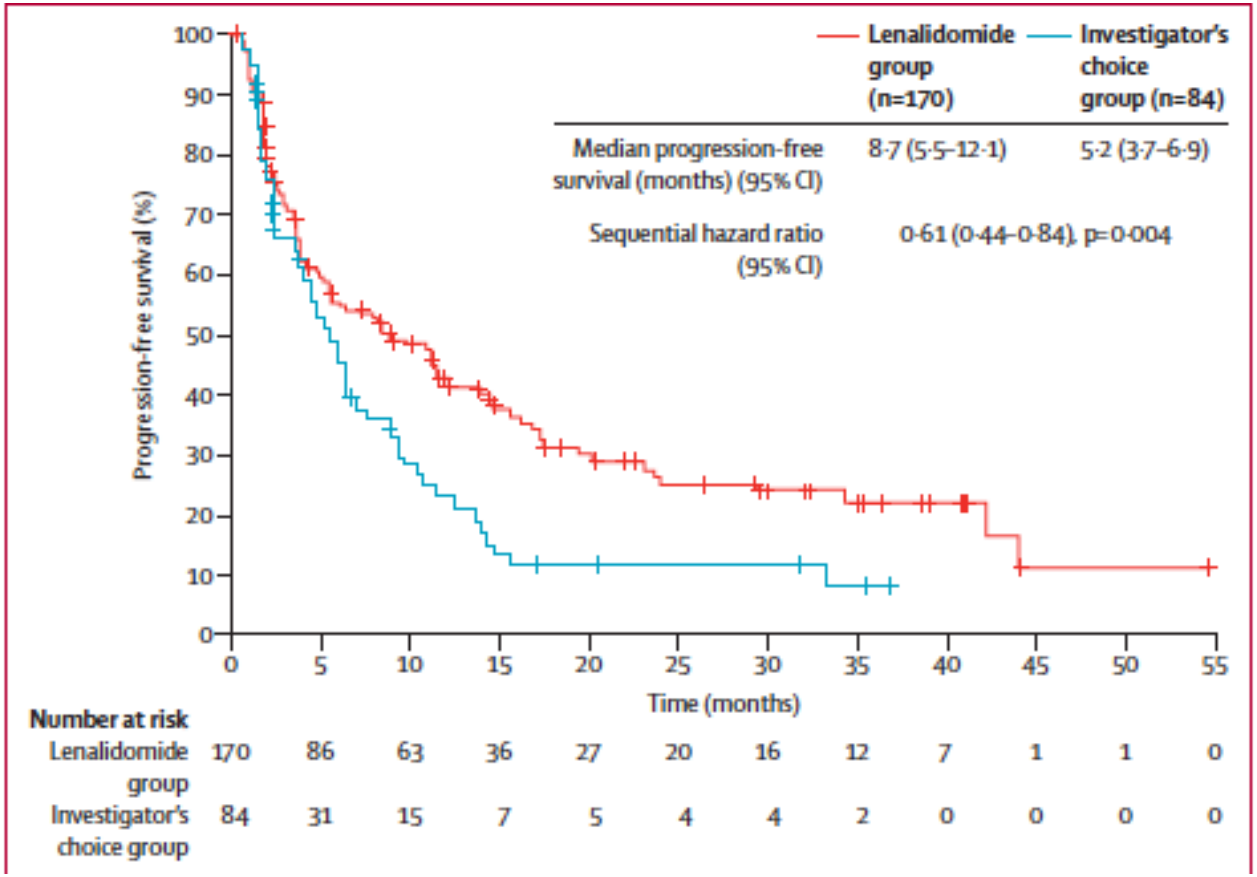

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Lancet Oncol 2016; 17: 319–31

	Lenalidomide (n=167)			Investigator's choice (n=83)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Haematological						
Anaemia	34 (20%)	12 (7%)	2 (1%)	13 (16%)	5 (6%)	1 (1%)
Thrombocytopenia	31 (19%)	25 (15%)	5 (3%)	10 (12%)	16 (19%)	7 (8%)
Leucopenia	15 (9%)	11 (7%)	2 (1%)	9 (11%)	5 (6%)	4 (5%)
Neutropenia	12 (7%)	40 (24%)	33 (20%)	1 (1%)	13 (16%)	15 (18%)
Febrile neutropenia	0	7 (4%)	3 (2%)	0	2 (2%)	0
Non-haematological						
Fatigue	33 (20%)	2 (1%)	0	4 (5%)	0	0
Diarrhoea	32 (19%)	5 (3%)	1 (1%)	8 (10%)	0	0
Constipation	28 (17%)	1 (1%)	0	5 (6%)	0	0
Nasopharyngitis	25 (16%)	0	0	5 (6%)	0	0
Asthenia	24 (14%)	2 (1%)	0	11 (13%)	0	0
Pyrexia	24 (14%)	3 (2%)	1 (1%)	9 (11%)	1 (1%)	0
Upper respiratory tract infection	19 (11%)	1 (1%)	0	4 (5%)	1 (1%)	0
Cough	19 (11%)	0	0	3 (4%)	1 (1%)	0
Decreased appetite	18 (11%)	1 (1%)	0	3 (4%)	0	0
Nausea	18 (11%)	0	0	12 (14%)	0	0
Rash	18 (11%)	0	0	3 (4%)	0	0
Peripheral oedema	16 (10%)	1 (1%)	0	9 (11%)	0	0
Vomiting	10 (6%)	0	0	9 (11%)	0	0
Pneumonia	5 (3%)	5 (3%)	1 (1%)	2 (2%)	2 (2%)	0

Data are n (%).

