Conclusiones de "The American Society of Hematology,53nd Annual Meeting". Madrid 25 y 26 de Enero del 2013, X Edición.

Tratamiento de otros linfomas indolentes (No Folicular)

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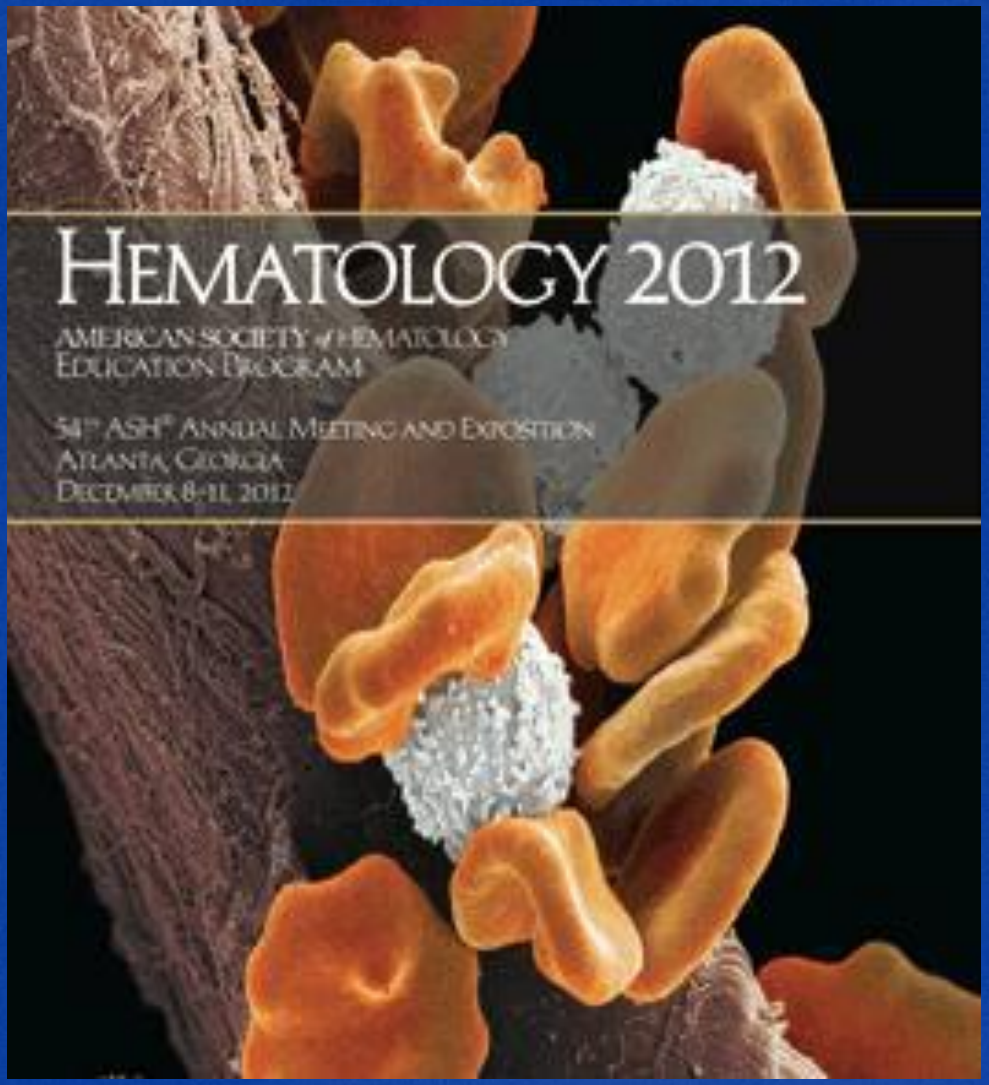
The many faces of marginal zone lymphoma

Pier Luigi Zinzani[1]



Linfomas marginales (LM)

1.-Linfomas MALT (70% de los LNH- Marginales)

(7-8% LNH-B)

2.-Linfomas Esplénicos (20% de los LNH Marginales)

3.- Linfomas marginal nodal (10% de los LNH Marginales)

