Impact of the microenvironment on the pathogenesis of mucosa-associated lymphoid tissue lymphomas

Barbara Uhl, Katharina T Prochazka, Karoline Fechter, Katrin Pansy, Hildegard T Greinix, Peter Neumeister, Alexander JA Deutsch

ORCID number: Barbara Uhl 0000-0002-8460-8771; Katharina T Prochazka 0000-0002-7201-5987; Karoline Fechter 0000-0002-6894-2438; Katrin Pansy 0000-0001-6972-4937; Hildegard T Greinix 0000-0002-2780-3306; Peter Neumeister 0000-0002-2761-5334; Alexander JA Deutsch 0000-0003-0914-2809.

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Barbara Uhl, Katharina T Prochazka, Karoline Fechter, Katrin Pansy, Hildegard T Greinix, Peter Neumeister, Alexander JA Deutsch, Division of Hematology, Medical University of Graz, Graz 8036, Austria

Corresponding author: Alexander JA Deutsch, PhD, Research Assistant Professor, Division of Hematology, Medical University of Graz, Auenbruggerplatz 38, Graz 8036, Austria. alexander.deutsch@medunigraz.at

Abstract
Approximately 8% of all non-Hodgkin lymphomas are extranodal marginal zone B cell lymphomas of mucosa-associated lymphoid tissue (MALT), also known as MALT lymphomas. These arise at a wide range of different extranodal sites, with most cases affecting the stomach, the lung, the ocular adnexa and the thyroid. The small intestine is involved in a lower percentage of cases. Lymphoma growth in the early stages is associated with long-lasting chronic inflammation provoked by bacterial infections (e.g., Helicobacter pylori or Chlamydia psittaci infections) or autoimmune conditions (e.g., Sjögren’s syndrome or Hashimoto thyroiditis). While these inflammatory processes trigger lymphoma cell proliferation and/or survival, they also shape the microenvironment. Thus, activated immune cells are actively recruited to the lymphoma, resulting in either direct lymphoma cell stimulation via surface receptor interactions and/or indirect lymphoma cell stimulation via secretion of soluble factors like cytokines. In addition, chronic inflammatory conditions cause the acquisition of genetic alterations resulting in autonomous lymphoma cell growth. Recently, novel agents targeting the microenvironment have been developed and clinically tested in MALT lymphomas as well as other lymphoid malignancies. In this review, we aim to describe the composition of the microenvironment of MALT lymphoma, the interaction of activated immune cells with lymphoma cells and novel therapeutic approaches in MALT lymphomas using immunomodulatory and/or microenvironment-targeting agents.

Key Words: Mucosa-associated lymphoid tissue lymphoma; Tumor microenvironment; Microenvironment; Helicobacter pylori; Activated immune cells

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ACQUIRED GENETIC ABNORMALITIES

In MALT lymphomas, recurrent chromosomal aberrations, such as trisomies, amplifications and deletions, chromosomal translocations, somatic point mutations, and promoter hypermethylation, have been described. The most common cytogenetic alterations are trisomies 3, 12, and/or 18, which are present in 20%-35% of cases, and they are often associated with one of the four main translocations [10-13]. Trisomies 3 and 18 and losses at 6q23 occur in MALT lymphomas primarily involving the stomach, orbital adnexa, thyroid, salivary glands, and lung [13]. Several promising candidate genes are located on chromosome 3, such as the proto-oncogene BCL6 and the transcription factor FOXP1 [14]. Additionally, the chemokine receptor CCR4, genomically located on chromosome 3 (3p24), is highly expressed in trisomy 3-positive MALT lymphomas [15]. Furthermore, genome-wide DNA profiling revealed deletions in 1p and 6q, as well as gains on chromosomes 3 and 18 and the short arm of chromosome 6 [10].

The most common chromosomal translocations associated with the pathogenesis of MALT lymphomas are t(1;14)(p22;q32) (involving the IGHV and BCL10 genes), t(11;18)(q21;q21) (involving BIRC3/MALT1), t(14;18)(q32;q21) (involving IGH/BCL2) and t(3;14)(p14.1;q32) (involving IGHV-FOXPI) [8,10,16]. The frequency of genetic aberrations is dependent on the primary site of disease [10,17]. At least three translo-
cations, t(11;18), t(14;18) and t(1;14), involve the BCL10 and MALT1 genes and lead to activation of the NF-xB pathway in lymphocytes, thus indicating that these aberrations are oncogenic events[18,19].

We observed somatic missense mutations in PIM1 and cMYC in 46% of gastric and 30% of extragastric MALT lymphomas[20]. In addition, missense and frameshift mutations in p53 were described in 20.8% of MALT lymphomas (mainly of gastric origin)[10]. Moreover, whole exome sequencing of extragastric MALT lymphomas identified recurrent novel somatic mutations in PIK3CD, TET2, and TNFRSF14 and in two G protein-coupled receptors (GPR34 and CCR6), which have not been reported to be somatically mutated in human tumors thus far. In addition, recurrent mutations were found in two genes (TBLIXR1 and NOTCH1), for which somatic mutations were already reported in ocular adnexal MALT lymphomas. The mutation frequencies of these genes were remarkably variable among MALT lymphomas affecting different sites[21]. Sequencing of NF-xB signaling pathway-related genes — A20, Card11, CD79B, and Myd88, known to be frequently mutated in aggressive lymphomas[10,22] — demonstrated that 6% of MALT lymphoma cases exhibited missense or frameshift mutations in the Myd88 locus. A total of 28.6% of the ocular adnexal MALT lymphomas had mutations in the A20 locus[10,23]. Card11 and CD79B were not affected in ocular adnexal MALT lymphomas[10].

Finally, promoter hypermethylation of the tumor suppressor genes p16 and p57 has been reported in low-grade MALT lymphoma cases[24]. CpG hypermethylation of A20 has been detected in 26% of investigated MALT lymphomas, including ocular adnexal cases and lymphomas located in the salivary and thyroid glands[10].