Table 3: **Treatment-emergent haematological and non-haematological adverse events (≥10% grade 1–2, ≥5% grade 3–4)**

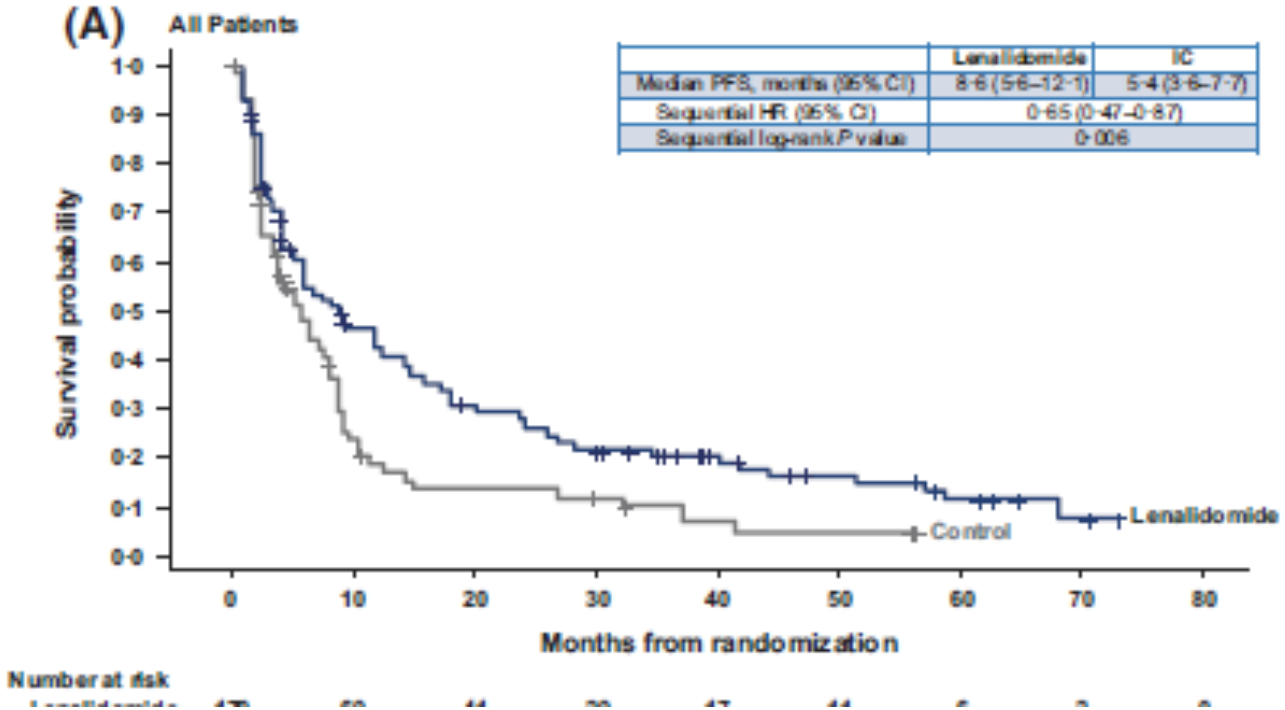
bjh research paper

Prospective subgroup analyses of the randomized MCL-002 (SPRINT) study: lenalidomide *versus* investigator's choice in relapsed or refractory mantle cell lymphoma

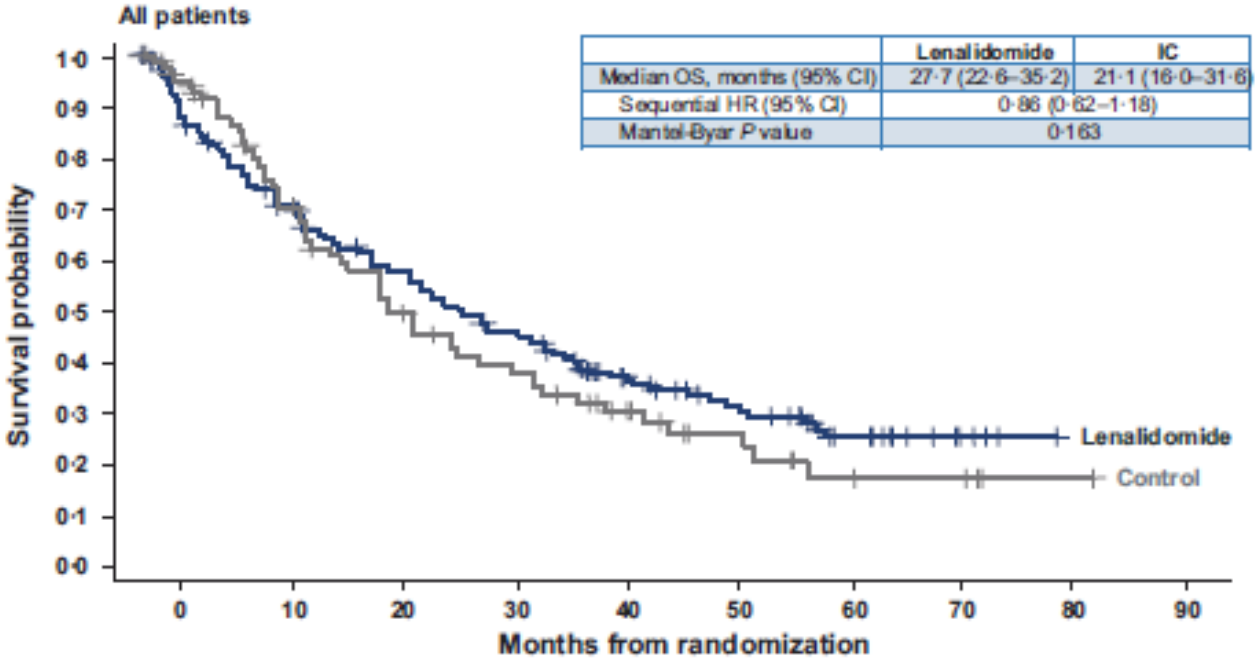
Luca Arcaini,[1,2] Thierry Lamy,[3] Jan Walewski,[4] David Belada,[5] Jiri Mayer,[6] John Radford,[7] Wojciech Jurczak,[8] Franck Morschhauser,[9] Julia Alexeeva,[10] Simon Rule,[11] José Cabeçadas,[12] Elias Campo,[13] Stefano A. Pileri,[14] Tsvetan Biyukov,[15] Meera Patturajan,[16] Marie-Laure Casadebaig Bravo,[15] and Marek Trněný,[17] on behalf of the SPRINT Trial Investigators

