Leitlinienprogramm Onkologie

Konsultationsfassung Leitlinienreport zur S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit einem follikulären Lymphom

Version 0.1 – August 2019
AWMF-Registernummer: 018/033OL

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Leitlinienreport

Bitte senden Sie Kommentare, Hinweise und Verbesserungsvorschläge zu dieser Leitlinie unter Verwendung des Kommentierungsbogens bis zum 25.09.2019 an:
follikulaeres-lymphom@leitlinienprogramm-onkologie.de
oder per Fax an: 030 322932966

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1. Informationen zum Leitlinienreport

1.1. Autoren des Leitlinienreports

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1.2. Herausgeber

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1.3. Federführende Fachgesellschaft(en) der Leitlinie

Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO) e.V.

1.4. Finanzierung der Leitlinie

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Leitlinienprogramms Onkologie gefördert.

1.5. Kontakt

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1.6. Zitierweise des Leitlinienreports

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Diagnostik, Therapie und Nachsorge für Patienten mit einem follikulären Lymphom, Leitlinienreport 0.1 (Konsultationsfassung), 2019, AWMF-Registernummer: 018/033OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/follikulaeres-lymphom/ (abgerufen am: TT.MM.JJJJ)

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1.7. Weitere Dokumente zur Leitlinie

Die Leitlinie liegt als Lang- und Kurzversion vor. Außerdem gibt es eine Patientenleitlinie (Laienversion der Leitlinie). Alle Dokumente zur Leitlinie sind über die folgenden Seiten zugänglich:

- AWMF (http://www.awmf.org/leitlinien/aktuelle-leitlinien.html)
- Leitlinienprogramm Onkologie http://www.leitlinienprogramm-onkologie.de/OL/leitlinien.html
- Deutsche Krebsgesellschaft http://www.krebsgesellschaft.de/wub_llevidenzbasiert,120884.html
- Deutsche Krebshilfe (http://www.krebshilfe.de/)
- Guidelines International Network (www.g-i-n.net)

fassung

1.8. Abkürzungsverzeichnis

Tabelle 1: Abkürzungsverzeichnis

Abkürzung	Erläuterung
AG	Arbeitsgruppe
AG PRiO	Prävention und integrative Onkologie
AkdÄ	Arzneimittelkommission der deutschen Ärzteschaft
AOI	Arbeitsgemeinschaft Internistische Onkologie in der Krebsgesellschaft e. V.
ASORS	Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BNHO	Berufsverband der Niedergelassenen Hämatologen und Onkologen in Deutschland e. V.
CT	Computertomographie
DAG KBT	Deutsche Arbeitsgemeinschaft für Knochenmark- und Blutstammzelltransplantation
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin
DEGRO	Deutsche Gesellschaft für Radioonkologie
DEGUM	Deutsche Gesellschaft für Ultraschall in der Medizin e.V.
DGHO	Deutsche Gesellschaft für Hämatologie und Onkologie e.V.
DNEbM	Deutsches Netzwerk Evidenzbasierte Medizin
DRG	Deutsche Röntgengesellschaft e.V.
DGKL	Deutsche Gesellschaft für klinische Chemie und Laboratoriumsmedizin
DGE BV	Deutsche Gesellschaft für Endoskopie und Bildgebende Verfahren e.V.
DGIM	Deutsche Gesellschaft für Innere Medizin
DGN	Deutsche Gesellschaft für Nuklearmedizin e.V.
DKG	Deutsche Krebsgesellschaft e. V.
DKH	Deutsche Krebshilfe
DLH	Deutsche Leukämie- und Lymphomhilfe e. V.
EK	Expertenkonsens
e.V.	Eingetragener Verein
FL	Follikuläres Lymphom
GDMS	Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V.
GEKID	Gesellschaft der epidemiologischen Krebsregister in Deutschland e. V.
G-I-N	Guidelines International Network

Abkürzung	Erläuterung
GKV	Gesetzliche Krankenversicherung
GLSG	Deutsche Studiengruppe Niedrigmaligne Lymphome
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KCO	Kompetenz-Centrum Onkologie
KK	Konsensus Konferenz
KML	Kompetenznetz Maligne Lymphome
KOK	Konferenz Onkologischer Kranken- und Kinderkrankenpflege
LA	Leitlinienadaptation
MDK	Medizinischer Dienst der Krankenversicherung
MRD	Minimal residual disease
NGC	National Guideline Clearinghouse
OL	Leitlinienprogramm Onkologie
OSHO	Ostdeutsche Studiengruppe für Hämatologie und Onkologie
PET	Positronen-Emissions-Tomographie
PSO	Deutsche Arbeitsgemeinschaft für Psychoonkologie
RCT	Randomisierte kontrollierte Studie
SR	Systematische Recherche
WINHO	Wissenschaftliches Institut der Niedergelassenen Hämatologen und Onkologen GmbH

Konsultat

2. Geltungsbereich und Zweck der Leitlinie

2.1. Adressaten

Primäre Zielgruppe der Leitlinie sind Ärzte und Angehörige anderer Gesundheitsberufe, die Patienten mit follikulärem Lymphom behandeln oder sie im Rahmen der Nachsorge langfristig betreuen. Dazu zählen u.a. Onkologen, Hämatologen, Internisten, Allgemeinmediziner, Strahlentherapeuten, Radiologen, Pathologen, Nuklearmediziner, Radioonkologen, Psychoonkologen und Pflegekräfte genannt. Der Anwendungsbereich für die Leitlinie gilt sowohl für den ambulanten als auch für den stationären Versorgungs- und Rehabilitationssektor.

Zielgruppe der Leitlinie sind auch Patienten ab dem 18. Lebensjahr mit einem follikulären Lymphom, die direkt durch eine optimierte Versorgung profitieren werden.

Weitere Adressaten der Leitlinie sind:

- Medizinisch-wissenschaftliche Fachgesellschaften
- Gesundheitspolitische Entscheidungsträger
- Krankenhäuser
- Krankenkassen sowie Vertragsverantwortliche von Integrierten Versorgungsverträgen
- Qualitätssicherungseinrichtungen

2.2. Zielsetzung

Das primäre Ziel dieser S3-Leitlinie ist es, die Diagnostik, Therapie und Nachsorge von Patienten mit einem follikulären Lymphom zu standardisieren und zu optimieren, um sowohl bei der Ersterkrankung als auch beim Rezidiv ein individuell adaptiertes qualitätsgesichertes Therapiekonzept zu gewährleisten.

Das follikuläre Lymphom ist nach den diffus großzelligen B-Zell-Lymphomen die häufigste bösartige Neubildung aus dem Bereich der malignen Lymphome in den Ländern der westlichen Welt. Die Inzidenz beträgt zwischen 15 und 20 Fällen pro 100.000 Einwohner pro Jahr und hat in den letzten Jahren zugenommen. Die Erkrankung tritt vor allem im höheren Lebensalter auf (Durchschnittsalter bei Diagnosestellung > 60 Jahre) und ist durch ein individuell sehr heterogenes klinisches Erscheinungsbild und eine stark variierende Prognose gekennzeichnet. Einige Patienten haben über Jahre keine oder nur minimale Symptome, die keiner Behandlung bedürfen und eine annähernd normale Lebenserwartung haben. Andere Patienten weisen hingegen bereits bei Diagnosestellung oder kurz darauf Symptome auf und sterben trotz einer Immunochemotherapie innerhalb weniger Jahre.

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Folgende Fragestellungen zur Diagnostik, Therapie und Nachsorge des follikulären Lympoms werden kontrovers diskutiert und unterschiedlich in der Patientenversorgung umgesetzt:

- Einsatz und Umfang der Strahlentherapie
- Indikation zur Erstlinientherapie
- Wahl der Erstlinientherapie
- Wahl der Rezidivtherapie
- Stellenwert der autologen Transplantation
- Therapie der malignen Transformation in ein hochmalignes Lymphom
- Therapie von FL Grad IIIb
- Zeitplan und Umfang der Nachsorge

Mittels der Beantwortung der Fragen zu diesen Themen in dieser S3-Leitlinie werden richtungsweisende Standards etabliert. Auf diesem Weg soll die Qualität der Versorgung verbessert werden. Zudem kann die Berücksichtigung der Empfehlungen zu einer Effizienzsteigerung und damit zur Kostendämpfung im Gesundheitswesen beitragen.

2.3. Gültigkeitsdauer und Aktualisierungsverfahren

Die S3-Leitlinie wird nach Abschluss der Konsulation und Publikation der Version 1 bis zur nächsten Aktualisierung oder maximal für 5 Jahre gültig sein.

Vorgesehen sind regelmäßige Aktualisierungen der Leitlinien. Bei dringendem Änderungsbedarf sind jedoch auch punktuelle kurzfristige Änderungen möglich. Kommentare und Hinweise für den Aktualisierungsprozess sind ausdrücklich erwünscht und können an das Leitliniensekretariat adressiert werden: follikulaeres-lymphom@leitlinienprogramm-onkologie.de

Konsultationfassung

3. Zusammensetzung der Leitliniengruppe

Die Zusammensetzung der Leitliniengruppe ist im Kapitel 1.9 der Langversion detailliert beschrieben.

4. Fragestellungen und Gliederung

Innerhalb der Leitliniensteuergruppe wurde die grundsätzliche inhaltliche Ausrichtung der Leitlinie (geplante Gliederung) erarbeitet.

Im Rahmen des Kick-Off-Meetings wurden die Gliederung und die Leitfragen konsentiert und die Art der Bearbeitungsweise festgelegt. Es wurden für jedes Kapitel eine verantwortliche Kapitelleitung bestimmt, sowie Unterpunktleitungen und Arbeitsgruppen zu den einzelnen Fragestellungen benannt. Die festgelegten Themen und die geplante primäre Bearbeitungsweise (Systematische de-novo-Recherche [SR], Leitlinienadaptation [LA] oder Expertenkonsens [EK]) sind in Tabelle 2 aufgeführt. Eine ausführliche Darstellung der konkreten Frágestellungen zu den Themen befindet sich in Kapitel 14.2. Die Fragestellungen wurden im Rahmen Kick-Off-Meetings konsentiert. Im Rahmen der weiteren Bearbeitung innerhalb der Arbeitsgruppen konnten - basierend auf inhaltlichen Aspekten - Leitfragen sprachlich angepasst und redaktionelle Änderungen wie Zusammenfassung von Unterpunkten vorgenommen werden. Dies wurde auf dem Leitliniensteuergruppen-Kapitelleiter Meeting 02./03.05.2018 in München im Detail besprochen und von der Leitliniensteuergruppe befürwortet.

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Tabelle 2: Schlüsselfragen und geplante Methode der Beantwortung

AG	Fragestellung	SR	LA	EK
Epidemiologie, Risikofaktoren				
Initiale Diagnostik, Stadieneinteilung und Verlaufsbeurteilung	Typischen Symptome			X
	Histologische Diagnostik			X
	Anforderung an die Diagnostik			X
	Prognostische / prädiktive Faktoren			X
	Prognostische Relevanz in Initial- und Verlaufsdiagnostik von PET CT, CT und MRD	X		
	Stadieneinteilung			X
	Psycho-Onkologie			X
	Fertiliätsprotektive Maßnahmen			X
Aufklärung des Patienten und Therapieplanung	Aufklärung und Diagnosemitteilung			X
	Therapieplanung			X

AG	Fragestellung	SR	LA	EK
Therapie des frühen Stadiums	Watch and Wait	X		
	Alleinige Strahlentherapie	X		
	Antikörper Therapie	X		
Therapie des fortgeschrittenen Stadiums	Watch and Wait	X		
	Tumorlast und Symptomatische Erkrankung			X
	Induktionstherapie	X		
Erhaltungstherapie	Erhaltungstherapie nach der Firstline Therapie	X		
	Radio-Immuntherapie	X		
	Konsolidierung mit autologer Stammzelltransplantation	X		
Subgruppen	Follikuläres Lymphom in situ			X
	Follikuläres Lymphom Grad 3a			X
	Follikuläres Lymphom Grad 3b			X
	Extranodales follikuläres Lymphom			X
	Intestinales follikuläres Lymphom			X
	Cutanes follikuläres Lymphom			X
	Stark begleiterkrankte Patienten			X
Rezidiv	Diagnostik			X
	Histologische Diagnostik			X
	Anforderung an die Diagnostik			X
	Prognostische / prädiktive Faktoren			X
	Stadieneinteilung			X
	Therapie Indikation			X
Therapie des Rezidivs	Neue Substanzen	X		
	(Chemo)-Immuntherapie	X		
	Strahlentherapie	X		

AG	Fragestellung	SR	LA	EK
	Autologe Transplantation	X		
	Allogene Transplantation	X		
	Erhaltungstherapie	X		
Nachsorge und Rehabilitation	Nachsorge zur Rezidivfrüherkennung			X
	Stellenwert des CT / PET CT / Sonographie / Körperliche Untersuchung hinsichtlich Rezidiv Detektion	X		
	Rezidiv-Verdacht			X
	Früherkennung für Sekundärneoplasien			X
	Rehabilitation			X
Supportivmaßnahmen, Palliativmedizin und komplementäre Verfahren	Supportivtherapie			X
	Palliativtherapie			X
	Komplementäre Verfahren			X
Forschungsziele				X

Abkürzungen: EK = Expertenkonsens, LA = Leitlinienadaptation, SR = Systematische Recherche

Konsultation

5. Methodisches Vorgehen

5.1. Leitlinienadaptation

Die Bewertung der identifizierten Leitlinien erfolgte nach einem formalisierten Verfahren zunächst durch die methodisch ausgewiesenen Mitarbeiter der Klinik I für Innere Medizin Universität Köln (Arbeitsgruppe Evidence-based Oncology).