Zinzani Educ Book ASH 2012

Alteraciones genéticas de los LM

Alteración	Gen	Frecuencia	Localización
t(11;18)(q21;q21)	BIRC3-MALT1	15%-40%	Stomach, lung
t(14;18)(q32;q21)	IGHV-MALT1	20%	Lung, salivary gland, skin, ocular adnexa
t(1;14)(p22;q32)	IGHV-BCL10	5%	Stomach, lung
t(3;14)(p13;q32)	IGHV-FOXP1	<5%	Unclear
3/3q		20-40%	No differences
18/18q		20-40%	No differences
6q23	TNFAIP3	15-30%	No differences

Zinzani Educ Book ASH 2012

Diferencias entre subtipos de LHN Marginal

	MALT	Esplénico	Nodal
Edad media	60	65	50-60
Patogenia	Hp,C jejuni,C psittaci, B burgdorferi	Unknown, HCV	Unknown, HCV
Alteración genética	t(11;18)(q21;q21)	3q and gains of 12q	No typical abnormality
Características clínicas	Stage IE disease	Abnormal blood cell count, splenomegaly	Disseminated peripheral and abnormal nodal involvement

Zinzani, Educ Book, ASH 2012

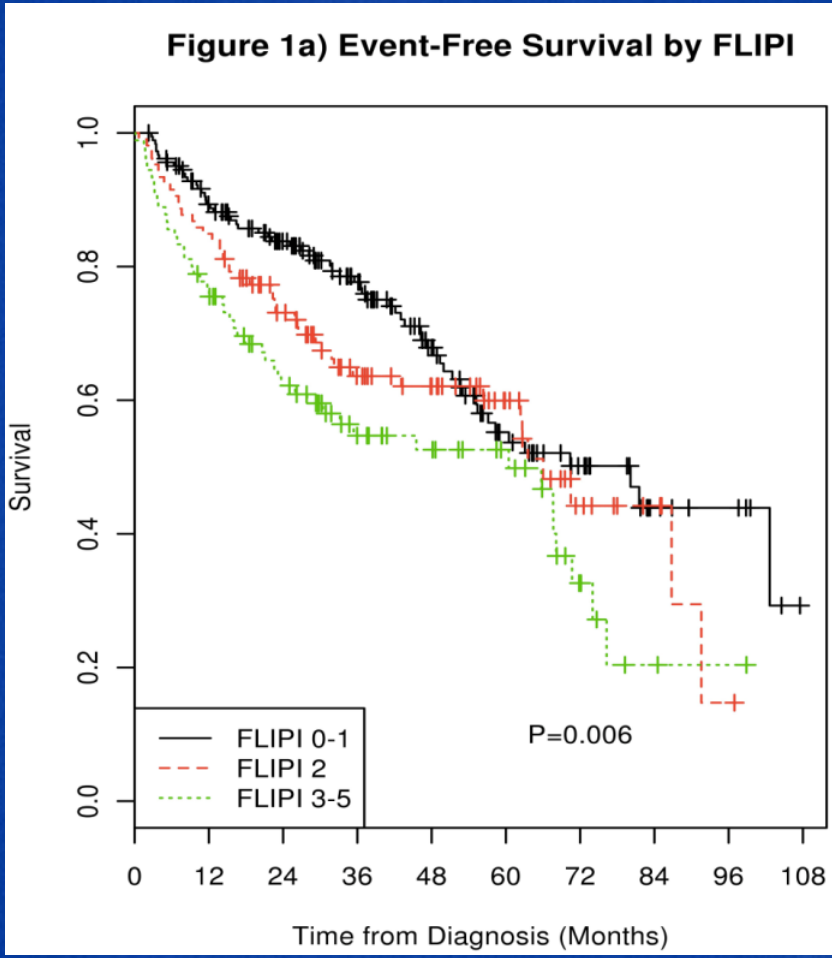
Indices pronósticos

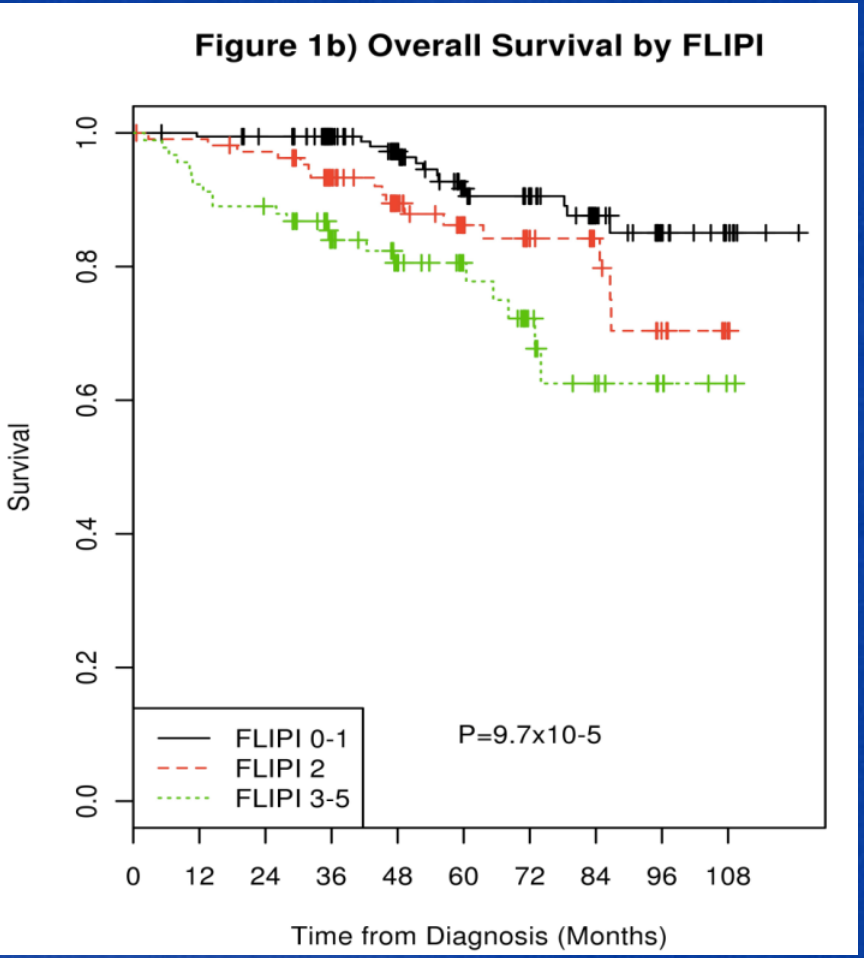
