special article

ESMO Consensus conferences: guidelines on malignant lymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-cell lymphoma

M. Dreyling[1]*, C. Thieblemont[2], A. Gallamini[3], L. Arcaini[4], E. Campo[5], O. Hermine[6],
J. C. Kluin-Nelemans[7], M. Ladetto[8], S. Le Gouill[9], E. Iannitto[10], S. Pileri[11],
J. Rodriguez[12], N. Schmitz[13], A. Wotherspoon[14], P. Zinzani[15] & E. Zucca[16]

[1]Department of Medicine III, University Hospital, LMU Munich, Germany; [2]Department of Hematology, APHP-Saint-Louis Hospital, Paris Diderot University, Sorbonne, France; [3]Department of Hematology, S. Croce e Carle Hospital, Cuneo; [4]Department of Hematology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [5]Department of Pathology, Hospital Clinic, University of Barcelona, Barcelona, Spain; [6]Department of Hematology, Hospital Necker University Paris Descartes, Paris, France; [7]Department of Hematology, University Medical Center Groningen, Groningen, Netherlands; [8]Department of Oncologia Medicine and Oncology, Università di Torino, Turin, Italy; [9]Department of Hematology, CHU de Nantes, Nantes, France; [10]Department of Oncohematology, Hospital S.G. Moscati, ASL, Taranto; [11]Department of Pathologic Anatomy and Haematopathology, Bologna University, Bologna, Italy; [12]Department of Oncology, University Hospital Severo Ochoa, Madrid, Spain; [13]Department of Hematology, Asklepios Hospital St. Georg, Hamburg, Germany; [14]Department of Histopathology, Royal Marsden Hospital, London, UK; [15]Institute of Hematology and Oncology, Bologna University, Bologna, Italy; [16]Onbcology Institute of Southern Italy, Bellinzona, Switzerland

To complement the existing treatment guidelines for all tumour types, ESMO organizes consensus conferences to focus on specific issues in each type of tumour. In this setting, a consensus conference on the management of lymphoma was held on 18 June 2011 in Lugano, next to the 11th International Conference on Malignant Lymphoma. The conference convened ~30 experts from all around Europe, and selected six lymphoma entities to be addressed; for each of them, three to five open questions were to be addressed by the experts. For each question, a recommendation should be given by the panel, referring to the strength of the recommendation based on the level of evidence. This consensus report focuses on the three less common lymphoproliferative malignancies: marginal zone lymphoma, mantle cell lymphoma, and peripheral T-cell lymphomas. A first report had focused on diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukaemia.
Key words: malignant lymphoma guidelines, mantle cell lymphoma, marginal zone lymphoma, T-cell lymphoma

Methodology

The conference convened ~30 experts from all around Europe, and selected six lymphoma entities to be addressed; for each of them, three to five open questions were to be addressed by the experts. For each question, a recommendation should be given by the panel, referring to the strength of the recommendation based on the level of evidence. This consensus report focuses on the three less common lymphoproliferative malignancies: marginal zone lymphoma (MZL), mantle cell lymphoma (MCL), and peripheral T-cell lymphomas (TCLs). A first report had focussed on diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukaemia (CLL). Level of evidence and grade of recommendation have been adapted from the Infectious Diseases Society of American-United States Public Health Service Grading System (Table 1).

Correspondence to: Dr M. Dreyling, Department of Medicine III, University Hospital /LMU, Marchioninistr. 15, 81377 Munich, Germany. Tel: +49-89-7095-2202; Fax: +49-89-7095-2201; E-mail: martin.dreyling@med.uni-muenchen.de

1. Marginal zone lymphoma

In the last WHO classification, the MZL including the extra-nodal MZL of MALT type (MALT lymphoma), the splenic MZL (SMZL) (with or without villous lymphocytes), and nodal MZL NMZL (with or without monocytoid B cells) are three distinct clinical entities with specific diagnostic criteria and different behaviour and therapeutic implications [1]. A committee of experts including haematologists/oncologists and haematopathologists has defined three crucial issues to manage patients with MZLs: to make the correct diagnosis and evaluate the biological prognosis of the disease; to distinguish between localized disease, essentially MALT lymphomas, and disseminated disease, SMZL and NMZL; and to propose the best treatment.

1.1 Pathology and prognosis of MZL
The diagnosis should be in accordance with the current WHO classification [1]. The diagnosis of MZL, as in other

Table 1. Level of evidence (Infectious Diseases Society of American-United States Public Health Service Grading System)

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials of large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Grade for recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

lymphomas should be confirmed by review by an expert haematopathologist. Differentiation from other lymphomas that can mimic MZLs should be confirmed (Table 2).

For *extra-nodal* MZL assessment of a potential associated large B-cell lymphoma is essential by analysis of extra-follicular components for transformed large B cells. Of particular note is the fact that the presence of lymphoepithelial lesions is neither essential for the diagnosis of extra-nodal MZL nor is their presence absolutely specific for this entity as they can be seen both in some reactive conditions and in other low-grade lymphomas.

The diagnosis of *SMZL* at present does not strictly require a splenectomy [2]. Characteristic features to allow this have been established following the review of a large series of cases in which the diagnosis has been confirmed by review of splenic histology [3].

In some cases, the definitive diagnosis may not be possible. Of note is the fact that cytoplasmic villi will not be seen in all cases (and may be lost if the blood has been store for prolonged period with anticoagulant) and not all lymphoproliferations where the cells have villi equate to SMZL.

No consistent prognostic markers have been identified that are sufficiently significant to alter initial clinical management in MZL. Studies for t(11;18)(p21; p21) would be considered

Table 2. Recommended procedures for initial staging and follow-up of patients with disseminated marginal zone lymphoma

Procedures	Recommendations		Expected results
	At diagnosis	Follow-up	
Full blood count	M	M	Presence or absence of anaemia, thrombocytopenia, neutropenia, lymphocytosis
Reticulocytes–DAT	R	O	
Blood cytology	M	O	Small lymphoid cells having a round nucleus with condensed chromatin and basophilic cytoplasm, with frequent short villi
Blood flow cytometry (FCM)	M	R	Mandatory: CD5−, CD10−, CD19+, CD23−, CD27+, CD43−, FMC7±, kappa/lambda
			Optional: CD20+, CD79b+, CD43±, CD103−, bcl-2+, annexin A1−, moderate to strong intensity of IgM and IgD or Ig M alone; in rare cases, IgG or IgA—expression of CD5 in 15%–20%—expression of CD23 in 30% of case—Score Matutes ≤3
Serology for HCV	M	O	If HCV positive, RT-PCR for HCV-RNA and virus genotyping
Cryoglobulins	M if HCV+	O	
Serology for HBV and HIV	M	O	
CT scan	M	M	SMZL: massive splenomegaly—NMZL: disseminated disease
GD endoscopy + ENT evaluation	R	O	Detection of occult localization at MALT sites
BM aspirate: cytology and FC	M	O	Identical to blood
BM biopsy	M	O	See morphology section
Splenectomy	O	O	See morphology section
Lymph node biopsy	O	O	See morphology section
Autoimmune screening	O	O	ANA, anti-DNA, AMA, anti-thyroid, RF; If clinical symptoms circulating anticoagulant (lupic or cardiolipidic), acquired vWD, acquired deficit in C1 ester.
FISH and cytogenetics	O	O	SMZL: trisomy 3q (85%) del or translocation of 7q32 (40%) trisomy 18, 17q isochromosome, 13q14 deletion, and structural abnormalities of chr 1; xclusion of t (11;14)
			NMZL: gains of chr 3 and 18q23—lack of 7q loss
IgVH status	O	O	IgVH mutated in two-third of the cases—IgVH unmutated in one-third of the cases
			Biased usage: SMZL: $V_H1.2$, $V_H1–2$, $V_H3–23$, $V_H4–34$ genes; NMZL V_H4-34

M, mandatory; R, recommended; O, optional; IgM, immunoglobulin M; IgD, immunoglobulin D; Ig, immunoglobulin; IgA, immunoglobulin A; IgG, immunoglobulin G; CT, computer tomography; ENT, ear nose and throat.

optional in the assessment of gastric MALT lymphoma, as they may give an indication of the likelihood of response of the lymphoma to *Helicobacter pylori* eradication alone.

1.1 Consensus statement
In all cases, but particularly for NMZL, the histological diagnosis must be established in knowledge of the full clinical and radiological presentation.
   Level of evidence: IV
   Grade of recommendation: A

1.2 Consensus statement
A minimum panel of immunocytochemical stains should include CD20, CD10, CD5, and cyclinD1.
   Level of evidence: IV
   Grade of recommendation: B

1.3 Consensus statement
The diagnosis of SMZL can be confidently achieved by the combination of peripheral blood and bone marrow aspirate morphology and flow cytometry (FC) and of the findings of bone marrow trephine biopsy histology with immunocytochemistry by expert haematopathologists and haematologists/oncologists [3].
   Level of evidence: IV
   Grade of recommendation: B

1.2 Localized marginal zone lymphoma: Diagnostic and therapeutic measures
Localized MZL is mainly represented by extra-nodal MZL of MALT type, that can however be disseminated in 25% of the cases [4–6]. We focused on two important issues for the management of the patients with extra-nodal MZL of MALT type: the staging and the treatment.

1.2.1 INITIAL STAGING PROCEDURES
The following procedures are considered mandatory in gastric MALT lymphoma:
   Gastroduodenal endoscopy with multiple biopsies taken from each region of the stomach, duodenum, gastro-oesophageal junction and from any abnormal-appearing site; *H. pylori* status must be evaluated. If clinically indicated, head and neck magnet resonance tomography (MRT) studies and other imaging may be performed.
   The following procedures are recommended in:

- *Gastric MALT lymphoma*: endoscopic ultrasound to evaluate the regional lymph nodes and gastric wall infiltration. Optional: fluorescence *in situ* hybridization (FISH) for the t(11;18) translocation.

   For specific sites such as:

- *Small intestine* (immunoproliferative small intestinal disease, IPSID): *Campylobacter Jejuni* search in the tumour biopsy by polymerase chain recation (PCR), immunohistochemistry or in situ hybridization may be carried out.
- *Large intestine*: colonoscopy.
- *Lung*: Bronchoscopy + bronchoalveolar lavage.

- *Salivary glands: Ear/nose/throat* examination and ultrasound. Association with Sjögren syndrome to eliminate (anti-SSA or anti-SSB antibodies) should be investigated.
- *Thyroid*: echography ± computer tomography (CT) scan of the neck and thyroid function tests.
- *Ocular adnexa*: MRT (or CT scan) and ophthalmologic examination. *Chlamydia psittaci* in the tumour biopsy and blood mononuclear cells by PCR may be considered.
- *Breast*: mammography and MRT (or CT scan).
- *Skin*: Borrelia Burgdorferi in the tumour biopsy by PCR (in endemic areas) may be considered.

   The value of positron emission tomography (PET) scan is controversial and has uncertain clinical utility and is not recommended.

1.4 Consensus statement
The following exams are mandatory: history and physical exam [including lymph node regions, eye and ear, nose and throat (ENT) areas, liver and spleen evaluation; complete blood counts and basic biochemical studies], including evaluation of renal and liver function, lactate dehydrogenase (LDH) and β2-microglobulin, serum protein immunofixation, human immundeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) serology; CT scan of the chest, abdomen, and pelvis; bone marrow aspirate and biopsy recommended.
   Level of evidence: IV
   Grade of recommendation: B

1.2.2 TREATMENT
Treatment has been discussed considering two specific scenarios: gastric MALT lymphoma, *H. pylori* positive, stage I–II, and the others MALT lymphoma (non-gastric MALT lymphoma and gastric patients who failed to respond to *H. pylori* eradication.

- *Gastric MALT lymphoma, H. pylori positive, stage I–II*

   H. pylori eradication therapy must be given to all gastric MALT lymphomas, independently of stage or histological grade. The outcome of H pylori eradication therapy should be checked by urea breath test (or by a monoclonal stool antigen test) at least 6 weeks after eradication therapy and at least 2 weeks after PPI withdrawal.

- *Non-gastric MALT lymphoma and gastric patients who failed to respond to H. pylori eradication*

   Involved Field Radiotherapy may be a reasonable option only for localized stage. Chemotherapy, or immunotherapy or in combination are effective in patients with MALT lymphoma of all stages. There is no definitive evidence in favour of one of these two modalities in localized gastric MALT lymphoma, but the preferred choice depends very much on the local expertise of the attending physicians. An important issue is that patients with t(11;18) will most probably be unresponsive to alkylating agents as sole treatment.
   As in other disseminated low-grade lymphomas, rituximab plus chemotherapy would be the best choice when treatment is

needed, but there is not yet a standard best chemotherapy to be recommended.

If clinical trials are available, patients should be included. Besides clinical trials, a therapeutic approach similar to other indolent lymphomas is always a good decision. Eradication therapy with antibiotics in MALT lymphoma arising outside the stomach remains investigational.

1.5. Consensus statement

In gastric MALT lymphoma the first step of treatment should be H Pylori eradication (PPI + clarithromycin-based triple therapy with either amoxicillin or metronidazole for 10–14 days).

Level of evidence: III
Grade of recommendation: A
H. pylori-negative patients with gastric MALT lymphoma may also receive anti-H pylori treatment
Level of evidence: IV
Grade of recommendation: C

1.2.3 FOLLOW-UP/MONITORING

While non-gastric sites can be re-evaluated as any other low-grade lymphoma (clinical exam, laboratory work-up, imaging, biopsy of residual lesions), sequential evaluation of gastric biopsies remains an essential follow-up procedure for gastric MZL to exclude the possibility of persistent significant disease, even if mucosa is normal and to look for early epithelial changes, which may be related to gastric carcinoma, particularly in patients with persistent *H. pylori* infection.

