Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-421 Zanubrutinib

Stand: Januar 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Zanubrutinib
[zur Behandlung des Marginalzonenlymphoms (MZL), nach mindestens einer vorherigen anti-CD20-basierte Therapie]

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“.* Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung zur Behandlung hochmaligner Non-Hodgkin-Lymphome.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Strahlentherapie - Chirurgische Resektion (z. B. Splenektomie) - Allogene und autologe Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Stand: 01.04.2020): - Off-Label-Indikation für Fludarabin: Fludarabin in Kombination mit Cyclophosphamid, Mitoxantron und Rituximab (FCM-R) bei geeigneten Patienten mit niedrig oder intermediär malignen Non-Hodgkin-Lymphomen der B-Zellreihe (CD20 positive NHL, u.a. lymphozytisch, lymphoplasmozytisch, lymphoplasmazytoid, follikulär Grad 1 oder 2, Mantelzell-, Marginalzonen-, nicht multiples Myelom, nicht Haarzellleukämie) und Resistenz auf CHOP (mit oder ohne Rituximab).
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:	
Zanubrutinib L01EL03 Brukinsa®	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Brukinsa® ist für die Behandlung erwachsener Patienten mit Marginalzonenlymphom (MZL) indiziert, die mindestens eine vorherige anti-CD20-basierte Therapie erhalten haben.
Non-Hodgkin-Lymphom	
Bendamustin L01AA09 generisch	Monotherapie bei indolenten Non-Hodgkin-Lymphomen bei Patienten mit Progression während oder innerhalb von 6 Monaten nach Behandlung mit Rituximab oder mit einer Rituximab-haltigen Therapie.
Bleomycin L01DC01 generisch	Non-Hodgkin-Lymphome von intermediärem oder hohem Malignitätsgrad im Erwachsenenalter. Bleomycinsulfat wird bei diesen Erkrankungen üblicherweise in Kombination mit anderen Zytostatika verwendet.
Chlorambucil L01AA02 generisch	niedrig maligne Non-Hodgkin-Lymphome
Cyclophosphamid L01AA01 generisch	Das Arzneimittel ist 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 generisch	Cytarabin wird in Kombination mit anderen Zytostatika in konventionellen Dosen eingesetzt zur: - Behandlung von Non-Hodgkin-Lymphomen von intermediärem und hohem Malignitätsgrad im Erwachsenenalter Cytarabin wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: - refraktären Non-Hodgkin-Lymphomen
Dexamethason H02AB02 generisch	Behandlung von symptomatischen multiplem Myelom, akuter lymphatischer Leukämie, Hodgkin-Lymphom und Non-Hodgkin-Lymphom in Kombination mit anderen Arzneimitteln.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Doxorubicin L01DB01 generisch	— Non-Hodgkin-Lymphom
Etoposid L01CB01 generisch	Etoposid ist in Kombination mit anderen zugelassenen Chemotherapeutika angezeigt zur Behandlung von Non-Hodgkin-Lymphomen bei erwachsenen und pädiatrischen Patienten.
Methotrexat L01BA01 generisch	Non-Hodgkin-Lymphome: - im Erwachsenenalter: Zur Behandlung von Non-Hodgkin-Lymphomen von intermediärem oder hohem Malignitätsgrad in Kombination mit anderen zytostatischen Arzneimitteln
Methylprednisolon H02AB04 generisch	Blutkrankheiten/Tumorerkrankungen - Autoimmunhämolytische Anämie - Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen, Anwendung im Rahmen antiemetischer Schemata
Mitoxantron L01DB07 generisch	Mitoxantron ist indiziert zur Behandlung des Non-Hodgkin-Lymphoms.
Prednisolon H02AB06 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome
Prednison H02AB07 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome
Trofosfamid L01AA07 Ixoten	Dieses Arzneimittel ist ein Zytostatikum. Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet.
Vinblastin L01CA01 generisch	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	Vincristin wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01CA02 generisch	- malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen
Arzneimittel mit explizierter Zulassung für das Marginalzonenlymphom:	
Keine Arzneimittel mit expliziter Zulassung für das Marginalzonenlymphom vorhanden	

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-421 (Zanubrutinib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12. Januar 2022

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Abkürzungsverzeichnis

AHS	Alberta Health Services
BCCA	British Columbia Cancer Agency
AMED	Allied and Complementary Medicine Database
AM-RL	Arzneimittel-Richtlinie
ASCO	American Society of Clinical Oncology
ATG	Antithymozytenglobulin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BEAM	BCNU, Etoposid, Cytarabin, Melphalan
B-NHL	B-Zell-Non-Hodgkin-Lymphom
CAR	Chimärer Antigenrezeptor
CCO	Cancer Care Ontario
CHOP	Cyclophosphamid, Doxorubicin, Vincristin, Prednison
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CLL	Chronisch lymphatische Leukämie
CNS	Zentrales Nervensystem
CR	Komplette Remission
CT	Computertomographie
CTCL	Kutanes T-Zell-Lymphom
CVP	Cyclophosphamid, Vincristin, Prednison
DLBCL	Diffus großzelliges B-Zell-Lymphom
DSG	Disease Site Group
Embase	Excerpta Medica Database
ESMO	European Society for Medical Oncology
FCM	Fludarabin, Cyclophosphamid, Mitoxantron
FDA	U.S. Food and Drug Administration
FDG	Fluordesoxyglukose
FISH	Fluoreszenz-in-situ Hybridisierung
G-BA	Gemeinsamer Bundesausschuss
GC	Guideline Committee
GI	gastrointestinal
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluati
Gy	Gray
HDCT	Hochdosis-Chemotherapie

HDT	Hochdosistherapie
HIV	Humanes Immundefizienz-Virus
IPI	International Prognostic Index
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRT	Involved Site-Strahlentherapie
LDH	Lactatdehydrogenase
LoE	Level of Evidence
LPL	Lymphoplasmozytisches Lymphom
MALT	Mucosa Associated Lymphoid Tissue
MCL	Mantelzelllymphom
MDS	Myelodysplastisches Syndrom
MF	Mycosis fungoides
MIPI	International Prognostic Index, modifiziert
MZL	Maginalzonenlymphom
NCCN	National Comprehensive Cancer NetworkF
NHL	Non-Hodgkin-Lymphom
NICE	National Institute for Health and Care Excellence
NMZL	Nodales Marginalzonenlymphom
NR	Non-Response
PAC	Lansoprazol, Clarithromycin, Amoxicillin
PCBCL	Primär kutanes B-Zell-Lymphom
PCDLBCL	Primär kutanes diffus-großzelliges B-Zell-Lymphom
PCFCL	Primär kutanes follikuläres B-Zell-Lymphom
PCMZL	Primär kutanes Marginalzonen-B-Zell-Lymphom
PCTLD	Primär kutane CD30+ lymphoproliferative Erkrankung
PET	Positronenemissionstomographie
PFS	Progressionsfreies Überleben
PI3K	Phosphatidylinositol-3-Kinase
PR	Partielle Remission
PTCL	Peripheres T-Zell-Lymphom
RCT	Randomisierte kontrollierte Studie
R-FCM	Rituximab, Fludarabin, Cyclophosphamid, Mitoxantron
RT	Radiotherapie
R-TBM	Rituximab, Thiotepa, Busulfan, Melphalan
SAGE	Standards and Guidelines Evidence
SCI-Expanded	Science Citation Index Expanded

SIGN	Scottish Intercollegiate Guidelines Network
SLL	Kleinzelliges lymphozytisches Lymphom
SMZL	Splenisches Marginalzonenlymphom
SS	Sézary-Syndrom
SSCI	Social Sciences Citation Index
TBI	Ganzkörperbestrahlung
TRIP	Turn Research into Practice Database
TTP	Zeit bis zur Progression
WHO	World Health Organization

1 Indikation

Behandlung erwachsener Patienten mit Marginalzonen-Lymphom (MZL), die mindestens eine vorherige Therapie erhalten haben.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Marginalzonenlymphom durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 14.12.2021 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 178 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.2 Systematische Reviews

Es konnten keine relevanten systematischen Reviews identifiziert werden.

3.3 Leitlinien

National Institute for Health and Care Excellence (NICE), 2016 [5].

Non-Hodgkin's lymphoma: diagnosis and management

Zielsetzung

This guideline covers diagnosing and managing non-Hodgkin's lymphoma in people aged 16 years and over. It aims to improve care for people with non-Hodgkin's lymphoma by promoting the best tests for diagnosis and staging and the most effective treatments for 6 of the subtypes. Tests and treatments covered include excision biopsy, radiotherapy, immunochemotherapy and stem cell transplantation.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- The following databases were included in the literature search: Cochrane Library, Medline and Premedline, Excerpta Medica (Embase), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, Allied and Complementary Medicine (AMED).
- In accordance with the 'NICE guidelines manual' (NICE 2012) searches were updated and re-run 8 weeks before the guideline was submitted to NICE for stakeholder consultation […]. Any evidence published after this date was not included. For the purposes of updating this guideline, 1st September 2015 should be considered the starting point for searching for new evidence.

LoE

Tabelle 1: 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.

GoR

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. Some recommendations were made with more certainty than others. Recommendations were based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence.

For all recommendations, it is expected that a discussion will take place with the patients about the risks and benefits of the interventions, and their values and preferences […].

Terms used within this guideline are:

- 'Offer' – for the vast majority of patients, and intervention will do more good than harm (based on high quality evidence)
- 'Do not offer' – the intervention will not be of benefit for most patients (based on high quality evidence)
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients (based on poor quality evidence or no evidence). The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Empfehlungen

4 Management

4.2 Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma

4.2.1 First line treatment

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

Gastric MALT lymphoma: localised disease

Offer 1 or more lines of Helicobacter pylori eradication therapy, without any concurrent therapy, to people with H. pylori-positive gastric MALT lymphoma.

Consider H. pylori eradication therapy for people with H. pylori-negative gastric MALT lymphoma.

Consider 'watch and wait' (observation without therapy) for people with gastric MALT lymphoma that responds clinically and endoscopically to H. pylori eradication therapy but

who have residual disease shown by surveillance biopsies of the stomach, unless high-risk features are present.

For people with residual MALT lymphoma after H. pylori eradication therapy who are at high risk of progression [H. pylori-negative at initial presentation or t(11:18) translocation], consider a choice of the following, in discussion with the person:

- chemotherapy (for example, chlorambucil or CVP) in combination with rituximab[b] or
- gastric radiotherapy

For people with progressive gastric MALT lymphoma, offer a choice of:

- chemotherapy (for example, chlorambucil or CVP) in combination with rituximab[c] or
- gastric radiotherapy.

[b] At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented […].

[c] At the time of publication (July 2016) rituximab did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented […].

Quality of the evidence

The quality of the evidence ranged from very low to high quality for individual outcomes as assessed using GRADE. Evidence was downgraded for imprecision, indirectness and for study limitations.

Specific issues with the evidence included:

- Underpowered randomised control trials
- Non-randomised comparative studies
- Non-comparative study designs
- Variation in measurement of outcomes (e.g. lymphoma regression, complete response)
- Variation in the diagnostic tests for helicobacter pyloridetection
- […]

Trade-off between clinical benefits and harms

Patients with Gastric MALT lymphoma

The GC made a strong reocmmendation for helicobacter pylori antibiotic eradication therapy in all patients with gastric MALT lymphoma because they thought it was important to reduce the use of toxic systemic therapies in some of these patients. There was evidence for the use of helicobacter eradication therapy in patients with gastric MALT lymphoma positive for helicobacter pylori. However, the evidence base for the use of helicobacter eradication therapy in patients with gastric MALT lymphoma negative for helicobacter pylori was limited but suggested that in these patients around 15% will not require further treatment with systemic therapies. In addition, the GC considered that the detection of helicobacter pylori can vary depending on the diagnostic test used. Therefore, the GC used their clinical judgement to make a recommendation to use helicobacter eradication therapy in patients with gastric MALT lymphoma negative for helicobacter eradication therapy (in case this indicates a false negative).

In patients with gastric MALT lymphoma who received antibiotic therapy, the GC considered that the recommendation for these patients needed to include assessment of response to antibiotic therapy in order to inform further treatment in these patients […].

The use of toxic systemic therapies is associated with treatment related morbidity and toxic side effects, and while the GC acknowledged that for some patients this is unavoidable due to the requirement for toxic systemic therapies, they considered that

the recommendations for patients with gastric MALT lymphoma will reduce the number of patients needing to receive toxic systemic treatment overall […].

The GC considered that in patients with gastric MALT lymphoma who receive helicobacter eradication therapy but do not respond or have progression in their lymphoma resulting in a need for systemic therapies, there was no evidence to suggest that the delay in starting intensive systemic therapies as a result of undergoing helicobacter eradication therapy first, is unlikely to impact on overall survival rates.

Clinical evidence

4.2.1.1.6 What is the most effective management strategy for patients with Gastric MALT lymphoma after treatment for helicobacter pylori infection eradication?

No response to antibiotic therapy

One systematic review (Zullo et al. 2010) provided evidence from 29 studies of low quality evidence assessing treatment of low-grade Gastric MALT lymphoma (stage IE1-IE28 or IIE1 according to Ann Arbor classification as modified by Musshof) unresponsive to helicobacter pylori eradication therapy. The 29 studies (21 prospective, 8 retrospective) provided evaluable data from 329 patients, of which 315 underwent oncologic therapy due to lymphoma persistence (successful eradicated patients n=233, infection persistence despite one or more antibiotic therapy n=45, lymphoma relapse at follow-up n=37). A total of 68 (21.6%) received chemotherapy, 112 (35.6%) received radiotherapy, 27 received rituximab (11.6%) and 80 underwent surgery (25.4%). Radiotherapy achieved a significantly higher remission rate (97.3%) compared to chemotherapy (85.3%, p=0.007). Remission rates for surgery (92.5%) were comparable to radiotherapy (p=0.2) and chemotherapy (p=0.2). Following monotherapy, lymphoma remission rate (59.3%) was significantly lower as compared with radiotherapy (p<0.001), surgery (p=0.004) and chemotherapy (p=0.006). When comparing the lymphoma remission rates achieved by a single therapy (overall considered: 287 patients) with that of combined treatments no statistically significant differences emerged (89.6% versus 96.4%, p=0.6). Zullo et al. (2010) reported that radiotherapy alone was both the most frequently chosen therapy and the most effective in patients with low grade gastric MALT lymphoma unresponsive to anti-helicobacter therapy. However, Zullo et al. (2010) also reported that of the 329 evaluable patients 14 (4.2%) had a reported remission at follow-up without any further therapy following H. pylori eradiation.