Non-Follicular Low Grade B-Cell Lymphomas: Patterns of Presentation and Management with Comparative Prognostic Utility of IPI and FLIPI

FLIPI N=382	LMEN N=198	LMN N=22	LME N=47	Linfopl asm. N=48	Inclas. N=67
0,1	(67%)	(36%)	(21%)	(23%)	(31%)
2	(22%)	36%	(30%)	(31%)	(40%)
3	(11%)	(27%)	(49%)	(46%)	(28%)

Jacobus, ASH 2012 abtr 1563

Non-Follicular Low Grade B-Cell Lymphomas: Patterns of Presentation and Management with Comparative Prognostic Utility of IPI and FLIPI





Jacobus, ASH 2012 abtr 1563

Tratamiento

Tratamiento del linfoma MALT gástrico

Número	Estadio I,IIvsIII/IV	Tratamiento	Respuesta
24	71%/29%	Ciclofosfamida o clorambucilo	75% CR
83	100%/0%	CHOP 3 CVP 4	100% CR
4	50%/50%	Oxaliplatin	50% CR, 25% PR
19	100%/0%	2CdA	100% CR
27	86%/14%	Rituximab	46% CR, 31% PR
7	57%/43%	R-CHOP/R-CNOP	100% CR
13	100%/0%	Bortezomib	46% CR, 15% PR

Hammel, Aviles, Raderer, Jager, Martinelli, Raderer, Conconi. Educational Book ;Zinzani ,ASH 2012

Radiotherapy in Stage I and II Extranodal Marginal Zone B-Cell Lymphoma of MALT : Surveillance, Epidemiology, and End Results (SEER)