Unfortunately, the interpretation of lymphoid infiltrate in post-treatment gastric biopsies can be very difficult and there are no uniform criteria for the definition of histological remission. Comparison with previous biopsies should be carried out to assess response, and we recommend the GELA scoring system as a reproducible method for this [7]. The clinical decision should always be the result of close interaction between clinicians and pathologists. *H. pylori* eradication should be documented at least 6 weeks after the antibiotic treatment. Then, a strict endoscopic follow-up is recommended, with multiple biopsies taken 2–3 months after treatment, and subsequently, at least twice per year for 2 years, to monitor the histological regression of the lymphoma. Gastric MALT lymphomas have limited tendency to distant spreading and to histological transformation. Transient apparent histological local relapses are occasionally observed but they have to be maintained in order to consider a relapse, as the changes reflect the limitations of small tissue and in addition tend to be self-limiting, especially in the absence of *H. pylori* reinfection [8].

Nevertheless, a long-term careful endoscopic and systemic (clinical exam, blood counts and minimal adequate radiological or ultrasound examinations) follow-up every 12 (−18) months is recommended for all patients. Indeed, the risk of gastric adenocarcinoma among patients diagnosed with gastric MALT lymphoma has been reported to be six-fold higher than in the general population. Of important note, if only microscopic gastric lesion is seen during follow-up, no treatment should be initiated.

1.6 Consensus statement

In case of persistent but stable residual disease or histological relapse (without distant dissemination and/or gross endoscopic tumour), a watch-and-wait policy appears to be safe [9].

Level of evidence: IV
Grade of recommendation: C

1.3 Disseminated MZL

Disseminated MZL include SMZL, which is associated with blood and bone marrow infiltration in more than 95% of the cases, and NMZL, presenting with more or less extended systemic lymphadenopathy in the vast majority of the cases. Important questions about the management of these lymphomas are staging, prognostic factors and treatment.

1.3.1 STAGING

Mandatory initial staging includes full blood and differential counts, biochemistry including renal and liver function tests, protein electrophoresis, calcium, LDH and β2-microglobulin, serum and urine immunofixation, FC, bone marrow aspirate with morphology and FC, bone marrow trephine biopsy, complete chest and abdominal CT scan (alternatively, in some occasions NMR), serology for HCV (if positive, including PCR for HCV-RNA in and virus genotyping), cryoglobulins and cryocrit if HCV positivity, HBV markers and HIV serology and *H. pylori* (in case of gastric symptoms).

There are no data supporting the clinical utility of abdominal sonography and PET in the routine staging of disseminated MZL [10]. Abdominal sonography could be considered in complement of CT scan for the detection of splenic focal lesions while PET scan investigation may be considered in selected cases (i.e. if clinical and/or laboratory data suggest a transformation to high-grade histology, or to guide the decision which lymph node should be biopsied).

We also recommend to perform the following exams: blood smear examination, reticulocyte count + direct antiglobulin test (DAT), gastroduodenal endoscopy + ENT evaluation if clinically indicated especially in NMZL to exclude extra-nodal localizations.

We consider autoimmune screening, FISH, and cytogenetics optional.

1.7 Consensus statement

Recommended procedures for initial staging of patients with disseminated MZL are based on well-described clinico-pathological case series of SMZL [10–15], NMZL [4, 16, 17, 18–22], and non-MALT MZL [17] (Table 1).

Level of evidence: III
Grade of recommendation: C

1.3.2 PROGNOSTIC FACTORS

The Integruppo Italiano Linfomi analysed 309 patients with SMZL and proposed a prognostic score validated in a split sample [10]. This score, using three variables (haemoglobin level <12 g/dl, LDH level greater than normal and albumin level <3.5 g/dl) allows the identification of a low-, intermediate, and high-risk group of patients [10]. Progression may be associated or not with histological transformation to DLBCL, and is more frequent in presence of peripheral lymph node involvement [23, 24].

NMZL reports have been limited to small series of patients, and specific prognostic factors are lacking.

1.8 Consensus statement

Regarding the prognostic assessment of SMZL, high lymphocyte count, abnormal levels of β2-microglobulin and LDH, or infiltration of non-haematopoietic sites have been found to be associated with shorter overall survival (OS) and progression-free survival (PFS) [11–15].

Level of evidence: IV
Grade of recommendation: C.

1.3.3 TREATMENT

For NMZL, no specific recommendation is available, but the disease is usually disseminated and treatment should be planned according to the therapeutic principles adopted for FL.

For SMZL, therapeutic options are splenectomy [12, 25], chemotherapy [10, 26, 27], rituximab alone [28–30], or rituximab–chemotherapy [15, 27, 28]. Rituximab therapy produces a quick response with a high overall (>80%) and complete (>40%) response rate with negligible toxicity but optimal schedule and long-term outcome have not been defined yet. Rituximab at 375 mg/m^2 × 4 weekly doses is a reasonable first-line therapy and a real and less traumatic alternative to splenectomy.

1.9 Consensus statement

Criteria for initiating treatment in SMZL are the following: [3] progressive or painful splenomegaly; one of the following symptomatic/progressive cytopenias: haemoglobin <10 g/dl, platelets <80 000/μl; neutrophils <1000/μl. Of note, AHA should be specifically treated.

Level of evidence V
Grade of recommendation: B

1.10 Consensus statement

Immunochemotherapy is indicated for fit patients with disseminated disease, constitutional symptoms, and/or signs of high-grade transformation.

Level of evidence: IV
Grade of recommendation: C

Regarding treatment of NMZL, in advanced stage immunochemotherapy should be the treatment of choice.

Level of evidence: IV
Grade of recommendation: C

1.11 Consensus statement

In patients with NMZL or SMZL and concurrent HCV-related chronic hepatitis who do not need immediately conventional treatment of lymphoma, antiviral treatment with pegylated interferon and ribavirin should be considered as first treatment [31–33].

Level of evidence: IV
Grade of recommendation: C

1.3.4 RESPONSE CRITERIA

Considering the peculiar clinical presentation of SMZL, we recommend to employ following specific criteria for response assessment: [3]

Complete response

- Resolution of organomegaly (spleen longitudinal diameter < 13 cm).
- Haemoglobin >12 g/dl, platelets >100 × 10^9/l, and neutrophils >1.5 × 10^9/l.
- No evidence of circulating clonal B cells by FC (light chain-restricted B cells).
- No evidence of BM infiltration detected by immunohistochemistry.
- Optional: negative DAT and normal PET scan (if positive at diagnosis).

Partial response

- Regression of ≥50% in all the measurable disease manifestations.
- No new sites of disease.
- Improvement of cytopenias.
- Decrease of infiltration and improvement of haemopoietic reserve at BM biopsy.

No response

- <10% improvement on the disease manifestations.

Progression

- >50% of measurable signs of the disease from nadir.

Relapse

- re-appearance of any measurable sign of the disease.

1.3.5 FOLLOW-UP/MONITORING

For asymptomatic patients with disseminated MZL, we recommend physical examination, blood counts, and biochemistry every 6 months. The interval between controls should be shortened in case of increasing splenomegaly and/or occurrence of cytopenia(s). A CT scan or bone marrow biopsy is not indicated unless signs of disease progression are identified. For treated patients, we recommend to check blood counts and laboratory work-up every 4–6 weeks during the first 3 months, and every 6 months thereafter.

2. Mantle cell lymphoma

2.1. Diagnosis and molecular risk factors

Diagnosis

The diagnosis of MCL is established according to the criteria of the WHO classification of haematological neoplasms and requires the detection of cyclin D1 expression or the t(11;14) translocation in the context of a mature B-cell proliferation [1]. The diagnosis of MCL, as in other lymphomas should be confirmed by review by an expert haematopathologist.

Most tumours have a classic morphology of small-medium sized cells with irregular nuclei, dense chromatin, and unapparent nucleoli. However, the tumour cells may present with a spectrum of morphological variants, including small round, marginal zone-like, pleomorphic, and blastoid cells that may raise some difficulties in the differential diagnosis with chronic lymphocytic leukaemia, MZLs, large B-cell lymphomas, or blastic haematological proliferations.

The tumour cells are clonal mature B cells that express strong immunoglobulin M/immunoglobulin D and frequently CD5 whereas CD23, CD10, and BCL6 are usually negative. Although the phenotype may be suggestive of the disease the confirmation of the diagnosis requires the demonstration of the cyclin D1 expression or the presence of the t(11;14) translocation because a number of cases may have atypical phenotypes such as CD5 negativity or expression of CD10 [34, 35]. SOX11, a transcription factor involved in neural development, has been recently identified as a reliable marker of MCL since it is expressed in ∼90% of MCL, and it is negative in virtually all B-cell lymphoid neoplasms with the exception of 30% of Burkitt lymphomas and lymphoblastic lymphomas [36, 37].

The presence of cyclin D1 positive B cells in the mantle zone of an otherwise reactive lymphoid tissue may be found incidentally in asymptomatic individuals or in lymph nodes biopsied for other pathologies. These lesions should not be considered and treated as overt lymphomas and they should be managed with caution.

A cyclin D1-negative variant of MCL has been recognized [38]. These cases have a similar morphology and phenotype but lack the expression of cyclin D1 and the t(11;14) translocation. These cases have a similar profile of gene expression and genomic alterations than conventional cyclin D1-positive MCL but the number of cases examined is still very limited [38–40]. SOX11 is expressed in cyclin D1 MCL, and therefore, it may be a reliable marker to identify this variant [36].

2.1 Consensus statement

Although the phenotype may be suggestive of the disease the confirmation of the diagnosis requires the demonstration of the cyclin D1 expression or the presence of the t(11;14) translocation.

Level of evidence: III
Grade of recommendation: A

2.2 Prognosis

The clinical evolution of MCL is very variable with some patients following a rapid course whereas others may have a relatively indolent disease. Many studies have analysed the clinical and biological prognostic parameters in MCL (See review in [41]). The most consistent biological prognostic parameter is the proliferative activity of the tumours. All different measurements of proliferation such as the mitotic index, Ki-67 index, gene expression proliferation signature, or other proliferation-related markers have revealed their prognostic value in patients with MCL with different discriminative power [41]. Most other biological parameters with prognostic value are usually related to proliferation and lose their independent significance in multivariate analysis when compared with proliferation, or have not been properly evaluated in comparison to proliferation [41–43]. The evaluation of the Ki-67 proliferative antigen is the most applicable and discriminative method to evaluate proliferation [44]. However, the major limitation to use this marker in clinical practice is the difficulties in the reproducibility of quantitative scores among different pathologists [45].

In clinical studies, the Ki67 index should be evaluated consistently by the same observer using recommended evaluating guidelines [44].

TP53 mutations have been confirmed to be of prognostic significance in large series of patients. Some studies have reported molecular and genetic alterations that maintain their prognostic prediction independently of the proliferation of the tumours. The quantitative evaluation of the expression of small panels of genes, including MYC seems to improve the prognostic value of the tumour proliferation [46, 47]. Similarly, the concomitant inactivation of the two regulatory pathways INK4a/CDK4 and ARF/p53 in MCL was associated with a poor survival that was independent of Ki-67 proliferation index [48]. Interestingly, the impact of the chromosome 3q gains and 9q losses on survival is independent of the microarray proliferation signature [39]. However, these results have not been confirmed by independent studies in larger series of patients and therefore are not recommended for clinical use.

2.2 Consensus statement

Ki67 staining is recommended in the routine practice as a prognostic indicator but the results should be evaluated with caution particularly when comparing studies from different institutions.

Level of evidence: I
Grade of recommendation: A

2.3 Indolent forms of mantle cell lymphoma

Most patients with MCL follow an aggressive clinical course. However, some studies indicate that a subset of patients may have a more indolent evolution. Studies of prognostic factors in MCL have indicated that tumours with very low proliferation fraction, limited-stage, or a mantle zone pattern may have a significant better prognosis with longer survival than the global series of patients [49, 50]. In addition, some observations recognized a subgroup of patients with MCL with an indolent behaviour that presented with a non-nodal disease, frequent splenomegaly, and a leukemic phase. These cases seem to have also different biological features including a different gene expression signature that includes SOX11 [35, 51]. This biomarker is positive in 90% of the conventional MCL and negative in a subset of MCL with a non-nodal disease and indolent clinical behaviour [35, 52]. SOX11-negative MCL with nodal disease and TP53 mutations may correspond to transformed cases and have an aggressive clinical evolution. However, the clinical and biological studies on this form of MCL are still limited. Further studies are needed to clarify these issues. As there are no markers to definitely predict indolent behaviour, a course of watch and wait under close observation may be appropriate in individual suspected cases with low tumour burden.

2.3 Consensus statement

At the present moment, it is not possible to establish definitive recommendations on the diagnosis and management of indolent MCL.

Level of evidence: IV
Grade of recommendation: C

2.4 Clinical risk factors

Since its histological identification, MCL has always been considered as a disease with a uniformly poor outcome [1, 53, 54]. This notion together with its rarity has limited efforts aimed at identifying prognostic parameters in this tumour up to the end of the millennium. With the introduction of more effective treatments, the prognosis of MCL has improved not only in terms of PFS but also in terms of OS. The study from Herrmann et al. [55] has shown that patients treated in clinical trials between 1996 and 2004 had a 5-year OS of 47% compared with 22% observed in previous studies.