5.1.1. Recherche

Im Januar 2017 wurde in der Datenbank des Guideline International Networks (www.g-i-n.net) und MEDLINE (www.pubmed.org) mit dem Suchbegriff „lymphoma“ nach relevanten Leitlinien gesucht.

5.1.2. Auswahl der Leitlinien

Die Einschlusskriterien für die detaillierte Betrachtung einer Leitlinie waren, dass sie evidenzbasierte Empfehlungen für die Diagnose oder Therapie von Patienten mit einem follikulären Lymphom geben sollten.

5.1.3. Leitlinienbewertung

Von den 26 Suchtreffern zu den teilweise noch in Erstellung befindlichen Leitlinien ist eine Leitlinie zum follikulären Lymphom potentiell relevant und bereits publiziert: [1]. Da die Suche in dieser Leitlinie nur bis 2008 ging, ist davon auszugehen, dass die Evidenz und somit die Empfehlungen nicht mehr aktuell sind. So wurde z.B. 2012 ein Cochrane Review von Schaaf et al. [2] erstellt, das die Evidenz zu dieser Fragestellung systematisch aufarbeitet und in einer Meta-analyse zusammenfasst und als Evidenzgrundlage für die Beantwortung der Schlüsselfrage in der vorliegenden Leitlinie verwendet wird.

5.1.4. Adaptierungsprozess

Da keine Leitlinie methodisch geeignet war, eine der Schlüsselfragen der S3-Leitlinie *Follikuläres Lymphom* zu beantworten, wurde keine Leitlinienadaption vorgenommen.

5.2. Systematische Recherchen

Die systematische Literatursuche basiert auf dem Prinzip der besten verfügbaren Evidenz. Die methodischen und inhaltlichen Ein- und Ausschlusskriterien wurden prospektiv definiert und von einer in der medizinischen Terminologie erfahrenen Bibliothekarin in sensitiven und hochkomplexen Suchstrategien für die jeweilig zu durchsuchende Datenbanken MEDLINE und CENTRAL der Cochrane Library umgesetzt. Für alle Suchstrategien wurden neben dem Datum der Suche auch die Anzahl der erzielten Treffer dokumentiert.

Bei der Literatur-Recherche wurde je nach klinischer Fragestellung nach Volltextpublikationen randomisierter kontrollierter Studien (RCTs), kontrollierter Studien, Kohorten (Nachsorge) und Testgütestudien gesucht. Dazu wurden durch eine Bibliothekarin Suchstrategien erstellt. Der Suchzeitraum deckt die Zeit von 1994 bis 2017 ab.

Konsultationfassung

5.2.1. Suchstrategien

Für therapeutische Fragestellungen aller Kapitel, die mittels randomisierter Studien oder systematischer Übersichtsarbeiten beantwortet werden sollten, wurde nur mittels eines Krankheitsfilters (Lymphom) und eines Studienfilters gesucht. Es wurde nicht nach spezifischen Interventionen gesucht. Zur Identifikation der Primärpublikationen wurden die Datenbanken MEDLINE (über OVID) und die Cochrane Library inklusive CENTRAL und die Referenzlisten von systematischen Übersichtsarbeiten durchsucht. Insgesamt ergaben die Suchen vom 07. und 08.11.2016 5948 Treffer in allen MEDLINE Datenbanken und 3768 CENTRAL. Ohne Dubletten ergaben sich so insgesamt 8508 Treffer.

5.2.1.1. MEDLINE/Ovid Suchstrategie für Systematische Übersichtsarbeiten und Meta-Analysen vom 08.11.2016

#	Suchen
1	exp LYMPHOMA, NON-HODGKIN/
2	(non-hodgkin$ or non hodgkin$ or nonhodgkin$ or no hodgkin$ or nhl).tw,kf,ot.
3	(lymph$ adj2 sarcom$).tw,kf,ot.
4	lymphosarcom$.tw,kf,ot.
5	(reticulum adj2 sarcom$).tw,kf,ot.
6	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$)).tw,kf,ot.
7	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$ or diffus$)).tw,kf,ot.
8	or/1-7
9	LYMPHOMA, FOLLICULAR/
10	(follicul$ adj2 lymph$).tw,kf,ot.
11	(nodular$ adj2 lymph$).tw,kf,ot.
12	((small$ or large$) adj4 (follicul$ adj2 lymph$)).tw,kf,ot.
13	((low-grad$ or low grad$) adj lymph$).tw,kf,ot.
14	((centro blast$ or zentroblast$) adj (centrocyst$ or zentrozyt$) adj lymph$).tw,kf,ot.
15	(follic$ adj2 (center$ or centro$) adj lymph$).tw,kf,ot.
16	(brill-symmer$ or brill symmer$).tw,kf,ot.
17	*Lymphoma, B-Cell/
18	(indolent$ adj2 lymph$).tw,kf,ot.
19	or/9-18
20	8 or 19
21	(review or review,tutorial or review, academic).pt.
22	(medline or medlars or embase or pubmed or cochrane).tw,sh.

ssung

#	Suchen
23	(scisearch or psychinfo or psycinfo).tw,sh.
24	(psychlit or psyclit).tw,sh.
25	cinahl.tw,sh.
26	((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
27	(electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
28	(pooling or pooled or mantel haenszel).tw,sh.
29	(peto or dersimonian or der simonian or fixed effect).tw,sh.
30	(retraction of publication or retracted publication).pt.
31	or/22-30
32	21 and 31
33	meta-analysis.pt.
34	meta-analysis.sh.
35	(meta-analys$ or meta analys$ or metaanalys$).tw,sh.
36	(systematic$ adj5 review$).tw,sh.
37	(systematic$ adj5 overview$).tw,sh.
38	(quantitativ$ adj5 review$).tw,sh.
39	(quantitativ$ adj5 overview$).tw,sh.
40	(quantitativ$ adj5 synthesis$).tw,sh.
41	(methodologic$ adj5 review$).tw,sh.
42	(methodologic$ adj5 overview$).tw,sh.
43	(integrative research review$ or research integration).tw.
44	or/33-43
45	32 or 44
46	20 and 45

5.2.1.2. Ovid/MEDLINE Suchstrategie am 07.11.2016 für den Zeitraum von 1946 – 07.11.2016 für randomisierte kontrollierte Studien zum follikulären Lymphom:

#	Suchen
1	exp Lymphoma, Non-Hodgkin/
2	(non-hodgkin$ or non hodgkin$ or nonhodgkin$ or no hodgkin$ or nhl).tw,kf,ot.
3	(lymph$ adj2 sarcom$).tw,kf,ot.

#	Suchen
4	lymphosarcom$.tw,kf,ot.
5	(reticulum adj2 sarcom$).tw,kf,ot.
6	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$)).tw,kf,ot.
7	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$ or diffus$)).tw,kf,ot.
8	or/1-7
9	Lymphoma, Follicular/
10	(follicul$ adj2 lymph$).tw,kf,ot.
11	(nodular$ adj2 lymph$).tw,kf,ot.
12	((small$ or large$) adj4 (follicul$ adj2 lymph$)).tw,kf,ot.
13	((low-grad$ or low grad$) adj lymph$).tw,kf,ot.
14	((centro blast$ or zentroblast$) adj (centrocyst$ or zentrozyt$) adj lymph$).tw,kf,ot.
15	(follic$ adj2 (center$ or centro$) adj lymph$).tw,kf,ot.
16	(brill-symmer$ or brill symmer$).tw,kf,ot.
17	*Lymphoma, B-Cell/
18	(indolent$ adj2 lymph$).tw,kf,ot.
19	or/9-18
20	8 or 19 → Follikuläres Lymphom
21	randomized controlled trial.pt.
22	controlled clinical trial.pt.
23	randomi?ed.ab.
24	placebo.ab.
25	drug therapy.fs.
26	randomly.ab.
27	trial.ab.
28	groups.ab.
29	or/21-28
30	humans.sh.
31	29 and 30
32	20 and 31 → Follikuläres Lymphom und RCT
33	randomized controlled trial.pt.

#	Suchen
34	controlled clinical trial.pt.
35	randomi?ed.ab.
36	placebo.ab.
37	clinical trials as topic.sh.
38	randomly.ab.
39	trial.ti.
40	or/33-39
41	humans.sh.
42	40 and 41
43	20 and 42 → Follikuläres Lymphom und RCT, klein

5.2.1.3. Ovid/MEDLINE Suchstrategie am 08.11.2017 für "In-Process & Other Non-Indexed Citations"

#	Suchen
1	exp Lymphoma, Non-Hodgkin/
2	(non-hodgkin$ or non hodgkin$ or nonhodgkin$ or no hodgkin$ or nhl).tw,kf,ot.
3	(lymph$ adj2 sarcom$).tw,kf,ot.
4	lymphosarcom$.tw,kf,ot.
5	(reticulum adj2 sarcom$).tw,kf,ot.
6	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$)).tw,kf,ot.
7	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$ or diffus$)).tw,kf,ot.
8	or/1-7
9	Lymphoma, Follicular/
10	(follicul$ adj2 lymph$).tw,kf,ot.
11	(nodular$ adj2 lymph$).tw,kf,ot.
12	((small$ or large$) adj4 (follicul$ adj2 lymph$)).tw,kf,ot.
13	((low-grad$ or low grad$) adj lymph$).tw,kf,ot.
14	((centro blast$ or zentroblast$) adj (centrocyst$ or zentrozyt$) adj lymph$).tw,kf,ot.
15	(follic$ adj2 (center$ or centro$) adj lymph$).tw,kf,ot.
16	(brill-symmer$ or brill symmer$).tw,kf,ot.
17	*Lymphoma, B-Cell/

#	Suchen
18	(indolent$ adj2 lymph$).tw,kf,ot.
19	or/9-18
20	8 or 19
21	randomized controlled trial.pt.
22	controlled clinical trial.pt.
23	randomi?ed.ab.
24	placebo.ab.
25	clinical trials as topic.sh.
26	randomly.ab.
27	trial.ti.
28	or/21-27
29	humans.sh.
30	28 and 29

5.2.1.4. Suchstrategie für den Cochrane Central Register of Controlled Trials am 08.11.2016

ID	Suche
#1	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees
#2	non-hodgkin* or non hodgkin* or nonhodgkin* or no hodgkin* or nhl
#3	lymph* near/2 sarcom*
#4	lymphosarcom*
#5	reticulum near/2 sarcom*
#6	(lymphom* near/2 (cleaved* or noncleaved* or grad* or mixed-cell* or pleomorphic*))
#7	(lymphom* near/2 (cleaved* or noncleaved* or grad* or mixed-cell* or pleomorphic* or diffus*))
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	MeSH descriptor: [Lymphoma, Follicular] explode all trees
#10	(follicul* near/2 lymph*)
#11	(nodular* near/2 lymph*)
#12	((small* or large*) near/4 (follicul* adj2 lymph*))
#13	((low-grad* or low grad*) near/1 lymph*)
#14	((centro blast* or zentroblast*) near/1 (centrocyst* or zentrozyt*) adj lymph*)
#15	(follic* near/2 (center* or centro*) near/1 lymph*)

ID	Suche
#16	(brill-symmer* or brill symmer*)
#17	MeSH descriptor: [Lymphoma, B-Cell] explode all trees
#18	(indolent* near/2 lymph*)
#19	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20	#8 or #19
#21	#20 in Trials

5.2.1.5. Medline/Ovid Suchstrategie für klinische Studien der Phasen I, II, III und IV sowie Follow-Up Studien am 11.01.2017

Für einige Fragestellungen wurden auch nicht randomisierten Studien gesucht und der Suchfilter entsprechend angepasst (siehe Tabelle 2). Die Suche am 01.11.2017 ergab 6649 Treffer in MEDLINE. Es konnten 531 Studien indentifiziert werden, die den Autoren zur Verfügung gestellt wurden.

