LA TERAPIA DEL LINFOMA GASTRICO

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Disclosures of Name Surname

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KIOWA KIRIN						x	
MSD						x	
SERVIER						x	

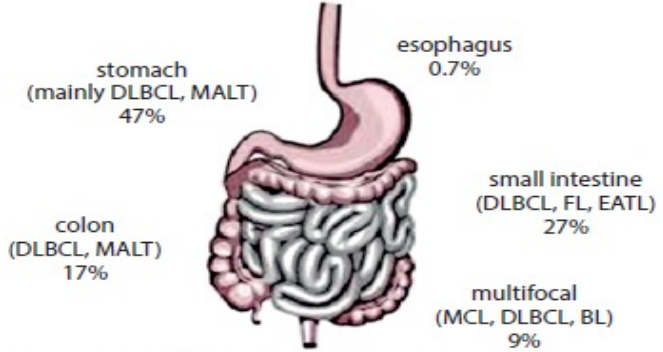

Fig. 1. Gastrointestinal lymphoma topography

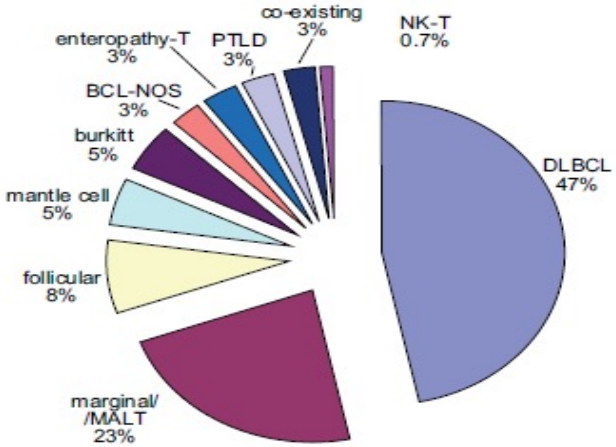

Fig. 2. Gastrointestinal lymphoma distribution

Olszewska-Szopa M, Wróbel T. Gastrointestinal non-Hodgkin lymphomas. *Adv Clin Exp Med*. 2019;28(8):1119–1124. doi:10.17219/acem/94068

- Patologia caratteristica dell'età adulta-avanzata, senza chiara predilezione di genere
- Sintomatologia aspecifica
- Riscontro spesso occasionale in corso di indagini endoscopiche.

Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆

E. Zucca[1,2,3], L. Arcaini[4,5], C. Buske[6], P. W. Johnson[7], M. Ponzoni[8], M. Raderer[9], U. Ricardi[10], A. Salar[11], K. Stamatopoulos[12], C. Thieblemont[13], A. Wotherspoon[14] & M. Ladetto[15], on behalf of the ESMO Guidelines Committee*

- 5%/15% di tutti i linfomi non Hodgkin nel mondo occidentale.
- ~60% EMZL
- qualsiasi sito extranodale
- stimolazione antigenica cronica (infezioni, autoimmunità).
- Lo stomaco è la sede più comune, seguito dagli annessi oculari, dai polmoni e dalle ghiandole salivari.
- ~20% SMZL
- <10% NMZL
- Incidenza in incremento negli ultimi due decenni (probabilmente a causa di una migliore diagnosi patologica), nonostante un calo dell'incidenza di MZL gastrici associati a Helicobacter pylori.

Ann Oncol. 2013;24 (suppl. 6):vi144-vi148.

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- EMZL localizzato per un periodo prolungato, ma spesso multifocale, coinvolgimento dei linfonodi regionali e di più sedi mucose.
- L'infiltrazione del midollo osseo è stata descritta nel 2%-20% dei casi, più comune nei linfomi non gastrici.
- Gli EMZL con coinvolgimento linfonodale o midollare alla presentazione hanno una prognosi peggiore; la multifocalità non ha significato prognostico.
- Le procedure iniziali di stadiazione della MZL gastrica devono includere: esofagogastroduodenoscopia (EGDS) con biopsie multiple di mappatura. L'EGDS di routine può anche essere consigliabile per i pazienti con MZL non gastrointestinale, in particolare le donne, quelli con coinvolgimento primario del polmone, delle vie aeree superiori e delle ghiandole salivari e IPI elevato, livelli sierici elevati di β2M o infezione da H. Pylori, indipendentemente dal sito primario.

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•La stadiazione iniziale obbligatoria per tutti i sottotipi MZL dovrebbe includere:
•obiettività in particolare per occhi e orecchie, naso e gola
•citometria a flusso del sangue periferico obbligatoria in NMZL e SMZL e facoltativa per EMZL, immunofissazione sierica e urinaria,
•sierologia per il virus dell'epatite C (HCV) e se positivo anche PCR e genotipizzazione del virus +crioglobuline e criocrito
•marcatori del virus dell'epatite B (HbsAg, ac. antiHbsAg, ac antiHbc)
•HIV
•L'aspirato midollare (con morfologia e citometria a flusso) altamente raccomandati in EMZL, in particolare nel linfoma non gastrico e quando è previsto solo un trattamento locale.
•La tomografia computerizzata (TC) completa del torace e dell'addome o RMN.
•La PET-CT. Può essere utile nei casi in cui è previsto solo un trattamento localizzato e nei casi sospetti di trasformazione in istologia di alto grado anche per guidare la biopsia. L'ecografia endoscopica (US) per MZL gastrica può essere utilizzata per definire l'infiltrazione della parete gastrica e il coinvolgimento dei linfonodi perigastrici.

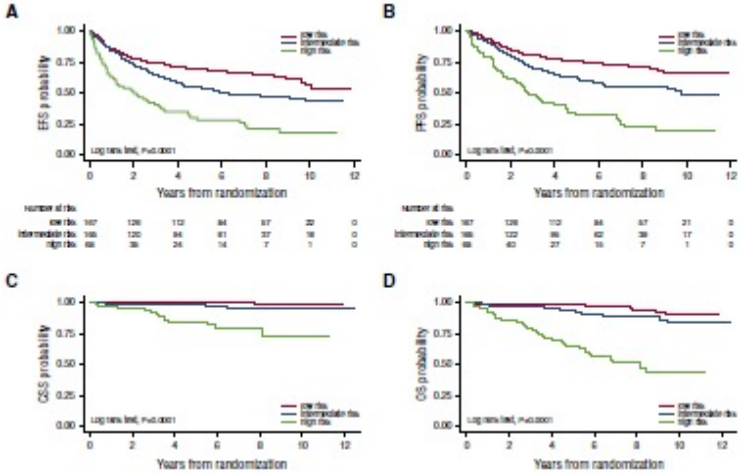
Ann Oncol. 2013;24 (suppl. 6):vi144-vi148.

A MALT lymphoma prognostic index

Catherine Thieblemont,[1] Luciano Cascione,[2,3] Annarita Conconi,[3,4] Barbara Kiesewetter,[5] Markus Raderer,[5]

Table 2. Final model for EFS generated by stepwise Cox regression used to build the MALT-IPI

N = 400	HR	Standard Error	95% CI	*P*
Stage III-IV	1.79	0.26	1.35-2.38	<.001
Age >70 y	1.72	0.27	1.26-2.33	.001
LDH >UNL	1.87	0.37	1.27-2.77	.002



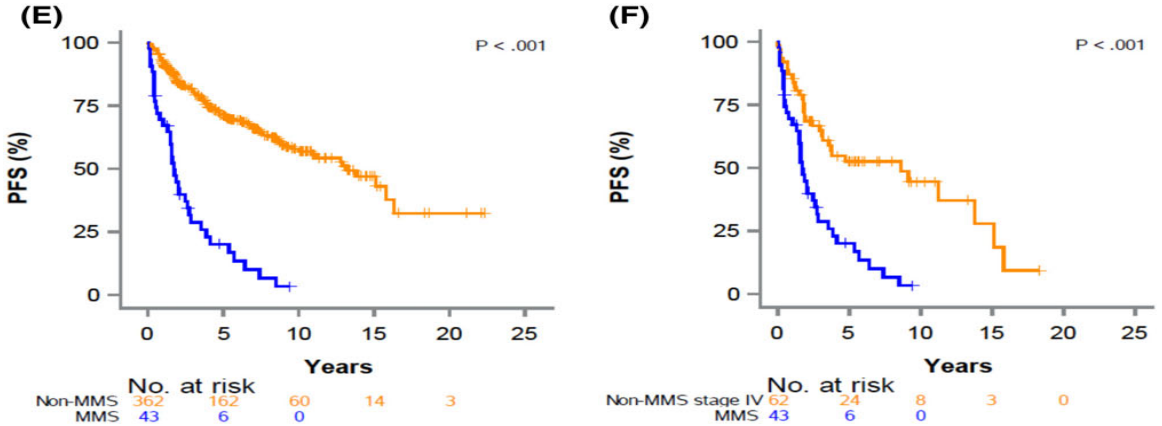
Blood. 2017;130(12):1409-1417

Risk factors

Short survival and frequent transformation in extranodal marginal zone lymphoma with multiple mucosal sites presentation. Alderuccio JP, Zhao W, Desai A, et al. Am J Hematol. 2019;94:585–596. https://doi.org/10.1002/ajh.25446.

«…MALT-IPI ≥2 (HR = 2.47 and 4.75), FLIPI >2 (HR = 1.65 and 2.09), and IPI >2 (HR = 2.09 and 1.73) were associated with shorter PFS and OS, respectively. Higher grade transformation (HGT) occurred in 11 (25.6%) MMS patients with a 5-year cumulative incidence of 13.2% (95% CI 4.7-26.1%). EMZL patients with MMS presentation represent a novel clinical subset associated with shorter PFS, OS, and higher incidence of HGT that needs novel therapeutic approaches.

Kaplan–Meier curves for progression-free survival (PFS) in 405 patients with EMZL.
- E: by the presence of MMS
- F: by MMS vs non-MMS in stage IV;



Risk factors

Early progression as a predictor of survival in marginal zone lymphomas: an analysis from the FIL-NF10 study. Luminari S et al. Blood. 2019;134(10):798-801DOI 10.1182/blood. 2019001088.

