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: 2025-B-317 Epcoritamab

Stand: Februar 2026

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

Epcoritamab
[rezidiviertes/refraktäres follikuläres Lymphom]

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 und follikulärer Lymphome Grad 3B.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Strahlentherapie - Allogene und autologe Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Odronextamab (Beschluss vom 22. Januar 2026) - Lisocabtagen maraleucel (Beschluss vom 2. Oktober 2025) - Epcoritamab (Beschluss vom 6. März 2025) - Zanubrutinib (Beschluss vom 6. Juni 2024) - Axicabtagen-Ciloleucel (Beschluss vom 21. Dezember 2023) - Mosunetuzumab (Beschluss vom 15. Dezember 2022) - Tisagenlecleucel (Beschluss vom 01. Dezember 2022) - Duvelisib (Beschluss vom 21. Juli 2022) - Obinutuzumab (Beschluss vom 04.11.2021) - Idelalisib (Beschluss vom 19. März 2015) Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Stand: 28.10.2022): - 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-,

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

Epcoritamab [rezidiviertes/refraktäres follikuläres Lymphom] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
	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:	
Epcoritamab L01FX27 Tepkinly	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Epcoritamab wird angewendet in Kombination mit Rituximab und Lenalidomid zur Behandlung von erwachsenen Patienten mit einem rezidivierenden oder refraktären follikulären Lymphom (FL).
Antineoplastische Arzneimittel	
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	Non-Hodgkin-Lymphome von intermediärem oder hohem Malignitätsgrad im Erwachsenenalter.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01DC01 generisch	Bleomycinsulfat wird bei diesen Erkrankungen üblicherweise in Kombination mit anderen Zytostatika verwendet.
Carmustin L01AD01 generisch	Als Einzelwirkstoff oder in Kombination mit anderen antineoplastischen Mitteln und/oder anderen therapeutischen Maßnahmen (Strahlentherapie, chirurgischer Eingriff): - Zweittherapie bei Non-Hodgkin-Lymphom und Morbus Hodgkin.
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
Doxorubicin L01DB01 generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: - Non-Hodgkin-Lymphome
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
Mitoxantron L01DB07	Mitoxantron ist indiziert zur Behandlung des Non-Hodgkin-Lymphoms.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	
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 L01CA02 generisch	Vincristin wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen
Glucocorticoide	
Dexamethason H02AB02 generisch	Prophylaxe und Therapie von postoperativem oder Zystostatika-induzierten Erbrechen im Rahmen antiemetischer Schemata
Methylprednisolon H02AB04 generisch	Blutkrankheiten/Tumorerkrankungen - Autoimmunhämolytische Anämie - Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen, Anwendung im Rahmen antiemetischer Schemata
Prednisolon H02AB06 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome
Prednison H02AB07 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome

II. Zugelassene Arzneimittel im Anwendungsgebiet

Arzneimittel mit expliziter Zulassung für das follikuläre Lymphom:	
PI3K-Inhibitoren	
Idelalisib L01EM01 Zydelig	Zydelig wird als Monotherapie zur Behandlung von erwachsenen Patienten mit follikulärem Lymphom (FL), das refraktär nach zwei vorausgegangenen Therapielinien ist, angewendet.
Duvelisib[1] L01EM04 Copiktra	Eine Copiktra-Monotherapie wird angewendet zur Behandlung von erwachsenen Patienten mit: - follikulärem Lymphom (FL), das gegenüber mindestens zwei vorherigen systemischen Therapien refraktär ist.
Immunmodulatoren	
Lenalidomid L04AX04 Revlimid	Follikuläres Lymphom Revlimid in Kombination mit Rituximab (Anti-CD20-Antikörper) ist indiziert für die Behandlung von erwachsenen Patienten mit vorbehandeltem follikulärem Lymphom (Grad 1 – 3a).
Antikörper	
Epcoritamab L01FX27 Tepkinly	Tepkinly wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit einem rezidivierenden oder refraktären follikulären Lymphom (FL) nach mindestens 2 Linien einer systemischen Therapie
Mosunetuzumab L01FX24 Lunsumio	Lunsumio als Monotherapie ist angezeigt für die Behandlung von erwachsenen Patienten mit rezidivierendem oder refraktärem follikulärem Lymphom (FL), die bereits mindestens zwei vorherige systemische Behandlungen erhalten haben
Obinutuzumab L01FA03 Gazyvaro	Follikuläres Lymphom (FL) Gazyvaro in Kombination mit Bendamustin, gefolgt von einer Gazyvaro Erhaltungstherapie, wird angewendet bei Patienten mit FL, die auf eine Behandlung mit Rituximab oder einem Rituximab-haltigen Regime nicht angesprochen haben oder während bzw. bis zu 6 Monate nach der Behandlung progredient wurden.

[1] Die Zulassung von Duvelisib ist auf Antrag des pharmazeutischen Unternehmers mit Wirkung vom 16. Februar 2026 widerrufen worden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Odronextamab L01FX34 Rotspone	Ordspono als Monotherapie wird angewendet zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem follikulärem Lymphom (r/r FL) nach zwei oder mehr systemischen Therapielinien
Rituximab L01FA01 MabThera	Non-Hodgkin-Lymphom (NHL): - MabThera ist als Monotherapie für die Behandlung von Patienten mit follikulärem Lymphom im Stadium III – IV angezeigt, die gegen eine Chemotherapie resistent sind oder nach einer solchen einen zweiten oder neuerlichen Rückfall haben.
Tafasitamab L01FX12 Minjuvi	Minjuvi ist in Kombination mit Lenalidomid und Rituximab zur Behandlung erwachsener Patienten mit rezidiviertem oder refraktärem follikulärem Lymphom (FL) (Grad 1 – 3a) nach mindestens einer systemischen Therapielinie indiziert.
CAR-T-Zellen	
Tisagenlecleucel L01XL04 Kymriah	Behandlung erwachsener Patienten mit rezidiviertem oder refraktären follikulärem B-Zell-Lymphom der Grade 1 bis 3a nach zwei oder mehr Vortherapien.
Axicabtagen-Ciloleucel L01XL03 Yescarta	Yescarta wird angewendet zur Behandlung von erwachsenen Patienten mit r/r follikulärem Lymphom (FL) nach drei oder mehr systemischen Therapien.
Lisocabatagen maraleucel Breyanzi L01XL08	Breyanzi wird angewendet zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem follikulären Lymphom (FL) nach zwei oder mehr Linien einer systemischen Therapie.

Bruton-Tyrosinkinase-(BTK)-Inhibitoren	
Zanubrutinib L01EL03 Brukinsa	Brukinsa wird in Kombination mit Obinutuzumab zur Behandlung von erwachsenen Patienten mit refraktärem oder rezidiviertem follikulärem Lymphom (FL) angewendet, die mindestens zwei vorherige systemische Therapien erhalten haben.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-317 (Beratung nach § 35a SGB V) Epcoritamab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. Dezember 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

ASCR	Autologous stem cell rescue
ASCT	Autologous stem cell transplant
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CHOP	Cyclophosphamid, Doxorubicin, Vincristin, Prednison
CR	Complete response
CRS	Cytokine release syndrome
CT	Computertomographie
CVP	Cyclophosphamid, Vincristin, Prednison
DLBCL	Diffuses großzelliges B-Zell-Lymphom
ECOG	Eastern Cooperative Oncology Group
ECRI	Emergency Care Research Institute
EFS	Event-free survival
FL	Follikuläres Lymphom
GIN	Guidelines International Network
GLSG	German Low Grade Lymphoma Study Group
GoR	Grade of recommendations
GRADE	Grading of recommendations assessment, development and evaluation
HCT	Hematopoietic cell transplant
HDCT	High-dose chemotherapy
HDT	High-dose therapy
ICANS	Immune effector cell-associated neurotoxicity syndrome
IFRT	Involved field radiation therapy
LoE	Level of evidence
mAb	Monoklonaler Antikörper
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin-Lymphom
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PET	Positronen-Emissions-Tomographie
PFS	Progression-free survival
POD	Progression of disease
PR	Partial response
RCT	Randomized controlled trial
RI	Rituximab induction
RM	Rituximab maintenance
SCT	Stem cell transplant
SIGN	Scottish Intercollegiate Guidelines Network
TEAE	Treatment-emergent adverse event
TRIP	Turn Research into Practice Database
TRM	Transplant-related mortality
TTNT	Time to next treatment

W&W	Watch & wait
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit einem rezidivierenden oder refraktären follikulären Lymphom (FL).

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 *B-Zell-Lymphome* 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), 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 der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 20.10.2025 abgeschlossen. Am 08.12.2025 erfolgte eine Überprüfung der iterativen Handsuche. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 1361 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. 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 2 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.3 Leitlinien

Leitlinien der AWMF

Die S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit einem follikulären Lymphom befindet sich derzeit in Überarbeitung mit geplanter Fertigstellung bis Ende Juni 2026.

National Comprehensive Cancer Network (NCCN), 2025 [2].

B-Cell Lymphomas, Version 3.2025 – August 18, 2025

Zielsetzung/Fragestellung

The National Comprehensive Cancer Network (NCCN®) Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas were developed as a result of meetings convened by a multidisciplinary Panel of experts, with the aim to provide recommendations for diagnostic workup, treatment, and surveillance strategies for the most common subtypes of B-cell lymphomas, in addition to a general discussion on the classification systems and supportive care considerations.

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund limitierter Evidenz hinsichtlich der Behandlung des rezidivierenden oder refraktären FL und aufgrund ihrer Aktualität wird die Leitlinie ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: **Trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft teilweise zu** – Eine systematische Recherche wurde durchgeführt, aber Angaben zu den Auswahlkriterien und der kritischen Bewertung der Literatur fehlen (siehe Recherche/Suchzeitraum).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft teilweise zu** – Konsensusprozesse werden dargelegt, aber es gibt kein externes Begutachtungsverfahren
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft teilweise zu** – In den Therapiealgorithmen werden die Evidenzgrade der Empfehlungen angegeben und es gibt einen Hintergrundtext. Jedoch fehlt eine konkrete Beschreibung der Empfehlungen.

- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu** – The NCCN Guidelines are reviewed and updated on an ongoing basis to ensure that the recommendations reflect the most current evidence and clinical practice. All NCCN Guidelines are reviewed and updated at least annually. Interim Guidelines updates may also occur based upon new evidence or regulatory approvals of new drugs or biologics that may change clinical practice. The need for an interim Guidelines update is determined by the Panel leadership in conjunction with the NCCN Guidelines Team.

Recherche/Suchzeitraum:

- Prior to the update of this version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas an electronic search of the PubMed database was performed to obtain key literature in FL published since the previous Guidelines update.
- The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles deemed relevant to these Guidelines and discussed by the Panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts).

LoE/GoR

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

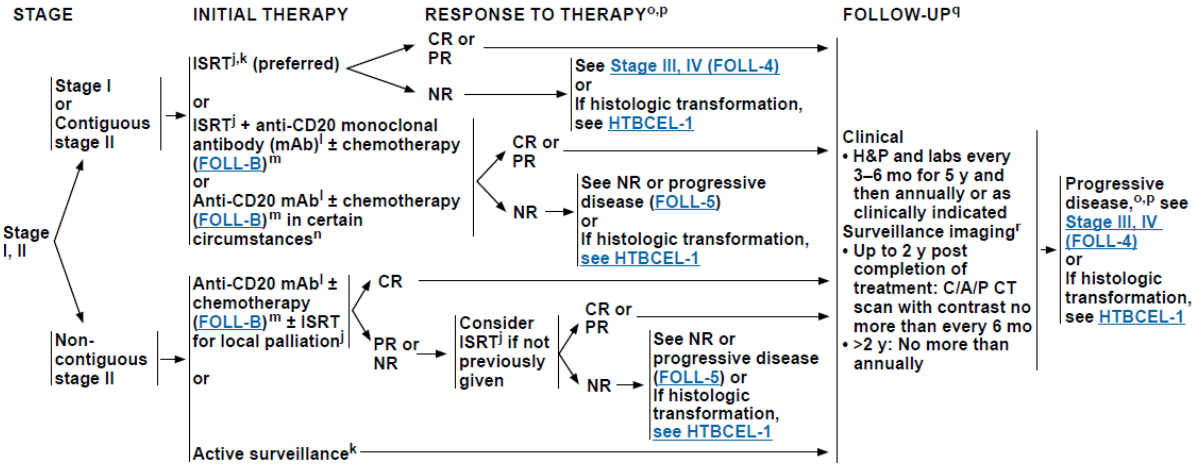
All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Klassifikation gemäß WHO-Klassifikation 2024, 5. Edition