**Aberrant somatic hypermutation is associated with genetic lesions in malt lymphomas**

Aberrant somatic hypermutation (ASHM) has been identified to be crucial for the development of lymphoid neoplasms. ASHM occurs commonly in diffuse large B cell lymphomas but is rare in indolent lymphomas[10,25,26]. The pathogenesis of most lymphomas is associated with distinct genetic lesions arising from mistakes during class switch recombination (CSR) and somatic hypermutation (SHM)[10,27]. Activation-induced cytidine deaminase (AID) is an enzyme required for CSR and SHM. Mis-targeting of AID to known proto-oncogenes combined with a breakdown of protective high-fidelity repair mechanisms has been shown to be a principal contributor to the pathogenesis of B-NHL[10]. Our research group has demonstrated that the expression levels of AID are associated with the mutational load caused by ASHM in MALT lymphomas[23]. However, the mechanism causing the upregulation of AID has not been identified thus far. It has been demonstrated that *H. pylori* infection upregulates AID expression *via* NF-xB in gastric cells *in vitro* and *in vivo*, resulting in the accumulation of p53 mutations[28]. Hence, it might be speculated that *H. pylori* infection is also participates in the upregulation of AID in B cells, leading to the accumulation of genetic alterations.

**CHRONIC INFLAMMATION SHAPES THE MICROENVIRONMENT AND THEREBY PLAYS A KEY ROLE IN MALT LYMPHOMAGENESIS**

It is well known that MALT lymphomas are commonly associated with long-lasting chronic inflammation caused by microbial pathogens and/or autoimmune diseases that trigger sustained lymphoid proliferation. The low activation threshold of MZ B cells may predispose them to neoplastic transformation[29].

Gastric MALT lymphomas show a strong association with chronic *H. pylori* infection[30]. Other infectious associations have been reported for *Borrelia burgdorferi* (skin)[31], *Campylobacter jejuni* (intestine)[32], *Achromobacter xylosidans* (lung)[33], *Chlamydia psittaci* (ocular, nongastrointestinal MALT lymphomas)[34-36] and hepatitis C virus (splenic marginal zone lymphoma)[37]. The strength of these associations shows vast geographical discrepancies[38-40]. In addition, an association of MALT lymphomas with chronic inflammation induced by autoimmune disease is found in primary Sjögren’s syndrome (pSS)[41-43] and Hashimoto thyroiditis[44].

Long-lasting chronic inflammation, e.g., induced by *H. pylori* infection or pSS, is the trigger for a multistage process in the evolution of MALT lymphomas due direct effects on B cell proliferation and/or survival and/or indirect effects on the activation of innate and adaptive immune cells[9,43,45] as shown in Figure 1.
Helicobacter pylori (H. pylori), other bacteria and/or autoantigens (auto-AGs) support an immune regulatory microenvironment promoting mucosa-associated lymphoid tissue (MALT) lymphomagenesis in different organs. First, regulatory T cells are activated and suppress the immune response by maintaining *H. pylori* colonization and influencing cytotoxic T cells, which possess malfunctions and therefore cannot inhibit the expansion of MALT lymphoma cells. Second, eosinophils and macrophages express a proliferation-inducing ligand (APRIL) and B cell-activating factor, supporting lymphomagenesis. The production of APRIL is induced by *H. pylori* antigens and *H. pylori*-specific T cells. Third, T helper cells and their cytokines (IL-4, IL-5, and IL-10) promote the growth and differentiation of lymphoma cells and are stimulated by *H. pylori* and/or auto-AGs. MALT: Mucosa-associated lymphoid tissue; *H. pylori*: Helicobacter pylori; Tregs: Regulatory T cells; CTL: Cytotoxic T cell; Auto-AG: Autoantigen; Th: T helper.

*H. pylori* strains expressing cytotoxin-associated gene A (CagA) are associated with the lymphomagenesis of gastric MALT lymphoma[46,47]. CagA is involved in the promotion of proliferation and the inhibition of apoptosis of B lymphocytes through activation of extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK) and upregulation of BCL-2 and BCL-xL[47]. Second, the CagA tyrosine phosphorylation-independent pathway impairs p53 via AKT serine/threonine kinase 1 (AKT1) and human homolog of double minute 2 (HDM2)[9,45]. In general, cell wall lipopolysaccharide has been shown to be responsible for triggering a pattern of mucosal inflammation via Toll-like receptor signaling, resulting in activation of MAPK, phosphoinositide 3-kinase (PI3K) and NF-κB pathways in *H. pylori* infection[48,49].

As already mentioned, long-lasting chronic inflammatory processes might also influence MALT lymphomagenesis through the direct (auto) antigen-mediated interaction of lymphoma cells with immune cells and/or the secretion of soluble factors like cytokines. In this case, a direct immune cell-lymphoma cell interaction and subsequent activation result. Activated T cells targeting *H. pylori* represent cells targeting autoantigens in the case of pSS, and these T cells are present in MALT lymphomas and are able to promote lymphoma cell growth via CD40-mediated signaling and T helper (Th) type-2 cytokine (IL-4, IL-5, and IL-10) effects[50,51]. Examples of two cytokines are a proliferation-inducing ligand (APRIL) and B cell-activating factor (BAFF), which are members of the tumor necrosis factor family and play a key role in B cells and autoimmunity. Both cytokines are secreted by eosinophils and/or macrophages and stimulate MALT lymphoma cells[52-54]. Both the CD40/CD40L interaction and APRIL and/or BAFF signaling cause the activation of important downstream signaling pathways, e.g., NF-κB and/or MAPK[55,56], and

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**Figure 1** Graphical depiction of the interplay of mucosa-associated lymphoid tissue lymphoma cells with their microenvironment. *Helicobacter pylori* (H. pylori), other bacteria and/or autoantigens (auto-AGs) support an immune regulatory microenvironment promoting mucosa-associated lymphoid tissue (MALT) lymphomagenesis in different organs. First, regulatory T cells are activated and suppress the immune response by maintaining *H. pylori* colonization and influencing cytotoxic T cells, which possess malfunctions and therefore cannot inhibit the expansion of MALT lymphoma cells. Second, eosinophils and macrophages express a proliferation-inducing ligand (APRIL) and B cell-activating factor, supporting lymphomagenesis. The production of APRIL is induced by *H. pylori* antigens and *H. pylori*-specific T cells. Third, T helper cells and their cytokines (IL-4, IL-5, and IL-10) promote the growth and differentiation of lymphoma cells and are stimulated by *H. pylori* and/or auto-AGs. MALT: Mucosa-associated lymphoid tissue; *H. pylori*: Helicobacter pylori; Tregs: Regulatory T cells; CTL: Cytotoxic T cell; Auto-AG: Autoantigen; Th: T helper.
thereby have an important impact on MALT lymphomagenesis.