«…assessment of POD24 predicts subsequent outcome in MZL in need of therapy and its association with OS is confirmed for the main MZL subtypes…»

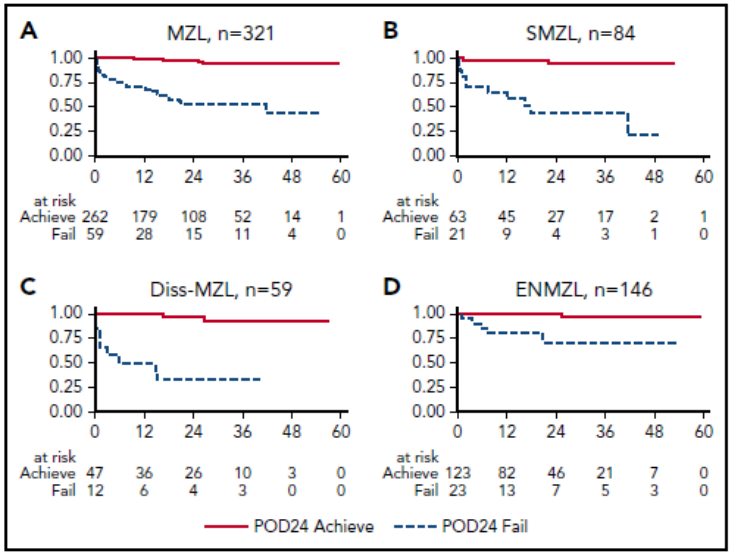


Figure 1. OS by POD24 and by MZL subtypes. OS from a risk-defining event after diagnosis in patients with MZL who were immediately treated after diagnosis. (A) Patients with MZL: POD24 rate, 18%; 3-year OS POD24, achieve 95% vs fail 53% ($P < .001$) (HR, 19.5; 95% CI, 8.40-45.4). (B) Patients with SMZL: POD rate, 25%; 3-year OS POD24, achieve 95% vs fail 44% ($P < .001$). (C) Patients with disseminated MZL (Diss-MZL): POD rate, 20%: 3-year OS POD24, achieve 93% vs fail 33% ($P < .001$). (D) Patients with ENMZL: POD rate, 16%; 3-year OS POD24, achieve 98% vs fail 71% ($P < .001$). Association of POD24 with OS could not be assessed for NMZL patients because too few events have been reported in this subgroup to do any inference.

Risk factors

The utility of prognostic indices, early events, and histological subtypes on predicting outcomes in non-follicular indolent B-cell lymphomas. Tracy SI, Larson MC, Feldman AL, et al. Am J Hematol. 2019;94:658–666. https://doi.org/10.1002/ajh.25473

•«…The divergent long-term outcomes experienced by patients who do or do not attain EFS12 suggest there exists a subset of patients who harbor high risk disease. Future research efforts should focus on methods to identify these patients at the time of diagnosis, in order to enable risk-tailored therapy.”

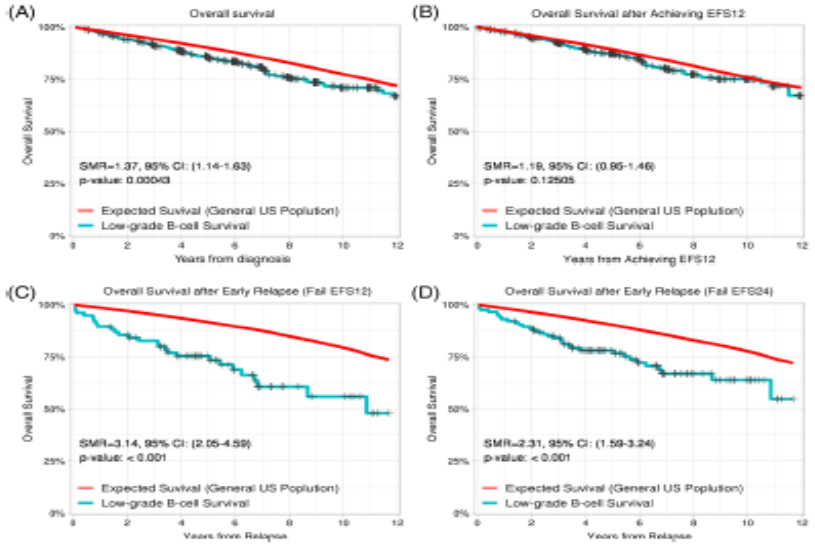


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Table 2. Comparison of the Lugano and Paris staging systems for gastrointestinal tract lymphoma[7,16]

	Lugano staging system	Paris staging system	Tumour extension
Stage I	Confined to the GI tract (single primary or multiple, non-contiguous)	T1m N0 M0 T1sm N0 M0 T2 N0 M0 T3 N0 M0	Mucosa Submucosa Muscularis propria Serosa
Stage II	Extending into abdomen		
II1	Local nodal involvement	T1—3 N1 M0	Perigastric lymph nodes
II2	Distant nodal involvement	T1—3 N2 M0	More distant regional nodes
Stage IIE	Penetration of serosa to involve adjacent organs or tissues	T4 N0—2 M0	Invasion of adjacent structures with or without abdominal lymph nodes
Stage IV	Disseminated extranodal involvement or concomitant supra-diaphragmatic nodal involvement	T1—4 N3 M0 T1—4 N0—3 M1 T1—4 N0—3 M2	Extra-abdominal lymph nodes Distant (non-contiguous) GI sites involvement Non-GI sites involvement

Table 3. Specific staging and work-up procedures for EMZL at different primary anatomic sites

Site	Exam	Notes
Stomach	EGD	Mandatory
	Endoscopic US	Optional, to evaluate the regional lymph nodes and gastric wall infiltration
	IHC	Mandatory, to evaluate *Helicobacter pylori* status. Faecal antigen or breath test and serology studies are recommended when the results of histology are negative
	FISH or PCR assay	Optional, to detect *t(11;18)* translocation

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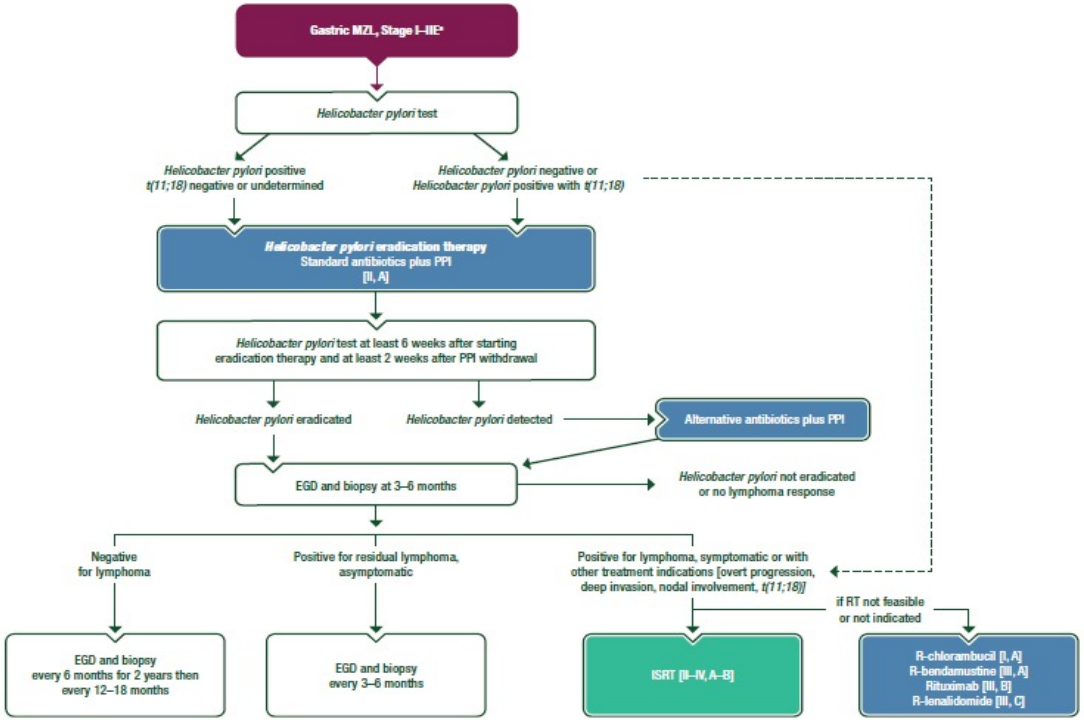

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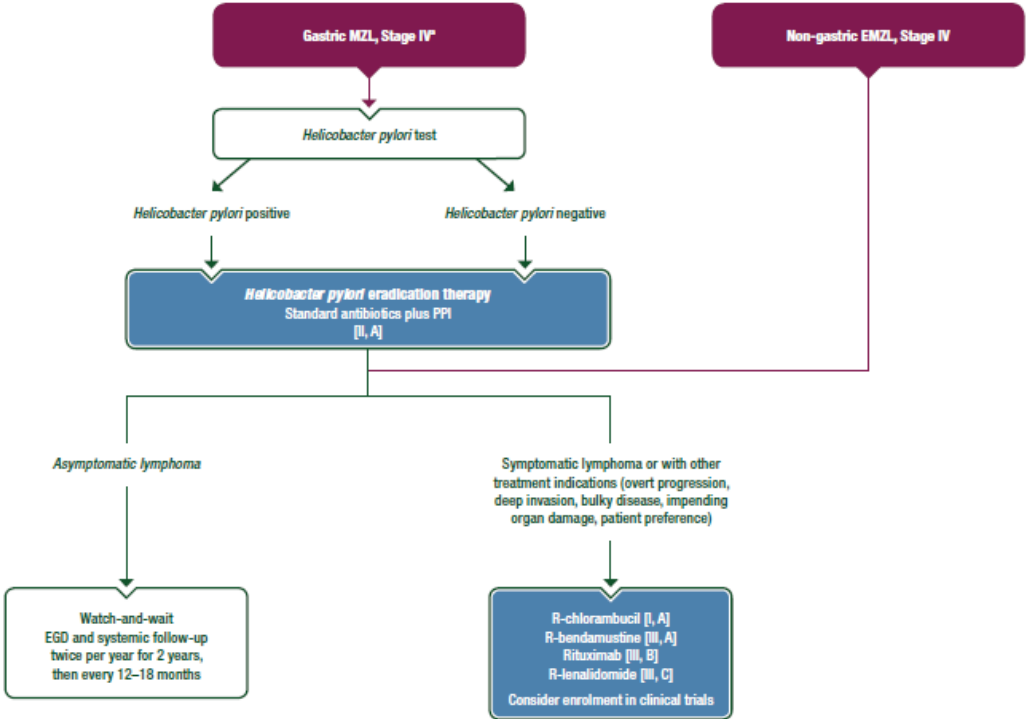