The improved outcome and the perception that the clinical history of MCL was as heterogeneous as that of most lymphoproliferative disorders led to increased efforts aiming at investigating histological, clinical, and biological outcome predictors. Although several candidate prognostic markers have been investigated, only the following have been adequately addressed to warrant consideration in the clinical setting:

- histological predictors, particularly proliferative index [35, 56]
- the MCL International Prognostic Index (MIPI) [57]
- minimal residual disease (MRD) [58]

Outcome prediction based on simple clinical scores proved highly successful in disparate clinical settings, including FL and DLBCL [59–61]. Some studies have addressed the predictive value in MCL of prognostic scores 'imported' from other lymphomas but prognostic discrimination was sub-optimal [50, 62–64]. This led to the development of the MIPI in 2008 [57]. This score takes into account four parameters (age, performance status, lactate dehydrogenase, and leukocyte count). It was originally devised using a mathematical algorithm to balance the weight of different predictors, but proved effective also in its simplified version, where all predictors were categorized [57, 65]. The MIPI score allows to discriminate three prognostic subgroups: median OS was not reached in the low risk group with a 5-year OS of 60%, and it was 51 and 29 months in the intermediate risk group and the high-risk group, respectively. The MIPI score is highly applicable, showed remarkable reliability and complemented histological and PCR-based predictors [57, 58]. Moreover, several independent studies succeeded in validating the MIPI score in different clinical and therapeutic contexts, with the only exceptions observed in underpowered single-institution series [65–71] (supplementary Table S1, available at *Annals of Oncology* online).

PCR-based evaluation of MRD has also shown remarkable predictive value in MCL. Since the 1990s, MRD has been used in several studies documenting the improved performances of rituximab and Ara-C-based regimens compared with less innovative approaches [72–77] (supplementary Table S2, available at *Annals of Oncology* online). The first paper clearly documenting the prognostic value of MRD in MCL was a retrospective analysis from Pott et al. [58] mainly focusing on young patients undergoing autologous transplantation [78]. Superior evidence on the predictive value of MRD was provided by the prospective MRD analysis of two European MCL network trials. In this analysis, MRD proved as a powerful independent outcome predictor together with MIPI. Most notably the predictive value of MRD detection was observed both in young patients treated intensively and in elderly patients receiving conventional treatment and maintenance either with interferon-α (IFN-α) or rituximab.

MRD detection by PCR is not devoid of costs and is usually carried out in centralized laboratories with considerable 'know-how' in the field. These aspects still represent limitations to a widespread use of MRD results in the clinical practice. On the other hand, considerable effort is ongoing with the aim of developing standardized rules that will ensure greater applicability and reproducibility of results [79]. Moreover, further validation of the results from Pott et al. [58] will be necessary from independent patient series. Several ongoing phase III clinical studies are investigating MRD determination and results will be available in the next few years.

Based on the reliability of MRD detection in MCL, tailored treatment based on PCR results has been employed in at least two reports [80–82] (supplementary Table S3, available at *Annals of Oncology* online). In these studies, molecular relapses of autografted MCL patients were treated with rituximab. This led to re-induction of molecular remission in the vast majority of patients. In particular, based on the larger Nordic study, this seemed to provide clinical benefit to patients undergoing pre-emptive treatment [81, 82]. These results are of great importance as they might provide an effective way to deliver additional tailored treatment only in subjects who actually require it. However, the broad applicability of such approaches still need to be proven, and their efficacy need to be formally assessed in phase III trials. In general, there is some evidence that risk-adapted treatment is feasible and useful, but should not be used in the clinical practice. Its optimal use should be investigated in clinical trials.

2.4 Consensus statement

MIPI is highly applicable and has been validated in most independent series. Is the use should be encouraged in the clinical practice.

Level of evidence: I
Grade of recommendation: A

2.5 Consensus statement

MRD detection by PCR is a powerful independent predictor. However, because of limitations of applicability, reproducibility and validation its use is not recommended in routine clinical practice outside of clinical trials.

Level of evidence: IV
Grade of recommendation: C

2.5. Elderly patients

Treatment of elderly patients with MCL is a major challenge. With a median age of 60–65 years at presentation, more than half of the patients with newly diagnosed MCL fall into the category 'elderly'. Whereas the prognosis of younger patients (e.g. aged <65 years) has largely improved with the introduction of high-dose cytarabine followed by upfront autologous stem-cell transplantation (SCT), these therapeutic options are thus far considered not feasible for the higher age group.

Monitoring for MRD has shown that patients—independent of age—who have obtained a complete molecular response can enjoy longstanding event-free survival [58]. Consequently, it seems important to obtain a complete response (CR), not only for younger patients, but also for the elderly ones. Treatment of elderly patients requires careful balancing between toxicity and efficacy. A good performance status and the absence of co-morbidity are required for any treatment aiming at complete remission. Therefore, a common approach consists of an upfront stratification of patients into elderly fit and elderly frail categories [83].

2.5.1 Elderly fit patients

A randomized, controlled trial comparing combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) versus R-CHOP showed that R-CHOP was significantly superior to CHOP in terms of overall response rate (ORR; 94% versus 75%; $P = 0.0054$), complete remission rate (34% versus 7%; $P = 0.00024$), and the time to treatment failure (TTF; median, 21 versus 14 months; $P = 0.0131$). No differences were observed for PFS [84]. However, a meta-analysis comprising three randomized, controlled trials involving 260 patients with MCL summarized that the addition of rituximab improved OS in patients with MCL (HR for mortality 0.60; 95% CI 0.37–0.98) [85, 86].

Only one randomized, controlled trial has been carried out for elderly patients with MCL comparing R-CHOP with rituximab, fludarabine, cyclophosphamide (R-FC), followed by a second randomization focusing on maintenance therapy [87]. Of 560 patients, 457 were assessable for response to induction. Whereas CR rates after R-FC and R-CHOP were similar (38% versus 34% CR), the ORR was lower after R-FC (78% versus 87%; $P = 0.0508$). Progressive disease was more frequent during R-FC (15% versus 5%). The median OS was significantly inferior after R-FC (40 versus 64 months; $P = 0.0072$). More patients in the R-FC arm died due to lymphoma or to infections.

In the above-mentioned RCT, in addition to less efficacy, it appeared that haematologic grade 3–4 toxic effects were more frequent during R-FC, especially thrombocytopenia (40% versus 17%). This toxicity hampered continuation of treatment and start of maintenance therapy. Thus, the use of upfront R-FC should be discouraged. In contrast a recent trial has suggested that R-bendamustine seem to be as effective, but is better tolerated than R-CHOP [88].

In the above-mentioned RCT, 310 patients underwent the second randomization focusing on maintenance therapy. Rituximab maintenance almost doubled the remission duration compared with IFN-α (at 4 years, 57% versus 26% in remission; HR 0.54, 95% CI 0.35–0.87; $P = 0.0109$). OS did not differ between both maintenance arms ($P = 0.17$). However, the sub-cohort of R-CHOP-treated patients showed a significant advantage after rituximab maintenance (4-year OS 87% versus 57% after IFN; $P = 0.0061$).

2.5.2 Elderly frail patients

Induction therapy could consist of mild chemo-immunotherapy, for example chlorambucil combined with rituximab [89, 90]. Single-agent therapy with rituximab (four gifts at weekly intervals) for treatment-naive patients is not recommended as only very low overall responses of 27% with 3% complete remissions have been obtained [91]. Thus, treatment of elderly frail patients should aim at palliation knowing that cure will not be obtained.

2.6 Consensus statement

Rituximab should be part of any induction chemotherapy regimen.
   Level of evidence: I
   Grade of recommendation: A

2.7 Consensus statement

Rituximab maintenance (one dose every 2 months until progression) should be offered to all patients responding upon R-chemotherapy, especially R-CHOP induction.
   Level of evidence: I
   Grade of recommendation: A

2.6 Younger patients with MCL

Retrospective analysis of MD Anderson experience using intensive induction regimen in MCL has shown that rituximab increases response rate and PFS [92]. In addition, a randomized, controlled trial comparing CHOP versus R-CHOP showed that R-CHOP was significantly superior to CHOP in terms of ORR ($P = 0.0054$), complete remission rate ($P = 0.00024$), and TTF ($P = 0.0131$) [84]. A meta-analysis comprising three randomized, controlled trials involving 260 patients with MCL summarized that the addition of rituximab improved OS in patients with MCL (HR for mortality 0.60) [85].

Several phase II studies have suggested that incorporation of high-dose Ara-C in the induction chemotherapy regimen before autologous transplantation (ASCT) increase the CR rate and PFS [76, 94–96]. In a recent trial, comparing six courses of CHOP plus rituximab followed by ASCT versus alternating courses of 3 × CHOP and 3 × DHAP plus rituximab followed by a high-dose cytarabine-containing myeloablative regimen experienced a significantly longer TTF in the experimental arm ($P = 0.0384$) mainly due to a lower number of relapses, whereas the rate of ASCT-related deaths was similar in both arms, but OS was similar in both arms [97]. Impact of cytarabine on the PFS rate seems to be linked with the quality of molecular remission, which was significantly higher after induction. Thus, the results of this trial demonstrate definitively the value of adding high-dose cytarabine in the induction regimen of MCL, and suggest this new standard of treatment in young patients [97, 98].

Patients under 60–65 years are usually considered as young patients and may benefit of intensive therapies. However, this paradigm may change since a recent publication show that up to 70 years old, fit patients with no co-morbidity may benefit from intensive therapies as do young patients with similar efficacy and safety [99]. The landmark trial of the *EMCL* is the only randomized study comparing ASCT following a conditioning regimen with total body irradiation (TBI) and high-dose cyclophosphamide to maintenance therapy with IFN-α [93]. Patients responder to CHOP-like induction have a longer PFS in the ASCT arm (median, 39 versus 17 months, $P = 0.0108$). In addition, after long-term follow-up OS is

superior in the ASCT arm. This benefit is detectable in the low- and intermediate risk patients according to MIPI, who represent the vast majority of younger patients with MCL. Other phase II have shown that ASCT improves PFS in MCL [94–96]. Thus, ASCT should be carried out in first-line therapy in young patients.

Currently, conditioning regimen used in MCL are those used in other lymphoma subtypes. The benefit effect of additional rituximab for *in vivo* purging has not been demonstrated in randomized studies and/or in meta-analysis. Due to the radiosensitivity of MCL cell lines, the role of TBI remains an important question. A small retrospective study have suggested that patients who did receive a conditioning regimen with TBI, when compared with those that received BEAM did better with a significant improvement of 4-year disease-free survival (DFS; 71% versus 0%) and OS (89% versus 60%) [100]. An EBMT retrospective study showed that TBI may benefit only for the group of patients that are in partial response (PR) but not in CR [overall response (OR) 0.52 versus OR 1.03 for relapse incidence] but with no significant improvement of OS [101]. Taken together, these studies suggest that TBI is not mandatory in patients in first CR but should be discussed in patients in PR. Conditioning regimen using radioimmunoconjugate are currently investigated in the *Nordic MCL-3* study in patients who are not achieving CR after induction chemotherapy, but currently there is no clear evidence that they improve outcome of MCL (reviewed in [54]).

Another dose-intensified approach (Hyper-CVAD) with alternating CHOP-like and high-dose methotrexate/cytarabine cycles also showed very high response rates in a mono-centre phase II study. However, these excellent results could not be replicated in a multicentre approach and were never tested in a randomized, phase III trial. Moreover, this regimen is hampered by a significant therapy-associated toxicity, which led to a high drop-up rate in the multicenter trial.

Difficulties to obtain a plateau with conventional chemotherapy regimens as well as the importance of clearing MRD raise the question of maintenance therapy in MCL. Rituximab maintenance after R-CHOP induction should be considered the new standard for elderly patients with MCL, to which new regimens should be compared. However, these data should be confirmed for the young patients in the context of intensive chemotherapy and ASCT. This question is currently addressed in the *Lyma* trial, in which maintenance by rituximab versus no maintenance after treatment by four R-DHAP followed by ASCT is randomized. However, data generated are insufficient to establish treatment guidelines but encourage further investigations in this direction. Thus, so far, maintenance therapy with rituximab cannot be uniformly recommended in young patients with MCL after ASCT.

The first randomized studies documenting molecular response after combined immunochemotherapy in a significant fraction of patients were the trials of the European MCL network. These trials investigated different immunochemotherapy protocols followed by ASCT in younger patients or maintenance treatment in patients >65 years or ineligible for ASCT [58]. Molecular response resulted in a significantly improved response duration ($P < 0.0043$) and

emerged as an independent prognostic factor for response duration ($P < 0.027$). Molecular response was highly predictive for prolonged response duration independent of clinical response ($P < 0.0015$). Thus, in addition to clinical CR, molecular studies should be carried out and negativity of MRD assessed by RQ-PCR should be a goal to achieve.

Techniques of molecular biology allow detecting sub-clinical relapses. In 2006, Ladetto et al. [80] report four patients treated in first molecular relapsed after ASCT by 4–6 rituximab perfusion. All patients obtain a new molecular remission. After 3–32 months of follow-up, one patient developed a new relapse, again sensitive to rituximab. Andersen et al. published a phase II on the use of rituximab in molecular relapse after ASCT [81, 82]. Among 160 patients, 26 patients received pre-emptive rituximab, allowing a new molecular remission in 92% of patients. After this treatment the median molecular DFS was 1.5 years and the median clinical-relapse-free survival was 3.7 years. These results are promising but there's a lack of randomized trials to compare this attitude to the conventional treatment.

