Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2016-B-080 (Obinutuzumab)

Stand: August 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Obinutuzumab zur Erstlinientherapie des follikulären Lymphoms und Marginalzonen-Lymphoms	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Strahlentherapie • Chirurgische Resektion (Marginalzonen-Lymphom)
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*keine*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Obinutuzumab L01XC15 Gazyvaro®	Zu bewertendes Anwendungsgebiet Gazyvaro® in Kombination mit Chemotherapie, gefolgt von einer Gazyvaro® Erhaltungstherapie bei Patienten mit einem Therapieansprechen, wird angewendet bei Patienten mit nicht vorbehandeltem fortgeschrittenem FL
Follikuläres Lymphom:	
Ibritumomab V10XX02 Zevalin®	[^{90}Y]-radiomarkiertes Zevalin ist indiziert als Konsolidierungstherapie nach Remissionsinduktion bei zuvor nicht therapierten Patienten mit follikulärem Lymphom. Der Nutzen von Zevalin nach Rituximabbehandlung in Kombination mit Chemotherapie ist nicht belegt. [^{90}Y]-radiomarkiertes Zevalin ist indiziert zur Behandlung von erwachsenen Patienten mit einem nach einer Behandlung mit Rituximab rezidivierenden oder refraktären CD20-positiven follikulären Non-Hodgkin-Lymphom (NHL) vom B-Zell-Typ.
Interferon alfa-2a L03AB04 Roferon-A®	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: - Follikuläres Non-Hodgkin-Lymphom.
Interferon alfa-2b L03AB05 IntronA®	Follikuläre Lymphome Therapie follikulärer Lymphome mit großer Tumormasse zusätzlich zu geeigneter Kombinations-Chemotherapie zur Induktion wie CHOP-ähnliche Behandlungsschemata. Eine große Tumormasse liegt vor, wenn mindestens eines der folgenden Kriterien zutrifft: Tumorgröße über 7 cm („bulky disease“), Beteiligung von 3 oder mehr Lymphknoten (jeder > 3 cm), Allgemeinsymptome (Gewichtsverlust > 10 %, Pyrexie > 38 °C für mehr als 8 Tage oder Nachtschweiß), über den Nabel hinausgehende Milzvergrößerung, ausgeprägte Organobstruktion oder Kompressionssyndrom, orbitale oder epidurale Beteiligung, seröser Erguss oder Leukämie.
Rituximab L01XC02 MabThera®	Follikuläres Lymphom: MabThera ist in Kombination mit einer Chemotherapie für die Erstbehandlung von Patienten mit follikulärem Lymphom im Stadium III – IV angezeigt. Eine MabThera Erhaltungstherapie ist angezeigt zur Behandlung von Patienten mit follikulärem Lymphom, die auf eine Induktionstherapie angesprochen haben. MabThera ist als Monotherapie für die Behandlung von Patientenmit follikulärem Lymphom im Stadium III – IV angezeigt, die gegen eine Chemotherapie resistent sind oder nach einer solchen einen zweiten oder neuerlichen Rückfall haben.
Marginalzonen-Lymphom:	
keine Arzneimittel mit expliziter Zulassung für das Marginalzonen-Lymphom	

Non-Hodgkin-Lymphome:	
Chlorambucil L01AA02 Leukeran®	niedrig maligne Non-Hodgkin-Lymphome
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Non-Hodgkin-Lymphome (in Abhängigkeit vom histologischen Typ und vom Krankheitsstadium auch als Monotherapie)
Cytarabin L01BC01 Alexan®	Alexan 20 mg/ml wird in Kombination mit anderen Zytostatika in konventionellen Dosen eingesetzt zur […] • Behandlung von Non-Hodgkin-Lymphomen von intermediärem und hohem Malignitätsgrad im Erwachsenenalter • Behandlung von Non-Hodgkin-Lymphomen im Kindesalter.
Doxorubicin L01DB01 Adrimedac®	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: […] – Non-Hodgkin-Lymphome
Etoposid L01CB01 Etopophos®	Etopophos ist in Kombination mit anderen antineoplastisch wirksamen Arzneimitteln bei der Behandlung folgender bösartiger Neubildungen angezeigt: […] – Non-Hodgkin-Lymphome von intermediärem und hohem Malignitätsgrad;
Methotrexat L01BA01 Bendatrexat®	Non-Hodgkin-Lymphome: – im Erwachsenenalter: Zur Behandlung von Non-Hodgkin-Lymphomen von intermediärem oder hohem Malignitätsgrad in Kombination mit anderen zytostatischen Arzneimitteln
Mitoxantron L01DB07 Onkotrone®	Intermediäre und hochmaligne Non-Hodgkin Lymphome (NHL) des Erwachsenen in der Kombinationstherapie.
Prednisolon H02AB06 Dermosolon®	Hämatologie/Onkologie: Non-Hodgkin-Lymphome
Prednison H02AB07 Cutason®	Hämatologie/Onkologie: Non-Hodgkin-Lymphome
Vinblastin L01CA01 Vinblastinsulfat Teva®	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: - maligne Non-Hodgkin-Lymphome

Vincristin L01CA02 Vincristinsulfat HEXAL®	Vincristinsulfat HEXAL wird bei folgenden Indikationen in der Regel in der Kombinationschemotherapie angewendet: […] • Non-Hodgkin-Lymphome
Vindesin L01CA03 Eldisine®	Kombinationschemotherapie: aggressives Non-Hodgkin-Lymphom (Stadium I oder II).

Quellen: AMIS-Datenbank, Fachinformationen

Hinweis: Einige Wirkstoffe mit Zulassung für Non-Hodgkin-Lymphome sind nur für aggressive Formen zugelassen.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2016-B-080 (Obinutuzumab)

Datum: 22.07.2016

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation follikuläres und Marginalzonenlymphom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 23.06.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 709 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 14 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Obinutuzumab in Kombination mit Chemotherapie wird bei erwachsenen Patienten mit nicht vorbehandeltem fortgeschrittenem follikulärem Lymphom und Marginalzonenlymphom angewendet, gefolgt von einer Obinutuzumab-Erhaltungstherapie.

Berücksichtigte Wirkstoffe/Therapien:

Siehe Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen:

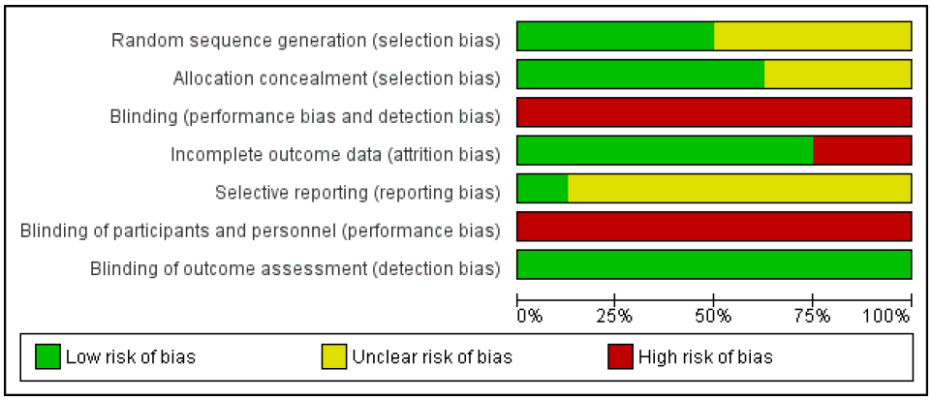
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG-Berichte/G-BA-Beschlüsse

Es konnten keine relevanten IQWiG-Berichte/G-BA-Beschlüsse im betreffenden AWG identifiziert werden.

Cochrane Reviews

Itchaki G et al., 2013 [5]. Anthracycline -containing regimens for treatment of follicular lymphoma in adults	1. Fragestellung To compare the efficacy of ACRs to other chemotherapy regimens, in the treatment of FL.
	2. Methodik Population: adult patients over 18 years of age, with a histologically confirmed diagnosis of FL, without gender or ethnicity restriction. Intervention: Anthracyclines (doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone, and pixantrone) regardless of additional agents, with or without radiotherapy; Komparator: non-ACR, as a single agent or multiple agents, regardless of dose Endpunkte: Primary outcomes: overall survival (OS); Secondary outcomes: progression-free survival (PFS), Complete response (CR), overall response rate (ORR), remission duration (RD), relapse, disease control, quality of life (QoL), adverse events (AE) Suchzeitraum (Aktualität der Recherche): 01/1966 -04/2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs/2636 Patienten Qualitätsbewertung der Studien: Two review authors independently assessed the risk of bias in included studies and extracted the data into the electronic table. We used a domain-based evaluation as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*. *Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies:*



3. Ergebnisdarstellung

Summary of findings for the main comparisons:

ACR compared to non-ACR for treatment of follicular lymphoma in adults

Patient or population: adults receiving treatment for follicular lymphoma
Settings:
Intervention: Aanthracycline
Comparison: no anthracycline same chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No anthracycline same chemotherapy	Anthracycline				
Overall survival number of dead patients Follow-up: median 50 months	538 per 1000	535 per 1000 (449 to 631)	HR 0.99 (0.77 to 1.29)	464 (3 studies)	⊕⊕⊕○ **moderate**[1]	
Mortality at 3 years	260 per 1000	239 per 1000 (174 to 327)	RR 0.92 (0.67 to 1.26)	465 (3 studies)	⊕⊕⊕○ **moderate**[1]	
Overall response	839 per 1000	889 per 1000 (839 to 940)	RR 1.06 (1 to 1.12)	622 (3 studies)	⊕⊕⊕○ **moderate**[2]	
Disease control number of patients with progression Follow-up: median 30 months	492 per 1000	356 per 1000 (297 to 423)	HR 0.65 (0.52 to 0.81)	759 (4 studies)	⊕⊕⊕⊕ **high**	
Progression/relapse at 3 years	544 per 1000	397 per 1000 (343 to 463)	RR 0.73 (0.63 to 0.85)	724 (4 studies)	⊕⊕⊕⊕ **high**	
Neutropenia grade 3-4	190 per 1000	368 per 1000 (277 to 485)	RR 1.94 (1.46 to 2.56)	533 (2 studies)	⊕○○○ **very low**[1,2,3]	
Cardiotoxicity**	2 per 1000	8 per 1000 (2 to 40)	RR 4.55 (0.92 to 22.49)	1412 (3 studies)	⊕○○○ **very low**[4,5]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Includes all trials, irrespectively of the comparison (' ' same chemotherapy"; ' ' different chemotherapy").
CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Small number of events
[2] Moderate heterogeneity
[3] Different reporting methods
[4] Not consistently reported
[5] Wide confidence interval

Overall survival

- OS data were analyzed for 464 patients included in three studies (Jones 1983; Lepage 1990; Taylor 2006).
- The pooled HR for OS was 0.99 (95% CI 0.77 to 1.29; Figure 3), indicating that there was no advantage to ACR chemotherapy compared with other chemotherapy.