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2021

Extranodal Marginal Zone B-Cell Lymphoma

Gastric MALT Lymphoma

NCCN Guidelines Index
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Discussion

ADDITIONAL DIAGNOSTIC TESTING[a,b]

ESSENTIAL:

- Diagnosis of gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis[c]
  - IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1,[d] BCL6 with or without
  - Cell surface marker analysis by flow cytometry with peripheral blood and/or biopsy specimen: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter pylori (H. pylori) stain (gastric), if positive, then PCR or FISH for t(11;18)[e]

USEFUL UNDER CERTAIN CIRCUMSTANCES:

- Molecular analysis to detect: antigen receptor gene rearrangements; *MYD88* mutation status to differentiate WM versus MZL if plasmacytic differentiation present
- Karyotype or FISH: t(1;14); t(3;14); t(11;14);[d] t(11;18)
- FISH or PCR: t(14;18)

→

WORKUP

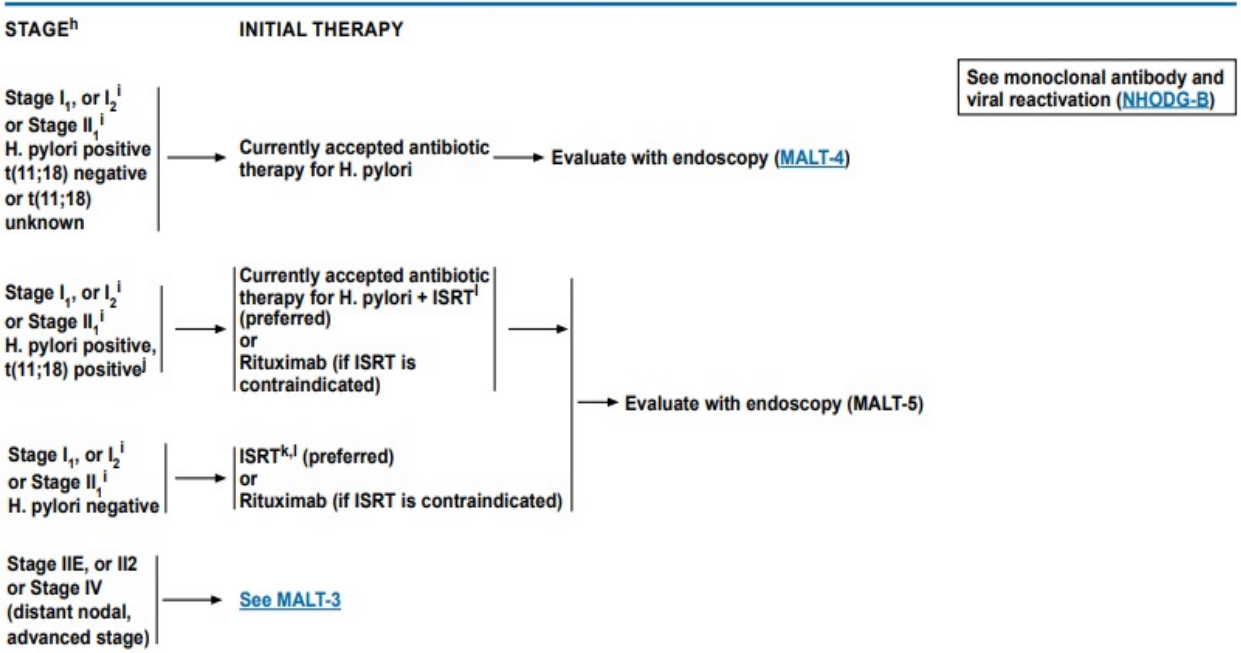
ESSENTIAL:

- Physical exam
- Performance status
- CBC with differential
- Comprehensive metabolic panel
- LDH
- If H. pylori negative by histopathology, then use noninvasive H. pylori testing (stool antigen test or urea breath test)
- Hepatitis B testing[f] if rituximab contemplated
- Hepatitis C testing
- C/A/P CT with contrast of diagnostic quality
- Pregnancy testing in women of childbearing age (if chemotherapy or RT planned)

USEFUL IN SELECTED CASES:

- Bone marrow biopsy ± aspirate
- PET/CT scan (including neck) (especially if ISRT anticipated)
- Echocardiogram or MUGA scan if anthracycline or anthracenedione-based regimen is indicated
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites[g]
- Discussion of fertility issues and sperm banking
- SPEP

→ See Initial Therapy (MALT-2)



[h] See Lugano Staging System for Gastrointestinal Lymphomas (MALT-A).
[i] Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.
[j] t(11;18) is a predictor for lack of tumor response (<5%) to antibiotics. Antibiotics are used in these patients to eradicate the H. plyori infection. These patients should be considered for alternative therapy of the lymphoma. Liu H, et al. Gastroenterology 2002;122:1286-1294.
[k] If H. pylori negative by both histology and serum antibodies, RT is recommended.
[l] See Principles of Radiation Therapy (NHODG-D).

NCCN Guidelines Version 4.2021

Extranodal Marginal Zone B-Cell Lymphoma

Gastric MALT Lymphoma

NCCN Guidelines Index
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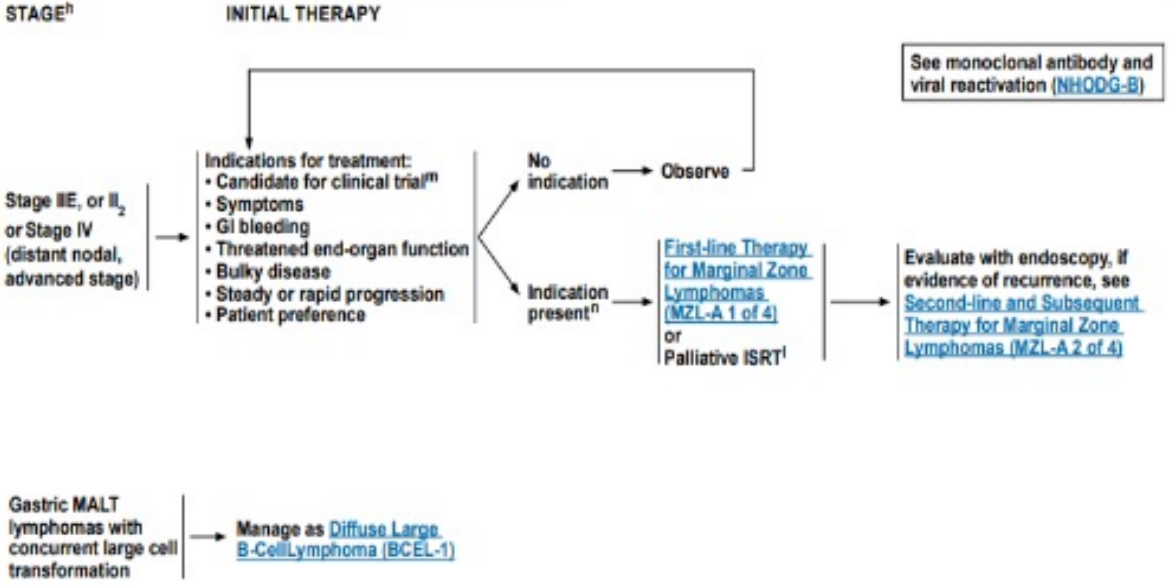
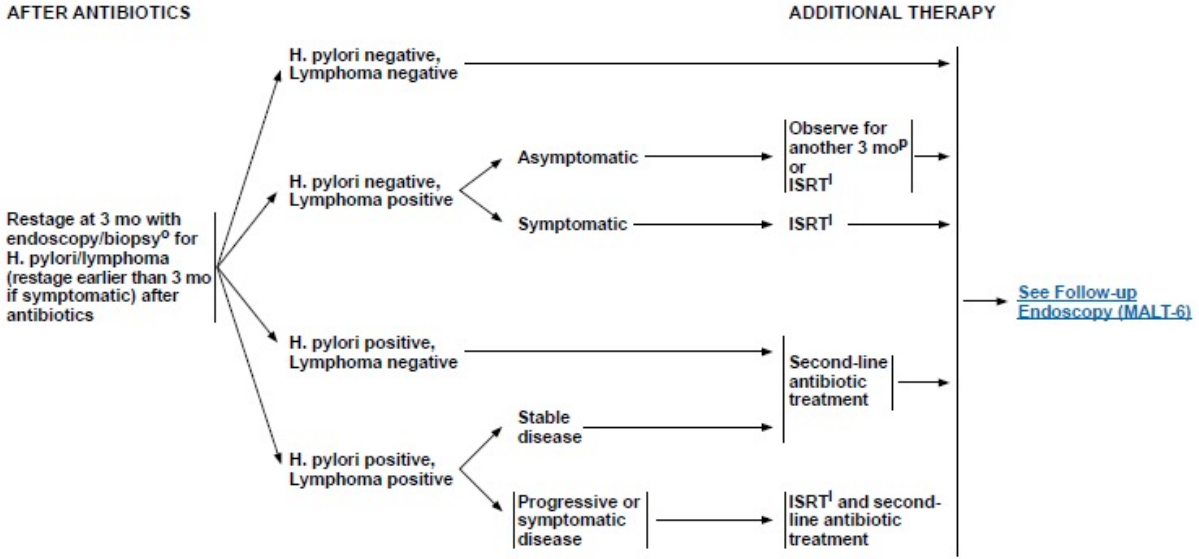


[h] See Lugano Staging System for Gastrointestinal Lymphomas (MALT-A).
[l] See Principles of Radiation Therapy (NHODG-D).
[m] Given incurability with conventional therapy, consider investigational therapy as first line of treatment.
[n] Surgical resection is generally limited to specific clinical situations (ie, life-threatening hemorrhage).