Empfehlungen

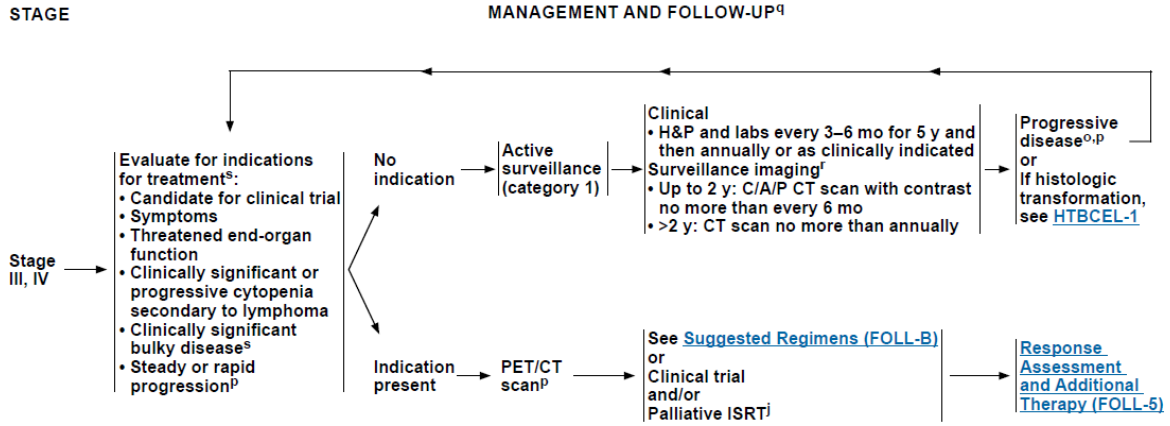
Classic Follicular Lymphoma



[j] Principles of Radiation Therapy (NHODG-D).
[k] Active surveillance may be appropriate in circumstances where potential toxicity of ISRT or systemic therapy outweighs potential clinical benefit in consultation with a radiation oncologist.
[l] Anti-CD20 mAbs include rituximab or obinutuzumab. Obinutuzumab is not indicated as single-agent therapy.
[m] Initiation of systemic therapy can improve failure-free survival (FFS), but has not been shown to improve overall survival. These are options for initial therapy.
[n] Eg, for patients with bulky intra-abdominal or mesenteric stage I disease.
[o] Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET Five-Point Scale (5-PS).
[p] 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, treatment options should be directed towards the large cell transformation, see HTBCEL-1.
[q] 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.
[r] Surveillance imaging is used for monitoring asymptomatic patients. 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.

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

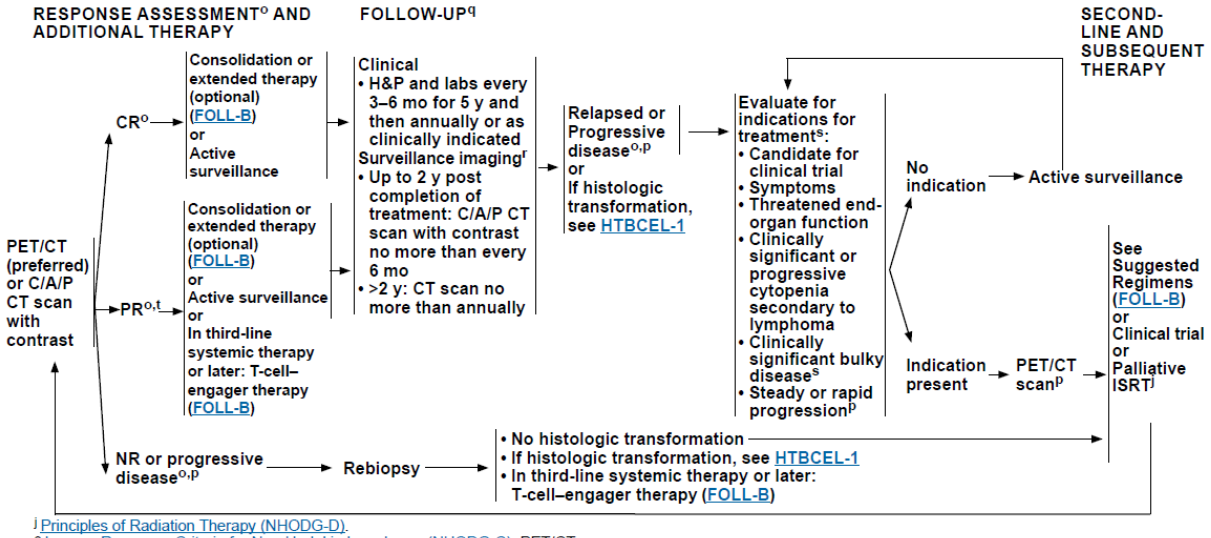
FOLL-3



[j] Principles of Radiation Therapy (NHODG-D).
[o] Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET 5-PS.
[p] 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, options should be directed towards the large cell transformation, see HTBCEL-1.
[q] 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.
[r] Surveillance imaging is used for monitoring asymptomatic patients. 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.
[s] GELF criteria (FOLL-A).

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

FOLL-4



[j] Principles of Radiation Therapy (NHODG-D).

[o] Lugano Response Criteria for Non-Hodgkin Lymphoma (NHODG-C). PET/CT scan should be interpreted via the PET 5-PS.

[p] 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,treatment options should be directed towards the large cell transformation, see HTBCEL-1.

[q] 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.

[r] Surveillance imaging is used for monitoring asymptomatic patients. 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.

[s] GELF criteria (FOLL-A).

[t] A PET-positive PR is associated with a shortened progression-free survival (PFS) (Discussion); however, additional treatment at this juncture has not been shown to change outcome.

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

FOLL-5

SUGGESTED TREATMENT REGIMENS[a,b,c]

SECOND-LINE THERAPY[h]

Preferred regimens (in alphabetical order)
- Bendamustine[d,i] + obinutuzumab[j] or rituximab (not recommended if treated with prior bendamustine)
- CHOP + obinutuzumab[j] or rituximab
- CVP + obinutuzumab[j] or rituximab
- Lenalidomide + rituximab
- Tafasitamab-cxix[k] + lenalidomide + rituximab (≥1 prior systemic therapy including an anti-CD20 mAb)

Other recommended regimens (in alphabetical order)
- Lenalidomide (if not a candidate for anti-CD20 mAb therapy)
- Lenalidomide + obinutuzumab
- Obinutuzumab
- Rituximab

SECOND-LINE THERAPY FOR OLDER OR INFIRM
(if none of the therapies are expected to be tolerable in the opinion of treating physician)

Preferred regimens
- Rituximab (375 mg/m^2 weekly for 4 doses)
- Tazemetostat[l] (irrespective of *EZH2* mutation status)

Other recommended regimen
- Cyclophosphamide ± rituximab

SECOND-LINE EXTENDED THERAPY (optional)

Preferred regimens
- Rituximab maintenance 375 mg/m^2 one dose every 12 weeks for 2 years (category 1)
- Obinutuzumab maintenance for rituximab-refractory disease (1 g every 8 weeks for total of 12 doses)

SECOND-LINE CONSOLIDATION THERAPY (optional)
- High-dose therapy with autologous stem cell rescue (HDT/ASCR)

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

Footnotes on FOLL-B 4 of 6
See Third-Line and Subsequent Therapy on FOLL-B 3 of 6

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

FOLL-B 2 OF 6

SUGGESTED TREATMENT REGIMENS[a,b,c]

THIRD-LINE AND SUBSEQUENT THERAPY **Subsequent systemic therapy options include second-line therapy regimens (FOLL-B 2 of 6) that were not previously given.**	
Preferred regimens (in alphabetical order)	**Other recommended regimens**
• T-cell engager therapy ‣ Bispecific antibody therapy[l,m] ◊ Epcoritamab-bysp ◊ Mosunetuzumab-axgb ‣ Chimeric antigen receptor (CAR) T-cell therapy[n] ◊ Axicabtagene ciloleucel (CD19-directed) ◊ Lisocabtagene maraleucel (CD19-directed) ◊ Tisagenlecleucel (CD19-directed)	• EZH2 inhibitor ‣ Tazemetostat[l] (irrespective of EZH2 mutation status) • BTK inhibitor (BTKi) ‣ Zanubrutinib[l] + obinutuzumab • Loncastuximab tesirine-lpyl + rituximab (category 2B)[k]

THIRD-LINE CONSOLIDATION THERAPY
Useful in Certain Circumstances
• Allogeneic hematopoietic cell transplantation (HCT) in selected cases[o]

Footnotes on FOLL-B 4 of 6

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

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

SUGGESTED TREATMENT REGIMENS
FOOTNOTES

[a] See references for regimens on FOLL-B 5 of 6 and FOLL-B 6 of 6.
[b] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. 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.
[c] 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.
[d] In the GALLIUM study, there was an increased risk of mortality from opportunistic infections and secondary malignancies in patients receiving bendamustine. Increased risk of mortality occurred over the entire treatment program and extending beyond maintenance. Prophylaxis for pneumocystis jirovecii pneumonia (PJP) and varicella zoster virus (VZV) should be administered; see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[e] The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data.
[f] Rituximab may be appropriate if active surveillance was initial therapy and for patients with progression of low tumor burden disease not meeting GELF criteria (FOLL-A). Immediate initial therapy with rituximab in patients not meeting GELF criteria has not improved overall survival (Ardeshna K, et al. Lancet Oncol 2014;15:424-435).
[g] This is based on the PRIMA study for patients with high tumor burden following treatment with RCVP and RCHOP. There are no data for rituximab maintenance following other regimens.
[h] Generally, a first-line regimen is not repeated.
[i] In patients intended to receive CAR T-cell therapy or CD3 x CD20 bispecific antibody therapy, bendamustine should be used with caution. Delay bendamustine until after CAR-T leukapheresis.
[j] The clinical trial evaluating this regimen included obinutuzumab maintenance. The use without maintenance was an extrapolation of the data. Obinutuzumab is preferred in patients with rituximab refractory disease, which includes disease progressing on or within 6 months of prior rituximab therapy.
[k] It is unclear if tafasitamab-cxix or loncastuximab tesirine-lpyl or if any other CD19–directed therapy would have a negative impact on the efficacy of subsequent anti-CD19 CAR T-cell therapy.
[l] Refer to package insert for full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[m] In the setting of CD20-negative lymphomas, the activity of CD3 x CD20 bispecific antibody therapy is unclear. Rebiopsy to confirm CD20 positivity is recommended prior to initiating CD3 x CD20 bispecific antibody therapy.
[n] Guidance for Treatment of Patients with Chimeric Antigen Receptor (CAR) T-Cell Therapy (NHODG-E).
[o] Selected cases include mobilization failures and persistent bone marrow involvement.

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

Version 3.2025, 08/18/25 © 2025 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

SUGGESTED TREATMENT REGIMENS
REFERENCES

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.

Lenalidomide ± rituximab
Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol 2015;33:3635-3640.
Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol 2019;37:1188-1199.

Lenalidomide + obinutuzumab
Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol 2019;6:e429-e437.

Rituximab
McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998;16:2825-2833.
Ghielmini M, Schmitz SH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416-4423.

Tafasitamab-cxix + lenalidomide + rituximab
Tafasitamab Plus Lenalidomide and Rituximab for Relapsed or Refractory Follicular Lymphoma: Results from a Phase 3 Study (inMIND) [abstract]. Blood 2024:Abstract LBA-1.

Tazemetostat
Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol 2020;21:1433-1442.

Second-line Consolidation or Extended Dosing

Rituximab maintenance
van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-hodgkin's lymphoma: Long-term outcome of the EORTC 20981 Phase III randomized Intergroup Study. J Clin Oncol 2010;28:2853-2858.

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.

Third-line and Subsequent Therapy

Loncastuximab tesirine-lpyl + rituximab
Alderuccio JP, Alencar AJ, Schatz JH, et al. Loncastuximab tesirine with rituximab in patients with relapsed or refractory follicular lymphoma: A single-centre, single-arm, phase 2 trial. Lancet Haematol 2025;12:e23-e34.

Zanubrutinib + obinutuzumab
Zinzani PL, Mayer J, Flowers CR, et al. ROSEWOOD: A phase II randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma. J Clin Oncol 2023;41:5107-5117.

T-Cell–Engager Therapy

CAR T-Cell Therapy

Axicabtagene ciloleucel
Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). Blood 2024;143:496-506.

Lisocabtagene maraleucel
Morschhauser F, Dahiya S, Palomba ML, et al. Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study. Nat Med 2024;30:2199–2207.

Tisagenlecleucel
Dreyling M, Fowler NH, Dickinson M, et al. Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update. Blood 2024;143:1713-1725.

Bispecific Antibody Therapy

Epcoritamab-bysp
Linton KM, Vitolo U, Jurczak W, et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. Lancet Haematol 2024;11:e593–e605.