Gilson D et al., 2019 [2].

British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018

Zielsetzung/Fragestellung

to provide up-to-date, evidence-based recommendations on the management of primary cutaneous lymphoma in the U.K.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium ohne Patientenvertreter;
- Interessenkonflikte dargelegt, keine Angaben zur Finanzierung der Leitlinie;
- Systematische Suche, Auswahl und Bewertung der Evidenz;

- Wenig Angaben zu Konsensusprozessen und externen Begutachtungsverfahren, Patientenvertreter konnten die Leitlinie kommentieren;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Unklar, ob regelmäßige Überprüfung der Aktualität gesichert ist.

Recherche/Suchzeitraum:

- PubMed, MEDLINE and Embase databases and the Cochrane Library,
- to February 2018

LoE

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, 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, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal*
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*Studies with a level of evidence '-' should not be used as a basis for making a recommendation.

GoR

Class	Evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	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 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+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT: randomized controlled trial; NICE: National Institute for Health and Care Excellence.

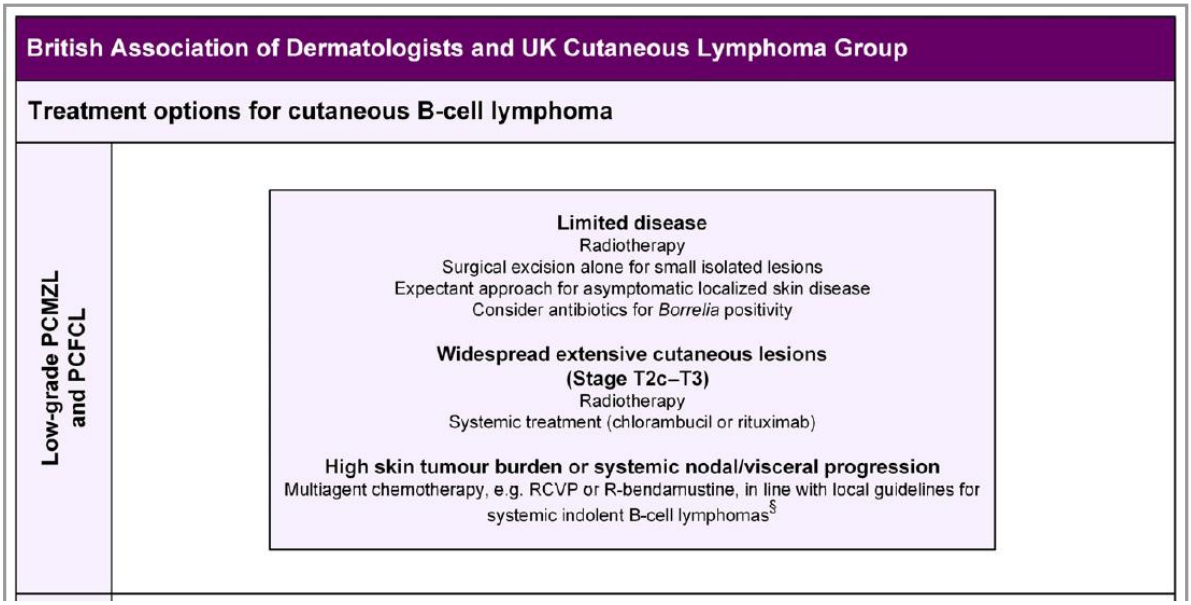
Sonstige methodische Hinweise

- These guidelines were first produced jointly by the British Association of Dermatologists and the U.K. Cutaneous Lymphoma Group (2003); reviewed and updated 2018.

Empfehlungen

8.0 Treatment of primary cutaneous B-cell lymphomas

Abbildung 1: Treatment guidelines for cutaneous B-cell lymphoma.



8.1 Primary cutaneous marginal zone and follicle centre lymphoma

Solitary lesions should be treated with the intention of cure. (Strength of recommendation B)

Small individual skin lesions can be completely excised and monitored, but treatment with radiotherapy (tumour or scar with a 2-cm margin of skin to define CTV) is preferred to reduce the risk of local relapse. (Strength of recommendation B)

Following a diagnostic biopsy, the first-line treatment for individual skin lesions should be radiotherapy. The radiotherapy CTV should be the tumour plus a 1_5-cm margin of normal skin around the tumour. (Strength of recommendation B)

8.1.1 Excision

Complete surgical excision may be considered for small lesions for both diagnosis and therapy, but there is no literature to guide margins of resection. In patients with PCMZL and PCFCL treated with complete excision, over 40% are reported to relapse.[11] Where the lesion has been excised completely, a policy of monitoring or radiotherapy to the scar with a 1_5-cm margin to CTV around the scar[238] can be considered to reduce the risk of local recurrence. In larger lesions where complete excision would result in a significant cosmetic scar or functional defect, a diagnostic biopsy should be performed and followed by radiotherapy.

8.1.2 Antibiotics

In patients with PCMZL and positive B. burgdorferi serology there are reports of complete response following antibiotic treatment.[11] The U.K. Health Protection Agency guidance on treatment for Borrelia with oral antibiotics should be followed before considering other therapies.

8.1.3 Radiotherapy

Radiotherapy is the standard treatment for both PCMZL and PCFCL. The EORTC consensus recommendations[11] reported data on 132 patients with PCMZL and 460 with PCFCL treated with radiotherapy. Of the patients with PCMZL, 99% achieved complete remission and only 46% of patients showed one or more relapses. Extracutaneous progression was reported in only three of 132 patients, one of whom died of lymphoma. The radiotherapy doses reported varied from 10 Gy to 50 Gy, and most studies used a treatment margin around the tumour of 1–5 cm.

Of the patients with PCFCL, almost all achieved complete response with radiotherapy. Three major studies in PCFCL combining 147 patients reported a relapse rate of 30% when margins > 2 cm were used.[248–250] This differs from the

relapse rate of 67% in a small study that used margins of 0_5– 1 cm, where frequent in-field and marginal recurrences were reported.[251] On the basis of this evidence, it is recommended that the radiotherapy CTV should be the tumour plus a 1_5- cm margin of normal skin around the tumour.[238]

In the U.K., the standard radiotherapy dose for indolent non-Hodgkin lymphoma is 24 Gy in 12 fractions, based on the results of a multicentre, prospective RCT comparing 40 Gy vs. 24 Gy in 2-Gy fractions for indolent follicular and marginal zone lymphoma.[252] Lower doses or shorter fractionation schedules (e.g. 8 Gy in two fractions for multiple lesions; 15 Gy in five fractions for solitary lesions) have been used in many centres with good results.[253] The Leiden group have reported complete response rates of 72% and re-treatment rates of 29% with 4 Gy in two fractions, and complete response achieved in all patients retreated with 20 Gy in eight fractions.[106] A U.K. RCT has shown that 4 Gy in two fractions can be effective in the palliative setting, with an ORR of 74,1% (complete response rate 44_3%). However, this was significantly inferior to 24 Gy in 12 fractions, with an ORR of 81% and complete response rate of 60_3%.[254] The OS rate was the same with both fractionations but there were fewer patients with PCMZL or PCFCL in this study.

Active monitoring is an option for patients with asymptomatic disease. (Strength of recommendation D (GPP))

Systemic chemotherapy should be reserved for patients with widespread extensive lesions or high tumour burden (stage T2c–T3), or patients with nodal or visceral progression. Treatment is palliative, and for disease confined to the skin consideration should be given to single-agent rituximab, or chlorambucil, as this is well tolerated and effective. Further choice of chemotherapy should be in line with local guidelines for the management of indolent lymphomas. (Strength of recommendation C)

8.1.5 Rituximab

The limited data on rituximab are based on case reports and small case series. Treatment is either as systemic therapy 375 mg m^{-2} intravenously weekly for 4–8 weeks, or as intralesional therapy 5–30 mg one to three times per week. For intralesional therapy, the complete response rates for both PCMZL and PCFCL are reported to be 70–90%, with relapse rates of 40–60%.256 Systemic therapy is preferred for more widespread disease. For systemic therapy, the complete response rates for PCMZL and PCFCL are similar, ranging from 67% to 87,5%, but again the relapse rates are relatively high, with a median time to relapse of 25 months.257,258

8.1.6 Chemotherapy

There are relatively little data published on the results of chemotherapy for PCMZL and PCFCL. For PCMZL, chlorambucil for multifocal skin lesions is associated with a complete response rate of 64% and relapse rate of 33%, based on reports of 14 patients. CHOP is associated with a complete response rate of 85% and relapse rate of 57%.11 For PCFCL, cumulative data on 104 patients from eight studies treated with CHOP or CHOP-like regimens for widespread skin lesions or high skin tumour burden give a complete response rate of 85% with a relapse rate of 48%.11 Only five patients received chemotherapy without an anthracycline (COP or CVP; see section 6_3_2). There is a lack of data on the efficacy of rituximab–CVP and rituximab–bendamustine, which are the most commonly used regimens in nodal or systemic indolent lymphomas, in disease confined to the skin.

As for systemic indolent lymphomas, it is appropriate to manage patients with disease confined to the skin with watchful waiting. Current evidence supports a role for single-agent chemotherapy or rituximab for those patients with extensive cutaneous disease and no systemic involvement. Patients with systemic disease or high disease burden failing to respond to single-agent systemic therapy should be managed according to local guidelines for the management of systemic disease.

Patients who relapse with nodal or visceral lymphoma should be treated according to local and national management guidelines for systemic lymphoma. (Strength of recommendation B)

Referenzen aus Leitlinien

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National Comprehensive Cancer Network (NCCN), 2021 [3].

B-Cell Lymphomas

Zielsetzung

The National Comprehensive Cancer Network (NCCN®) Guidelines (NCCN® Guidelines) were developed […] with the aim to provide recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of NHL […].

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund limitierter höherwertiger Evidenz zu Behandlungsmethoden für Patientinnen und Patienten mit Marginalzonenlymphom wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; (⇨ NCCN Guidelines Panel Disclosures)
- Systematische Suche erwähnt, aber keine Details beschrieben (z. B. Suchzeitraum), keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Konsensfindung erwähnt, aber nicht detailliert beschrieben, externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind eindeutig, Literaturverknüpfung mit Evidenzbewertung im Hintergrundtext[1];
- Weder Gültigkeit, noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

Prior to the update of this version of the NCCN Guidelines® for B-cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in FL [and] MLZs published since the previous Guidelines update […].

LoE/GoR

Tabelle 2: NCCN Categories of Evidence and Consensus

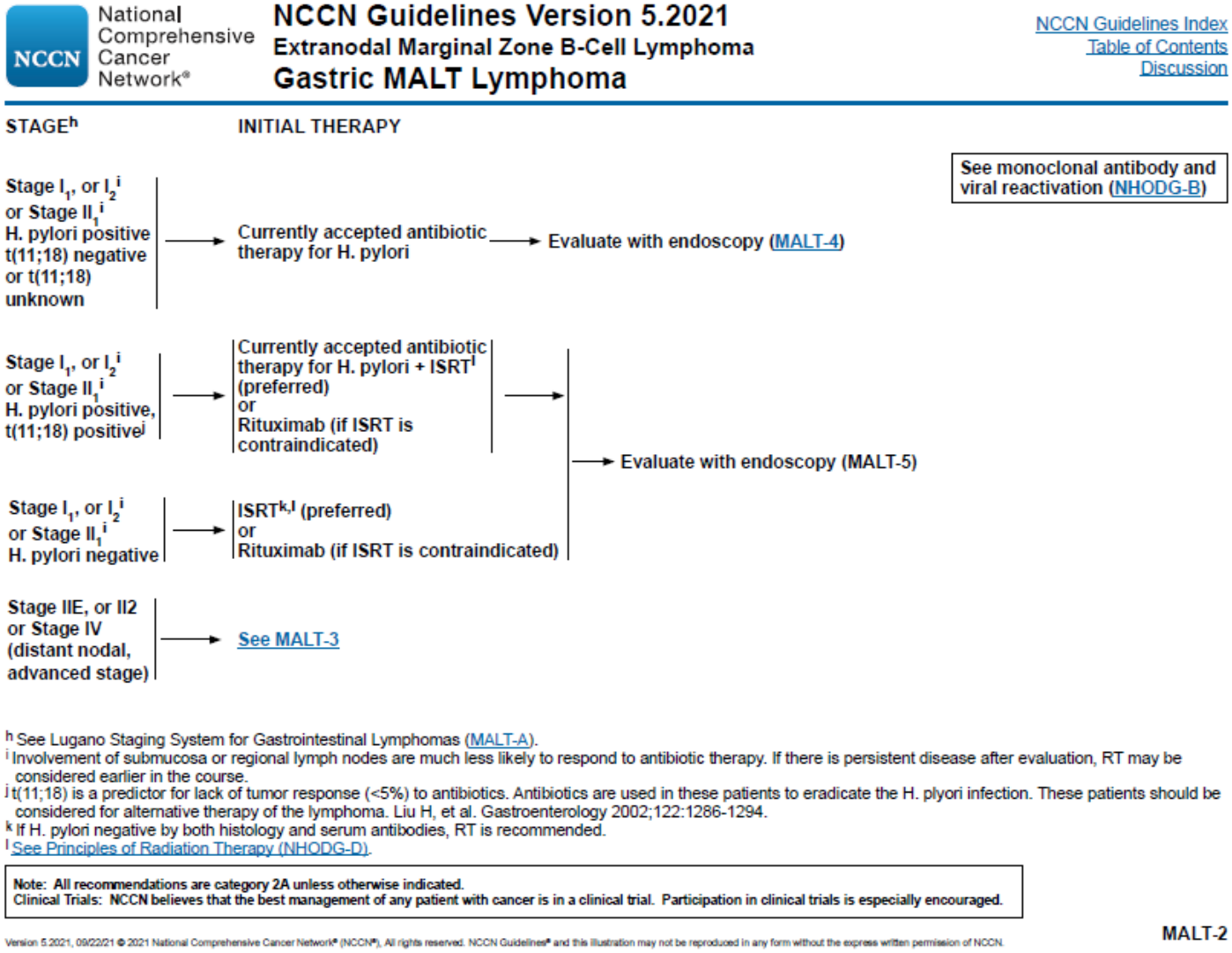
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Sonstige methodische Hinweise

Note: All recommendations are category 2A unless otherwise indicated.