(A)

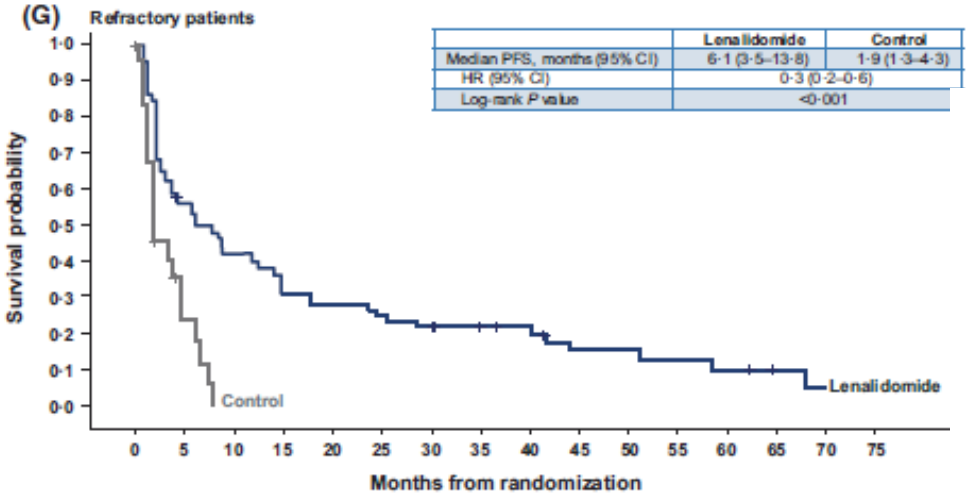
Subgroup		PFS HR (95% CI)	Patients, *n/N* Len	Patients, *n/N* IC	Median PFS, months Len	Median PFS, months IC	Log rank *P*
MIPI score at diagnosis	Low		**41/61**	**27/35**	**7·5**	**5·7**	**0·035**
	Intermed·		37/51	17/22	8·4	6	0·255
	High		36/40	12/14	5·7	2·1	0·549
MIPI score at baseline	Low		28/42	15/21	16·4	5·7	0·159
	Intermed·		**46/66**	**27/37**	**12·1**	**6·4**	**0·033**
	High		**52/60**	**23/25**	**3·7**	**2·1**	**0·037**
Age	<65 years		41/55	21/27	5·7	6·8	0·637
	≥65 years		**86/115**	**45/57**	**10·7**	**4·3**	**0·001**
ECOG PS	0-1		**107/142**	**55/73**	**8·6**	**5·9**	**0·025**
	2		**20/27**	**11/11**	**9·0**	**1·9**	**0·019**
LDH	Low		0/2	2/2	NA	4·6	0·157
	Normal		**67/94**	**35/51**	**12·2**	**7·8**	**0·049**
	High		**59/73**	**28/30**	**3·8**	**2·0**	**0·016**
WBC ($x10^9$/l)	<6·7		**55/79**	**37/46**	**8·1**	**4·4**	**0·011**
	6·7-<10		42/56	20/27	11·5	7·4	0·085
	10-<15		15/19	5/7	8·4	8·4	0·804
	≥15		14/15	4/4	2·9	3·9	0·731