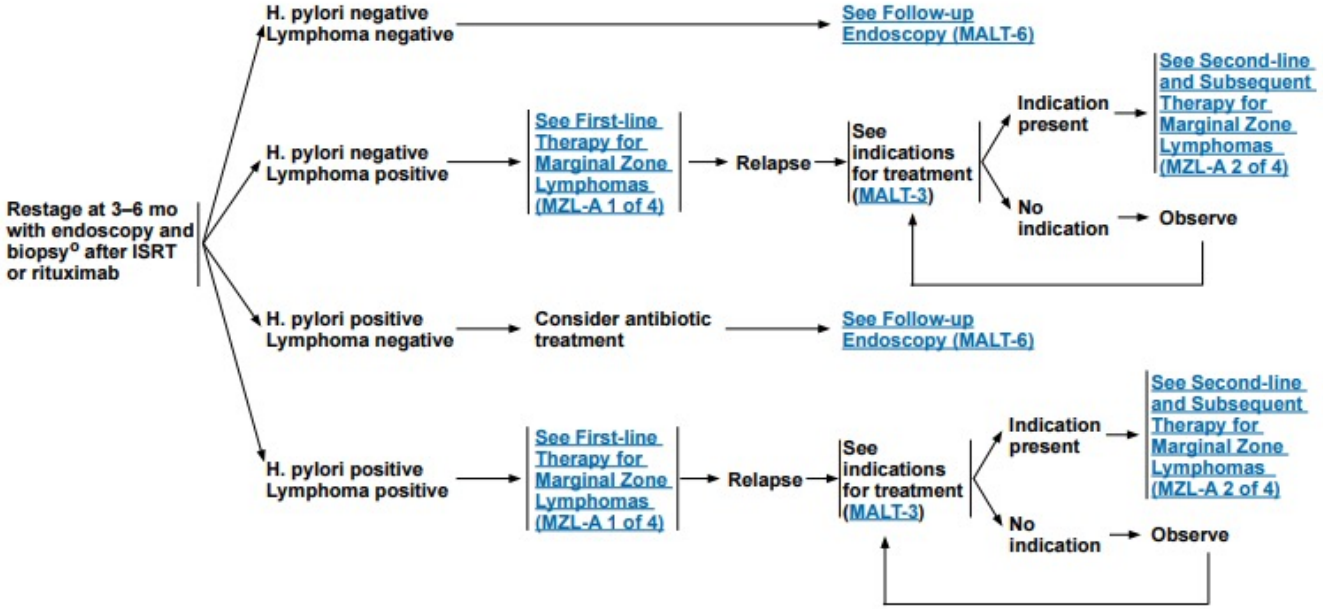


[I] See Principles of Radiation Therapy (NHODG-D).
[O] Reassessment to rule out H. pylori by institutional standards. Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated as DLCBL (BCEL-1).
[P] If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. Complete responses may be observed as early as 3 months after antibiotic treatment but can take longer to achieve (up to 18 months) (category 2B).

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.

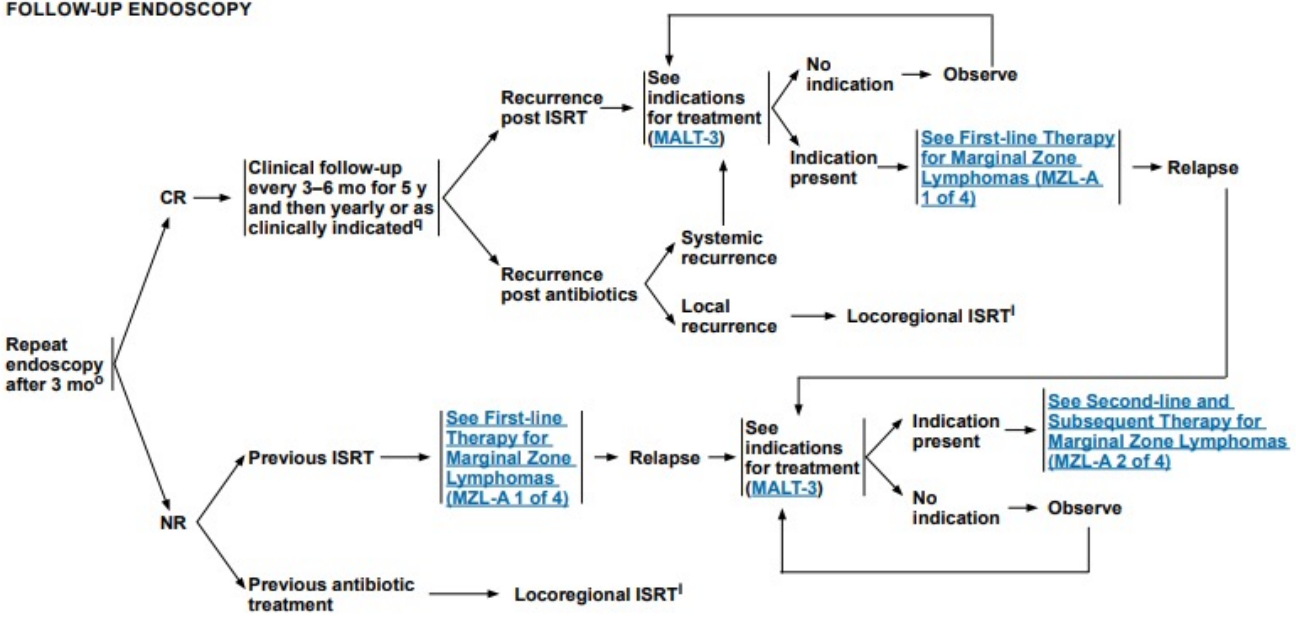
3- TO 6-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER ISRT OR RITUXIMAB **ADDITIONAL THERAPY**



[o] Reassessment to rule out H. pylori by institutional standards. Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated as DLCBL (BCEL-1).

FOLLOW-UP ENDOSCOPY



[l] See Principles of Radiation Therapy (NHODG-D).
[o] Reassessment to rule out H. pylori by institutional standards. Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated as DLCBL (BCEL-1).
[q] Optimal interval for follow-up endoscopy and imaging is not known. At NCCN Member Institutions, follow-up endoscopy and imaging using the modalities performed during workup is driven by symptoms.

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Table 4. GELA grading system proposed to define the histological response of gastric MZL after *Helicobacter pylori* eradication[72]

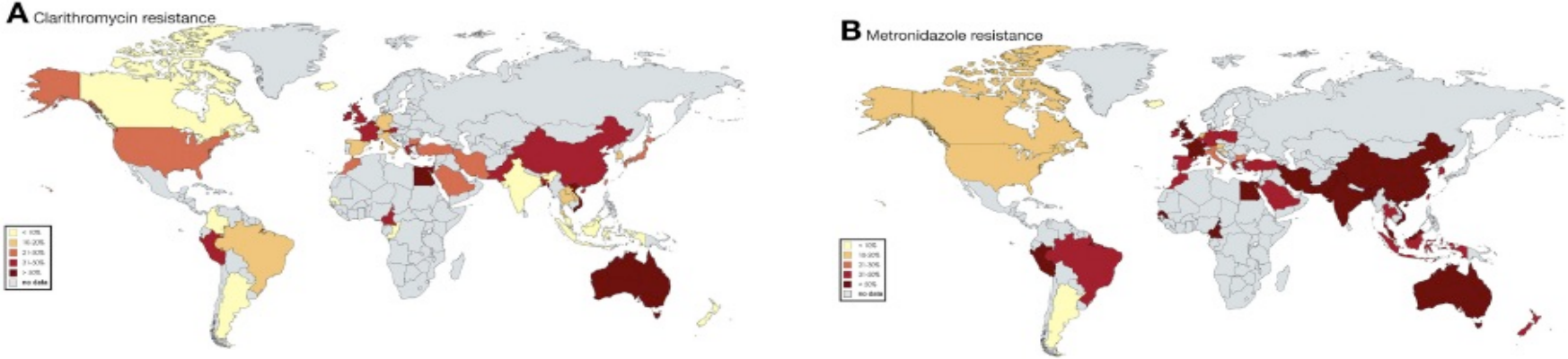
Response (score)	Description	Histological characteristics
CR	Complete histological remission	Normal or empty LP and/or fibrosis with absent or scattered plasma cells and small lymphoid cells in the LP, no LEL
pMRD	Probable minimal residual disease	Empty LP and/or fibrosis with aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM, no LEL
rRD	Responding residual disease	Focal empty LP and/or fibrosis with dense, diffuse or nodular lymphoid infiltrate, extending around glands in the LP, focal LEL or absent
NC	No change	Dense, diffuse or nodular lymphoid infiltrate, LEL usually present

GELA, Groupe d'Etude des Lymphomes de l'Adulte; LEL, lymphoepithelial lesion; LP, lamina propria; MM, muscularis mucosa; MZL, marginal zone B-cell lymphoma; SM, submucosa.

Ann Oncol. 2013;24 (suppl. 6):vi144-vi148.

Eradicazione HP e antibiotico resistenza

Le indicazioni di terapia secondo ACG e Maastricht V/Florence consensus Guidelines prevedono, ove la prevalenza di resistenza a macrolide risulti > 15%, l'indicazione, non alla Clarithromicin-based-therapy (Claritromicina+ amoxicillina o metronidazolo in caso di allergia + PPI), ma a Bismuth Quadruple Therapy (bismuto, metronidazolo tetraciclina + PPI).



Guevara B. Digestive Diseases and Sciences (2020) 65:1917–1931 https://doi.org/10.1007/s10620-020-06193-7
Savoldi A. Gastroenterology 2018;155:1372–1382; https://doi.org/10.1053/j.gastro.2018.07.007

IL RUOLO DEL MACROLIDE

- Ferreri HD-K PhII Ann Oncol 2015. Claritromicina 2 g/die d1-14 ogni 3 settimane per 4 cicli: 3 MALT gastrici. ORR 52%.
- Ferreri BJH 2018: Claritromicina 2 g/die d1-14 ogni 3 settimane per 4 cicli,

oppure 1000 mg/die per 6 mesi, oppure tre cicli 1000 mg/die d1-21 ogni 35 gg..): 9 MALT gastrici. ORR 47%.