[1] Der Hintergrundtext zu den Empfehlungen wird zurzeit überarbeitet.

Empfehlungen



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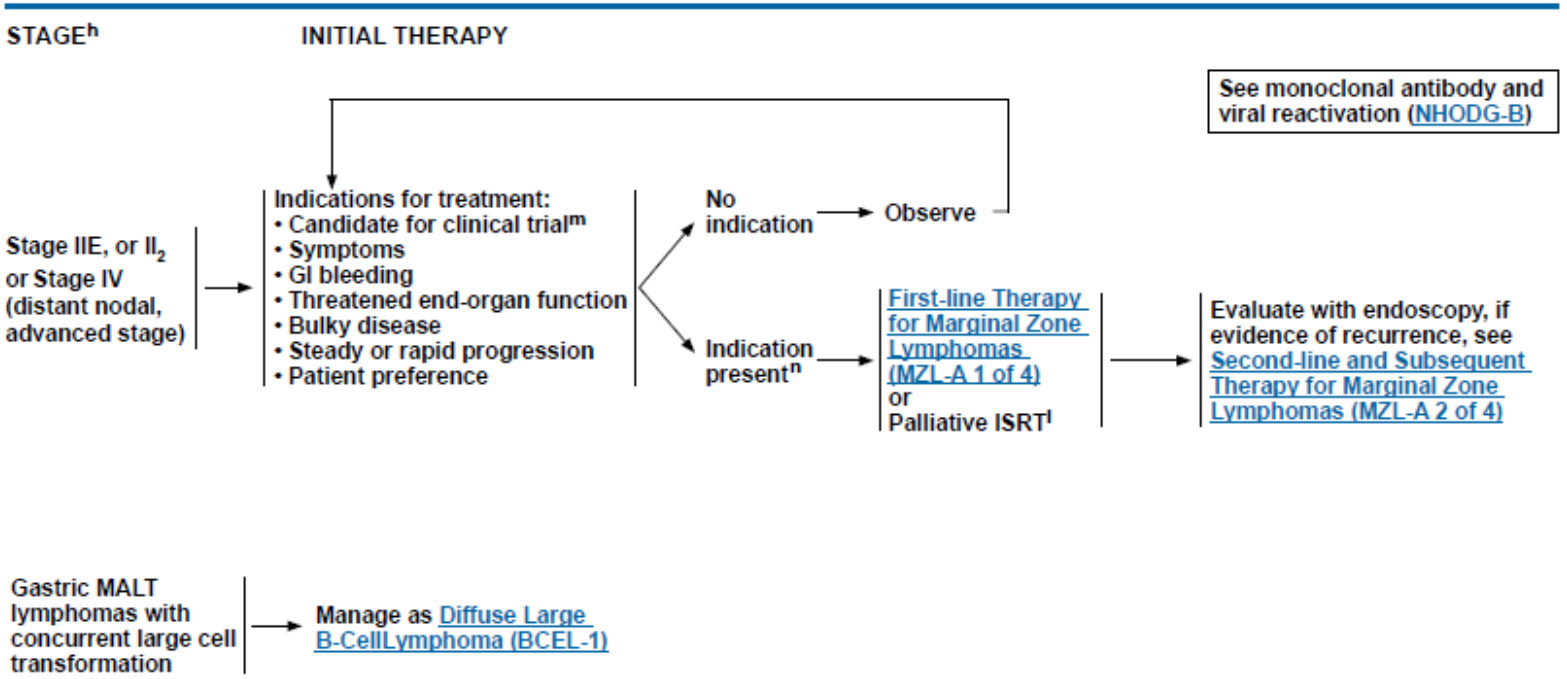

[h] See Lugano Staging System for Gastrointestinal Lymphomas (MALT-A).
[l] See Principles of Radiation Therapy (NHODG-D).
[m] Given incurability with conventional therapy, consider investigational therapy as first line of treatment.
[n] Surgical resection is generally limited to specific clinical situations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

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

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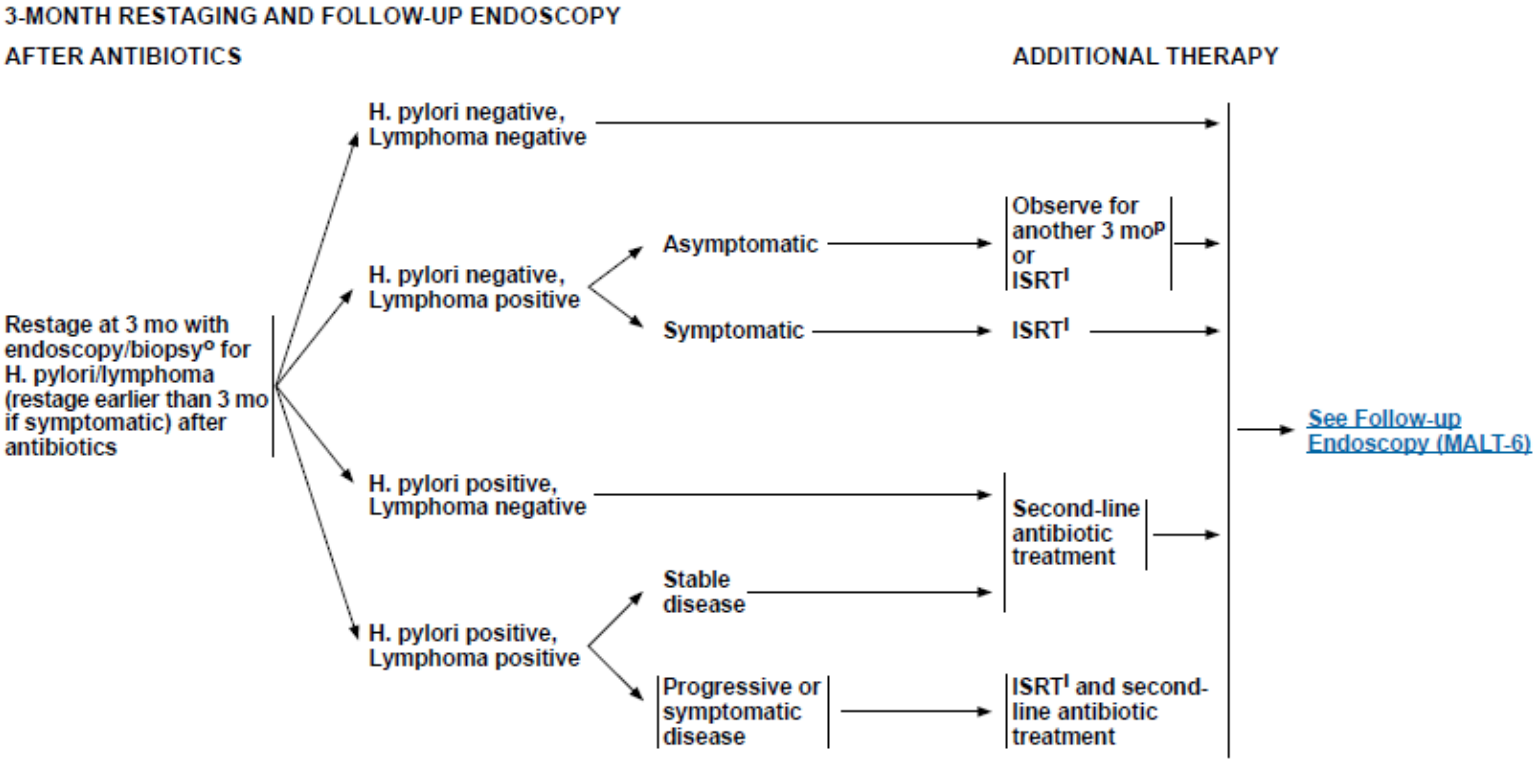

[l] See Principles of Radiation Therapy (NHODG-D).
[o] Reassessment to rule out H. pylori by institutional standards. Biopsy to rule out large cell lymphoma. Any area of DLBCL should be treated as DLCBL (BCEL-1).
[p] If re-evaluation suggests slowly responding disease or asymptomatic nonprogression,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

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

MALT-4

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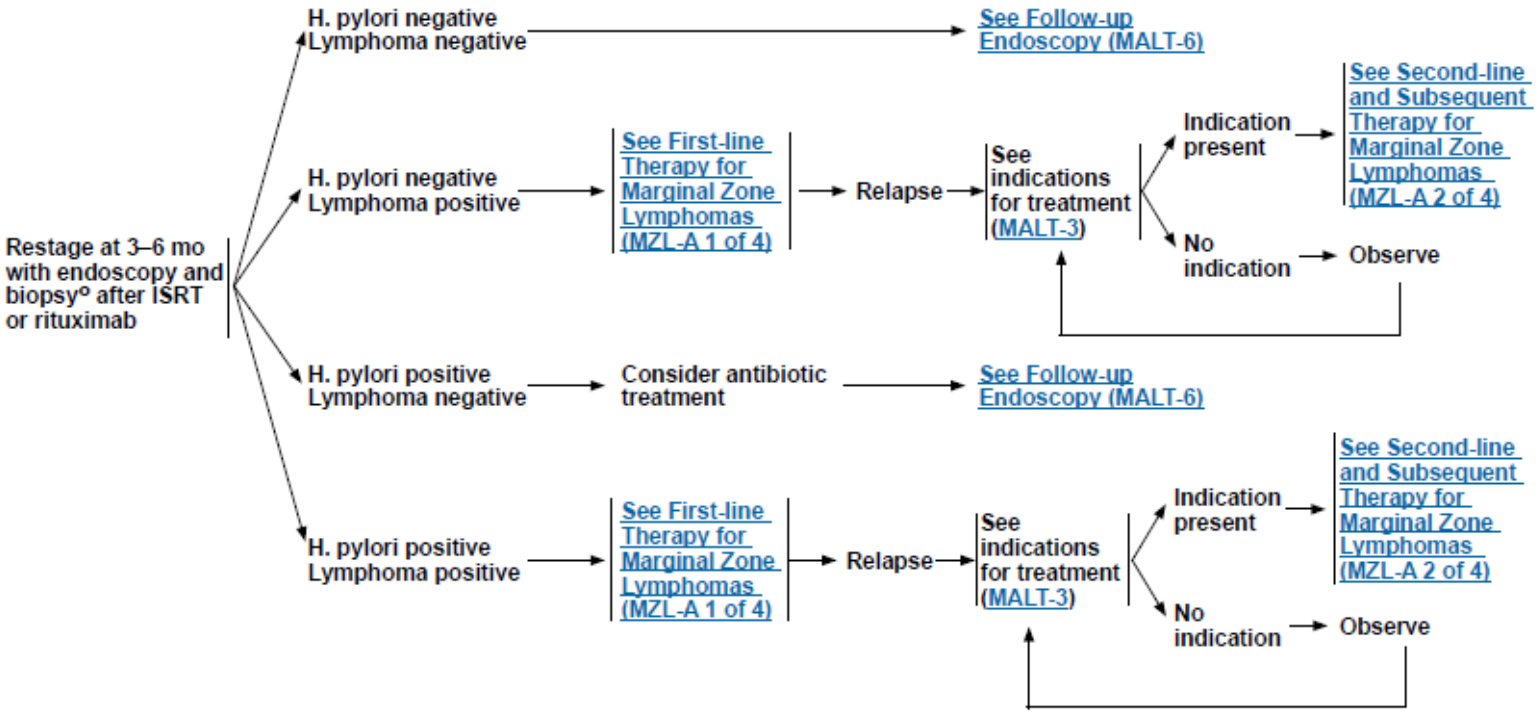
3- TO 6-MONTH RESTAGING AND FOLLOW-UP ENDOSCOPY

AFTER ISRT OR RITUXIMAB — ADDITIONAL THERAPY



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

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

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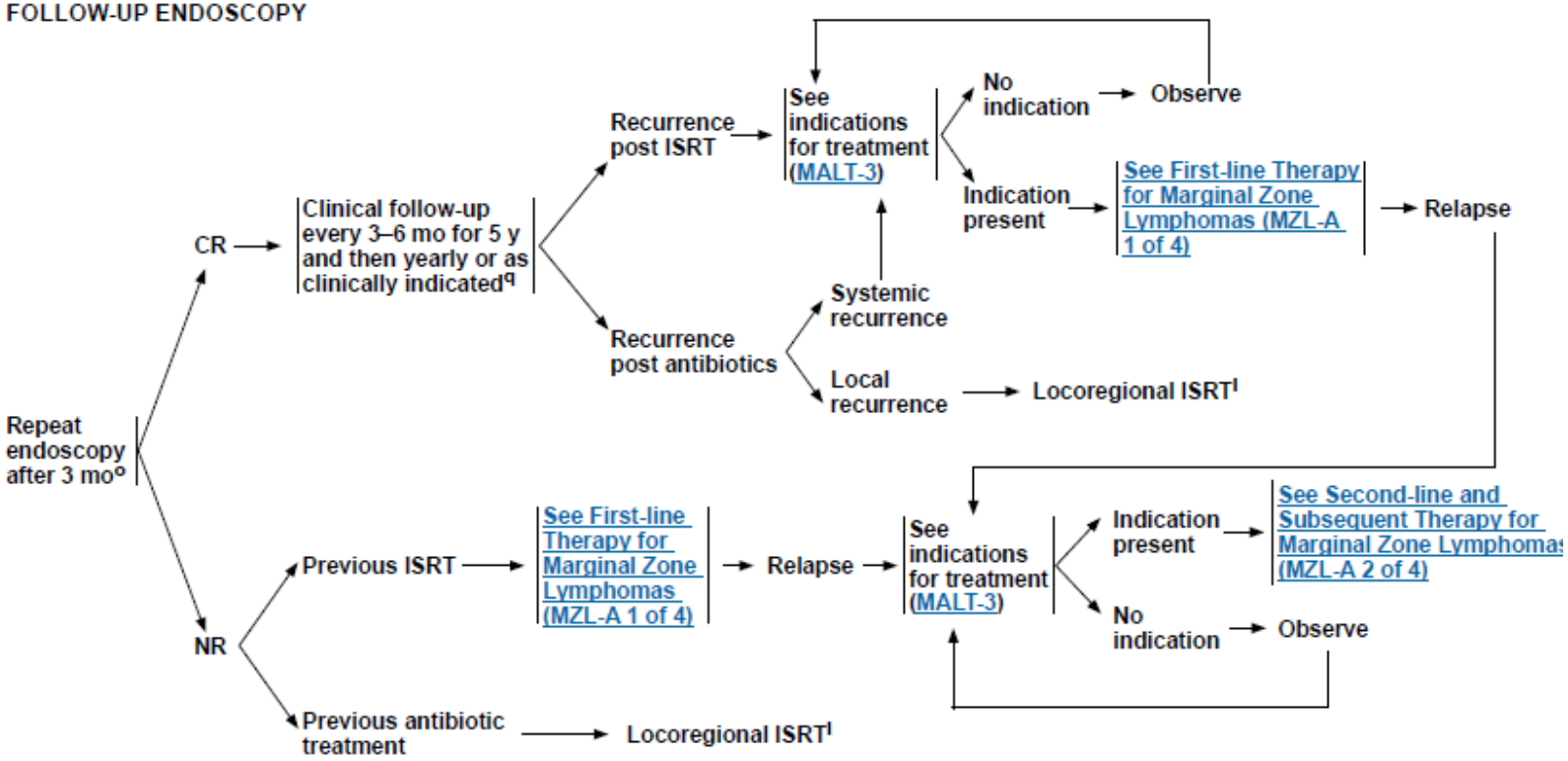
FOLLOW-UP ENDOSCOPY



