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Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Follicular lymphomas (FLs) are the second most frequent subtype of nodal lymphoid malignancies in Western Europe. The annual incidence of this disease has rapidly increased during recent decades and has risen from 2–3/100 000 during the 1950s to 5/100 000 recently [1].

diagnosis and pathology/molecular biology

Diagnosis should be based on a surgical specimen/excisional lymph node biopsy. Core biopsies should only be carried out in patients without easily accessible lymph nodes (e.g. retroperitoneal bulk), keeping in mind the possible heterogeneity of FL grading can be difficult to appreciate on core biopsies and re-biopsy may be required if the material is not adequate. Fine needle aspirations are inappropriate for a reliable diagnosis.

The histological report should give the diagnosis according to the World Health Organization (WHO) classification. Grading of lymph node biopsies is carried out according to the number of blasts/high-power field (Table 1). FL grade 3A (with sheets of blasts) is considered an aggressive lymphoma and treated as such [2], whereas grade 1, 2 and 3A should be treated as indolent disease [3]. Review, especially of grade 3A or 3B, by an expert haematopathologist is advised if the infiltration pattern is atypical (diffuse areas, even with small cells).

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staging and risk assessment

Since treatment largely depends on the stage of the disease, initial staging should be thorough, particularly in the small proportion of patients with early stages I and II (10%–15%) (Table 2). Initial work-up should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy (Table 3). Positron emission tomography (PET)–CT improves the accuracy of staging for nodal and extranodal sites and thus should be recommended for routine staging in FL [IV, C] [4]. This is particularly important to confirm localised stage I/II before involved-field radiotherapy.

A complete blood count, routine blood chemistry including lactate dehydrogenase (LDH), β2 microglobulin and uric acid as well as screening tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C are required. The staging is carried out according to the Ann Arbor classification system (Table 2), with mention of bulky disease (>7 cm) when appropriate.

For prognostic purposes, a 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI, Table 4) has been established [I, A] [6]. A revised FLIPI 2 (incorporating β2 microglobulin, diameter of largest lymph node, bone marrow involvement and haemoglobin level) has been suggested for patients requiring treatment which may be more informative on progression-free survival (PFS) [7].

Extended gene-expression profiling of tumour biopsy suggests a more favourable clinical course in cases with infiltrating T cells, in comparison with cases with non-specific macrophage bystander cells [5]. Recently, a clinicogenetic risk score (m7-FLIPI) has been proposed based on mutation status of seven candidate genes (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP* and *CARD11*) [8]; however, none of the techniques are yet established in clinical routine practice. In addition, several recent immunohistochemistry studies have reported conflicting data; hence, biological parameters are still investigational for

Table 1. Grading of follicular lymphoma (FL)

Grade	Description
1	≤5 blasts/high-power field
2	6–15 blasts/high-power field
3A	>15 blasts/high-power field, centroblasts with intermingled centrocytes
3B	>15 blasts/high-power field, pure sheets of blasts

Table 2. Ann Arbor classification

Stage	Area of involvement
I (I_E)	One lymph node region or extralymphatic site (I_E)
II (II_E)	Two or more lymph node regions or at least one lymph node region plus a localised extralymphatic site(II_E) on the same side of the diaphragm
III (III_E, III_S)	Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (III_E) or spleen (III_S)
IV	Diffuse or disseminated extralymphatic organ involvement

A: no symptoms.
B: unexplained fever of >38°C, drenching night sweats; or loss of >10% body weight within 6 months.

Table 3. Diagnostic work-up

History	B symptoms
Physical examination	Peripheral lymph nodes, liver, spleen
Laboratory work-up	Blood and differential count Optional: FACS on peripheral blood, PCR for BCL2 rearrangement LDH, uric acid Electrophoresis (optional: immune fixation) β_2 microglobulin (FLIPI 2)
Serology	Hepatitis B, C and HIV serology
Imaging	CT neck, chest, abdomen, pelvis Recommended: PET–CT[a] Optional: abdominal ultrasound
Bone marrow[b]	Histology Cytology Optional: FACS, PCR for BCL2 rearrangement
Toxicity	Electrocardiogram, cardiac ultrasound (before anthracyclines, ASCT) Creatinine clearance Reproductive counselling in young patients

[a]To confirm localised disease or in the case of suspected transformation.
[b]If clinically indicated.
FACS, fluorescence-activated cell sorting; PCR, polymerase chain reaction; LDH, lactate dehydrogenase; FLIPI 2, Follicular Lymphoma International Prognostic Index 2; HIV, human immunodeficiency virus; CT, computed tomography; PET–CT, positron emission tomography–computed tomography; ASCT, autologous stem cell transplantation.