	- There was no heterogeneity among trials (P = 0.37; I2 = 0%) All-cause mortality - There was no difference between ACR and non-ACR chemotherapy for mortality at three years (RR 0.92; 95% CI 0.67 to 1.26; three trials), and no heterogeneity among trials (P = 0.48; I2 = 0%). - five-year mortality (RR 0.95; 95%CI 0.77 to 1.18; three trials; 539 patients) Data regarding 10-year all-cause mortality were reported only in Taylor 2006, where there was no benefit to anthracyclines Response rate (CR and ORR) - All trials contributed to the analysis of CR, and all reported response data for FL patients separately. Use of ACR was not statistically significantly better than non-ACR (RR 1.05; 95% CI 0.94 to 1.18) - there was moderate heterogeneity between trials (P = 0.12; I2 = 46%) Disease control - Disease control measures were reported in four trials using same chemotherapy (Jones 1983; Zinzani 2000; Taylor 2006; Federico 2013) - ACRs were superior to non-ACRs with a pooled HR of 0.65 (95% CI 0.52 to 0.81) - heterogeneity (I2 = 46%; P = 0.14) Progression or relapse - Progression or relapse was chosen as a complementary dichotomous measure of disease control, relevant in patients with FL - This outcome was assessed in four trials (Jones 1983; Zinzani 2000; Taylor 2006; Federico 2013) - The pooled RR for previously untreated FL was 0.73 (95% CI 0.63 to 0.85; little heterogeneity I2 = 7%) Toxicity Neutropenia - Four trials reported neutropenia as a serious event, but only two (Taylor 2006; Federico 2013) were amenable for meta-analysis, demonstrating a higher rate of grade 3-4 neutropenia with ACR (RR 1.94; 95% CI 1.46 to 2.56) Infection - The types of infection reported varied considerably between any infection, serious infection, and neutropenic fever. Three trials were included in a meta-analysis considering the infection reported in the study (Jones 1983;Taylor 2006; Federico 2013) - The pooled RR of anthracyclines was 1.16 (95% CI 0.75 to 1.80) Quality of life - QoL was not assessed in the included trials. However, nausea and vomiting, diarrhea, and mucositis were reported more often with ACR Subgroup analysis for different anthracyclines: - doxorubicin (Jones 1983; Lepage 1990) - There was no evidence of survival benefit to either type of anthracycline - Disease control measures were reported in two trials employing doxorubicin (Jones 1983; Federico 2013) - The advantage of anthracyclines in disease control was preserved regardless of type of anthracycline used

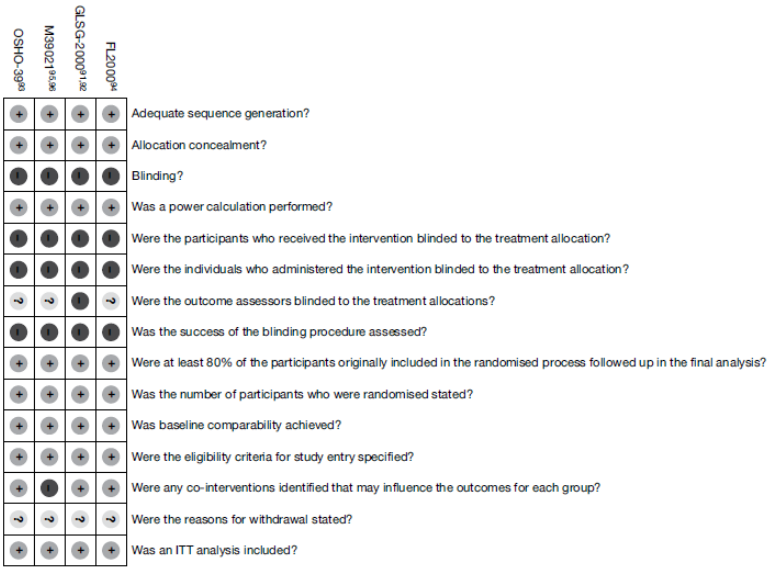
	4. Anmerkungen/Fazit der Autoren The use of anthracyclines in patients with FL has no demonstrable benefit on overall survival, although it may have been mitigated by the more intense regimens given in the control arms of three of five trials. ACR improved disease control, as measured by PFS and RD with an increased risk for side effects, notably cardiotoxicity. The current evidence on the added value of ACR in the management of FL is limited. Further studies involving immunotherapy during induction and maintenance may change conclusion. 5. Hinweise durch FB Med - Zugelassene Antracycline im AWG sind ausschließlich Doxorubicin und Mitoxantron - 8 RCTs wurden in die qualitative Analyse eingeschlossen (SR) - 5 RCTs wurden in die quantitative Analyse eingeschlossen (MA)

Systematische Reviews

Hua Q et al., 2015 [4]. Severe and fatal adverse events risk associated with rituximab addition to B-cell non-Hodgkin's lymphoma (B-NHL) chemotherapy: a meta-analysis.	1. Fragestellung To assess the risk of severe and fatal AEs related to the addition of rituximab to chemotherapy in B-NHL, here we conducted a metaanalysis, including data from recent published randomized control trials (RCTs).
	2. Methodik Population: B-NHL expressing CD20 antigen detectable by immunohistochemical methods Intervention: rituximab Komparator: k.A. Endpunkt: severe AEs (defined as Grade 3 or 4 AEs, fatal AE defined as Grade 5 AE) Suchzeitraum: over the last 10 years Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs/k.A. Qualitätsbewertung der Studien: Jadad scale Heterogenitätsanalysen: x^2 and I^2 Funnel plots were used to assess the publication bias.
	3. Ergebnisdarstellung (Studienübersicht siehe „Table 1“ im Anhang) – no statistically significant rituximab-associated increased risk in 13 severe adverse events (SAEs): infection, fever, anaemia, thrombocytopaenia, granulocytopenia, liver toxicity, cardiac toxicity, neurologic toxicity, lung toxicity, mucositis, nausea/vomiting, diarrhoea, alopecia – except leukocytopenia (36.4% versus 31%; RR=1.13; 95%CI, 1.01–1.27; P=0.03) – incidences of fatal AEs: noteworthy difference between rituximab group and control group: RR=1.45; 95% CI, 1.04–2.02; P=0.03 – funnel plots of severe and fatal AEs symmetrical: no publication bias

	4. Anmerkungen/Fazit der Autoren This meta-analysis indicates that there was no proof of statistically higher incidence of most SAEs in rituximab containing group compared with chemotherapy alone. However, fatal infections were more frequently observed in patients who received rituximab. Considering the low-incidence infection induced death during the treatment period, the effects of rituximab on infections need further investigation. *5. Hinweise durch FB Med* • *Funding None.* • *None of the authors declare any conflicts of interest.* • *nur bei einer Primärstudie angegeben, dass es sich um relapsed/refractory handelt, allerdings nicht in welcher Linie* *in Metaanalyse wird der Vergleich von verschiedenen Therapieregimen zusammengefasst; immer Rituximab + Kontrollregime vs. Kontrollregime*
Wang B et al., 2013 [13]. Intensified therapy followed by autologous stem-cell transplantation (ASCT) versus conventional therapy as first-line treatment of follicular lymphoma: a meta-analysis.	1. Fragestellung Our aim was to define the treatment effect of intensified therapy followed by ASCT compared with conventional therapy as first-line treatment of patients with FL in terms of overall survival (OS) and event-free survival (EFS).
	2. Methodik Population: patients with FL in the first-line setting Intervention: intensified therapy followed by ASCT Komparator: conventional therapy Endpunkte: primary outcome OS; event-free survival (EFS) Suchzeitraum (Aktualität der Recherche): 1985 -06/2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4/941 patients Qualitätsbewertung der Studien: Two reviewers (L.D.W. and Z. X. S.) independently assessed the quality of selected studies using the following criteria: (1) generation of allocation concealment; (2) description of dropouts; (3) masking of randomization, intervention and outcome assessment; and (4) intention-to-treat (ITT) analyses. Each criterion was rated as yes, no or unclear. Thirdly, the quality of a meta-analysis is always subject to the quality of included studies. None of included trials was double blinded.
	3. Ergebnisdarstellung - The random-effects summary HR by comparing the treatment effect on OS between intensified and conventional therapy was 0.95 [0.70, 1.30] (p = 0.75), indicating that no additional survival benefit was derived from the intensified therapy followed by ASCT. - A significant benefit of intensified therapy followed by ASCT as first-line treatment was detected in terms of EFS: the random-effects summary HR (intensified versus conventional therapy) was 0.59 [0.44, 0.79] (p<0.001).
	4. Anmerkungen/Fazit der Autoren In conclusion, despite its superior EFS, intensified therapy followed by

	ASCT does not improve OS compared with conventional therapy. So, ASCT should not be recommended as first-line treatment of FL.
Papaioannou D et al., 2012 [11]. Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation.	1. Fragestellung The aim of this assessment is to systematically evaluate and appraise the clinical effectiveness and cost-effectiveness of rituximab (in its licensed indication) in combination with chemotherapy compared with non-rituximab-containing chemotherapy, for the first-line treatment of symptomatic stage III–IV FL.
	2. Methodik Population: The population comprised adults with symptomatic stage III–IV FL who had not received any previous treatment. Intervention*:* Rituximab in combination with any of the following chemotherapy regimens: CVP, CHOP, CNOP, CHVP, MCP, FCM, FM, bendamustine, fludarabine or chlorambucil. Komparator: The comparator was chemotherapy without rituximab, which for this review was considered to be one of the following: CVP, CHOP, CNOP, CHVP, MCP, FCM, FM, bendamustine, fludarabine or chlorambucil. Endpunkte: The primary outcome of interest for this appraisal in relation to clinical effectiveness was OS. Secondary outcomes were PFS, response rates (CR, PR and ORR), duration of disease remission/ response duration, and adverse/toxic effects of treatment. Suchzeitraum (Aktualität der Recherche): Searches were not restricted by language or publication date. Anzahl eingeschlossene Studien/Patienten (Gesamt): 4/k.A. (Studien: M39021 trial by Marcus *et al*., GLSG-2000 by Hiddemann *et al*., OSHO-39 trial by Herold *et al*. and the FL2000 trial by Salles *et al*.) Qualitätsbewertung der Studien: The methodological quality of each included study was assessed by one reviewer and checked by a second reviewer, according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination (CRD) for RCTs.