#	Suchen
1	exp LYMPHOMA, NON-HODGKIN/
2	(non-hodgkin$ or non hodgkin$ or nonhodgkin$ or no hodgkin$ or nhl).tw,kf,ot.
3	(lymph$ adj2 sarcom$).tw,kf,ot.
4	lymphosarcom$.tw,kf,ot.
5	(reticulum adj2 sarcom$).tw,kf,ot.
6	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$)).tw,kf,ot.
7	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$ or diffus$)).tw,kf,ot.
8	or/1-7
9	indolent*.tw,kf,ot.
10	8 and 9
11	LYMPHOMA, FOLLICULAR/
12	(follicul$ adj2 lymph$).tw,kf,ot.
13	(nodular$ adj2 lymph$).tw,kf,ot.
14	((small$ or large$) adj4 (follicul$ adj2 lymph$)).tw,kf,ot.
15	((low-grad$ or low grad$) adj lymph$).tw,kf,ot.
16	((centro blast$ or zentroblast$) adj (centrocyst$ or zentrozyt$) adj lymph$).tw,kf,ot.
17	(follic$ adj2 (center$ or centro$) adj lymph$).tw,kf,ot.
18	(brill-symmer$ or brill symmer$).tw,kf,ot.

#	Suchen
19	*LYMPHOMA, B-CELL/
20	(indolent$ adj2 lymph$).tw,kf,ot.
21	or/11-20
22	10 or 21
23	exp Clinical Trial/
24	(clinical* adj25 trial*).tw.
25	clinical trial.pt.
26	((singl* or double* or trebl* or tripl* or quadrupl*) adj25 (blind* or mask*)).tw.
27	PLACEBOS/
28	placebo*.tw.
29	RESEARCH DESIGN/
30	RANDOM ALLOCATION/
31	"therapeutic".hw.
32	or/23-31
33	COMPARATIVE STUDY/
34	exp EVALUATION STUDIES/
35	FOLLOW-UP STUDIES/
36	PROSPECTIVE STUDIES/
37	(control* or prospectiv* or volunteer*).tw.
38	or/33-37
39	exp CLINICAL TRIALS AS TOPIC/
40	"clinical trial, phase i".pt.
41	clinical trial, phase i.pt.
42	clinical trial, phase ii.pt.
43	clinical trial, phase iii.pt.
44	clinical trial, phase iv.pt.
45	MULTICENTER STUDIES AS TOPIC/
46	"multicenter study".pt.
47	or/39-46
48	CONTROLLED CLINICAL TRIALS AS TOPIC/
49	controlled clinical trial.pt.
50	(controlled adj3 trial*).kf,tw,ot.

#	Suchen
51	or/48-50
52	humans.sh.
53	(32 or 38 or 47 or 51) and 52
54	22 and 53

5.2.1.6. Updatesuche MEDLINE/Ovid Suchstrategie für klinische Studien der Phasen I, II, III und IV sowie Follow-Up Studien am 29.11.2017 für den Zeitraum 11.01.2017-29.11.2017

Die Updatesuche am 29.11.2017 ergab erneute 482 Treffer. Von diesen werden 37 Publikationen ebenfalls zur Datenextraktion aufgenommen und den Autoren zur Verfügung gestellt.

#	Suchen
1	exp LYMPHOMA, NON-HODGKIN/
2	(non-hodgkin$ or non hodgkin$ or nonhodgkin$ or no hodgkin$ or nhl).tw,kf,ot.
3	(lymph$ adj2 sarcom$).tw,kf,ot.
4	lymphosarcom$.tw,kf,ot.
5	(reticulum adj2 sarcom$).tw,kf,ot.
6	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$)).tw,kf,ot.
7	(lymphom$ adj2 (cleaved$ or noncleaved$ or grad$ or mixed-cell$ or pleomorphic$ or diffus$)).tw,kf,ot.
8	or/1-7
9	indolent*.tw,kf,ot.
10	8 and 9
11	LYMPHOMA, FOLLICULAR/
12	(follicul$ adj2 lymph$).tw,kf,ot.
13	(nodular$ adj2 lymph$).tw,kf,ot.
14	((small$ or large$) adj4 (follicul$ adj2 lymph$)).tw,kf,ot.
15	((low-grad$ or low grad$) adj lymph$).tw,kf,ot.
16	((centro blast$ or zentroblast$) adj (centrocyst$ or zentrozyt$) adj lymph$).tw,kf,ot.
17	(follic$ adj2 (center$ or centro$) adj lymph$).tw,kf,ot.
18	(brill-symmer$ or brill symmer$).tw,kf,ot.
19	*Lymphoma, B-Cell/
20	(indolent$ adj2 lymph$).tw,kf,ot.

#	Suchen
21	or/11-20
22	10 or 21
23	exp CLINICAL TRIAL/
24	(clinical* adj25 trial*).tw.
25	clinical trial.pt.
26	((singl* or double* or trebl* or tripl* or quadrupl*) adj25 (blind* or mask*)).tw.
27	PLACEBOS/
28	placebo*.tw.
29	RESEARCH DESIGN/
30	RANDOM ALLOCATION/
31	"therapeutic".hw.
32	or/23-31
33	COMPARATIVE STUDY/
34	exp EVALUATION STUDIES/
35	FOLLOW-UP STUDIES/
36	PROSPECTIVE STUDIES/
37	(control* or prospectiv* or volunteer*).tw.
38	or/33-37
39	exp Clinical Trials as Topic/
40	"clinical trial, phase i".pt.
41	clinical trial, phase i.pt.
42	clinical trial, phase ii.pt.
43	clinical trial, phase iii.pt.
44	clinical trial, phase iv.pt.
45	MULTICENTER STUDIES AS TOPIC/
46	"multicenter study".pt.
47	or/39-46
48	CONTROLLED CLINICAL TRIALS AS TOPIC/
49	controlled clinical trial.pt.
50	(controlled adj3 trial*).kf,tw,ot.
51	or/48-50
52	humans.sh.

#	Suchen
53	(32 or 38 or 47 or 51) and 52
54	22 and 53
55	limit 54 to ed=20170111-20171129

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5.2.2. Auswahl der Literatur

Die durch die systematische Suche gefundenen Referenzen wurden durch zwei Methodiker unabhängig voneinander auf Relevanz für die vorliegende Leitlinie gescreent. Hierbei wurden systematische Übersichtsarbeiten, sowie Einzelstudien berücksichtigt. Gemäß den Cochrane-Richtlinien wurden Studien nicht ausgeschlossen, in denen vordefinierte Endpunkte nicht berichtet wurden, die aber ansonsten der definierten Fragestellung entsprach.

In einem Arbeitsgruppentreffen im Juni 2017 wurden alle identifizierten Referenzen vorgestellt. Anschließend wurden je Kapitel Online-Meetings vereinbart, in denen die Vollständigkeit der Literatur mit den Arbeitsgruppenleiten geprüft und die Fragestellungen je Kapitel spezifiziert wurden. Studien und systematische Übersichtsarbeiten, die als Volltext publiziert waren und zur Beantwortung einer der Schlüsselfragen beitrugen, wurden folgend in Evidenztabellen extrahiert. Wenn systematische Übersichtsarbeiten gefunden wurden, die zur Beantwortung der Fragestellungen herangezogen werden konnten, wurden diese extrahiert. Die enthaltenden Einzelstudien wurden dann nicht zusätzlich extrahiert. Im Anschluss wurden die Evidenzkörper je Fragestellung nach dem GRADE-Schema bewertet und den Autoren zur Verfügung gestellt.

Entsprechend der Kapitel, für die eine Literaturrechereche durchgeführt werden sollte (Kapitel 2e, 5, 6, 7, 10, 12a), wurden die Referenzen mitsamt pdf-Volltexten in dem Literaturverwaltungsprogramm EndNote in Ordner sortiert. So konnten letztendlich für das Unterkapitel 2e (Prognostische Relevanz in Initial- und Verlaufsdiagnostik von PET CT, CT und MRD) 72 relevante Publikationen identifiziert werden. Die Daten von sechs systematischen Übersichtsarbeiten wurden extrahiert, sowie von 32 Einzelstudien. Dabei ist hier darauf hinzuweisen, dass für dieses Kapitel die Extraktion der bereits in den systematischen Üersichtsarbeiten und Meta-Analysen enthaltenen Einzelstudien explizit vereinbart wurde, da die für die Beantwortung der Schlüsselfragen als ungeeignet eingestuft wurden. Für das Kapitel 5 (Therapie des frühen Stadiums) konnten 42 Referenzen gefunden werden. Davon wurden acht Studien zur Beantwortung der Schlüsselfragen extrahiert. Für Kapitel 6 (Therapie des fortgeschrittenen Stadiums) wurden 106 Referenzen identifiziert. Zur Beantwortung der Schlüsselfragen wurden 6 systematische Übersichtsarbeiten und 21 Einzelstudien herangezogen und extrahiert. Die Suche für Kapitel 7 (Erhaltungstherapie) ergab 95 relevante Referenzen. Extrahiert wurden Daten aus 15 systematischen Übersichtsarbeiten und zehn weitere Einzelstudien. Von den 102 relevanten Referenzen, die für Kapitel 10 (Therapie des Rezidivs) identifiziert wurden, konnten Daten aus neun systematische Übersichtsarbeiten und weiteren 58 Einzelstudien extrahiert werden, die zur Beantwortung der Schlüsselfragen potenziell relevant waren. Die Schlüsselfragen zu den einzelnen neuen Substanzen wurden nach Abstimmung bei der zweiten Konsenuskonferenz zusammengefasst, sodass die Evidenz nicht für einzelne Empfehlungen zugrundegelegt wurde. Für das Unterkapitel 12a (Nachsorge zur Rezidivfrüherkennung) ergab die Suche nach Evidenz zur Beantwortung der Schlüsselfragen keine ausreichende Grundlage. Nach Rücksprache mit den Arbeitsgruppenleitern und der Leitlinienkoordination wurden die Empfehlungen dieses Unterkapitels mittels Expertenenkonsens entwickelt.

5.2.3. Bewertung der Evidenz

Die Bewertung der Evidenz erfolgte nach einem formalisierten Verfahren durch die Methodiker der Klinik 1 für Innere Medizin der Universität Köln (Evidence-based Oncology) entsprechend den Kriterien der EbM. Die in den systematischen

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Suchrecherchen identifizierte Literatur wurde von methodisch tätigen Wissenschaftlern (PD Dr. Nicole Skoetz, Tina Jakob, Marius Goldkuhle) in Evidenztabellen extrahiert, Unstimmigkeiten geklärt, gegebenenfalls unter Hinzuziehung eines dritten Experten.

Die Resultate der Bewertung sind in Kapitel 10 aufgeführt (siehe Thema Initiale Diagnostik, Stadieneinteilung und Verlaufsbeurteilung: 10.1, Therapie der frühen Stadien: 10.2, Zeitpunkt und Wahl der Erstlinientherapie Stadien III und IV: 10.3, Systemische Postinduktions-Therapien in der Erstlinientherapie 10.4, Therapie des Rezidivs: 10.5) in Form von Evidenztabellen zusammenfassend dargestellt und boten die Diskussionsgrundlage zur internen Validität der Studienergebnisse im Hinblick auf die zu beantwortende Frage. Weiterhin wurde die Bewertung des Vertrauens in die Evidenz nach dem GRADE-Systems angewendet, um die jeweils gesamte Evidenz, die einer spezifischen Empfehlung zugrunde liegt, standardisiert und formalisiert zu bewerten.

Die Studien wurden zusammen mit den formal standardisierten Evidenztabellen als Evidenzgrundlage für die Empfehlungen den Experten der Arbeitsgruppen zur Verfügung gestellt.

5.2.3.1. Bewertung des Vertrauens in die Evidenz gemäß GRADE

Die Bewertung der den Empfehlungen zugrundeliegenden Evidenz erfolgte gemäß dem GRADE-Schema [3]. Dazu wurden zunächst die Endpunkte für die jeweilige Fragestellung beim Kick-Off Meeting priorisiert. In die Qualitätsbewertung der Evidenz gehen die als wichtig und patienten-relevant erachteten Endpunkte (sogenannte kritische Endpunkte) ein, für die jeweils das Vertrauen in die zugrundeliegende Evidenz mittels des GRADE-Systems ermittelt wird. Für therapeutische Fragestellungen sind diese Endpunkte insbesondere das Gesamtüberleben, das progressionsfreie Überleben, die Lebensqualität, und akute oder Langzeitnebenwirkungen und die behandlungsbedingte Mortalität.

Zur Abwertung des Vertrauensgrades führen folgende Studien- oder Qualitätscharakteristika [4]:

- Ein nicht-randomisiertes Studiendesign [4]
- Ein potentiell hohes Verzerrungsrisiko des zugrundeliegenden Evidenzkörpers [5]
- Heterogenität oder Inkonsistenz eines Ergebnisparameters in den betrachteten Einzelstudien [6]
- Ein unpräzise geschätzter Effekt mit einem breiten Konfidenzintervall [7]
- Ein Ergebniswert der indirekt auf die Zielpopulation oder den untersuchten Ergebnisparameter zu übertragen ist [8]
- Ein Hinweis auf Publikationsbias [9]

Folgende Charakteristika führten zur Aufwertung der Qualität des zugrundeliegenden Evidenzkörpers [10]

- Eine Dosis-Wirkungsbeziehung
- Ein sehr ausgeprägter Effekt
- Residuelles Confounding

Bedeutung der Evidenzgraduierung gemäß der GRADE Working Group (www.gradepro.org):

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Tabelle 3: Vertrauen in den Evidenzkörper gemäß GRADE

Qualität der Evidenz	Beschreibung	Symbol
Hohe Qualität	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderate Qualität	Wir haben mäßig viel Vertrauen in den Effektschätzer: der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.	⊕⊕⊕⊖
Geringe Qualität	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringe Qualität	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

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5.3. Formulierung der Empfehlungen und formale Konsensusfindung

5.3.1. Schema der Empfehlungsgraduierung

In der Leitlinie wird zu allen Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in der Leitlinie drei Empfehlungsgrade unterschieden (siehe Tabelle6), die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.