2.8 Consensus statement
Rituximab should be used in induction chemotherapy regimen in MCL.
   Level of evidence: I
   Grade of recommendation: A

2.9 Consensus statement
Induction with high-dose cytarabine regimen is superior to R-CHOP in young patients with MCL.
   Level of evidence: I
   Grade of recommendation: B

2.10 Consensus statement
Autologous stem transplantation should be carried out in first-line therapy.
   Level of evidence: I
   Grade of recommendation: B

2.11. Consensus statement
No conditioning regimen has shown a clear superiority; However, TBI may improve PFS in patients in PR after induction.
   Level of evidence: IV
   Grade of recommendation: C

2.12 Consensus statement
Therapy of MRD driven strategies cannot yet be recommended outside of clinical trials.
   Level of evidence: III
   Grade of recommendation: C

2.7 Molecular approaches in relapsed MCL
During the last decade, important insights have been gained into the molecular lymphomagenesis of MCL, and based on the identified signal pathways, numerous antibody-based and other targeted approaches are currently being explored in MCL [49, 102]. Especially, mTOR inhibitors, proteasome inhibitors, and immune-modulatory molecules (IMIDs) have shown high efficacy in relapsed MCL. In addition, the B-cell receptor has

Table 3. Moleculars in mantle cell lymphoma

References	Regimen/single dose	Prior lines (median)	Pat no	OR/CR	Median TTP/PFS
103	Temsirolimus 250 mg	3	35	38/3	6.5 months
	Temsirolimus 25 mg	4	29	41/4	6 months
104	Temsirolimus 25 mg, rituximab	2.5	71	59/19	9.7 months
105	Temsirolimus 175/75 mg	3.5	54	22/–	4.8 months
106	Bortezomib 1.3 mg/m^2	1	155	32/8	6.7 months
107	Bortezomib 1.5 mg/m^{2*}, R-HAD	4	8	50/25	5.5 months
108	Bortezomib 1.3 mg/m^2, R-CHOP	0	36	91/72	64% (2 years)
109	Lenalidomide 25 mg	3	57	42/21	5.7 months
102	PCI 3265 560 mg	2	51	69/16	na

*Phase III trial.

been recently identified as a crucial signal pathway in MCL, and small molecules targeting this pathway have achieved high response rates in relapsed disease even as oral monotherapy (PCI, Cal-101) [103]. Thus, due to the only short-term remissions after conventional chemotherapy, such molecular approaches have been already generally recommended in relapsed MCL [54].

Temsirolimus

The mTOR inhibitor temsirolimus has achieved response rates of 38%–41% in two phase II studies and even up to 63% in combination with rituximab [104, 105]. In the only randomized trial carried out so far, temsirolimus achieved a significant higher response rate and PFS to investigators choice of monotherapy (mostly purine analoga, gemcitabine). Accordingly, temsirolimus is the only biological registered for relapsed MCL in EU, but response was only 22% in a high-risk patient population (Table 3) [106]. Thus, future studies will focus on combined approaches to further explore the benefits of mTOR inhibition.

2.13 Consensus statement

Temsirolimus should be considered in advanced relapses (greater than second line). The recommended dose monotherapy is 75 mg, whereas data on the 175-mg induction dose are inconclusive.

Level of evidence: II
Grade of recommendation: B

Temsirolimus may be especially considered in relapsed non-fit patients.

Level of evidence: IV
Grade of recommendation: C

Bortezomib

The proteasome inhibitor has achieved response rates of 29%–46% in numerous phase II studies including a large international trial with >150 patients with relapsed MCL [107]. Accordingly, bortezomib monotherapy is registered in relapsed MCL in the United States. However, data from randomized trials are missing. Toxicity is reasonable, but median PFS is only in the range of 6–9 months. Current trials have reported long-lasting remissions in combination with immunochemotherapy, especially cytarabine-containing regimens [108, 109].

Lenalidomide

The second-generation immune modulatory compound lenalidomide has achieved response rates of 38%–50% in various phase II studies including a large international trial with 57 patients with relapsed MCL but data from randomized trials are missing [110]. Toxicity seems to be favourable besides some moderate myelotoxicity, and median PFS under continuous medication may extend 6–9 months. Current trials investigate monotherapy or consolidation after immunochemotherapy induction as explored in multiple myeloma.

2.14 Consensus statement

Bortezomib and lenalidomide may be considered in advanced relapses (greater than second line)

Level of evidence: III
Grade of recommendation: B

2.8 Allogeneic stem-cell transplantation in MCL

Up to now, the question of allogeneic SCT (allo-SCT) in MCL has only been addressed in monocentric (including several reports from the same institution) or registry based retrospective studies but no phase III or prospective trials have been carried out. Thus, the role and place of allo-SCT in MCL according to evidence-based medicine remains a challenging issue.

In the late 1990s and early 2000s, the first experiences of allo-SCT in patients with relapsed or refractory MCL used myeloablative-conditioning regimens [111–118]. Patient age and allo-SCT toxicity and efficiency were major concerns. These studies covered only small numbers of highly selected patients with MCL with median ages <50 years at the time of allo-SCT [99, 115–126] (Table 4). At D100 after allo-SCT, toxicity-related mortality (TRM) was between 0% and 32% [111–118]. The 3-year PFS rates were 41% and 55%, respectively, in Kasamon's and Khouri's reports [114, 115].

More recently, extended use of reduced-intensity conditioning regimen (RIC-allo) improved the feasibility of allogeneic transplant in patients with MCL aged >50 years [119–126]. Further investigations have dealt with RIC-allo in patients with MCL, and the number of patients has increased (with a median age at transplant >55 years in some studies) (Table 5). However, the result of RIC-allo in MCL varies much

Table 4. Results from published reports about myeloablative allo-SCT in MCL

References	Year	N	Median age (years)	Median FU	PFS or EFS	OS	TRM
114	1999	14	52 (30–60)	24 months	55% (3 years)	55% (3 years)	31%
110	2001	9	46 (26–61), *not only patients with MCL*	25 months, *not only patients with MCL*	50%, all patients	–	46%, all patients
116	2005	5	46.8 (36.5–54.8), at diagnosis	4.3 years	No relapse	100%	0%
111	2005	17	47 (36–57)	33 months, *not only patients with MCL*	44% (5 years)	49% (5 years)	19%, D100
115	2006	10	48 (37–62), *not only patients with MCL*	32 months, *not only patients with MCL*	50% (5 years)	49% (5 years)	29% (5 years)
113	2005	18	≤55	23 months	42% (3 years)	37% (3 years)	32%, D100
117	2006	10	23 patients of the entire cohort were >50	69 months	40% (2 years)	50% (2 years)	–
112	2009	11	46 (22–63), *not only patients with MCL*	5 years for all surviving patients with NHLs	18% (5 years)	18% (5 years)	–

FU, follow-up; PFS, progression-free survival; EFS, event-free survival; TRM, toxicity-related mortality.

from one study to the other. TRM at 1 year varies between 9% to 46%. Two-year OS varies between 12.8% to 65% and 2-year PFS from 0% to 60% (Table 5). Prognostic factors regarding OS, PFS, risk of relapse, and TRM also vary. The nature of conditioning regimen, disease status at transplantation, and the monocentric or multicentric nature of the reports partially explains the discrepancies. Almost all authors highlight the fact that RIC-allo can provide patients with refractory/relapsed MCL with long-term DFS, although risk of relapse is higher for patients with transplanted MCL than for other NHL patients. Interestingly, conditioning regimens with T-depletion seem to increase relapse.

Although most authors agree that RIC-allo may be curative for some patients with MCL, the paucity of literature and the relatively small number of patients per study do not allow for any strong recommendations for allo-SCT in MCL.

Is there enough evidence of graft-versus-MCL effect to support allo-SCT in MCL?

GVD-MCL is documented by several reports and supported by the following:

- long-term CR in refractory/relapsed patients is achievable after allo-SCT,
- relapsed patients can reach prolonged CR, including molecular CR, after allo-SCT, and donor lymphocyte infusions (DLIs),
- the risk of relapse increases for transplanted patients undergoing T-cell depletion, which abrogates the effect of GVD,
- withdrawal of immunosuppression can reduce tumour progression.

When is allo-SCT to be used in MCL?

Reports describe allo-SCT carried out in patients with relapse or refractory MCL. It has never been proved that allo-SCT is superior to auto-SCT, neither upfront, nor at the time of relapse. Auto-SCT and intensive chemotherapy regimens, e. g. hyper-CVAD, upfront have been shown to give lower TRM than allo-SCT.

2.15 Consensus statement
Possible GVD-MCL supports the use of allo-SCT in MCL
Level of evidence: III
Grade of recommendation: C

2.16 Consensus statement
Allo-SCT is not recommended upfront in MCL but may be considered for fit patients with MCL experiencing either relapse or refractory disease after appropriate line(s) of treatment.
Level of evidence: III
Grade of recommendation: C

3. Peripheral T-cell lymphoma

3.1 Diagnostic procedures and tools
According to the 4th edition of the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, peripheral natural killer (NK)/TCLs account for about 12% of lymphoid malignancies (supplementary Table S4, available at *Annals of*

Table 5. Results from published reports about RIC-allo-SCT in MCL

References	Year	N	Median age (years)	Disease status at the time of transplantation	Median FU	PFS or EFS	OS	TRM/toxicity
125	2002	22	52 (44–57)	Chemosensitive 73% Chemoresistant 14% and unknown	283 days, *not only patients with MCL*	48.2% (1 year) 0% (2 years)	12.8% (2 years)	13.6%, D100 46% (1 year) 82% (2 years)
122	2004	33	53.5 (32.6–69.6)	CR, *n* = 13 PR, *n* = 13	24.6 months	60% (2 years)	65% (2 years)	24% (2 years)
119	2010	70	52.2 (34.7–68.8)	CR1 30% ≥CR2 21.5% PR1 13% ≥PR2 17.5%	37 months	14% (5 years)	37% (5 years) 60% at 3 years for patients in CR at transplantation	11%, D100, NRM 18% (1 year) 21% (5 years)
120	2007	14		One CR PR, *n* = 7 Refractory, *n* = 6	33 months, *not only patients with MCL*	33% (3 years)	45% (3 years)	32% (3 years), NRM
121	2003	18	56.5 (46–64)	CR 44% PR 44% SD 12%	33 months, *not only patients with MCL*	33% (3 years)	45% (3 years)	0%, D100
123	2004	10	48 (18–73), *not only patients with MCL*	CR 40% PR 50% Refractory 10%	26 months	82% (3 years)	85.5% (3 years)	20% (3 years), NRM
118	2008	15	51 (34–64), *all patients*	All patients: 27% in CR and 49% in PR	36 months, *not only patients with MCL*	50% (3 years)	60% (3 years)	37% (3 years), NRM
91	2009	35	58 (43–68)	Chemosensitive 83%	26 months, *not only patients with MCL*	22% (3 years)	40% (3 years)	0% (3 months) and 9% (1 year)
124	2002	6			2 years	Failure-free survival: 60%	77% for all patients	

FU, follow-up; PFS, progression-free survival; EFS, event-free survival; TRM, toxicity-related mortality; NRM, non-relapse mortality; CR, complete response; PR, partial response.

Oncology online) [1]. They stem from NK- or γδ T cells that take part in the innate immune response or, more frequently, from different subsets of αβ T lymphocytes that belong to the adaptive immune reaction. Basically, these subsets correspond to naïve, effector, memory, and follicular T helper (FTH) cells. NK/TCLs include 22 entities (listed in Table S4, available at *Annals of Oncology* online, with their acronyms), 4 of which provisional. They can be recorded in every part of the World, although same varieties occur endemically (i.e. ATLL in Southern Japan and Caribbean basin, ENKTL/NT in Far East and native Americans, EATL in UK and Scandinavian countries).

In principle, their diagnosis should always be made by an expert haematopathologist and relies on a tissue bioptic specimen, unless the process is leukaemic. Cytology on fluid aspirates ought be avoided or considered insufficient. According to the criteria of the WHO Classification, the identification of NK/TCL as well as the distinction among different entities requires the integration of clinical picture, morphology, immunohistochemistry, FC, cytogenetics, and molecular biology [1].

While in B-cell lymphomas the monotypic restriction of κ and λ Ig light chains represents a surrogate of monoclonality, in TCLs the stains for CD4 and CD8 do not play the same role: in fact, they can turn double negative or double positive in a significant proportion of cases [127]. Thus, the indication of the neoplastic nature of a given T-cell population is based on morphology as well as the lack of one or more of the T-cell-associated antigens, this implying the application of a panel from CD2 to CD8. On this respect, CD5 and CD7 are the most frequently defective markers [1, 127]. In particular, the aberrant phenotypic profile, possibly integrated by the detection of clonal re-arrangement of the genes encoding for the T-cell receptor by the BIOMED-2 approach, is pivotal for the distinction between partial lymph node involvement by TCL and paracortical T-cell hyperplasia [128].