3. Ergebnisdarstellung

Clinical efficacy outcomes reported in four studies

Study	PFS	OS	ORR	CR	PR	RD	EFS	TTF	TTNT	DFS	TTP
M39021[95,96]		✓	✓	✓	✓	✓		✓	✓	✓	✓
GLSG-2000[91,92]		✓	✓	✓	✓	✓		✓	✓		
OSHO-39[93]	✓	✓	✓	✓	✓	✓	✓		✓		
FL2000[94]		✓	✓	✓	✓	✓	✓				

RD, response duration; TTF, time to treatment failure;TTNT, time to next antilymphoma treatment. Cells in grey represent the primary outcome of the trial.

Response to treatment:

- ORR was significantly improved for patients receiving R-chemotherapy than those who received chemotherapy alone in three studies
- The ORR in the four studies ranged from 81% to 97% for the R-chemotherapy arm and from 57% to 91% for the chemotherapy-only arm.
- The difference in ORR between the treatment and comparator arms in each of the four studies ranged between 5% and 24%; the greatest difference was between the R-CVP and CVP arm.
- R-CHOP, R-CHVPi and R-MCP were the regimens that provided the highest ORR of 96%, 94% and 92%, respectively.
- CHOP alone provided a high ORR of 91%

Overall survival:

- The OS rate in the four studies ranged from 83% to 90% in the R-chemotherapy arms and from 77% to 84% in the chemotherapy-alone arms
- The difference in OS rate was significantly improved in three trials when R-chemotherapy was compared with chemotherapy alone; the exception being the FL2000 trial (p = 0.1552)
- The median OS was reported as not reached in three studies and was not reported in the FL2000 trial
- The OS data from the GLSG- 2000and OSHO-39 trials were confounded owing to the effects of subsequent therapy provided to all responders to first-line treatment
- The FL2000 trial also provided additional treatment (interferon-alpha)

	to both treatment arms during the 6-month remission induction phase - In addition, the FL2000 trial provided a further 12-month treatment phase in which the chemotherapy-alone arm received bimonthly CHVP and both treatment arms received interferon-alpha - The hazard ratios (HRs) for OS were not available in the manuscripts for each of the individual trial *Progression-free survival:* - The median PFS was significantly prolonged in OSHO-39 trial93 for the R-chemotherapy arm (R-MCP) (28.8 months MCP vs median not reached R-MCP; $p < 0.0001$) - PFS was not reported in the other three trials Safety data *Grade 3 and 4 adverse events:* - All fours studies reported grade 3 and 4 AEs; the GSLG-200092 and OSHO-3993 trials reported grade 3 and 4 AEs separately, whereas the M39021 and FL2000 trials combined the numbers of grade 3 or 4 AEs. - The most common AEs observed in the four trials were related to the blood and bone marrow, including leucocytopenia, neutropenia and granulocytopenia. - For two trials, the most common grade 3 and 4 AEs were reduced leucocyte (white blood cell) levels; this was observed in 69% of R-CHOP and 61% CHOP patients in the GLSG-2000 trial and 72% R-MCP and 58% MCP patients in the OSHO-39 trial. *Death and life-threatening adverse events:* - Overall, there were very few AEs reported as life-threatening or leading to death within the trials. - The M39201 trial reported that five patients experienced a total of six life-threatening events following R-CVP; however, no treatment-related deaths occurred. The remaining three studies did not report whether or not AEs were either life-threatening or led to death.
	4. Anmerkungen/Fazit der Autoren In conclusion, the addition of rituximab to chemotherapy results in better clinical outcomes for patients when compared with chemotherapy alone, for all chemotherapeutic backbones examined in this review, i.e. CVP, CHOP, MCP and CHVPi. This is achieved with minimal additional AEs or toxicity, which are deemed to be clinically relevant.

National Institute for Health and Care Excellence (NICE), 2016 [9]. Non-Hodgkin's Lymphomas: diagnosis and management. Version 01/2016 Draft version: noch nicht in Kraft	Fragestellung/Zielsetzung: The scope was drafted by the GC Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2012). The purpose of the scope was to: - set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C - inform professionals and the public about the expected content of the guideline - provide an overview of the population and healthcare settings the guideline would include and exclude - specify the key clinical issues that will be covered by the guideline - inform the development of the review questions and search strategies.
	Methodik Grundlage der Leitlinie: The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2012, NICE 2014). A team of health professionals, lay representatives and technical experts known as the Guideline Committee (GC) (Appendix F), with support from the NCC-C staff, undertook the development of this clinical guideline. From each of the key clinical issues identified in the scope, the GC formulated a review question. For intervention questions the PICO framework was used. This structured approach divides each question into four components: P – the population (the population under study); I – the intervention(s) (what is being done); C – the comparison (other main treatment or test options); O – the outcomes (the measures of how effective the interventions have been). Literature searches were repeated for all of the review questions at the end of the guideline development process, allowing any relevant papers published before 1st September 2015 to be considered. Future guideline updates will consider evidence published after this cut-off date. LoE und GoR **GRADE (Grading of Recommendations, Assessment, Development and Evaluation)** For interventional questions, studies which matched the inclusion criteria were evaluated and presented using GRADE (NICE 2012; http://gradeworkinggroup.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (very low, low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared. Each outcome was examined for the quality elements defined in Table 2 and subsequently graded using the quality levels listed in Table 3. **Table 2: Descriptions of quality elements of GRADE**

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect
Inconsistency	Inconsistency refers to unexplained heterogeneity of results
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

Freitext/Empfehlungen/Hinweise

First line treatment

Clinical question: What is the most effective first-line treatment for people with stage IIA follicular lymphoma?

Recommendation:

- Offer involved field radiotherapy as first-line treatment to people with localised stage IIA follicular lymphoma.
- Consider 'watch and wait' (observation without therapy) as first-line treatment for people with stage IIA follicular lymphoma who are asymptomatic and for whom treatment with a single radiotherapy volume is not suitable.
- Offer the same treatment as for advanced-stage (stages III and IV) disease to people with stage IIA follicular lymphoma who are symptomatic and for whom radiotherapy is not suitable.

Relative value placed on the outcomes considered:

- The critical outcomes for this topic were disease specific survival and overall survival. Other important outcomes of interest included progression free survival, treatment related mortality and morbidity, health related quality of life and patient preference, although no useful evidence was found for treatment related mortality, treatment related morbidity, health related quality of life or patient preference.

Quality of the evidence:

- The evidence for this topic was assessed using GRADE and ranged from very low to low quality overall. The evidence was downgraded due to low sample sizes, low numbers of events, limited descriptions of methods, indirectness of populations (limited data on stage IIA) and non-comparative study designs.
- It was not possible to compare outcomes across studies as each study compared different interventions, thus making it difficult to summarise across the evidence base.
- Although there was an absence of high quality, randomised trial evidence, the GC felt that radiotherapy should be recommended strongly because it has low toxicity, potential curative benefit (indicated by a large SEER dataset showing a 9% improvement in overall survival at ten years with radiotherapy for stage II follicular lymphoma) and further trials are unlikely in this area.

Treating advanced-stage asymptomatic follicular lymphoma

Clinical question: Is immediate treatment or deferred chemotherapy (watch and wait) the more effective treatment for people with advanced asymptomatic follicular lymphoma?

Recommendation:

- Offer rituximab induction therapya to people with advanced-stage (stages III and IV) follicular lymphoma who are asymptomatic.

Relative value placed on the outcomes considered:

- Overall survival was considered the most important clinical outcome when drafting recommendations.

Quality of the evidence:

- The quality of the evidence for this topic was low to very low as assessed using GRADE. The main issues with the evidence were: low imprecision and outcome assessment was not blinded. Although time to next treatment is an unusual primary endpoint due to its subjective component the results for progression free survival were similar, giving the GC more confidence in the evidence.
- The rituximab induction treatment arm was stopped early in Ardesha (2014) due to the publication of other rituximab induction and maintenance studies affecting recruitment and resulting in a loss of equipoise. The GC, however, still considered this trial as useful evidence.

Treating advanced-stage symptomatic follicular lymphoma

Recommendation:

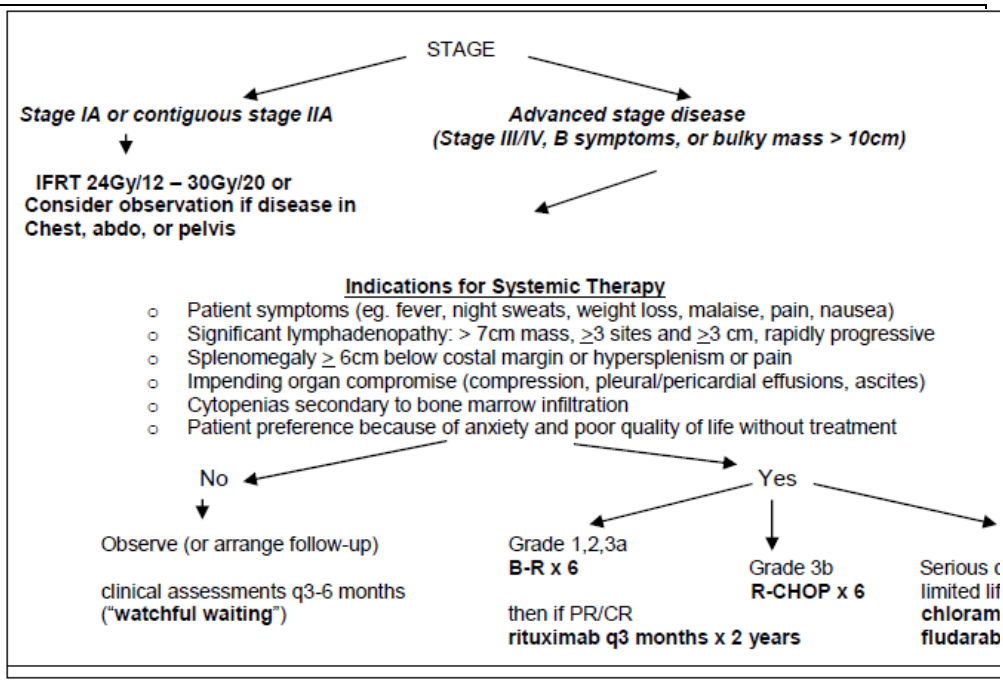
Rituximab, in combination with:

- cyclophosphamide, vincristine and prednisolone (CVP)
- cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)
- mitoxantrone, chlorambucil and prednisolone (MCP)
- cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α (CHVPi) or
- chlorambucil

is recommended as an option for the treatment of symptomatic stage III

	and IV follicular lymphoma in previously untreated people. [This recommendation is from Rituximab for the first-line treatment of stage III-IV follicular lymphoma] - These recommendations are from Rituximab for the first-line treatment of stage III-IV follicular lymphoma (NICE technology appraisal guidance 243). They were formulated by the technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/TA243.
National Comprehensive Cancer Network, 2016 [8]. Non-Hodgkin's Lymphomas. Version 03/2016	Fragestellung Nicht spezifiziert
	Methodik Grundlage der Leitlinie: Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - Diskussion der Literatur und Empfehlungen im Expertenpanel - eigenes Graduierungssystem (siehe unten) - industriefinanziert - Angaben zu CoI in zugehörigen Publikationen des JNCCN zu finden Literatursuche (Update): in PubMed zwischen 06/2014 und 10/2015 (search terms: diffuse large B-cell lymphoma, aggressive B-cell lymphoma, primary mediastinal B-cell lymphoma, double-hit lymphoma, gray zone lymphoma) GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert. **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.** Sonstige methodische Hinweise • *„discussion update in progress“* *Therapieempfehlungen überwiegend nicht zugelassen*

	Freitext/Empfehlungen/Hinweise Siehe Anhang Evidenzsynopse
Alberta Provincial Hematology Tumour Team, 2016 [1]. Lymphoma.	Fragestellung/Zielsetzung: - What are the diagnostic criteria for the most common lymphomas? - What are the staging and re-staging procedures for Hodgkin and non-Hodgkin lymphomas? - What are the recommended treatment and management options for Hodgkin and non-Hodgkin lymphomas? - What are the recommended follow-up procedures for patients with malignant Hodgkin and non-Hodgkin lymphoma? Target population: The following guidelines apply to adults over 18 years of age. Different principles may apply to pediatric and adolescent patients.
	Methodik Grundlage der Leitlinie: A detailed description of the methodology followed during the guideline development and updating process can be found in the Guideline Resource Unit Handbook. The original guideline was developed in March 2006 and was revised on the following dates: May 2007, June 2009, November 2009, January 2011, December 2011, September 2012, April 2013, December 2014, December 2015, February 2016 and April 2016. Literatursuche: 1950-10/2015 LoE und GoR The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
	Freitext/Empfehlungen/Hinweise **Follicular Lymphoma** Throughout the following suggested treatment approach, three over-riding principles should be considered: 1. These are guidelines only. This disease often carries a long, incurable, remitting/relapsing natural history and, therefore, several treatment approaches are reasonable. 2. The mere presence of disease does not alone imply the need for treatment. 3. If therapy is required for predominantly localized disease, IFRT should be considered in lieu of systemic pharmacological treatment as long as the radiotherapy can be done with minimal early or delayed side-effects (e.g., xerostomia, severe nausea/vomiting) and without eliminating future treatment options (e.g., should not radiate >25% bone marrow). Figure 2 outlines the treatment algorithm for follicular lymphoma. *Treatment algorithm for follicular lymphoma*



Initial therapy of advanced stage disease (stage III/IV, B symptoms, or bulky stage I/II). Indications for systemic therapy (usually stage III/IV or bulky stage I/II) include:

- Patient symptoms (fever, night sweats, weight loss, malaise, pain, nausea)
- Significant lymphadenopathy (> 7 cm mass, > 3 sites and > 3cm, rapidly progressive)
- Splenomegaly > 6 cm below costal margin, or hypersplenism, or pain
- Impending organ compromise (compression, pleural/pericardial effusions, ascites)
- Cytopenias secondary to bone marrow infiltration
- Patient preference because of anxiety and poor quality of life without treatment

For patients who do not have any of the above indications for therapy, the recommended approach is to observe with (or arrange) follow-up clinical assessments every 3-6 months ("watchful waiting").
For grades 1,2,3a follicular lymphoma who have an indication for therapy, the recommended therapy involves 6 cycles of B-R (bendamustine-rituximab) chemotherapy, followed in responding patients by 2 years of maintenance rituximab (375mg/m2 IV single dose every 3 months for total of eight doses). In patients with previously untreated indolent lymphoma, B-R can be considered as a prefered first-line treatment approach to R-CHOP because of increased progression-free survival and fewer side-effects. Patients who have limited life-expectancy from serious co-morbid illness, or who do not want intravenous therapy, may be treated with oral chlorambucil or fludarabine monotherapy.
For grade 3b follicular lymphoma or DLBCL with areas of follicular lymphoma, R-CHOP should be used. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell lymphoma, and therefore is not recommended.

National Institute for	Fragestellung/Zielsetzung: Nicht spezifiziert

Health and Care Excellence (NICE), 2011 [10]. Rituximab for the first-line maintenance treatment of follicular non-Hodgkin's lymphoma. Version 06/2011	Methodik Grundlage der Leitlinie: This guidance was developed using the NICE single technology appraisal process.
	Freitext/Empfehlungen/Hinweise *Key conclusion:* Rituximab maintenance therapy is recommended as an option for the treatment of people with follicular non-Hodgkin's lymphoma that has responded to first-line induction therapy with rituximab in combination with chemotherapy. *Evidence for clinical effectiveness:* *Availability, nature and quality of evidence:* The manufacturer derived efficacy data primarily from the PRIMA trial that compared rituximab maintenance with observation in people whose disease had responded to first-line induction therapy. The Committee noted that the most recent data from this trial were available from the post-study observational follow-up period, which had a median follow-up of 38 months. The Committee heard from the clinical specialists that the results from the PRIMA trial inform clinical practice in the UK. The Committee was aware that the trial stopped earlier than originally planned on advice from a Data and Safety Monitoring Committee, but heard from the ERG that evidence suggests that studies which stop earlier than planned often overestimate the clinical benefit. However, the Committee was satisfied, after advice from the clinical specialists, that progression-free survival for people treated with rituximab maintenance therapy in the PRIMA trial reflected the clinicians' observations from clinical practice. *Uncertainties generated by the evidence:* The Committee noted that because of the small number of deaths during the trial period, overall survival associated with rituximab maintenance treatment could not be estimated. The Committee noted that the manufacturer assumed in the base case that the clinical benefit of rituximab maintenance would last for 6 years (2 years of treatment and 4 years of sustained benefit once treatment was stopped). The Committee noted the ERG's concerns that patient-level data for rituximab maintenance treatment from the PRIMA trial indicated that the duration of treatment effect appears to be 28 months. The Committee heard from the clinical specialists that data from the PRIMA trial indicated that rituximab maintenance treatment is clinically effective to at least 36 months and there is no evidence that the effect diminishes over time; therefore assuming a duration of benefit of only 28 months, as suggested by the ERG, may underestimate the actual effect of treatment. The Committee heard from the clinical specialists that rituximab is likely to provide a benefit for 3 to 4 years (that is, 1 to 2 years beyond treatment); however, it was not possible to predict a definite time period.
Prica A et al.,	Fragestellung 1. In patients with lymphoma of any type or stage, is rituximab used alone

2015 [12]. Cancer Care Ontario (CCO). Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline [online].	or in combination with chemotherapy more effective than non–rituximab-containing regimens for improving overall survival (OS), disease control (as assessed by measures such as progression-free survival [PFS], event-free survival [EFS], time-to-treatment failure [TTF] , or response duration [RD]), response rate, or quality of life (QOL)? 2. What are the adverse events associated with the use of rituximab used alone or in combination with chemotherapy compared with non–rituximab-containing regimens? 3. Which patients with lymphoma are more or less likely to benefit from treatment with rituximab compared with those treated with non–rituximab-containing regimens? TARGET POPULATION Lymphoma Adult patients with lymphoma of any type, at any stage, and with any histology.
	Methodik Grundlage der Leitlinie: systematische Evidenzaufbereitung (inklusive Leitlinien) - Evidenzklassifizierung und Empfehlungsgraduierung mit verschiedenen Systemen (in Evidenztabellen dargestellt) - formale Konsensusprozesse nicht regelhaft - standardisiertes Reviewverfahren (intern und extern) - Interessenkonflikterklärungen dargelegt Update: this report is an update of a previous CCO guideline Suchzeitraum: updated search executed in October 2013 UPDATING (All Program in Evidence-Based Care documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC *Document Assessment and Review Protocol*, available on the Cancer Care Ontario (CCO) website at: https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=122178) *Sonstige methodische Hinweise* • *when clinically homogenous results from two or more trials were available, a meta-analysis was conducted* • *Therapieempfehlungen teilweise nicht zugelassen*
	Freitext/Empfehlungen/Hinweise **Recommendation 2** *Indolent histology B-cell lymphomas: first-line, second-line, and maintenance treatment and patients with asymptomatic CD20-positive B-cell lymphomas* - ***Previously Untreated Patients*** Previously untreated patients with indolent histology CD20-positive B-cell lymphomas, excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive their chemotherapy in combination with rituximab. - For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who are candidates for therapy, but not combination chemotherapy, rituximab monotherapy is a reasonable option. ***Previously Untreated Patients*** - Ten studies, represented by 23 publications, were included. Five studies reported a nonsignificant difference in OS [21,22,24,27,32]: rituximab (alone or in combination) was compared with chorambucil

	[24], with watchful waiting [27], with cyclophosphamide, mitoxantrone, vincristine, and prednisone (CNOP), with cyclophosphamide, adriamycin, etoposide and prednisolone plus interferon 2α (CHVP+I) [22], and with CHOP [32]. Four studies reported a statistically significant OS benefit for rituximab [18,33-35]; rituximab and various rituximab combinations were compared with CHOP [33], with cyclophosphamide, vincristine, and prednisone (CVP) [34], with CHOP and iodine-131-tositumomab [35], and with mitoxantrone, chlorambucil, and prednisone (MCP) [18]. Lengths of follow-up ranged from 18 months to 4.9 years. - Three studies reported on EFS [18,22,24]. Herold et al [18] reported a statistically significant (p=0.0001) benefit for rituximab in combination with MCP (R-MCP) compared with MCP alone at 47 and 60 months; Salles et al [22] found a statistically significant benefit of rituximab in combination with CHVP+I compared with CHVP+I alone (p=0.001), and Zucca et al [24] found a statistically significant benefit of rituximab combined with chlorambucil compared with cholrambucil alone at five-year follow up (p=0.002); a third, rituximab-only arm of this trial was still ongoing at the time of publication in 2013. - Five studies reported on PFS [18,23-25,27]. Herold et al [18] reported statistically significant longer PFS for R-MCP compared with MCP alone; Salles et al [22] reported a median of 35 months survival in the CHVP+I alone arm while median was not reached in the rituximab combination arm. Press et al [23] reported no statistically significant difference between R-CHOP compared with CHOP and iodine-131-tositumumab at two and 4.9 years follow-up. Zucca et al [24] reported no statistically significant difference between rituximab plus chlorambucil and chlorambucil alone (p=0.057). Hoster et al [25] and Lenz et al [32] did not find a statistically significant difference between R-CHOP and CHOP alone (p=0.31). Ardeshna et al [27], in a conference abstract reporting a study that was stopped early for benefit at 18 months follow-up, detected a statistically significant difference of rituximab treatment, and of rituximab treatment and maintenance compared with watchful waiting (log rank test p<0.001). - One study [34] detected a statistically significant benefit for rituximab combined with CVP compared with CVP alone for disease-free survival rates (DFS) (p=0.0001). - One study in abstract form [21] did not find a significant difference in disease-free survival rates (DFS) when comparing rituximab alone, rituximab combined with CNOP, or CNOP alone at 24 months follow-up (p values not reported). - Two studies [18,27], of which one was reported in abstract form [27], reported a statistically significant benefit of rituximab for time to next treatment at 18 and 60 months follow-up, respectively, when comparing R-MCP versus MCP alone and weekly rituximab alone, rituximab treatment, and rituximab maintenance versus watchful waiting (respectively, p=0.0002 and p value of log rank test <0.001). - Four studies [22,32-34] detected a benefit in time to treatment failure. Marcus et al [34] reported a statistically significant benefit of rituximab combined with CVP compared with CVP alone at 53 months follow-up (p<0.0001); Hiddeman et al [33] and Salles et al [22], at five-year follow-up, reported a statistically significant benefit for R-CHOP versus CHOP alone and for rituximab plus CHVP+I versus CHVP+I alone (p<0.0001 and p=0.003, respectively). - Six studies reported a statistically significant benefit for CR