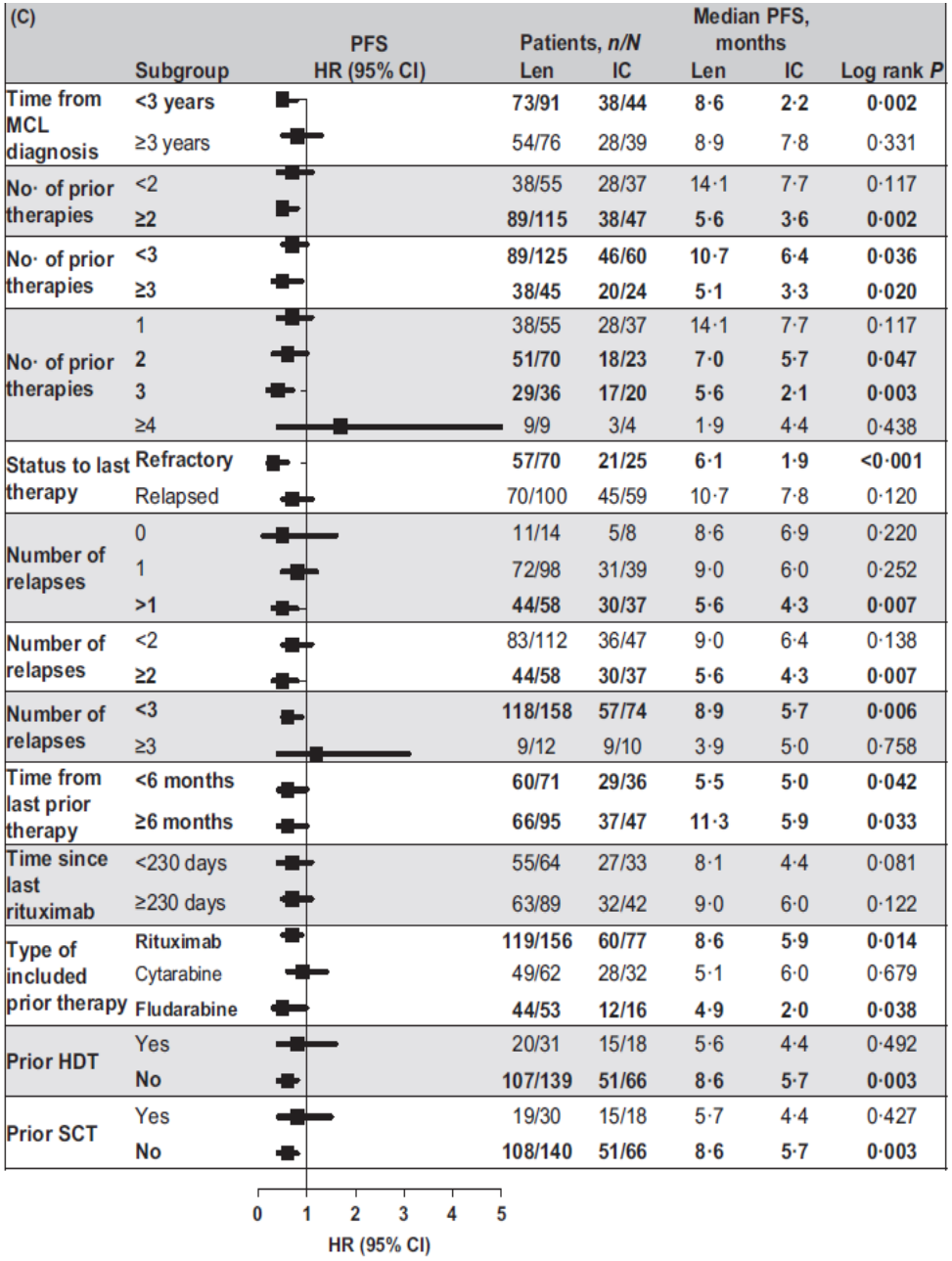


	Lenalidomide	IC
Median PFS, months (95% CI)	8·6 (5·6–12·1)	5·4 (3·6–7·7)
Sequential HR (95% CI)	0·65 (0·47–0·87)	
Sequential log-rank *P* value	0·006	



	Lenalidomide	IC
Median OS, months (95% CI)	27·7 (22·6–35·2)	21·1 (16·0–31·6)
Sequential HR (95% CI)	0·86 (0·62–1·18)	
Mantel-Byar *P* value	0·163	


(G)
Refractory patients
Lenalidomide
Control
Median PFS, months (95% CI)
6·1 (3·5–13·8)
1·9 (1·3–4·3)
HR (95% CI)
0·3 (0·2–0·6)
Log-rank P value
<0·001
Survival probability
1·0
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0·0
Control
Lenalidomide
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75
Months from randomization


(C)
Subgroup
PFS HR (95% CI)
Patients, n/N
Len
IC
Median PFS, months
Len
IC
Log rank P
Time from MCL diagnosis
<3 years 73/91 38/44 8·6 2·2 0·002
≥3 years 54/76 28/39 8·9 7·8 0·331
No· of prior therapies
<2 38/55 28/37 14·1 7·7 0·117
≥2 89/115 38/47 5·6 3·6 0·002
No· of prior therapies
<3 89/125 46/60 10·7 6·4 0·036
≥3 38/45 20/24 5·1 3·3 0·020
No· of prior therapies
1 38/55 28/37 14·1 7·7 0·117
2 51/70 18/23 7·0 5·7 0·047
3 29/36 17/20 5·6 2·1 0·003
≥4 9/9 3/4 1·9 4·4 0·438
Status to last therapy
Refractory 57/70 21/25 6·1 1·9 <0·001
Relapsed 70/100 45/59 10·7 7·8 0·120
Number of relapses
0 11/14 5/8 8·6 6·9 0·220
1 72/98 31/39 9·0 6·0 0·252
>1 44/58 30/37 5·6 4·3 0·007
Number of relapses
<2 83/112 36/47 9·0 6·4 0·138
≥2 44/58 30/37 5·6 4·3 0·007
Number of relapses
<3 118/158 57/74 8·9 5·7 0·006
≥3 9/12 9/10 3·9 5·0 0·758
Time from last prior therapy
<6 months 60/71 29/36 5·5 5·0 0·042
≥6 months 66/95 37/47 11·3 5·9 0·033
Time since last rituximab
<230 days 55/64 27/33 8·1 4·4 0·081
≥230 days 63/89 32/42 9·0 6·0 0·122
Type of included prior therapy
Rituximab 119/156 60/77 8·6 5·9 0·014
Cytarabine 49/62 28/32 5·1 6·0 0·679
Fludarabine 44/53 12/16 4·9 2·0 0·038
Prior HDT
Yes 20/31 15/18 5·6 4·4 0·492
No 107/139 51/66 8·6 5·7 0·003
Prior SCT
Yes 19/30 15/18 5·7 4·4 0·427
No 108/140 51/66 8·6 5·7 0·003
0 1 2 3 4 5
HR (95% CI)