Mosunetuzumab-axgb
Sehn LH, Bartlett NL, Matasar MJ, et al. Long-term 3-year follow-up of mosunetuzumab in relapsed or refractory follicular lymphoma after >/=2 prior therapies. Blood 2025;145:708–719.

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

Backgroundinfos aus Leitlinien:

Relapsed or Progressive Disease

Frequently, patients with disease relapse or progression of disease (POD) after first-line therapy will benefit from a second period of active surveillance. Considerations and indications for treatment of relapsed/refractory or progressive disease include: symptoms attributable to FL (not limited to B symptoms); threatened end-organ function; clinically significant or progressive cytopenia secondary to lymphoma; clinically significant bulky disease (any nodal or extranodal tumor mass with a diameter of ≥7 cm); and steady or rapid progression. Progressive disease should be histologically documented to exclude transformation, especially in the presence of raising LDH levels, disproportional growth in one area, development of extranodal disease, or development of new constitutional symptoms. Areas of high SUV, especially in values in excess of 13, should raise suspicion for the presence of transformation.46 However, a positive PET/CT scan does not replace a biopsy; rather, the results of the PET/CT scan should be used to direct the optimal site of biopsy for histologic confirmation to enhance the diagnostic yield from the biopsy.

POD ≤24 months of diagnosis and inability to achieve EFS at 12 months (EFS12) after initial treatment with chemoimmunotherapy have been identified as prognostic indicators of poor survival.100-102 In the National LymphoCare Study, the 5-year OS rate was 50% for patients with POD ≤2 years after first-line therapy with RCHOP compared with 90% for those with POD >2 years.100 In a population-based analysis of relative survival of patients with FL compared to age-and-sex-matched controls (from U.S. and French datasets), the group of patients achieving EFS12 following initial management had similar OS outcomes compared to age-and-sex-matched general populations, whereas patients who did not achieve EFS12 had lower subsequent OS.101 Systemic therapy options for patients with FL at first relapse with high tumor burden or symptomatic disease include alternate non–cross-resistant, CD20-directed, mAb-based chemoimmunotherapy or a combination of lenalidomide and rituximab.103-107 The phase III AUGUMENT trial (discussed below) established lenalidomide + rituximab as an effective second-line therapy option for patients with previously treated FL that is not refractory to rituximab.107 Duration of response (DOR) to first-line therapy is an important factor in the selection of second-line therapy. Rituximab monotherapy may be appropriate for patients with late relapse as well, particularly if disease burden is low. Patients with POD ≤2 years after first -line therapy should be considered for treatment with lenalidomide-based regimens, novel approaches including clinical trials, or referral for the consideration of HDT/ASCR.108-110 PI3K inhibitors including copanlisib, duvelisib, idelalisib, and umbralisib had previously received accelerated FDA approval for relapsed/refractory FL based on the improved ORR and PFS as shown in

preliminary clinical trials.111-115 However, there was later a voluntary withdrawal of this FDA indication for copanlisib, duvelisib, idelalisib, and umbralisib based on the substantial toxicity of PI3K inhibitors having a detrimental impact on OS in recent clinical trials; these are not recommended for the treatment of relapsed/refractory FL.116 Allogeneic hematopoietic cell transplant (HCT) results in lower relapse rates than HDT/ASCR, but it is associated with high transplant-related mortality (TRM) rate.117-119 Allogeneic HCT may also be considered as third-line consolidation therapy in selected patients.

Second-Line Therapy: Preferred Regimens

Chemoimmunotherapy With CD20-Directed Monoclonal Antibody

In a randomized phase III study of 230 patients with relapsed or refractory indolent lymphoma or MCL (114 patients assigned to BR and 105 patients assigned to FR [fludarabine + rituximab]), BR was more effective than FR in terms of PFS.120 At a median follow-up of 96 months, the median PFS was 34 months and 12 months, respectively, for BR and FR. Obinutuzumab-based chemoimmunotherapy has also been evaluated in atients with relapsed or refractory FL.103-105

The safety and efficacy of CHOP + obinutuzumab in patients with relapsed or refractory FL was demonstrated in a randomized study (56 patients were randomized to obinutuzumab in combination with CHOP or FC [fludarabine and cyclophosphamide]).103 The ORRs were 96% and 93%, respectively, for CHOP + obinutuzumab and FC + obinutuzumab. The corresponding CR rates were 39% and 50%, respectively. In the CHOP + obinutuzumab group, 25% of patients with rituximab-refractory disease achieved CR and in the FC + obinutuzumab group, 30% achieved CR. All of the patients with rituximab-refractory disease achieved at least PR. FC + obinutuzumab was associated with more TEAEs than CHOP + obinutuzumab.

The phase III randomized trial (GADOLIN) compared bendamustine + obinutuzumab versus bendamustine monotherapy in patients with rituximab-refractory indolent lymphoma (413 patients; 335 patients had FL; 164 patients were randomized to bendamustine + obinutuzumab; 171 patients were randomized to bendamustine monotherapy).104,105 Patients without POD in the bendamustine + obinutuzumab group received obinutuzumab maintenance. After a median follow-up of 32 months, the median PFS was significantly longer with bendamustine + Obinutuzumab than with bendamustine monotherapy (26 vs. 14 months; P < .001) in patients with FL.112 The median OS was not reached in the bendamustine + obinutuzumab group compared to 54 months for the bendamustine group. The most frequent grade ≥3 TEAEs were neutropenia (33% for bendamustine + obinutuzumab vs. 26% for bendamustine monotherapy), thrombocytopenia (11% vs. 16%), anemia (8% vs. 10%), and infusion-related reactions (11% vs. 6%). Given the concerns for increased incidences of opportunistic infections and secondary malignancies after first-line therapy with BR,87,88 BR is not recommended as an option for second-line therapy if it was previously used as first-line therapy.

Lenalidomide + Rituximab

In the multicenter, double-blind, randomized phase III study (AUGMENT; n = 358; 295 patients had FL), lenalidomide + rituximab was superior to rituximab monotherapy in terms of PFS in all histologic subtypes of previously treated indolent lymphomas except MZL.107 At median follow-up of 28 months, the median PFS was 39 months for lenalidomide + rituximab compared to 14 months for rituximab monotherapy (P < .0001) in the subgroup of patients with previously treated FL. The ORRs were 80% (35% CR) and 55% (20% CR), respectively (P < .0001). The estimated 2-year OS rates were 95% and 86%, respectively, for lenalidomide + rituximab and rituximab monotherapy. Infections (63% vs. 49%), cutaneous reactions (32% vs. 12%), constipation (26% vs. 14%), thrombocytopenia (15% vs. 4%), and tumor flare reaction (11% vs. 1%) were more common with lenalidomide + rituximab, with neutropenia (50% vs. 13%) and leukopenia (7% vs. 2%) being the most common grade 3 or 4 toxicities.

Tafasitamab + Lenalidomide + Rituximab

Tafasitamab is a CD19-directed mAb approved for the treatment of relapsed or refractory DLBCL in combination with lenalidomide. The results of the phase III randomized inMIND study demonstrated that the addition of tafasitamab to lenalidomide + rituximab resulted in significantly improved PFS compared to lenalidomide + rituximab in patients with relapsed or refractory FL.121 In this study, 548 patients were randomly assigned to tafasitamab + lenalidomide + rituximab (n = 272) and lenalidomide + rituximab + placebo (n = 275). After a median follow-up of 14 months, the median PFS was not reached for patients assigned to tafasitamab + lenalidomide + rituximab vs. 16 months for lenalidomide + rituximab (P < .0001). The PFS benefit was consistent across all subgroups of patients including those with POD24, refractory disease to multiple prior therapies including anti CD20 mAb. Tafasitamab + lenalidomide + rituximab also resulted in higher ORR (84% vs. 72%; P = 0.0014), CR rate (49% vs. 40%; P = .029), improved DOR (21 months vs.14 months), and longer TTNT (not reached vs. 29 months). The incidences of TEAEs, including rates of grade 3–4 neutropenia and infection, were similar between treatment arms.

Based on the results of this trial, the Panel agreed that tafasitamab + lenalidomide + rituximab is an appropriate option for relapsed or refractory FL in patients who are considered candidates for lenalidomide + rituximab, and the Panel consensus supported the inclusion of this combination as a preferred treatment option (in addition to lenalidomide + rituximab). Loss of CD19/CD20 expressions has

been suggested as a possible mechanism of resistance to CD19- and CD20-directed mAb therapy and may also have an impact on response to CAR T-cell therapy.122,123 The Panel acknowledged that the potential risk of loss of CD19 expression in patients with relapsed or refractory disease should be considered and emphasized that further follow-up is needed to confirm the incidences of relapse and loss of CD19 expression following treatment with tafasitamab + lenalidomide + rituximab. At the present time, it is unclear whether treatment with CD19-directed mAb therapy would have a negative impact on the efficacy of subsequent CD19-directed CAR T-cell therapy. Rebiopsy to confirm CD19 positivity is recommended prior to the initiation of CD19-directed CAR T-cell therapy.

Second-Line Therapy: Other Recommended Regimens

Lenalidomide ± Obinutuzumab

In a phase II trial of patients with relapsed/refractory indolent NHL (n = 43), lenalidomide monotherapy induced an ORR of 23% (7% CR).124 The ORR was 27% among the subgroup of 22 patients with FL. The median DOR was >16 months and has not been reached. Median PFS for all patients was 4 months. Lenalidomide monotherapy is recommended for patients who are not candidates for CD20-directed mAb therapy. The efficacy of lenalidomide + obinutuzumab in patients with relapsed/refractory FL was established in the phase II GALEN study (n = 89), including those with early relapse.125 The ORR was 87% (38% CR) among the 86 patients evaluable for efficacy. At the median follow-up of 3 years, the 2-year PFS and OS rates were 65% and 87%, respectively. Asthenia (61%), neutropenia (43%; grade ≥3, 5%), bronchitis (41%), diarrhea (40%), and muscle spasms (39%) were the most common TEAEs. Lenalidomide monotherapy is an option for patients who are not candidates for anti-CD20 mAb therapy.

Rituximab or Obinutuzumab

Monotherapy with rituximab and obinutuzumab also has demonstrated activity in patients with relapsed or refractory disease and are included as options for second-line therapy (other recommended regimens).126-128 In a multiinstitutional study of 166 patients with relapsed/refractory FL, rituximab monotherapy resulted in a response rate of 48%.126 The median follow-up of 12 months and the estimated median time to progression was 13 months in patients with responding disease. Grade ≥3 infusion-related reactions were reported in 12% of patients. The phase II randomized GAUSS study evaluated the efficacy of obinutuzumab and rituximab in patients with relapsed indolent lymphomas with previous response to a rituximab-containing regimen (n = 175; FL, n = 149).128 ORR was higher with obinutuzumab compared to rituximab in patients with FL (45% vs. 33%; P = .08). However, this did not translate into improvement in PFS. At a median follow-up period of 32 months, the 2-year PFS rates were 46% (median PFS was 18 months) and 50% (median PFS was 25 months) for obinutuzumab and rituximab, respectively. Obinutuzumab was also associated with a higher rate of infusion-related reactions (74% vs. 51%) than rituximab.

Second-Line Consolidation or Extended Dosing

Two large, randomized trials have demonstrated a PFS advantage with rituximab maintenance over observation following second-line therapy.129,130 In a prospective phase III randomized study by the German Low Grade Lymphoma Study Group (GLSG), rituximab maintenance after second-line treatment with RFCM significantly prolonged DOR in the subgroup of patients with recurring or refractory FL (n = 81); median PFS with rituximab maintenance was not reached compared with 26 months in the observation arm (P = .035).129 In a phase III randomized Intergroup trial (EORTC 20981) in patients with relapsed or resistant FL (n = 334) responding to CHOP or RCHOP induction therapy, rituximab maintenance significantly improved median PFS (4 years vs. 1 year; P < .001) compared with observation alone.130 This PFS benefit was observed regardless of the induction therapy employed (CHOP or RCHOP). With a median follow-up of 6 years, the 5-year OS rate was not significantly different between study arms (74% vs. 64%, respectively).130 In the GADOLIN study (discussed above), obinutuzumab maintenance following second-line therapy with bendamustine + obinutuzumab improved PFS in patients with rituximab-refractory FL.104,105 In a randomized study that evaluated the benefit of rituximab maintenance versus rituximab retreatment at progression in patients with indolent lymphomas previously treated with chemotherapy (n = 114), rituximab maintenance significantly improved PFS compared with rituximab retreatment (31 vs. 7 months; P = .007).131 However, the duration of benefit was similar in both treatment groups (31 vs. 27 months). Therefore, either approach (maintenance or rituximab retreatment at progression) could be beneficial for this patient population.