<table>
<tr><td></td><td>[18,22,24,32-34] while four studies did not find a significant difference for CR, for OR, or for both [21,24,26,35].
- The majority of the studies did not report on grade ≥3 adverse events or reported nonsignificant between-group differences. Three studies reported statistically significant higher rates of lymphopenia or granulocytopenia in the rituximab arm compared with the chemotherapy-alone arm [22,26,32] (p<0.001; p=0.01 [granulocytopenia]; and p=0.02, respectively). One study reported a higher rate of infections and neutropenia in the rituximab arm when rituximab combined with CNOP was compared with CNOP alone [21], and one study reported a higher rate of thrombocytopenia in the rituximab arm compared with chemotherapy alone [35]. One study [23] reported a statistically significant difference in favour of the non-rituximab arm for cardiac adverse effects (p=0.08), while no statistically significant differences were reported for neurological adverse effects, nausea, and vomiting [23,26,33].</td></tr>
<tr><td rowspan="2">Bron D et al., 2014 [2].

BHS guidelines for the treatment of marginal zone lymphomas.

und

Debussche S et al., 2012 [3].

Guidelines of the Belgian Hematological Society for newly diagnosed and relapsed follicular lymphoma 2012.</td><td>Fragestellung/Zielsetzung:
Marginal zone lymphomas are a heterogeneous subtype of indolent B-non-Hodgkin Lymphoma that includes three distinct diseases: Extranodal mucosa associated lymphoid tissue lymphoma, nodal marginal zone lymphoma and splenic marginal zone lymphoma lymphocytes +/- villous lymphocytes. The different diagnosis, work up and treatment options are discussed in these guidelines.</td></tr>
<tr><td>Methodik
Grundlage der Leitlinie: nicht spezifiziert

LoE und GoR
Level of evidence (Infectious Diseases Society of American-United States Public Health Service Grading System)
<table>
<tr><td>I</td><td>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</td></tr>
<tr><td>II</td><td>Small randomised trials of large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity</td></tr>
<tr><td>III</td><td>Prospective cohort studies</td></tr>
<tr><td>IV</td><td>Retrospective cohort studies or case–control studies</td></tr>
<tr><td>V</td><td>Studies without control group, case reports, experts opinions</td></tr>
<tr><td colspan="2">Grade for recommendation</td></tr>
<tr><td>A</td><td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td></tr>
<tr><td>B</td><td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td></tr>
<tr><td>C</td><td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events,</td></tr>
</table></td></tr>
</table>

	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

Freitext/Empfehlungen/Hinweise

Extended (III-IV) disease
Extended (III-IV) disease should be treated according to follicular NHL approaches.
28. Debussche S, Van Hoof A, Sonnet A, et al. Guidelines of the Belgian Hematological Society for newly diagnosed and relapsed follicular lymphoma 2012. Belg J Hematol 2012;3:41-50.

Treatment: Initiation of treatment beyond curative intent

- In patients with stage III-IV and stage II non-contiguous disease, current treatments are not considered curative. Nevertheless patients may remain very stable over a long period of time and spontaneous regressions have been described to occur.18 There is no uniform consensus on the criteria to initiate therapy.
- The BHS Lymphoproliferative group recom - mends to use either the Groupe d'Etude des Lymphomes Folliculaires (GELF) or the German Low grade lymphoma Study Group (GLSG) criteria, since they have been used in validated randomised clinical trials and are the basis for claims made at evidence I level.
- The BHS lymphoproliferative group advises R-chemo in patients with newly diagnosed FL fulfilling the GELF or GLSG criteria. R- CHOP (6+2) or R-CVP (8) should be used in patients up to grade 3a with an advan - tage for R-CHOP in terms of PFS but not OS. R-CHOP should be preferred in suspected or documented transformed lymphoma.

Key messages for clinical practice

1. Extranodal MALT lymphoma arises in a variety of tissue but primarily in the stomach. They are usually localised and often associated with chronic antigenic stimulation by microbial pathogens. Eradication of the pathogen is part of the first line therapy. Prognosis is excellent and radiotherapy (when feasible) is curative in early stages. In advanced stages, observation, anti CD20 antibodies and/or cytostatic drugs (such as chlorambucil or fludarabine) are therapeutic approaches.
2. Nodal MZL is usually confined in lymph node, bone marrow and peripheral blood. A monoclonal gammopathy (IgG, IgM) is often produced by the lymphoma cells. Because of the lack of RCTs in this population, there are no guidelines and they should be managed as follicular lymphomas.
3. Splenic MZL lymphocytes +/- villous lymphocytes are a unique entity involving the spleen, the bone marrow and the blood. These lymphomas have an indolent behaviour and only symptomatic patients should be treated by splenectomy and/or rituximab (after control for hepatitis C status).

Zinzani PL et

Fragestellung/Zielsetzung:
- When to start treatment (consensus-based recommendations)
- First line therapy (evidence–based recommendations)

al., 2013 [14]. SIE, SIES, GITMO revised guidelines for the management of follicular lymphoma.	o In asymptomatic stage II–IV non bulky patients is rituximab alone better than watchful waiting? o In patients with stage II–IV deserving treatment, is chemoimmunotherapy better than chemotherapy? o In patients candidates to frontline chemoimmunotherapy, which chemotherapy regimen should be chosen? o In patients candidates to frontline chemoimmunotherapy, high-dose chemoimmunotherapy with autologous stem cell support is better than standard chemoimmunotherapy?
	Methodik: evidenz- und konsensbasierte LL Grundlage der Leitlinie: - systematische Literatursuche und Bewertung (anhand vom GRADE-Schema), - Empfehlungen durch formale Konsensusmethoden verabschiedet (nominaler Gruppenprozess) Suchzeitraum: bis Juli 2011 (limited to English-language publications edited after 2005) Weitere Kriterien für die Qualität einer Leitlinie: - Empfehlungen durch Hintergrundtexte mit Quellenangaben verknüpft LoE/GoR: GRADE *Sonstige methodische Hinweise:* - *The SIE administered all aspects of the meetings. The funding sources had no role in identifying statements, abstracting data, synthesizing results, grading evidence, or preparing the manuscript or in the decision to submit the manuscript for publication.*
	Freitext/Empfehlungen/Hinweise Issue 2: When to start treatment (consensus-based recommendations) - Treatment can be started in patients with Stage II–IV disease in case of one of the following features occurs: systemic symptoms, high tumor burden (i.e., >3 lymph nodes measuring >3 cm or a single lymph node >7 cm), extranodal disease, cytopenia due to marrow involvement, spleen involvement (516 cm by CT), leukemic phase, serous effusion, symptomatic or life endangering organ involvement, rapid lymphoma progression, consistently increased LDH levels. A policy of watchful waiting is not recommended in patients with Stage I–II disease, with the exception of patients with a short life expectancy due to severe comorbidity or with contraindications to therapy. 1. Barosi G, Carella A, Lazzarino M, et al. Management of nodal indolent (non marginal-zone) nonHodgkin's lymphoma: Practice guidelines from the Italian Society of Haematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. Haematologica 2005;90:1237– 1257. 25. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: A randomized controlled trial. Lancet 2003;362:516– 522. 26. Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin containing regimen with or without interferon alfa 2b for advanced follicular lymphomas: Final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaire 86 trial. J Clin Oncol 1998;16:2332–2338. Issue 3: First line therapy (evidence–based recommendations) - In asymptomatic stage II–IV non bulky patients is rituximab alone better than watchful waiting?

- For asymptomatic Stage II–IV, non bulky patients watchful waiting remains the standard of care and rituximab cannot be recommended (quality of evidence, low; strength of recommendation, weak).

27. Ardeshna K, Qian W, Smith P, et al. An intergroup randomized trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (grades 1, 2 and 3a). A preliminary analysis. Blood (ASH Annual Meeting Abstracts) 2010;116:6.
28. Ardeshna KM, Quian W, Stephens R, et al. Preliminary results of quality of life (QOL) analyses from the intergroup phase III randomized trial of Rituximab vs. a watch and wait approach in patients with advanced stage, asymptomatic, non-bulky follicular lymphoma (FL). Ann Oncol 2011;22:19.

In patients with stage II–IV deserving treatment, is chemoimmunotherapy better than chemotherapy?

- Patients with Stage III–IV should receive front-line chemoimmunotherapy. No evidence indicates chemoimmunotherapy in Stage II disease. However, the panel agreed that these patients should receive chemoimmunotherapy when there is high tumor burden or high-risk scoring system (quality of evidence, moderate; strength of recommendation, strong).

1. Barosi G, Carella A, Lazzarino M, et al. Management of nodal indolent (non marginal-zone) nonHodgkin's lymphoma: Practice guidelines from the Italian Society of Haematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. Haematologica 2005;90:1237– 1257.
30. Herold M, Pasold R, Srock S, et al. Results of a prospective randomized open label phase III study comparing rituximab plus mitoxantrone, chlorambucile, prednisolone chemotherapy (R-MCP) versus MCP alone in untreated advanced indolent non-Hodgkin's lymphoma (NHL) and Mantle- Cell-lymphoma (MCL). ASH Annual Meeting Abstracts 2004;104:584.
31. Hiddman W, Kneba M, Dreyling M, et al. Frontline therapy with Rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725–3732.
32. Buske C, Hoster E, Dreyling M, et al. Rituximab in combination with CHOP in patients with follicular lymphoma: Analysis of treatment outcome of 552 patients treated in a randomized trial of the German Low Grade Lymphoma Study Group (GLSG) after a follow up of 58 months. Blood (ASH Annual Meeting Abstracts) 2008;112:2599.
33. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417–1423.