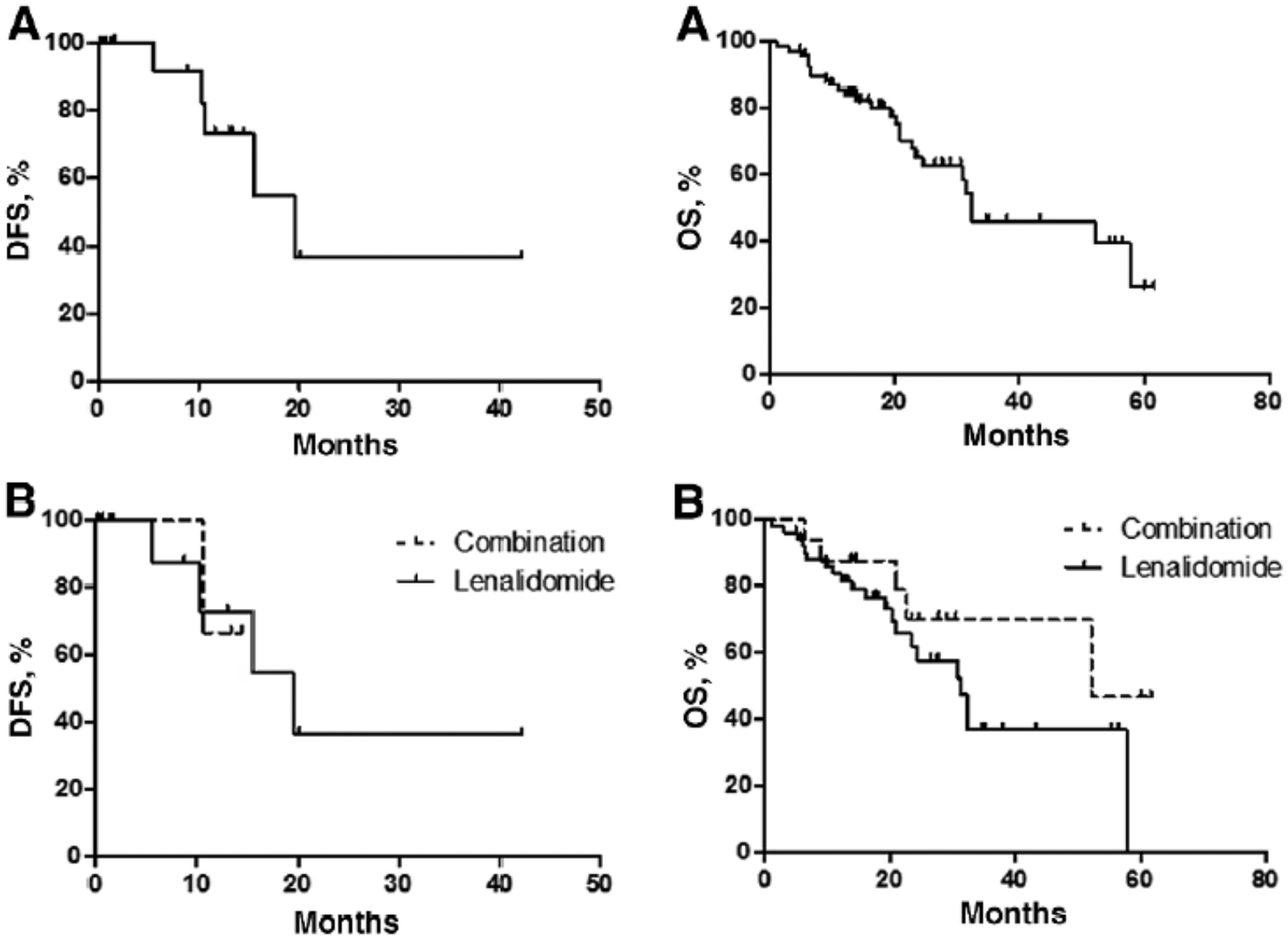
The Oncologist®

Hematologic Malignancies

Lenalidomide in Pretreated Mantle Cell Lymphoma Patients: An Italian Observational Multicenter Retrospective Study in Daily Clinical Practice (the Lenamant Study)

Vittorio Stefoni,[a] Cinzia Pellegrini,[a] Alessandro Broccoli,[a] Luca Baldini,[b] Monica Tani,[c] Emanuele Cencini,[d] Amalia Figuera,[e] Michela Ansuinelli,[f] Elisa Bernocco,[g] Maria Cantonetti,[h] Maria Christina Cox,[i] Filippo Ballerini,[j] Chiara Rusconi,[k] Carlo Visco,[l] Luca Arcaini,[m] Angelo Fama,[n] Roberto Marasca,[o] Stefano Volpetti,[p] Alessia Castellino,[q] Catello Califano,[r] Marina Cavaliere,[s] Guido Gini,[t] Anna Marina Liberati,[u] Gerardo Musuraca,[v] Anna Lucania,[w] Giuseppina Ricciuti,[x] Lisa Argnani,[a] Pier Luigi Zinzani[a]

