

Mantle Cell lymphoma: Update on pathobiology



Stefano A. Pileri



MANTLE CELL LYMPHOMA: NOW and BEYOND

ROME June 27, 2022

Disclosures of Stefano Pileri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BeiGene						x	
Roche					x		
Takeda						x	
Diatech						х	
Morphosys			X				

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International Agency for Research on Cancer (IARC)

Revised 4th Edition

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues

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KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

Patients	N = 68		
Characteristics			
Median no. of prior therapies (range)*	3 (1-5)		
≥ 3 prior lines of therapy, n (%)	55 (81)		
Anthracycline or bendamustine, n (%)	67 (99)		
Anthracycline	49 (72)		
Bendamustine	37 (54)		
BTKi, n (%)	68 (100)		
Ibrutinib	58 (85)		
Acalabrutinib	16 (24)		
Both	6 (9)		
Relapsed/refractory subgroup, n (%)			
Relapsed after autologous SCT	29 (43)		
Refractory to last prior therapy	27 (40)		
Relapsed after last prior therapy	12 (18)		
BTKi relapsed/refractory status, n (%)	68 (100)		
Refractory to BTKi	42 (62)		
Relapsed on BTKi	18 (26)		
Relapsed after BTKi	5 (7)		
Intolerant to BTKi ⁺	3 (4)		

brexucabtagene autoleucel (KTE-X19, brexu-cel) was successfully manufactured for 71 patients (96%) and administered to 68 patients (92%)

Median time from leukapheresis to delivery of KTE-X19 to the study site was 16 days



The NEW ENGLAND JOURNAL of MEDICINE

Wang M. J. et al. KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma N Eng J Med, April 2020



Aberrant expression of CD10 and BCL6 in mantle cell lymphoma

Marco Pizzi,¹ Claudio Agostinelli,² Simona Righi,² Anna Gazzola,² Claudia Mannu,² Francesca Galuppini,¹ Matteo Fassan,¹ Andrea Visentin,³ Francesco Piazza,³ Gianpietro C Semenzato,³ Massimo Rugge¹ & Elena Sabattini²

CD5-negative Mantle Cell Lymphoma

Clinicopathologic Correlations and Outcome in 58 Patients

Yuan Miao, MD, PhD,*† Pei Lin, MD,* Annapurna Saksena, MD,* Jie Xu, MD, PhD,* Michael Wang, MD,‡ Jorge Romaguera, MD,‡ C. Cameron Yin, MD, PhD,* L. Jeffrey Medeiros, MD,* and Shaoying Li, MD* (Am J Surg Pathol 2019;00:000–000)

CD23 expression in mantle cell lymphoma is associated with CD200 expression, leukemic non-nodal form, and a better prognosis $\overset{\circ}{\sim}, \overset{\circ}{\sim} \overset{\circ}{\sim}$



Annapurna Saksena MD^{a,b}, C. Cameron Yin MD, PhD^a, Jie Xu MD, PhD^a, Jingyi Li MD^{a,c}, Jiehao Zhou MD, PhD^d, Sa A. Wang MD^a, Pei Lin MD^a, Guilin Tang MD, PhD^a, Lifu Wang MD^{a,e}, Michael Wang MD^f, Roberto N. Miranda MD^a, L. Jeffrey Medeiros MD^a, Shaoying Li MD^{a,*}

LYMPHOID NEOPLASIA

CCND2 and CCND3 hijack immunoglobulin light-chain enhancers in cyclin D1⁻ mantle cell lymphoma

David Martín-Garcia,^{1,2,*} Alba Navarro,^{1,2,*} Rafael Valdés-Mas,³ Guillem Clot,^{1,2} Jesús Gutiérrez-Abril,³ Miriam Prieto,^{1,2} Inmaculada Ribera-Cortada,⁴ Renata Woroniecka,⁵ Grzegorz Rymkiewicz,⁶ Susanne Bens,^{7,8} Laurence de Leval,⁹ Andreas Rosenwald,^{10,11} Judith A. Ferry,¹² Eric D. Hsi,¹³ Kai Fu,^{14,15} Jan Delabie,^{16,17} Dennis Weisenburger,¹⁸ Daphne de Jong,¹⁹ Fina Climent,²⁰ Sheila J. O'Connor,²¹ Steven H. Swerdlow,²² David Torrents,^{23,24} Sergi Beltran,²⁵ Blanca Espinet,^{26,27} Blanca González-Farré,^{2,28} Luis Veloza,²⁸ Dolors Costa,^{2,28} Estella Matutes,²⁸ Reiner Siebert,^{7,8} German Ott,^{29,30} Leticia Quintanilla-Martinez,³¹ Elaine S. Jaffe,³² Carlos López-Otín,^{2,3} Itziar Salaverria,^{1,2} Xose S. Puente,^{2,3,†} Elias Campo,^{1,2,28,33,†} and Sílvia Beà^{1,2,†}