- Lagler Hematol/Oncol 2018: Azitromicina 1500 mg una volta a settimana ogni

7 gg 4 dosi settimanali = 1 ciclo fino a 6 cicli. 2 MALT gastrici: nessuna risposta clinica.

The impact of t(11;18) on clinical outcomes

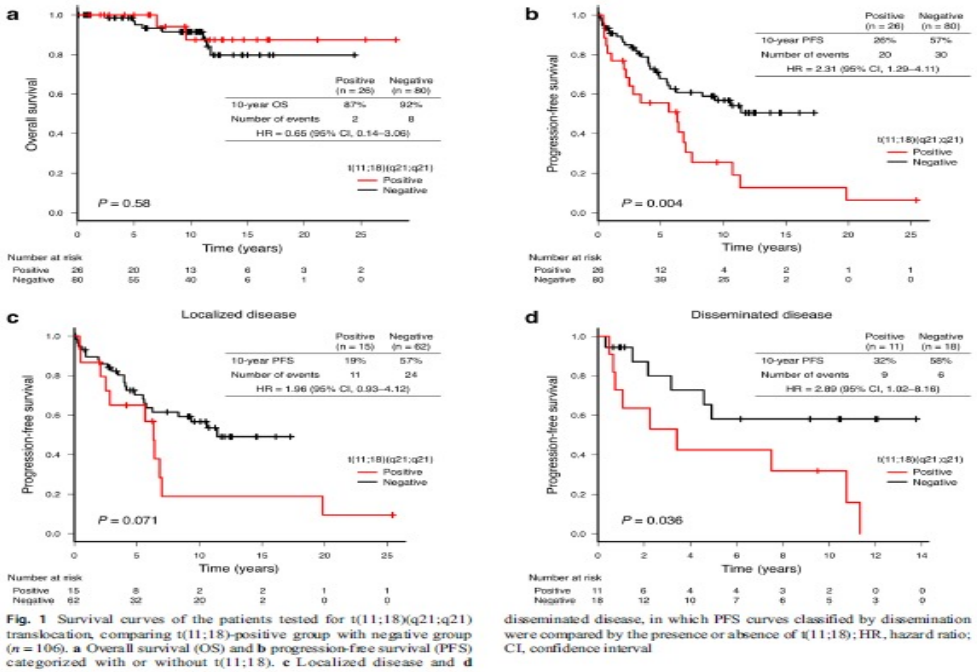


Fig. 1 Survival curves of the patients tested for t(11;18)(q21;q21) translocation, comparing t(11;18)-positive group with negative group ($n = 106$). **a** Overall survival (OS) and **b** progression-free survival (PFS) categorized with or without t(11;18). **c** Localized disease and **d** disseminated disease, in which PFS curves classified by dissemination were compared by the presence or absence of t(11;18); HR, hazard ratio; CI, confidence interval

- Single-institute retrospective analysis of 464 patients with newly diagnosed MALT NHL
- 26 patients with MALT lymphoma and t(11;18).
- PFS at 10 years; 26% vs. 57%; p=0.004) compared to those without t(11;18).
- Similar overall survival or incidence of HT.
- (11;18) positive MALT lymphoma showed disseminated disease and refractoriness to H. pylori eradication therapy.
- Usually unresponsive to alkylating agents as sole treatment but sensitive to purine analogues or rituximab.
- Patients with t(11;18) had more frequent MGUS, especially of IgM subtype.

Toyoda Annals of Hematology (2019) 98:1675–1687

LENALIDOMIDE

Ref	n	Study design	sedi	Tx	ORR (%)	Detailed response (%)	PFS	FU
Kiesewetter 2015	18	PhII	28% gastric 72% extragastric	Len 25 mg d1-21/28 (max. 6 cycles)	61%	CR 33 PR 28 SD 17 PD 11	n.a.	20
Kiesewetter 2017	46	PhII	30% gastric 70% extragastric	R 375 mg/mq d1, Len 20 mg d1-21/28 (max 8 cycles)	80%	CR 54 PR 26 SD 17 PD 2	91% 27 m	27
Kiesewetter 2019	50	ret	32% gastric 68% extragastric	Len (n = 32%) or R-Len (n = 68%)	72%	CR 48 PR 24 SD 22 PD 6	median 72 m	68
AUGMENT Leonard 2019	31	PhIII	14 EMZL 17 MZL	Len 20 mg d1-21 R 375 mg/m1 d1, 8, 15, 22 (cycle 1) day 1 cycles 2 to 5 every 28 days. vs. R placebo (max 12 cycles)	65	29	20,2	28,3

Kiesewetter B. Hematological Oncology. 2020;38:417–424. https://doi.org/10.1002/ hon.2754

Bendamustina

Ref	N	Study design	tx	ORR/CR (%)	PFS (%)	FU
Morigi 2020 MZL 1L	65	Ret	6 RB	89,2/58,5	71,8 at 6 yrs	44,6
Cencini 2019 MALT gastrici R/R: 10 HP+	13	Ret.	6 RB	100/100	100	30
Vannata 2021 in press MZL R/R	15	PhII	6 Ofa/B	92,9/57,1	77 (2 yrs)	24

MOLECULAR TARGETED TX

Ref	n	Study design	sedi	tx	ORR (%)	Detailed response (%)	PFS	FU
Zucca 2017 IELSG19 R ± Clb	138	Phase III	44% gastric, 56% extragastric	R 375 mg/m2 weekly × 4, followed by every 4 weeks × 4	78	CR 56 PR,23 SD 12 PD 9	5-year EFS 50%	68
Conconi 2003 R single agent	35	Phase II	43% gastric, 57% extragastric	R 375 mg/m2 weekly × 4	73	CR 44 PR 29 SD 18 PD 9	n.a.	15
Martinelli 2005 R single agent	26 R/R	Phase II	100% gastric	R 375 mg/m2 weekly × 4	77	CR 46 PR 31 SD 23	n.a.	33
Lossos 2007 R single agent	12 naïve	Phase II	25% gastric, 75% extragastric	R 375 mg/m2 weekly × 4	67	CR 17 PR 50 SD 25 PD 8	n.a.	20
Kiesewetter 2018 Ofatumumab	16	Phase II	31% gastric, 69% extragastric	Ofa 1000 mg weekly × 4 followed by every 8 weeks × 4	81	CR 50 PR 31 SD 19	n.a.	25 (13-37)
Sehn GAUSS 2015 Obinutuzumab	26	PhII	MZL (11)	4 once-per-week iv O 1.000 mg or R 375 mg/mq. maintenance therapy	50 vs. 17	CR 29 vs. 0 PR 29 vs. 3	n.a.	n.a.

Kiesewetter B. Hematological Oncology. 2020;38:417–424. https://doi.org/10.1002/ hon.2754

MOLECULAR TARGETED TX

Ref	N	Study design	sedi	tx	ORR	Detailed response	PFS	FU
Hofmann 2011 90Y-ibritumomab Tiuxetan	6	Retrosp.	50% gastric, 50% extragastric	0.4 mCi/kg on d7	83 %	CR 67%, PR 17% SD 17%	n.a.	9-29
Vanazzi 2014 90Y-ibritumomab Tiuxetan	30	Phase II	43% gastric, 57% extragastric	0.4 mCi/kg on d7	90 %	CR 77%, PR 13% SD 7%, PD 3%	median not reached	64
Conconi 2011 Bortezomib	32	Phase II	44% gastric, 56% extragastric	1.3 mg/mq d1/4/8/11 every 3 weeks (max. 6 cycles)	48 %	CR 31% PR 17% SD 31%, PD 21%(	median 25 m	24
Troch 2015 Bortezomib	16	Phase II	25% gastric, 75% extragastric	1.5 mg/m2 d1/4/8/11 every 3 weeks (max. 8 cycles)	80 %	CR 44% (7/16), PR 37% (6/16), SD 19% (3/16)	median 22 m	23

Kiesewetter B. Hematological Oncology. 2020;38:417–424. https://doi.org/10.1002/ hon.2754

PATOGENESI

•Gli elementi neoplastici nei MZL esprimono gene IGHV mutati per selezione antigenica in seguito ad attivazione di BCR, con anomalia di espressione dei geni IGHV ed espressione di recettori BCR di tipo stereotipato. Spesso è presente attività tipo Fattore Reumatoide ma non reattività verso altri autoAg (insulina, tireoglobulina ecc). Le Ig non legano direttamente antigeni microbici e l'agente infettivo agisce primariamente con segnale costimolatorio senza attivare direttamente il BCR.

•E' caratteristica l'attivazione delle kinasi SRC e le anomalie geniche più frequenti potenzialmente amplificano

1) l'attivazione canonica di NFkB Ig: mutazioni inattivanti di TNFAIP3/A20 (10-30%) o di KLF2 (17-40%), CARD11

2) l'attivazione non canonica di NFkB: MAP3K14.

Della Bella Int J Mol Sci 2021,22,9459
Troppan Gast Res Pract 2015. http://dx.doi.org/10.1155/2015/102656
Younes Apll Immunoistochem Mol Morphol 2021; 29(1) 56.