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

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

MALT-6

Nongastric MALT Lymphoma (Noncutaneous)

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Nongastric MALT Lymphoma (Noncutaneous)

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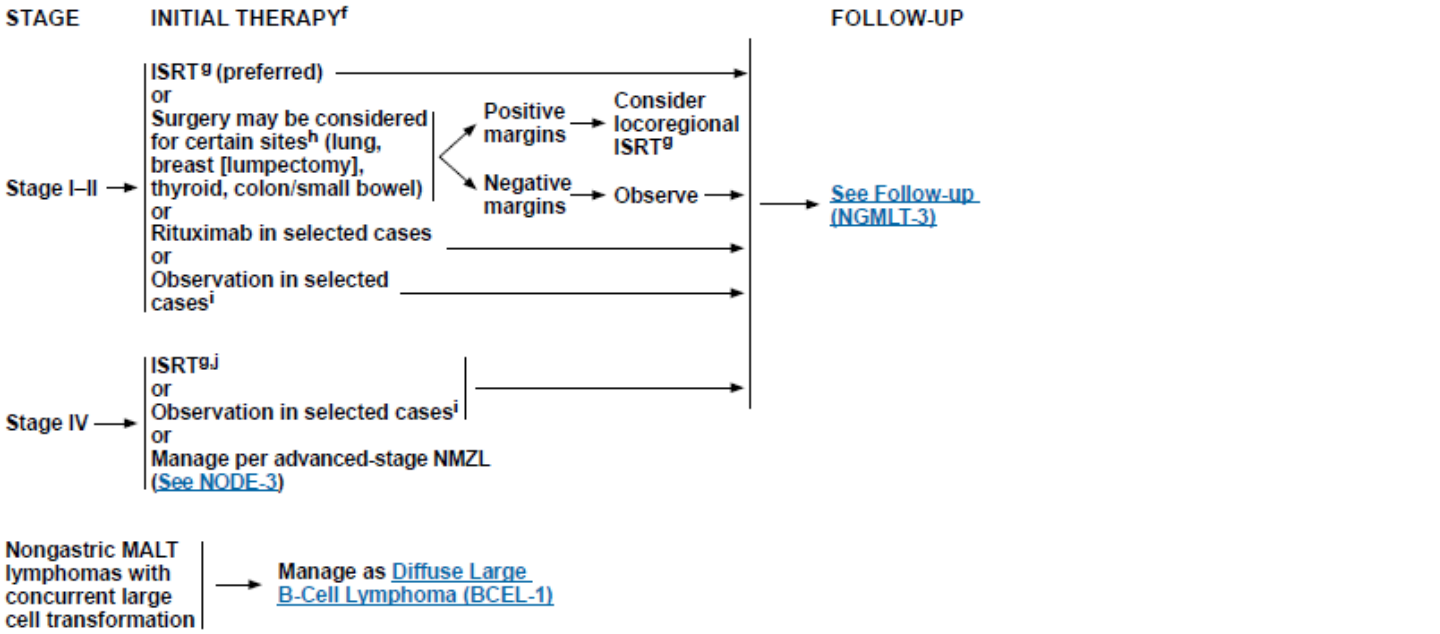

[f] Based on anecdotal responses to antibiotics in ocular and cutaneous marginal zone lymphomas, some physicians will give an empiric course of doxycycline prior to initiating other therapy.
[g] See Principles of Radiation Therapy (NHODG-D).
[h] Surgical excision for adequate diagnosis may be appropriate treatment for disease.
[i] Observation may be considered for patients whose diagnostic biopsy was excisional, or where RT could result in significant morbidity.
[j] Definitive treatment of multiple sites may be indicated (eg, bilateral orbital disease without evidence of disease elsewhere) or palliative treatment of symptomatic sites.

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

NGMLT-2

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Extranodal Marginal Zone B-Cell Lymphoma

Nongastric MALT Lymphoma (Noncutaneous)

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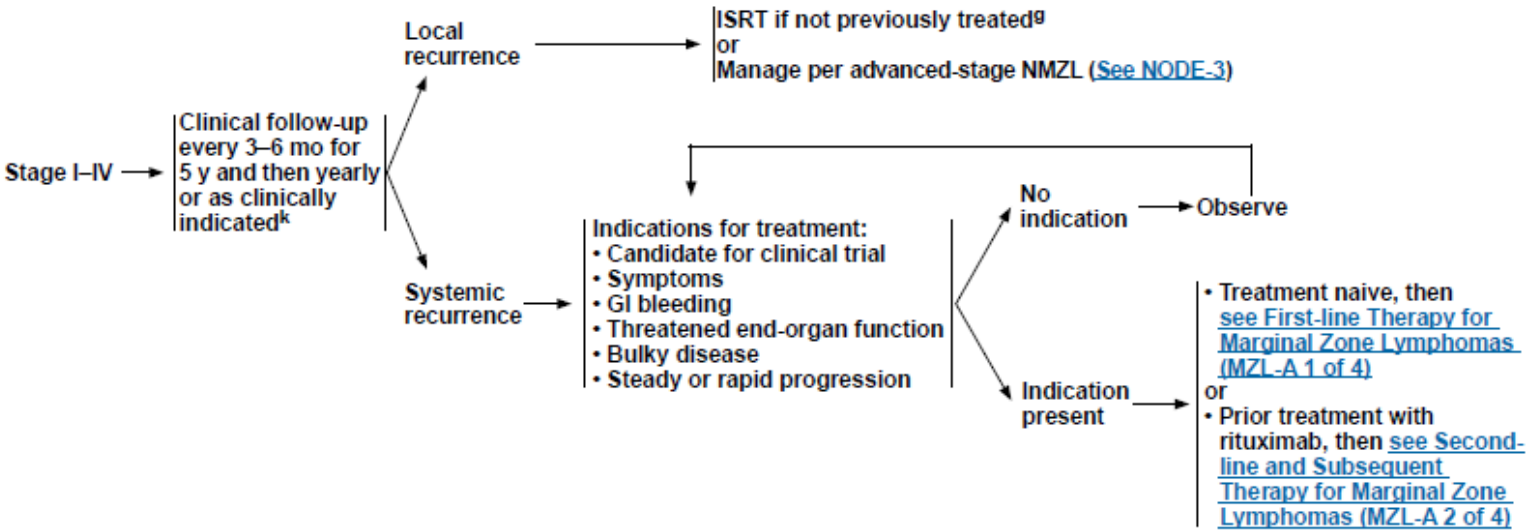
STAGE FOLLOW-UP

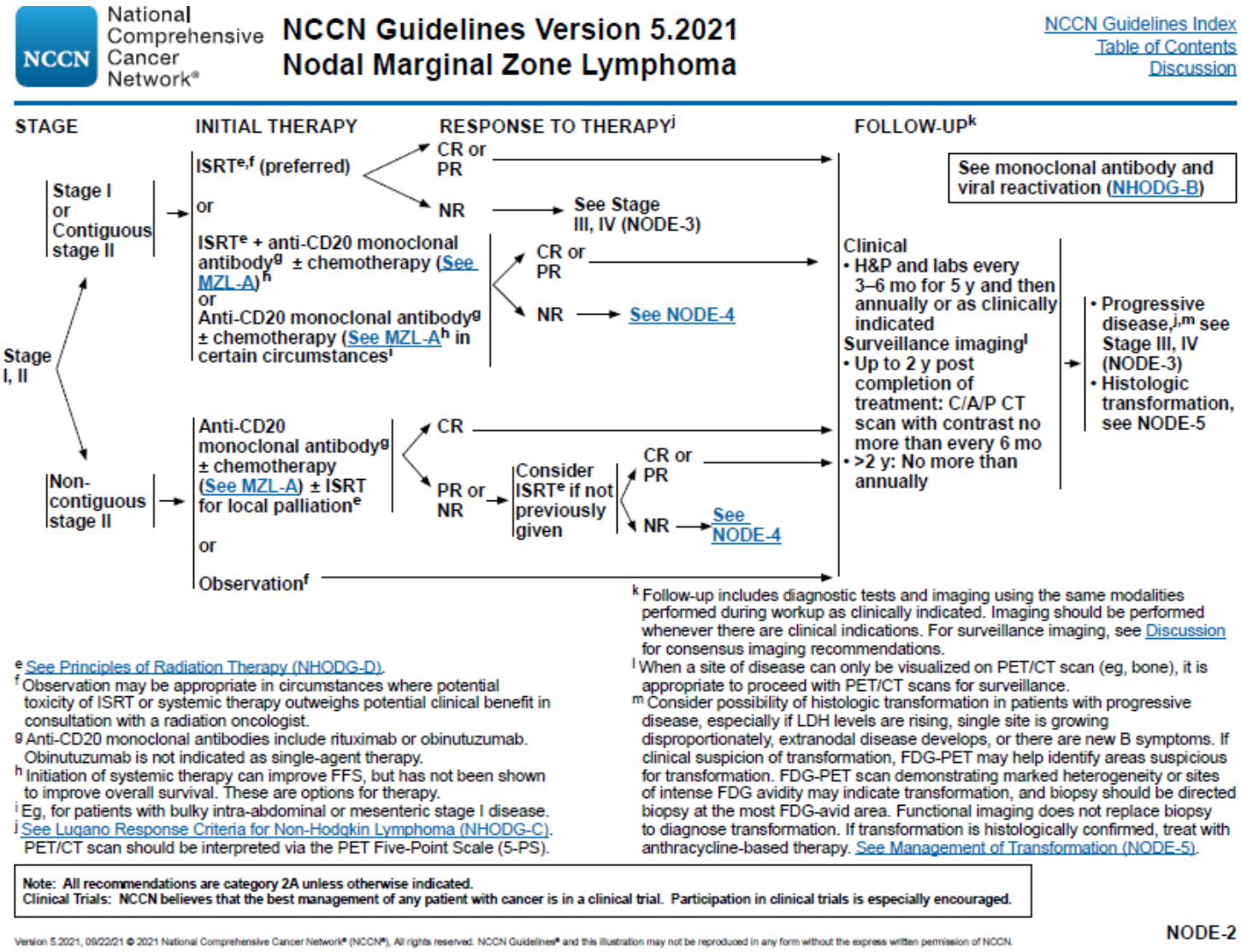


[g] See Principles of Radiation Therapy (NHODG-D).
[k] Follow-up includes diagnostic tests and imaging previously used as clinically indicated.

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

NGMLT-3

Nodal Marginal Zone Lymphoma



[e] See Principles of Radiation Therapy (NHODG-D).
[f] Observation may be appropriate in circumstances where potential toxicity of ISRT or systemic therapy outweighs potential clinical benefit in consultation with a radiation oncologist.
[g] Anti-CD20 monoclonal antibodies include rituximab or obinutuzumab. Obinutuzumab is not indicated as single-agent therapy.
[h] Initiation of systemic therapy can improve FFS, but has not been shown to improve overall survival. These are options for therapy.
[i] Eg, for patients with bulky intra-abdominal or mesenteric stage I disease.
[j] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS).
[k] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated. Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[l] When a site of disease can only be visualized on PET/CT scan (eg, bone), it is appropriate to proceed with PET/CT scans for surveillance.
[m] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (NODE-5).