Chronic inflammatory processes in MALT lymphomas not only promote B cell growth/proliferation but also actively induce immunosuppressive conditions, which also play a major role in the development and progression of this B cell malignancy. These effects are partially mediated by recruited regulatory T cells (Tregs)[57,58], which suppress anticancer immunity by secreting anti-inflammatory cytokines and/or expressing immune inhibitory surface receptors[59,60]. Furthermore, activated tumor-infiltrating T cells have dysfunctional cytolytic capacity in MALT lymphomas[61,62].

It has been demonstrated that T cells, macrophages and neutrophils recruited during long-lasting chronic inflammation contribute to the formation of genetic aberrations, DNA damage and genetic instability in B cells, leading to antigen-independent lymphoma cell growth. These effects are mediated by activation of ASHM and class-switching recombination in MALT lymphomas[63] and are associated with epigenetic and genetic changes in p57[64,65], p16[66,67] and p53[68,69] as well as chromosomal translocation of cMYC and BCL6[10,69].

**TUMOR MICROENVIRONMENT-TARGETING THERAPIES**

As already described, MALT lymphomas with long-lasting chronic infections cause B cell proliferation and/or survival either directly and/or indirectly via activation of immune cells[9,43,45,66]. Therefore, these interactions provide multiple potential targets for new immunomodulatory treatments beyond the established treatment options for *H. pylori* eradication by antibiotics, radiation, chemotherapy and treatment with the anti-CD20 antibody therapy rituximab[67].

Immunomodulatory drugs (IMiDs) represent a novel therapeutic approach to target the tumor microenvironment of MALT lymphomas. IMiDs, consisting of thalidomide, lenalidomide and pomalidomide, are approved for the treatment of multiple myeloma, and lenalidomide is approved for the treatment of relapsed follicular lymphoma[53,68-70]. IMiDs exert anti-inflammatory effects, such as decreased production of cytokines and increased production of Th1 type cytokines; furthermore, they decrease vascular endothelial growth factor (VEGF) levels and show modulating effects on basic cellular mechanisms (T cell costimulation and alteration of FOXP3+ Tregs and natural killer cells) [65,69]. The efficacy of lenalidomide in MALT lymphomas has been reported in studies with induction of remission after treatment for up to 32 mo[71]. Raderer and Kiesewetter[53] conducted a phase II study with a combination therapy consisting of lenalidomide and rituximab, which achieved an overall response rate of 80% and a complete remission rate of 54%.

Further therapeutic targets are related to Tregs, which are recruited into the microenvironment of MALT lymphoma[58,72] and suppress antitumor immune reactions[58,60,73,74]. It has been shown that the Bruton’s kinase inhibitor ibrutinib reduces the number of Tregs in the early course of treatment in chronic lymphocytic leukemia (CLL), in addition to inhibiting the BCR pathway[75]. Ibrutinib has been tested in relapsed/refractory marginal zone B cell lymphoma (MZL) and possesses a remarkable response rate with tolerable toxicity[53]. However, no data are available thus far for the treatment of MALT lymphoma.

As reported in section 3, in MALT lymphoma cells, the NF-κB pathway is strongly activated by genetic alterations[18,76,77] or by interaction with activated immune cells via the CD40/CD40L[52-54,56] and/or APRIL axes[77-79].

Bortezomib, a proteasome inhibitor with inhibitory effects on the NF-κB signaling pathway[10], showed promising response rates in MALT lymphoma patients in phase II trials[80]. Furthermore, bortezomib was reported to reverses the tumor-induced dysfunction of CD8+ T cells by increasing the expression of Notch cascade genes[81]. Moreover, bortezomib enacts immunostimulatory effects by activating tumor-infiltrating CD8+ T cells[51,62]. Taken together, these findings suggest that the anti-lymphoma effects of bortezomib are mediated by NF-κB inhibition and by reversal of the observed T cell malfunction[52-54].

Another possibility to suppress NF-κB activation in MALT lymphoma cells is the disruption of the APRIL axis[82] with use of an anti-APRIL antibody; one such antibody was developed by Guadagnoli al et al[82] and has shown promising results in CLL in a preclinical setting[83-89]. However, this strategy has not been tested in MALT lymphoma patients thus far.

It has also been demonstrated that macrolides, which are used for eradication of bacterial infection in MALT lymphomas, have certain immunomodulatory effects, e.g., they decrease the number and inhibit the function of neutrophils as well as eosinophils
and inhibit Th2 cell functions. Thus, it is likely that the immunomodulatory effects significantly impact the response rates of MALT lymphomas when these antimicrobial drugs are used.

CONCLUSION

MALT lymphomas represent a heterogeneous group of lymphoid neoplasms arising at different extranodal sites and are associated with a variety of long-lasting chronic infections. In the current pathogenic model, (auto) antigen stimuli trigger lymphoma cell growth, survival, and recruitment of immune cells to the microenvironment, which in turn stimulate lymphoma cells directly via surface receptor interactions and/or indirectly via cytokine secretion. Moreover, it has been shown that inflammatory processes may lead to the acquisition of further genetic alterations resulting in lymphoma cell growth independent of (auto) antigen stimuli. Many agents targeting/blocking the interaction of immune cells of the microenvironment with lymphoma cells, as well as eradicating the antigen stimuli, have been developed within recent years, indicating that the basis for novel therapeutic strategies is already available. Despite these advances, the number of comprehensive studies on the microenvironment composition and its interaction with lymphoma cells needs to be significantly increased to gain further knowledge on targets for innovative and efficient therapy.