Several markers can be used for the identification of the T-cell subset, which the tumour is related to. Thus, TIA1, granzyme B, and perforin stand for a cytotoxic profile and are usefully applied to define a more aggressive subset of TCL/NOS or to construct diagnostic profiles [see, for instance HSTL, CD8+ PCAECTL or anaplastic large cell lymphoma (ALCL), both ALK+ and ALK−]. CD10, Bcl6, CXCL13, PD1, SAP, ICOS, and CCR5 are characteristically carried by FTH cells [1, 129]. Such markers can be used for the identification of neoplasms stemming from this compartment. However, in doing this, one should consider that (i) at least three of them must be detected to ascertain an FTH derivation, because a single positivity can be the result of cell plasticity;[130] (ii) their expression is not restricted to AITL, as there is now evidence that the same phenotype can be found also in tumours of the NOS type that like the former consist of clear cells [131].

Therefore, the diagnosis of AITL should be based on the characteristic clinical picture, hyperplasia of CD21+ follicular dendritic cells (FDC), arborizing high endothelial venules and B-cell component in part represented by EBV-infected blasts, besides the expression of FTH-related markers.

FoxP3 is carried by regulatory T cells: it is typically observed in the HTLV1-associated ATLL along with positivities for

CD25 and CCR4 and negativity for CD7 [1]. CD16, CD56, and CD57 in variable combinations and often in association with cytotoxic markers assist in diagnosing T-LGL, NK-CLPD, NK-AL, ENKTCL/NT, type II EATL, and HSTL [1]. Notably, true NK cases show intra-cytoplasmic positivity for the ε-chain of CD3 in contrast to TCLs that carry CD3 positivity at the cytoplasmic membrane level [1]. CD56 does also concur to the differentiation between γδ+/CD8+ PCAECTL and αβ+/SCPLTL that turn, respectively, positive and negative [1]. CD30 plays a basic role in the recognition of ALCLs, CD30+ CTLPD, and the rare CD30+ TCLs/NOS, provided with a very poor behaviour [132]. ALCLs that are systematically PAX5−, frequently EMA+ and in one-third of the cases CD45−, are further distinguished in ALK+ and ALK− depending on the occurrence or not of the t(2;5) translocation and variants [1]. These chromosomal aberrations lead to the formation of hybrid genes and fusion proteins involving the anaplastic large-cell lymphoma kinase (ALK) [1]. The latter can be revealed by specific antibodies that produce variable positivities (nuclear and cytoplasmic, intra-cytoplasmic or bound to the cytoplasmic membrane) depending on the type of fusion gene. The anomalous expression of ALK—that is provided with oncogenic properties—does not occur in ALK− ALCL. The latter is morphologically and phenotypically indistinguishable from the ALK+ form and this might reflect the occurrence of genetic aberrations other than t(2;5) and variants but producing the same downstream effects. The distinction between ALK+ and ALK− ALCLs is of practical relevance, since the former behave much better than the latter [1, 133].

In this setting, additional markers that can contribute to the diagnosis of NK/TCLs, are CD20, PAX5, CD21, CD68, and MIB1. CD20 and PAX5 allow the identification of B-cell components as can help in distinguishing ALK− ALCL from morphologically aggressive classical Hodgkin lymphoma (PAX5+); CD21 highlights the content of FDCs in AITL; CD68 reveals the histiocytic component that can at times obscure the neoplastic one (e.g. lympho-epithelioid TCL or Lennert's lymphoma and ALCL, lympho-histiocytic variant). The Ki-67 marking does represent another relevant tool, being potentially provided of prognostic value, as suggested by gene expression profiling data and the inclusion in a clinico-pathologic score [129, 134]. In particular, the latter corresponds to a modified PIT in which bone-marrow involvement is substituted by a Ki-67 rate higher than 80% [135].

Finally, the search for EBV, especially by EBER *in situ* hybridization, has an important role in PNK/TCL diagnosing. Some entities (e.g. EBV+ ANKL, EBV+ LPD-C, and ENKTL/NT) as well as a variable proportion of TCLs/NOS, in fact, show positivity of neoplastic cells for EBV [1]. Notably, all these neoplasms are characterized by a very aggressive clinical behaviour.

3.1 Consensus statement

The diagnosis of peripheral TCL requires the review by an experienced haematopathologist, the panel of mandatory markers are listed in Table 6. In the light of that fact that

Table 6. List of markers applicable to formalin-fixed, paraffin-embedded tissue sections for the diagnosis of peripheral NK-/TCLs

---

Mandatory diagnostic T-cell markers
CD2, CD3, CD4, CD5, CD7, CD8, (βF1), (TCRγ)
Optional markers for subtype distinction
Cytotoxic markers: TIA1, granzyme B, perforin
FTH markers: CD10, Bcl6, PD1, CXCL13, SAP, ICOS, CCR5
T$_{reg}$ markers: FoxP3
NK-cell markers: CD16, CD56, CD57
Activation markers: CD25, CD30
Others: CCR4, ALK, EMA, CD45
Proliferation: MIB1/Ki-67
B-cell markers: CD20, BSAP/PAX5
Follicular dendritic cells: CD21
Histiocytes and epithelioid elements: CD68/PG-M1
EBV: EBER ISH, LMP1, EBNA2

FTH, follicular helper T cell; ISH, *in situ* hybridization; TCR, T-cell receptor.

conventional microscopy may be elusive, a cytologic spectrum being commonly seen within each category.

> Level of evidence: IV
> Grade of recommendation: A

3.2 Prognostic models

In the literature published so far, the 5-year OS of TCL patients treated with doxorubicin-based chemotherapy ranges between 25% and 45% [134].

Different prognostic systems have been proposed. Morphology does not always correlate with outcome, and the significance of the international prognostic index (IPI) is controversial, although most investigators agree on its relevance [136, 137]. Moreover, different from other prognostic scores, IPI seems to predict treatment outcome in all TCL subtypes, included NK/T-cell nasal-type subtype and ATLL [138, 139]. Later on, in 2004, a clinical score called peripheral T-cell index (PIT) has been proposed to improve prognostic stratification of TCL/U patients [135]. As in IPI age, performance status and LDH were confirmed as prognostic factors but bone-marrow involvement was more relevant then advanced stage or extra-nodal sites. Recently, a modified version of this prognostic model has been proposed, where bone marrow attainment was substituted with Ki-67 (mPIT) [127]. This proposal has been made with the aim of substituting bone marrow involvement by lymphoma with a more reproducible, operator-independent variable, such as the mitotic Index assessed by immunoperoxydase. The International T-cell Project has been risen to retrospectively evaluate the prognosis of TCL in a cohort of patients in whom the diagnosis was centrally reviewed: a new model has been proposed incorporating age, performance status and platelets [140]. However, the value of these models is limited since the 5-years OS ranges between 37% and 5% for the low and high-risk classes, respectively. In patients with TCL treated with alemtuzumab, CD 52 expression has been evaluated [141].

Although preliminary studies have been done in very limited series of patients, CD 52 expression did not seemed to correlate with treatment outcome [142].

3.2 Consensus statement

IPI should be applied in peripheral TCL
> Level of evidence: IV
> Grade of recommendation: C

3.3 First-line treatment

In first-line, as well as in second-line treatment patients should be enrolled, whenever possible and feasible, in clinical trials.

First-line treatment of all TCL subtypes but NK/TCL, nasal type, should be based on Anthracycline-containing regimens such as CHOP/CHOEP and CHOP-like regimens. An exception to this assumption could probably made for enteropathy-associated T-cell lymphoma (EATL) that has been treated with a specific regimen according to the Scottish Lymphoma Group.

3.3 Consensus statement

For NK/T-cell nasal-type lymphoma the treatment should include L-asparaginase and local (nasopharyngeal) radiotherapy.
> Level of evidence: III
> Grade of recommendation: B

3.4 Consensus statement

For patients with poor-risk TCL (IPI or PIT ≥2) with a chemosensitive disease (in CR or PR) after induction chemotherapy ASCT should be delivered.
> Level of evidence: III
> Grade of recommendation: B

3.4 Relapsed TCL treatment

Incidence: Around 70% of patients with TCL are refractory to first-line therapy or relapse of their disease. Relapsing TCL can have an aggressive course with the development of life threatening complications. Hence diagnostic procedures, staging and therapeutic decision might be done in emergency and hectic situations. Histological verification should be obtained in any situation, but it would be mandatory in relapses of more than 12 months of the initial diagnosis. Immunophenotype and level of expression of some markers with therapeutic relevance should be investigated (CD30, CD52, CD4, etc). Staging and risk assessment should be carried out as per first diagnosis procedures.

The treatment choice differs depending on age and fitness. Owing to the dismal prognosis of these malignancies in this setting, an allogeneic transplant procedure is contemplated in patients either with high-risk feature or in relapse after front-line autologous SCT.

In the elderly and/or unfit patients, the treatment will be palliative, although due to the favourable therapeutic index of some new drugs used in monotherapy, these patients may be enrolled in clinical trials with these agents.

Salvage therapy before ASCT
Conventional platinum-based regimens such as DHAP, ESHAP, or ICE as used in DLBCL larger group may be offered

and are usually applied in such patients. The efficacy of these regimens in TCL is not well known as no large published study is available in these lymphomas. In general terms the response rate might not exceed 50% with a small number of CRs with a short duration of response.

The addition of gemcitabine in these combinations is based on strong activity as a single agent in cutaneous TCL [143]. The GEM-P (gemcitabine, cis-platinum, and methylprednisolone) offer a 69% ORR and a 19% CR rate in a small series of relapsing patient [144]. The GIFOX combination (gemcitabine, ifosfamide, and oxaliplatin) recently tested in untreated TCL (ALCL excluded) with 86% ORR and 67% CR could also be an alternative [145].

Alemtuzumab the anti-CD52-targeted monoclonal antibody has been tested in monotherapy in relapsing TCL and in combination with various chemotherapy (including DHAP) [146, 147]. In the salvage setting, there is a 33%–61% response rate including 33%–39% CRs, however with substantial toxicity, a sizeable rate of fatal infections including EBV reactivation. A close monitoring of patients treated with alemtuzumab-containing regimens is warranted. ALCL whose CD52 expression on tumour cells is uncommon are not candidate for alemtuzumab treatment.

New agents used in monotherapy as pralatrexate, romidepsin, and bendamustine can provide a 29%–47% ORR with 11%–29% CR rate with acceptable toxicity [148–150]. Combinations of these agents with poly-chemotherapy have not been reported yet in TCL. Such agents could still be used in monotherapy, especially in the elderly patients. Brentuximab vedotin has shown promising activity in pre-treated ALCL ALK-negative patients, with >50% of the patients attaining durable CR (see Section 3.5 "new drugs"). In any case, there is no evidence that these new agents are superior to standard salvage regimens widely used in the treatment of DLBCL.

In young and elderly fit patients, intensive salvage therapy with cure intention should be undertaken. High-dose chemotherapy with autologous SCT consolidation for chemosensitive disease is the standard salvage therapy in relapse/refractory aggressive lymphoma patients able to tolerate this therapeutic modality. This strategy is implemented in TCL on the assumption of a similar outcome as in DLBCL.

Consolidation with autologous SCT

Autologous SCT in relapsing TCL appears to provide a 40%–80% CR and a reported OS at 5 years of 40%–70% in retrospective studies (see Table 7) [151, 152].

Most studies, especially those excluding ALK-positive TCL, showed PFS curves with no plateau; a complete remission status before auto-SCT is needed for a favourable outcome. Also, high-risk patients, such as those with a high IPI score, high β2-microglobulin, and chemorefractory disease have a very poor prognosis.

No risk system has been specifically designed to select patients that benefit from this therapeutic modality and conversely that do not benefit and other alternative should be undertaken. However, Rodriguez et al. proposed a risk system based on two discrete variables aa-IPI and β2-microglobulin able to segregate three groups of patients with distinct prognosis with ASCT. In fact, patients with no presence of

Table 7. Retrospective studies of auto-SCT in relapsed T-NHL

References	N	CR (%)	OS
152	64	ND	70% (5 years)
169	29	79	39% (3 years)
170	40	80	58% (3 years)
171	36	42	48% (3 years)
172	78	68	56% (5 years)
173	28	50	69% (3 years)
174	37	76	54% (5 years)
175	24	63	33% (5 years)
176	40	60	Median 11.5 months
177	64	ND	49% (2 years)
178	123	73	45% (5 years)
153	25	ND	45% (2 years)
179	55	ND	45% (5 years)

CR, complete response; N, number of patients; ND, not done; OS, overall survival.

aa-IPI >1 and normal level of β2-microglobulin benefit substantially of these therapeutic procedures. In contrast, no benefit is obtained in patients that present both variables at relapse [153]. The quality of the response to the salvage induction regimen before the transplant might also be important as patients in CR pre-transplant according to most series do better. However, with the current information, it is not known whether patients in PR or CR differ in the outcome with the transplant. A patients refractory to front-line therapy and chemorefractory relapses have a dismal prognosis with an autologous SCT, an allogeneic SCT is being studied in this population.

Allogeneic transplantation

Based on preliminary results, allo-SCT can be considered as a therapeutic option in the setting of relapsed T-cell lymphomas. Moreover, ongoing clinical trials are testing the hypothesis of allo-SCT as upfront strategy in patients affected by high-risk disease. The advantage provided by an allo-SCT may reside on two factors:

T cells can be a good target for donor-derived immune cells: the so called 'graft-versus-lymphoma' effect; allogeneic grafts are free from tumour cell contamination. Nevertheless, whether or not the postulated graft-versus-lymphoma effect may overcome the poor prognosis of patients with T-cell NHL has not yet been established. In fact, the assessment of the role of allo-SCT is limited by the following factors:

most of the studies are retrospective; the number of patients is usually limited; different histologic subtypes are often analysed together; many studies have included both refractory and relapsed patients.