Tabelle 4: verwendete Empfehlungsgrade

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Die Empfehlungsgrade berücksichtigen neben der Qualität der Evidenz auch die klinische Relevanz des Ergebnisparameters, das Ausmaß des Effektes und die Übertragbarkeit der Studienergebnisse auf die Patientenzielgruppe und das deutsche Gesundheitssystem. Bei der Empfehlungsgradierung innerhalb dieser Leitlinie wurde nicht der Evidence-to-decision Framework von GRADE angewendet, da dieses aufgrund der nur 2-stufigen Graduierung nicht direkt auf die Leitlinien des Onkologischen Leitlinienprogramms übertragbar ist.

Es wurden zudem Statements zu Fragestellungen gebildet, bei denen keine randomisierten Studien oder heterogene Evidenz vorhanden sind. Diese Statements wurden auf Grundlage von Expertenmeinungen oder Studienergebnissen gebildet und entsprechend der Vorgehensweise bei den Empfehlungen im Rahmen eines formalen Konsensusverfahrens als Statement oder als Expertenkonsens verabschiedet.

5.3.2. Festlegung des Empfehlungsgrades

Grundsätzlich erfolgte eine Anlehnung der evidenzbasierten Empfehlungen hinsichtlich ihres Empfehlungsgrades an die Bewertung des Vertrauens in die Evidenz gemäß GRADE. Hohes Vertrauen in die Evidenz bedeutet in diesem Fall, dass man sich sehr sicher sein kann, dass der wahre Effekt nahe dem Effektschätzer liegt. In solchen Fällen sollen die Empfehlungen in der Regel zu einer starken Empfehlung (Empfehlungsgrad A, „soll“) führen.

Zusätzlich wurden weitere Kriterien bei der Wahl des Empfehlungsgrades berücksichtigt. Diese folgenden berücksichtigten Kriterien konnten zu einem Abweichen der Empfehlungsstärke nach oben oder unten führen:

- Klinische Relevanz der Endpunkte und Effektstärken

Bsp.: Es liegen zwar Studien mit Ergebnissen in eine Richtung vor, jedoch wird die Bedeutung der gewählten Endpunkte und/oder Effektstärken als nicht relevant eingeschätzt.

- Nutzen-Risiko-Verhältnis

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Bsp.: Dem nachgewiesenen Nutzen einer Intervention steht ein relevanter Schadensaspekt gegenüber, der gegen eine uneingeschränkte Empfehlung spricht.

- Ethische Verpflichtungen

Bsp.: Downgrading: Aus ethischen Gründen kann eine Intervention mit nachgewiesenem Nutzen nicht uneingeschränkt angeboten werden. Upgrading: Starke Empfehlung auf Basis von z.B. Fall-Kontroll-Studien, da aus ethischen Gründen ein RCT nicht durchführbar ist.

- Patientenpräferenzen

Bsp.: Eine Intervention mit nachgewiesenem Nutzen wird nicht stark empfohlen, da sie von den Patienten als belastend oder nicht praktikabel abgelehnt wird.

- Anwendbarkeit, Umsetzbarkeit in der Versorgung

Bsp.: Eine Intervention mit nachgewiesenen positiven Effekten kann nicht empfohlen werden, weil sie im regionalen Versorgungssystem aus strukturellen Gründen nicht angeboten werden kann.

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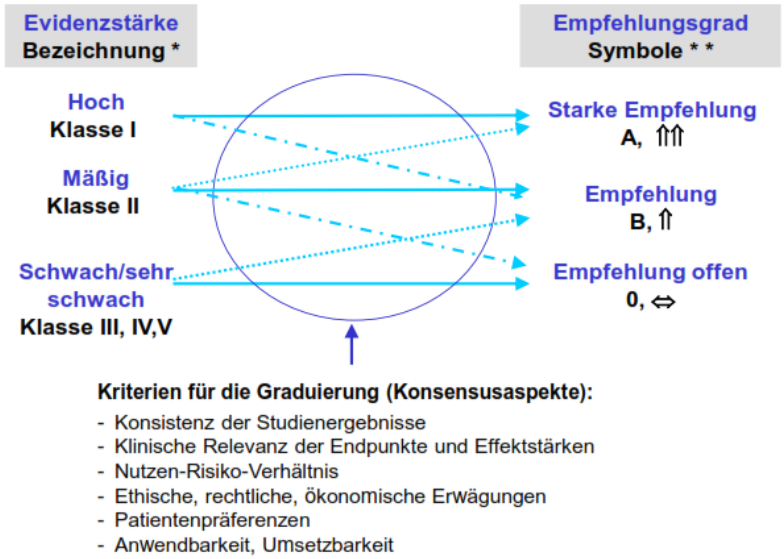
Abbildung 1: Schema zur Darstellung der Kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades.



*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford;
**: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden").

Quelle: modifiziert AWMF-Regelwerk [11]

5.3.3. Formale Konsensusverfahren und Konsensuskonferenz

Die Leitlinienentwicklung für die S3-Leitlinie fand in Anlehnung an die AWMF-Empfehlungen zur Erarbeitung von Leitlinien für Diagnostik und Therapie statt. Im Anschluss an die systematische Recherche wurde das verfügbare Wissen bewertet und über einen strukturierten interdisziplinären Konsens Handlungsempfehlungen abgeleitet. Der Prozess der Konsensusfindung wurde unter Beratung und Mitwirkung von zwei neutralen, in den Konsensustechniken geschulten und erfahrenen Moderatoren geführt. Eingesetzt wurden Techniken des nominalen Gruppenprozesses und der formalen Konsensuskonferenz.

Es fanden zwei Präsenz Konsensus Konferenzen statt. Im Vorfeld zu beiden Konferenzen wurden Online Abstimmungen durchgeführt und deren Ergebnisse den Teilnehmern im Vorfeld der Präsenz Treffen zur Verfügung gestellt.

Jeder schriftlich von der teilnehmende Fachgesellschaft / AG innerhalb der DKG sowie DLH ernannte Mandatsträger erhielt im Konsensusverfahren eine Stimme.

Ausschließlich die benannten Mandatsträger waren in den Abstimmungsprozessen stimmberechtigt. Die übrigen Mitglieder der Steuergruppe und hinzu geladene Experten hatten lediglich beratende Funktion und waren nicht stimmberechtigt.

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Eine Empfehlung galt ab einer Zustimmung von mindestens 75% als angenommen. Ab einer Zustimmung von mindestens 95% wurde der Konsens als starker Konsens bezeichnet. Siehe hierzu auch Tabelle 7.

Tabelle 5: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	>95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 – 75% der Stimmberechtigten
Dissens	<50% der Stimmberechtigten

5.4. Ablauf des Prozesses

5.4.1.1. Leitliniensteuergruppenmeeting 14.06.2016 / 17.11.2016 in München

Teilnehmer siehe Anhang 15.2

Das erste Leitliniensteuergruppenmeeting fand am 14.06.2016 in München statt. Hierbei wurde die Leitliniensteuergruppe von Professor Dr. W. Hiddemann über das Projekt informiert und die grundsätzliche Planung (Auswahl der an der Leitlinienerstellung beteiligten Organisationen, geplante Gliederung, Zeitplan) besprochen. Es wurde die methodische Begleitung und Übernahme der systematischen Recherche durch die Arbeitsgruppe Evidence-based Oncology, geleitet von Frau PD Dr. N. Skoetz, besprochen.

Im zweiten Leitliniensteuergruppenmeeting am 17.11.2016 in München wurden die Rückmeldungen der angeschriebenen Organisationen besprochen und die Vollständigkeit der beteiligten Organisationen diskutiert. Zur Vorbereitung des Kick-Off-Meetings wurden Schlüsselfragen entworfen, die Art der Bearbeitung diskutiert und der Zeitplan angepasst.

5.4.1.2. Kick-Off Meeting 08.02.2017 in München

Teilnehmer siehe Anhang 15.2

Das Kick-Off Meeting wurde von Herrn Prof. Dr. W. Hiddemann geleitet, aufgrund von Flugausfällen in Berlin konnten Herr T. Langer (Deutsche Krebsgesellschaft) und Frau Dr. M. Nothacker (AWMF) kurzfristig nicht teilnehmen. Herr Hiddemann stellte das Onkologische Leitlinienprogramm der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V. (AWMF), der Deutschen Krebsgesellschaft e.V. (DKG) und der Deutschen Krebshilfe vor. Hiernach wurden die Leitliniensteuergruppe der Leitlinie und die zur Mitarbeit eingeladenen Fachgesellschaften, Arbeitsgemeinschaften innerhalb der AWMF und der Krebsgesellschaft und sonstiger Organisationen vorgestellt und von den Teilnehmern bestätigt.

Frau PD Dr. N. Skoetz erläuterte die Methodik zur Leitfragenerstellung, die Syntax der Empfehlung, sowie die systematische Recherche und den Expertenkonsens.

Es wurden die Gliederung und Leitfragen durch Herrn Prof. Dr. W. Hiddemann präsentiert. Nach Diskussion und Ergänzungen wurden die Leitfragen verabschiedet, 37

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Leitfragen sollten als Experten Konsens beantwortet werden und für 16 Leitfragen sollte eine systematische Recherche durchgeführt werden.

Es wurden für jedes Kapitel eine Arbeitsgruppe mit Arbeitsgruppenleitern gegründet (siehe 4.1).

Herrn Prof. Dr. W. Hiddemann stellte den AWMF Leitfaden zum Umgang mit potentiellen Interessenkonflikten vor. Das durch die Leitliniensteuergruppe beschlossenen Prozedere, eine Kommission zur Bewertung der potentiellen Interessenkonflikte zu gründen, wurde angenommen. Weiterhin wurde beschlossen zum Ausschluss einer Beeinflussung des Abstimmungsergebnisses durch potentielle Interessenkonflikte bei den Konsensuskonferenzen, bei Empfehlungen bei denen ein potentieller Interssenkonflikt entstehen könnte, eine Doppelabstimmung (mit Stimmberechtigten mit moderaten Interessenkonflikten und ohne) durchzuführen (siehe auch 8).

Der weitere Zeitplan wurde festgelegt und ein Autorentreffen für den 30.06.2017 beschlossen.

5.4.1.3. Autorentreffen 30.06.2017 in München

Teilnehmer siehe Anhang 15.2

Das Autorentreffen wurde von Frau PD Dr. N. Skoetz geleitet. Frau PD Dr. N. Skoetz erläuterte den Ablauf der Erstellung von evidenzbasierten / Experten Konsens Empfehlungen, sowie die Schritte der Hintergrundtexterstellung und Literaturverweise mit Datenbanken. Im Anschluss erfolgte eine Diskussion mit den Teilnehmern zu der praktischen Anwendung bei der Leitlinienerstellung. Es wurde eine Erstellung der Kapitel Entwürfe bis 04/18 beschlossen.

5.4.1.4. Leitliniensteuergruppen-Kapitelleiter Meeting 02./03.05.2018 in München

Teilnehmer siehe Anhang 15.2

Das Treffen wurde von Herrn Prof. Dr. W. Hiddemann geleitet. Im Vorfeld des Treffens waren die Kapitelentwürfe in den Arbeitsgruppen erstellt worden und diese den Teilnehmern zur Verfügung gestellt worden. Die Kapitelleiter stellten ihre Kapitel vor, es folgte eine Diskussion durch alle Anwesenden. Frau PD Dr. N. Skoetz und Frau T. Jakob waren am 03.05.18 anwesend, um methodische Fragen zu diskutieren. Es wurde eine methodische Checkliste zur Anpassung der Kapitel für die Autoren erstellt und eine Fertigstellung bis August 2018 beschlossen, um im Vorfeld der Konsensuskonferenz eine Online Abstimmung durchführen zu können.