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

NODE-2

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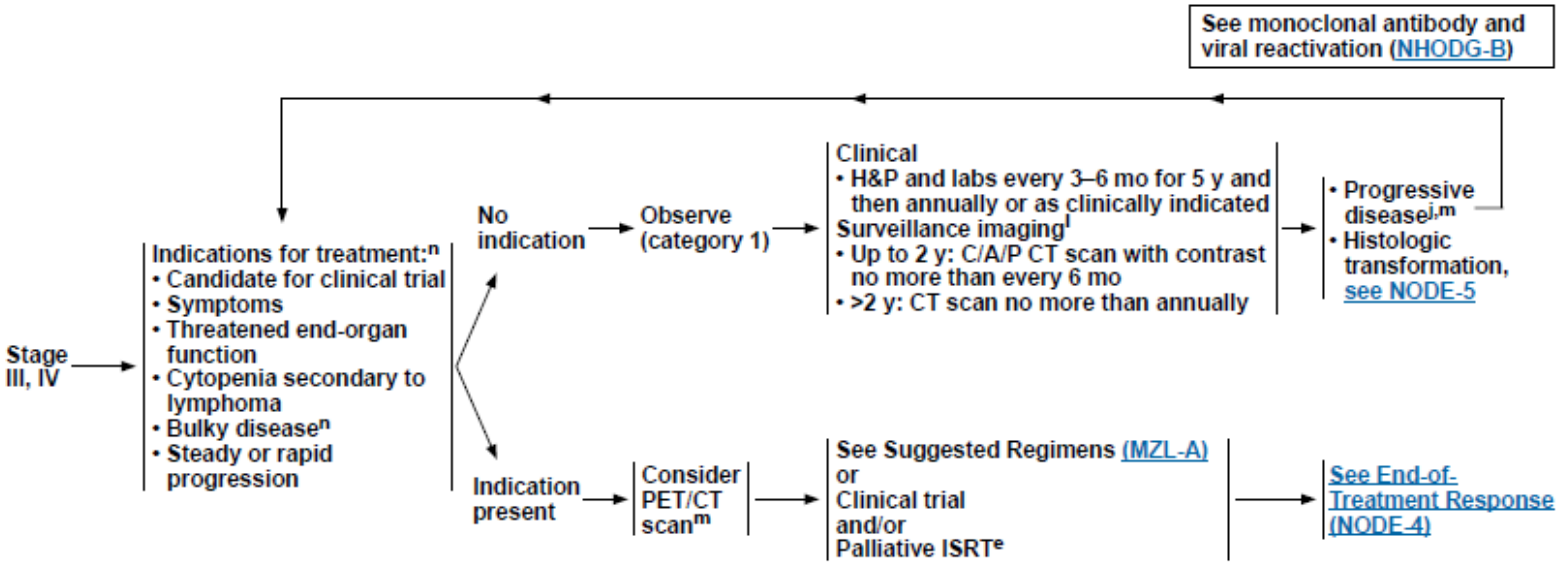
STAGE | **MANAGEMENT AND FOLLOW-UP[k]**



[e] See Principles of Radiation Therapy (NHODG-D).
[j] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS).
[k] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated. Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[l] When a site of disease can only be visualized on PET/CT scan (eg, bone), it is appropriate to proceed with PET/CT scans for surveillance.
[m] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (NODE-5).
[n] See GELF criteria (FOLL-A).

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

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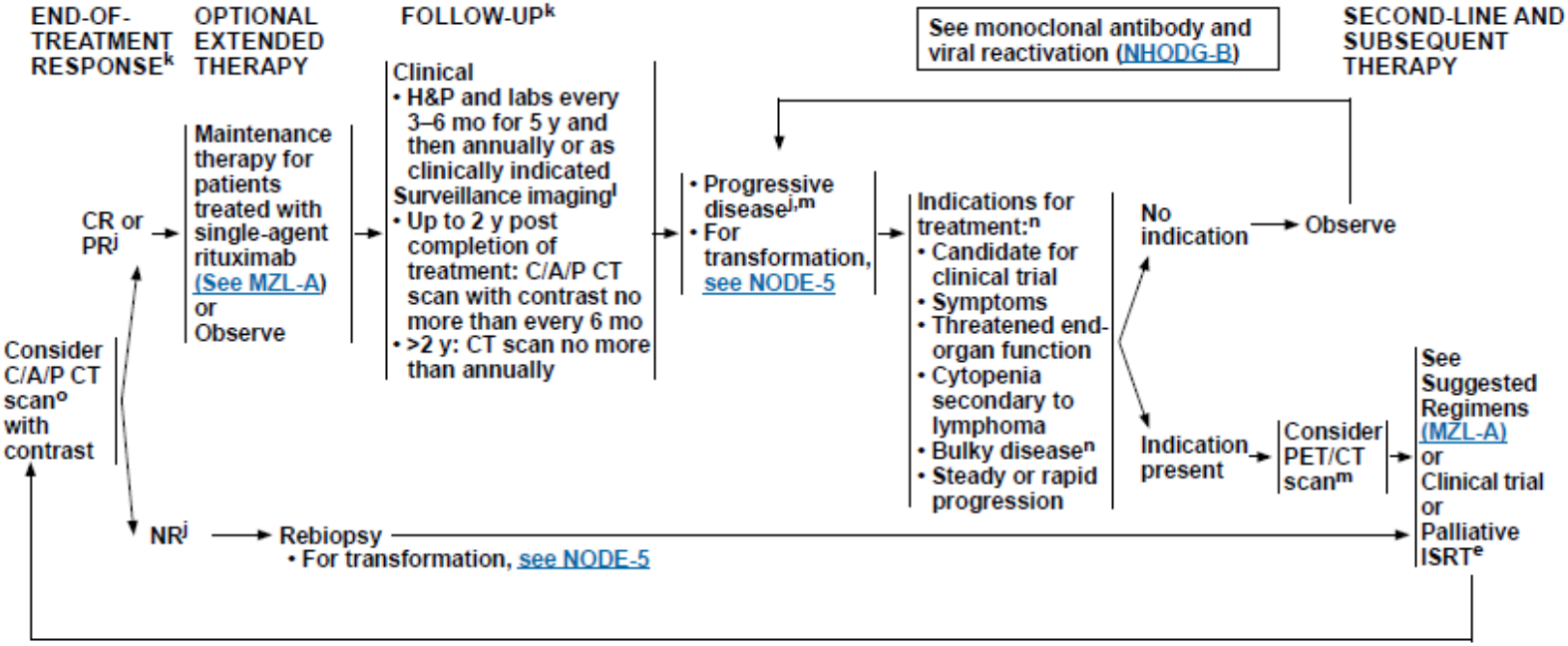
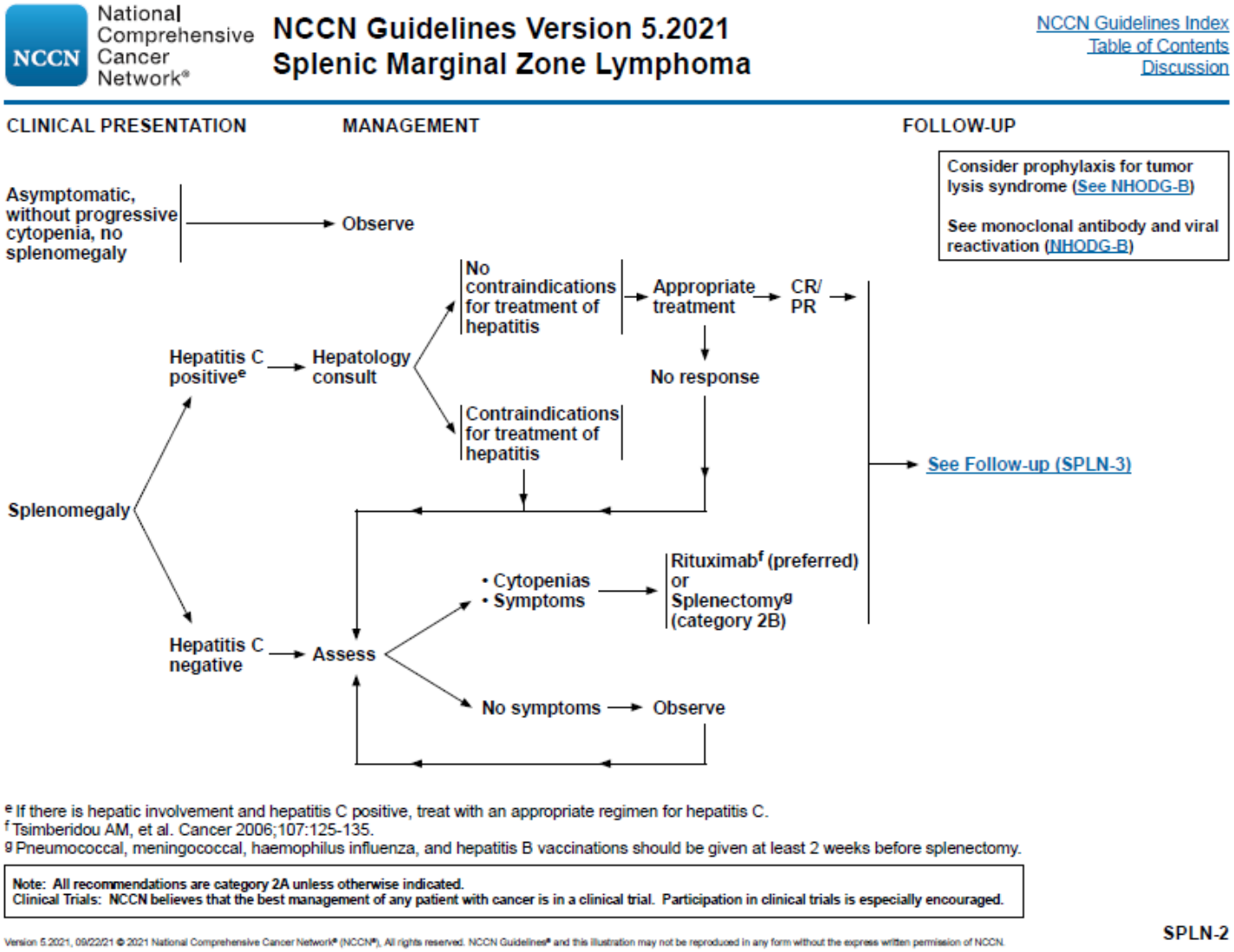


[e] See Principles of Radiation Therapy (NHODG-D).
[j] See Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS).
[k] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated. Imaging should be performed whenever there are clinical indications. For surveillance imaging, see Discussion for consensus imaging recommendations.
[l] When a site of disease can only be visualized on PET/CT scan (eg, bone), it is appropriate to proceed with PET/CT scans for surveillance.
[m] Consider possibility of histologic transformation in patients with progressive disease, especially if LDH levels are rising, single site is growing disproportionately, extranodal disease develops, or there are new B symptoms. If clinical suspicion of transformation, FDG-PET may help identify areas suspicious for transformation. FDG-PET scan demonstrating marked heterogeneity or sites of intense FDG avidity may indicate transformation, and biopsy should be directed biopsy at the most FDG-avid area. Functional imaging does not replace biopsy to diagnose transformation. If transformation is histologically confirmed, treat with anthracycline-based therapy. See Management of Transformation (NODE-5).
[n] See GELF criteria (FOLL-A).
[o] A PET-positive PR is associated with a shortened PFS (see Discussion); however, additional treatment at this juncture has not been shown to change outcome.

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

NODE-4

Splenic Marginal Zone Lymphoma

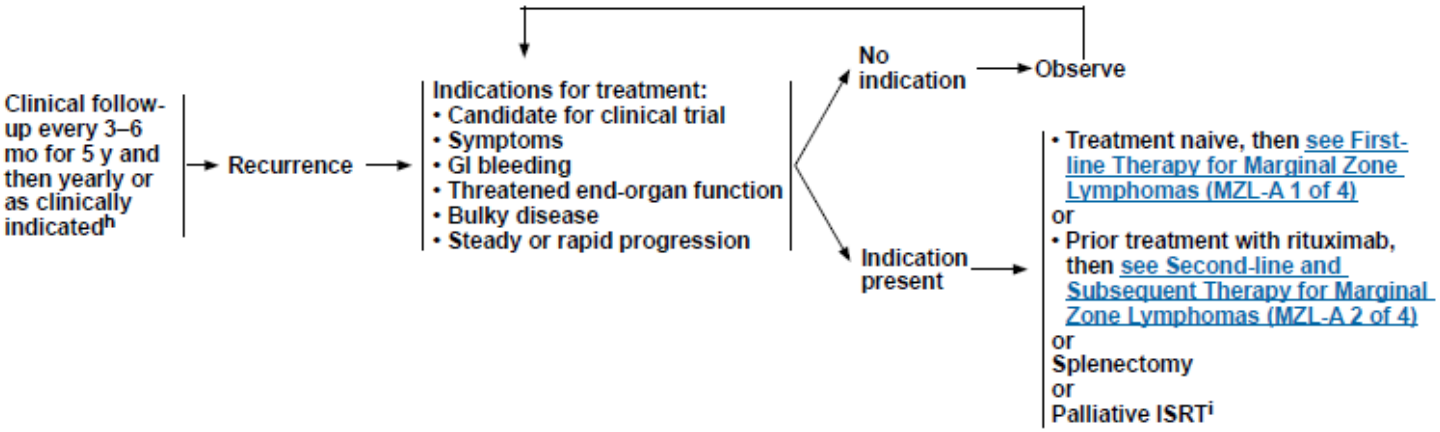


[e] If there is hepatic involvement and hepatitis C positive, treat with an appropriate regimen for hepatitis C.
[f] Tsimberidou AM, et al. Cancer 2006;107:125-135.
[g] Pneumococcal, meningococcal, haemophilus influenza, and hepatitis B vaccinations should be given at least 2 weeks before splenectomy.

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

SPLN-2

FOLLOW-UP



[h] Follow-up includes diagnostic tests and imaging using the same modalities performed during workup as clinically indicated.
[i] See Principles of Radiation Therapy (NHODG-D).

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

Suggested treatment regimens

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SUGGESTED TREATMENT REGIMENS[a,b,c]
An FDA-approved biosimilar is an appropriate substitute for rituximab.

FIRST-LINE THERAPY

Preferred regimens (in alphabetical order)
- Bendamustine + rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab
- Rituximab (375 mg/m² weekly for 4 doses) for SMZL[b]

Other recommended regimens
- Ibritumomab tiuxetan[d] (category 2B)
- Lenalidomide + rituximab (category 2B)
- Rituximab (375 mg/m² weekly for 4 doses) for extranodal (MALT) and nodal MZL

FIRST-LINE THERAPY FOR ELDERLY OR INFIRM
(if none of the above are expected to be tolerable in the opinion of treating physician)

Preferred regimen
- Rituximab (375 mg/m² weekly for 4 doses)

Other recommended regimens
- Chlorambucil ± rituximab
- Cyclophosphamide ± rituximab

FIRST-LINE EXTENDED THERAPY (optional)
- Consolidation with rituximab 375 mg/m² one dose every 8–12 weeks for up to 2 years

See Second-line and Subsequent Therapy on MZL-A 2 of 4

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

[a] See references for regimens (MZL-A 4 of 4).
[b] The choice of therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with ASCR). Therefore, treatment selection is highly individualized.
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[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 ibritumomab tiuxetan. If ibritumomab tiuxetan 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. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT. Cytogenetics/FISH assessment for MDS markers is recommended for patients receiving RIT.