Survival after myeloablative allo-SCT has been influenced by the high non-relapse mortality (NRM). Comparative trials of auto- versus allo-SCT have some selection bias because usually patients enrolled in the allograft cohort have more advanced disease, more prior therapies and/or bone marrow involvement. However, these studies demonstrated that allografting induced a lower relapse risk when compared with

auto-SCT, but the high NRM offset any survival benefit [154, 155].

Allo-SCT with RIC regimens is usually associated to a lower NRM compared with myeloablative transplants; therefore, this strategy can be offered to the elderly or heavily pre-treated patients. In a pilot prospective study, we, first, reported the outcome of 17 patients with relapsed TCL receiving a RIC allo-SCT based on thiothepa—fludarabine—cyclophosphamide [156].

In the recent literature on RIC-allotransplant in TCL, there were some clinical results suggesting the existence of a graft-versus-T lymphoma effect, because of achievement of durable response with allografting in patients relapsed after an auto-SCT and clinical responses to DLIs.

Recently, Dodero et al. have extended and corroborated their previous observation that allografting may overcome the unfavourable prognostic impact of T-cell phenotype reporting the retrospective results of 52 patients [157]. The cumulative incidence of NRM was 12% at 5 years. In multivariate analysis, refractory disease and age >45 years were independent adverse prognostic factors.

Other retrospective studies analysed the results of particular subtypes of T-cell NHL. The British group published the data about 45 patients affected by AITL underlying that more than half of the patients may experience long-term survival after an allo-SCT [158].

More limited experiences have been reported about acute T-cell leukaemia/lymphoma and NK-lymphoma, providing the evidence that allo-SCT is feasible and can produce responses also in these patients [159–161].

3.5 Consensus statement
Second-line treatment of refractory/relapsed TCL should contain one or more than one among the following drugs: platinum, gemcitabine.
Level of evidence: IV
Grade of recommendation: B

3.6 Consensus statement
Auto-SCT should be considered for relapsed/refractory TCL-NOS as well as ALK-negative ALCL and AITL.
Level of evidence: III
Grade of recommendation: B

3.7 Consensus statement
Allo-SCT in relapsed/refractory TCL (TCL-NOS, ALCL ALK−, and AITL) proved to be the only curative treatment of this patient subset (provided by retrospective studies).
Level of evidence: III
Grade of recommendation: A

3.5 New drugs
While current salvage regimens show some promise, what is more exciting is the expanding number of new drugs being studied specifically in TCL. In particular, available drugs such as alemtuzumab and bortezomib are being included in combination regimens for TCL [146, 147, 162]. Other agents such as nelarabine, clofarabine, lenalidomide, and mTOR inhibitors or new antibodies are either being studied or have shown anedoctal activity in TCL [163–166]. While these new

uses of approved drugs are adding to an elongating list of useful or promising therapies for TCL, there are currently only two drugs specifically studied and FDA approved for the treatment of relapsed/refractory TCL:

- Pralatrexate is a novel antifolate designed for higher affinity for RFC-1 (reduced folate carrier) and increased poly-glutamation, resulting in increased internalization and retention of the drug in tumours. Promising results was seen in a phase I–II trial. A multicentre registration phase II study of pralatrexate in 111 relapsed or refractory TCL has confirmed an ORR of 29% including 11% of CR [148].
- Romidepsin, a histone deacetylase inhibitor (HDACi), followed a similar pattern to pralatrexate with early activity seen in cutaneous TCL [167]. HDACi inhibit enzymes that regulate acetylation of core nucleosomal histones as well as other proteins. An international prospective multicentre phase II of romidepsin in 130 relapsed/refractory TCL has recently completed reporting an ORR of 30% and a CR rate of 16% [149].

Monoclonal antibodies being studied for TCL include especially anti-CD30 antibodies. CD30 is uniformly expressed in ALCL and in ~30% of cases of TCL—not otherwise specified. SGN-35, an antibody-drug conjugate brentuximab vedotin (SGN-35) delivers the highly potent anti-microtubule agent monomethyl auristatin E (MMAE) to CD30-positive malignant cells by binding specifically to CD30 on the cell surface and releasing MMAE inside the cell via lysosomal degradation. In particular, a phase II international multicentre study in 58 relapsed or refractory ALCL patients showed an ORR of 87% with a CR rate of 57% [168].

3.8 Consensus statement
Refractory relapsed TCL should be enrolled, whenever possible, in phase I or II prospective clinical trials aimed at exploring the efficacy of new drugs that have shown activity in pre-clinical studies.
Level of evidence: IV
Grade of recommendation: B

conflict of interest

M. Dreyling: scientific advisory boards: Celgene, Janssen, Pfizer, Roche. Speakers honoraria: Celgene, Mundipharma,

references

1. Swerdlow S, Campo E, Harris N et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: WHO 2008.

2. Franco V, Florena AM, Iannitto E. Splenic marginal zone lymphoma. Blood 2003; 101: 2464–2472.

3. Matutes E, Oscier D, Montalban C et al. Splenic marginal zone lymphoma proposals for a revision of diagnostic, staging and treatment criteria. Leukemia 2008; 22: 487–495.

4. Raderer M, Wohrer S, Streubel B et al. Assessment of disease dissemination in gastric compared with extragastric mucosa-associated lymphoid tissue lymphoma using extensive staging: a single-center experience. J Clin Oncol 2006; 24: 3136–3141.

5. Thieblemont C, Berger F, Dumontet C et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 2000; 95: 802–806.

6. Zucca E, Conconi A, Pedrinis E et al. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. Blood 2003; 101: 2489–2495.

7. Copie-Bergman C, Gaulard P, Lavergne-Slove A et al. Proposal for a new histological grading system for post-treatment evaluation of gastric MALT lymphoma. Gut 2003; 52: 1656.

8. Stathis A, Chini C, Bertoni F et al. Long-term outcome following Helicobacter pylori eradication in a retrospective study of 105 patients with localized gastric marginal zone B-cell lymphoma of MALT type. Ann Oncol 2009; 20: 1086–1093.

9. Fischbach W, Goebeler ME, Ruskone-Fourmestraux A et al. Most patients with minimal histological residuals of gastric MALT lymphoma after successful eradication of Helicobacter pylori can be managed safely by a watch and wait strategy: experience from a large international series. Gut 2007; 56: 1685–1687.

10. Arcaini L, Lazzarino M, Colombo N et al. Splenic marginal zone lymphoma: a prognostic model for clinical use. Blood 2006; 107: 4643–4649.

11. Troussard X, Valensi F, Duchayne E et al. Splenic lymphoma with villous lymphocytes: clinical presentation, biology and prognostic factors in a series of 100 patients. Groupe Francais d'Hematologie Cellulaire (GFHC). Br J Haematol 1996; 93: 731–736.

12. Chacon J, Mollejo M, Munoz E et al. Splenic marginal zone lymphoma: clinical characteristics and prognostic factors in a series of 60 patients. Blood 2002; 100: 1648–1654.

13. Thieblemont C, Felman P, Berger F et al. Treatment of splenic marginal zone B-cell lymphoma: an analysis of 81 patients. Clin Lymphoma 2002; 3: 41–47.

14. Parry-Jones N, Matutes E, Gruszka-Westwood AM et al. Prognostic features of splenic lymphoma with villous lymphocytes: a report on 129 patients. Br J Haematol 2003; 120: 759–764.

15. Arcaini L, Paulli M, Boveri E et al. Splenic and nodal marginal zone lymphomas are indolent disorders at high hepatitis C virus seroprevalence with distinct presenting features but similar morphologic and phenotypic profiles. Cancer 2004; 100: 107–115.

16. Traverse-Glehen A, Felman P, Callet-Bauchu E et al. A clinicopathological study of nodal marginal zone B-cell lymphoma. A report on 21 cases. Histopathology 2006; 48: 162–173.

17. Berger F, Felman P, Thieblemont C et al. Non-MALT marginal zone B-cell lymphomas: a description of clinical presentation and outcome in 124 patients. Blood 2000; 95: 1950–1956.

18. Camacho FI, Algara P, Mollejo M et al. Nodal marginal zone lymphoma: a heterogeneous tumor: a comprehensive analysis of a series of 27 cases. Am J Surg Pathol 2003; 27: 762–771.

19. 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.

20. Armitage J, Weisenburger D. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1998; 16: 2780–2795.

21. Nathwani B, Anderson J, Armitage J et al. Marginal zone B-cell lymphoma: a clinical comparison of nodal and mucosa-associated lymphoid tissue types. Non-Hodgkin's Lymphoma Classification Project. J Clin Oncol 1999; 17: 2486–2492.

22. Arcaini L, Burcheri S, Rossi A et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol 2007; 18: 346–350.

23. Camacho FI, Mollejo M, Mateo MS et al. Progression to large B-cell lymphoma in splenic marginal zone lymphoma—a description of a series of 12 cases. Am J Surg Pathol 2001; 25: 1268–1276.

24. Dungarwalla M, Appiah-Cubi S, Kulkarni S et al. High-grade transformation in splenic marginal zone lymphoma with circulating villous lymphocytes: the site of transformation influences response to therapy and prognosis. Br J Haematol 2008; 143: 71–74.

25. Thieblemont C, Felman P, Callet-Bauchu E et al. Splenic marginal-zone lymphoma: a distinct clinical and pathological entity. Lancet Oncol 2003; 4: 95–103.

26. Lefrere F, Hermine O, Belanger C et al. Fludarabine: an effective treatment in patients with splenic lymphoma with villous lymphocytes. Leukemia 2000; 14: 573–575.

27. Cervetti G, Galimberti S, Sordi E et al. Significant efficacy of 2-CdA with or without rituximab in the treatment of splenic marginal zone lymphoma (SMZL). Ann Oncol 2010; 21: 851–854.

28. Tsimberidou AM, Catovsky D, Schlette E et al. Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone. Cancer 2006; 107: 125–135.

29. Kalpadakis C, Pangalis GA, Dimopoulou MN et al. Rituximab monotherapy is highly effective in splenic marginal zone lymphoma. Hematol Oncol 2007; 25: 127–131.

30. Bennett M, Sharma K, Yegena S et al. Rituximab monotherapy for splenic marginal zone lymphoma. Haematologica 2005; 90: 856–858.

31. Hermine O, Lefrere F, Bronowicki J et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 2002; 11: 89–94.

32. Saadoun D, Boyer O, Trebeden-Negre H et al. Predominance of type 1 (Th1) cytokine production in the liver of patients with HCV-associated mixed cryoglobulinemia vasculitis. J Hepatol 2004; 41: 1031–1037.

33. Kelaidi C, Rollot F, Park S et al. Response to antiviral treatment in hepatitis C virus-associated marginal zone lymphomas. Leukemia 2004; 18: 1711–1716.

34. Zanetto U, Dong H, Huang Y et al. Mantle cell lymphoma with aberrant expression of CD10. Histopathology 2008; 53: 20–29.

35. Fernandez V, Salamero O, Espinet B et al. Genomic and gene expression profiling defines indolent forms of mantle cell lymphoma. Cancer Res 2010; 70: 1408–1418.

36. Mozos A, Royo C, Hartmann E et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. Haematologica 2009; 94: 1555–1562.

37. Dictor M, Ek S, Sundberg M et al. Strong lymphoid nuclear expression of SOX11 transcription factor defines lymphoblastic neoplasms, mantle cell lymphoma and Burkitt's lymphoma. Haematologica 2009; 94: 1563–1568.

38. Fu K, Weisenburger DD, Greiner TC et al. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. Blood 2005; 106: 4315–4321.

39. Salaverria I, Zettl A, Bea S et al. Specific secondary genetic alterations in mantle cell lymphoma provide prognostic information independent of the gene expression-based proliferation signature. J Clin Oncol 2007; 25: 1216–1222.

40. Hartmann EM, Campo E, Wright G et al. Pathway discovery in mantle cell lymphoma by integrated analysis of high-resolution gene expression and copy number profiling. Blood 2010; 116: 953–961.

41. Jares P, Campo E. Advances in the understanding of mantle cell lymphoma. Br J Haematol 2008; 142: 149–165.

42. Rosenwald A, Wright G, Wiestner A et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 2003; 3: 185–197.

43. Royo C, Salaverria I, Hartmann E et al. The complex landscape of genetic alterations in mantle cell lymphoma. Semin Cancer Biol; 2011; 21(5): 322–334.

44. Klapper W, Hoster E, Determann O et al. Ki-67 as a prognostic marker in mantle cell lymphoma-consensus guidelines of the pathology panel of the European MCL Network. J Hematop 2009; 2(2): 103–111.

45. De Jong D, Rosenwald A, Chhanabhai M et al. Immunohistochemical prognostic markers in diffuse large B-cell lymphoma: validation of tissue microarray as a prerequisite for broad clinical applications—a study from the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 2007; 25: 805–812.

46. Kienle D, Katzenberger T, Ott G et al. Quantitative gene expression deregulation in mantle-cell lymphoma: correlation with clinical and biologic factors. J Clin Oncol 2007; 25: 2770–2777.

47. Hartmann E, Fernandez V, Moreno V et al. Five-gene model to predict survival in mantle-cell lymphoma using frozen or formalin-fixed, paraffin-embedded tissue. J Clin Oncol 2008; 26: 4966–4972.

48. Hernandez L, Bea S, Pinyol M et al. CDK4 and MDM2 gene alterations mainly occur in highly proliferative and aggressive mantle cell lymphomas with wild-type INK4a/ARF locus. Cancer Res 2005; 65: 2199–2206.

49. Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: perspectives for new targeted therapeutics. Nat Rev Cancer 2007; 7: 750–762.

50. Tiemann M, Schrader C, Klapper W et al. Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol 2005; 131: 29–38.

51. Orchard J, Garand R, Davis Z et al. A subset of t(11;14) lymphoma with mantle cell features displays mutated IgVH genes and includes patients with good prognosis, nonnodal disease. Blood 2003; 101: 4975–4981.

52. Ondrejka SL, Lai R, Kumar N, Smith SD, Hsi ED. Indolent mantle cell leukemia: clinicopathologic variant characterized by isolated lymphocytosis, interstitial bone marrow involvement, kappa light chain restriction, and good prognosis. Haematologica 2011; 96(8): 1121–1127.

53. Nickenig C, Dreyling M, Hoster E et al. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group. Cancer 2006; 107: 1014–1022.

54. Dreyling M, Hiddemann W. Current treatment standards and emerging strategies in mantle cell lymphoma. American Society of Hematology Education Program Book. Hematology 2009: 542–554.

55. Herrmann A, Hoster E, Zwingers T et al. Improvement of overall survival in advanced stage mantle cell lymphoma. J Clin Oncol 2009; 27: 511–518.

56. Determann O, Hoster E, Ott G et al. Ki-67 predicts outcome in advanced-stage mantle cell lymphoma patients treated with anti-CD20 immunochemotherapy: results from randomized trials of the European MCL Network and the German Low Grade Lymphoma Study Group. Blood 2008; 111(4): 2385–2387.

57. Hoster E, Dreyling M, Klapper W et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008; 111: 558–565.

58. Pott C, Hoster E, Delfau-Larue MH et al. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. Blood 2010; 115: 3215–3223.

59. Solal-Céligny P, Roy P, Colombat P et al. Follicular lymphoma international prognostic index. Blood 2004; 104: 1258–1265.

60. Federico M, Bellei M, Marcheselli L et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009; 27: 4555–4562.

61. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987–994.

62. Velders GA, Kluin-Nelemans JC, De Boer CJ et al. Mantlecell lymphoma: a population-based clinical study. J Clin Oncol 1996; 14: 1269–1274.

63. Argatoff LH, Connors JM, Klasa RJ et al. Mantle cell lymphoma: a clinicopathologic study of 80 cases. Blood 1997; 89: 2067–2078.

64. Møller MB, Pedersen NT, Christensen BE. Mantle cell lymphoma: prognostic capacity of the Follicular Lymphoma International Prognostic Index. Br J Haematol 2006; 133: 43–49.

65. Geisler CH, Kolstad A, Laurell A et al. The Mantle Cell Lymphoma International Prognostic Index (MIPI) is superior to the International Prognostic Index (IPI) in predicting survival following intensive first-line immunochemotherapy and autologous stem cell transplantation (ASCT). Blood 2010; 115(8): 1530–1533.

66. Shah JJ, Fayad L, Romaguera J. Mantle Cell International Prognostic Index (MIPI) not prognostic after R-hyper-CVAD. Blood 2008; 112(6): 2583; Author reply 2583–2584.

67. Salek D, Vasova I, Pytlik R et al. Mantle Cell Lymphoma International Prognostic Score is valid and confirmed in unselected cohort of patients treated in rituximab era. Blood 2008; 112(Suppl. 1): Abstract 3745.

68. Eve HE, Gambell J, Smith P et al. The Simplified Mantle-Cell Lymphoma International Prognostic Index predicts overall survival but not progression-free survival in patients with mantle-cell lymphoma treated with fludarabine and cyclophosphamide +/− rituximab: results of a randomized phase II trial. Leuk Lymphoma 2009; 50(10): 1709–1711.

69. van de Schans SA, Janssen-Heijnen ML, Nijziel MR et al. Validation, revision and extension of the Mantle Cell Lymphoma International Prognostic Index in a population-based setting. Haematologica 2010; 95(9): 1503–1509.

70. Chiappella A, Puccini B, Ferrero S et al. Retrospective analysis of 206 mantle cell lymphoma patients at diagnosis: Mantle Cell International Prognostic Index (MIPI) is a good predictor of death event in patients treated either with rituximab-chemotherapy or rituximab-high-dose-chemotherapy. Blood 2010; 116(Suppl. 1): Abstract 1784.

71. Budde LE, Guthrie KA, Till BG et al. Mantle cell lymphoma International Prognostic Index but not pretransplantation induction regimen predicts surviva for patients with mantle-cell lymphoma receiving high-dose therapy and autologous stem-cell transplantation. J Clin Oncol 2011; 29(22): 3023–3029.

72. Magni M, Di Nicola M, Devizzi L et al. Successful in vivo purging of CD34-containing peripheral blood harvests in mantle cell and indolent lymphoma: evidence for a role of both chemotherapy and rituximab infusion. Blood 2000; 96: 864–869.

73. Howard OM, Gribben JG, Neuberg DS et al. Rituximab and CHOP induction therapy for newly diagnosed mantle-cell lymphoma: molecular complete responses are not predictive of progression-free survival. J Clin Oncol 2002; 20(5): 1288–1294.

74. Gianni AM, Magni M, Martelli M et al. Long-term remission in mantle cell lymphoma following high-dose sequential chemotherapy and in vivo rituximab-purged stem cell autografting (R-HDS regimen). Blood 2003; 102: 749–755.

75. Brugger W, Hirsch J, Grünebach F et al. Rituximab consolidation after highdose chemotherapy and autologous blood stem cell transplantation in follicular and mantle cell lymphoma: a prospective, multicenter phase II study. Ann Oncol 2004; 15: 1691–1698.

76. Geisler CH, Kolstad A, Laurell A et al. Long-term progression—free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivopurged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood 2008; 112: 2687–2693.

77. Sachanas S, Pangalis GA, Vassilakopoulos TP et al. Combination of rituximab with chlorambucil as first line treatment in patients with mantle cell lymphoma: a highly effective regimen. Leuk Lymphoma 2011; 52(3): 387–393.

78. Pott C, Schrader C, Gesk S et al. Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma. Blood 2006; 107: 2271–2278.

79. van der Velden VH, Cazzaniga G, Schrauder A et al. Analysis of minimal residual disease by Ig/TCR gene rearrangements: guidelines for interpretation of real-time quantitative PCR data. Leukemia 2007; 21: 604–611.

80. Ladetto M, Magni M, Pagliano G et al. Rituximab induces effective clearance of minimal residual disease in molecular relapses of mantle cell lymphoma. Biol Blood Marrow Transplant 2006; 12: 1270–1276.

81. Andersen NS, Pedersen LB, Laurell A et al. Pre-emptive treatment with rituximab of molecular relapse after autologous stem cell transplantation in mantle cell lymphoma. J Clin Oncol. 2009; 27: 4365–4370.

82. Geisler CH. Front-line treatment of mantle cell lymphoma. Haematol 2010; 95(8): 1241–1243.

83. Kluin-Nelemans HC, Doorduijn JK. Treatment of elderly patients with mantle cell lymphoma. Semin Hematol 2011; 48: 208–213.

84. Lenz G, Dreyling M, Hoster E et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005; 23(9): 1984–1992.

85. Schulz H, Bohlius J, Skoetz N et al. Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Cochrane Database Syst Rev 2007; (4): CD003805.

86. Schulz H, Bohlius JF, Trelle S et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007; 99(9): 706–714.

87. Kluin-Nelemans HC, Hoster E, Hermine O et al. Treatment of older patients with mantle cell lymphoma. NEJM 2012; 367(6): 520–531.

88. Rummel MJ, Niederle N, Maschmeyer G et al. Bendamustin plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: final results of a randomized phase III study of the StiL. Blood 2009; 114: Abstract 405.

89. Ghielmini M, Zucca E. How I treat mantle cell lymphoma. Blood 2009; 114(8): 1469–1476.

90. Bauwens D, Maerevoet M, Michaux L et al. Activity and safety of combined rituximab with chlorambucil in patients with mantle cell lymphoma. Br J Haematol 2005; 131(3): 338–340.

91. Ghielmini M, Hsu Schmitz SF, Cogliatti S et al. Effect of single-agent rituximab given at the standard schedule or as prolonged treatment in patients with mantle cell lymphoma: a study of the Swiss Group for Clinical Cancer Research (SAKK). J Clin Oncol 2005; 23: 705–711.

92. Tam CS, Bassett R, Ledesma C et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood 2009; 113(18): 4144–4152.

93. Dreyling M, Lenz G, Hoster E et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood 2005; 105(7): 2677–2684.

94. Rodriguez J, Gutierrez A, Obrador-Hevia A et al. Therapeutic concepts in mantle cell lymphoma. Eur J Hematol 2010; 85: 371–386.

95. Goy A, Kahl B. Mantle cell lymphoma: the promise of new treatment options. Crit Rev Oncol Hematol 2011; 80(1): 69–86.

96. Harel S, Delarue R, Ribrag V et al. Treatment of younger patients with mantle cell lymphoma. Sem Hematol 2011; 48(3): 194–208.

97. Hermine O, Hoster E, Walewski J et al. Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: results of the MCL younger trial of the European Mantle Cell Lymphoma Network (*MCL net*). Blood (ASH Annual Meeting Abstracts) 2010; 116: Abstract 110.

98. Pott C, Hoster E, Beldjord K et al. R-CHOP/R-DHAP Compared to R-CHOP induction followed by high dose therapy with autologous stem cell transplantation induces higher rates of molecular remission in MCL: results of the *MCL Younger* Intergroup Trial of the *European MCL Network*. Blood (ASH Annual Meeting Abstracts) 2010; 116: Abstract 965.

99. Jantunen E, Canals C, Attal M et al. Autologous stem-cell transplantation in patients with mantle cell lymphoma beyond 65 years of age: a study from the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol 2012: 23(1): 166–171.

100. Milpied N, Gaillard F, Moreau P et al. High-dose therapy with stem cell transplantation for mantle cell lymphoma: results and prognostic factors, a single center experience. Bone Marrow Transplant 1998; 22(7): 645–650.

101. Rubio MT, Boumendil A, Luan JJ et al. Is there still a place for total body irradiation (TBI) in the conditioning regimen of autologous stem cell transplantation in mantle cell lymphoma?: a retrospective study from the lymphoma working party of the EBMT. Blood (ASH Annual Meeting Abstracts) 2010; 116: Abstract 688.

102. Pérez-Galán P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. Blood 2011; 117(1): 26–38.

103. Wang L, Martin P, Blum KA et al. The Bruton's kinas inhibitor PCI-32765 is highly active as single-agent therapy in previously-treated mantle cell lymphoma (MCL): preliminary results of a phase II trial. Blood (ASH Annual Meeting Abstracts) 2011: Abstract 442.

104. Ansell SM, Inwards DJ, Rowland KM et al. Low-dose, single-agent temsirolimus for relapsed mantle cell lymphoma: a phase 2 trial in the North Central Cancer Treatment Group. Cancer 2008; 113(3): 508–514.

105. Ansell SM, Tang H, Kurtin PJ et al. Temsirolimus and rituximab in patients with relapsed or refractory mantle cell lymphomas: a phase II study. Lancet 2011; 12: 361–368.

106. Hess G, Herbrecht R, Romaguera J et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. JCO 2009; 27: 3822–3829.

107. Goy A, Bernstein SH, Kahl BS et al. Bortezomib in patients with relapsed or refractory mantle cell lymphoma: updated time-to-event analyses of the multicenter phase 2 PINNACLE study. Ann Oncol 2009; 20: 520–525.

108. Weigert O, Weidmann E, Mück R et al. A novel regimen combining high dose cytarabine and bortezomib has activity in multiple relapsed and refractory mantle cell lymphoma—long term results of a multicenter observation study. Leuk Lymphoma 2009; 50: 716–722.

109. Ruan J, Martin P, Furmann M et al. Bortezomib plus CHOP-rituximab for previously untreated diffuse large B-cell lymphoma an mantle cell lymphoma. JCO 2011; 29: 690–697.

110. Witzig TE, Vose JM, Zinzani PL et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non Hodgkin lymphoma. Ann Oncol 2011; 22: 1622–1627.

111. Berdeja JG, Jones RJ, Zahurak ML et al. Allogeneic bone marrow transplantation in patients with sensitive low-grade lymphoma or mantle cell lymphoma. Biol Blood Marrow Transplant 2001; 7: 561–567.

112. Ganti AK, Bierman PJ, Lynch JC et al. Hematopoietic stem cell transplantation in mantle cell lymphoma. Ann Oncol 2005; 16: 618–624.

113. Hamadani M, Benson DM, Jr, Hofmeister CC et al. Allogeneic stem cell transplantation for patients with relapsed chemorefractory aggressive non-hodgkin lymphomas. Biol Blood Marrow Transplant 2009; 15: 547–553.

114. Kasamon YL, Jones RJ, Diehl LF et al. Outcomes of autologous and allogeneic blood or marrow transplantation for mantle cell lymphoma. Biol Blood Marrow Transplant 2005; 11: 39–46.

115. Khouri IF, Lee MS, Romaguera J et al. Allogeneic hematopoietic transplantation for mantle-cell lymphoma: molecular remissions and evidence of graft-versus-malignancy. Ann Oncol 1999; 10: 1293–1299.