5.4.1.5. Erste Online Vorabstimmung 30.09.2018- 25.10.2018

In der ersten Online Vorabstimmung wurden aus allen Kapiteln der Leitlinie durch das OL- Office der DKG die Empfehlungen extrahiert und in das online Portal surveymonkey® zur Abstimmung und Kommentierung eingestellt. Allen Teilnehmern wurden alle Kapitel in Gänze zur Verfügung gestellt. Alle Teilnehmer der Leitlinie wurden über die Online Abstimmung informiert und um Abstimmung und Kommentierung der Empfehlungen gebeten. In der Folge waren die Empfehlungen 14 Tage für die online Abstimmung verfügbar. Hierbei hatten alle beteiligten Fachexperten, die Möglichkeit den Empfehlungsvorschlägen zuzustimmen oder diese abzulehnen und Verbesserungsvorschläge einzubringen. Nach Ende der Online Vorabstimmung wurden alle Kommentare extrahiert und alle Abstimmungsergebnisse ausgewertet. Von 29 Mandatsträgern hatten 28 (nicht abgestimmt: Mandatsträgerin der KOK) über alle

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Empfehlungen abgestimmt. Hieraus wurde eine Zusammenfassung generiert, die die Prozentzahl der Zustimmung und alle Kommentare enthielt. Diese wurde den Arbeitsgruppen zur Verfügung gestellt um zur Konsensus Konferenz Vorschläge zur Umformulierung der Empfehlung / Erwiderungen zu den Kommentaren zu formulieren.

5.4.1.6. Erste Konsensus Konferenz 16.11.2018 in München

Teilnehmer siehe Anhang 15.2

Die Moderation erfolgte durch Herrn Dr. M. Follmann (DKG) und Frau Dr. M. Nothacker (AWMF). Wie auf dem Kick-Off Treffen vereinbart, wurde beschlossen eine Doppelabstimmung (mit Enthaltung bei potenziellem Interessenkonflikt der Mandatsträger und ohne Enthaltung) durchzuführen. Es gab keine Gegenstimme gegen dieses Vorgehen, die Teilnehmer wurden einzeln über die Empfehlungen, bei denen ein potenzieller Interessenkonflikt bestehen könnte, informiert. Frau Dr. M. Nothacker stellte die Empfehlungsgraduierung und die strukturierte Konsensfindung für AWMF-Leitlinien dar und erläuterte den Abstimmungsprozesses der KK.

Unter der Moderation von Herrn Dr. M. Follmann und Frau Dr. M. Nothacker wurden die Empfehlungen, die in der Online Vorabstimmung weniger als 95% Zustimmung der Mandatsträger erhalten hatten oder zu der ein inhaltlicher Kommentar abgegeben wurde unter Anwendung des Prozederes zur Strukturierten Konsensfindung diskutiert und abgestimmt.

Empfehlungen, die in der Online-Vorabstimmung einen starken Konsens erreicht hatte und zu der es keinen inhaltlichen Kommentar gab, wurden – sofern es keine Einwände von den anwesenden Personen gab - als formal angenommen gewertet. Wenn Einwände formuliert wurden, erfolgte die Diskussion und Abstimmung unter Anwendung des Prozederes zur Strukturierten Konsensfindung.

Eine Empfehlung galt in der Konsensuskonferenz ab einer Zustimmung von mehr als 75% als angenommen. Ab einer Zustimmung von mehr als 95% wurde der Konsens als starker Konsens bezeichnet.

Der Konsensusprozess während der Konferenz fand wie folgt statt:

- Vorstellung der vorgeschlagenen Empfehlung inkl. des Hintergrundes ihrer Ent-wicklung im Rahmen der AGs, der Evidenzgrundlage und der Begründung des Empfehlungsgrades durch die jeweiligen AG-Leiter/Fachexperten;
- Rückfragen und Diskussion durch das Plenum mit ggf. Einbringen von neuen Vorschlägen bzw. Änderungen (alle Kommentare aus der Online-Vorabstimmung waren sichtbar in der Präsentation aufgeführt);
- Abstimmung im anonymen Verfahren mittels TED-Systems;
- Bei fehlendem Konsens: Fortführung der Diskussion und erneute Abstimmung.

Unter Anwendung des vereinbarten Umgangs mit Interssenkonflikten, erfolgte eine Doppelabstimmung im Kapitel „Therapie des Rezidivs“, die keinen Einfluss auf das Ergebnis hatte.

Im Kapitel Supportivtherapie, Palliativmedizin und Komplementärmedizin, Empfehlung „Betroffene, die am follikulären Lymphom erkrankt sind, sollen unabhängig vom Krankheitsstadium Zugang zu Informationen über Palliativversorgung (z.B. Auslage von Flyern) haben“ lag die Zustimmung der Online Vorabstimmung der Mandatsträger bei 88%. In der vor Ort Diskussion konnte sich die Leitliniengruppe nicht auf eine Übernahme in diese Leitlinie einigen. Der Vertreter der Deutschen Gesellschaft für Palliativmedizin

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erläuterte die Empfehlung auf Basis der gleichlautenden Empfehlung in der S3 Leitlinie Palliativmedizin für Patienten mit einer nicht-heilbaren Krebserkrankung (AWMF-Registernummer 128/001OL) ausführlich. Insbesondere durch die beiden anwesenden Patientenvertreter wurde eine Verunsicherung der Patienten bezüglich des zu erwartenden Krankheitsverlaufes durch eine ausdrückliche Empfehlung auf einfachen Zugang zu Informationen zu palliativmedizinischen Behandlungs- und Versorgungsmöglichkeiten befürchtet.

Nach ausführlicher Diskussion wurde der Übernahme der Originalempfehlung der Querschnittsleitlinie in die vorliegende Leitlinie nicht mehrheitlich zugestimmt. Der Aufnahme in den Hintergrundtext wurde im Konsens (80% Zustimmung) zugestimmt.

Nach Abstimmung aller Empfehlungen, die in der ersten Online Vorabstimmung unter 95% Zustimmung erhalten hatten, wurde dasweitere Prozedere mit einer erneuten Online Vorabstimmung gefolgt von einer 2. Konsensus Konferenz festgelegt.

5.4.1.7. Zweite Online Vorabstimmung 10.01.2019- 27.01.2019

In der Vorbereitung zur zweiten Online Vorabstimmung erstellten die Arbeitsgruppen eine überarbeitete Version der verbliebenen Empfehlungen, die zwar über 95% Zustimmung in der ersten Online Vorabstimmung erhalten hatten aber inhaltlich kommentiert worden waren. Die Kommentare aus der ersten Online Vorabstimmung wurden hierbei entweder einzeln beantwortet oder ein Fazit zu den Kommentaren in Summe erstellt. Diese überarbeitete Version der Empfehlungen wurde allen Teilnehmern zur zweiten Online Abstimmung zur Verfügung gestellt.

Durch das OL-Office der DKG wurden die Empehlungen in das Online Portal surveymonkey® zur Abstimmung und Kommentierung eingestellt. Alle Teilnehmer der Leitlinie wurden über die Online Abstimmung informiert und um Abstimmung und Kommentierung der Empfehlungen gebeten. In der Folge waren die Empfehlungen für mindestens 14 Tage in der online Abstimmung verfügbar. Hierbei hatten alle beteiligten Fachexperten, die Möglichkeit den Empfehlungsvorschlägen zuzustimmen oder diese abzulehnen und Verbesserungsvorschläge einzubringen. Nach Ende der Online Vorabstimmung wurden alle Kommentare extrahiert und alle Abstimmungsergebnisse ausgewertet. Von 29 Mandatsträgern hatten 26 über alle Empfehlungen abgestimmt (nicht abgestimmt: Mandatsträgerin der KOK, Mandatsträger der Deutsche Gesellschaft für klinische Chemie und Laboratoriumsmedizin, Mandatsträger AG Radiologische Onkologie). Hieraus wurde eine Zusammenfassung generiert, die die Prozentzahl der Zustimmung und alle Kommentare enthielt. Diese wurde den Arbeitsgruppen zur Verfügung gestellt um zur Konsensus Konferenz Vorschläge zur Umformulierung der Empfehlung / Erwiderungen zu den Kommentaren zu formulieren.

5.4.1.8. Zweite Konsensus Konferenz 22.02.2019 in München

Teilnehmer siehe Anhang 15.2

Im Rahmen der zweiten Konsensus Konferenz wurden alle verbliebenden Empfehlungen unter der Moderation von Herrn Dr. M. Follmann und Frau Dr. M. Nothacker konsentiert. Dabei wurde der Konsensusprozess analog der ersten Konsensus Konferenz angewandt. Unter Anwendung des vereinbarten Umgangs mit Interessenkonflikten, erfolgte bei vier Empfehlungen im Kapitel „Therapie des Rezidivs“ eine Doppelabstimmung, woraus sich bei einer Empfehlung die Konsenstärke änderte (93% Zustimmung bei der Abstimmung mit Enthaltung der Mandatsträger mit potentiellem Interesenkonflikt, 96% Zustimmung bei der Abstimmung mit allen Mandatsträgern). Im Vorfeld der zweiten Konsensus Konferenz erreichte die Leitlinienkoordination eine Einlassung des KCO zu ausgesuchten

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konsentierten Empfehlungen der ersten Konsensus Konferenz. Die Einlassung des KCO wurde allen Teilnehmern der Leitlinie zur Verfügung gestellt. Unter der Moderation von Frau Dr. M. Nothacker diskutierte der Vertreter der KCO ebendiese Empfehlungen mit allen Anwesenden. Nach der Diskussion wurde eine erneute Abstimmung über die bereits konsentierten Empfehlungen durch die Mandatsträger abgelehnt.

5.4.1.9. Schlussredaktion und Review

Im Anschluss an die zweite Konsensus Konferenz wurden die Kommentare aus den Konferenzen und Online Abstimmungen zur Ergänzung von Hintergrundtexten oder redaktionellen Anpassungen an die jeweiligen Arbeitsgruppen versandt und innerhalb der Arbeitsgruppen finalisiert. Anschließend wurden die Kapitel zum Review an die Zuständigen der DKG, AWMF, DGHO und der Arbeitsgruppe Evidence-based Oncology übergeben. Nach dem Erhalt der Rückmeldungen wurden inhaltliche Kommentare an die betroffenen Kapitelleitern und Autoren weitergeleitet und dadurch entstehende Anpassungen aufgenommen.

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6. Ableitung der Qualitätsindikatoren

Im Rahmen des Leitlinienprogramms Onkologie werden Qualitätsindikatoren in einem standardisierten Prozess aus den Empfehlungen der Leitlinien abgeleitet. Die detaillierte Beschreibung der Methodik findet sich auf der Homepage des Leitlinienprogramms Onkologie [12].

Die Generierung der Qualitätsindikatoren wurde in folgenden Schritten durchgeführt.

6.1. Bestandsaufnahme

Bei der Suche nach bereits definierten internationalen und nationalen Qualitätsindikatoren außerhalb des OL-Verfahrens erfolgte eine Einschränkung des Suchzeitraums: 01.01.2009 bis 24.04.2019. Es erfolgte keine Einschränkung der Sprache.

Die Suche wurde in folgenden Quellen durchgeführt:

- Literaturdatenbanken: Medline über https://www.ncbi.nlm.nih.gov/ & Cochrane über http://www.cochranelibrary.com/
- Webseiten von nationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Webseiten von internationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Internetrecherche via www.google.de

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und sind in der Anlage 1 aufgeführt.

Die Recherche führte zu einer Reihe internationaler Qualitätsindikatoren, die ebenfalls in dem Dokument zusammengefasst wurden (siehe Kapitel).

6.2. Vorbereitung Anwesenheitstreffen (Erstellung einer Primärliste potenzieller Qualitätsindikatoren)

Soweit möglich, wurden im Vorfeld des Anwesenheitstreffens (siehe 1.3) aus den starken Empfehlungen der Leitlinie (n= 53) potenzielle Indikatoren mit Definition von Zähler und Nenner abgeleitet. Diese Liste und das Dokument mit den internationalen Qualitätsindikatoren wurden den Mitgliedern der Arbeitsgruppe im Vorfeld des Anwesenheitstreffens zugesandt.

6.3. Anwesenheitstreffen (Diskussion und primäre Sichtung)

Das Treffen der Arbeitsgruppe Qualitätsindikatoren (AG QI), die aus Mitgliedern der Leitliniengruppe und je einem Vertreter der klinischen Krebsregister, des Zertifizierungssystems und des OL bestand, fand am 07.05.2019 statt. In dem Treffen wurde den Teilnehmern der Prozessablauf der Erstellung von Qualitätsindikatoren sowie das Bewertungsinstrument des OL erläutert. In dem Treffen wurde die unter 1.2 generierte Zusammenstellung aus den weiteren starken Empfehlungen der Leitlinie und den internationalen Qualitätsindikatoren diskutiert und entschieden, ob aus der

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jeweiligen Empfehlung ein potenzieller Qualitätsindikator generiert werden könne. Folgende Ausschlusskriterien kamen bei diesem ersten Screening zur Anwendung.

Tabelle 6: Gründe für einen Ausschluss der Empfehlung aus der Liste der potenziellen Qualitätsindikatoren

Nr.	1	2	3	4
Begründung	Empfehlung ist nicht operationalisierbar (Messbarkeit nicht gegeben)	Fehlender Hinweis auf Verbesserungs potenzial	Fehlende Verständlichkeit u/o großer Erhebungsaufwand in Verhältnis zu Nutzen	Sonstiges (mit Freitexteingabe in Liste der Empfehlungen)

Die Diskussion und primäre Sichtung ergab ein Set von drei potenziellen Qualitätsindikatoren.