(Blood. 2019;133(9):940-951)

Insights into the mechanisms underlying aberrant SOX11 oncogene expression in mantle cell lymphoma

Roser Vilarrasa-Blasi (D^{1,2}^{\vee}, Núria Verdaguer-Dot¹, Laura Belver^{3,4}, Paula Soler-Vila⁵, Renée Beekman¹, Vicente Chapaprieta (D¹, Marta Kulis¹, Ana C. Queirós¹, Maribel Parra (D⁴, María José Calasanz (D^{6,7}, Xabier Agirre (D^{6,7}, Felipe Prosper (D^{6,7,8}, Sílvia Beà^{1,2,7}, Dolors Colomer (D^{1,2,7}, Marc A. Marti-Renom^{5,9}, Adolfo Ferrando (D³, Elías Campo (D^{1,2,7} and José Ignacio Martin-Subero (D^{1,2,7,9})

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ORIGINAL REPORT

Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network

Ewa Hoster, Andreas Rosenwald, Françoise Berger, Heinz-Wolfram Bernd, Sylvia Hartmann, Christoph Loddenkemper, Thomas F.E. Barth, Nicole Brousse, Stefano Pileri, Grzegorz Rymkiewicz, Roman Kodet, Stephan Stilgenbauer, Roswitha Forstpointner, Catherine Thieblemont, Michael Hallek, Bertrand Coiffier, Ursula Vehling-Kaiser, Réda Bouabdallah, Lothar Kanz, Michael Pfreundschuh, Christian Schmidt, Vincent Ribrag, Wolfgang Hiddemann, Michael Unterhalt, Johanna C. Kluin-Nelemans, Olivier Hermine, Martin H. Dreyling, and Wolfram Klapper







Variable Expression of Proliferation Signature Genes in Mantle Cell Lymphoma





Rosenwald A et LLMPP, Cancer Cell 2003; 3(2):185-97.



Virchows Arch. 2020 August; 477(2): 259-267. doi:10.1007/s00428-020-02750-7.

Reproducibility of histologic prognostic parameters for mantle cell lymphoma: cytology, Ki67, p53 and SOX11

Giorgio A. Croci^{1,2}, Eva Hoster^{3,4}, Sílvia Beà^{5,6}, Guillem Clot^{5,6}, Anna Enjuanes^{5,6}, David W. Scott⁷, José Cabeçadas⁸, Luis Veloza⁹, Elias Campo^{5,6,9}, Erik Clasen-Linde¹⁰, Rashmi S. Goswami¹¹, Lars Helgeland¹², Stefano Pileri¹³, Grzegorz Rymkiewicz¹⁴, Sarah Reinke¹, Martin Dreyling⁴, Wolfram Klapper¹

MCL*				
Conventional	Leukemic nonnodal			
Naive B-cell–like	Memory B-cell-like			
Unexperienced†	Experienced†			
Naive-like	Memory-like			
98.7 (±2.6)†	95.1 (±1.5)†			
IGHV4-34	IGHV4-34			
IGHV5-51	IGHV5-51			
IGHV3-21	IGHV1-8			
IGHV3-23	IGHV4-59			
ATM, CDKN2A del	CCND1, TLR2			

LYMPHOID NEOPLASIA

Coding and noncoding drivers of mantle cell lymphoma identified through exome and genome sequencing

Prasath Pararajalingam,^{1,*} Krysta M. Coyle,^{1,*} Sarah E. Arthur,¹ Nicole Thomas,¹ Miguel Alcaide,¹ Barbara Meissner,^{2,3} Merrill Boyle,^{2,3} Quratulain Qureshi,¹ Bruno M. Grande,¹ Christopher Rushton,¹ Graham W. Slack,^{2,3} Andrew J. Mungall,⁴ Constantine S. Tam,^{5,6} Rishu Agarwal,⁵ Sarah-Jane Dawson,^{5,6} Georg Lenz,⁷ Sriram Balasubramanian,⁸ Randy D. Gascoyne,^{2,3} Christian Steidl,^{2,3} Joseph Connors,^{2,3} Diego Villa,^{2,3} Timothy E. Audas,¹ Marco A. Marra,^{2,3} Nathalie A. Johnson,⁹ David W. Scott,^{2,3} and Ryan D. Morin^{1,4}

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KEY POINTS

- RNA-binding proteins with roles in regulating alternative splicing, DAZAP1, EWSR1, HNRNPH1, are frequently mutated in MCL.
- Most somatic HNRNPH1 mutations are intronic and disrupt regulation of HNRNPH1 through alternative splicing.