116. Laudi N, Arora M, Burns L et al. Efficacy of high-dose therapy and hematopoietic stem cell transplantation for mantle cell lymphoma. Am J Hematol 2006; 81: 519–524.

117. Rifkind J, Mollee P, Messner HA, Lipton JH. Allogeneic stem cell transplantation for mantle cell lymphoma—does it deserve a better look? Leuk Lymphoma 2005; 46: 217–223.

118. Rodriguez R, Nademanee A, Ruel N et al. Comparison of reduced-intensity and conventional myeloablative regimens for allogeneic transplantation in non-Hodgkin's lymphoma. Biol Blood Marrow Transplant 2006; 12: 1326–1334.

119. Armand P, Kim HT, Ho VT et al. Allogeneic transplantation with reduced-intensity conditioning for Hodgkin and non-Hodgkin lymphoma: importance of histology for outcome. Biol Blood Marrow Transplant 2008; 14: 418–425.

120. Cook G, Smith GM, Kirkland K et al. Outcome following reduced-intensity allogeneic stem cell transplantation (RIC AlloSCT) for relapsed and refractory mantle cell lymphoma (MCL): a study of the British society for blood and marrow transplantation. Biol Blood Marrow Transplant 2010; 16: 1419–1427.

121. Corradini P, Dodero A, Farina L et al. Allogeneic stem cell transplantation following reduced-intensity conditioning can induce durable clinical and molecular remissions in relapsed lymphomas: pre-transplant disease status and histotype heavily influence outcome. Leukemia 2007; 21: 2316–2323.

122. Khouri IF, Lee MS, Saliba RM et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol 2003; 21: 4407–4412.

123. Maris MB, Sandmaier BM, Storer BE et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood 2004; 104: 3535–3542.

124. Morris E, Thomson K, Craddock C et al. Outcomes after alemtuzumab-containing reduced-intensity allogeneic transplantation regimen for relapsed and refractory non-Hodgkin lymphoma. Blood 2004; 104: 3865–3871.

125. Perez-Simon JA, Kottaridis PD, Martino R et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. Blood 2002; 100: 3121–3127.

126. Robinson SP, Goldstone AH, Mackinnon S et al. Chemoresistant or aggressive lymphoma predicts for a poor outcome following reduced-intensity allogeneic progenitor cell transplantation: an analysis from the Lymphoma Working Party of the European Group for Blood and Bone Marrow Transplantation. Blood 2002; 100: 4310–4316.

127. Went P, Agostinelli C, Gallamini A et al. Marker expression in peripheral T-cell lymphoma: a proposed clinical-pathologic prognostic score. J Clin Oncol 2006; 24: 2472–2479.

128. Brüggemann M, White H, Gaulard P et al. Powerful strategy for polymerase chain reaction-based clonality assessment in T-cell malignancies Report of the BIOMED-2 Concerted Action BHM4 CT98–3936. Leukemia 2007; 21: 215–221.

129. Iqbal J, Weisenburger DD, Greiner TC et al. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. Blood 2010; 115: 1026–1036.

130. Laurent C, Fazilleau N, Brousset P. A novel subset of T-helper cells: follicular T-helper cells and their markers. Haematologica 2010; 95: 356–358.

131. Agostinelli C, Hartmann S, Klapper W et al. Peripheral T-cell lymphomas with follicular T-helper phenotype: a new basket or a distinct entity? Revising Karl Lennert's personal archive. Histopathology 2011; 59(4): 679–691.

132. Savage KJ, Harris NL, Vose MJ et al. ALK-negative anaplastic large-cell lymphoma (ALCL) is clinically and immunophenotypically different from both ALK-positive ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008; 111: 5496–5504.

133. Cuadros M, Dave SS, Jaffe ES et al. Identification of a proliferation signature related to survival in nodal peripheral T-cell lymphomas. J Clin Oncol 2007; 25: 3321–3329.

134. Abouyabis AN, Shenoy PJ, Flowers J, Lechowicz MJ. Response and survival rates in patients with peripheral T-cell lymphoma treated with anthracyclines-based regimens: a comprehensive meta-analysis [Abstract]. Blood 2007; 110 (11): Abstract 3452.

135. Gallamini A, Stelitano C, Calvi R et al. Peripheral T-cell lymphoma unspecified (TCL-U): a new prognostic model from a retrospective multicentric clinical study. Blood 2004; 103: 2474–2479.

136. Vose J, Armitage J, Weisemburger D. International peripheral T-cell natural killer/T-cell lymphoma study: pathology findings and clinical outcome. J Clin Oncol 2008; 26(25): 4124–4139.

137. Foss F, Zinzani PL, Vose JM et al. Peripheral T-cell lymphoma. Blood 2011; 117(25): 6756–6767.

138. Schmitz N, Trümper L, Ziepert M et al. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010; 116: 3418–3425.

139. Suzumiya J, Ohshima K, Tamura K et al. for the International Peripheral T-cell Lymphoma Project The International Prognostic Index predicts outcome in aggressive adult T-cell leukemia/lymphoma: analysis of 126 patients from the International Peripheral T-cell Lymphoma Project. Ann Oncol 2009; 20: 715–721.

140. Vose JM. International peripheral T-cell lymphoma (TCL) clinical and pathologic review project: poor outcome by prognostic indices and lack of efficacy with anthracyclines. Blood 2005; 106: Abstract 811.

141. Rodig SJ, Abramson JS, Pinkus GS et al Heterogeneous CD52 Expression among hematologic neoplasms: implications for the use of alemtuzumab (CAMPATH-1H). Clin Canc Res 2006; 12(23): 7174–7179.

142. Gallamini A, Zaja F, Patti C et al. Alemtuzumab (Campath-1H) and CHOP chemotherapy as first-line treatment of peripheral T-cell lymphoma: results of a GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) prospective multicenter trial. Blood 2007; 110: 2316–2323.

143. Zinzani PL, Baliva G, Magagnoli M et al. Gemcitabine treatment in pretreated cutaneous T-cell lymphoma: experience in 44 patients. J Clin Oncol 2000; 18(13): 2603–2606.

144. Arkenau HT, Chong G, Cunningham D et al. Gemcitabine, cisplatin and methylprednisolone for the treatment of patients with peripheral T-cell lymphoma: the Royal Marsden Hospital experience. Haematologica 2007; 92(2): 271–272.

145. Corazzelli G, Frigeri F, Marcacci G et al. Gemcitabine, ifosfamide, oxaliplatin (GIFOX) as first-line treatment in high-risk peripheral T-cell/NK lymphomas: a phase II trial. Blood 2010; 116: Abstract 2829.

146. Enblad G, Hagberg H, Erlanson M et al. A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas. Blood 2004; 103(8): 2920–2924.

147. Zinzani PL, Alinari L, Tani M et al. Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma. Haematologica 2005; 90(5): 702–703.

148. O'Connor OA, Pro B, Pinter-Brown L et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. J Clin Oncol 2011; 29(9): 1182–1189.

149. Coiffier B, Pro B, Prince HM et al. Results from a pivotal open-label phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy. J Clin Oncol 2012; 30: 631–636.

150. Damaj G, Gressin R, Bouabdallah K et al. Preliminary results from an open-label, multicenter, phase II study of bendamustine in relapsed or refractory T-cell lymphoma from the french GOELAMS group : the BENTLY trial. Ann Oncol 2011; 22(Suppl 4): iv125.

151. Rodriguez J, Conde E, Gutierrez A et al. The results of consolidation with autologous stem-cell transplantation in patients with peripheral T-cell lymphoma (TCL) in first complete remission: the Spanish Lymphoma and Autologous Transplantation Group experience. Ann Oncol 2007; 18(4): 652–657.

152. d'Amore F, Jantunen E, Relander T. Hemopoietic stem cell transplantation in T-cell malignancies: who, when, and how? Curr Hematol Malig Rep 2009; 4(4): 236–244.

153. Rodriguez J, Conde E, Gutierrez A et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. Haematologica 2007; 92(8): 1067–1074.

154. Dhedin N, Giraudier S, Gaulard P et al. Allogeneic bone marrow transplantation in aggressive non-Hodgkin's lymphoma (excluding Burkitt and lymphoblastic lymphoma): a series of 73 patients from the SFGM database. Societ Francaise de Greffe de Moelle. Br J Haematol 1999; 107(1): 154–161.

155. Doocey RT, Toze CL, Connors JM et al. Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma. Br J Haematol 2005; 131(2): 223–230.

156. Corradini P, Dodero A, Zallio F et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol 2004; 22(11): 2172–2176.

157. Dodero A, Spina F, Narni F et al. Allogeneic transplantation following a reduced-intensity conditioning regimen in relapsed/refractory peripheral T-cell lymphomas (TCL): long-term remissions and response to donor lymphocyte infusions support the role of a graft-versus-lymphoma effect. Leukemia 2012; 26(3): 520–526.

158. Kyriakou C, Canals C, Finke J et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol 2009; 27(24): 3951–3958.

159. Choi I, Tanosaki R, Uike N et al. Long-term outcomes after hematopoietic SCT for adult T-cell leukemia/lymphoma: results of prospective trials. Bone Marrow Transplant 2011; 46(1): 116–118.

160. Murashige N, Kami M, Kishi Y et al. Allogeneic haematopoietic stem cell transplantation as a promising treatment for natural killer-cell neoplasms. Br J Haematol 2005; 130(4): 561–567.

161. Ennishi D, Maeda Y, Fujii N et al. Allogeneic hematopoietic stem cell transplantation for advanced extranodal natural killer/T-cell lymphoma, nasal type. Leuk Lymphoma 2011; 52(7): 1255–1261.

162. Zinzani PL, Musuraca G, Tani M et al. Phase II trial of proteasome inhibitor bortezomib in patients with relapsed or refractory cutaneous T-cell lymphoma. J Clin Oncol 2007; 25: 4293–4297.

163. Czuczman MS, Porcu P, Johnson J et al. Results of a phase II study of 506U78 in cutaneous T-cell lymphoma and peripheral T-cell lymphoma: CALGB 59901. Leuk Lymphoma 2007; 48: 97–103.

164. D'Amore F, Radford J, Relander T et al. Phase II trial of zanolimumab (HuMax-CD4) in relapse or refractory non-cutaneous peripheral T cell lymphoma. Br J Haematol 2010; 150: 565–573.

165. Zinzani PL, Pellegrini C, Broccoli A et al. Lenalidomide monotherapy for relapsed/refractory peripheral T-cell lymphoma not otherwise specified. Leuk Lymphoma 2011; 52(8): 1585–1588.

166. Dueck G, Chua N, Prasad A et al. Interim report of a phase 2 clinical trial of lenalidomide for T-cell non-Hodgkin lymphoma. Cancer 2010; 116(19): 4541–4548.

167. Piekarz RL, Robey RW, Zhan Z et al. T-cell lymphoma as a model for the use of histone deacetylase inhibitors in cancer therapy: impact of depsipeptide on molecular markers, therapeutic targets, and mechanisms or resistance. Blood 2004; 103: 4636–4643.

168. Shustov AR, Advani R, Brice P et al. Complete remissions with brentuximab vedotin (SGN-35) in patients with relapse or refractory systemic anaplastic large cell lymphoma. Blood 2010; 116: Abstract 961.

169. Fanin R, Ruiz de Elvira MC, Sperotto A et al. Autologous stem cell transplantation for T and null cell CD30-positive anaplastic large cell lymphoma: analysis of 64 adult and paediatric cases reported to the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 1999; 23(5): 437–442.

170. Rodriguez J, Munsell M, Yazji S et al. Impact of high-dose chemotherapy on peripheral T-cell lymphomas. J Clin Oncol 2001; 19(17): 3766–3770.

171. Blystad AK, Enblad G, Kvaloy S et al. High-dose therapy with autologous stem cell transplantation in patients with peripheral T cell lymphomas. Bone Marrow Transplant 2001; 27(7): 711–716.

172. Song KW, Mollee P, Keating A, Crump M. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol 2003; 120(6): 978–985.

173. Rodriguez J, Caballero MD, Gutierrez A et al. High dose chemotherapy and autologous stem cell transplantation in patients with peripheral T-cell lymphoma not achieving complete response after induction chemotherapy. The GEL-TAMO experience. Haematologica 2003; 88: 1372–1377.

174. Jagasia M, Morgan D, Goodman S et al. Histology impacts the outcome of peripheral T-cell lymphomas after high dose chemotherapy and stem cell transplant. Leuk Lymphoma 2004; 45(11): 2261–2267.

175. Jantunen E, Wiklund T, Juvonen E et al. Autologous stem cell transplantation in adult patients with peripheral T-cell lymphoma: a nation-wide survey. Bone Marrow Transplant 2004; 33(4): 405–410.

176. Kewalramani T, Zelenetz AD, Teruya-Feldstein J et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol 2006; 134(2): 202–207.

177. Kim MK, Kim S, Lee SS et al. High-dose chemotherapy and autologous stem cell transplantation for peripheral T-cell lymphoma: complete response at transplant predicts survival. Ann Hematol 2007; 86(6): 435–442.

178. Feyler S, Prince HM, Pearce R et al. The role of high-dose therapy and stem cell rescue in the management of T-cell malignant lymphomas: a BSBMT and ABMTRR study. Bone Marrow Transplant 2007; 40(5): 443–450.

179. Smith SD, Bolwell BJ, Rybicki LA et al. Autologous hematopoietic stem cell transplantation in peripheral T-cell lymphoma using a uniform high-dose regimen. Bone Marrow Transplant 2007; 40(3): 239–243.