6.4. Bewertung

Die potenziellen Qualitätsindikatoren wurden mit dem Bewertungsinstrument des Leitlinienprogramms Onkologie durch die Mitglieder der AG QI bewertet. Jeweils mit dem unten abgebildeten Bogen erhielten die Bewertenden seitens der Krebsregister und des Zertifizierungssystems der DKG für den Indikatorvorschlag die Informationen zur Datenverfügbarkeit. Angenommen wurden die Qualitätsindikatoren, bei denen mind. 75% der Teilnehmer die Kriterien 1,2,3 und 5 mit „Ja“ und das Kriterium 4 mit „Nein“ bewertet haben. Die Auswertung dieser Abstimmungen erfolgte durch einen Methodiker, der nicht am Qualitätsindikatoren-Entwicklungsprozess teilgenommen hatte.

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Tabelle 7: Bewertungsinstrument des Leitlinienprogramms Onkologie

QI-Nr.	Möglicher Qualitätsindikator		Empfehlung	Angaben der S3 Leitlinie im Hinblick auf a) Qualitätsziel und b) Evidenzgrundlage
1.	Z			
	N			
Information zur Datenverfügbarkeit (Stand 06/2019**):** **[dies wird von den Registern und den Zentren ausgefüllt]** Die Erfassung ist seitens der Klinischen Krebsregister über den einheitlichen Onkologischen Basisdatensatz und seiner Module gewährleistet: ja / nein Die Erfassung ist Teil des Zertifizierungssystems der DKG: ja / nein Ggf. welche Ergänzungen wären erforderlich?				
			Nein	**Ja**
Kriterium: Der Qualitätsindikator erfasst für den Patienten relevante Verbesserungspotenziale.				
Kriterium: Der Indikator ist klar und eindeutig definiert.				
Kriterium: Der Qualitätsindikator bezieht sich auf einen Versorgungsaspekt, der von den Leistungserbringern beeinflusst werden kann.				
Kriterium: Gibt es Risiken zur Fehlsteuerung durch den Indikator, die nicht korrigierbar sind?				
Kriterium: Die Daten werden beim Leistungsbringer routinemäßig dokumentiert oder eine zusätzliche Erhebung erfordert einen vertretbaren Aufwand				

Zusätzlich bestand die Möglichkeit, zu den im Folgenden genannten Kriterien Kommentare abzugeben:

	Kommentar
Risikoadjustierung Können spezifische Merkmale von Patienten z.B. Alter, Komorbidität oder Schweregrad der Erkrankung die Ausprägung des QI beeinflussen?	
Implementierungsbarrieren Gibt es Implementierungsbarrieren, die es zu beachten gilt?	

6.5. Telefonkonferenz

Nach der schriftlichen Bewertung erfolgte am 29.05.2019 eine moderierte Telefonkonferenz, in der die Ergebnisse der Bewertung diskutiert wurden. Auf Basis der Bewertungen und der Diskussion wurde ein finales Set von drei Qualitätsindikatoren konsentiert.

Die Primärliste der potenziellen Qualitätsindikatoren inklusive der Ausschlussgründe, die o.g. Zusammenstellung der internationalen Qualitätsindikatoren und die Ergebnisse der schriftlichen Bewertung sind auf Anfrage im Leitliniensekretariat oder Office des Leitlinienprogramms Onkologie erhältlich.

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7. Reviewverfahren und Verabschiedung

Die Leitlinie kann im Rahmen einer 6-wöchigen Konsultationsphase durch die (Fach)Öffentlichkeit kommentiert werden. Weiterhin wird die formale Zustimmung der beteiligten Fachgesellschaften zur Publikation der Leitlinien eingeholt. Die Ergebnisse des Konsultationsverfahren werden bei Publikation der Version 1.0. an dieser Stelle detailliert beschrieben.

8. Unabhängigkeit und Umgang mit Interessenkonflikten

Der Umgang mit Interessenkonflikten bei der Leitlinienerstellung ist im Kapitel 2.2.5. der Langversion beschrieben. Die von den beteiligten Personen offengelegten Interessenkonflikterklärungen sind in Kapitel 14.5 aufgeführt.

9. Verbreitung und Implementierung

Die Leitlinie wird nach Abschluss des Konsultationsverfahrens in den in Kapitel 1 genannten und näher dargestellten Formaten publiziert werden:

- Kurzfassung in deutscher Sprache
- Langfassung in deutscher Sprache
- Patientenleitlinie
- Leitlinienreport
- OL-App

Alle genannten Formate der Leitlinie werden über die Internetseiten der folgenden Gesellschaften und Organisationen verfügbar sein:

- AWMF (www.leitlinien.net),
- Leitlinienprogramm Onkologie (http://www.leitlinienprogramm-onkologie.de/OL/leitlinien.html),
- „Guidelines International Network“ (www.g-i-n.net)

Intensive Öffentlichkeitsarbeit mittels Beiträgen in Fachzeitschriften, Buchbeiträgen, Vorträgen auf Kongressen, Symposien, Schulungen und Fortbildungen wird die Verbreitung und Implementierung der Leitlinie unterstützen.

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10. Evidenztabellen und Bewertung der Evidenz mittels GRADE Methodik

10.1. Kapitel 4 Initiale Diagnostik, Stadieneinteilung und Verlaufsbeurteilung

10.1.1. Evidenztabellen

10.1.1.1. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
[13]	**A systematic review Database:** PubMed/MEDLINE (from inception to March 20, 2015) **Inclusion criteria:** Original studies reporting on prognostic value of interim or end-of-treatment FDG-PET in indolent follicular lymphoma during or after first-line therapy **Exclusion criterias**	**Interim and end-of-treatment** PET/CT in follicular lymphoma	1. To systematically review published data on the prognostic value of in- terim and end-of-treatment FDG-PET in follicular lymphoma **2. PFS** 3. **OS**	**1. Included studies:** 8 studies (2 prospective, 6 retrospective) **2. Results** • **Interim FDG-PET PFS** 2 of 3 studies: No significant difference in PFS between PET /CT positive and negative patients 1 of 3 studies: FDG-PET positive patients have significantly worse PFS than FDG-PET negative patients • **Interim FDG-PET OS** 2 of 3 studies: No significant difference in OS between FDG-PET positive & negative patients • **End of treatment FDG-PET PFS** 5 of 6 studies: FDG-PET	Systematic Review 2a 1. **N** = N/A **2. Bias:** • High risk for domains of study participation & confounding in 1 study • High risk for domain of prognostic factor measurement in 4 studies • Moderate risk for domain of prognostic factor measurement in 3 studies • High risk for outcome measurement in 8 studies 3. **Rando:** N/A 4. **Blinding:** N/A	Lu et al. 2014 *(Ann Nucl Med)* Luminari et al. 2014 *(Ann Oncol)* Zinzani et al. 2013 *(Am J Hematol)* Dupuis et al. 2012 *(J Clin Oncol)* Trotman et al. 2011 *(J Clin Oncol)* Le Dortz et al. 2010 *(Eur J Nucl Med Mol Imaging)* Bishu et al. 2007 *(Leuk Lymphoma)*

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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	• Language restrictions, guidelines, letters, editorials, meta analyses, conference abstracts • N < 10 • studies including patients with refractory disease • studies with patients receiving second-line therapy studies with tailored therapy on the basis of the interim or end-of-treatment PET/CT result			positive patients significantly worse PFS than FDG-PET negative patients 1 of 6 studies: No significant difference in PFS between positive & negative FDG-PET patients • **End of treatment FDG-PET OS** 3 of 4 studies: PET/CT positive patients have significantly worse OS than PET/CT negative patients.	5. **Follow-up:** N/A 6. **Financing:** Alpe d'HuZes/Dutch Cancer Society Bas Mulder Award for T.C.K. (grant number 5409). **Methodological Flaws:** No numbers given for results	Zinzani et al. 2007 *(Clin Lymphoma Myeloma)*
[14]	Search: MEDNLINE/PubMed April 2015 Inclusion Criteria: original studies on topic, **newly diagnosed FL** (exclusion if: less than 10 pts FL or no FL-subgroup results or refractory or only FDG-PET without control)	Additional value of FDG-PET to CT in Staging (Ann Arbor and FLIPI) BMB+CT vs. BMB+FDG-PET Or CT vs PET/CT Or	Changes in Stage (Ann Arbor or FLIPI)	Included studies: 7; N=349 Results: FGD-PET induced Changes in Ann Arbor Stage 18,7 % (95% CI 10,8%-40,4%) No FGD-PET-induced changes in FLIPI score reported Heterogeneity: I2=75.5% with regard to the proportion of pts with FDG-PET-induced changes in Ann Arbor stage	**SR&MA, 2a** **Study quality:** "overall studies of very poor quality, with lack of histological verification of additionally detected lesions at FDG-PET" "1 study exclusively included pts with CT-based limited no bulky stage I&II disease" ***About this Review:*** No report of double screening or double data extraction; probably biased by subjective judgment	• Cho 2015 Kaohsiung J Med Sci • Luminari 2013 Ann Oncol • Le Dortz 2010 Eur J Nucl Med Mol Imaging • Ngeow 2009 Ann Oncol

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
		Clinical examination + BMB + CT vs. the same + FDG-PET (one study: Clinical examination + x-ray + rhinoscopy + gastroscopy + BMB + CT vs. the same + FDG-PET)			**Randomization:** not reported **Blinding:** one reported it as yes, others unclear or no **Financing:** Supported by an Alpe d'HuZes/Dutch Cancer Society Bas Mulder Award for T.C.K. (grant number 5409). Data collection, data analysis, interpretation of data, writing of the article, and decision to submit were left to the authors' discretion and were not influenced by Alpe d'HuZes/Dutch Cancer Society. The authors declare no conflict of interest. Bias of included studies: high or unknown	• Janikova 2008 Clin Lymphoma Myeloma • Wirth 2008 Int J Radiat Oncol Biol Phys Karam 2006 Cancer
[15]	N=185 pts with **FL, with high tumor burden 92% advanced stages** 37% FLIPI score: 3-5 31% FLIPI2 score: 3-5	Prognostic value of total metabolic tumor volume (TMTV) measured at baseline with PET/CT and it's added value to existing clinical prognostic models TMTV was obtained by summing the metabolic volumes	prognostic impact of the TMTV measured with PET/CT OS PFS	• Overall: 5y PFS: 55% • Overall OS: 92% • Median TMTV 297cm3 • optimal cutoff identified was **510 cm³**, with a markedly inferior survival in the **29% of patients with TMTV >510 cm³**: ○ **5y PFS** was 33% vs. 65% (HR=2.9; P<0.001) ○ **5y OS** was 85% vs. 95% (HR=3.45; P<0.010)	**Pooled analysis of 3 multicenter studies,** **Retrospective** **2a** **Median follow up: 64 months** **Randomization:** not applicable **Blinding:** two nuclear medicine physicians blinded to patient outcome computed TMTV	Salles 2011 Lancet Federico 2013 J Clin Oncol Dupuis 2012 J Clin Oncol