PATOGENESI

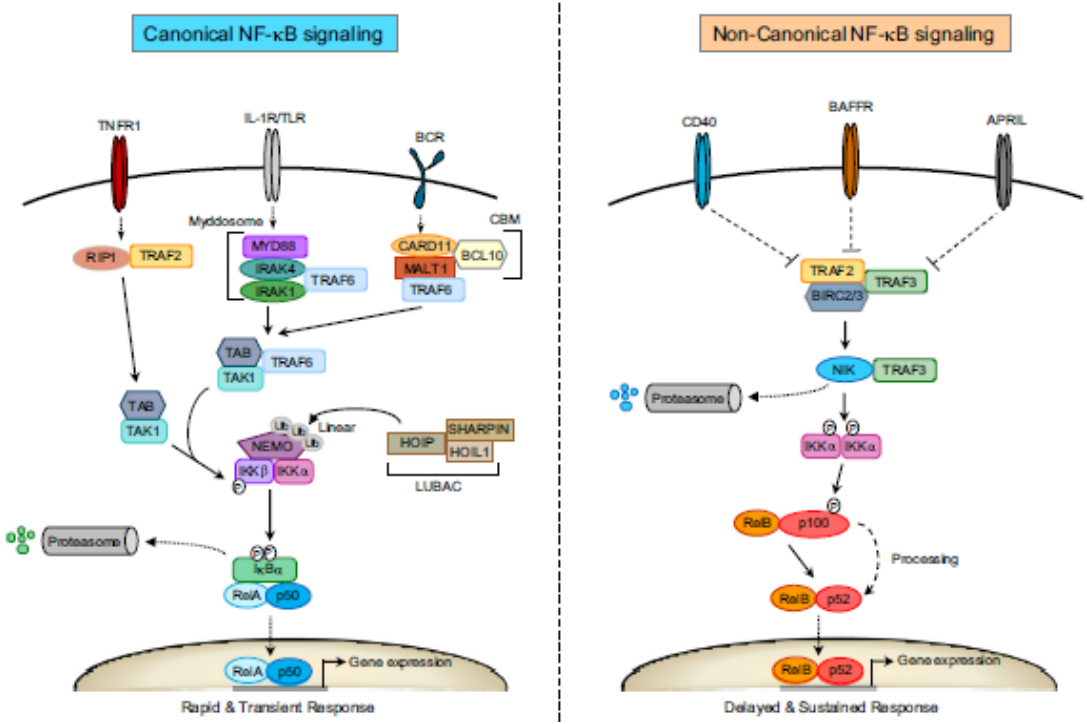
•HP induce un'intensa risposta infiammatoria, la proteina CagA attiva il rilascio di citochine infiammatorie, stimola i macrofagi a produrre il proliferation-inducing ligand (APRIL) che concorre, assieme a BAFF, all'attivazione non canonica di NFKB sui B linfociti ed alla linfomagenesi.

•E' presente un infiltrato T che agisce ritardando la risposta infiammatoria, contribuendo alla persistenza del patogeno e cronicizzando la stimolazione antigenica. La proteina CagY di HP è uno dei target immunodominanti dei T linfociti che è presente solo nei MALT ma non nella gastrite cronica non complicata. Lo spettro di citochine secrete dai Th1 e Th17 (IL4, IL17, γIFN) concorre a cronicizzare il quadro.

•La proteina CagA viene traslocata nei B linfociti di MALT HP correlati e DLBCL. CagA comporta un'attivazione costitutiva di 3K/AKT tramite upregulation della ciclina A2 e downregulation di PTEN (tumor suppressor gene).

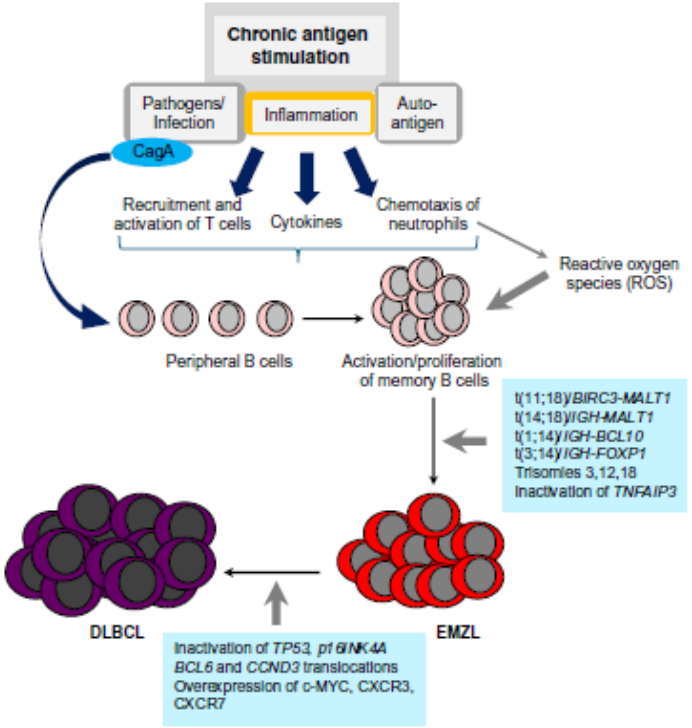
Della Bella Int J Mol Sci 2021,22,9459
Troppan Gast Res Pract 2015. http://dx.doi.org/10.1155/2015/102656
Younes Apll Immunoistochem Mol Morphol 2021; 29(1) 56.

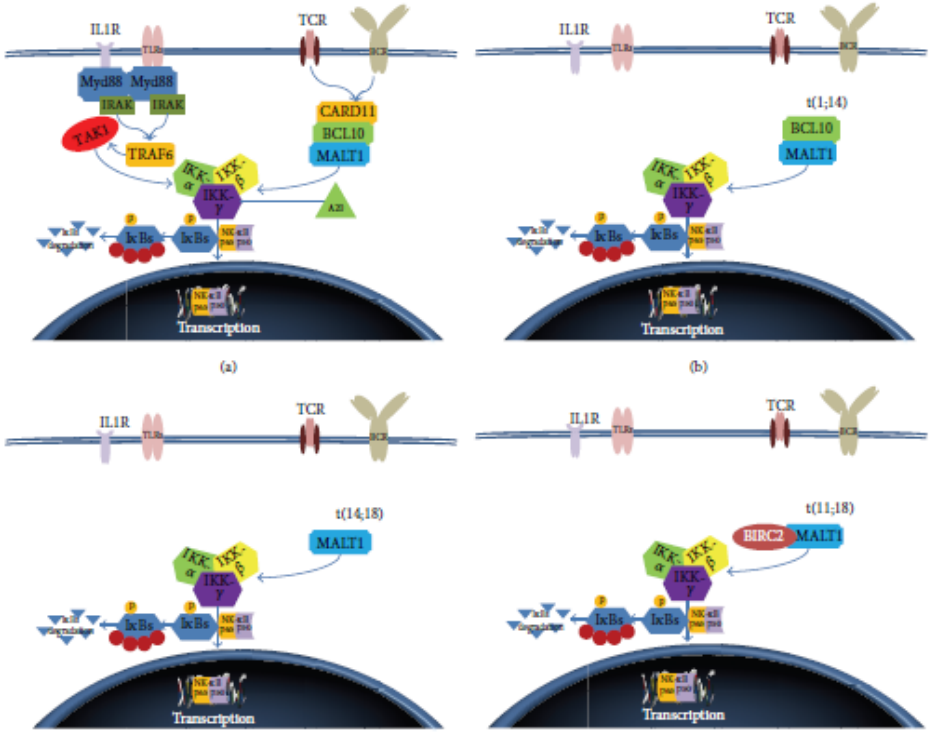
PATOGENESI



Schreuder MI J Hematopathol (2017) 10:91–107 DOI 10.1007/s12308-017-0302-2

PATOGENESI





Schreuder MI. J Hematopathol (2017) 10:91–107 DOI 10.1007/s12308-017-0302-2
Troppan Gast Res Pract 2015. http://dx.doi.org/10.1155/2015/102656

MALT1

•La t(11;18)(q21;q21) ha una frequenza variabile nell'ambito dei linfomi MALT e comporta la generazione di un gene di fusione BIRC3 (API2)–MALT1 (mucosa-associated lymphoid tissue lymphoma translocation). La proteina API2/MALT1 attiva sia la via canonica che non canonica di di NF-κB.

•Descritte mutazioni di TRAF3 e BIRC3 che comportano a valle l'attivazione della via non canonica di NF-κB. Si associa generalmente a malattia multifocale e/o disseminata. E' prevalente nella localizzazione polmonare (oltre 50%) e gastrica (~30%) dove è caratteristica la refrattarietà all'eradicazione di HP.

•La t(14;18)(q32; q21) comporta la fusione di MALT1 la regione enhancer di IGH comportandone una sovraespressione: è più frequente nelle localizzazioni NON gastrointestinali (polmone, annessi oculari).

•La t(3;14)(p14.1;q32) è più frequente nel Linfoma MALT della tiroide, annessi oculari e cute.

•La t(1;14)(p22;q32) è presente nel 5% del Linfoma MALT a localizzazione intestinale, la fusione di BCL10 con il locus IGH deregolando l'espressione di BCL10.

Onaindia Modern Pathology (2017) 30, 1338–1366
Toyoda Annals of Hematology (2019) 98:1675–1687

New drugs

- ***Ibrutinib*** Blood Noy 2017: 63 patients, mFU 19.4 m, ORR/CR= 48/3 mDOR not reached, mPFS 14,2 m
- ***Idelalisib*** (PI3Kδ) Leuk Lymph Wagner-Johnston 2020: mFU 6 years 15 patients, ORR/CR=7/1, mDOR 18,4 m, PFS 6,6 m
- ***Duvelisib*** (PI3Kγ-δ) DYNAMO JCO Flinn 2019: 18 patients, ORR 38,9%, mDOR 10 m
- ***Parsaclisib*** (PI3Kδ) Blood Forero-Torres 2019: 9 patients, ORR/CR 7/3
- ***Copanlisib*** (PI3Kα-δ) Am J Hem Dreyling 2020: 23 patients ORR/CR 18/3
- ***Umbralisib*** (PI3Kδ) JCO Fowler 2021: 69 patients ORR/CR 34/11, FU 27,7 m, mDOR e mPFS not reached.
- ***Entospletinib*** (Syk inhibitor) BJH Andorsky 2019: 17 patients, 0 CR, 2 PR, 12 SD, PFS a 24 m 46,2%.

New drugs

•***MALT1 inhibitors.*** There is preclinical evidence of anti-tumor activity in MZL models as a single agent or in combination (copanlisib).