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REFERENCES

1. Isaacsen P, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. *Cancer* 1983; 52: 1410-1416 [PMID: 6193858 DOI: 10.1002/1097-0142(19831015)52:8<1410::AID-CANC2820520813>3.0.CO;2-3]
2. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. *Blood* 1997; 89: 3909-3918 [PMID: 9168687 DOI: 10.1182/blood.v89.11.3909]
3. Olszewski AJ, Castillo JJ. Survival of patients with marginal zone lymphoma: analysis of the Surveillance, Epidemiology, and End Results database. *Cancer* 2013; 119: 629-638 [PMID: 22893605 DOI: 10.1002/cncr.27773]
4. Isaacsen PG, Du MQ. MALT lymphoma: from morphology to molecules. *Nat Rev Cancer* 2004; 4: 644-653 [PMID: 15286744 DOI: 10.1038/nrc1409]
5. Swerallew SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H. World Health Organization. WHO classification of tumours of haematopoietic and lymphoid tissues. [cited 12 January 2021]. In: International Agency for Research on Cancer [Internet]. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017
6. Efremov DG, Turkalj S, Laurenti L. Mechanisms of B Cell Receptor Activation and Responses to B Cell Receptor Inhibitors in B Cell Malignancies. *Cancers (Basel)* 2020; 12 [PMID: 32481736 DOI: 10.3390/cancers12061396]
7. Cerutti A, Cols M, Puga I. Marginal zone B cells: virtues of innate-like antibody-producing lymphocytes. *Nat Rev Immunol* 2013; 13: 118-132 [PMID: 23348416 DOI: 10.1038/nri3383]
8. Zucca E, Bertoni F, Vannata B, Cavalli F. Emerging role of infectious etiologies in the pathogenesis of marginal zone B-cell lymphomas. *Clin Cancer Res* 2014; 20: 5207-5216 [PMID: 25320370 DOI: 10.1158/1078-0432.CCR-14-0496]
9. Kiesewetter B, Raderer M. Immunomodulatory treatment for mucosa-associated lymphoid tissue lymphoma (MALT lymphoma). *Hematol Oncol Clin North Am* 2020; 38: 417-424 [PMID: 32469432 DOI: 10.1016/j.hoc.2020.02.003]
10. Troppan K, Wenzl K, Neumeister P, Deutsch A. Molecular Pathogenesis of MALT Lymphoma. *Gastroenterol Res Pract* 2015; 2015: 102656 [PMID: 25922601 DOI: 10.1155/2015/102656]
11. Krugmann J, Tzanov A, Dimhofer S, Fend F, Wolf D, Siebert R, Erdel M. Complete or partial trisomy 3 in gastro-intestinal MALT lymphomas co-occurs with aberrations at 18q21 and correlates with advanced disease stage: a study on 25 cases. *World J Gastroenterol* 2005; 11: 7384-7385 [PMID: 16437648 DOI: 10.3748/wjg.v11.i46.7384]
12. Taji S, Nomura K, Matsumoto Y, Sakabe H, Yoshida N, Mitsufuji S, Nishida K, Horiike S,
Nakamura S, Morita M, Taniwaki M. Trisomy 3 may predict a poor response of gastric MALT lymphoma to Helicobacter pylori eradication therapy. *World J Gastroenterol* 2005; 11: 89-93 [PMID: 15609403 DOI: 10.3748/wjg.v11.i1.89]

13 **Kwee I**, Rancoita PM, Rinaldi A, Ferreri AJ, Bhagat G, Gascoyne RD, Canzoni V, Gaidano G, Doglioni C, Zucca E, Ponzoni M, Bertoni F. Genomic profiles of MALT lymphomas: variability across anatomical sites. *Haematologica* 2011; 96: 1064-1066 [PMID: 21459788 DOI: 10.3324/haematol.2011.040402]

14 **Dierlamm J**, Wlodarska I, Michaux L, Stefanova M, Hinz K, Van Den Berghhe H, Hagenemeier A, Hossfeld DK. Genetic abnormalities in marginal zone B-cell lymphoma. *Hematol Oncol* 2000; 18: 1-13 [PMID: 10797525 DOI: 10.1002/(SICI)1099-1069(200003)18:1<1::AID-HON647-3.0.CO;2-G>

15 **Deutsch AJ**, Aigelsreiter A, Steinbauer F, Frühwirth M, Kerl H, Beham-Schmid C, Schaider H, Neumeister P. Distinct signatures of B-cell homeostatic and activation-dependent chemokine receptors in the development and progression of extragastrointestinal MALT lymphomas. *J Pathol* 2008; 215: 431-444 [PMID: 18561120 DOI: 10.1002/path.2372]

16 **Willis TG**, Jadayel DM, Du MQ, Peng H, Perry AR, Abdul-Rauf M, Price H, Karran L, Majekodunmi O, Wlodarska I, Pan L, Crook T, Hamoudi R, Isaacson PG, Dyer MJ. Bcl10 is involved in t(1;14)(p22;q32) of MALT B cell lymphoma and mutated in multiple tumor types. *Cell* 1999; 96: 35-45 [PMID: 9989495 DOI: 10.1016/S0092-8674(00)80957-5]

17 **Bertoni F**, Zucca E. Delving deeper into MALT lymphoma biology. *J Clin Invest* 2006; 116: 22-26 [PMID: 16395939 DOI: 10.1172/JCI27476]

18 **Luca PC**, Yonezumi M, Inohara N, McAllister-Lucas LM, Abazeed ME, Chen FF, Yamaoka S, Seto M, Numer G. Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. *J Biol Chem* 2001; 276: 19012-19019 [PMID: 11262391 DOI: 10.1074/jbc.M099983200]

19 **Uren AG**, O’Rourke K, Aravind LA, Psaharros MT, Seshagiri S, Koonin EV, Dixit VM. Identification of paracaspases and metacaspases: two ancient families of caspase-like proteins, one of which plays a key role in MALT lymphoma. *Mol Cell* 2000; 6: 961-967 [PMID: 11090634 DOI: 10.1016/s1074-2765(00)00049-0]

20 **Deutsch AJ**, Frühwirth M, Aigelsreiter A, Cerroni L, Neumeister P. Primary cutaneous marginal zone B-cell lymphomas are targeted by aberrant somatic hypermutation. *J Invest Dermatol* 2009; 129: 476-479 [PMID: 18704108 DOI: 10.1038/jid.2008.243]