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

MZL-A
1 OF 4

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SUGGESTED TREATMENT REGIMENS[a,b,c]

An FDA-approved biosimilar is an appropriate substitute for rituximab.

SECOND-LINE AND SUBSEQUENT THERAPY

Preferred regimens (in alphabetical order)
- Bendamustine + obinutuzumab (not recommended if treated with prior bendamustine)
- Bendamustine + rituximab (not recommended if treated with prior bendamustine) (may be considered for both nodal MZL and extranodal [MALT] lymphoma)
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab
- Ibrutinib[e,f]
- Lenalidomide + rituximab (may be considered for both nodal MZL and extranodal [MALT] lymphoma)
- Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen)[e,f]

Other recommended regimens (in alphabetical order)
- CHOP + obinutuzumab (category 2B)
- CVP + obinutuzumab (category 2B)
- Ibritumomab tiuxetan[d] (category 2B)
- Lenalidomide + obinutuzumab (category 2B)
- PI3K inhibitors
  - Relapsed/refractory after 2 prior therapies[e]
    - Copanlisib
    - Duvelisib
    - Idelalisib
  - Relapsed/refractory after at least one prior anti-CD20-mAB-based regimen
    - Umbralisib[e]
- Rituximab (if longer duration of remission)

SECOND-LINE AND SUBSEQUENT THERAPY FOR ELDERLY OR INFIRM
(if none of the above are expected to be tolerable in the opinion of treating physician)

Preferred regimens (in alphabetical order)
- Ibrutinib[e,f]
- Lenalidomide + rituximab
- Rituximab (375 mg/m² weekly for 4 doses)
- Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen)[e,f]

Other recommended regimens (in alphabetical order)
- Chlorambucil ± rituximab
- Cyclophosphamide ± rituximab
- Umbralisib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen)[e]

See Second-Line Consolidation or Extended Dosing on MZL-A 2 of 4
See Anti-CD19 CAR T-cell Therapy on MZL-A 2 of 4

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

[a] See references for regimens (MZL-A 4 of 4).
[b] The choice of therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with ASCR). Therefore, treatment selection is highly individualized.
[c] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan.
[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 ibritumomab tiuxetan. If ibritumomab tiuxetan 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. As of 2010, updates suggest a trend towards an increased risk of MDS with RIT. Cytogenetics/FISH assessment for MDS markers is recommended for patients receiving RIT.
[e] See Special Considerations for the Use of Small-Molecule Inhibitors (NHODG-E).
[f] Consider alternate BTKi (acalabrutinib or zanubrutinib) in patients with intolerance or contraindications to ibrutinib.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2021
Marginal Zone Lymphomas

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SUGGESTED TREATMENT REGIMENS[a,b]

SECOND-LINE CONSOLIDATION OR EXTENDED DOSING (optional)

Preferred regimen
- If treated with bendamustine + obinutuzumab for recurrent disease then obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

Other recommended regimens
- High-dose therapy with autologous stem cell rescue
- Allogeneic hematopoietic cell transplant for highly selected patients

HISTOLOGIC TRANSFORMATION OF NODAL MZL TO DLBCL

- Anti-CD19 CAR T-cell therapy (only after ≥2 prior chemoimmunotherapy regimens)[g,h]
  - Axicabtagene ciloleucel
  - Lisocabtagene maraleucel[i]
  - Tisagenlecleucel
- Loncastuximab tesirine[i] (only after ≥2 lines of systemic therapy)

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

[a] See references for regimens (MZL-A 4 of 4).
[b] The choice of therapy requires consideration of many factors, including age, comorbidities, and future treatment possibilities (eg, HDT with ASCR). Therefore, treatment selection is highly individualized.
[g] See Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-F).
[h] Patients should have received at least one anthracycline or anthracenedione-based regimen, unless contraindicated.
[i] Lisocabtagene maraleucel and loncastuximab tesirine are indicated for DLBCL transformed from MZL.

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

SUGGESTED TREATMENT REGIMENS

REFERENCES

First-line Therapy

Chlorambucil ± rituximab

Zucca E, Conconi A, Martinelli G, et al. Final results of the IELSG-19 randomized trial of mucosa-associated lymphoid tissue lymphoma: Improved event-free and progression-free survival with rituximab plus chlorambucil versus either chlorambucil or rituximab monotherapy. J Clin Oncol 2017;35:1905-1912.

RCHOP/RCVP/BR

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. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944-2952.

Salar A, Domingo-Domenech E, Panizo C, et al. Long-term results of a phase 2 study of rituximab and bendamustine for mucosa-associated lymphoid tissue lymphoma. Blood 2017;130:1772-1774.

Ibritumomab tiuxetan

Lossos IS, Fabregas JC, Koru-Sengul T, et al. Phase II study of (90)Y Ibritumomab tiuxetan in patients with previously untreated marginal zone lymphoma. Leuk Lymphoma 2015;56:1750-1755.

Lenalidomide + rituximab

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

Rituximab (preferred for SMZL)

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

Else M, Marin-Niebla A, de la Cruz F, et al. Rituximab, used alone or in combination, is superior to other treatment modalities in splenic marginal zone lymphoma. Br J Haematol 2012;159:322-328.

Kalpadakis C, Pangalis GA, Angelopoulou MK, et al. Treatment of splenic marginal zone lymphoma with rituximab monotherapy: progress report and comparison with splenectomy. Oncologist 2013;18:190-197.

First-line Extended Therapy (optional)

Extended dosing with rituximab

Williams ME, Hong F, Gascoyne RD, et al. Rituximab extended schedule or retreatment trial for low tumour burden non-follicular indolent B-cell non-Hodgkin lymphomas: Eastern Cooperative Oncology Group Protocol E4402. Br J Haematol 2016;173:867-875.

Second-line and Subsequent Therapy

Bendamustine + obinutuzumab

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2016;17:1081-1093.

Copanlisib

Dreyling M, Panayiotidis P, Follows GA, et al. Long-term efficacy and safety of copanlisib in multiply relapsed or refractory patients with marginal zone lymphoma [abstract]. Blood 2019;134:Abstract 1531.

Duvelisib

Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: A phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. J Clin Oncol 2019; 37:912-922.

Ibritumomab tiuxetan

Vanazzi A, Grana C, Crosta C, et al. Efficacy of (9)(0)Yttrium-ibritumomab tiuxetan in relapsed/refractory extranodal marginal-zone lymphoma. Hematol Oncol 2014;32:10-15.

Ibrutinib

Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood 2017;129:2224-2232.

Idelalisib

Gopal A, Kahl B, De Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018.

Lenalidomide + rituximab

Witzig TE, Wiernik PH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin's Lymphoma. J Clin Oncol 2009;27:5404-5409.

Sacchi S, Marcheselli R, Bari A, et al. Safety and efficacy of lenalidomide in combination with rituximab in recurrent indolent non-follicular lymphoma: final results of a phase II study conducted by the Fondazione Italiana Linfomi. Haematologica 2016;101:e196.

Umbralisib

Zinzani PL, Samaniego F, Jurczak W, et al. Umbralisib, the once daily dual inhibitor of PI3Kδ and casein kinase-1ε demonstrates clinical activity in patients with relapsed or refractory indolent non-Hodgkin lymphoma: Results from the Phase 2 Global Unity-NHL Trial [abstract]. Blood 2020;136:34-35.

Zanubrutinib

Opat S, Tedeschi A, Linton K, et al. The Magnolia trial: zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clinical Cancer Res 2021; Online ahead of print.

Second-line Consolidation or Extended Dosing (optional)

Obinutuzumab maintenance for rituximab refractory disease

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2016;17:1081-1093.

CAR T-Cell Therapy

Axicabtagene ciloleucel

Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017;377:2531-2544.

Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol 2019;20:31-42.

Lisocabtagene maraleucel

Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.

Tisagenlecleucel

Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2019;380:45-56.

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

National Comprehensive Cancer Network (NCCN), 2021 [4].

Primary Cutaneous Lymphomas

Zielsetzung

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment.

The most common subtypes of PCL that are covered in the NCCN guidelines are listed below:

Cutaneous B-Cell Lymphomas:

- Primary cutaneous marginal zone lymphoma (PCMZL);
- Primary cutaneous follicle center lymphoma (PCFCL); and
- Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, leg type)

Cutaneous T-Cell Lymphomas:

- Mycosis fungoides (MF) and Sézary syndrome (SS)
- Primary cutaneous CD30+ T-cell lymphoproliferative disorders (PCTLD)

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund fehlender höherwertiger Evidenz zu Behandlungsmethoden für Patientinnen und Patienten mit primär kutanem Marginalzonenlymphom wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, unklar, ob Patientenvertretungen einbezogen wurden;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; (⇨ NCCN Guidelines Panel Disclosures)
- Systematische Suche erwähnt, aber keine Details beschrieben (z. B. Suchzeitraum), keine Angaben zur systematischen Auswahl und Bewertung der Evidenz;
- Konsensfindung erwähnt, aber nicht detailliert beschrieben, externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind eindeutig, Literaturverknüpfung mit Evidenzbewertung im Hintergrundtext;
- Weder Gültigkeit, noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

Prior to the update of this version of the NCCN Guidelines® for Primary Cutaneous Lymphomas, a literature search was performed to obtain key literature on PCBCL published since the previous Guidelines update […].

LoE/GoR

Tabelle 3: NCCN Categories of Evidence and Consensus

Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

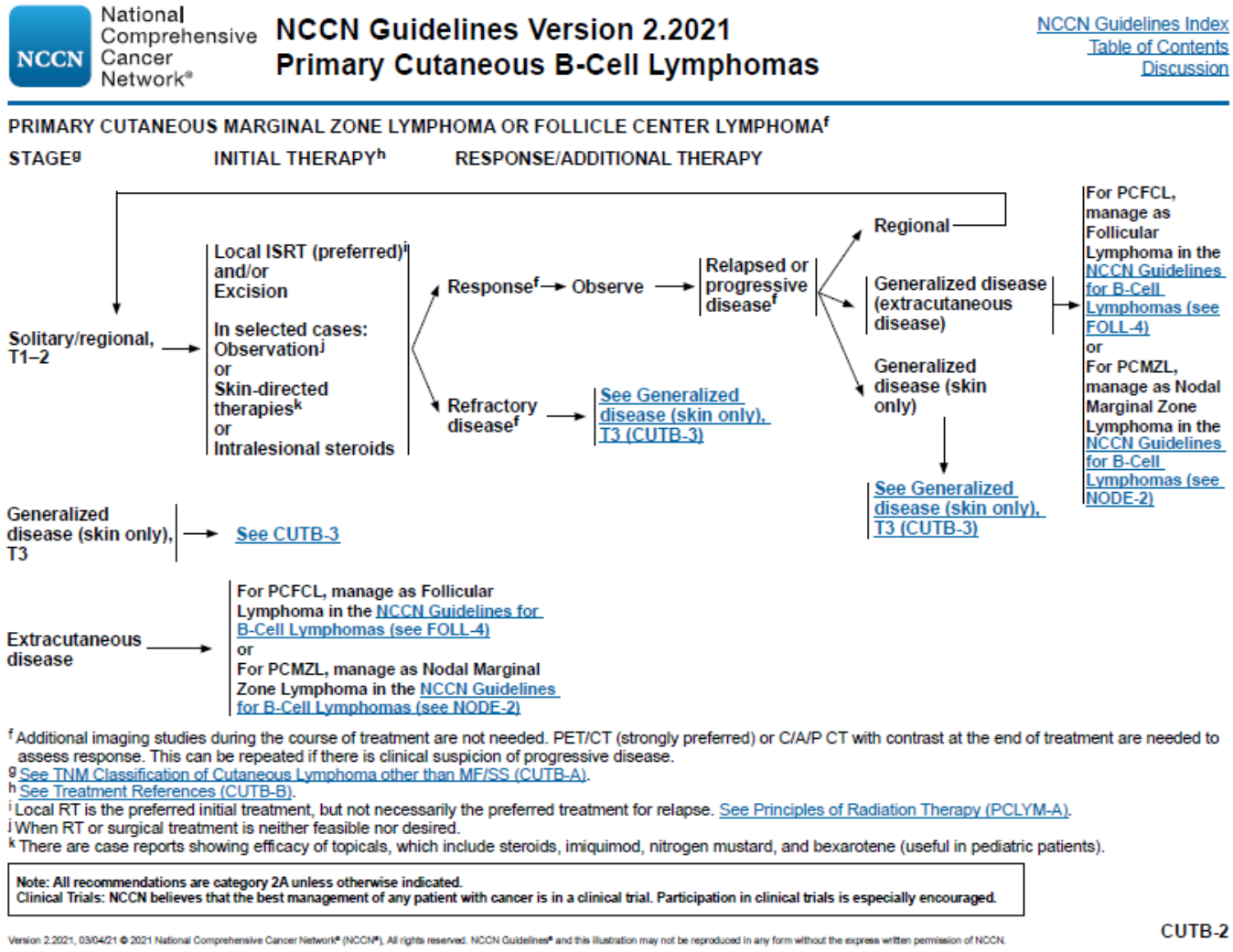
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Sonstige methodische Hinweise

Note: All recommendations are category 2A unless otherwise indicated.

Empfehlungen

Primary Cutaneous Marginal Zone Lymphoma or Follicle Center Lymphoma[f]



[f] Additional imaging studies during the course of treatment are not needed. PET/CT (strongly preferred) or C/A/P CT with contrast at the end of treatment are needed to assess response. This can be repeated if there is clinical suspicion of progressive disease.
[g] See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[h] See Treatment References (CUTB-B).
[i] Local RT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. See Principles of Radiation Therapy (PCLYM-A).
[j] When RT or surgical treatment is neither feasible nor desired.
[k] There are case reports showing efficacy of topicals, which include steroids, imiquimod, nitrogen mustard, and bexarotene (useful in pediatric patients).