• ***second mitochondria-derived activator of caspase (SMAC) mimetics.*** The BIRC3 gene, fused to MALT1 in the t(11;18) of EMZL, and recurrently mutated in the other MZLs, codes for the cellular inhibitor of apoptosis 2 (cIAP2) protein, an E3 ubiquitin ligase important for the activation of the CBM complex. LCL-161 has shown anti-tumor activity in MZL primary cells.

•***MYD88-IRAK4 Axis.*** Attempts to target MYD88 has largely been unsuccessful as it is difficult to inhibit. Only preclinical dataST2825 suppress the growth of lymphoma cell lines, but has off target effects. Clinical trials ongoing: IRAK4 kinase inhibitors, IRAK4 degraders.

Jennifer K. Lue Ann Lymphoma 2020;4:7|http://dx.doi.org/10.21037/aol-20-20

New drugs

•***NOTCH signaling:*** no clinical data is available.
•***Methylation and chromatin remodeling.*** 25% of SMZL cases are associated with a very high degree of promoter hypermethylation, leading to silencing of tumor suppressor genes and over-expression of potential therapeutic targets (NF-κB, PI3K and BCR signaling; PRC2-complex, that is EZH2 and others). This phenotype is associated with inferior outcomes and a higher risk of histologic transformation. High prevalence of somatic mutations in the TET2 gene in primary thyroid EMZLs is associated with increased DNA promoter methylation in genes targeted by the PRC2 complex members. Interestingly, the transcriptome of TET2 DLBCL mutants have important overlaps with the transcriptome of CREBBP DLBCL mutants, and CREBBP mutants are sensitive to HDAC3 inhibitors. In fact, silencing of TET2 sensitizes DLBCL cells to HDAC3 inhibitors. Therefore, considering that CREBBP mutations are also common in MZL, there is a clear rationale to explore HDAC3 and other epigenetic drugs in MZL.

Jennifer K. Lue Ann Lymphoma 2020;4:7|http://dx.doi.org/10.21037/aol-20-20

Primary gastric DLBCL (PGDLBCL)

- Costituisce circa il 40-70% dei linfomi gastrici
- Forma secondaria o con concomitante componente MALT
- Forma «*de novo*»

✓ Dati contrastanti di distribuzione per COO
✓ Affidabilità degli algoritmi inferiore rispetto alle forme nodali
✓ Non disponibili dati numericamente significativi se studiati in GE

- La forme non GCB spesso seguono o concomitano a MALT.

✓ Talvolta variante DE (15%)
✓ Le forme GCB non sono correlabili a MALT ma possono associarsi a HP+: non è chiaro il significato né le implicazioni operative conseguenti.
✓ Rare le forme DH/TH anche se MYC può risultare riarrangiato
✓ Rarissima la presenza di mutazione MYD88.

- Da trattare secondo protocolli RCHOP like, **nessuna indicazione alla chirurgia se non in caso di emergenza.**

Kisha LL;2008;49(9):1717-23, Kawajiri, Blood Cancer J 2016;6, e477, Nagakita Path Int; 2016:66:44-52, Hallas Leuk Res 2019; 76:107-11

Leukemia Research 76 (2019) 107–111

Contents lists available at ScienceDirect

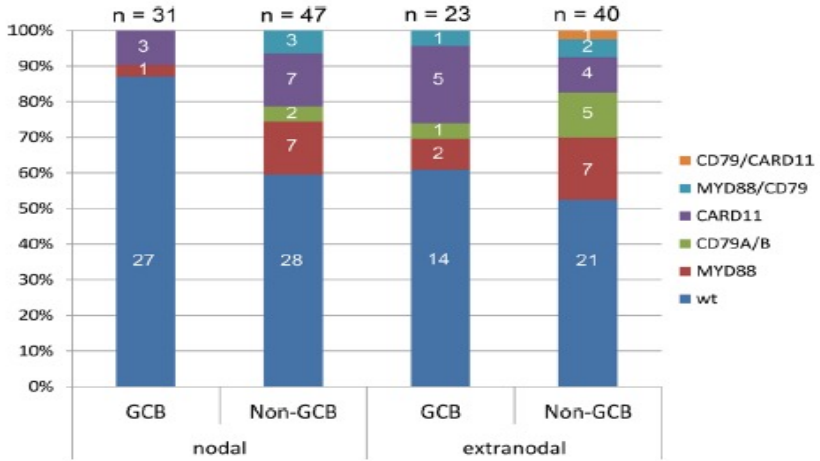
Leukemia Research

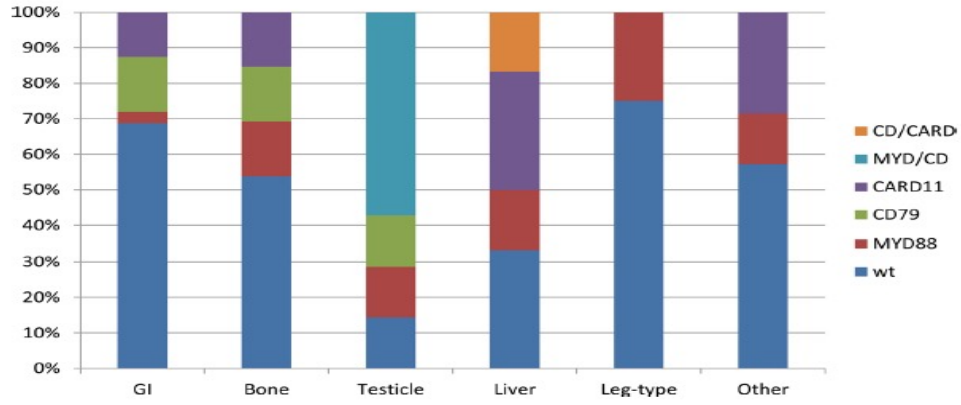
journal homepage: www.elsevier.com/locate/leukres

Research paper

Immunohistochemical distinction of ABC and GCB in extranodal DLBCL is not reflected in mutation patterns

Cora Hallas*, Michael Preukschas, Markus Tiemann





La chirurgia ha ancora un ruolo?

Surgical re **treat**

diffuse lar

Conclusion e (>90%)

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The Impact **ymphoma:**

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significant

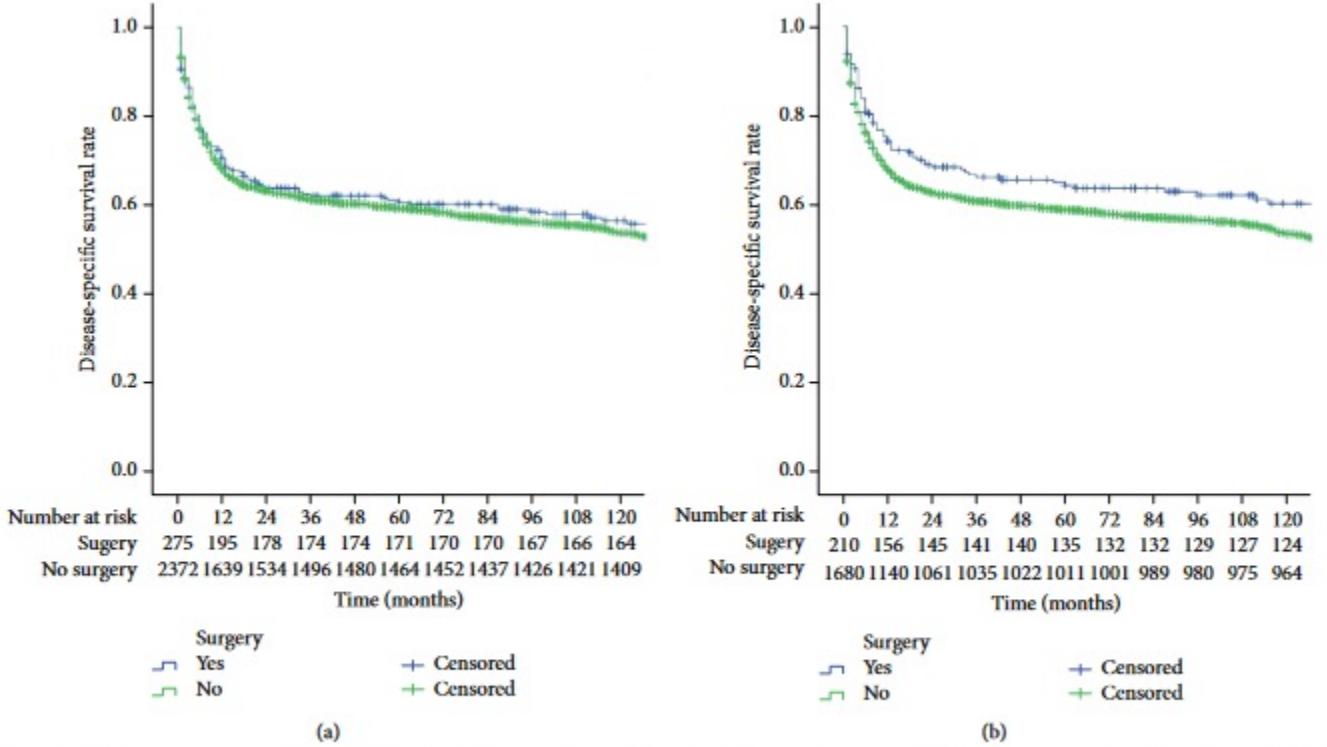


FIGURE 1: (a) Comparison of 5-year CSS between the surgical and conservative treatment groups before propensity matching ($P = 0.952$); (b) comparison of 5-year CSS between the surgical and conservative treatment groups after propensity matching ($P = 0.0462$).

PGDLBCL and HP eradication

- HP induce una cross reazione immunologica con trasferimento di CagA sulle cellule linfomatose.
- In genome wide expression è stato confermato che HP determina incremento dei livelli di miR200 un inibitore di ZEB1 (promoter di progressione via down regulation di BCL6).
- Le forme dipendenti da HP si associano a positività per CD86+, CD4-CD56- Treg, p16INKaA;
- markers di non riposta: t11;18 e t1;14, espressione nucleare aberrante di BCL10, CXCR3, MAD2, miR203, miR142-5p e miR155

PGDLBCL and HP eradication

- Morgner 2001, Chen 2001: in stadio I-IIE1, «la trasformazione non è necessariamente associata a perdita della dipendenza da HP»

- Chen 2005. 24 tDLBCL early stage HP+: CR 80%, a 5 yrs 3 relapses.