Sitio	**Número**	**% que reciben RT**	**SG (5 a) No RT** *(95 CI)*	**SG (5 a) SI RT** *(95 CI)*	**p**
Estómago	2499	27	0,87	0,92	**0,0002**
Ocular	1013	67	0,84	0,99	**0,0004**
Gl.salivales	615	44	0,87	0,98	0,14
Intestino	600	11	0,88	0,87	0,45
Piel	514	51	0,90	1.0	**0,007**
Pulmón	496	9	0,87	0,92	0,28
Mama	210	41	0,86	0,62	0,17
Tiroides	164	39	0,90	0,95	0,24

Olszewski, ASH 2012, abtr 2053

FMR Regimen in previously untreated patients with indolent lymphoma: Efficacy, safety and PET data on 285 patients (143 Non Follicular)

- LCP 31 pacientes y L. Marginal 111 pacientes
- Fludarabina 25/m2 mg días 2,3,4 + Mitoxantrone 10 mg /m2 día 2 + Rituximab 375 mg día 1 + , 6 ciclos c/28 días
- Respuesta: RG 85%; RC 74% (LCP 52% y LM 80% de RC)
- Mediana de seguimiento 40 m (12-144)
- SG a 11 años 79%, SLE 73% y S LP 72 % en la serie global ,sin diferencia entre Folicular y No Folicular.
- Toxicidad hematológica grado >3 : 31%.
- Neoplasias secundarias : 3 , a los 8 m (LLA), 9 m (SMD), y 11 m (LLA)

Zinzani et al , ASH Atlanta 2012,abtr 2736

FMR Regimen in previously untreated patients with indolent lymphoma: Efficacy, safety and PET data on 285 patients (143 Non Follicular)

- PET al diagnóstico y tras el tratamiento en 75 L. Foliculares y 57 No Foliculares
- PET + al final del tratamiento se asocia a peor SG (71% vs 98%) (p<0,0001)
- SLP no diferente

Zinzani et al , ASH Atlanta 2012,abtr 2736

Final Results of a Multicenter Phase II Trial with Bendamustine and Rituximab as First Line Treatment for Patients with MALT Lymphoma (MALT-2008-01). (Abstract 3691)

Inclusion criteria:

- histologically proven CD20+ MALT lymphoma arisen at **any extranodal site**, of any **stage (Ann Arbor I-IV)**
- either **de novo,** or **relapsed disease following local therapy in gastric or cutaneous lymphoma** (in well-defined circunstances)
- no evidence of histologic transformation
- measurable or evaluable disease
- age ≥ 18
- life expectancy of at least 1 year
- ECOG performance status 0-2
- no prior chemotherapy or prior immunotherapy with any anti-CD20 monoclonal antibody or prior radiotherapy in the last 6 weeks
- written informed consent

Exclusion criteria:

- concurrent malignancy (except CIN1 or NM skin Ca)
- active infection requiring systemic therapy
- active HBV and/or HCV infection or serology for HIV
- pregnant or breast feeding
- significant concurrent medical diseases

GELTAMO

- Prospective, multicenter, non-randomized, phase II trial
- EUDRACT code: 2008-007725-39

Benda-R en Linfomas MALT

STUDY DESIGN

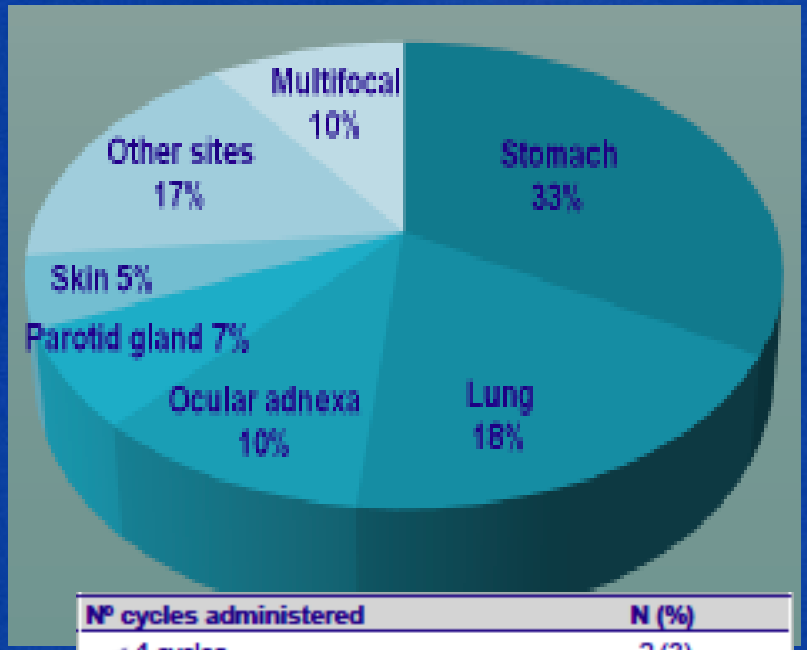
- Prospective, multicenter, non-randomized, phase II trial
- EUDRACT code: 2008-007725-39