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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
		of all local (L) nodal and extranodal lesions Total metabolic tumor volume computed by using 41% maximum standardized uptake value thresholding method; optimal cutoff for survival prediction was determined (intervention: immunochemotherapy)		• TMTV (HR=2.3; P< 0.001) and FLIPI2 (HR=2.2; P<0.002) were independent predictors of PFS bone marrow involvement on biopsy and b2-microglobulin level were prognostic of PFS but not OS	**Financing:** some authors reported different sources of pharmaceutical funding Disclosures provided by the authors are available with this article at www.jco.org. **Methodological Flaws:** no systematic search was conducted, data from 3 existing and known studies were taken	
[16]	**Database:** Ovid-MEDLINE & EMBASE (from inception to February 28, 2012) **Inclusion criteria** • Patients with follicular lymphoma who underwent **end-therapy PET** after chemo • All observational studies (retrospective or prospective) and clinical trials with survival analysis data such as HR or	Predictive value of FDG-PET in predicting outcome of follicular lymphoma after chemo	1. To quantitatively compare the predictive value of **PET/CT & CT in PFS** of patients	1. **Included studies:** 8 studies 2. **Results** • **End therapy PET /CT PFS** Pooled HR patients with positive vs negative PET 5.1 (95% CI, 3.7– 7.2) • **End therapy CT PFS** Pooled HR patients with positive vs negative CT 2.6 (95% CI 1.2-5.8) • **PET based response** Pooled complete remission rates 75% (95% CI, 70-79%) • **CT based response** Pooled complete remission rates 63% (95% CI, 53-73%)	A Systematic Review and Meta-analysis 2a (retrospective and prospective analysis) 1. **N** = 577 2. **Bias**: No publication bias in the included studies 3. **Rando:** N/A 4. **Blinding:** N/A 5. **Follow-up:** not reported **Financing:** No potential conflicts of interest were disclosed by all authors.	Bishu et al. 2007 *(Leuk Lymphoma)* Dupuis et al. 2012 *(J Clin Oncol)* Janikova et al. 2008 *(ClinLymphoma Myeloma)* Le Dortz et al. 2010 *(Eur J Nucl Med Mol Imaging)* Lopci et al. 2010 *(Ann Oncol)* Lopci et al. 2012 *(Eur J Nucl Med Mol Imaging)*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Kaplan –Meier curves **Exclusion criterias** • Case reports, case series, review articles, editorials, letters, comments, conference abstracts • Studies with insufficient survival analysis & without specific follicular lymphoma data			• **Heterogeneity** No substantial heterogeneity (I^2 = 0%; P = 0.438, Q test)	The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact	Trotman et al. 2011 *(J Clin Oncol)* Zinzani et al. 2007 *(Clin Lymphoma Myeloma)*
[17]	Pooled analysis (3 multicenter prospective studies) **Duration:** • Dec 24, 2004 – Sept 22, 2010 **Inclusion Criteria:** • patients with PET done up to 3 months after the last dose of induction R (with/without chemo) • FL pts with high tumor burden	Prognostic value of post-induction PET/CT and confirm primary role of PET/CT response assessment in FL PET/CT scans defined as positive by a 5 point Deaville score of 4 (“FDG update moderately higher than uptake in the liver”) or higher (complementary analyses with 5 point Deauvilee score of 3 = positive PET was done)	Primary: 1. PFS 2. OS (in accordance with PET/CT status 4 or greater) Secondary: 1. PFS 2. OS (in accordance with PET/CT status 3 or greater)	**1. Included studies:** 439 patients enrolled in 3 studies (but some not eligible for this analysis) • 41(17%) of 246 patients positive post-induction PET scan (according to 4 point or higher 5 point Deauville scale) **2. Results** (PET/CT cutoff at 4 pf 5 point Deauville score) **PFS** • At median follow up: 16.9 months (95% CI 10.8–31.4) for patients with a positive PET scan versus 74.0 months (54.7–not reached) for those with a negative - PET scan HR (Patients with positive PET vs	1. **Pooled analysis (3 multicenter prospective studies)** **2a** 2. **Rando:** not applicable 3. **Blinding:** assessment by 3 masked reviewers 4. **Follow-up:** 54.8 months (IQR 39.7-68; range 7.7-90.1) 5. **Financing:** Grouped’Etude des Lymphomes de l’Adulte (Paris, France), now LYSA (Lymphoma Study Association), Direction de la Recherche Clinique de l’Assistance Publique–Hôpitaux de Paris, Fondazione Italiana Linfomi, & Italian Ministry of Health.	Salles et al. 2011 *(Lancet)* Dupuis et al. 2012 *(J Clin Oncol)* Federico et al. 2013 *(J Clin Oncol)*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
		Baseline pt and disease characteristics (FLIPI and FLIPI2 prognostic) + conventional staging and response assessment + survival data were obtained for all pts		Negative PET) 3.9 (95% CI 2.5-5.9 ; p<0.0001) • PFS at 4 years: Patients with positive PET 23.2% (95% CI 11.1-3.9), Patients with negative PET 63.4% (95% CI 55.9-70). P-value (p<0.0001) **OS** • HR 6.7 (2.4-18.5; p = 0.0002) • OS at 4 years: Patients with positive PET 87.2% (95% CI 71.9-94.5), Patients with negative PET 97.1% (95% CI 93.2-98.8). P-value (p<0.0001) Conventional CT-based response (ie, complete response or unconfirmed complete response vs partial response) was weakly predictive of progression-free survival (HR 1・7 [95% CI 1・1–2・5]; p=0・017)	Members of the funding cooperative groups participated in study design, data collection, data analysis, data interpretation, and writing of the report Statisticians (SB and LM) had full access to the raw data from all three studies contributing to this pooled analysis and all authors had access to the data and statistical results.	

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10.1.1.2. Einzelstudien

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[18]	multicenter prospective registry	N=953 All FL	To detect patterns of PET/CT use in grade 1-2 FL initial staging: Underwent FDG-PET at initial diagnosis Yes: N=532 No: N=421 "Data were obtained from the National Comprehensive Cancer Network Non-Hodgkin Lymphoma Outcomes database"	• newly diagnosed patients with grade 1 – 2 FL • median age was 56.4 years Exclusion criteria: • grade 3 or transformed FL as they are often treated as patients with DLBCL • HIV-positive • less than 6 months of follow-up	At least 6 months	• patterns of use of FDG-PET	• FDG-PET is used for initial staging in 56% of patients • Among pts who underwent PET/CT for initial staging, 438 (82%) received early treatment compared to 259 (61.5%) of those staged without FDG-PET ($p < 0.0001$) • Of all pts with stage I FL (n = 100), 47% were treated with RT alone, and the choice of initial treatment strategy for stage I FL did not vary sign by use of FDG-PET (p = 0.22)	R: N/A B: N/A I: N/A F: National Comprehensive Cancer Network M: Register Analysis
[19]	prospective multicentre study	N= 116 FL:	One arm	Inclusion criteria: • patients aged 8 years or older	N/A	• Diagnostic accuracy	• Sensitivity whole-body MRI in all lymphomas 45.5 % [95 % CI: 29.8–62.0 %]	R: N/A

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		N=23		• newly diagnosed (histologically proven) Hodgkin or non-Hodgkin lymphoma • written informed consent before the start • of the study • blind BMB had to have been performed before • sufficient time for whole-body MRI before the start of treatment Exclusion criteria: • contraindication for MRI • physically or psychologically unable to undergo whole-body MRI • previous malignancy • Pregnancy • Nursing • therapy had already started			• Sensitivity whole-body MRI in aggressive lymphoma [88.9 % (95 % CI: 54.3–100 %)] significantly higher (P=0.0029) than in indolent lymphoma [23.5 % (95 % CI: 9.1–47.8 %)] • Sensitivity of FDG-PET in aggressive lymphoma [83.3 % (95 % CI: 41.8–98.9 %)] also significantly higher (P=0.026) than that in indolent lymphoma [12.5 % (95 % CI: 0–49.2 %)]	B: Partial (blinded interpretation of biopsy) I: N/A F: not reportes M: no specifity/PPV/NPV reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
(Adams 2014)	Retrospective, single-center study	N=22 All FLL BMB+: N=8 BMB-: N=14	Arm 1: BMB + (positive BMB or FDG-PET/CT bone marrow result) Arm 2:BMB – (negative BMB or FDG-PET/CT bone marrow result)	• Newly diagnosed grade I-IIIA follicular lymphoma • pretreatment FDG-PET/CT and BMB Exclusion criteria: • previously treated/ relapsed lymphoma • coexistence of another lymphoma subtype in the same diagnostic biopsy • another previousmalig-nancy within the past 5 years • patients in whom BMB was done before FDG-PET/CT, interval between FDG-PET/CT • BMB >30 days, non-diagnostic BMB, and start of therapy (chemotherapy, radiation therapy) and/or hematopoietic growth	No Only around 12-13.1 days between BMB and FDG-PET/CT	• Sensitivity • Specifity • PPV • NPV • SUV (mean) • SUV (max) • SUV (peak)	• Sensitivity: 0 % (95 % CI: 0–32.4 %) • Specifity: 100 % (95 % CI: 78.5–100 %) • PPV: Not calculated • NPV: (95%CI: 43.0–80.3 %) • SUV (mean): BMB+ 1.7±0.4 vs. BMB- 1.1±0.3 • SUV (max): BMB+ 2.5±0.54 vs. BMB- 1.7±0.4 • SUV (peak): BMB+ 2.0±0.4 vs. BMB- 1.4±0.4	R: No B: No I: No F: Alpe d'HuZes/ DutchCancer Society, ZonMW M: retrospective, small sample

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				factor injections before FDG-PET/CT or BMB.				
[20]	Prospecti ve study	N=68 FL: N=10	One arm	• median age: 42 years Inclusion criteria: • Age over 14 • absence of contraindications to MRI • histologically confirmed newly diagnosed FDG-avid lymphoma • performance status with values from 0 to 2 according to ECOG scale	N/A	• Comparability MRI and PET	• Excellent agreement between WB-MRI and FDGPET/CT stage (k = 0.88; p < 0.05) and WB-MRI stage was equal to those of FDG-PET/CT in 91.2% (62/68; in particular 35/37Hodgkin lymphoma, 27/31 Non Hodgkin lymphoma). • The agreement was better in patients with Hodgkin lymphoma (k = 0.92) than in those	R: N/A B: Partial (“reviewer … unaware of the type and grade of lymphoma and findings of other imaging modalities”) I: N/A F: N/A
[21]	Retrospec tive cohort study	N=59	PET/CT after salvage treatment prior to ASCT	• Relapsed/refractory FL pts after R-CHOP • chemosensitive (as evaluated by CT) to salvage treatment and who proceeded to ASCT • Median Age: 55 years (28-57)	Median: 37.5 months	• 3yrs-OS • 3yrs-PFS • prognostic value of PET/CT after salvage treatment prior to ASCT	• 3-year PFS and OS for the whole population were 63.1 % (50.9 – 78.3) and 90.5 % (82.8 – 98.8) • PFS was significantly lower in PET/CT-positive patients (3-year PFS of 45.5 %	R: N/A B: N/A I: N/A F: CAPTOR project (partial)

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							• (26.6 – 77.8 %) versus 72.6 % (58.5 – 90.0 %; p=0.039) • In the univariate analysis, PET-negativity and R-CHOP refractoriness were correlated with PFS, but not with OS • Of 43 patients who achieved CR/CRu, 8 • (18.6 %) still had a positive PET/CT according to the IHP criteria and of 10 patients (80.0 %) achieving PR, 8 remained PET-positive before ASCT • "PET/CT after salvage treatment before ASCT is a strong prognostic factor in patients with first chemosensitive relapse of FL"	

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[22]	Retrospective	**n= 31 FL-1 or FL-2 pts** 95 PET examinations **Patient underwent PET:** 1999-2006	Predictive value and diagnostic accurancy of FDG-PET in FL grade 1 and 2 PET for: • initial staging • mid-induction • post-treatment (PET examination 60 minutes after the intravenous administration of 370-740 MBq of FDG)	**Eligibility Criteria:** • Biopsy proven diagnosis of FL-1 or FL-2 • Pre-treatment PET and CT examinations positive for malignancy • PET and CT obtained at each re-staging, with each examination performed within 4 weeks of the other, and without intervening therapy • Minimum follow-up of 6 months or until disease progression **Exclusion Criteria:** • Transformation to diffuse large B-cell lymphoma during the study	Median 28 months	**Endpoints:** • Response duration • **PFS** • DFS	• PET has high sensitivity (95%) and specificity (88%) for detecting lesions in treated FL-1 and FL-2 (p value, ≤0.001) • post-induction **mean PFS** PET positive 29.5 months (95% 22-38 months) and PET negative 5.8 months (95% 2-9 months) (p value, 0.00015) • relapse rate PET negative: 7% (1/14) vs. PET pos. 100% (2/2) • trend towards longer **mean response** duration among post-salvage PET negative patients (p-value, 0.09) • post-treatment PET positive patients are likely to relapse prior	R: N/A (retrospective) B: N/A I: N/A F: not reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							to PET negative patients • Compared with aggressive NHL, the clinical relevance of post-therapy PET results in FL-1/FL-2 are less clear •	
[23]	Monocentric, prospective study	N=38 Of these FL=23	PET/CT identifies aggressive transformation sites of indolent lymphomas and can guide biopsies HT (histological transformation) was confirmed if the histological and	Adult patients presenting with clinical and/or biological signs of histological transformation (such as: B symptoms, localized tumor mass enlargement, high levels of LDH…)	Median 12 months	• Sensitivity • Specificity • PET/CT as guide for biopsies • Minimal and maximal SUVmax	• median minimal SUVmax was 5.5 (range, 2.0-17.0) in FL patients vs. 2.9 (1.7-5.8) in non-FL patients (p<0.001) • median maximal SUVmax was 13.6 (range, 7.1-41.2) in FL patients vs. 9.2 (1.7-23.2) in non-FL patients (p<0.028) • Histopathological analysis showed a HT in 17 cases: 15 DLBCL ,1 HD and 1 composite lymphoma case	R: N/A B: of analysts, not reported I: N/A F: not reported M: no control

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			immunophenotypical analysis showed diffuse large B lymphoma (DLBCL)				• Sensitivity and positive predictive value (PPV) made up 93.9%, and specificity and negative predictive value (NPV) 95.3%. • study confirms PET/CT can be used as an accurate guide for biopsies in suspected transformed tissues • statistical analysis proved tumor size was not predictive of HT (p=0.094) • SUVmax < than 11.7 is always associated with indolent lymphoma, whereas a SUVmax >17 is always associated with histological transformation	
[24]	Retrospective analysis	N= 185	PET/CT BMB	**Inclusion Criteria:**	Not reported	18F-FDG PET/CT as staging tool and	• PET/CT was found to be useful in the differentiation of	R: N/A