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

CUTB-2

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Primary Cutaneous B-Cell Lymphomas

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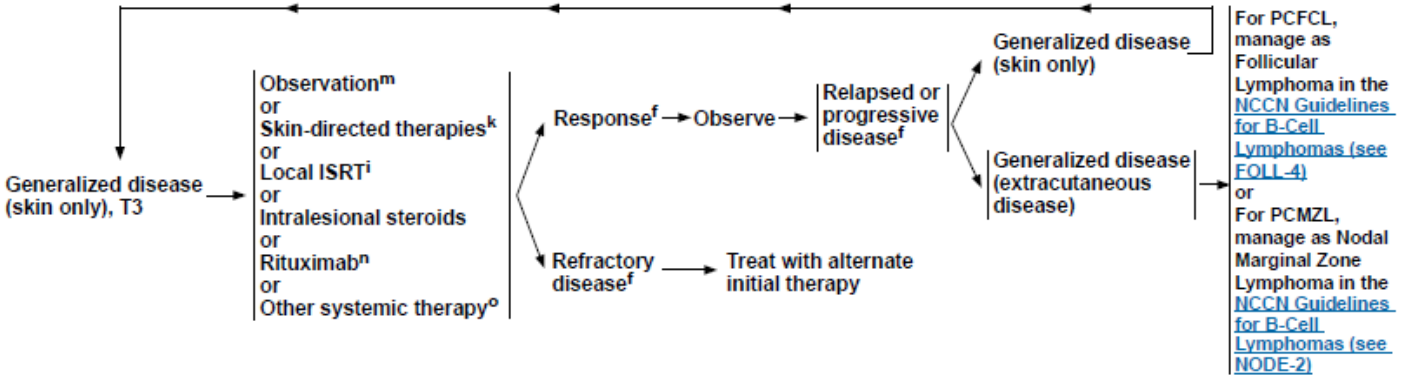
PRIMARY CUTANEOUS MARGINAL ZONE LYMPHOMA OR FOLLICLE CENTER LYMPHOMA[f]

STAGE[g] | **INITIAL THERAPY[h,l]** | **RESPONSE/ADDITIONAL THERAPY**



[f] Additional imaging studies during the course of treatment are not needed. PET/CT (strongly preferred) or C/A/P CT with contrast at the end of treatment are needed to assess response. This can be repeated if there is clinical suspicion of progressive disease.
[g] See TNM Classification of Cutaneous Lymphoma other than MF/SS (CUTB-A).
[h] See Treatment References (CUTB-B).
[i] Local ISRT is the preferred initial treatment, but not necessarily the preferred treatment for relapse. See Principles of Radiation Therapy (PCLYM-A).
[k] There are case reports showing efficacy of topicals, which include steroids, imiquimod, nitrogen mustard, and bexarotene (useful in pediatric patients).
[l] See monoclonal antibody and viral reactivation (See NCCN Guidelines B-Cell Lymphomas).
[m] Considered appropriate in asymptomatic patients.
[n] Rituximab and hyaluronidase human injection for subcutaneous use may be substituted for rituximab after patients have received the first full dose of rituximab by intravenous infusion. This substitution cannot be made for rituximab used in combination with ibritumomab tiuxetan. An FDA-approved biosimilar is an appropriate substitute for rituximab.
[o] In rare circumstances for very extensive or refractory disease, other combination chemotherapy regimens listed in NCCN Guidelines for B-Cell Lymphomas, FOLL-B are used.

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

Alberta Health Services (AHS), 2019 [1].

Lymphoma

Fragestellungen

- 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?

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund limitierter höherwertiger Evidenz zu Behandlungsmethoden für Patientinnen und Patienten mit Marginalzonenlymphom wird die Leitlinie jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Multidisziplinäre Leitliniengruppe, aber keine Einbeziehung von Patientenvertretungen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Angaben zur systematischen Auswahl und kritischen Bewertung der Literatur fehlen;
- Verfahren zur Konsensfindung (formal und informell) erwähnt, externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind identifizierbar, Angaben zu Literaturverknüpfungen, Evidenzbewertung und Graduierung der Empfehlungen fehlen;
- Beschreibung des Verfahrens zur Überwachung und Aktualisierung ist widersprüchlich[2].

Recherche/Suchzeitraum:

- Medical journal articles were searched using Medline (1950 to October Week 1, 2015), EMBASE (1980 to October Week 1, 2015), Cochrane Database of Systematic Reviews (3rd Quarter, 2015), and PubMed electronic databases. An updated review of the relevant existing practice guidelines for lymphoma was also conducted by accessing the websites of the National Comprehensive Cancer Network (NCCN), Cancer Care Ontario (CCO), the British Columbia Cancer Agency (BCCA), the European Society for Medical Oncology (ESMO), and the British Committee for Standards in Haematology.

[2] A formal review of the guideline will be conducted at the Annual Provincial Hematology Tumour Team Meeting in 2015. If critical new evidence is brought forward before that time […] the guideline working group members will revise and update the document accordingly. (siehe 'Maintenance')

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. (siehe 'Development and Revision History')

LoE

Tabelle 4: Levels of Evidence

Level		Description of Evidence
I		evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias meta-analyses of RCTs without heterogeneity
II		small RCTs phase II RCTs large RCTs with potential bias or meta-analyses including such RCTs with heterogeneity
III		prospective cohort studies post-hoc and ad-hoc analyses of RCTs
IV		retrospective cohort studies case-control studies instrument validation studies (note: could be level III, based on size of population, methods)
V		studies without a control group case reports expert opinions review articles or narrative reviews Delphi studies cross-sectional studies (interviews, focus groups, surveys)

GoR

Tabelle 5: Strength of Recommendations

A	Strongly recommended; strong evidence for efficacy with a substantial clinical benefit.
B	Generally recommended; strong or moderate evidence for efficacy but with a limited clinical benefit.
C	Optional; insufficient evidence for efficacy or benefit does not outweigh the risks/disadvantages.
D	Generally not recommended; moderate evidence against efficacy or for adverse outcomes.
E	Never recommended; strong evidence against efficacy or for adverse outcomes.

Sonstige methodische Hinweise

Die Feststellung der Stärke der Evidenz und eine Graduierung der Empfehlungen nach den oben aufgeführten Klassifikationsschema erfolgt bei der Leitlinienerstellung durch das Alberta Provincal Hematology Tumour Team, gemäß Methodenpapier, erst seit Ende 2019.

Empfehlungen

III. Treatment of non-Hodgkin Lymphomas

Splenic Marginal Zone Lymphoma

Although existing evidence is inadequate to conclude which treatment approach is superior, we propose the following strategy for managing SMZL:

1. Rituximab monotherapy is recommended as frontline therapy for most patients. A standard regimen is rituximab 375 mg/m² once weekly for 4 weeks, followed by a response assessment 4-6 weeks later.
   a. Those achieving at least a partial response, defined by conventional response criteria[123], should subsequently receive maintenance rituximab (375 mg/m² every 3 months for 2 years).
   b. Non-responders or those with progressive disease should proceed with either:
      - Splenectomy if the spleen is the major site of disease or
      - BR for those with additional nodal disease, extensive bone marrow involvement, or non-operative candidates, then followed by maintenance rituximab (375 mg/m² every 3 months for 2 years).
2. Select patients who require a splenectomy to establish the diagnosis and have no bone marrow, peripheral blood, or nodal involvement, do not require maintenance rituximab and may simply be observed.

Gastric MALT lymphoma

[…] Stage IAE low grade gastric MALT should be treated with omeprazole 20mg twice daily, clarithromycin 500mg twice daily and either metronidazole 500mg twice daily or amoxicillin 1000mg twice daily for one week, or an equally effective regimen such as the Hp-PAC. After treatment with antibiotics, patients should undergo repeat gastroscopy at 3 months, then every 6 months for 2 years, then annually for 3 years. Biopsies should be taken for lymphoma and H pylori each time. One re-treatment should be tried if H pylori persists. MALT lymphoma may slowly regress over 12-18 months after H pylori eradication.

If lymphoma recurs or persists more than 12-18 months after eradication of H pylori, the patient should receive upper abdominal irradiation (30 Gy/20 fractions with POP if anatomy permits, otherweise 4-5 field plan with superior portion AP/PA and inferior portion AP, R lateral and L lateral). Patients with localized MALT lymphomas are reported to have excellent clinical outcomes after moderate-dose radiation, significantly less risk of distant recurrence, and good overall survival.[201] […] Stage IIAE or greater gastric MALT should be managed as advanced low grade lymphoma plus eradication of H pylori with antibiotics. Stage IIAE or greater gastric MALT should be managed as advanced low grade lymphoma plus eradication of H pylori with antibiotics.

Referenzen

90. Witzig TE, Molina A, Gordon LI, Emmanouilides C, Schilder RJ, Flinn IW, et al. Long-term responses inpatients with yttrium 90 ibritumomab tiuxetan. Cancer 2007;109(9):1804-1810.
112. Oh DH, Li H, Duan Q, Villa D, Peters A, Chua N, et al. Quantifying benefit of autologous transplantation for relapsed follicular lymphoma patients via instrumental variable analysis. Biol Blood Marrow Transplant 2016;22(5):941-948.
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123. Matutes E, Oscier D, Montalban C, Berger F, Callet-Bauchu E, Dogan A, et al. Splenic marginal zone lymphoma proposals for a revision of diagnostic, staging and therapeutic criteria. Leukemia 2008;22(3):487-495.

201. Goda JS, Gospodarowicz M, Pintilie M, Wells W, Hodgson DC, Sun A, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. Cancer 2010;116(16):3815-3824.

IV. Cutaneous Lymphomas

Treatment of other types of non-MF cutaneous lymphomas

CTCL Subtype	First line treatment	Second or third line treatment
Primary Cutaneous Marginal Zone Lymphoma		
Solitary lesion	Surgical excision Local radiotherapy (15-35 Gy)	Intralesional corticosteroids Intralesional rituximab (5-20 mg per lesion q4 week x 3-6 cycles)* Treat as systemic (R-Bendamustine x 6)
Multifocal lesions	Observation Chlorambucil Rituximab monotherapy*	
B. burgdorferi associated pcMZL	Antibiotics (cephalosporin or doxycycline)	
* Manufacturer application required for access. Drug not funded.		

VI. HDCT and hematopoietic stem cell transplantation for lymphoma

Eligibility

- Patient: age ≤ 70 years, ECOG 0-2, adequate organ function, no active infections
  ⇨ HIV not contraindication if CD4 > 100 and meet other eligibility criteria
- Lymphoma: chemosensitive: partial response (PR) or better to last chemotherapy
  No active secondary CNS disease (eligible if CNS in PR/CR to salvage therapy)

HDCT regimen for autologous stem cell transplantation

- Indolent (Follicular, SLL/CLL, MZL, LPL) and Mantle Cell: melphalan 180 mg/m² + TBI 5 Gy
- Aggressive systemic non-Hodgkin lymphoma (DLBCL, PTCL):
  (R)BEAM or Etoposide/Melphalan
- Hodgkin lymphoma: melphalan 200 mg/m² or Etoposide/Melphalan
- Primary CNS lymphoma: thiotepa 600 mg/m² + busulfan 9.6 mg/kg
- Secondary CNS lymphoma: (R-TBM) thiotepa 500 mg/m² + busulfan 9.6 mg/kg + melphalan 100 mg/m²

HDCT regimen for allogeneic stem cell transplantation

- Majority of patients: fludarabine 250 mg/m² + busulfan 12.8 mg/kg, 400 cGy TBI + ATG
- Reduced intensity: fludarabine 120 mg/m² + melphalan 140 mg/m² ± ATG
  ⇨ co-morbidities (liver, lung, nervous system), prior busulfan, prior ASCT after BEAM or TBI
  ⇨ slowly progressive, non-bulky lymphoma

Indications for HDCT and autologous stem cell transplantation

1. Indolent non-Hodgkin lymphoma
   - Follicular, Marginal Zone, Small Lymphocytic, Lymphoplasmacytic Lymphoma
     ⇨ chemosensitive first or second chemotherapy failure
   - Mantle Cell Lymphoma (especially low or low-intermediate risk MIPI score)

⇨ first partial remission (PR) or first complete remission (CR)

2. Aggressive non-Hodgkin lymphoma
   - Part of first salvage therapy for chemosensitive first relapse or first remission-induction failure
   - Part of initial therapy for high IPI = 4 – 5 risk patients or double hit Lymphoma
   - ⇨ first PR/CR following completion of full induction (i.e. R-CHOP x 6)
   - ⇨ high-dose sequential remission-induction therapy
3. Hodgkin lymphoma
   First chemotherapy failure (relapse or 1^0 refractory)

Indications for HDCT and allogeneic stem cell transplantation

1. Indolent non-Hodgkin lymphoma
   - Follicular, Marginal Zone, Small Lymphocytic/CLL, Lymphoplasmacytic Lymphoma
     - ⇨ chemosensitive second to fourth chemotherapy failure (last time to progression <2 years), usually after prior autologous SCT
   - Mantle Cell Lymphoma
     - ⇨ first remission for high risk MIPI score, blastoid variant, or heavy blood/marrow involvement
     - ⇨ chemosensitive first chemotherapy failure
2. Aggressive non-Hodgkin lymphoma
   - Diffuse large B-cell or peripheral T-cell lymphomas
     - ⇨ chemosensitive relapse following HDCT/ASCT if time to relapse >1 year and aaIPI = 0-1
   - Lymphoblastic lymphoma
     - ⇨ first remission after induction and CNS therapy if prior blood/marrow involvement and high LDH
     - ⇨ chemosensitive first chemotherapy failure
3. Hodgkin lymphoma
   Chemosensitive relapse following HDCT/ASCT if time to relapse >1 year
4. Any lymphoma with indication for HDCT/ASCT but unable to collect adequate autograft

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1. Pfreundschuh M, Zwick C, Zeynalova S, Duhrsen U, Pfluger KH, Vrieling T, et al. Dose-escalated CHOEP for the treatment of young patients with aggressive non-Hodgkin's lymphoma: II. Results of the randomized high-CHOEP trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Ann Oncol. 2008;19(3):545-552.
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Prica A et al., 2017 [6].