Table 4. 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI) risk factors

Parameter	Definition of risk factors	
	FLIPI 1	FLIPI 2
Nodal sites	>4 lymph node regions (definition in [5])	Long diameter of largest lymph node >6 cm
Age	>60 years	>60 years
Serum marker	Elevated LDH	Elevated β2 microglobulin
Stage	Advanced (III–IV according to Ann Arbor classification)	Bone marrow involvement
Haemoglobin	<12 g/dl	<12 g/dl

0–1 risk factors, low risk; 2 risk factors, intermediate risk; 3–5 risk factors, high risk.
LDH, lactate dehydrogenase.

Table 5. High tumour burden criteria in FL [Groupe d'Etude des Lymphomes Folliculaires (GELF)

Parameter	High tumour burden criteria
Lymph nodes	Bulk (>7 cm) or 3 lymph nodes in distinct areas >3 cm
Spleen	Symptomatic splenic enlargement
(Potential) complication	Organ compression by tumour, pleural or peritoneal effusion
Serum markers	Elevated LDH or elevated β_2-microglobuline
Clinical presentation	B symptoms (see Table 2)

LDH, lactate dehydrogenase.

prognostic assessment and are not yet suitable for clinical decision-making [9]. If possible, additional biopsy material should be stored fresh frozen to allow for the possible future application of additional molecular analyses.

treatment

first line

stage I–II. In the small proportion of patients with limited non-bulky stages I–II, radiotherapy (involved field, 24 Gy) is the preferred treatment with a potentially curative potential, whereas the 2 × 2 Gy schedule is inferior and is merely palliative [II, B] [10]. In selected cases, watchful waiting or rituximab monotherapy may be considered to avoid the side-effects of radiation (e.g. cervical: sicca syndrome, hypothyroidism; abdominal: mucositis, myeloablative suppression) [11, 12].

In stage I–II patients with large tumour burden, adverse clinical or biological prognostic features or when local radiotherapy is not applicable (e.g. lung, liver), systemic therapy as indicated for advanced stages should be applied [IV, B] [12].

stage III–IV

induction: In the majority of patients with advanced stage III and IV disease, no curative therapy is yet established. Since the

natural course of the disease is characterised by spontaneous regressions in 10%–20% of cases and varies significantly from case to case, therapy should be initiated only upon the occurrence of symptoms, including B symptoms, haematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression (Table 5) [I, A].

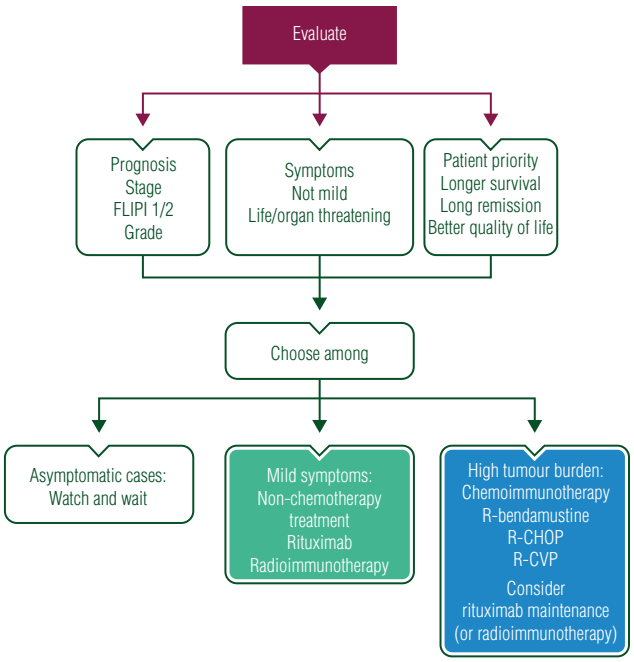

Figure 1. Therapeutic algorithm. R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone; R-CVP, rituximab, cyclophosphamide, vincristine and prednisolone.

In three randomised trials before the rituximab era, an early initiation of therapy in asymptomatic patients did not result in any improvement of disease-specific survival or overall survival (OS) [13]. In a more recent study, early initiation of rituximab resulted in improved PFS (80% versus 48%, P <0.001), but no survival benefit has been determined so far [14], and the benefit of rituximab maintenance in this setting appears doubtful [15]. Thus, the current therapeutic approach is based on clinical risk factors, symptoms and patient perspective (Figure 1).