- Kuo 2012. 50 tDLBCL/de novo: CR 56.3%/68.8%, PFS a 7.7 yrs 100%

- Ferreri 2012. 16 tDLBCL/de novo: CR 8 (+3 dopo R), mPFS 83 m, OS a 5 yrs 94%

Morgner JCO 2001; 19(7):2041, Chen JCO 2001; 22(15):4245, Chen JNCI 2005;97(18): 1345; Kuo Blood 2012;119(21):4838, Ferreri Blood 2012; 120(18):3858

Il ruolo dei virus

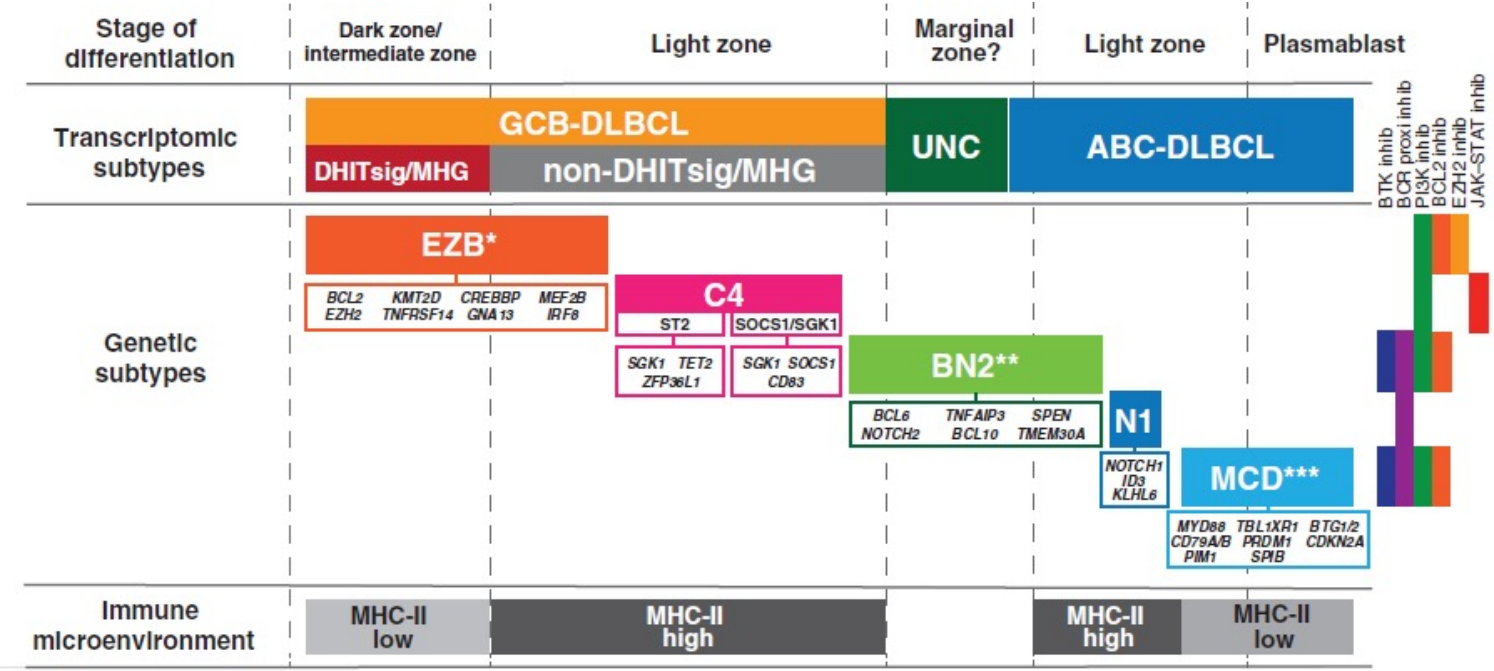
- HCV: il PGDLBCL è la III sede in ordine di frequenza dopo Milza e Fegato, spesso CD5+, pochi dati riguardo COO e sottogruppi citogenetici. Esprimono PD-L1
- EBV: pochi dati riguardo COO e sottogruppi citogenetici. Esprimono PD-L1, ambito non sicuramente assimilabile al DLBCL nodale EBV correlato, prognosi peggiore anche in multivariata.

Defrancesco I Clin and Exp Med 2020, 20:321.https://doi.org/10.1007/s10238-020-00615-6
Ishikawa E. Cancer Med. 2018;7:3510. https://doi.org/10.1002/ cam4.1595

Toward a New Molecular Taxonomy of Diffuse Large B-cell Lymphoma

Cancer Discov 2020;10:1267–81
doi: 10.1158/2159-8290.CD-20-0174

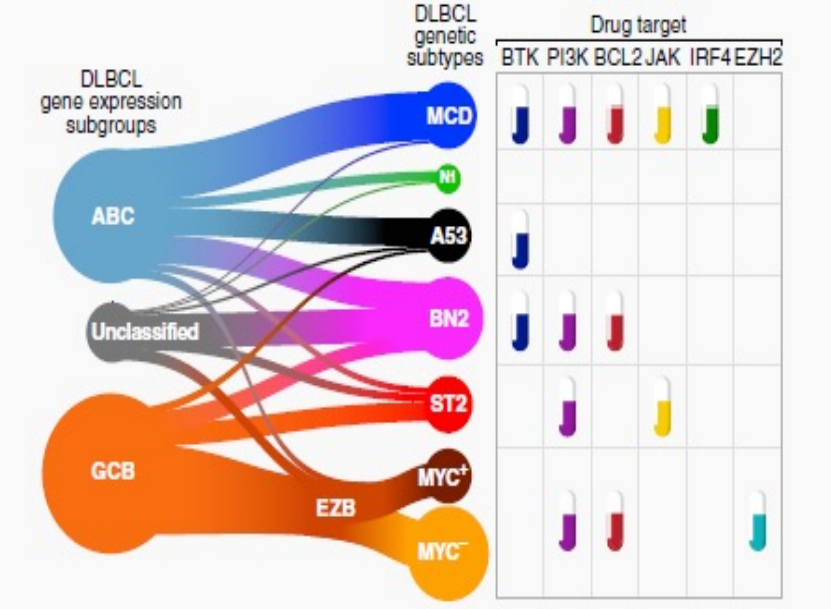
Daisuke Ennishi[1], Eric D. Hsi[2], Christian Steidl[1], and David W. Scott[1]



A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications

George W. Wright,[1] Da Wei Huang,[2] James D. Phelan,[2] Zana A. Coulibaly,[2] Sandrine Roulland,[2] Ryan M. Young,[2]

Cancer Cell 37, 551–568, April 13, 2020



Dan L. Longo, M.D., Editor

Diffuse Large B-Cell Lymphoma

N Engl J Med 2021;384:842-58.
DOI: 10.1056/NEJMra2027612

Laurie H. Sehn, M.D., M.P.H., and Gilles Salles, M.D., Ph.D.

Biologic Features of DLBCL

Cell of Origin Classification	**Germinal Center B-Cell–Like** Germinal center regulatory program reminiscent of light zone germinal center centrocytes Immunoglobulin somatic hypermutation Genetic lesions: t(14;18), *BCL2, PTEN*, miR-17-92, *GNA13, EZH2, KMT2D, CREBBP, EP300* (chromatin modifiers)…		**Unclassifiable**	**Activated B-Cell–Like** Early plasmacytic regulatory program reminiscent of plasmablasts Enhanced BCR signaling Genetic lesions: *CARD11, CD79A/B, TNFAIP3* (constitutive NF-κB activation), *PRDM1, BCL2* (gain), *CDKN2A, MYD88*…		
Potential correspondences						
LymphGen Classification	**EZB**	**ST2**	**BN2**	**A53**	**N1**	**MCD**
Potential correspondences	HGBCL-DH/TH					
DLBCL Clusters	**C3**	**C4**	**C1**	**C2**		**C5**
Genetic Hallmarks	*BCL2, EZH2, TNFSFR14, CREBBP, KMT2D* (and *MYC* in DH/TH cases)	*TET2, SGK1, DUSP2, ZFP36L1, ACTG1, ACTB, ITPKB, NFKBIA*	*BCL6, NOTCH2, TNFAIP3, DTX1*	*TP53*, aneuploidy	*NOTCH1, IRF2BP2*	*MYD88, CD79B, PIM1, HLA-B, BTG1, CDKN2A, ETV6, SPIB, OSBPL10*
Biologic Pathways Deregulated	Epigenetic; PI3K signaling; cell migration; immune cell interactions	JAK/STAT signaling	NOTCH2 signaling; immune evasion	Genetic instability; immune evasion	NF-κB activation	B-cell receptor and NF-κB signaling
Patient Prognosis	Favorable; poor if EZB-MYC+ or HGBCL-DH/TH	Favorable	Intermediate	Poor or intermediate	Unknown	Poor or intermediate
Genetic Similarities with Other Lymphoma Entities	Follicular lymphoma	Marginal zone lymphoma	Nodular lymphocyte predominant HL T-cell or histiocyte-rich B-cell lymphoma		Chronic lymphocytic leukemia	Primary extranodal (CNS, testis, skin) Lymphoplasmacytic lymphoma

CONCLUSIONI

- Il Linfoma gastrico è un modello peculiare di linfomagenesi che integra elementi già noti per le forme nodali.
- Sia nell'istotipo MALT che PGDLBCL sono auspicabili dati di NGS sia per finalità di stratificazione prognostica che di strategia terapeutica.
- La «secondarietà» a infezioni virali/batteriche identifica istotipi differenti rispetto a forme secondarie a malattie autoimmuni?
- La «curabilità» con antivirali/antibiotici di forme «parainfettive» modifica la nostra concezione di DLBCL come malattia «aggressiva»?
- I presupposti biologici sottendono anomalie funzionali e non strutturali?
- Il concetto di neoplasia in queste situazioni acquisisce nuovi significati?