Characteristics	Whole population, $n = 70$, n (%)	Patients in continuous complete remission, $n = 14$, n (%)
Median age, years (range)	67 (45–85)	63 (45–79)
<65 years	57 (81.4)	8 (57.1)
≥65 years	13 (18.6)	6 (42.9)
Male	50 (71.4)	8 (57.1)
Stage		
I/II	14 (20.0)	4 (28.6)
III	5 (7.1)	1 (7.1)
IV	51 (72.9)	9 (62.3)
ECOG performance status		
0/1	47 (67.1)	12 (85.7)
2	17 (24.3)	2 (14.3)
3	2 (2.9)	—
4	1 (1.4)	—
B symptoms	10 (14.3)	1 (7.1)
Refractory to most recent therapy	32 (45.7)	4 (37.7)
Refractory to first-line therapy	16 (22.8)	9 (62.3)
Median number of previous therapies (range)	2.5 (1–10)	2 (1–5)
Prior autologous stem cell transplant	36 (51.4)	8 (57.1)
Lenalidomide single agents	52 (74.3)	8 (57.1)
Lenalidomide in combination	18 (25.7)	6 (42.9)



The Oncologist 2018;23:1033–1038

Initial Treatment with Lenalidomide Plus Rituximab for Mantle Cell Lymphoma: 5-year Follow-up and Correlative Analysis from a Multi-center Phase II Study

J Ruan, P Martin, P Christos, L Cerchietti, B Shah, SJ Schuster, W Tam, A Rodriguez, D Hyman, N Calvo-Vidal, L Roman-Gonzalez, S Smith, J Svoboda, RR Furman, M Coleman, JP Leonard

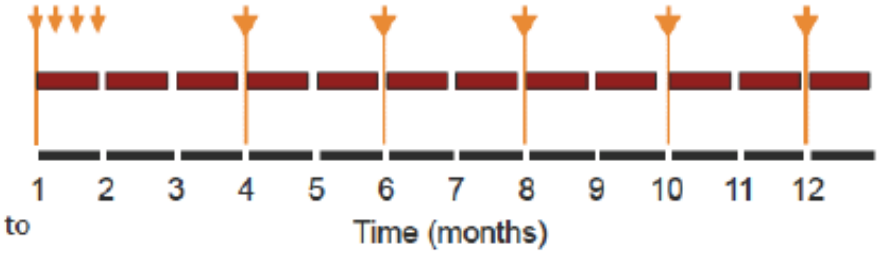
Weill Cornell Medicine; Moffitt Cancer Center; U Penn Abramson Cancer Center; U Chicago Medical Center

Study Design

Induction (cycles 1-12)

Rituximab
375 mg/m^2

Lenalidomide
20 mg*
Days 1-21 q 28

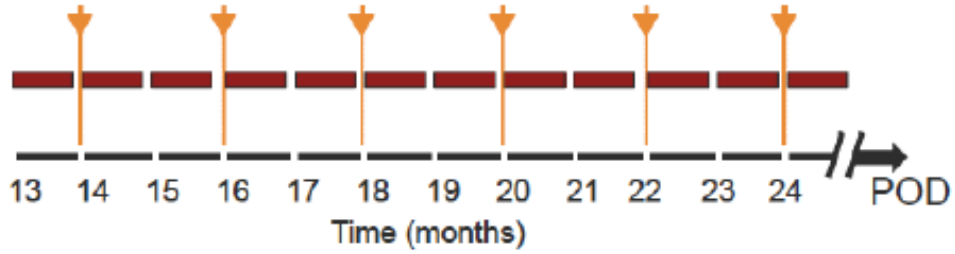


* Dose escalation to 25 mg allowed

Maintenance (cycle 13 - POD)

Rituximab
375 mg/m^2

Lenalidomide
15 mg
Days 1-21 q 28



Response assessment: Cheson 2007; DVT prophylaxis: ASA
Scan frequency: every 3 months Y1-2, every 6 month Y3 & beyond

Ruan et al, ASH 2017

Baseline Patient and Disease Characteristics

Clinical Characteristics	Number	Percentage
Number of patients	38	100%
Median age in year (range)	65 (42-86)	
Gender Male	27	71%
Female	11	29%
ECOG 0-1	37	97%
> 1	1	3%
Stage III-IV	38	100%
LDH Elevated	14	37%
Bone marrow involvement	34	89%
MIPI score		
Low risk (score < 5.7)	13	34%
Intermediate risk (5.7≤score<6.2)	13	34%
High risk (score ≥ 6.2)	12	32%
Ki67		
< 30%	26	68%
≥ 30%	8	21%

Ruan et al, ASH 2017

Efficacy: Objective Best Responses

Response	No. of patients	ITT (n=38)	Evaluable (n=36)
Overall response	33	87%	92%
CR	23	61%	64%
PR	10	26%	28%
SD	1	3%	3%
PD	2	5%	6%
Inevaluable#	2		
Median follow-up	61 months (range 21-74)		
Median time to PR	3 months (range 3-13)		
Median time to CR	11 months (range 3-22)		

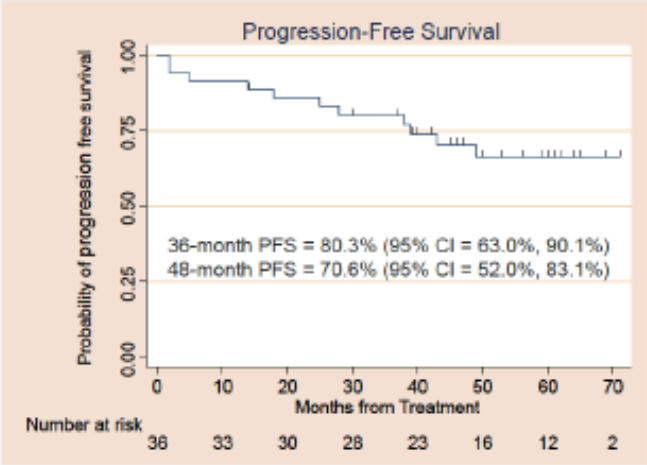
ITT: Intent-to-treat

#: Treatment was discontinued in 2 patients due to tumor flare without progression before tumor response evaluation.