Four prospective first-line trials, two salvage trials and a systematic meta-analysis confirmed an improved overall response, PFS and OS if rituximab was added to chemotherapy (Table 6) [16–20]. If complete remission and long PFS is to be achieved, rituximab in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine should be used [I, B] [17, 21]. CVP (cyclophosphamide, vincristine and prednisone) is not as effective as these two regimens with respect to PFS but not OS [22]. Full courses of purine analogue-based schemes [FC (fludarabine and cyclophosphamide) or FM (fludarabine and mitoxantrone)] are not recommended due to higher haematological toxicities, but a brief course of chemoimmunotherapy with full rituximab course is an alternative in elderly patients, with good efficacy and low toxicity [II, B] [22, 23]. If there is evidence (histological grade 3B or clinical signs of transformation) of more aggressive lymphoma, an anthracycline-based regimen [rituximab, cyclophosphamide,

Table 6. Combined chemoimmunotherapy in FL (first line)

Study	Total no. of patients	Median follow-up	Overall response	Time to treatment failure (months)	Overall survival
Marcus et al. [16]	159	53 months	81%	27	83% (4 years)
R-CVP			(P < 0.0001)	(P < 0.0001)	(P = 0.029)
Hiddemann et al. [17]	223	58 months	96%	NR	90% (2 years)
R-CHOP				(P < 0.001)	(P = 0.0493)
Herold et al. [18]	105	48 months	92%	NR	87% (4 years)
R-MCP			(P = 0.0009)	(P < 0.0001)	(P = 0.0096)
Bachy et al. [19]	175	99 months	81%	66	79% (8 years)
R-CHVP-IFN			(P = 0.035)	(P = 0.0004)	(P = 0.076)
Rummel et al. [21]	139	34 months	93%	NR	84% (4 years)
BR					
Federico et al. [22]		34 months			95% (3 years)
R-CVP	178		88%	46% (3 years)	
R-CHOP	178		93%	62% (3 years)	
R-FM	178		91%	59% (3 years)	
+ R maintenance					
Vitolo et al. [23]	234	42 months	86%	NR	89% (3 years)
4× R-FND + 4× R					
± R maintenance					

P, significance levels in comparison with chemotherapy only.
FL, follicular lymphoma; R-CVP, cyclophosphamide, vincristine and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-MCP: mitoxantrone, chlorambucil, prednisone; R-CHVP-IFN, rituximab, cyclophosphamide, doxorubicin, etoposide, prednisone, interferon; BR, bendamustine–rituximab; R-FM, rituximab, fludarabine and mitoxantrone; R-FND, cyclophosphamide, vincristine and prednisolone; NR, not reached.

Table 7. Recommended follow-up after end of therapy

Examination	Details	Year 1–2	Year 3–5	Year >5
History	B symptoms	Every 3–4 months	Twice annually	Annually
Physical examination	Particular: peripheral lymph nodes, liver, spleen	Every 3–4 months	Twice annually	Annually
Laboratory work-up	Blood and differential count	Every 3–4 months	Twice annually	Annually
	LDH	Every 3–4 months	Twice annually	If progress suspected
Imaging	Abdominal ultrasound	Twice annually	Every 12 months	If progress suspected
	CT neck, chest, abdomen, pelvis	Optional: 6–12 months	Optional: 12–24 months	If progress suspected

LDH, lactate dehydrogenase; CT, computed tomography.

doxorubicin, vincristine and prednisolone (R-CHOP)] should be applied.

Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remain alternatives for patients with a low-risk profile or when conventional chemotherapy is contraindicated [III, B] [24, 25].

In patients with positive hepatitis B serology including occult carrier (HBS Ag negative and anti-core positive), prophylactic antiviral medication and regular monitoring of HBV DNA are strongly recommended [I, A] [26].

consolidation/maintenance

Rituximab maintenance for 2 years improves PFS (59% versus 43% after 6 years, $P < 0.0001$) [I, B] [27], whereas a shorter maintenance period results in inferior benefit [28].

Radioimmunotherapy consolidation also prolongs PFS after chemotherapy, but its benefit seems to be inferior in comparison with rituximab maintenance for 2 years [II, B] [29, 30].