In patients candidates to frontline chemoimmunotherapy, which chemotherapy regimen should be chosen?

- There is evidence that many frontline chemotherapy regimens, whether antracycline-based polychemotherapy (CHOP or CHOP like regimens) or fludarabine- based polychemotherapy, or CVP regimen or bendamustine can be used in association with rituximab (quality of evidence, low; strength of recommendation, weak).

34. Federico M, Luminari S, Dondi A, et al. R-CVP vs. R-CHOP vs. R-FM for the initial treatment of patients with advanced stage follicular lymphoma. Preliminary results of FOLL05 trial. Ann Oncol 2011;22:135.
35. Rummel M, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab 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 AtiL (Study Group Indolent Lymphomas, Germany). Blood 2009;114:404.

In patients candidates to frontline chemoimmunotherapy, high-dose chemoimmunotherapy with autologous stem cell support is better than standard chemoimmunotherapy?

- Upfront high-dose chemoimmunotherapy with autologous stem cell support cannot be recommended (quality of evidence, low; strength of recommendation, strong).

36. Al Khabori M, de Almeida JR, Guyatt GH, et al. Autologous stem cell transplantation in follicular lymphoma: A systematic review and meta-analysis. J Natl Cancer Inst 2012;104:18–28.

<table>
<tr><td></td><td>37. Ladetto M, De Marco F, Benedetti F, et al. Gruppo Italiano Trapianto di Midollo Osseo (GITMO); Intergruppo Italiano Linfomi (IIL). Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: The superior disease control of R-HDS does not translate into an overall survival advantage. Blood 2008;111:4004–4013.</td></tr>
<tr><td>McNamara C et al., 2012 [7].

Guidelines on the investigation and management of follicular lymphoma.</td><td>Guideline of the British Society for Haematology
Fragestellung
Management of patients with follicular lymphoma.
Hier: relapsed/refractory patients</td></tr>
<tr><td></td><td>Methodik
Grundlage der Leitlinie:
Guideline group was selected to be representative of UK-based medical experts and patient’s representatives.
Systematic literature review
writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology
External review process by 50 UK haematologists, the BCSH and the British Society for Haematology Committee
Suchzeitraum: 1980 – 2010
LOE/GoR: GRADE approach:
quality of evidence graded as very low, low, moderate or high
Strength of Recommendation: strong (‘recommend’) or weak (‘suggest’)
GoR (Strength of Recommendation)
Strong (grade 1): Strong recommendations are made if clinicians are very certain that benefits do, or do not, outweigh risks and burdens.
Grade 1 recommendations can be applied uniformly to most patients and words such as “recommend”,“offer” and “should” are appropriate.
Weak (grade 2): Weak recommendations are made if clinicians believe that benefits and risks and burdens are finely balanced, or appreciable uncertainty exists about the magnitude of benefits and risks. In addition, clinicians are becoming increasingly aware of the importance of patient values and preferences in clinical decision making. When, across the range of patient values, fully informed patients are liable to make different choices, guideline panels should offer weak recommendations.
Grade 2 recommendations require judicious application to individual patients and words such as “suggest”and “consider” are appropriate.
LoE (Quality of Evidence)
The quality of evidence is graded as high(A), moderate(B), low (C) or very low (D), and although these categories are descriptively defined as
(A) High:further research is very unlikely to change our confidence in the estimate of effect,
(B) Moderate:further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate,
(C) Low:further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate,
(D) Very Low: any estimate of effect is very uncertain,
the objective criteria for assigning the quality of evidence shown in the table below should be used.
Criteria for assigning the quality of evidence in GRADE<table><tr><td>Type of evidence</td><td>Randomized trial = high (A)
Observational study = low (C)
Any other evidence = very low (D)</td></tr></table></td></tr>
</table>

	<table><tr><td>Decrease* grade if</td><td>• Serious or very serious limitation to study quality • Important inconsistency • Some or major uncertainty about directness • Imprecise or sparse data • High probability of reporting bias *Each quality criteria can reduce the quality by one or, if very serious, by two levels</td></tr><tr><td>Increase grade if</td><td>• Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) • Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2) • Evidence of a dose response gradient (+1) • All plausible confounders would have reduced the effect (+1)</td></tr></table> It should be noted that a strong recommendation (1) can be made when the quality of the evidence is low (C) or very low (D).
	Freitext/Empfehlungen/Hinweise **Management of patients with newly diagnosed FL** *Treatment of advanced stage disease: Advanced stage, asymptomatic FL/Treatment of symptomatic advanced stage FL/ Rituximab maintenance following first line chemoimmunotherapy/ Autologous stem cell transplantation (ASCT) and newly diagnosed FL/ Radioimmunotherapy (RIT) in the newly diagnosed FL patient* - Observation remains an appropriate approach in patients with asymptomatic, advanced stage FL in an attempt to delay the need for chemotherapy (Strong, Moderate). - Rituximab, in combination with chemotherapy, should be used in patients with newly diagnosed, symptomatic advanced stage FL who require therapy (Strong, High). There is no strong evidence to support one regimen over another (Strong, Moderate). - Rituximab maintenance after successful induction therapy prolongs PFS and is recommended in patients responding to first line rituximab-based chemotherapy (Strong, Moderate). - Autologous stem cell transplantation has no role in first line therapy for FL outside a clinical trial (Strong, Moderate). - There is no conclusive evidence that radio-immunotherapy prolongs OS in patients and insufficient data to routinely recommend RIT after rituximab-based induction therapy (Weak, Low).
Lopez-Guillermo A et al., 2011 [6]. National Catalog of Clinical Practice	Fragestellung … giving preference to randomized clinical trials and meta-analyses, these clinical practice guidelines (CPG) have been developed to offer therapeutic recommendations for patients with FL, based on the best available clinical evidence.
	Methodik: Grundlage der Leitlinie: Repräsentativität des Gremiums unklar, CoI liegen vor, systematische Suche, Auswahl und Bewertung der Literatur, Konsensusprozesse ohne formale Verfahren beschrieben LoE, GoR: recommendations have different grades (A, B, C and D),

Guidelines of the Spanish national health	depending on the level of evidence on which they are based (where there is no scientific evidence, they follow the consensus of Good Clinical Practice: see Appendix)

system.

Clinical practice guidelines for first-line/after-relapse treatment of patients with follicular lymphoma.

Appendix. Key to evidence statements and grades of recommendation (SIGN) [7,8].

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation	
A	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence consisting principally of studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+

Notes:

- The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.
- Studies rated as *1−* and *2−* are avoided in the process of developing recommendations due to the high risk of bias.

Good Clinical Practice	
✓*	Recommended best practice based on the clinical experience of the guideline development group

*Sometimes, the working group observes that there is an important practical aspect that should be emphasized but which is probably not supported by any scientific evidence. In general, these cases are related to some aspect of the treatment that is considered Good Clinical Practice and that no one would usually question. These aspects are evaluated as points of Good Clinical Practice. Such recommendations are not an alternative to those based on scientific evidence and should only be considered when there is no other way to highlight that aspect.

Freitext/Empfehlungen/Hinweise

	Induction treatment in first-line *Treatment objectives* - Patients with localized-stage follicular lymphoma are recommended to have locoregional radiotherapy. **Grade of recommendation B** - In asymptomatic patients with no risk factors or with " low tumor burden, " whatever the stage of disease, it is recommended to delay systemic treatment until disease progression, especially in elderly patients or in those with concomitant diseases. **Grade of recommendation C** - In patients who require treatment (symptomatic or with " high tumor burden " criteria), immunotherapy or immunochemotherapy with rituximab is the best therapeutic option; however, it has not yet been established which polychemotherapy regimen – cyclophosphamide, vincristine and prednisone (CVP); CVP and adriamycin (CHOP); or combinations with fludarabine or bendamustine – should be prescribed along with rituximab. **Grade of recommendation A** - In patients over 70 years of age, it is recommended to evaluate carefully their comorbidities, and where there is a cardiopathy or ventricular ejection fraction less than 50%, fi rst-line induction therapy should not include anthracyclines. **Good Clinical Practice** **Post-induction treatment in first-line** *Post-induction treatment options* - In patients with treatment criteria, in complete or partial response after first-line induction immunochemotherapy, maintenance treatment with rituximab (375 mg/m 2 every 2 months for 2 years) significantly prolongs PFS and EFS compared with observation alone (see Table II for clinical trial evidence). **Grade of recommendation A** *Evaluation and follow-up of patients during maintenance phase* - During first-line maintenance treatment, it is recommended to perform clinical evaluation every 2 months (coinciding with every administration) and assessment of imaging results (computed tomography [CT] scan) every 6 months. Furthermore, it is also suggested to quantify immunoglobulins every 6 months. A positron emission tomography (PET) scan is not recommended for FL follow-up. **Grade of recommendation D** - At the end of the maintenance phase, it is recommended to re-evaluate the patient, with the repetition of all tests which gave abnormal values before the start of maintenance. From that time, it is recommended to monitor the patient every 4 – 6 months for 5 years and thereafter on an annual basis. History, physical examination and laboratory results will be repeated at every visit. There is no agreement on the use of imaging tools (CT scan) during follow-up; it is reasonable that these scans be performed annually in the early years. **Grade of recommendation D** *When should the possibility of changing treatment be contemplated?* - During the maintenance phase, whatever the therapeutic regimen, if disease progression is demonstrated, usually by clinical or imaging data (CT scan), or if there is serious treatment-related toxicity, a therapeutic change should be considered (" salvage treatment "). **Grade of recommendation D**

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 21.06.2016**

#	Suchfrage
1	MeSH descriptor: [Lymphoma, Follicular] explode all trees
2	MeSH descriptor: [Lymphoma, B-Cell, Marginal Zone] explode all trees
3	MeSH descriptor: [Lymphoma, Non-Hodgkin] this term only
4	MeSH descriptor: [Lymphoma, B-Cell] this term only
5	(follicular or marginal or mucosa or malt) and lymphom*:ti,ab,kw (Word variations have been searched)
6	((non next hodgkin*) or nonhodgkin*) and lymphom*:ti,ab,kw (Word variations have been searched)
7	(b next cell) and (lymphom* or malignanc*):ti,ab,kw (Word variations have been searched)
8	mzl or nhl or inhl:ti,ab,kw (Word variations have been searched)
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 21.06.2016