Rituximab: 375 mg/m² i.v. day 1
Bendamustine: 90 mg/m² i.v. day 1 and 2
x 3 cycles

Stable disease Progression → Withdrawal of study

Complete remission (CR o uCR) → Rituximab 375 mg/m² d1, Bendamustine 90 mg/m² d1-2, x 1 cycle (4 total)

Parcial remission (PR) → Rituximab 375 mg/m² d1, Bendamustine 90 mg/m² d1-2, x 3 cycles (6 total)



Nº cycles administered	N (%)
< 4 cycles	2 (3)
4 cycles	44 (73)
> 4 cycles	14 (23)

	N	Median [Q1 , Q3]
RDI Rituximab		
≤ 4 cycles	46	0.99 [0.95 , 1.01]
> 4 cycles	14	0.98 [0.98 , 1.01]
RDI Bendamustine		
≤ 4 cycles	46	0.99 [0.95 , 1.00]
> 4 cycles	14	0.98 [0.97 , 1.00]

Delayed cycles	N (%)
Yes	17 (6)
Cause of delay	
Hematologic toxicity	6 (21)
Non-hematologic toxicity	10 (35)
Both	1 (4)

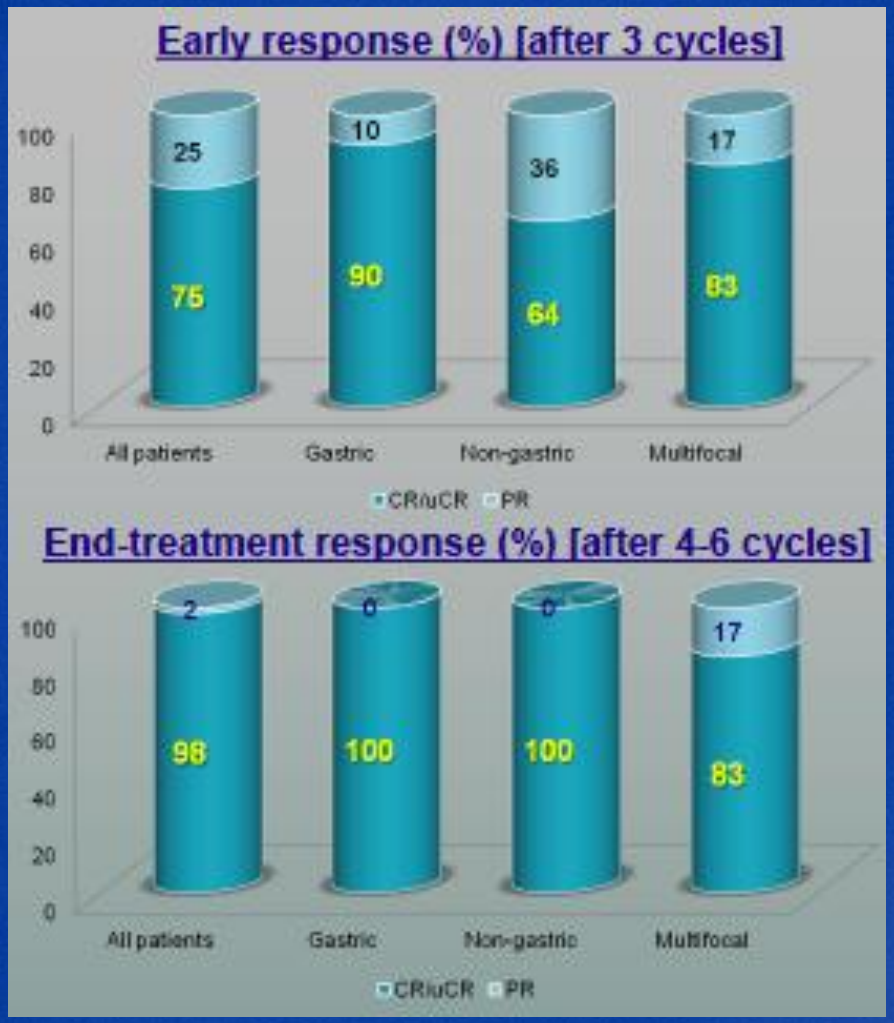
Salar et al, abtr 3691

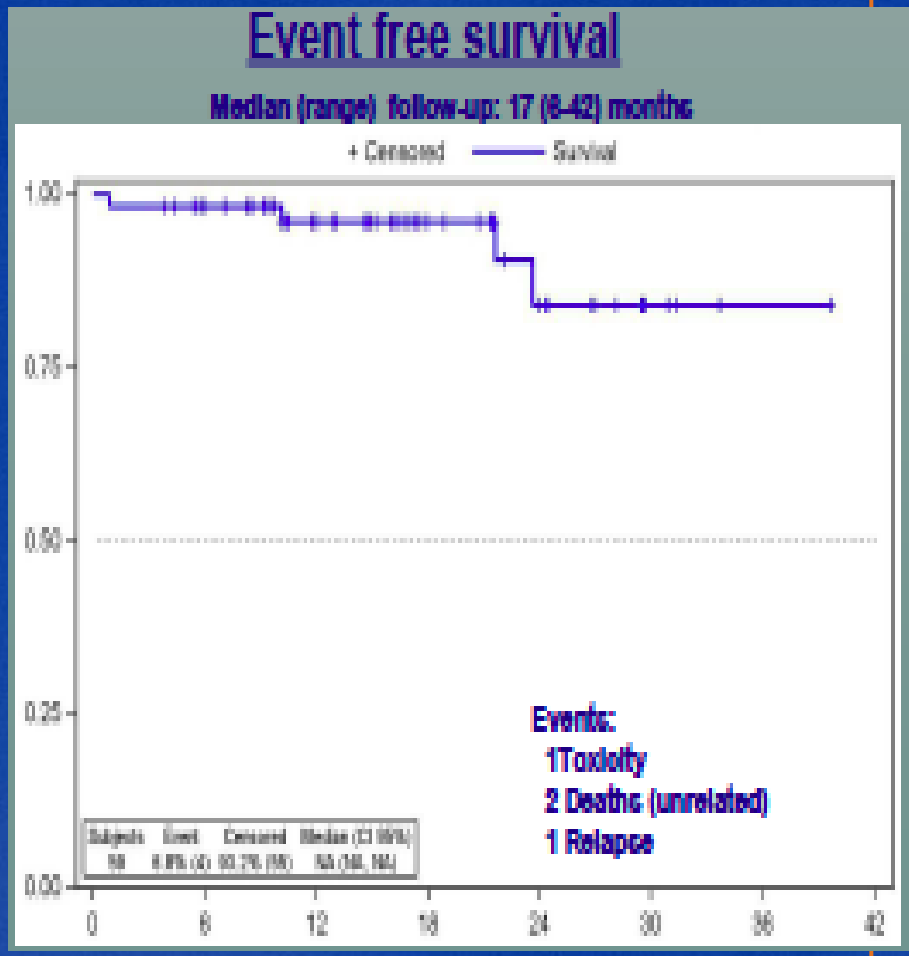
Benda-R en Linfomas MALT

Adverse events Grade 3-4 by cycle (N=264)	Grade 3	Grade 4	Grade 3-4
Hematologics			
Lymphocytopenia	25 (9.47)	1 (0.38)	26 (9.85)
Neutropenia	6 (2.27)	8 (3.03)	14 (5.30)
Leucopenia	4 (1.52)	2 (0.76)	6 (2.27)
Febril neutropenia	1 (0.38)	1 (0.38)	2 (0.76)
Non-hematologics			
Infections	4 (1.52)	1 (0.38)	5 (1.89)
Fever	2 (0.76)	0 (0.00)	2 (0.76)