Myeloablative consolidation followed by autologous stem cell transplantation (ASCT) prolongs PFS after chemotherapy, but its benefit after a rituximab-containing induction is minor and no OS has been observed [31]. Therefore, such an approach is not recommended in first-line therapy of responding patients [I, D].

relapsed disease

At relapse, it is strongly recommended to obtain a new biopsy in order to exclude transformation into an aggressive lymphoma. It may be useful to target the biopsy based on PET scanning.

As at first presentation, observation is an accepted approach in asymptomatic patients with low tumour burden.

Selection of salvage treatment depends on efficacy of prior regimens. In early relapses (<12–24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or vice versa). Other options, including fludarabine-based, platinum salts-based or alkylating agents-based regimens, could also be useful. Rituximab should be added if the previous antibody-containing scheme achieved >6- to 12-month duration of remission [IV, B]. On the other hand, obinutuzumab has recently received a positive recommendation for approval by the European Medicines Agency for rituximab-refractory cases based on an improved PFS in comparison with bendamustine only [I, B] [32].

In symptomatic cases with low tumour burden, rituximab monotherapy may be applied.

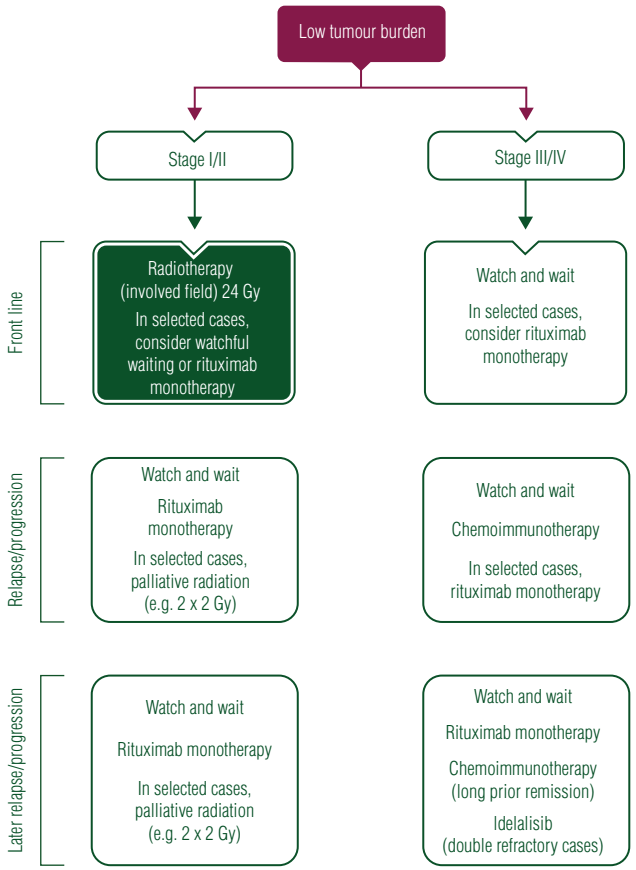

Figure 2. Consensus-driven recommendations outside of clinical studies—low tumour burden.

Radioimmunotherapy (^{90}yttrium–ibritumomab–tiuxetan) may represent an effective therapeutic approach in elderly patients with comorbidities not appropriate for chemotherapy [IV, B].

Rituximab maintenance for up to 2 years has a favourable side-effect profile and, based on a systematic meta-analysis, substantially prolongs PFS and OS in relapsed disease, even after antibody-containing induction in patients who have not received antibody as first-line therapy [I, A] [33]. A second-line maintenance treatment has not been investigated in the setting of maintenance use in first line and probably should not be used for those patients who had relapsed during their first maintenance period [IV, D].

High-dose chemotherapy with ASCT prolongs PFS and OS and should be considered, especially in patients who experience short-lived first remissions (<2–3 years) after rituximab-containing regimens, which usually have a much worse long-term outcome, but its general role in the rituximab era has to be redefined [I, B] [34–37]. A subsequent rituximab maintenance may achieve some improvement in PFS [II, B] [38].

In later relapses, monotherapy is an established option with palliative intent [II, B]. The PI3K inhibitor idelalisib has been registered in double-refractory FL, based on a phase II study [39]. Recent analyses suggest an increased mortality risk as a consequence of pulmonary morbidity (atypical pneumonias/pneumonitis), so appropriate prophylaxis (cotrimoxazole/acyclovir) is strongly recommended. Cytomegalovirus monitoring may be also advised.