Patients achieving CR or PR to second-line or subsequent therapy can either be observed or treated with optional consolidation or extended therapy.

- Rituximab maintenance (one dose every 12 weeks up to 2 years) is included with a category 1 recommendation.129,130,132 However, the Panel recognizes that the efficacy of rituximab maintenance in the second-line setting would likely be impacted by a patient's response to first-line maintenance with rituximab. The clinical benefit of rituximab maintenance in the second-line setting

is likely very minimal in patients with POD during or within 6 months of first-line maintenance with rituximab.
- Obinutuzumab maintenance (1 g every 8 weeks for a total of 12 doses) is preferred for patients with rituximab refractory disease, which includes POD on or within 6 months of prior rituximab therapy.104,105
- HDT/ASCR as consolidation therapy has been shown to prolong OS and PFS in patients with relapsed or refractory disease and is an appropriate consolidation therapy for patients with second or third remission.119,133-137 Clinical follow-up with a complete physical exam and laboratory assessment (every 3 to 6 months for the first 5 years, and then annually [or as clinically indicated]) is recommended. Surveillance imaging with CT scans can be performed no more than every 6 months up to the first 2 years following completion of treatment, and then no more than annually (or as clinically indicated) thereafter.

Third-Line Therapy: Preferred Regimens

CAR T-Cell Therapy

Axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel are the CD19-directed CAR T-cell therapies that are FDA-approved for the treatment of relapsed/refractory FL following ≥2 lines of systemic therapy based on the results of the ZUMA-5, ELARA, and TRANSCEND FL trials (described below). ZUMA-5 was a phase II trial that evaluated the efficacy of axicabtagene ciloleucel in patients with relapsed/refractory indolent lymphoma (FL, n = 127; MZL, n = 31) after ≥2 prior lines of systemic therapy. Axicabtagene ciloleucel resulted in an ORR of 92% (74% CR) among the 104 patients with indolent lymphoma evaluable for efficacy (FL, n = 84; MZL, n = 20).138 The ORR was 94% (80% CR) for patients with FL (median age was 61 years; 38% of patients had ECOG PS 1; 86% of patients had stage III/IV disease). Cytopenias and infections were the most common grade ≥3 TEAEs reported in 70% and 18% of patients, respectively.138 Grade ≥3 CRS and neurologic events were reported in 7% and 19% of patients, respectively. Notably, deaths due to TEAEs occurred in 3% patients, one of which was due to treatment-related multisystem organ failure. After median follow-up of 42 months for patients with FL, the ORR was 94% (similar to that reported in the primary analysis) and the median PFS was 40 months.139 In an updated analysis, with a median follow-up of 5 years, the median PFS was 62 months and the estimated 60-month PFS rate was 50% for patients with FL, consistent regardless of the presence of high-risk features including POD24.140 The 60-month OS rate was 69% for patients with FL. The phase II ELARA trial evaluated tisagenlecleucel in patients with relapsed/refractory FL after ≥2 lines of systemic therapy including a CD20-directed mAb and an alkylating agent or disease relapse after HDT/ASCR. At a median follow-up of 29 months, among the 94 evaluable patients, the ORR was 86% (68% CR) and the median PFS was not reached.141 The estimated 24-month PFS and OS rates were 57% and 88%, respectively. Elevated tumor burden at baseline, POD24, and >4 nodal areas at inclusion were associated with inferior long-term outcomes. After a median follow-up of 17 months, grade ≥3 CRS, neurological events, and immune effector cell-associated neurotoxicity syndrome (ICANS) were reported in 49%, 37%, and 4% of patients, respectively (with no safety signals reported with longer follow-up).

Lisocabtagene maraleucel was evaluated in the phase II TRANSCEND FL trial in patients with relapsed or refractory FL (n = 101).142 After a median follow-up of 19 months, lisocabtagene maraleucel resulted in an ORR of 97% (94% CR) in patients with relapsed or refractory FL after ≥2 prior lines of therapy. The median DOR and median PFS were not reached after a median follow-up of 17 months and 18 months, respectively. At 12 months, response was maintained in 82% of patients and the 12-month PFS rate was 81%. The median OS was not reached, and the 12-month OS rate was 96%. Neutropenia (grade ≥3; 65%), prolonged cytopenia (grade ≥3; 22%), infection (grade ≥3; 5%), CRS (grade 3; 58%), and neurological events (grade 3; 15%) were the most common TEAEs. The 2-year follow-up data also confirmed the safety and efficacy of lisocabtagene maraleucel for patients with relapsed or refractory FL after ≥2 prior lines of therapy.143

Axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel are included as options for third-line and subsequent therapy for relapsed/refractory FL in fir patients.

Bispecific Antibodies

Mosunetuzumab

Mosunetuzumab (CD3 X CD20 bispecific antibody) is FDA-approved for relapsed/refractory FL.144,145 In a single-arm, multicenter, phase II study (n = 90), mosunetuzumab (intravenous; fixed-duration treatment) resulted in high response rates and durable remissions in patients with relapsed or refractory FL after ≥2 lines of therapy including an CD20-directed mAb and an alkylating agent.144 The ORR assessed by the institutional review committee (IRC) was 80% (60% CR). Patients achieving a CR after 8 cycles completed treatment with no additional cycles, whereas those with a PR or stable disease received a total of 17 cycles. Mosunetuzumab resulted in favorable response rates across all subgroups including those with high-risk disease and EZH2 mutated FL. At the median follow-up of 18 months, IRC-assessed median PFS was 18 months. The estimated EFS and OS rates were 61% and 90%, respectively. In addition, the efficacy of

mosunetuzumab was also better compared to the patient's last prior therapy. The updated follow-up data also confirmed durability of responses and safety profile of mosunetuzumab.145 After a median follow-up of 37 months, the investigator-assessed ORR was 78% (60% CR) and the median PFS was 24 months for mosunetuzumab. The estimated 36-month OS rate was 82%. Peripheral blood B-cell depletion following treatment with mosunetuzumab occurred in all patients and B-cell recovery was observed after a median of 18 months following end of treatment. Cytokine release syndrome (CRS; 42%), fatigue (37%), headache (30%), and pyrexia (28%) were the most common grade 1–2 events. Grade 3–4 neutropenia was reported in 13% of patients.144 CRS (grade 1–2) was predominantly confined to cycle 1 of step-up dosing. Among the 42% of patients who developed CRS, grade 3 was reported in 2% of patients and it resolved in all patients. Corticosteroids or tocilizumab were used for the management of CRS in 15% and 8% of patients, respectively, and combination of both was used in 10% of patients. ICANS were very rare, and all were low grade (grade 1–2 confusion rate was reported in 3% of patients with no incidences of aphasia, seizures, encephalopathy, or cerebral edema). The safety profile enables the outpatient administration of mosunetuzumab, and the safety profile after long-term follow-up was similar to that reported in the primary analysis. Mosunetuzumab is included as an option for relapsed/refractory FL after ≥2 prior lines of therapy. Loss of CD20 expression has been suggested as a possible mechanism of resistance to CD20-directed mAb therapy (including bispecific antibody therapy).146 The efficacy of CD3 x CD20 bispecific antibody therapy is unclear in the setting of CD20-negative lymphomas. Rebiopsy to confirm CD20 positivity is recommended prior to the initiation of CD3 x CD20 bispecific antibody therapy.

Epcoritamab

In the EPCORE NHL-1 trial, epcoritamab (subcutaneous; CD3 x CD20 bispecific antibody) resulted in an ORR of 82% (63% CR) in patients with relapsed or refractory FL after ≥2 prior lines of therapy (n = 128).147 The ORRs were consistent across prespecified high-risk subgroups including double refractory FL (76%; 56% CR), refractory disease to last prior therapy (74%; 51% CR), and POD24 (79%; 64% CR). At 18 months after initiation of therapy, the estimated PFS rate was 49% for all patients and 74% for those with a CR. CRS (grades 1–2, 65%; grade 3, 2%), injection-site reaction (57%), fatigue (grades 1–2, 28%; grade 3, 2%), neutropenia (grades 1–2, 3%; grade 3, 13%; grade 4, 13%), diarrhea (grades 1–2, 25%; grade 3, 2%), pyrexia (grades 1–2, 23%; grade 3, 2%), and headache (20%) were the most common TEAEs. ICANS was reported in 6% of patients and resolved without leading to discontinuation of treatment.

Epcoritamab is included as an option for relapsed/refractory FL after ≥2 prior lines of therapy. As discussed earlier with the use mosunetuzumab, the activity of CD3 x CD20 bispecific antibody therapy is unclear in the setting of CD20-negative lymphomas. Rebiopsy to confirm CD20 positivity is recommended prior to the initiation of CD3 x CD20 bispecific antibody therapy.

Third-Line Therapy: Other Recommended Regimens

Tazemetostat

Tazemetostat (EZH2 inhibitor) is FDA-approved for relapsed/refractory FL after ≥2 prior systemic therapies and it is an appropriate third-line treatment option for patients who are not eligible for CAR T-cell therapy.148 In a phase II trial of 99 patients with relapsed/refractory FL (45 patients with EZH2-mutated FL; 54 patients with EZH2 wild-type) after ≥2 systemic therapies including PI3K inhibitor or an immunomodulatory drug, tazemetostat resulted in an ORR of 69% (13% CR; 56% PR; 29% stable disease) in the EZH2-mutated cohort (median follow-up was 22 months) and 35% (4% CR; 31% PR; 33% stable disease) in the EZH2 wild-type cohort.148 With a median follow-up of 36 months, the median PFS was 14 months and 11 months for EZH2-mutated and EZH2 wild-type cohorts, respectively. The median OS was not reached in either cohort. The ORR was higher for patients with EZH2-mutated FL than those with EZH2 wild-type FL in all subgroups: POD within 24 months of diagnosis (POD 24; 63% vs. 25%); double-refractory disease (no objective response to rituximab-based regimen and relapse within 6 months or refractory to alkylating agent-based chemotherapy; 78% vs. 27%); and refractory to rituximab (no objective response to rituximab-based regimens or progressive disease within 6 months of completion of rituximab-based therapy; 59% vs. 31%). Notably, this study was not designed to compare the outcomes based on the EZH2 mutation status. Tazemetostat had a favorable safety profile, with thrombocytopenia (3%), neutropenia (3%), and anemia (2%) being the most common grade ≥3 TEAEs and serious TEAEs reported in only 4% of patients. Tazemetostat is included as an option for third-line and subsequent therapy for patients with relapsed/refractory FL irrespective of EZH2 mutation status. Testing for EZH2 mutation status for patients with relapsed/refractory FL after 2 prior therapies is feasible using paraffin-embedded tissue and should be performed by an approved sequencing assay.

Zanubrutinib + Obinutuzumab

The combination of zanubrutinib and obinutuzumab is FDA-approved for relapsed/refractory FL after ≥2 prior systemic therapies based on the results of the phase II randomized ROSEWOOD trial (217 patients; zanubrutinib + obinutuzumab, n = 145; obinutuzumab, n = 72).149 ORR and CR rates were significantly higher with zanubrutinib + Obinutuzumab (69%; 39% CR) compared to obinutuzumab (46%; 19% CR). After a median follow-up of 20 months, the median PFS was 28 months for zanubrutinib + obinutuzumab and

10 months for obinutuzumab. Grade ≥3 thrombocytopenia (15% vs. 7%), pneumonia (10% vs. 4%), diarrhea (3% vs. 1%), and dyspnea (2% vs. 0%) were more frequent with zanubrutinib + obinutuzumab whereas grade ≥3 neutropenia (24% vs. 23%) and anemia (5% vs. 6%) were similar between the treatment arms. The incidence of grade ≥3 infusion-related reactions and pyrexia were substantially lower with zanubrutinib + obinutuzumab. This combination was also associated with lower incidences of atrial fibrillation and hypertension (both reported in 3% of patients) and this safety profile was consistent with that observed in studies that have evaluated Zanubrutinib in other B-cell malignancies. Zanubrutinib + obinutuzumab is included as an option for third-line and subsequent therapy for patients with relapsed/refractory FL.

Loncastuximab Tesirine + Rituximab

In a phase II single-arm trial (39 patients with relapsed or refractory FL including those presenting with POD24 after first-line therapy and transformed FL relapsing with indolent component), the combination of loncastuximab tesirine + rituximab resulted in a CR rate of 67%.150 Patients met one or more GELF criteria (92%) or had POD24 after the first line of therapy (51%). After a median follow-up of 18 months, the median DOR was 16 months and the 12-month PFS rate was 95%. Lymphopenia (21%) and neutropenia (13%) were the most common grade ≥3 treatment-related toxicities. Given the availability of FDA-approved third-line therapy options for relapsed or refractory FL that have been evaluated in prospective randomized trials (eg, CAR T-cell therapy, bispecific antibody therapy, zanubrutinib + obinutuzumab), a few Panel members felt that loncastuximab + tesirine should not be included as a treatment option at this time, citing the single-arm trial design with the small sample size and the need for these findings to be confirmed in a prospective randomized trial.