Asthenia	1 (0.38)	0 (0.00)	1 (0.38)
Pharyngeal edema/pain	3 (1.14)	0 (0.00)	3 (1.14)
Gastrointestinal disorders	2 (0.76)	0 (0.00)	2 (0.76)
Neurologic disorders	0 (0.00)	2 (0.76)	2 (0.76)
Hypotension	1 (0.38)	1 (0.38)	2 (0.76)
Eye disorders	1 (0.38)	0 (0.00)	1 (0.38)
Hepatobiliar disorders	0 (0.00)	1 (0.38)	1 (0.38)
Anorexia	1 (0.38)	0 (0.00)	1 (0.38)
Hypocalcemia	1 (0.38)	0 (0.00)	1 (0.38)
Neoplasms	1 (0.38)	0 (0.00)	1 (0.38)

Salar et al, abtr 3691

Benda –R en Linfomas MALT





Salar et al, abtr 3691

Comentarios

- The combination of Bendamustine and Rituximab in first line treatment of MALT lymphoma has a manageable safety profile, being safe and well accepted by patients.
- This regimen achieved an overall response of 100% after only 3 cycles and the complete remission rate was 98% after completing treatment plan.
- All but one (93%) patient in partial remission after 3 cycles converted to complete remission after 6 cycles.
- Of note, a large majority of patients (77%) required only 4 cycles to achieve complete remission.

Lenalidomide and Rituximab for Untreated Indolent Lymphomas

Histología	PGR	Enf estable	RP	RC/RCi	RG	SLP a 36 meses
LCP n=30	7%	13%	53%	27%	80%	66%