In selected younger patients with later relapses of high-risk profile or relapse after ASCT, a potentially curative allogeneic stem cell transplantation (preferably with dose-reduced conditioning) may be considered, especially in patients with early relapse and refractory disease [IV, B] [36].

innovative approaches

In recent years, new approaches, including lenalidomide–rituximab and additional inhibitors of the B-cell signalling pathway, have proved active in phase II studies, but to date their benefit

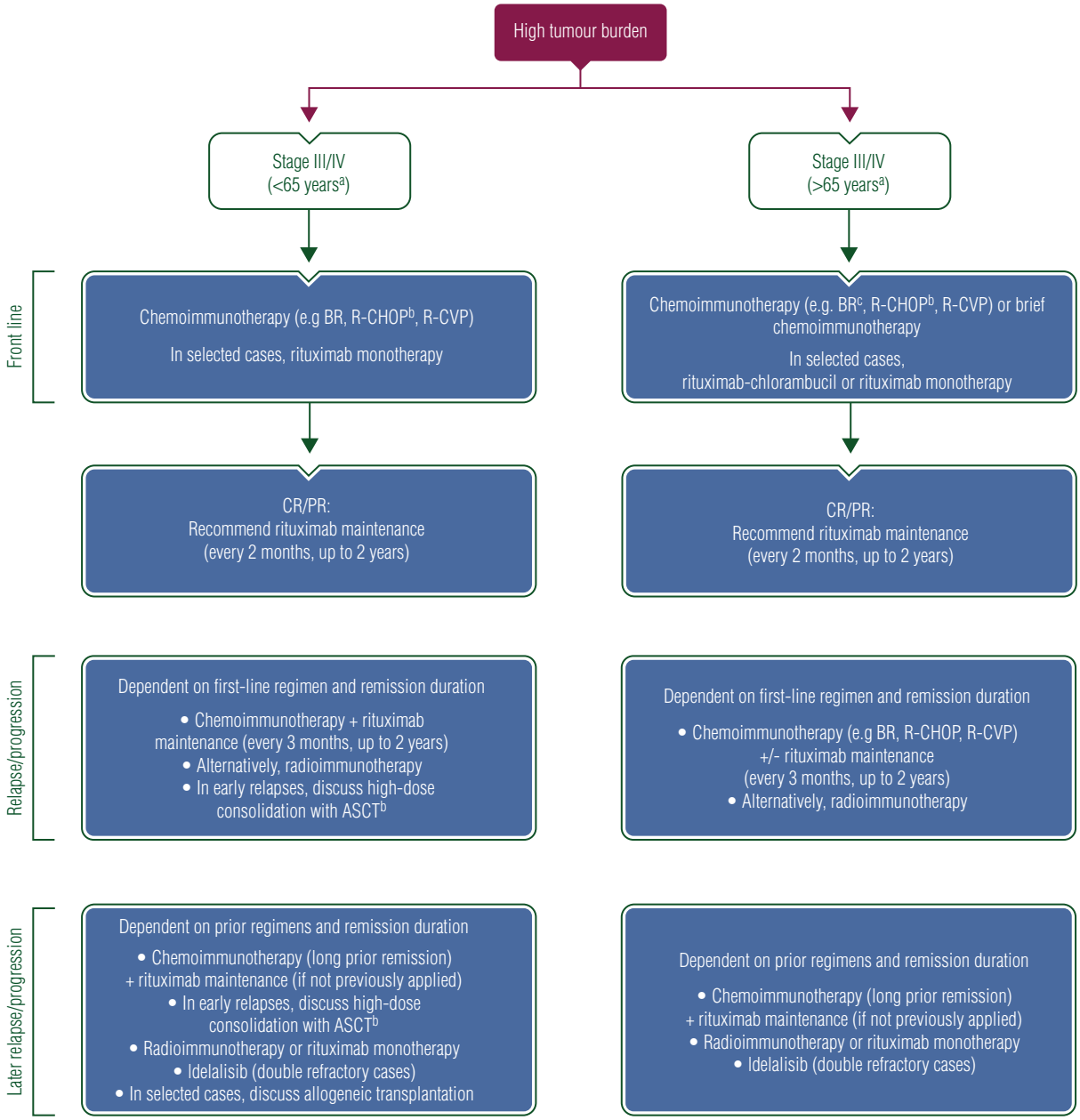

Figure 3. Consensus-driven recommendations outside of clinical studies—high tumour burden. R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, cyclophosphamide, vincristine and prednisolone; BR, bendamustine–rituximab; CR, complete response; PR, partial response; ASCT, autologous stem cell transplantation. [a]According to biological age; [b]especially if transformation is suspected; [c]70–90 mg/m^2, 4–6 cycles [42].

has yet to be confirmed in randomised phase III studies. The combination of bortezomib–rituximab has shown only a minor benefit compared with antibody monotherapy [I, D].

response evaluation

Appropriate imaging evaluation should be carried out midterm and after completion of chemotherapy. Patients with an inadequate response [less than partial response (PR)] should be evaluated for early salvage regimens. PR patients may convert to complete response (CR) under rituximab maintenance.