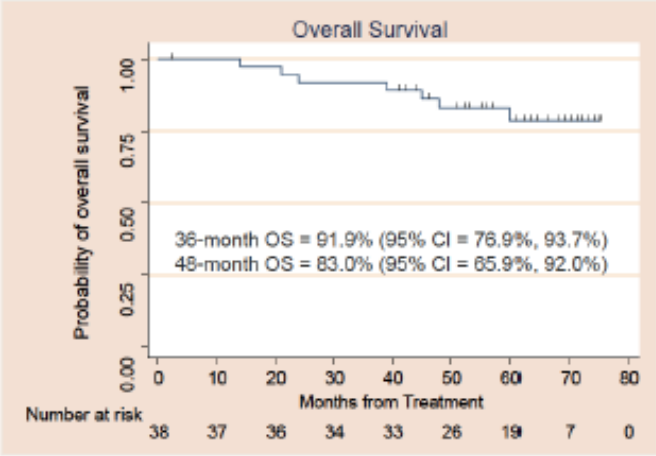
Ruan et al, ASH 2017

Rituximab + Lenalidomide For Newly Diagnosed MCL

Efficacy: Progression-Free Survival



Efficacy: Overall Survival



Ruan et al, ASH 2017

Wang et al. Journal of Hematology & Oncology (2017) 10:171
DOI 10.1186/s13045-017-0537-5

Journal of Hematology & Oncology

RESEARCH Open Access

Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004)

Michael Wang[1*], Stephen J. Schuster[2], Tycel Phillips[3], Izidore S. Lossos[4], Andre Goy[5], Simon Rule[6], Mehdi Hamadani[7], Nilanjan Ghosh[8], Craig B. Reeder[9], Evelyn Barnett[10], Marie-Laure Casadebaig Bravo[11] and Peter Martin[12]

Table 1 Patient characteristics at study entry

Characteristic	L (*n* = 13)		L + R (*n* = 11)		L + other (*n* = 34)		Overall (*N* = 58)	
	No.	%	No.	%	No.	%	No.	%
Median age, years (range)	67 (54–83)		70 (58–84)		71 (50–89)		71 (50–89)	
≥ 65	6	46	9	82	26	76	41	71
Sex								
Male	11	85	8	73	25	74	44	76
Female	2	15	3	27	9	26	14	24
ECOG PS								
0–1	7	54	5	45	16	47	28	48
2–4	3	23	1	9	4	12	8	14
Missing	3	23	5	45	14	41	22	38
Tumor burden[a]								
High	4	31	1	9	12	35	17	29
Low	1	8	5	45	13	38	19	33
Missing	8	62	5	45	9	26	22	38
Bulky disease[b]								
Yes	2	15	0	0	6	18	8	14
No	2	15	6	55	17	50	25	43
Missing	9	69	5	45	11	32	25	43
Time from diagnosis to first lenalidomide dose, months								
Median	58		47		46		49	
Range	15–144		6–105		4–214		4–214	
Time from end of last prior antilymphoma therapy to first dose of lenalidomide, weeks								
Median	0.7		0.3		0.7		0.7	
Range	0.1–3.5		0.1–21.7		0.1–12.6		0.1–21.7	

Table 2 Treatment history of enrolled patients

	L (*n* = 13)		L + R (*n* = 11)		L + other (*n* = 34)		Overall (*N* = 58)	
	No.	%	No.	%	No.	%	No.	%
No. of prior antilymphoma treatment regimens								
Median	4		3		4		4	
Range	3–7		2–8		1–13		1–13	
No. of prior antilymphoma therapies								
1	0	0	0	0	1	3	1	2
2	0	0	4	36	2	6	6	10
3	5	38	3	27	10	29	18	31
≥ 4	8	62	4	36	21	62	33	57
Missing	0	0	0	0	0	0	0	0
Type of ibrutinib treatment								
Combination regimen	1	8	1	9	10	29	12	21
Monotherapy	12	92	10	91	24	71	46	79
Ibrutinib status at study inclusion								
Relapse/PD	6	46	2	18	15	44	23	40
Refractory	2	15	8	73	15	44	25	43
Intolerant	3	23	0	0	3	9	6	10
Missing	2	15	1	9	1	3	4	7
Duration of ibrutinib treatment, months								
Median	4.8		3.9		4.3		4.3	
Range	1.2–13.9		2.0–16.6		0.5–47.6		0.5–47.6	
Best response on ibrutinib								
CR	2	15	0	0	6	18	8	14
PR	5	38	2	18	11	32	18	31
SD	0	0	1	9	0	0	1	2
Relapse/PD	5	38	8	73	15	44	28	48
Unknown	1	8	0	0	2	6	3	5
Primary reason for ibrutinib discontinuation								
Lack of efficacy	9	69	11	100	31	91	51	88
Toxicity to ibrutinib	3	23	0	0	2	6	5	9
Toxicity attribution unknown	0	0	0	0	1	3	1	2
Completed ibrutinib treatment	1	8	0	0	0	0	1	2
Time from end of last dose of ibrutinib to first dose of lenalidomide, weeks[a]								
Median	1.4		0.4		1.3		1.3	
Range	0.1–7.4		0.1–21.7		0.1–16.8		0.1–21.7	