#	Suchfrage
1	lymphoma, follicular[MeSH Terms]
2	lymphoma, b-cell, marginal zone[MeSH Terms]
3	"Lymphoma, Non-Hodgkin"[Mesh:NoExp]
4	"Lymphoma, B-Cell"[Mesh:NoExp]
5	(((((follicular[Title/Abstract]) OR marginal[Title/Abstract]) OR mucosa[Title/Abstract]) OR malt[Title/Abstract])) AND lymphom*[Title/Abstract]
6	(((non hodgkin*[Title/Abstract]) OR nonhodgkin*[Title/Abstract])) AND lymphom*[Title/Abstract]
7	(b cell[Title/Abstract]) AND ((lymphom*[Title/Abstract]) OR malignanc*[Title/Abstract])
8	((mzl[Title/Abstract]) OR nhl[Title/Abstract]) OR inhl[Title/Abstract]
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
11	(((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))

12	(#10) OR #11
13	(#9) AND #12
14	(#13) AND ("2011/06/01"[PDAT] : "2016/06/21"[PDAT])

Leitlinien in Medline (PubMed) am 21.06.2016

#	Suchfrage
1	lymphoma, follicular[MeSH Terms]
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6	(((non hodgkin*[Title/Abstract]) OR nonhodgkin*[Title/Abstract])) AND lymphom*[Title/Abstract]
7	(b cell[Title/Abstract]) AND ((lymphom*[Title/Abstract]) OR malignanc*[Title/Abstract])
8	((mzl[Title/Abstract]) OR nhl[Title/Abstract]) OR inhl[Title/Abstract]
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]
11	(#9) AND #10
12	(#11) AND ("2011/06/01"[PDAT] : "2016/06/21"[PDAT])

Gemeinsamer Bundesausschuss

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1. **Alberta Provincial Hematology Tumour Team.** Lymphoma [online]. Edmonton (CAN): Cancer Control Alberta; 04.2016. [Zugriff: 21.06.2016]. (Clinical practice guideline; Band LYHE-002 version 10). URL: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe002-lymphoma.pdf.

2. **Bron D, Van den Neste E, Kentos A, Offner F, Schroyens W, Bonnet C, et al.** BHS guidelines for the treatment of marginal zone lymphomas Belg J Hematol 2014;5(1):12-21.

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4. **Hua Q, Zhu Y, Liu H.** Severe and fatal adverse events risk associated with rituximab addition to B-cell non-Hodgkin's lymphoma (B-NHL) chemotherapy: a meta-analysis. J Chemother 2015;27(6):365-370.

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8. **National Comprehensive Cancer Network (NCCN).** NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas, Version 3.2016 [online]. Fort Washington (USA): NCCN; 2016. [Zugriff: 20.06.2016]. URL: https://www.nccn.org/professionals/physician_gls/pdf/nhl.pdf.

9. **National Institute for Health and Care Excellence (NICE).** Non-Hodgkin's lymphoma: diagnosis and management [online]. London (GBR): NICE; 01.2016. [Zugriff: 20.06.2016]. (NICE in development; Band GID-CGWAVE0671). URL: https://www.nice.org.uk/guidance/GID-CGWAVE0671/documents/draft-guideline.

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11. **Papaioannou D, Rafia R, Rathbone J, Stevenson M, Buckley Woods H, Stevens J.** Rituximab for the first-line treatment of stage III-IV follicular lymphoma (review of Technology Appraisal No. 110): a systematic review and economic evaluation. Health Technol Assess 2012;16(37):1-253, iii-iv.

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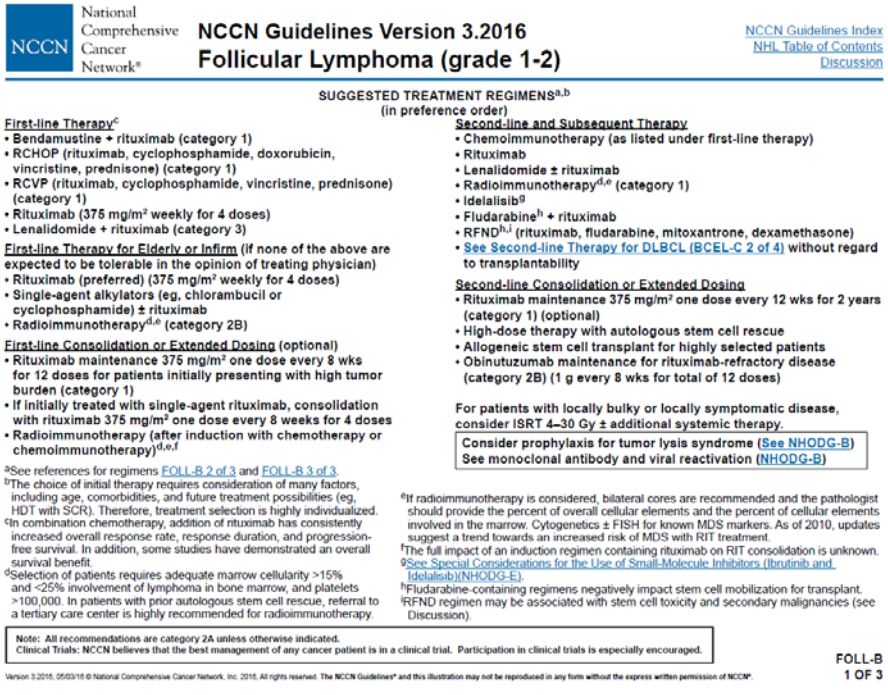
Gemeinsamer Bundesausschuss

Anhang:



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Follicular Lymphoma (grade 1-2)

SUGGESTED TREATMENT REGIMENS[a,b]
(in preference order)

First-line Therapy[c]
- **Bendamustine + rituximab (category 1)**
- **RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)**
- **RCVP (rituximab, cyclophosphamide, vincristine, prednisone) (category 1)**
- **Rituximab (375 mg/m² weekly for 4 doses)**
- **Lenalidomide + rituximab (category 3)**

First-line Therapy for Elderly or Infirm (if none of the above are expected to be tolerable in the opinion of treating physician)
- **Rituximab (preferred) (375 mg/m² weekly for 4 doses)**
- **Single-agent alkylators (eg, chlorambucil or cyclophosphamide) ± rituximab**
- **Radioimmunotherapy[d,e] (category 2B)**

First-line Consolidation or Extended Dosing (optional)
- **Rituximab maintenance 375 mg/m² one dose every 8 wks for 12 doses for patients initially presenting with high tumor burden (category 1)**
- **If initially treated with single-agent rituximab, consolidation with rituximab 375 mg/m² one dose every 8 weeks for 4 doses**
- **Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)[d,e,f]**

Second-line and Subsequent Therapy
- **Chemoimmunotherapy (as listed under first-line therapy)**
- **Rituximab**
- **Lenalidomide ± rituximab**
- **Radioimmunotherapy[d,e] (category 1)**
- **Idelalisib[g]**
- **Fludarabine[h] + rituximab**
- **RFND[h,i] (rituximab, fludarabine, mitoxantrone, dexamethasone)**
- **See Second-line Therapy for DLBCL (BCEL-C 2 of 4) without regard to transplantability**

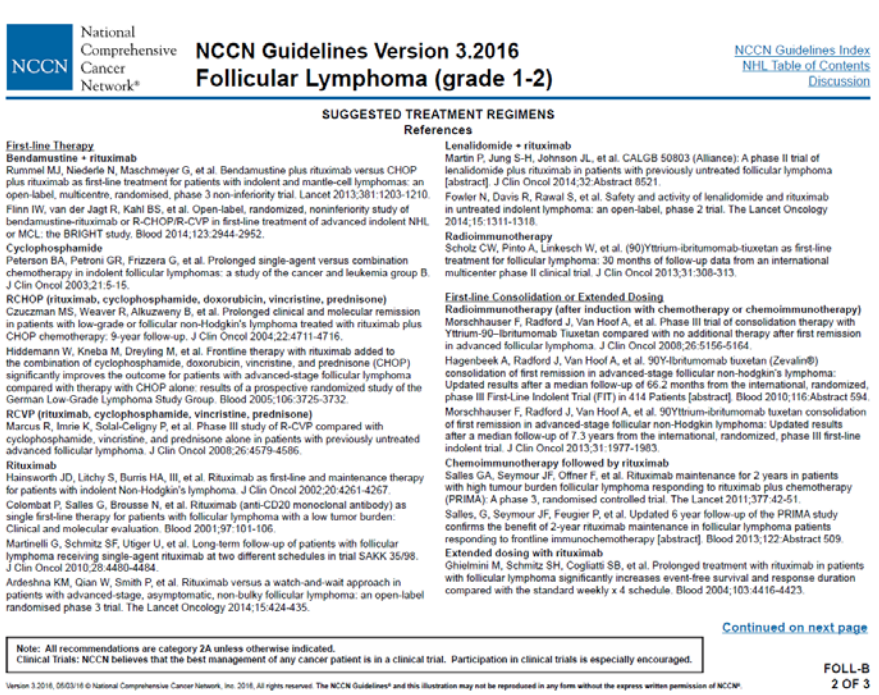
Second-line Consolidation or Extended Dosing
- **Rituximab maintenance 375 mg/m² one dose every 12 wks for 2 years (category 1) (optional)**
- **High-dose therapy with autologous stem cell rescue**
- **Allogeneic stem cell transplant for highly selected patients**
- **Obinutuzumab maintenance for rituximab-refractory disease (category 2B) (1 g every 8 wks for total of 12 doses)**

For patients with locally bulky or locally symptomatic disease, consider ISRT 4–30 Gy ± additional systemic therapy.

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)
See monoclonal antibody and viral reactivation (NHODG-B)

[a] See references for regimens FOLL-B 2 of 3 and FOLL-B 3 of 3.
[b] The choice of initial therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with SCR). Therefore, treatment selection is highly individualized.
[c] In combination chemotherapy, addition of rituximab has consistently increased overall response rate, response duration, and progression-free survival. In addition, some studies have demonstrated an overall survival benefit.
[d] Selection of patients requires adequate marrow cellularity >15% and <25% involvement of lymphoma in bone marrow, and platelets >100,000. In patients with prior autologous stem cell rescue, referral to a tertiary care center is highly recommended for radioimmunotherapy.
[e] If radioimmunotherapy is considered, bilateral cores are recommended and the pathologist should provide the percent of overall cellular elements and the percent of cellular elements involved in the marrow. Cytogenetics ± FISH for known MDS markers. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT treatment.
[f] The full impact of an induction regimen containing rituximab on RIT consolidation is unknown.
[g] See Special Considerations for the Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib)(NHODG-E).
[h] Fludarabine-containing regimens negatively impact stem cell mobilization for transplant.
[i] RFND regimen may be associated with stem cell toxicity and secondary malignancies (see Discussion).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Follicular Lymphoma (grade 1-2)

SUGGESTED TREATMENT REGIMENS
References

First-line Therapy

Bendamustine + rituximab
Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203-1210.

Flinn IW, van der Jagt R, Kahl BS, et al. Open-label, randomized, noninferiority study of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of advanced indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.