Mantle cell lymphoma (MCL) is an uncommon B-cell non-Hodgkin lymphoma (NHL) that is incurable with standard therapies. The genetic drivers of this cancer have not been firmly established, and the features that contribute to differences in clinical course remain limited. To extend our understanding of the biological pathways involved in this malignancy, we performed a large-scale genomic analysis of MCL using data from 51 exomes and 34 genomes alongside previously published exome cohorts. To confirm our findings, we resequenced the genes identified in the exome cohort in 191 MCL tumors, each having clinical follow-up data. We confirmed the prognostic association of *TP53* and *NOTCH1* mutations. Our sequencing revealed novel recurrent noncoding mutations surrounding a single exon of the *HNRNPH1*gene. In RNA-seq data from 103 of these cases, MCL tumors with these mutations had a distinct imbalance of *HNRNPH1* isoforms. This altered splicing of HNRNPH1 was associated with inferior outcomes in MCL and showed a significant increase in protein expression by immunohistochemistry. We describe a functional role for these recurrent noncoding mutations in disrupting an autoregulatory feedback mechanism,

thereby deregulating HNRNPH1 protein expression. Taken together, these data strongly imply a role for aberrant regulation of messenger RNA processing in MCL pathobiology. (*Blood*. 2020;136(5):572-584)



Circulating tumor DNA predicts therapeutic outcome in mantle cell lymphoma

Rahul Lakhotia,¹ Christopher Melani,¹ Kieron Dunleavy,² Stefania Pittaluga,³ Nakhle Saba,⁴ Liza Lindenberg,⁵ Esther Mena,⁵ Ethan Bergvall,⁶ Andrea Nicole Lucas,⁷ Allison Jacob,⁸ Erik Yusko,⁸ Seth M. Steinberg,⁹ Elaine S. Jaffe,³ Adrian Wiestner,¹⁰ Wyndham H. Wilson,^{1,*} and Mark Roschewski^{1,*}

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Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study

Yuqin Song,¹ Keshu Zhou,² Dehui Zou,³ Jianfeng Zhou,⁴ Jianda Hu,⁵ Haiyan Yang,⁶ Huilai Zhang,⁷ Jie Ji,⁸ Wei Xu,⁹ Jie Jin,¹⁰ Fangfang Lv,¹¹ Ru Feng,¹² Sujun Gao,¹³ Haiyi Guo,¹⁴ Lei Zhou,¹⁵ Jane Huang,¹⁶ William Novotny,¹⁶ Pil Kim,¹⁶ Yiling Yu,¹⁴ Binghao Wu,¹⁴ and Jun Zhu¹

KEY POINTS

- Zanubrutinib demonstrated deep and durable responses and a favorable safety profile in R/R MCL at median 35.3 months follow-up.
- Zanubrutinib provided a high response rate (84% [78% CR]) and extended PFS (median 33.0 months) in patients with R/R MCL.



Genomic and Gene Expression Profiling Defines Indolent Forms of Mantle Cell Lymphoma

Verònica Fernàndez¹, Olga Salamero², Blanca Espinet³, Francesc Solé³, Cristina Royo¹, Alba Navarro¹, Francisca Camacho⁴, Sílvia Beà¹, Elena Hartmann⁵, Virginia Amador¹, Luis Hernández¹, Claudio Agostinelli⁶, Rachel L. Sargent⁷, Maria Rozman¹, Marta Aymerich¹, Dolors Colomer¹, Neus Villamor¹, Steven H. Swerdlow⁷, Stefano A. Pileri⁶, Francesc Bosch², Miguel A. Piris⁴, Emili Montserrat², German Ott⁸, Andreas Rosenwald⁵, Armando López-Guillermo², Pedro Jares¹, Sergi Serrano³, and Elías Campo¹

Molecular and Cellular Pathobiology

Cancer Research

Molecular Subsets of Mantle Cell Lymphoma Defined by the *IGHV* Mutational Status and SOX11 Expression Have Distinct Biologic and Clinical Features