LM n=27	0	11%	22%	67%	89%	80%

Neutopenia grado >3 : 40% de los pacientes (13% de los ciclos)
Trombopenia en el 4% de los pacientes

Fowler et al, OC, abtr 901, Atlanta ASH 2012

LR-CD: Efficacy of combination therapy with Lenalidomide for Untreated Indolent B-Cell Lymphoma

- Lenalidomide *20 D 1-21* + Rituximab *375 mg /m2 D1*+ ciclofosfamida *250 mg /m2 D1,8 y 15* + dexametasona 40 D1,8,15 y 22
- 31 pacientes con LF 28%, LM 25%,LPL/MWG 39% y LCP 4%
- Respuesta global 82% (39% RC)
- *Bien tolerado con similares toxicidades a Lena sola.*

Reeder , ASH 2012, abtr 2741

Results of a Phase II Study of Lenalidomide in combination with Rituximab for the treatment of Indolent Non Follicular NHL.

- LEN 20 mg D1-21+Rituxi D14 x 6 ciclos.
- LNH indolentes 2 o 3 líneas previas
- 39 pacientes. 19 LCP, 4 LME, 3 MALT, y 2 LMN

- RG 52% (5/27 pacientes alcanzan RC)

Sazzi , ASH 2012 , abtr 1645

Biología

Histologic Transformation in Marginal Zone Lymphomas

373 pacientes con Linfoma marginal, SG y SLP (15 y 8 años); con una mediana de 5 años

14 pacientes se transformaron (4%), LBDCG en 12 , LM en 1 y LH en 1 paciente. SG postransformación a los 2 años (38%)

186 (50%)