Cyclophosphamide
Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5-15.

RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
Czuczman MS, Weaver R, Alkuzweny B, et al. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol 2004;22:4711-4716.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725-3732.

RCVP (rituximab, cyclophosphamide, vincristine, prednisone)
Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 2008;26:4579-4586.

Rituximab
Hainsworth JD, Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent Non-Hodgkin's lymphoma. J Clin Oncol 2002;20:4261-4267.

Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: Clinical and molecular evaluation. Blood 2001;97:101-106.

Martinelli G, Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol 2010;28:4480-4484.

Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. The Lancet Oncology 2014;15:424-435.

Lenalidomide + rituximab
Martin P, Jung S-H, Johnson JL, et al. CALGB 50803 (Alliance): A phase II trial of lenalidomide plus rituximab in patients with previously untreated follicular lymphoma [abstract]. J Clin Oncol 2014;32:Abstract 8521.

Fowler N, Davis R, Rawal S, et al. Safety and activity of lenalidomide and rituximab in untreated indolent lymphoma: an open-label, phase 2 trial. The Lancet Oncology 2014;15:1311-1318.

Radioimmunotherapy
Scholz CW, Pinto A, Linkesch W, et al. (90)Yttrium-ibritumomab-tiuxetan as first-line treatment for follicular lymphoma: 30 months of follow-up data from an international multicenter phase II clinical trial. J Clin Oncol 2013;31:308-313.

First-line Consolidation or Extended Dosing

Radioimmunotherapy (after induction with chemotherapy or chemoimmunotherapy)
Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with Yttrium-90–Ibritumomab Tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 2008;26:5156-5164.

Hagenbeek A, Radford J, Van Hoof A, et al. 90Y-Ibritumomab tiuxetan (Zevalin®) consolidation of first remission in advanced-stage follicular non-hodgkin's lymphoma: Updated results after a median follow-up of 66.2 months from the international, randomized, phase III First-Line Indolent Trial (FIT) in 414 Patients [abstract]. Blood 2010;116:Abstract 594.

Morschhauser F, Radford J, Van Hoof A, et al. 90Yttrium-ibritumomab tuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: Updated results after a median follow-up of 7.3 years from the international, randomized, phase III first-line indolent trial. J Clin Oncol 2013;31:1977-1983.

Chemoimmunotherapy followed by rituximab
Salles GA, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial. The Lancet 2011;377:42-51.

Salles, G, Seymour JF, Feugier P, et al. Updated 6 year follow-up of the PRIMA study confirms the benefit of 2-year rituximab maintenance in follicular lymphoma patients responding to frontline immunochemotherapy [abstract]. Blood 2013;122:Abstract 509.

Extended dosing with rituximab
Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.

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NCCN Guidelines Version 3.2016
Extranodal Marginal Zone B-Cell Lymphoma
Gastric MALT Lymphoma

DIAGNOSIS

ESSENTIAL:
- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.[a,b]
- Diagnosis of gastric MALT lymphoma requires an endoscopic biopsy and an FNA is never adequate.
- Adequate immunophenotyping to establish diagnosis[c,d]
  - IHC Panel: CD20, CD3, CD5, CD10, BCL2, kappa/lambda, CD21 or CD23, cyclin D1, BCL6 with or without
  - Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD10
- Helicobacter pylori (H. pylori) stain (gastric), if positive, then PCR or FISH for t(11;18)[e]
- FISH or PCR: t(14;18)

USEFUL UNDER CERTAIN CIRCUMSTANCES:
- Molecular analysis to detect: antigen receptor gene rearrangements; MYD88 mutation status to differentiate WM versus MZL if plasmacytic differentiation present
- Cytogenetics or FISH: t(1;14); t(3;14); t(11;14);[f] t(11;18)

WORKUP

ESSENTIAL:
- Physical exam with attention to nongastric sites (eyes, skin)
- Performance status
- CBC, differential, platelets
- Comprehensive metabolic panel
- LDH
- If H. pylori negative by histopathology, then use noninvasive H. pylori testing (stool antigen test, urea breath test, blood antibody test)
- Hepatitis B testing[g] if rituximab contemplated
- Hepatitis C testing
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan (especially if ISRT anticipated)
- Pregnancy testing in women of child-bearing age (if chemotherapy planned)

USEFUL IN SELECTED CASES:
- Bone marrow biopsy ± aspirate
- MUGA scan/echocardiogram if anthracycline or anthracenedione-based regimen is indicated
- Endoscopy with ultrasound (if available) with multiple biopsies of anatomical sites[h]
- Discussion of fertility issues and sperm banking
- SPEP

→ See Initial Therapy (MALT-2)

[a]Nondiagnostic atypical lymphoid infiltrates that are H. pylori positive should be rebiopsied to confirm or exclude lymphoma prior to treatment of H. pylori.
[b]Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
[c]Typical immunophenotype: CD10-, CD5-, CD20+, cyclin D1-, BCL2- follicles.
[d]See Use of Immunophenotyping/Genetic Testing in Differential Diagnosis of Mature B-Cell and NK/T-Cell Neoplasms (NHODG-A).
[e]Locally advanced disease is more likely in patients with gastric MALT lymphoma with t(11;18), which is less likely to respond to antibiotics.
[f]If IHC for cyclin D1 is positive, FISH for t(11;14) is not necessary.
[g]Hepatitis B testing is indicated because of the risk of reactivation with immunotherapy + chemotherapy. Tests include hepatitis B surface antigen and core antibody for a patient with no risk factors. For patients with risk factors or previous history of hepatitis B, add e-antigen. If positive, check viral load and consult with gastroenterologist.
[h]This is particularly useful for H. pylori-positive cases because the likelihood of tumor response is related to depth of tumor invasion.

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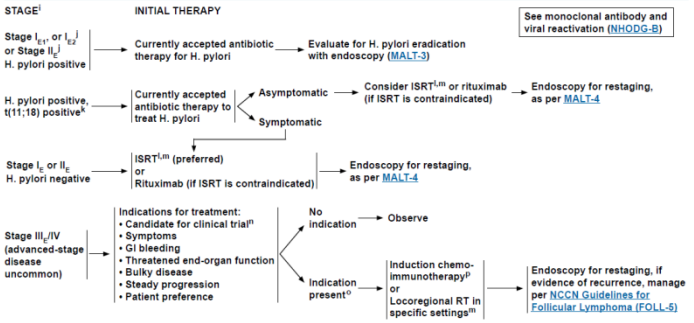
NCCN Guidelines Version 3.2016
Extranodal Marginal Zone B-Cell Lymphoma
Gastric MALT Lymphoma



[i]See Lugano Staging System for Gastrointestinal Lymphomas (MALT-A).
[j]Involvement of submucosa or regional lymph nodes are much less likely to respond to antibiotic therapy. If there is persistent disease after evaluation, RT may be considered earlier in the course.
[k]t(11;18) is a predictor for lack of tumor response (<5%) to antibiotics. Antibiotics are used in these patients to eradicate the H. pylori infection. These patients should be considered for alternative therapy of the lymphoma. Liu H, Ye H, Ruskone-Fourmestraux A, et al. t(11;18) is a marker for all stage gastric MALT lymphomas that will not respond to H. pylori eradication. Gastroenterology 2002;122:1286-1294.
[l]If negative by both histology and serum antibodies, RT is recommended.
[m]See Principles of Radiation Therapy (NHODG-D).
[n]Given incurability with conventional therapy, consider investigational therapy as first line of treatment.
[o]Surgical resection is generally limited to specific clinical situations (ie, life-threatening hemorrhage).
[p]See Suggested Treatment Regimens (FOLL-B).

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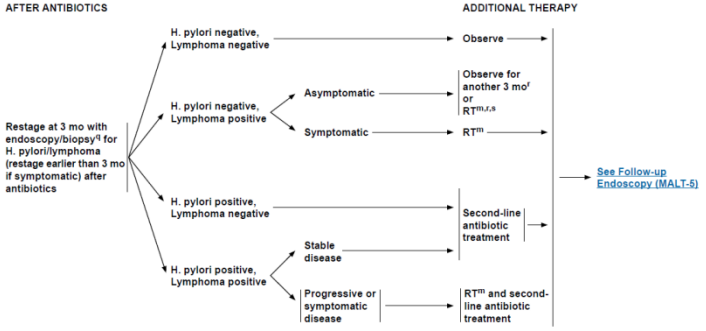
Extranodal Marginal Zone B-Cell Lymphoma
Gastric MALT Lymphoma

3-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY



[m]See Principles of Radiation Therapy (NHODG-D).
[q]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
[r]If re-evaluation suggests slowly responding disease or asymptomatic nonprogression, continued observation may be warranted. RT can be considered as early as 3 mo after observation but can be prolonged to 18 mo (category 2B).
[s]If patient originally had clinical Stage I_{E2} or Stage II_E, early RT should be considered if there is no response to antibiotics.

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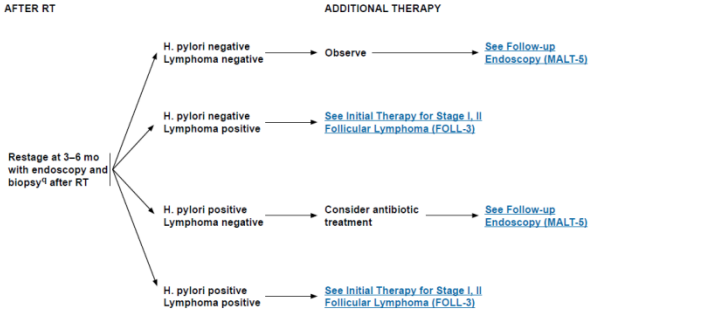
NCCN Guidelines Version 3.2016
Extranodal Marginal Zone B-Cell Lymphoma
Gastric MALT Lymphoma

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



[q]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).

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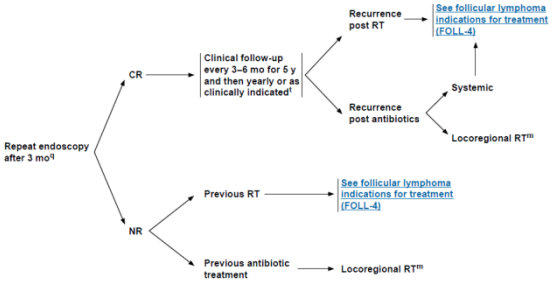
FOLLOW-UP ENDOSCOPY



[m]See Principles of Radiation Therapy (NHODG-D).
[q]Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated according to the NCCN Guidelines for Diffuse Large B-Cell Lymphoma (BCEL-1).
[t]Optimal interval for follow-up endoscopy and imaging is not known. Follow-up endoscopy and imaging at NCCN Member Institutions is driven by symptoms.

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