PET–CT after completion of chemotherapy induction has been recommended for prognostic reasons as persistent PET-positivity (using appropriate Deauville scales) identifies a small group (20%–25%) of patients with a worse prognosis [40], but therapeutic consequences remain undefined [II, B].

Minimal residual disease (MRD) analysis by polymerase chain reaction at the end of the treatment is an independent predictor of long-term outcome, but should not guide therapeutic strategies outside of clinical studies.

personalised medicine

As various therapeutic approaches may achieve durable responses in the vast majority of patients, the selection of optimal treatment is mainly based on clinical risk factors, symptoms and patient perspective (Figure 1). PET- and MRD-based tailored treatments are currently evaluated in studies but are not yet routine clinical practice.

Paediatric FL is an FL variant originally described in children, but occurs in adults as well. It is characterised by a localised disease, the absence of bcl-2 aberrations, lack of t(14;18), grade III and a high proliferation rate. It shows a much more indolent course and should be managed with local therapy only, despite displaying histologically more aggressive features [41].

follow-up and long-term implications and survivorship

The following minimal recommendations are based on consensus rather than on evidence (Table 7):

- After local radiotherapy: history and physical examination every 6 months for 2 years, subsequently once a year if clinically indicated.
- After (during continuous) systemic treatment: history and physical examination every 3–4 months for 2 years, every 6 months for 3 additional years, and subsequently once a year [V, D].
- Blood count and routine chemistry every 6 months for 2 years, then only as needed for evaluation of suspicious symptoms.
- Evaluation of thyroid function in patients with irradiation of the neck at 1, 2 and 5 years.
- Minimal adequate radiological or ultrasound examinations every 6 months for 2 years and optionally annually up to 5 years. Regular CT scans are not mandatory outside of clinical trials, especially if abdominal ultrasound is applicable. PET–CT should be not used for surveillance.
- MRD screening may be carried out in clinical studies but should not guide therapeutic strategies.

Table 8. Summary of recommendations

In localised stages: radiation (24 Gy)
In advanced stages: treatment depends on clinical risk factors, symptoms and patient perspective
Standard approach in asymptomatic advanced cases: watch and wait
In advanced symptomatic cases
Combined chemoimmunotherapy for long-term remissions
Recommend rituximab maintenance for consolidation
Relapse is frequently sensitive to conventional approaches
Autologous (and allogeneic) transplantation should be only discussed in relapse
Monotherapy (antibodies, idelalisib) is appropriate, especially in later relapses

methodology

These clinical practice guidelines were developed in accordance with the ESMO standard operating procedures for clinical practice guidelines development, http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommended treatment strategies outside of clinical studies is provided in Figures 2 and 3, and a summary of recommendations is provided in Table 8. Levels of evidence and grades of recommendation have been applied using the system shown in Table 9. Statements without grading were considered justified

Table 9. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of 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, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [43].

standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

conflict of interest

MD has reported institutional research support from Celgene, Janssen, Mundipharma, Pfizer and Roche; speaker's honoraria from Bayer, Celgene, Gilead, Janssen and Roche; advisory boards for Bayer, Celgene, Gilead, Janssen, Pfizer and Roche. MG has reported honoraria from Roche, Mundipharma, Gilead and Janssen. SR has reported research support from Janssen, Roche and Celgene; advisory boards for Janssen, Gilead, Roche, AstraZeneca and Celgene; speaker's honoraria from Janssen, Celgene and Roche. GS has reported personal fees for advisory boards or participation in meetings from Amgen, Celgene, Gilead, Janssen, Mundipharma, Novartis and Roche; grant support from Roche. UV has reported advisory boards for Roche and Janssen; honoraria for lectures from Roche, Janssen, Celgene, Takeda; conducting research as a global PI in multicentre studies sponsored by Roche and Celgene. ML has reported institutional research support from Celgene, Janssen, Mundipharma, Pfizer and Roche; speaker's honoraria from Bayer, Celgene, Gilead, Janssen and Roche; advisory boards for Bayer, Celgene, Gilead, Janssen, Pfizer and Roche.

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