21 **Moody S**, Thompson JS, Chuang SS, Liu H, Raderer M, Vassiliou G, Wlodarska I, Wu F, Cogliatti S, Robson A, Ashton-Key M, Bi Y, Goodlad J, Du MQ. Novel GPR34 and CCR6 mutation and distinct genetic profiles in MALT lymphomas of different sites. *Haematologica* 2018; 103: 1329-1336 [PMID: 29674500 DOI: 10.3324/haematol.2018.191601]

22 **Lenz G**, Davis RE, Ngo VN, Lam L, George TC, Wright GW, Dave SS, Zhao H, Xu W, Rosenwald A, Ott G, Muller-Hermelink HK, Gascoyne RD, Connors JM, Rimsza LM, Campo E, Jaffe ES, Delabi J, Smeland EB, Fisher RJ, Chan WC, Staudt LM. Oncogenic CARD11 mutations in human diffuse large B-cell lymphoma. *Science* 2008; 319: 1676-1679 [PMID: 18323416 DOI: 10.1126/science.1153629]

23 **Li ZM**, Rinaldi A, Cavalli A, Mensah AA, Ponzoni M, Gascoyne RD, Bhagat G, Zucca E, Bertoni F. MYD88 somatic mutations in MALT lymphomas. *Br J Haematol* 2012; 158: 662-664 [PMID: 22643646 DOI: 10.1111/j.1365-2457.2012.09176.x]

24 **Min KO**, Seo EJ, Kwon HJ, Lee EJ, Kim WI, Kang CS, Kim KM. Methylation of p16(INK4A) and p57(KIP2) are involved in the development and progression of gastric MALT lymphomas. *Mod Pathol* 2006; 19: 141-148 [PMID: 16357845 DOI: 10.1038/modpathol.3800505]

25 **Deutsch AJ**, Aigelsreiter A, Staber PB, Beham A, Linkesch W, Guelli C, Brezinsekch RL, Frühwirth M, Emberger W, Buettner M, Beham-Schmid C, Neumeister P. MALT lymphoma and extranodal diffuse large B-cell lymphoma are targeted by aberrant somatic hypermutation. *Blood* 2007; 109: 3500-3504 [PMID: 17197434 DOI: 10.1182/blood-2006-06-030494]

26 **Bödör C**, Bognár A, Reiniger L, Szepesi A, Töth E, Kopper L, Matolcsy A. Somatic hypermutation and expression of activation-induced cytidine deaminase mRNA in mediastinal large B-cell lymphoma. *Br J Haematol* 2005; 129: 373-376 [PMID: 15842661 DOI: 10.1111/j.1365-2457.2005.05454.X]

27 **Küppers R**, Dalla-Favera R. Mechanisms of chromosomal translocations in B cell lymphomas. *Annu Rev Genet* 2001; 35: 559-594 [PMID: 11607811 DOI: 10.1146/annurev.genet.35.1.120460]

28 **Matsumoto Y**, Marusawa H, Kinoshita K, Endo Y, Kuo T, Morisawa T, Azuma T, Okazaki M, Honjo T, Chiba T. Helicobacter pylori infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. *Nat Med* 2007; 13: 470-476 [PMID: 17401375 DOI: 10.1038/nm1566]

29 **Isaacsong PG**, Spencer J. The biology of low grade MALT lymphoma. *J Clin Pathol* 1995; 48: 395-397 [PMID: 7629280 DOI: 10.1136/jcp.48.5.395]

30 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; 338: 1175-1176 [PMID: 1682595 DOI: 10.1016/S0140-6736(91)92035-Z]

31 **Cerroni L**, Zöchling N, Pütz B, Kerl H. Infection by Borrelia burgdorferi and cutaneous B-cell lymphoma. *J Cutan Pathol* 1997; 24: 457-461 [PMID: 9331890 DOI: 10.1111/j.1600-0560.1997.tb01318.x]

32 **Parsonnet J**, Isaacson PG. Bacterial infection and MALT lymphoma. *N Engl J Med* 2004; 350: 213-
Uhl B et al. Microenvironment in MALT lymphomas

215 [PMID: 14724298 DOI: 10.1056/nejmp038200]

33 Adam P, Czepieński P, Colek S, Kosmidis P, Tousseny T, Sagaré X, Bouduvá K, Okoli K, Morresi-Hauf A, Agostinelli C, Pilieri S, Pruneri G, Martinelli G, Du MQ, Fend F. Prevalence of Achromobacter xylosidans in pulmonary mucosa-associated lymphoid tissue lymphoma in different regions of Europe. *Br J Haematol* 2014; 164: 804-810 [PMID: 24372375 DOI: 10.1111/bjh.12703]

Ferreri AJ, Guidoboni M, Pozzoni M, De Conciutiis C, Dell’Oro S, Fleischhuaker K, Caggiari L, Lettini AA, Dal Cin E, Ieri R, Freschi M, Villa E, Boiocchi M, Dolcetti R. Evidence for an association between Chlamydia psittaci and ocular adnexal lymphomas. *J Natl Cancer Inst* 2004; 96: 586-594 [PMID: 15100336 DOI: 10.1093/jnci/djh102]

Chauvet E, Adam P, Nicholson AG, Wouterspoon AC, Ranaldi R, Goteri G, Pilieri SA, Ye H, Müller-Hermelink HK, Du MQ, Chlamydiae and Mycoplasma infections in pulmonary MALT lymphoma. *Br J Cancer* 2007; 97: 949-951 [PMID: 17876330 DOI: 10.1038/sj.bjc.6603981]

Algesheimer G, Gerlza T, Deutsch AJ, Leitner E, Beham-Schmid C, Beham A, Popper H, Borel N, Pospisilch A, Raderer M, Kessler HH, Neumeister P. Chlamydia psittaci Infection in nongastrointestinal extranodal MALT lymphomas and their precursor lesions. *Am J Clin Pathol* 2011; 135: 70-75 [PMID: 21173126 DOI: 10.1309/AJCPXM0RT1S6KIV]

Negri E, Little D, Boiocchi M, La Vecchia C, Franceschi S. B-cell non-Hodgkin’s lymphoma and hepatitis C virus infection: a systematic review. *Int J Cancer* 2004; 111: 1-8 [PMID: 15185336 DOI: 10.1002/ijc.20205]