Wang et al. Journal of Hematology & Oncology (2017) 10:171
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RESEARCH Open Access

Observational study of lenalidomide in patients with mantle cell lymphoma who relapsed/progressed after or were refractory/intolerant to ibrutinib (MCL-004)

Michael Wang[1*], Stephen J. Schuster[2], Tycel Phillips[3], Izidore S. Lossos[4], Andre Goy[5], Simon Rule[6], Mehdi Hamadani[7], Nilanjan Ghosh[8], Craig B. Reeder[9], Evelyn Barnett[10], Marie-Laure Casadebaig Bravo[11] and Peter Martin[12]

Table 3 Efficacy outcomes with lenalidomide in patients with MCL after ibrutinib failure or intolerance

Outcome	L ($n = 13$)		L + R ($n = 11$)		L + other[a] ($n = 34$)		Overall ($N = 58$)	
	No.	%	No.	%	No.	%	No.	%
Best response by investigator's assessment								
ORR	2	15	3	27	12	35	17	29
95% CI	2–45%		6–61%		20–54%		18–43%	
CR	0	0	1	9	7	21	8	14
PR	2	15	2	18	5	15	9	15
SD	0	0	1	9	3	9	4	7
Relapse/PD	8	62	3	27	16	47	27	47
Unknown	3	23	2	18	3	9	8	14
Missing	0	0	2	18	0	0	2	3
Duration of response, weeks								
KM median	3		20		NA		20	
95% CI	NA to NA		NA to NA		16.4 to NA		2.9 to NA	

Paper No: 754

KTE-X19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Patients (Pts) With Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL): Results of the Phase 2 ZUMA-2 Study

Michael L. Wang, MD, The University of Texas MD Anderson Cancer Center

Disclosure: Please see Session Details (link below).

Results: As of May 30, 2018, 28 pts received KTE-X19 with = 1 year of follow-up (median 13.2 months [range, 11.5 – 18.5]). The median age was 65 years (range, 50 – 75) and 86% of pts were male. Forty-three percent of pts had ECOG score of 1, 21% had blastoid morphology, 82% had stage IV disease, 50% had intermediate/high-risk MIPI, 86% received a median of 4 (range, 1 – 5) prior therapies, and 57% were refractory to last prior therapy. In 20/28 pts with available data, the median Ki-67 index was 38% (range, 5% – 80%). Eight pts received bridging therapy; all had disease present post-bridging.

Investigator-assessed ORR was 86% (95% CI, 67% – 96%) with a CR rate of 57% (95% CI, 37% – 76%). As of May 30, 2018, 75% of responders remained in response and 64% of treated pts had ongoing responses. The 12-month estimates of DOR, PFS and OS were 83% (95% CI, 60% – 93%), 71% (95% CI, 50% – 84%), and 86% (95% CI, 66% – 94%), respectively and the medians were not reached. The most common Grade = 3 AEs (= 20% of pts) were anemia (54%), platelet count decreased (39%), neutropenia (36%), neutrophil count decreased (32%), white blood cell count decreased (29%), encephalopathy (25%), and hypertension (21%). Grade 3/4 cytokine release syndrome (CRS) assessed by Lee et al. (*Blood.* 2014) was reported in 18% of pts, most commonly manifesting as hypotension (14%), hypoxia (14%), and pyrexia (11%). Grade 3/4 neurologic events (NE) were reported in 46% of pts and included encephalopathy (25%), confusional state (14%), and aphasia (11%). No Grade 5 CRS or NE occurred. All CRS events and most NE (15/17 pts) were reversible. Median time to onset and resolution of CRS was 2 days (range, 1 – 7) and 13 days (range, 4 – 60), respectively. Median time to onset of NE was 6 days (range, 1 – 15) and median time to resolution was 20 days (range, 9 – 99). There was 1 Grade 5 AE of organizing pneumonia that was considered related to conditioning chemotherapy. Median CAR T cell levels as measured by peak and area under the curve were 99 cells/µL (range, 0.4 – 2589) and 1542 cells/µL (range, 5.5 – 27239), respectively. Peak CAR T cell expansion was observed between Days 8 and 15 and declined over time.

Conclusions: ZUMA-2 is the first multicenter Phase 2 study of CAR T cell therapy in pts with R/R MCL. With = 1 year of follow-up, KTE-X19 demonstrated significant and durable clinical benefit, including a majority of pts achieving CR, and a manageable safety profile in pts with R/R MCL for whom there are no curative treatment options.

Conclusioni

- La Lenalidomide ha mostrato attività duratura nei MCL con med DOR 16,7 mesi e med DOR 28 mesi nei pz in CR

- La risposta si ottiene anche in pazienti pesantemente pre-trattati e chemorefrattari

- Il ruolo della Lenalidomide potrebbe essere espanso ad altri setting di pazienti affetti da MCL quali mantenimento o in prima linea in caso di pazienti non candidabili a chemio-immunoterapia classica

Sperando di non avervi annoiato……

Invoco la vostra clemenza