While CAR T-cell therapy (requiring single infusion of CAR T cells) and mosunetuzumab are fixed-duration treatment options, epcoritamab and zanubrutinib are given continuously until disease progression. In terms of safety profile, CRS, ICANS, and prolonged cytopenias (which may be associated with the use of bridging chemotherapy required for disease control in the majority of patients) are common TEAEs of CAR T-cell therapy. Bispecific antibodies are “off-the-shelf” immunotherapies with a better overall safety profile and very few incidences of ICANS. They are also more readily available than CAR T cells, thus obviating the need for bridging chemoimmunotherapy. However, step-up-dosing schedule (over a period of time before reaching the effective target dose) is required for all bispecific antibodies to mitigate the risk of CRS, which can be challenging in patients with rapidly progressing disease.151 In addition, loss of CD20 expressions has been suggested as a possible mechanism of resistance to CD20-directed mAb therapy (including bispecific antibody therapy) and the activity of CD3 x CD20 bispecific antibody therapy in the setting of CD20-negative lymphomas is unclear.146

Based on the efficacy and the favorable safety profile demonstrated in the aforementioned phase II study, some Panel members felt that loncastuximab tesirine + rituximab is an appropriate third-line therapy option especially for patients who are either considered not candidates for CAR T-cell therapy or do not have access to CAR T-cell therapy or bispecific antibodies, acknowledging that long-term follow-up is needed to confirm that there is no loss of CD19 expression following treatment with this combination. The findings from the LOTIS-2 trial (that evaluated loncastuximab tesirine in patients with relapsed or refractory DLBCL) showed that CD19 antigen loss after loncastuximab tesirine is not common suggesting that the use of loncastuximab tesirine does not preclude responses to subsequent CD19-directed CAR T-cell therapy.152 However, these preliminary results need to be confirmed in a larger cohort of patients.

The Panel consensus supported the inclusion of loncastuximab tesirine + rituximab as an option for third-line therapy (other recommended regimens) with a category 2B recommendation. It is unclear if CD19-directed mAb therapy would have a negative impact on the efficacy of subsequent CD19-directed CAR T-cell therapy. Rebiopsy is recommended to confirm CD19 positivity prior to initiation of CD19-directed CAR T-cell therapy.

Suggested Treatment Regimens for Patients who are Older or Infirm

As discussed earlier, rituximab monotherapy has demonstrated single-agent activity in patients with previously untreated low-burden FL and advanced-stage FL as well as in patients with relapsed/refractory disease.79,80,126 In a retrospective study of 75 patients with newly diagnosed FL, chlorambucil + rituximab resulted in an ORR of 97% (75% CR). The 5-year EFS and OS rates were 71% and 98%, respectively.153 Single-agent cyclophosphamide was associated with similar OS and CR rates compared with cyclophosphamide-based combination chemotherapy.154 Rituximab monotherapy is the preferred first-line therapy for older or infirm patients who are not able to tolerate any of the chemoimmunotherapy regimens recommended for first-line therapy. Alkylating agent-based chemotherapy (cyclophosphamide or chlorambucil) with or without rituximab is included as an alternative option for first-line therapy. Rituximab monotherapy and tazemetostat are the preferred treatment options for second-line and subsequent therapy. Cyclophosphamide with or without rituximab is included as an alternate option.

Referenzen aus Leitlinie

100. Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. J Clin Oncol 2015;33:2516–2522. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26124482.
101. Maurer MJ, Bachy E, Ghesquieres H, et al. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. Am J Hematol 2016;91:1096–1101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27465588.
102. Casulo C, Dixon JG, Le-Rademacher J, et al. Validation of POD24 as a robust early clinical end point of poor survival in FL from 5225 patients on 13 clinical trials. Blood 2022;139:1684–1693. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34614146.
103. Radford J, Davies A, Cartron G, et al. Obinutuzumab (GA101) plus CHOP or FC in relapsed/refractory follicular lymphoma: results of the GAUDI study (BO21000). Blood 2013;122:1137–1143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23843495.
104. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27345636.
105. Cheson BD, Chua N, Mayer J, et al. Overall survival benefit in patients with rituximab-refractory indolent non-Hodgkin lymphoma who received obinutuzumab plus bendamustine induction and Obinutuzumab maintenance in the GADOLIN study. J Clin Oncol 2018;36:2259–2266. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29584548.
106. Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol 2015;33:3635–3640. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26304886.
107. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol 2019;37:1188–1199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30897038.
108. Casulo C, Friedberg JW, Ahn KW, et al. Autologous transplantation in follicular lymphoma with early therapy failure: A National LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. Biol Blood Marrow Transplant 2018;24:1163–1171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29242111.
109. Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous Stem Cell Transplantation for Patients with Early Progression of Follicular Lymphoma: A Follow-Up Study of 2 Randomized Trials from the German Low Grade Lymphoma Study Group. Biol Blood Marrow Transplant 2018;24:1172–1179. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29605716.
110. Smith SM, Godfrey J, Ahn KW, et al. Autologous transplantation versus allogeneic transplantation in patients with follicular lymphoma experiencing early treatment failure. Cancer 2018;124:2541–2551. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29645093.
111. Dreyling M, Santoro A, Mollica L, et al. Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study. Am J Hematol 2020;95:362–371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31868245.
112. 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. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30742566.
113. Gopal AK, Kahl BS, de Vos S, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008–1018. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24450858.
114. Gopal AK, Kahl BS, Flowers CR, et al. Idelalisib is effective in patients with high-risk follicular lymphoma and early relapse after initial chemoimmunotherapy. Blood 2017;129:3037–3039. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28325864.
115. Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib, a dual PI3Kdelta/CK1epsilon inhibitor in patients with relapsed or refractory indolent lymphoma. J Clin Oncol 2021;39:1609–1618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33683917.
116. Richardson NC, Kasamon Y, Pazdur R, Gormley N. The saga of PI3K inhibitors in haematological malignancies: survival is the ultimate safety endpoint. Lancet Oncol 2022;23:563–566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35429996.
117. Peniket AJ, Ruiz de Elvira MC, Taghipour G, et al. An EBMT registry matched study of allogeneic stem cell transplants for lymphoma: allogeneic transplantation is associated with a lower relapse rate but a higher procedure-related mortality rate than autologous transplantation. Bone Marrow Transplant 2003;31:667–678. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12692607.

118. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood 2003;102:3521–3529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12893748.
119. Evens AM, Vanderplas A, LaCasce AS, et al. Stem cell transplantation for follicular lymphoma relapsed/refractory after prior rituximab: a comprehensive analysis from the NCCN lymphoma outcomes project. Cancer 2013;119:3662–3671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23921646.
120. Rummel M, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol 2016;17:57–66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26655425.
121. Sehn LH, Luminari S, Scholz CW, et al. Tafasitamab plus lenalidomide and rituximab for relapsed or refractory follicular lymphoma: Results from a phase 3 study (inMIND) [abstract]. Blood 2024;144:Abstract LBA–1. Available at: https://doi.org/10.1182/blood-2024-212970.
122. Duell J, Leipold AM, Appenzeller S, et al. Sequential antigen loss and branching evolution in lymphoma after CD19- and CD20-targeted T-cell-redirecting therapy. Blood 2024;143:685–696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37976456.
123. Hueso T, Alchidiac J, Ghigna M-R, et al. Post-therapeutic tumor losses of B-cell receptor components CD20/CD19, a new challenge in the management of patients with relapsed/refractory diffuse large B-cell lymphoma [abstract]. Blood 2024;144:Abstract 474. Available at: https://doi.org/10.1182/blood-2024-203664.
124. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19805688.
125. Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol 2019;6:e429–e437. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31296423.
126. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: Half of patients respond to a four-dose treatment program. J Clin Oncol 2023;41:154–162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36603541.
127. Salles GA, Morschhauser F, Solal-Celigny P, et al. Obinutuzumab (GA101) in patients with relapsed/refractory indolent non-Hodgkin lymphoma: results from the phase II GAUGUIN study. J Clin Oncol 2013;31:2920–2926. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23835715.
128. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-hodgkin lymphoma: Final analysis of the GAUSS study. J Clin Oncol 2015;33:3467–3474. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26282650.
129. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003–4008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16946304.
130. van Oers MHJ, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28:2853–2858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20439641.
131. Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma—a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088–1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15657401.
132. Rule S, Barreto WG, Briones J, et al. Efficacy and safety assessment of prolonged maintenance with subcutaneous rituximab in patients with relapsed or refractory indolent non-Hodgkin lymphoma: results of the phase III MabCute study. Haematologica 2022;107:500–509. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34134469.
133. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol 2003;21:3918–3927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14517188.
134. Rohatiner AZS, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. J Clin Oncol 2007;25:2554–2559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17515573.

135. Sebban C, Brice P, Delarue R, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with follicular lymphoma: a GELA study. J Clin Oncol 2008;26:3614–3620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18559872.
136. Le Gouill S, De Guibert S, Planche L, et al. Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica 2011;96:1128–1135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21486862.
137. Metzner B, Pott C, Muller TH, et al. Long-term outcome in patients with follicular lymphoma following high-dose therapy and autologous stem cell transplantation. Eur J Haematol 2021;107:543–552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34288114.
138. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol 2022;23:91–103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34895487.
139. Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). Blood 2024;143:496–506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37879047.
140. Neelapu SS, Chavez JC, Sehgal AR, et al. 5-Year Follow-up Analysis from ZUMA-5: A Phase 2 Trial of Axicabtagene Ciloleucel (Axi-Cel) in Patients with Relapsed/Refractory Indolent Non-Hodgkin Lymphoma [abstract]. Blood 2024;144:Abstract 864. Available at: https://doi.org/10.1182/blood-2024-194627.
141. Dreyling M, Fowler NH, Dickinson M, et al. Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update. Blood 2024;143:1713–1725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38194692.
142. Morschhauser F, Dahiya S, Palomba ML, et al. Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study. Nat Med 2024;30:2199–2207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38830991.
143. Nastoupil L, Dahiya S, Palomba ML, et al. Lisocabtagene maraleucel (liso-cel) in patients (pts) with relapsed or refractory (R/R) follicular lymphoma (FL): Transcend FL 2-year follow-up [abstract]. Blood 2024;144:Abstract 4387. Available at: https://doi.org/10.1182/blood-2024-198509.
144. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. Lancet Oncol 2022;23:1055–1065. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35803286.
145. Sehn LH, Bartlett NL, Matasar MJ, et al. Long-term 3-year follow-up of mosunetuzumab in relapsed or refractory follicular lymphoma after >/=2 prior therapies. Blood 2025;145:708–719. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39447094.
146. Schuster SJ, Huw LY, Bolen CR, et al. Loss of CD20 expression as a mechanism of resistance to mosunetuzumab in relapsed/refractory B-cell lymphomas. Blood 2024;143:822–832. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38048694.
147. Linton KM, Vitolo U, Jurczak W, et al. Epcoritamab monotherapy in patients with relapsed or refractory follicular lymphoma (EPCORE NHL-1): a phase 2 cohort of a single-arm, multicentre study. Lancet Haematol 2024;11:e593–e605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38889737.
148. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol 2020;21:1433–1442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33035457.
149. Zinzani PL, Mayer J, Flowers CR, et al. ROSEWOOD: A phase II randomized study of zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma. J Clin Oncol 2023;41:5107–5117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37506346.
150. Alderuccio JP, Alencar AJ, Schatz JH, et al. Loncastuximab tesirine with rituximab in patients with relapsed or refractory follicular lymphoma: a single-centre, single-arm, phase 2 trial. Lancet Haematol 2025;12:e23–e34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39662486.
151. Crombie JL, Graff T, Falchi L, et al. Consensus recommendations on the management of toxicity associated with CD3xCD20 bispecific antibody therapy. Blood 2024;143:1565–1575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38252906.
152. Thapa B, Caimi PF, Ardeshna KM, et al. CD19 antibody-drug conjugate therapy in DLBCL does not preclude subsequent responses to CD19-directed CAR T-cell therapy. Blood Adv 2020;4:3850–3852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32797191.
153. Martinelli G, Montoro J, Vanazzi A, et al. Chlorambucil-rituximab as first-line therapy in patients affected by follicular non-Hodgkin's lymphoma: a retrospective single-centre study. Hematol Oncol 2015;33:129–135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25047267.
154. Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. J Clin Oncol 2003;21:5–15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12506163.

Alberta Health Service (AHS), 2025 [1].