Aoyama S, Masaki A, Sakamoto Y, Takino H, Murase T, Ohshima K, Yoshino T, Kato S, Inagaki H. Achromobacter Infection Is Rare in Japanese Patients with Pulmonary B-cell Lymphoma. *Intern Med* 2018; 57: 789-794 [PMID: 29151525 DOI: 10.2169/internalmedicine.9430-17]

Carugi A, Onnis A, Antonielli G, Rossi B, Mannucci S, Luzzi A, Lazzi S, Bellan C, Tosi GM, Sayed S, De Falco G, Leoncini L. Geographic variation and environmental conditions as cofactors in Helicobacter pylori CagA into Human B lymphocytes, the origin of mucosa-associated lymphoid tissue lymphoma. *Helicobacter* 2019; 24: 209-227 [PMID: 30820719 DOI: 10.1111/hcl.13192]

Wöhrer S, Zhou Y, Bacon CM, Wotherspoon AC, Müller-Hermelink HK, Adam P, Dong HY, de Jong D, Li Y, Wei R, Gong X, Wu Q, Ranaldi R, Goteri G, Pilieri SA, Ye H, Hamoudi RA, Liu H, Radford J, Du MQ. Chlamydia psittaci is variably associated with ocular adnexal MALT lymphoma in different geographical regions. *J Pathol* 2006; 209: 344-351 [PMID: 1658336 DOI: 10.1002/path.1984]

Wöhrrer S, Troch M, Streubel B, Zwerina J, Skrbas C, Formanek M, Hauff W, Hoffmann M, MÜLLER L, Chott A, Raderer M. MALT lymphoma in patients with autoimmune diseases: a comparative analysis of characteristics and clinical course. *Leukemia* 2007; 21: 1812-1818 [PMID: 17554381 DOI: 10.1038/sj.leu.2404782]

Ferraccioli GF, Sorrentino D, De Vita S, Casatta L, Labombarda A, Avellini C, Dolcetti R, Di Luca D, Beltrami CA, Boiocchi M, Bartoli E. B cell clonality in gastric lymphoid tissues of patients with Sjögren’s syndrome. *Ann Rheum Dis* 1996; 55: 311-316 [PMID: 8660105 DOI: 10.1136/ard.55.5.311]

Nocturne G, Mariette X. Sjögren Syndrome-associated lymphomas: an update on pathogenesis and management. *Br J Haematol* 2015; 168: 317-327 [PMID: 25316606 DOI: 10.1111/bjh.13192]

Tisch J, Woeber S, Streubel B, Weisell M, Hoffmann M, MÜLLER L, Chott A, Raderer M. Chronic autoimmune thyroiditis (Hashimoto’s thyroiditis) in patients with MALT lymphoma. *Ann Oncol* 2008; 19: 1336-1339 [PMID: 18334310 DOI: 10.1093/annonc/dnm049]

Umehara S, Higashi H, Ohnishi N, Asaka M, Hatakeyama M. Effects of Helicobacter pylori CagA protein on the growth and survival of B lymphocytes, the origin of MALT lymphoma. *Oncogene* 2003; 22: 8337-8342 [PMID: 14614457 DOI: 10.1038/sj.onc.1207028]

Kuo SH, Wu MS, Yeh KH, Lin CW, Hsu PN, Chen LT, Cheng AL. Novel Insights of Lymphomagenesis of Helicobacter pylori-Dependent Gastric Mucosa-Associated Lymphoid Tissue Lymphoma. *Cancers (Basel)* 2019; 11 [PMID: 30995581 DOI: 10.3390/cancers11040547]

Lin WC, Tsai HF, Kuo SH, Wu MS, Lin CW, Hsu PI, Cheng AL, Hsu PN. Translocation of Helicobacter pylori CagA into Human B lymphocytes, the origin of mucosa-associated lymphoid tissue lymphoma. *Cancer Res* 2010; 70: 5740-5748 [PMID: 20587516 DOI: 10.1158/0008-5472.CAN-09-4690]

Slomiany BL, Slomiany A. Syk: a new target for attenuation of Helicobacter pylori-induced gastric mucosal inflammatory responses. *Inflammopharmacology* 2019; 27: 203-211 [PMID: 30820719 DOI: 10.1007/s10787-019-00577-6]

Slomiany BL, Slomiany A. Role of LPS-elicited signaling in triggering gastric mucosal inflammatory responses to H. pylori: modulatory effect of ghrelin. *Inflammopharmacology* 2017; 25: 415-429 [PMID: 28516374 DOI: 10.1007/s10787-017-0360-1]

Clark EA, Ledbetter JA. How B and T cells talk to each other. *Nature* 1994; 367: 425-428 [PMID: 8107800 DOI: 10.1038/367425a0]

Nakamura H, Kawakami A, Tominaga M, Mgitza K, Kawabe Y, Nakamura T, Eguchi K. Expression of CD40/CD40 Ligand and Bcl-2 family proteins in labial salivary glands of patients with Sjögren’s syndrome. *Lab Invest* 1999; 79: 261-269 [PMID: 10092062]

Blosse A, Peru S, Levy M, Martben B, Floch P, Sifré E, Giese A, Prochazkova-Carlootti M, Azzi Martin L, Dubus P, Méraud F, Ruskone Fournestaux A, Fabiani B, Copie Bergman C, Robe C, Hahne M, Haard B, Lehours P. APRIL-producing cosinophils are involved in gastric MALT lymphomagenesis induced by Helicobacter sp infection. *Sci Rep* 2020; 10: 14858 [PMID: 32908188 DOI: 10.1038/s41598-020-71792-3]
A, Lehours P. Regulatory T cells may participate in Helicobacter pylori persistence in gastric MALT lymphoma. *J Clin Med* 2020; 9: [PMID: 32355238 DOI: 10.3390/jcm9123794]

Elguea R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. *Immunol Rev* 2009; 229: 152-172 [PMID: 19426221 DOI: 10.1111/j.1600-065X.2009.00782.x]