Alba Navarro¹, Guillem Clot¹, Cristina Royo¹, Pedro Jares¹, Anastasia Hadzidimitriou⁴, Andreas Agathangelidis^{4,5}, Vasilis Bikos⁴, Nikos Darzentas⁴, Theodora Papadaki⁷, Itziar Salaverria^{1,8}, Magda Pinyol¹, Xavier Puig², Jara Palomero¹, Maria Carmela Vegliante¹, Virgina Amador¹, Alejandra Martinez-Trillos¹, Lenka Stefancikova¹², Adrian Wiestner¹³, Wyndham Wilson¹³, Christiane Pott⁹, Maria Jose Calasanz³, Nicola Trim¹⁴, Wendy Erber¹⁵, Birgitta Sander¹⁶, German Ott¹⁰, Andreas Rosenwald¹¹, Dolors Colomer¹, Eva Giné¹, Reiner Siebert⁸, Armando Lopez-Guillermo¹, Kostas Stamatopoulos^{4,6}, Sílvia Beà¹, and Elías Campo¹



	cMCL (n=15)	iMCL (n=12)	P value
B symptoms (%)	33	0	0.03
Non-ambulatory performance status ECOG≥2 (%)	70	0	0.01
Nodal presentation (lymph nodes >1 cm) (%)*	93	17	<0.001
High serum LDH* (%)	46	0	0.03
Intermediate or high-risk MIPI	46	0	0.016
Morphology	13	67	0.007
Small cell (%)	74	33	
Classical Blastoid	13	-	
IGHV gene hypermutations (>5%)	20	70	< 0.04
Genomic Profile			
1.imbalance	13	100	<0.001
≥ 2 imbalances	87	0	
Chemotherapy at any time (%)	100	17	
Dead patients (%)	47	0	<0.001
5-year overall survival (%)	49	100	0.03







LNMCL shows a specific gene signature and SOX11 negativity







		L.	P value		
Variable	Total	cMCL	nnMCL	Undetermined	vs nnMCL)
Number of cases (%)	70	39 (56)	26 (37)	5 (7)	
Follow-up data					
Median follow-up, mo	43	35	88	30	.019
Mean time from diagnosis to sample (range), mo	16.6 (0-185)	2.8 (0-36)	36 (0-185)	22.8 (0-92)	.002
Dead patients, n (%)	24/70 (34)	16/39 (41)	7/26 (27)	1/5 (20)	.296
Treated at 3 y from diagnosis, % (95% Cl)	65 (51-75)	88 (70-96)	31 (9-48)	47 (0-79)	<.001
Treated at 3 y from sampling, % (95% Cl)	71 (57-80)	89 (73-96)	44 (19-62)	47 (0-79)	<.001
3-y OS, diagnosis, % (95% CI)	78 (69-89)	69 (55-86)	92 (81-100)	80 (52-100)	.006
3-y OS, sampling, % (95% CI)	72 (61-85)	68 (53-86)	79 (62-100)	80 (52-100)	.379



In-situ mantle cell lymphoma—a report of two cases

2008 Blackwell Publishing Ltd, Histopathology, 52, 239–262.

N Aqel F Barker K Patel K N Naresh

Departments of Histopathology and Haematology, Northwick Park Hospital, Hillingdon Hospital & Hammersmith Hospital, London, UK

In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior

by Alejandra Carvajal-Cuenca, Luz F. Sua, Nhora M. Silva, Stefania Pittaluga, Cristina Royo, Joo Y. Song, Rachel L. Sargent, Blanca Espinet, Fina Climent, Samuel A. Jacobs, Jan Delabie, Kikkeri N. Naresh, Adam Bagg, Pierre Brousset, Roger A. Warnke, Sergi Serrano, Nancy Lee Harris, Steven H. Swerdlow, Elaine S. Jaffe, and Elias Campo

Haematologica 2011 [Epub ahead of print]





LN with Cyclin D1+ In Situ Pattern

SOX11 negative

May be CD5 negative Rare event: <1% of LNs Low risk of Progression (<10%)

SOX11 positive

More often CD5 positive Higher risk of progression Similar pattern can be seen at relapse or at distant sites

Letter to the Editor Leukemia 23, 1190-1193 (June 2009) | doi:10.1038/leu.2009.31

t(11;14)-positive clones can persist over a long period of time in the peripheral blood of healthy individuals.

Y Lecluse, P Lebailly, S Roulland, A-C Gac, B Nadel and P Gauduchon

Abstract

Several lymphoma- and leukaemia-associated chromosomal translocations are present in the peripheral blood of healthy individuals (HI). Translocation t(14;18), the genetic hallmark of follicular lymphoma (FL) that juxtaposes the BCL2 proto-oncogene near the immunoglobulin heavy chain (IGH) locus, can be detected in most HI at highly variable frequency.