Lymphoma – Clinical Practice Guideline V20

Methodik

Die Leitlinie erfüllt die methodischen Anforderungen nicht ausreichend. Aufgrund limitierter Evidenz hinsichtlich der Behandlung des rezidivierenden oder refraktären FL und aufgrund ihrer Aktualität wird die Leitlinie ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: **Trifft teilweise zu** – Die Leitlinienarbeitsgruppe war multidisziplinär einschließlich Methodikexpertise, jedoch ist eine Patientenbeteiligung unklar
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft teilweise zu** – Die Finanzierung ist unabhängig, aber Interessenkonflikte des Expertengremiums werden nicht angegeben
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft teilweise zu** – Eine systematische Recherche wurde durchgeführt, aber Angaben zu den Auswahlkriterien und der kritischen Bewertung der Literatur fehlen (siehe Recherche/Suchzeitraum).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft teilweise zu** – Die Empfehlungen sind eindeutig, aber es wird keine Evidenz-/Empfehlungsgraduierung angegeben.
- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu**

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.

LoE

Table 3. 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 trials 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

Table 4. Strength of Recommendations

Grade	Description of Recommendation Strength
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.

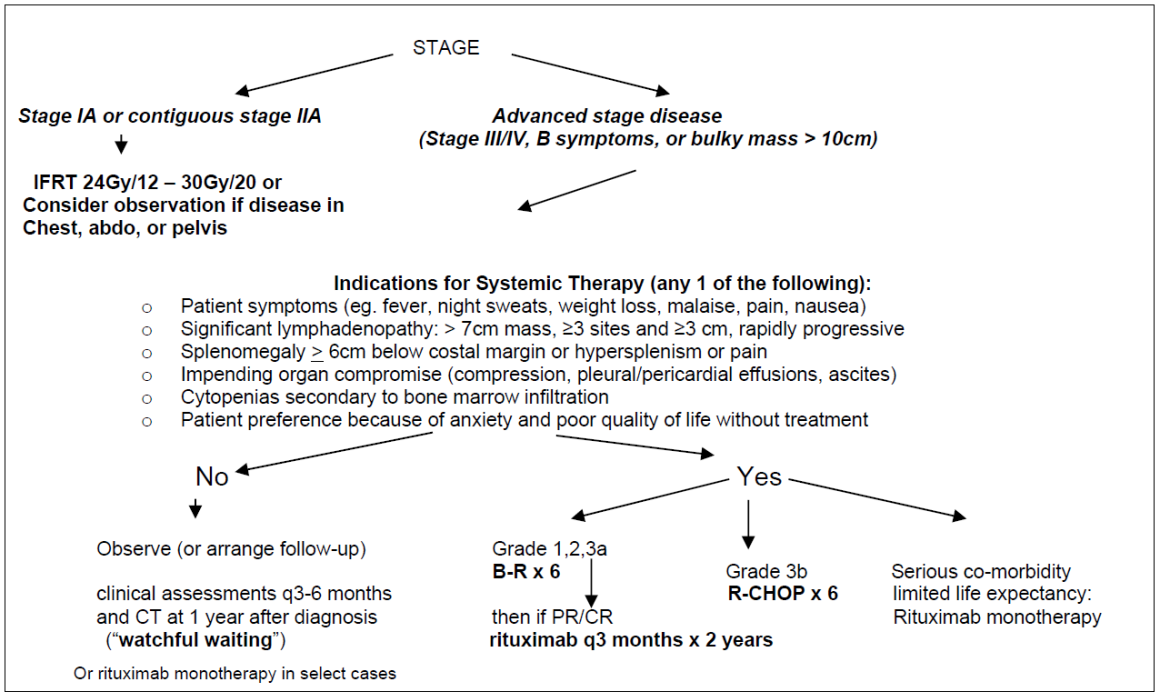
Sonstige methodische Hinweise

- Klassifikation gemäß WHO-Klassifikation 2024, 5. Edition

Empfehlungen

Follicular Lymphoma

Figure 2. Treatment algorithm for follicular lymphoma.



Throughout the following suggested treatment approach, three over-riding principles should be considered:

1. These are guidelines only. This disease often carries a long, incurable, remitting/relapsing natural history and, therefore, several treatment approaches are reasonable.
2. The mere presence of disease does not alone imply the need for treatment.
3. If therapy is required for predominantly localized disease, IFRT should be considered in lieu of systemic pharmacological treatment as long as the radiotherapy can be done with minimal early or delayed side-effects (e.g., xerostomia, severe nausea/vomiting) and without eliminating future treatment options (e.g., should not radiate ≥25% bone marrow). Figure 2 outlines the treatment algorithm for follicular lymphoma.

Initial therapy of stage IA and contiguous stage IIA:

IFRT 24Gy/12-30Gy/20 fractions is recommended for newly diagnosed patients with peripheral stage IA or contiguous non-bulky stage IIA follicular lymphoma, even if the patient is asymptomatic.

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

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

For patients who do not have any of the above indications for therapy:

The recommended approach is to observe with (or arrange) follow-up clinical assessments every 3-6 months ("watchful waiting"), and a CT CAP 1 year after diagnosis. For patients not meeting treatment criteria 1 year after diagnosis, another CT 1-2 years later could be considered. Patients who have progressive disease on follow-up should generally be treated, even if they do not fulfill any of the other indications for therapy to prevent the risk of clinical deterioration in the setting of known progressing lymphoma. A retrospective study of 238 Alberta follicular lymphoma patients managed with watchful waiting found that 24% developed transformed disease or significant organ dysfunction (at a median of 30months) prior to initiating initial therapy, and these patients had inferior survival rates compared to other patients requiring therapy who were initially managed with watchful waiting (10 yr OS 67.9% vs 85.7%, HR 3.000 (95%CI 1.696-7.126), p=0.0007). These watchful waiting patients did not undergo routine follow-up CT scans at 1 or 2 years to identify progression. It is possible that these adverse outcomes might have been avoided with closer monitoring by CT imaging and earlier initiation of chemoimmunotherapy 146.

Alternatively, a select population of advanced stage II-IV, asymptomatic patients could be considered for treatment with rituximab monotherapy (weekly x4) based on the long term follow up of the Ardeshna/Northend trial. This phase III trial randomized 379 patients with asymptomatic low tumour burden follicular lymphoma to (1) watch & wait (W&W) (2) rituximab induction (RI) or (3) RI followed by rituximab maintenance (RM). The median time to next treatment (TTNT) was 2.7 years (W&W), 9.9 years (RI) and not reached (RM). No significant differences in OS, histological transformation, or response to next line treatment were observed 147. This group may include elderly patients (age 70+ who will likely not require another treatment within their lifetime) or patients with profound anxiety regarding their diagnosis. This treatment needs to be weighed with the risk of immunosuppression during and at least 6 months post-therapy. Patients need to be made aware that there is no survival benefit by using this approach. Additionally, the AB drug benefit list includes rituximab monotherapy for FL only for those "who have contraindications to, or who cannot tolerate chemotherapy" so these conditions would need to be met in individuals selected for treatment with RI.

For grades 1,2,3a follicular lymphoma who have an indication for therapy:

The recommended therapy involves 6 cycles of B-R (bendamustine-rituximab) chemotherapy, followed in responding patients by 2 years of maintenance rituximab (every 3 months for total of eight doses).

Patients who have an indication for treatment but are unable to tolerate BR due to significant comorbidities or frailty can be considered for dose reduced bendamustine (ie. 70mg/m2 on D1 and D2 or 50% bendamustine, keeping D1 at 90mg/m2 and omitting D2). This may help to reduce infectious and cytopenia risks. Alternatively, rituximab monotherapy may be used, for 4 weekly doses, to debulk their disease and provide an element of disease control. Rare patients who have very limited life-expectancy from serious comorbid illness and who wish to avoid intravenous therapy could be treated with palliative oral fludarabine or chlorambucil or targeted radiotherapy.

The GALLIUM clinical trial investigated the value of obinutuzumab in combination with chemotherapy followed by maintenance therapy compared to standard therapy with rituximab chemo-immunotherapy plus maintenance in the first-line treatment of follicular lymphoma. The study demonstrated superiority of obinutuzumab over rituximab in terms of PFS (3-year PFS was 81.9% (95%CI: 77.9-85.2%) vs. 77.9% (95%CI: 73.8-81.4%), with acceptable increased toxicity. As no OS advantage has yet been demonstrated,

obinutuzumab is not funded in Canada for this indication and we continue to recommend rituximab 148.

Note: Grade 3b follicular lymphoma should be treated as DLBCL with R-CHOP. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell lymphoma, and therefore is not recommended.

Management of relapsed follicular lymphoma:

Note: treatment indications at relapse are the same as the indications for upfront treatment. Relapse and progression are expected for indolent lymphomas and again, only require treatment if meeting the criteria listed above.

Prior to moving to next line therapy for FL, if there is suspicion of transformation to aggressive lymphoma (ie. less than PR to initial therapy, systemic symptoms, or very early relapse), biopsy of the fastest growing (or most FDG-avid, if PET is performed) lesion should be done to rule out DLBCL.

Therapeutic recommendations for recurrent follicular lymphoma need to be individualized, and no one recommendation is suitable for all patients. Numerous factors need to be taken into consideration before recommending therapy for recurrent follicular lymphoma, including:

- Patient Factors: Age, co-morbidity, symptoms, short vs. long-term goals, preservation of future options, reimbursement/ability to pay for expensive treatments, acceptance of risks/toxicities of treatment option relative to potential benefit (RR, PFS, OS).
- Disease Factors: Stage, sites of involvement, grade, transformation, prior therapy, time from prior therapy (disease-free interval).

Autologous stem cell transplant:

For healthy patients, younger than 75 years old, HDCT/SCT maximizes the length of disease control, regardless of length of initial remission, and as such is a reasonable treatment option at first or second relapse for those who accept potential risks/toxicities.

This benefit of ASCT is most pronounced for patients who relapse within 2 years of initial chemotherapy (POD24) have more aggressive disease and higher rates of transformation to aggressive lymphoma. Their OS is < 5 years with standard therapy and several studies have shown improved PFS along with OS with ASCT for these patients.

A large retrospective study of consecutively treated relapsed follicular lymphoma patients in Alberta and BC reported 5 year overall survival rates following relapse of ~90% for those who received ASCT vs ~60% for those who did not receive ASCT. This marked difference in survival retained significance in multivariate as well as instrumental variable analyses149. Another long-term follow-up study from Alberta demonstrated that up to 50% of ASCT recipients may be functionally cured of FL 150.

Lenalidomide/rituximab:

For patients not suitable HDCT/SCT, lenalidomide and rituximab, based on the AUGMENT trial is approved for patients with relapsed/refractory disease. Progression-free survival was estimated at a median duration of 39.4 months (95% CI, 22.9 months to not reached) in this phase III trial 151.

CAR-T cellular therapy:
CAR-T is funded for patients with r/r FL grade 1-3A after ≥2 lines of therapy based on the ZUMA-5 and the ELARA trials 152,153. ORR and CR rates were upwards of 85% and 69% in both trials, respectively. Infection and cytopenias were the most common adverse effects. Patients need to be monitored for CRS and ICANS, though rates of same are generally lower than for DLBCL.

Repeat chemo-immunotherapy:
Some patients may be managed with repeating chemo-immunotherapy if they have achieved a long remission to first therapy. Rituximab maintenance should only be used once in the course of a patient's disease (first remission or first relapse).
A phase 3, open-label, two-arm parallel, randomized trial (GADOLIN), compared obinutuzumab and bendamustine followed by obinutuzumab maintenance to bendamustine alone in patients with rituximab-refractory, indolent non-Hodgkin lymphoma (failure to respond or progress during or within 6 months of a rituximab containing regimen). Both PFS (HR[95%CI]: 0.52[0.39,0.69]; p<0.0001) and OS (HR[95%CI: 0.58[0.39.0.86]; p=0.0061) were improved in the FL group treated with obinutuzumab. While there was no significant advantage reported for patients with other subtypes of iNHL, this was deemed to be based purely on the small numbers in other subgroups. Based on these results, it is recommended that obinutuzumab chemo-immunotherapy be considered in patients with rituximab-refractory iNHL. While the study used bendamustine as a chemotherapy backbone, few patients on the study had received bendamustine as their frontline therapy. Given current practice of BR for the frontline treatment of FL and the fact that there is no biological reason that the same clinical benefit of obinutuzumab would not be seen in combination with other chemotherapies, alternate NHL chemotherapy backbones can be considered for patients deemed inappropriate for bendamustine retreatment. Relatively frequent infections were noted so prophylactic antibiotics and antivirals should be considered, especially when obinutuzumab is combined with bendamustine.