Bosson C, Schneider P, BAFF, APRIL and their receptors: structure, function and signaling. *Semin Immunol* 2006; 18: 263-275 [PMID: 16914324 DOI: 10.1016/s0165-4608(06)004.006]

Craig VJ, Cogliatti SB, Arnold I, Gerke C, Balandat JE, Wünsch T, Müller A. B-cell receptor signaling and CD40 Ligand-independent T cell help cooperate in Helicobacter-induced MALT lymphomagenesis. *Leukemia* 2010; 24: 1186-1196 [PMID: 20428202 DOI: 10.1038/leu.2010.76]

García M, Bellissol sB, Sánchez-González B, García-Payárols F, Seoane A, Ferrer AM, Giné M, Barranco LE, Torner A, Solé F, Bessè sC, Serrano S, Salar A. Study of regulatory T-cells in patients with gastric malf lymphoma: influence on treatment response and outcome. *PLoS One* 2012; 7: e51681 [PMID: 23284739 DOI: 10.1371/journal.pone.0051681]

Curiel TJ. Regulatory T cells and treatment of cancer. *Curr Opin Immunol* 2008; 20: 241-246 [PMID: 18580251 DOI: 10.1016/coi.2008.04.008]

Togashi Y, Shi taka K, Nishikawa H. Regulatory T cells in cancer immunosuppression - implications for anticancer therapy. *Nat Rev Clin Oncol* 2019; 16: 356-371 [PMID: 30705439 DOI: 10.1038/s41571-019-0175-7]

D’Elios MM, Amedei A, Manghetti M, Costa F, Baldar i CT, Quazi AS, Telford JL, Romagnani S, Del Prete G. Impaired T cell regulation of B-cell growth in Helicobacter pylori–related gastric low-grade MALT lymphoma. *Gastroenterology* 1999; 117: 1105-1112 [PMID: 10535873 DOI: 10.1016/s0016-5085(99)70395-1]

Bergman MP, D’Elios MM. Cytotoxic T cells in H. pylori-related gastric autoimmunity and gastric lymphoma. *J Biomed Biotechnol* 2010; 2010: 104918 [PMID: 20617132 DOI: 10.1155/2010/104918]

Thieblemont C, Ber t oni F, Copie-Bergman C, Ferrer AJ, Pon zoni M. Chronic inflammation and extra-nodal marginal-zone lymphomas of MALT-type. *Semin Cancer Biol* 2014; 24: 33-42 [PMID: 24333758 DOI: 10.1016/j.semcancer.2013.11.005]

Neumeister P, Hoefler G, Beham-Schmidt C, Schmidt H, Apfelbeck U, Schiuder H, Linkesch W, Sill H. Deletion analysis of the p16 tumor suppressor gene in gastrointestinal mucosa-associated lymphoid tissue lymphomas. *Gastroenterology* 1997; 112: 1871-1875 [PMID: 9178679 DOI: 10.1053/gast.1997.v112.pm9178679]

Liang R, Chan WP, Kwong YL, Xu WS, Srivastava G, Ho FC. High incidence of BCL-6 gene rearrangement in diffuse large B-cell lymphoma of primary gastric origin. *Cancer Genet Cytogenet* 1999; 97: 114-118 [PMID: 9283593 DOI: 10.1016/s0165-4608(99)00338-3]

Hussell T, Isa conson PG, Crabtree JE, Spencer J. Helicobacter pylori-py lori-specific tumour-infiltrating T cells provide contact dependent help for the growth of malignant B cells in low-grade gastric lymphoma of mucosa-associated lymphoid tissue. *J Pathol* 1996; 178: 122-127 [PMID: 8683376 DOI: 10.1002/(SICI)1096-9896(199602)178:2<122::AID-JPATH486>3.0.CO;2-D]

Zucza E, Arcaini L, Busce c B, Johnson PW, Pon zoni M, Raderer M, Ricardi U, Salar A, Stamatopoulos K, Thieblemont C, Wotherspoon A, Ladetto M, ESMO Guidelines Committee. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; 31: 17-29 [PMID: 31912792 DOI: 10.1016/annonc.2019.10.010]

Kotla V, Goel S, Nischal S, Heuck C, Vivek K, Das B, Verma A. Mechanism of action of lenalidomide in hematological malignancies. *J Hematol Oncol* 2009; 2: 36 [PMID: 19674465 DOI: 10.1186/1758-8359-2-36]

Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, Prince HM. Mechanism of action of immunomodulatory drugs (ImiDS) in multiple myeloma. *Leukemia* 2010; 24: 22-32 [PMID: 19907437 DOI: 10.1038/leu.2009.236]

Leonard JP, Trinen M, Izutsu K, Fowler NH, Hong X, Zhu J, Zhang H, Offner F, Scheliga A, Nowakowski GS, Pinto A, Re F, Fogliatto LM, Scheinberg P, Finn JW, Moreira C, Cabeças das J, Liu D, Kalambakas S, Fustier P, Wu C; Gribben JG; AUGMENT Trial Investigators. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. *J Clin Oncol* 2019; 37: 1188-1199 [PMID: 30897038 DOI: 10.1200/JCO.19.00010]

Kiesewetter B, Troch M, Mayerhoefer ME, Dolak W, Simonitsch-Klupp I, Raderer M. Delayed Efficacy After Treatment With Lenalidomide or Thalidomide in Patients With Mucosa-Associated Lymphoid Tissue Lymphoma. *Oncologist* 2016; 21: 72-75 [PMID: 26621040 DOI: 10.1634/theoncologist.2015-0176]

Bagheri N, Azadegan-Dehkordi F, Rahimian G, Rafieian-Kopaei M, Shirzad H. Role of Regulatory T-cells in Different Clinical Expressions of Helicobacter pylori Infection. *Arch Med Res* 2016; 47: 245-254 [PMID: 27664483 DOI: 10.1016/j.arcmed.2016.07.013]

Laur AM, Floch P, Chambonnier L, Benejat L, Korolik V, Giese A, Dubus P, Mégraud F, Bandeira A, Lehours P. Regulatory T cells may participate in Helicobacter pylori persistence in gastric MALT lymphomas: lessons from an animal model. *Oncotarget* 2016; 7: 3394-3402 [PMID: 26657504 DOI: 10.18632/oncotarget.10208]
WJGO  |  https://www.wjnet.com