MALT
Transf 4%

88 (23%) esplénicos

Transf 6%

63 (17%) No clasif

Transf 2%

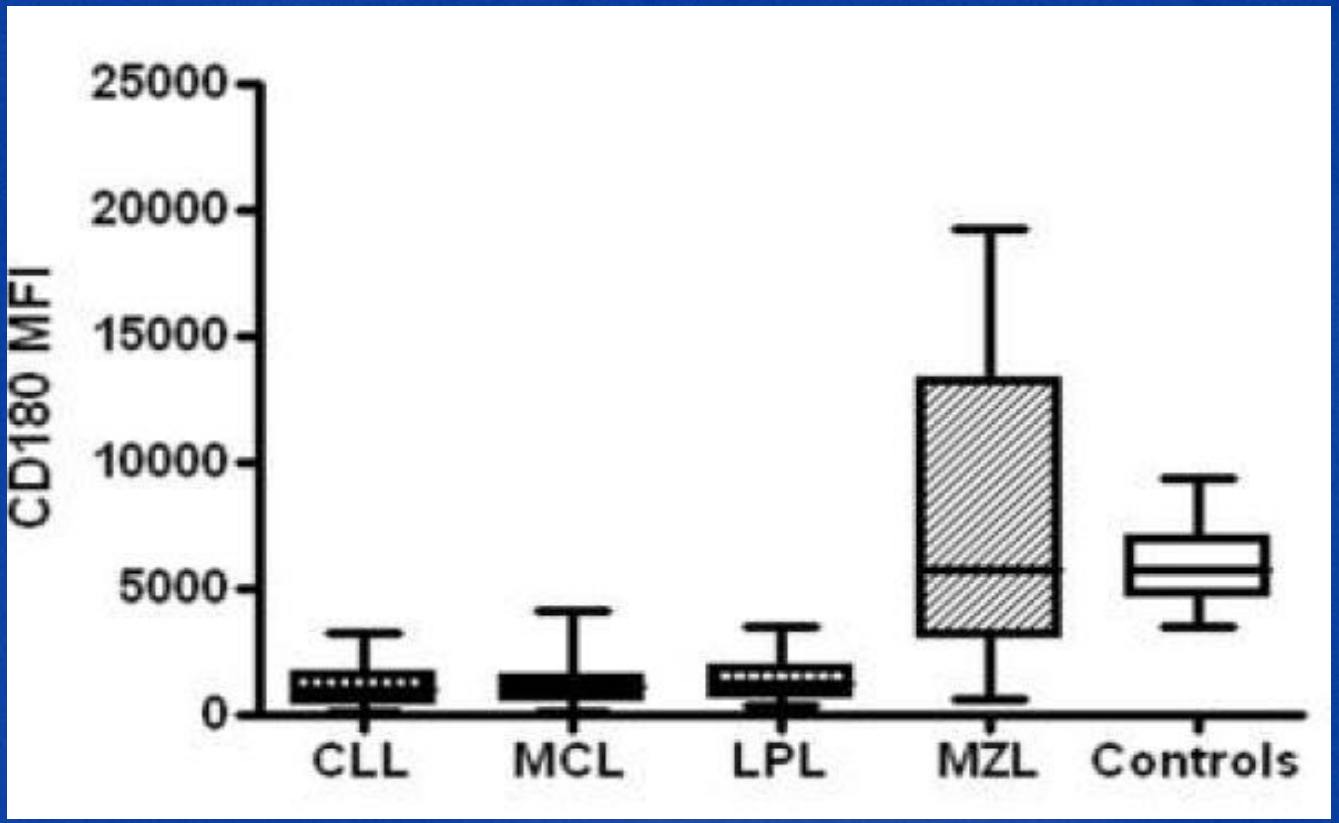
36 (10%)

Nodales

Franceschetti, ASH 2012 abtr 1571

Strong Cell Surface Expression of the Toll-Like Receptor Homolog CD180 Identifies Circulating Cells of Marginal Zone Lymphoma From Other B-Cell Malignancies

- 25 controles y 91 pacientes con LNH (30 L Marginales, 30 LLC ,13 L. Manto y 15 LPL)



Mauvieux , ASH 2012, abtr1542.

Prevalence and Clinical Significance of the *MYD88* (L265P) Somatic Mutation in Patients with Waldenström Macroglobulinemia, IgM-Monoclonal Gammopathy of Undetermined Significance or Other Mature B-Cell Neoplasms

	MGW	**GMSi(IgM)**	**LME**	**otros SLPB**
Número	58	77	84	52
% mutación	100	47	6	6

Sensibilidad 100%;
6/8 LME o SLPB con mutación tenían un CM IgM
2 p IgG /IgM (son MGW??)

Varetoni ,ASH 2012, abtr 2667

Mutational Status of Splenic Marginal Zone Lymphoma Revealed by Whole Exome Sequencing

Los linfomas marginales esplénicos contienen mutaciones somáticas que implican a genes reguladores del RCB , de las vías TLR/NFKB y de la remodelación de la cromatina

Nerea, ASH 2012 abtr 2698