Idelalisib:
Idelalisib, a PI3Kδ inhibitor has also shown efficacy in a Phase 2 study of double-refractory FL patients (patients with lack of response or progression within 6 months of both rituximab and an alkylator). Idelalisib can lead to durable remissions in a minority of patients and is currently funded. Infectious complications and immune toxicities are frequent and prophylactic antibiotics and anti-virals are required to reduce the risk of serious infections 154. Due to these risks and general poor tolerability, we recommend considering other therapeutic options first.

Palliative, symptomatic care (possibly including palliative IFRT 4Gy/2 fractions):
This is usually the best option for patients who were refractory to their two most recent treatment regimens, those with CNS involvement, or those with an ECOG score of 3-4.

Referenzen aus Leitlinien
100. Tsang RW, Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. *Hematol Oncol*. 2005;23(1):10-17. doi:10.1002/hon.743 [doi]
101. Tsang RW, Gospodarowicz MK. Low-grade non-hodgkin lymphomas. *Semin Radiat Oncol*. 2007;17(3):198-205. doi:S1053-4296(07)00017-3 [pii]

102. Mac Manus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. *J Clin Oncol*. 1996;14(4):1282-1290. doi:10.1200/JCO.1996.14.4.1282 [doi]
103. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. *J Clin Oncol*. 2004;22(8):1454-1459. doi:10.1200/JCO.2004.10.086 [doi]
104. Peterson BA, Petroni GR, Frizzera G, et al. Prolonged single-agent versus combination chemotherapy in indolent follicular lymphomas: a study of the cancer and leukemia group B. *J Clin Oncol*. 2003;21(1):5-15. doi:10.1200/jco.2003.05.128 [doi]
105. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. 1997;15(3):1110-1117. doi:10.1200/JCO.1997.15.3.1110 [doi]
106. Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin-containing regimen with or without interferon alfa-2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial. *J Clin Oncol*. 1998;16(7):2332-2338. doi:10.1200/JCO.1998.16.7.2332 [doi]
107. Coiffier B, Neidhardt-Berard EM, Tilly H, et al. Fludarabine alone compared to CHVP plus interferon in elderly patients with follicular lymphoma and adverse prognostic parameters: a GELA study. Groupe d'Etudes des Lymphomes de l'Adulte. *Ann Oncol*. 1999;10(10):1191-1197. doi:1008347425795 [doi]
108. Hagenbeek A, Eghbali H, Monfardini S. Fludarabine versus conventional CVP chemotherapy in newly diagnosed patients with stages III and IV low grade malignant non-Hodgkin's lymphoma. Preliminary results from a prospective randomized phase III clinical trial in 381 patients. *Blood*. 1998;ASH Annual Meeting Abstracts); 92:Abstract 1294.
109. Weisdorf DJ, Andersen JW, Glick JH, Oken MM. Survival after relapse of low-grade non-Hodgkin's lymphoma: implications for marrow transplantation. *J Clin Oncol*. 1992;10(6):942-947. doi:10.1200/JCO.1992.10.6.942 [doi]
110. Rohatiner AZ, Johnson PW, Price CG, et al. Myeloablative therapy with autologous bone marrow transplantation as consolidation therapy for recurrent follicular lymphoma. *J Clin Oncol*. 1994;12(6):1177-1184. doi:10.1200/JCO.1994.12.6.1177 [doi]
111. Bierman PJ, Vose JM, Anderson JR, Bishop MR, Kessinger A, Armitage JO. High-dose therapy with autologous hematopoietic rescue for follicular low-grade non-Hodgkin's lymphoma. *J Clin Oncol*. 1997;15(2):445-450. doi:10.1200/JCO.1997.15.2.445 [doi]
112. van Besien K, Sobocinski KA, Rowlings PA, et al. Allogeneic bone marrow transplantation for low-grade lymphoma. *Blood*. 1998;92(5):1832-1836.
113. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol*. 1998;16(8):2825-2833. doi:10.1200/JCO.1998.16.8.2825 [doi]
114. Maloney DG, Grillo-Lopez AJ, White CA, et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. *Blood*. 1997;90(6):2188-2195.
115. Davies AJ, Rohatiner AZ, Howell S, et al. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2004;22(8):1469-1479. doi:10.1200/JCO.2004.06.055 [doi]
116. Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2002;20(10):2453-2463. doi:10.1200/JCO.2002.11.076 [doi]
117. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. 2003;21(21):3918-3927. doi:10.1200/JCO.2003.10.023 [doi]
118. Brice P, Simon D, Bouabdallah R, et al. High-dose therapy with autologous stem-cell transplantation (ASCT) after first progression prolonged survival of follicular lymphoma patients included in the prospective GELF 86 protocol. *Ann Oncol*. 2000;11(12):1585-1590. doi:1008399623564 [doi]
119. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105(4):1417-1423. doi:2004-08-3175 [pii]
120. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26(28):4579-4586. doi:10.1200/JCO.2007.13.5376 [doi]
121. Hochster HS, Weller E, Gascoyne RD, Ryan TS, Habermann TM, Gordan LI. Maintenance Rituximab after CVP Results in Superior Clinical Outcome in Advanced Follicular Lymphoma (FL): Results of the E1496 Phase III Trial from the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B. ASH Annual Meeting Abstracts. *Blood*. 2005;106(11):349.
122. van Oers MH, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during

induction: results of a prospective randomized phase 3 intergroup trial. *Blood*. 2006;108(10):3295-3301. doi:blood-2006-05-021113 [pii]
123. van Oers MH, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol*. 2010;28(17):2853-2858. doi:10.1200/JCO.2009.26.5827 [doi]
124. Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2007;99(9):706-714. doi:99/9/706 [pii]
125. Cheung MC, Haynes AE, Meyer RM, Stevens A, Imrie KR, Members of the Hematology DSGotCCOPiE-BC. Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario. *Cancer Treat Rev*. 2007;33(2):161-176. doi:S0305-7372(06)00207-6 [pii]
126. Witzig TE, Molina A, Gordon LI, et al. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. *Cancer*. 2007;109(9):1804-1810. doi:10.1002/cncr.22617 [doi]
127. Morschhauser F, Radford J, Van Hoof A, et al. Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. *J Clin Oncol*. 2008;26(32):5156-5164. doi:10.1200/JCO.2008.17.2015 [doi]
128. Brown JR, Feng Y, Gribben JG, et al. Long-term survival after autologous bone marrow transplantation for follicular lymphoma in first remission. *Biol Blood Marrow Transplant*. 2007;13(9):1057-1065. doi:S1083-8791(07)00307-2 [pii]
129. Sebban C, Brice P, Delarue R, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with follicular lymphoma: a GELA study. *J Clin Oncol*. 2008;26(21):3614-3620. doi:10.1200/JCO.2007.15.5358 [doi]
130. Salles G, Mounier N, de Guibert S, et al. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: results of the GELA-GOELAMS FL2000 study. *Blood*. 2008;112(13):4824-4831. doi:10.1182/blood-2008-04-153189 [doi]
131. Hochster H, Weller E, Gascoyne RD, et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study. *J Clin Oncol*. 2009;27(10):1607-1614. doi:10.1200/JCO.2008.17.1561 [doi]
132. Gyan E, Foussard C, Bertrand P, et al. High-dose therapy followed by autologous purged stem cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by the GOELAMS with final results after a median follow-up of 9 years. *Blood*. 2009;113(5):995-1001. doi:10.1182/blood-2008-05-160200 [doi]
133. Nickenig C, Dreyling M, Hoster E, et al. Combined cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) improves response rates but not survival and has lower hematologic toxicity compared with combined mitoxantrone, chlorambucil, and prednisone (MCP) in follicular and mantle cell lymphomas: results of a prospective randomized trial of the German Low-Grade Lymphoma Study Group. *Cancer*. 2006;107(5):1014-1022. doi:10.1002/cncr.22093 [doi]
134. Sebban C, Mounier N, Brousse N, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood*. 2006;108(8):2540-2544. doi:blood-2006-03-013193 [pii]
135. Ladetto M, De Marco F, Benedetti F, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. *Blood*. 2008;111(8):4004-4013. doi:10.1182/blood-2007-10-116749 [doi]
136. Nickenig C, Dreyling M, Hoster E, et al. Initial chemotherapy with mitoxantrone, chlorambucil, prednisone impairs the collection of stem cells in patients with indolent lymphomas--results of a randomized comparison by the German Low-Grade Lymphoma Study Group. *Ann Oncol*. 2007;18(1):136-142. doi:mdl348 [pii]
137. Hagenbeek A, Eghbali H, Monfardini S, et al. Phase III intergroup study of fludarabine phosphate compared with cyclophosphamide, vincristine, and prednisone chemotherapy in newly diagnosed patients with stage III and IV low-grade malignant Non-Hodgkin's lymphoma. *J Clin Oncol*. 2006;24(10):1590-1596. doi:24/10/1590 [pii]
138. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106(12):3725-3732. doi:2005-01-0016 [pii]
139. Herold M, Schulze A, Niederwieser D, et al. Bendamustine, vincristine and prednisone (BOP) versus cyclophosphamide, vincristine and prednisone (COP) in advanced indolent non-Hodgkin's lymphoma and

mantle cell lymphoma: results of a randomised phase III trial (OSHO# 19). *J Cancer Res Clin Oncol*. 2006;132(2):105-112. doi:10.1007/s00432-005-0023-2 [doi]
140. Rohatiner AZ, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow-up. *J Clin Oncol*. 2007;25(18):2554-2559. doi:JCO.2006.09.8327 [pii]
141. Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 2011;377(9759):42-51. doi:10.1016/S0140-6736(10)62175-7 [doi]
142. Siddhartha G, Vijay P. R-CHOP versus R-CVP in the treatment of follicular lymphoma: a meta-analysis and critical appraisal of current literature. *J Hematol Oncol*. 2009;2:14-14. doi:10.1186/1756-8722-2-14 [doi]
143. Oliansky DM, Gordon LI, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2010;16(4):443-468. doi:10.1016/j.bbmt.2010.01.008 [doi]
144. 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(9873):1203-1210. doi:10.1016/S0140-6736(12)61763-2 [doi]
145. Rummel MJ, Kaiser U, Balser C, et al. Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab In Patients with Relapsed Follicular, Indolent and Mantle Cell Lymphomas – Final Results of the Randomized Phase III Study NHL 2–2003 on Behalf of the StiL (Study Group Indolent Lymphomas, Germany). *Blood*. 2010;116(21):856.
146. Davies G, Ghosh S, Oh D, et al. Significant Adverse Consequences of Initial Watchful Waiting for Follicular Lymphoma Patients: A Retrospective Analysis of Patients Diagnosed in Alberta from 1994-2011. *Blood*. 2017;130:4041.
147. Northend MW, W. Clifton-Hadley, L. Rana, Z. Martin, TL, Young, M. Miall, F. Long Term Follow-up of International Randomised Phase 3 Study of Rituximab Versus a Watch and Wait Approach for Patients with Asymptomatic, Low Tumour Burden Follicular Lymphoma Shows Rituximab Is Highly Effective at Delaying Time to New Treatment without Detrimental Impact Following Next Line of Therapy | Blood | American Society of Hematology. *Blood*. 2022;140(Supplement 1):1456-1458. doi:10.1182/blood-2022-156790
148. Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-Based Induction and Maintenance Prolongs Progression-Free Survival (PFS) in Patients with Previously Untreated Follicular Lymphoma: Primary Results of the Randomized Phase 3 GALLIUM Study. *Blood*. 2016;128(22):6.
149. Oh DH, Li H, Duan Q, 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. doi:10.1016/j.bbmt.2016.01.015 [doi]
150. Puckrin R, Chua N, Chin K, et al. Long-term follow-up demonstrates curative potential of autologous stem cell transplantation for relapsed follicular lymphoma. *Br J Haematol*. Apr 2023;201(2):319-325. doi:10.1111/bjh.18640
151. Leonard J, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 05/10/2019 2019;37(14)doi:10.1200/JCO.19.00010
152. Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Blood*. Feb 8 2024;143(6):496-506. doi:10.1182/blood.2023021243
153. Dreyling M, Fowler NH, Dickinson M, et al. Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update. *Blood*. Apr 25 2024;143(17):1713-1725. doi:10.1182/blood.2023021567
154. Gopal A, Kahl B, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. *The New England journal of medicine*. 03/13/2014 2014;370(11)doi:10.1056/NEJMoa1314583