Uhl B et al. Microenvironment in MALT lymphomas

10.18632/oncotarget.6492]

74 Isawa Y, Kobayashi M, Monose M, Hiraoka N, Sakai Y, Akamatsu T, Tanaka E, Ohtani H, Fukuda M, Nakayama J. High levels of FOXP3 regulatory T cells in gastric MALT lymphoma predict responsiveness to Helicobacter pylori eradication. Helicobacter 2013; 18: 356-362 [PMID: 23551894 DOI: 10.1111/hel.12051]

75 Podsherecka M, Goracy A, SZymczyk A, Kowal M, Ibanez B, Jankowska-Lecka O, Macheta A, Nowaczyńska A, Drab-Urbanek E, Chochołska S, Jawniak D, Hsu M. Changes in T-cell subpopulations and cytokine network during early period of ibrutinib therapy in chronic lymphocytic leukemia patients: the significant decrease in T regulatory cells number. Oncotarget 2017; 8: 34661-34669 [PMID: 28416773 DOI: 10.18632/oncotarget.16148]

76 Liu F, Karube K, Kato H, Arita K, Yoshida N, Yamamoto K, Tsuzuki S, Kim W, Ko YH, Seto M. Mutation analysis of NF-kB signal-related genes in ocular MALT lymphoma. Int J Clin Exp Pathol 2012; 5: 436-441 [PMID: 22808296]

77 McAllister-Lucas LM, Inohara N, Lucas PC, Ruland J, Benito A, Li Q, Chen S, Chen FF, Yamaoka S, Verma IM, Mak TW, Núñez G. Bimp1, a MAGUK family member linking protein kinase C activation to Bcl10-mediated NF-kappaB induction. J Biol Chem 2001; 276: 30589-30597 [PMID: 11387339 DOI: 10.1074/jbc.M103824200]

78 Hozák RR, Manji GA, Friesen PD. The BIR motifs mediate dominant interference and oligomerization of inhibitor of apoptosis Op-IAP. Mol Cell Biol 2000; 20: 1877-1885 [PMID: 10669762 DOI: 10.1128/mcb.20.5.1877-1885.2000]

79 Panwalkar A, Verstovsek S, Giles F. Nuclear factor-kappaB modulation as a therapeutic approach in hematologic malignancies. Cancer 2004; 100: 1578-1589 [PMID: 15073843 DOI: 10.1002/cncr.20182]

80 Thousoajom MC, Dudinah DF, Pellom ST Jr, Uzhaenko RN, Carbone DP, Dikov MM, Shanker A. Bortezomib enhances expression of effector molecules in anti-tumor CD8+ T lymphocytes by promoting Notch-nuclear factor-kB crosstalk. Oncotarget 2015; 6: 32439-32455 [PMID: 26431276 DOI: 10.18632/oncotarget.5857]

81 Pellom ST Jr, Dudinah DF, Thousoajom MC, Uzhaenko RN, Singhal A, Richardson A, Shanker A. Bortezomib augments lymphocyte stimulatory cytokine signaling in the tumor microenvironment to sustain CD8+ T cell antitumor function. Oncotarget 2017; 8: 8604-8621 [PMID: 28052005 DOI: 10.18632/oncotarget.14365]

82 Guadagnoli M, Kimberley FC, Phan U, Cameron K, Vink PM, Rodermond H, Eldering E, Kater AP, van Enenennam H, Medema JP. Development and characterization of APRIL antagonistic monoclonal antibodies for treatment of B-cell lymphomas. Blood 2011; 117: 6856-6865 [PMID: 21543761 DOI: 10.1182/blood-2011-01-330852]

83 Zimmermann P, Ziesenis VC, Curtis N, Ritz N. The Immunomodulatory Effects of Macrolides-A Systematic Review of the Underlying Mechanisms. Front Immunol 2018; 9: 302 [PMID: 29593707 DOI: 10.3332/ecancer.2015.513]

84 Ghosh N, Tucker N, Zahirak M, Wozney J, Borrello I, Huff CA. Clarithromycin overcomes resistance to lenalidomide and dexamethasone in multiple myeloma. Am J Hematol 2014; 89: E116-E120 [PMID: 24723438 DOI: 10.1002/ajh.23733]

85 Van Nuffel AM, Sukhatme V, Pantziarka P, Meheus L, Sukhatme VP, Bouche G. Repurposing Drugs in Oncology (ReDO)-clarithromycin as an anti-cancer agent. Ecancermedicalscience 2015; 9: 513 [PMID: 25792462 DOI: 10.3332/ecancer.2015.513]

86 Li L, Sun R, Miao Y, Tran T, Adams L, Roscoe N, Xu B, Manyam GC, Tan X, Zhang H, Xiao M, van Enenennam H, Medema JP. Development and characterization of APRIL antagonistic monoclonal antibodies for treatment of B-cell lymphomas. Blood 2011; 117: 6856-6865 [PMID: 21543761 DOI: 10.1182/blood-2011-01-330852]

87 Ferrerei AJ, Sassone M, Kiesewetter B, Giovi S, Scarfó L, Donadoni G, Raderer M. High-dose clarithromycin is an active monotherapy for patients with relapsed/refractory extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) the HD-K phase II trial. Ann Oncol 2015; 26: 1760-1765 [PMID: 25935794 DOI: 10.1093/annonc/mdv214]

88 Ferrerei AJM, Cecchetti C, Kiesewetter B, Sassone M, Calimeri T, Perrone S, Ponzoni M, Raderer M. Clarithromycin as a “repurposing drug” against MALT lymphoma. Br J Haematol 2018; 182: 913-915 [PMID: 28771670 DOI: 10.1111/bjh.14878]

89 Giovi S, Dognini GP, Licata G, Crocchiolo R, Resti AG, Ponzoni M, Ferreri AJ. Six-month oral clarithromycin regimen is safe and active in extranodal marginal zone B-cell lymphomas: final results of a single-centre phase II trial. Br J Haematol 2010; 150: 226-229 [PMID: 20433679 DOI: 10.1111/j.1365-2141.2010.08179.x]