Rituximab in Lymphoma and Chronic Lymphocytic Leukaemia: A Practice Guideline

Zielsetzung

[…] to systematically review and update the literature on rituximab in lymphoma and CLL given many recent publications and updates, and provide evidence-based consensus guidelines for its rational use.

Methodik

Grundlage der Leitlinie

- Unklar, ob Patientenvertretungen in die Leitlinienerstellung einbezogen wurden;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Konsensfindung erwähnt, aber nicht detailliert beschrieben, externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind identifizierbar, Evidenzbewertung und Graduierung der Empfehlungen fehlen;
- Weder Gültigkeit noch Verfahren zur Überwachung und Aktualisierung beschrieben.

Recherche/Suchzeitraum:

This evidentiary base is composed of three parts: the evidentiary base of Version 2, the results of the updated search executed in March 2012 and the content of a further update executed in October 2013.

For this update, a search for guidelines was undertaken in the Inventory of Cancer Guidelines (SAGE), the National Guideline Clearing House, the CMA Infobase and on the websites of international guidelines developers such as the National Institute for Clinical Excellence (UK) (NICE), the Scottish Intercollegiate Guideline Network (SIGN), the Australian National Health and Medical Research Council and the New Zealand Guidelines Group.

The literature was systematically searched using MEDLINE (Ovid, March 2006 to October 2013), EMBASE (Ovid, March 2006 to October 2013) and the Cochrane Library (22 October 2013). In addition, abstracts from the American Society of Clinical Oncology (ASCO) (2006-2013) were searched.

LoE

Keine Angaben

GoR

The working group developed a set of initial recommendations through consideration of the aggregate evidence quality, the potential for bias in the evidence and the probable benefits and harms of rituximab in patients with lymphoma and CLL.

Eine Graduierung der Empfehlungen konnte nicht identifiziert werden.

Empfehlungen

Indolent/Mantle Cell Lymphoma

Patients with relapsed/refractory disease

For previously treated patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL:

- Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab or as rituximab monotherapy.
- Patients who have previously received rituximab (including combination rituximab-chemotherapy, rituximab monotherapy, or maintenance rituximab) and who have achieved a response of at least one year's duration from the last rituximab administration and who are appropriate candidates for therapy should receive this therapy in combination with rituximab or as rituximab monotherapy.

Hintergrund

The DSG […] considered the role of rituximab beyond first-line therapy. Five studies [39-43], represented by nine publications, were included. Three studies had a population of patients with follicular lymphoma or MCL [41-43]; the other two studies included patients with NHL [39, 40]. The recommendation […] for previously treated rituximab-naive patients is based on the improved survival and time to progression (TTP) observed with the addition of rituximab to fludarabine, cyclophosphamide, and mitoxantrone (FCM) reported by Forstpointner et al. [41] and Dreyling et al. [70], and the improved TTP reported in the study of CHOP ± rituximab by van Oers et al. [42].

The role of rituximab in combination with chemotherapy for patients previously treated with rituximab (alone or in combination) is much less clearly defined. None of the randomised trials included patients who had previously received rituximab. The DSG is unable to offer definitive recommendations where no direct evidence exists, but recognises the need of practitioners and policy-makers for guidance in this situation. The addition of rituximab to chemotherapy in patients beyond first-line treatment is associated with improved TTP and, in one trial, survival. The re-use of therapies that have previously been effective for a given patient is a common strategy when managing patients with indolent lymphomas. Data from trials of rituximab monotherapy suggest that in a selected population of rituximab-sensitive patients, a response rate comparable to that observed in first-line treatment can be observed [65]. Cumulative toxicity from multiple treatments with rituximab is not expected. Based upon these data, and the consensus of the members of the Hematology DSG, the group recommends that patients previously treated with rituximab who remain sensitive to this agent, and who are appropriate candidates, should receive chemotherapy in combination with rituximab. Although no evidence-based definition of rituximab sensitivity exists, the DSG considers relapse 1 year or more after treatment with rituximab to be a reasonable threshold. In addition, the group considered patients who remained stable for 1 year after the last dose of maintenance rituximab to be rituximab-sensitive.

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Rituximab maintenance treatment

For patients with indolent histology CD20-positive B-cell lymphomas, excluding SLL, who respond to treatment with combination chemotherapy and/or rituximab, this treatment should be followed by the use of maintenance rituximab.

Hintergrund

Nine RCTs [42,60,63-67,71,72], represented by 22 publications, were included. Six studies had a population of patients with follicular lymphoma [42,61,63,67,71,72], two studies included patients with MCL [60,64] and two studies included patients with NHL or indolent lymphoma [65,66]. The Hainsworth et al. study [65] compared rituximab maintenance with rituximab re-treatment; all the other studies compared rituximab maintenance with observation. Two of the trials had two randomisations, the second of which tested for rituximab maintenance [42,67]. Therefore, depending on the trials' first phase, some patients in rituximab maintenance group had already been exposed to rituximab (all the patients from the PRIMA study [72], the FILML17638 study [63], the Forstpointner et al. study [64]).

Most studies have shown clinically important improvements in disease control and three trials have shown prolongation of survival [64,66,73]. In patients receiving therapy for relapsed follicular lymphoma, there are clear benefits in disease control and survival attained with the use of magnetic resonance. Six studies reported on PFS [42,63,65-67,72]. The meta-analysis showed a pooled hazard ratio for the six RCTs of 0.53 (95% confidence interval 0.47-0.59). The benefit in disease control is preserved even in patients who have received combination chemotherapy that includes rituximab. Following front-line therapy, magnetic resonance has similarly resulted in prolonged PFS and overall survival. However, this strategy has only been studied following combination chemotherapy without rituximab. The DSG believed strongly that the body of evidence to date supports extending the use of magnetic resonance to the front-line setting following chemotherapy with rituximab. The group consensus was influenced by the sizable magnitude of benefit in disease control in this setting and the preservation of this benefit following rituximab-based chemotherapy noted in the relapsed setting. Data are available

on the use of maintenance rituximab (MR) following rituximab monotherapy in both front-line and relapsed setting. Based on the improvement in PFS in those trials as well as the consistent benefit of this strategy, the DSG also recommends the use of MR in those patients initially receiving rituximab monotherapy.

Given the inclusion of a number of non-follicular indolent histologies in four of the six trials and the comparable activity of rituximab in follicular lymphoma and other non-follicular indolent histologies, the DSG recommends that data from follicular lymphoma be generalised to these histologies (including marginal zone lymphoma [MZL] and lymphoplasmacytic lymphoma) […].

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2021) am 14.12.2021

#	Suchfrage
1	[mh "lymphoma, b cell, marginal zone"]
2	(((marginal NEXT zone) OR malt OR mucosa) AND lymphom*):ti,ab,kw
3	(monocytoid AND (b NEXT cell) AND lymphom*):ti,ab,kw
4	(cutaneous AND (b NEXT cell) AND lymphom*):ti,ab,kw
5	#1 OR #2 OR #3 OR #4
6	#5 with Cochrane Library publication date from Dec 2016 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 14.12.2021

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	"lymphoma, b cell, marginal zone"[mh]
2	(marginal zone[tiab] OR malt[tiab] OR mucosa[tiab]) AND lymphom*[tiab]
3	monocytoid[tiab] AND b-cell[tiab] AND lymphom*[tiab]
4	cutaneous[tiab] AND b-cell[tiab] AND lymphom*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR

#	Suchfrage
	datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	(#6) AND ("2016/12/01"[PDAT] : "3000"[PDAT])
8	(#7) NOT "The Cochrane database of systematic reviews"[Journal]
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 14.12.2021

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	"lymphoma, b cell, marginal zone"[mh]
2	(marginal zone[tiab] OR malt[tiab] OR mucosa[tiab]) AND lymphom*[tiab]
3	monocytoid[tiab] AND b-cell[tiab] AND lymphom*[tiab]
4	cutaneous[tiab] AND lymphom*[tiab]
5	"Lymphoma, B-Cell"[mh:noexp]
6	"Lymphoma, Non-Hodgkin"[mh:noexp]
7	(non-hodgkin*[tiab] OR nonhodgkin*[tiab]) AND lymphom*[tiab]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(#8) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
10	(#9) AND ("2016/12/01"[PDAT] : "3000"[PDAT])
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 14.12.2021

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)

- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-421

Kontaktdaten

Fachgesellschaft
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Indikation gemäß Beratungsantrag

Behandlung erwachsener Patienten mit Marginalzonenlymphom (MZL), die mindestens eine vorherige Therapie, darunter mindestens eine anti-CD20-basierte Therapie, erhalten haben.

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Das Marginalzonenlymphom umfasst eine heterogene Gruppe von Erkrankungen. Formal werden unterschieden:

- extranodales Marginalzonen-Lymphom des Mukosa-assoziierten lymphatischen Gewebes (‚mucosa-associated lymphatic tissue', MALT)
- splenisches Marginalzonen-Lymphom
- nodales Marginalzonen-Lymphome

Die systemische Therapie im Rezidiv und bei Refraktärität orientiert sich am follikulären Lymphom. Eine Therapieindikation besteht erst beim Auftreten krankheitsassoziierter Symptome. Die Therapie erfolgt patientenindividuell nach Maßgabe der behandelnden Ärzt*innen in Abhängigkeit von der Primärtherapie, der Dauer der vorherigen Remission, der Verträglichkeit und Komorbiditäten.

Stand des Wissens

Die Marginalzonen-Lymphome gehören zu den reifzelligen indolenten Non-Hodgkin Lymphomen. Nach der aktuellen Version der WHO-Klassifikation werden folgende Subgruppen unterschieden [1]:

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- extranodales Marginalzonen-Lymphom des Mukosa-assoziierten lymphatischen Gewebes (‚mucosa-associated lymphatic tissue', MALT), 7% bis 8% aller neu diagnostizierten Lymphome [2]
- splenisches Marginalzonen-Lymphom (2% aller Lymphome)
- nodales Marginalzonen-Lymphome (1,5% bis 1,8 % aller Lymphome) [3]

Die Therapiekonzepte der Marginalzonen-Lymphome unterscheiden sich in der Primärtherapie dadurch, dass insbesondere beim extranodalen Marginalzonen-Lymphom lokale Maßnahmen wie die Strahlentherapie oder eine antibiotische Eradikationstherapie eine wichtige Rolle spielen [2-4].

In fortgeschrittenen Stadien und im Rezidiv bildet die systemische Therapie den Standard. Wie beim follikulären Lymphom wird auch das fortgeschrittene Marginalzonen-Lymphom nur bei krankheitsassoziierten Symptomen behandelt [2-4]. Die Rezidivtherapie folgt zumeist den Empfehlungen des follikulären Lymphoms.

Diese sind [2-4]:

- Im Rezidiv nach längerer (>2 Jahre) vorheriger Ansprechdauer wird eine erneute Rituximab/Chemotherapie empfohlen.
- Bei Frührezidiven ist bei geeigneten Patient*innen eine Hochdosistherapie mit autologer Stammzelltransplantation eine Therapieoption [5, 6].
- Eine wirksame Therapieoption sind BTK Inhibitoren. Zwei Studien belegen die Wirksamkeit der BTK Inhibition beim Marginalzonenlymphom: so induzierte Ibrutinib als Monotherapie in einer Phase II Studie bei rezidivierten/refraktären Marginalzonenlymphomen (n=63; 17 Patient*innen mit nodalen MZL) ein Gesamtansprechen von 48 % mit einem PFS von 14.2 Monaten [7]. Der Zweitgenerations – BTK Inhibitor Zanubrutinib erreichte ebenfalls in einer Phase II Studie bei 68 Patient*innen mit rezidivierten/refraktären MZL ein Gesamtansprechen von 68,2 %, wobei bei den 26 Patient*innen mit nodalem MZL ein OR von 76% erzielt wurde [8]. Bei beiden BTK-Inhibitoren handelt es sich formal um einen Off-Label-Use. Ibrutinib hat die Zulassung bei der CLL, beim Mantelzell-Lymphom und beim Morbus Waldenström, Zanubritinib hat seit November 2021 die Zulassung der EMA beim Morbus Waldenström.
- Bei Patient*innen, die auf zwei vorherige Behandlungen nicht angesprochen haben, ist der Einsatz des PI3K-Inhibitors Idelalisib als Monotherapie möglich. Im fortgeschrittenen Rezidiv haben PI3K-Inhibitoren (Idelalisib, Copanlisib) auch bei Rituximab-refraktären Rezidiven lang anhaltende Remissionen erzielt, so dass dieser Therapieansatz individuell zu diskutieren ist [9-11]. In einer Phase-II-Studie konnte bei Patient*innen mit follikulärem Lymphom, die gegen eine vorherige Therapie mit Rituximab und Alkylanzien refraktär waren, mit Idelalisib eine Ansprechrate von 56%

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erzielt werden [9]. Der Einsatz von Idelalisib ist formal Off-Label, wird aber in der Praxis analog zum Einsatz beim follikulären Lymphom durchgeführt.

- Eine andere, wirksame Substanzklasse sind Immunmodulatoren. Bei Patient*innen mit Rezidiv oder Refraktärität nach einer oder mehreren Vortherapien führte die Kombination von Lenalidomid mit Rituximab gegenüber einer Rituximab-Monotherapie (nach Anpassung der klinischen Risikofaktoren) zu einer Verlängerung des progressionsfreien Überlebens. Ein möglicher, positiver Einfluss von Lenalidomid/Rituximab auf die Gesamtüberlebenszeit ist wegen noch unreifer Daten nicht abschließend beurteilbar [12]. Anders als in den USA erfolgt der Einsatz dieser Kombination beim Marginalzonen-Lymphom im Off-Label-Use.

Eine allogene Transplantation spielt beim rezidivierten Marginalzonen-Lymphom nur eine nachgeordnete Rolle, ist aber eine Option.

Die patientenindividuelle Wahl des Therapieregimes hat insbesondere das zu erwartende Toxizitätsspektrum und eventuelle Komorbiditäten zu berücksichtigen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von *„erwachsenen Patienten mit Marginalzonenlymphom (MZL), die mindestens eine vorherige Therapie, darunter mindestens eine anti-CD20-basierte Therapie, erhalten haben“* die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, diese sind in einer patientenindividuellen Therapie nach Maßgabe der behandelnden Ärzt*innen enthalten.

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