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2025) am 16.10.2025

#	Suchschritt
1	[mh ^"lymphoma, non-hodgkin"]
2	(((non NEXT hodgkin*) OR nonhodgkin*) AND lymphoma*):ti,ab,kw
3	[mh ^"Lymphoma, B-Cell"] OR [mh "lymphoma, large b-cell, diffuse"]
4	(diffuse NEXT large NEXT cell NEXT lymphoma*):ti,ab,kw
5	(("b-cell" OR bcell OR "high-grade" OR highgrade OR "double-hit" OR "triple-hit" OR aggressive OR Burkitt*) AND lymphoma*):ti,ab,kw
6	((histiocytic OR "large lymphoid") AND lymphoma*):ti,ab,kw
7	(DLBCL OR BCL OR LBCL OR HGBCL OR HGBL):ti,ab,kw
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	[mh "lymphoma, follicular"] OR [mh ^"lymphoma, non-hodgkin"]
10	((follicular OR nodular OR "small cleaved cell") AND lymphoma*):ti,ab,kw
11	#9 OR #10
12	(PMBCL OR rrPMBCL OR ((primary NEXT mediastinal) AND lymphoma*)):ti,ab,kw
13	(THRBCL OR ("histiocyte-rich" AND lymphoma*)):ti,ab,kw
14	#8 OR #11 OR #12 OR #13
15	[mh "Lymphoma, B-Cell, Marginal Zone"] OR [mh ^"Lymphoma, B-Cell"]
16	((marginal NEXT zone) OR malt OR mucosa* OR splenic* OR nodal* OR extranodal*):ti,ab,kw AND (lymphoma* OR (lymphoid NEXT tissue)):ti,ab,kw
17	((monocytoid OR cutaneous) AND ((b NEXT cell) OR bcell)) AND lymphoma*):ti,ab,kw
18	#14 OR #15 OR #16 OR #17
19	#18 with Cochrane Library publication date from Oct 2020 to present
20	#19 with Cochrane Library publication date from Oct 2023 to present
21	#19 NOT #20

Leitlinien und systematische Reviews in PubMed am 16.10.2025

Hinweis: Vom 1. Oktober 2025 bis 13. November 2025 gab es eine Unterbrechung der staatlichen Finanzierung von Behörden in den USA. Die National Library of Medicine wies darauf hin, dass die Möglichkeit besteht, dass sich der Informationsbestand von PubMed nicht auf dem neuesten Stand befand bzw. befindet. Da währenddessen keine Unregelmäßigkeiten festgestellt wurden, erfolgte die Nutzung der Datenbank weiterhin.

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

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	"Lymphoma, Non-Hodgkin"[mh:noexp]
2	(non-hodgkin*[tiab] OR nonhodgkin*[tiab]) AND lymphoma*[tiab]
3	"Lymphoma, B-Cell"[mh:noexp] OR "Lymphoma, Large B-Cell, Diffuse"[mh]
4	diffuse[tiab] AND large[tiab] AND cell[tiab] AND lymphoma*[tiab]
5	(b-cell[tiab] OR bcell[tiab] OR high-grade[tiab] OR highgrade[tiab] OR ((double[tiab] OR triple[tiab]) AND hit[tiab]) OR aggressive[tiab] OR Burkitt*[tiab]) AND lymphoma*[tiab]
6	(histiocytic[tiab] OR (large[tiab] AND lymphoid[tiab])) AND lymphoma*[tiab]
7	DLBCL[tiab] OR BCL[tiab] OR LBCL[tiab] OR HGBCL[tiab] OR HGBL[tiab]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	lymphoma, follicular[mh] OR lymphoma, non-hodgkin[mh:noexp]
10	(follicular[tiab] OR nodular[tiab] OR small cleaved cell[tiab]) AND lymphoma*[tiab]
11	#9 OR #10
12	PMBCL[tiab] OR rrPMBCL[tiab] OR (primary mediastinal[tiab] AND lymphoma*[tiab])
13	THRBCL[tiab] OR (histiocyte rich[tiab] AND lymphoma*[tiab])
14	#8 OR #11 OR #12 OR #13
15	"lymphoma, b cell, marginal zone"[mh] OR "Lymphoma, B-Cell"[mh:noexp]
16	(marginal zone[tiab] OR malt[tiab] OR mucosa*[tiab] OR splenic*[tiab] OR nodal*[tiab] OR extranodal*[tiab]) AND (lymphoma*[tiab] OR lymphoid tissue[tiab])
17	(cutaneous[tiab] OR monocytoid[tiab]) AND (b-cell[tiab] OR bcell[tiab]) AND lymphom*[tiab]
18	#14 OR #15 OR #16 OR #17
19	(#18) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])

#	Suchschritt
20	(#19) AND ("2020/10/01"[PDAT] : "3000"[PDAT])
21	(#20) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
22	(#18) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
23	(#22) AND ("2020/10/01"[PDAT] : "3000"[PDAT])
24	(#23) NOT "The Cochrane database of systematic reviews"[Journal]
25	(#24) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
26	(#25) NOT (#21)
27	(#26) AND ("2023/10/01"[PDAT] : "3000"[PDAT])
28	#26 NOT #27

Iterative Handsuche nach grauer Literatur, abgeschlossen am 20.10.2025, überprüft am 08.12.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Alberta Health Services (AHS).** Lymphoma; version 20 [online]. Edmonton (CAN): AHS; 2025. [Zugriff: 08.12.2025]. (Clinical practice guideline; Band LYHE-002). URL: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe002-lymphoma.pdf.

2. **National Comprehensive Cancer Network (NCCN).** B-cell lymphomas; version 03.2025 [online]. Plymouth Meeting (USA): NCCN; 2025. [Zugriff: 08.12.2025]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

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

Verfahrens-Nr.: 2025-B-317

Verfasser	
Institution	DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie GLA German Lymphoma Alliance
Sachverständige	
Datum	30. Dezember 2025

Indikation
Behandlung von erwachsenen Patienten mit einem rezidivierenden oder refraktären follikulären Lymphom (FL)
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Das follikuläre Lymphom [FL] ist das häufigste indolente Lymphom. Der klinische Verlauf ist sehr variabel. Auch bei vorbehandeltem FL besteht eine Behandlungsindikation erst beim Auftreten krankheitsassoziierter Symptome.

Vor Einleitung einer Therapie im Rezidiv ist eine erneute Lymphknotenexstirpation oder -biopsie zur Histologiegewinnung anzustreben, um eine sekundäre Transformation in ein aggressives Lymphom auszuschließen.

Die Wahl des Therapieschemas erfolgt nach ärztlicher Maßgabe in Abhängigkeit von den vorhergehenden Therapien, der Dauer der vorherigen Remission, der Verträglichkeit und Komorbiditäten. Zu den Optionen beim behandlungspflichtigen r/r FL gehören entsprechend der Evidenz und den Zulassungsbestimmungen [1, 2]:

<u>1. Rezidiv</u>

- Tafasitamab / Rituximab / Lenalidomid
- Rituximab + Lenalidomid
- Anti-CD20 AK + Chemotherapie (Obinutuzumab oder Rituximab in Kombination mit Bendamustin, Rituximab in Kombination mit CVP oder CHOP), ggf. auch als Hochdosischemotherapie bei Hochrisiko

2. Rezidiv (zusätzlich)

- Bispezifische Antikörper: Epcoritamab oder Mosunetuzumab oder Odronextamab
- CAR-T-Zellen: Lisocabtagen Maraleucel oder Tisagenlecleucel
- Zanubrutinib + Obinutuzumab

3. Rezidiv (zusätzlich)

- CAR-T-Zellen: Axicabtagen Ciloleucel
- Idelalisib
- ggf. allogene Stammzelltransplantation

Fragestellung

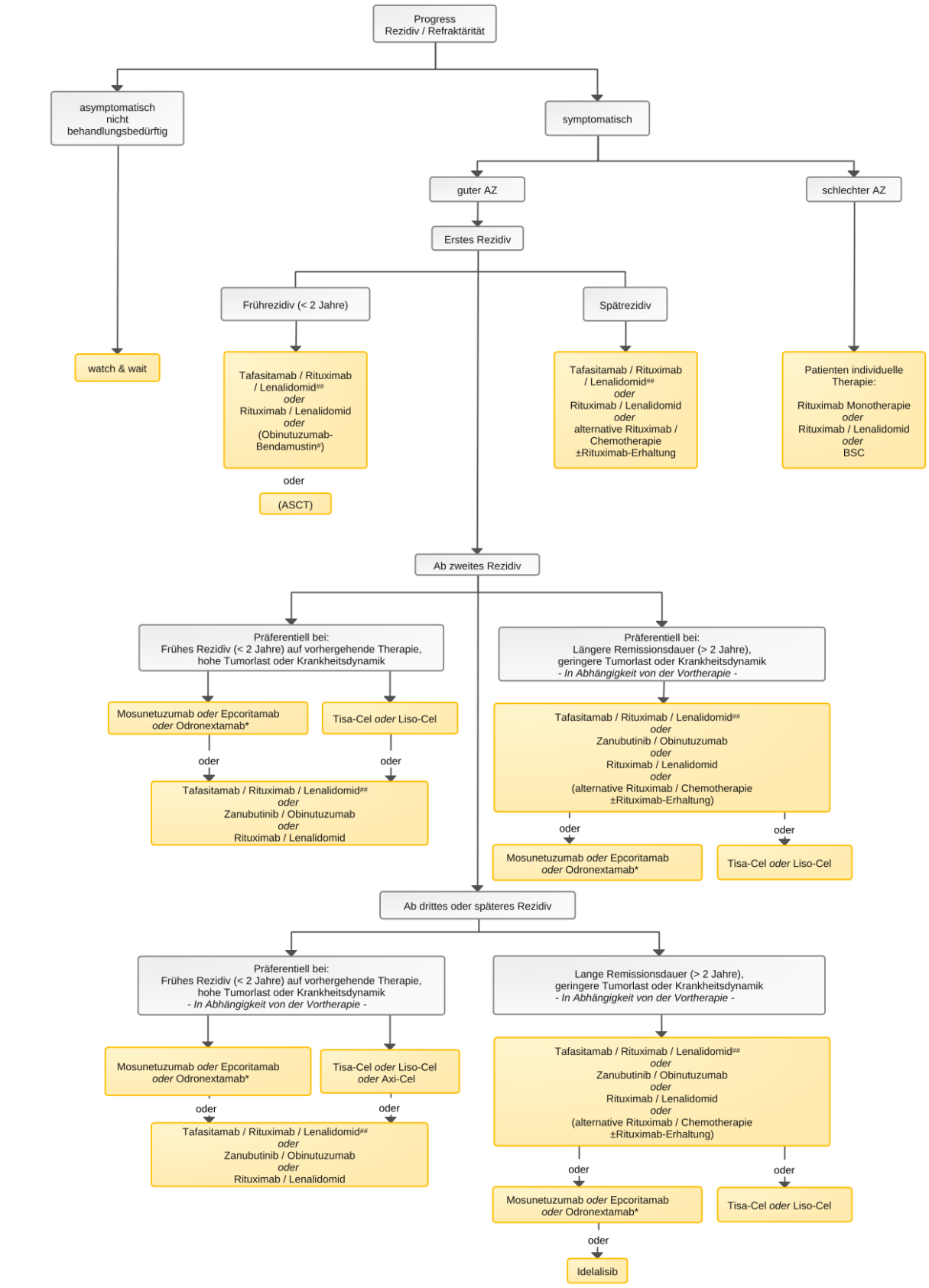
Die Fragestellung ist sehr weit gestellt. Wir schlagen bei einer Studienplanung und/oder bei einer Nutzenbewertung eine Differenzierung vor, bei der zumindest diese Behandlungsbedingungen beschrieben werden sollten:

- Anzahl der Vortherapie
- Zeit bis zum Progress (POD24)

Stand des Wissens

Ein Algorithmus ist in Abbildung 1 dargestellt [2].

Rezidivtherapie des Follikulären Lymphoms



Legende:
** derzeit nur in Deutschland verfügbar*
 # bei Rituximab Refraktärität, nur bei chemotherapiefreier Erstlinientherapie
keine Zulassung bislang

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
Ja, die Optionen sind oben dargestellt. Bei der Therapiesequenz ist zu berücksichtigen, dass eine zytostatische Vortherapie, z. B. mit Bendamustin die T-Zellfunktion supprimieren kann. Dies hat einen negativen Einfluss auf die Wirksamkeit einer nachfolgenden Immuntherapie, z. B. von bispezifischen Antikörpern mit Bindung an CD3 auf T-Zellen. Weiterhin wird im ersten Rezidiv nach initialer Immunchemotherapie insbesondere bei kurzer Remissionsdauer die erneute Verwendung einer Immunchemotherapie zurückhaltend gesehen.

Referenzliste:

1. AWMF S3 Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit einem follikulären Lymphom. Stand Juli 2025. https://www.awmf.org/uploads/tx_szleitlinien/018-033OLl_S3_Follikulaeres_Lymphom_2020-06.pdf
2. Buske C et al.: Follikuläres Lymphom, Juli 2025. https://www.dgho-onkopedia.de/de/onkopedia/leitlinien/follikulaeres-lymphom