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		30 of these with FL **Start of Study:** 2009 in Taiwan		• Patients with newly diagnosed and histology proven HL/NHL (30 of 185 FL pts) • ≥20 years old • Free of other previous or concurrent malignant disease **Patients Characteristics:** • Median age was 55.8 years • 108 males (58.4%) and 77 females (41.6%)		prediction of bone marrow involvement	aggressive lymphoma subtypes from the indolent subtype based on higher standardized uptake value (SUV) (16.67 vs. 7.98, p < 0.001) • high SUV level (SUV > 10) were predictive of aggressive B-cell NHL • A high concordance rate was found between aggressive B cell lymphoma and HL (88.1% and 93.8%, respectively) • results of BMB and PET/CT in the detection of bone marrow involvement were concordant	B: Nuclear medicine physician who was blinded to the pathological diagnoses from the bone marrow biopsy I: N/A F: Grant from the Kaohsiung Medical University Hospital (KMUH102-2M12)
[25]	Prospecti ve study	N= 121 **Patient Recruit ment Time:**	Prognostic Value Evaluation **PET:**	**Eligibility Criteria:** • 18-80 years of old • **Untreated FL** (grade 1, 2, or 3A)	Median follow-up 23 months	**Response** **PFS** • **OS**	• Intermin PET neg. in 76% of pts; • Final PET neg. in 78% of pts	R: No B: Physicians were not blinded to the results of local PET interpretation

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		September 18, 2007-November 18, 2009 in 1 Italian and 13 French centers	• Before treatment • after 4th cycle of R-CHOP (interim PET) • after the treatment (final PET) **Intervention:** 4 cycles of R-CHOP + 2 cycles of R-CHOP and 2 cycles of rituximab in case of response based on conventional criteria ([PR or CR]/ [CRu])	• ECOG performance status of ≤2 • Adequate hematologic function **Exclusion Criteria:** • FL of grade 3B/ transformation into DLBCL • CHS involvement • Life expectancy <6 months • History of cancer (except treated nonmelanoma skin or in situ cervical cancer) • Poor renal/hepatic function • HIV/active Hepatitis B or C virus infection **Patient Characteristics:** • Median age of 57 years • 63% were men			• 2-year PFS rates were 86% for interim PET–negative versus 61% for interim PET–positive patients (P =0 .0046) and 87% for final PET–negative versus 51% for final PET–positive patients (P<0.001) • 2-year OS significantly differed according to final PET results: 100% PET neg. vs 88% PET pos. (P =0 .0128)	I: Not applicable F: Not reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[26]	prospective, multicenter, randomized, comparative study	N=181 FL: N=37	Arm 1: PET/ceCT N=82 FL: N=19 Arm 2: ceCT64 N=99 FL: N=18	Inclusion criteria: • biopsy-pathology–Independent of the branch assigned • FDG PET/ceCTwas proven diagnosis of HL, DLBCL, or FL • not treated previously for lymphoma and without previous imaging tests for initial staging • signed informed consent • age older than 18 years. Exclusion criteria: • renal failure with a cre-atinine clearance below 30 mL/min • human immunodeficiency virus infection • known inflammatory or granulomatous disease • a life expectancy of less than 3months or poor	Mean follow-up: 16.2+-9,5 months	· diagnostic accuracy of PET/ceCT64	• Contrast-enhanced FDG PET/CT was concordant with the reference standard for staging in 97.8% of cases (88/90) with κ =0.96 (P < 0.001), and sensitivity and specificity for each stage were 98% to 100% and 98% to 100% • concordance with the reference standard in 97.8% of the cases (88/90) with κ =0.91 (P < 0.001), corresponding with a • CR in 83.3% (n = 75), a PR in 4.4% (n = 4), and a PD in 10% (n = 9), with good sensitivity and specificity for response assess	R: Yes B: N/A I: N/A F: Spanish Health Ministry M: No details on FL patients

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				general health (a Zubrod performance scale status >3) • known allergies to CT contrast agents • a positive pregnancy test • suspicion or confirmation of alcohol or drug abuse.				
[27]	Retrospective study	N=117 (181 PET/CT scans) Patient Treatment Time: 2002-2007	18F-FDG PET/CT at staging and post-treatment evaluation versus standard staging	Eligibility Criteria: • Patients with FL Patients Characteristics: • Grade I, II, IIIA and ubdetermined • Stage of 0, I, II, III, IV Median age of 57	Median follow-up of 27 months	• Differences in involvement and stage attribution • Prognostic value of PET	• PET showed more involvement than computed tomography (CT) with clinical examination in 41 of 82 patients (50%), less in 11 of 82 (13%); the same extension was found in 27 of 82 patients (33%), and 3 patients revealed discordant foci visible on PET only and lymphadenopathy without PET activity (P < .001)	R: N/A B: N/A I: N/A F: research grants NR8342-3/2005 and MSMT 0021622430 M: N/A

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							• The difference in relapse rates between PET-positive and PET-negative patients is statistically significant (P < .001) • 73 of 99 negative posttreatment PET scans; 54 of 73 PET-negative patients (74%) remain in complete remission (median follow-up, 27 months)	
[28]	Retrospective study	N= 103	18F-FDG PET/CT scanning	**Patients Characteristics:** • Biopsy-proven nontransformed and transformed FL, B-cell small-cell lymphocytic lymphoma (SLL/CLL), or marginal zone lymphoma (MZL) who Underwent PET and computed tomography (CT) scans within 3 weeks	Median follow-up of 26 months	Role of PET/CT in evaluation and follow-up of pts. Sensitivity • Specificity	• In FL, PET demonstrated 94% sensitivity and 100% specificity for staging • PET was more specific than CT for detecting recurrence or assessing therapeutic responses (91% vs. 50%)	R: N/A B: The pathologist was blinded to the PET findings I: N/A F: Not reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							• For MZL staging, PET had moderate sensitivity (71%) and outperformed CT alone in the depiction of extranodal sites (85% vs. 57% sensitivity) • In SLL/CLL, PET sensitivity was 53% and underestimated disease extent in 5 of 19 patients (26%) compared with CT • Nontransformed FL had a higher SUV (ANOVA, P<.05) compared with MZL and SLL/CLL. SUV was higher in transformed than in non transformed tumors (P<0.001, Student t test)	

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[29] GAUSS study	Post hoc exploratory analysis based on a multicenter phase II study	N=75 (all FL)	Pts treated with R or G as induction PET(CT before and after induction Could PET/CT results predict PFS and tumor response?	pts with relapsed, CD20-positive indolent B-cell lymphoma with a prior response to a R-containing regimen randomized to induction (either G (1000 mg) or R (375 mg/m2)) • Pts without evidence of progressive disease received G or R maintenance in their respective arms every 2 months for up to 2 years.	Median: 31.7 months	• predictive value of an end-of-Induction treatment PET scan with respect to PFS and tumor response	• HR for progression or death was 0.25 (95% CI:0.01–0.64; p¼0.0018) • 55/75 (73.3%) patients were PET-positive • the proportion of pts with a PFS event (progression or death) was sig lower in PET-negative than PET-positive pts with HRs of 0.25–0.44 (p<0.05 for all criteria) • pts with PR: there was a sign lower risk of PD in patients with PR who were PETnegative versus PET-positive (HR, 0.14; 95%CI: 0.02–1.09; logrank test p value, 0.0286)	R: N/A B: N/A I: N/A F: sponsored by F. Hoffmann-La Roche Ltd Conflict of interests: Disclosure forms provided by the authors are available online

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[30]	Retrospective study	N= 45 Untreated FL	**FDG PET/CT vs. CT** Before and after chemoimmuntherapy (**Intervention:** 4/6 cycles of R-CHOP (for 19 patients there was two injections of rituximab following 6 cycles of R-CHOP))	**Eligibility Criteria:** • Histologically **proven FL** • Chemoimmunotherapy **Exclusion Criteria:** • Localized stage(I/II) or low FLIPI • low tumour burden **Patient Characteristics:** • Mean age 60 years • 22 Male and 23 Female • Grade 1, 2, 3a • Ann Arbor stage of I/II, III, IV	Median follow-up of 36 months	Assess usefulness of PET/CT in staging, prognosis evaluation and restaging: • PFS • Staging-Differences • Prognostic Differences • Accuracy of PET/CT and CT	• **Median PFS** 48 months in t PET/CT-neg. group as compared with 17.2 months for the group with residual uptake ($p<10^{-4}$) • PET/CT detected more nodal (+51%) and extra-nodal (+89%) lesions than CT • PET/CT modified Ann Arbor staging in eight patients (18%) • 5 pts (11%) inititally considered early stage, treted as advanced stage • Initial PET/CT prognostic score sing. More accurate than FLIPI score in identifying pts with poor prognonsis (i.e. pts with incomplete	R: no B: Not mentioned I: not applicable F: Not mentioned

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							response or early relapse) • Accuracy of PET/CT for therapeutic response assessment was higher than that of CT (0.97 vs 0.64) • Post-treatment PET/CT was able to predict patients' outcomes	
[30]	Retrospective analysis	N= 45	Diagnostic and prognostic impact of 18F-fluorodeoxy-glucose PET/CT (FDG PET/CT) Vs. CT **Intervention:** 6 cycles of rituximab combined	**Patients Characteristics:** • Untreated biopsy-proven **FL** who underwent FDG-PET/CT and CT before and after chemo-immunotherapy **Exclusion criteria:** Localized stage (I/II) or low Follicular Lymphoma International Prognostic Index (FLIPI) and with low tumour burden	Median follow-up of 36 months	Usefulness of PET/CT in staging, prognosis evaluation and restaging	• PET/CT detected more nodal (+51%) and extranodal (+89%) lesions than CT • PET/CT modified Ann Arbor staging in eight patients (18%) • Five patients (11%) initially considered as being early stage (I/II) were eventually treated as advanced stage (III/IV)	R: N/A B: N/A I: N/A F: Not reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			with cyclophosphamide, doxorubicin, vincristine and prednisone				• initial PET/CT prognostic score was significantly more accurate than the FLIPI score • The accuracy of PET/CT for therapeutic response assessment was higher than that of CT (0.97 vs 0.64) • The median PFS was 48 months in the PET/CT negative group as compared with 17.2 months for the group with residual uptake ($p<10^{-4}$)	
[31]	Retrospective study	N=64 FL: N=unclear	One arm Interval between PET/CT and BMB was 4 ± 9 days	Inclusion criteria • All consecutive staging PET/CT examinations with histological confirmed treatment-naive newly diagnosed indolent NHL from April	N/A	Diagnostic accuracy	• The overall accuracy of PET/CT in detecting BMI was 89% (41/46), with a sensitivity of 84% (21/25), a specificity of 95% (20/21), PPV	R: N/A B: N/A I: N/A F: N/A M: small sample

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				2007 to March 2014 in one single centre Exclusion Criteria • history of previous radiation therapy • concurrent infection • recent granulocyte colony-stimulating factor injections that might affect marrow uptake were excluded			of 95% (21/22) and NPV of 83% (20/24). • In comparison, BMB had an accuracy of 98% (45/46), a sensitivity of 96% (24/25), a specificity of 100% (21/21), PPV of 100% (24/24) and NPV of 95% (21/22)	
[32]	Retrospective analysis	N=91 (all FL) 148 PET/CTs analysed	PET scanning 6–8 weeks after the last cycle of therapy "PET was performed according to a standard procedure by means of a hybrid PET/CT tomograph"	histologically proven FL • (first-line and relapse)	Mean: 3 yrs	• PFS • Patient outcome for PET result • Tumor grading • FLIPI • Disease stage • Number or relapses • Remission or disease	• pts presented a mean PFS of 35 months (range 3–86), with a relapse rate of 42% • PET/CT performance at the end of treatment was as follows: 100% sensitivity, 99% specificity, 89% positive predictive value and 100% negative predictive value	R: N/A B: N/A I: N/A F: not reported

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			"almost half of our patients underwent different therapeutic regimens"				• The Kaplan-Meier analysis demonstrated a stat. sign. correlation with PFS for PET (p<0.0001), FLIPI score (0–1 versus ≥2) (p00.0451) and number of relapses (none versus ≥1) (p00.0058). (univariate analysis) • Multivariate analysis: Pet and number of relapse independent predictive factors for PFS	
[33]	Retrospective study	N= 57 Indolent FL (grade 1, 2, 3a) **Patient Recruitment Time:** 2002-	**PET or PET/CT, but not analyzed separately** Mid- and post-treatment *"scans reported as complete*	**Exclusion Criteria:** • Grade 3b FL • Patients treated with tumour excision and/or radiotherapy without induction chemotherapy **Patient Characteristics:**	Median follow-up of 57.6 months	Evaluate predictive value of mid- and post-teatment PET **PFS** **OS** • .	• OS: Post-treatment PET was predictive of OS (mean OS 95.2 vs. 45.0 months for PET-neg. vs. PET-pos., p<0.001) • PFS: post treatment PET-neg. 74.4 vs.	R: no B: Not mentioned I: not applicable F: The authors declare that there are no conflict of interests

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		2011 at the Sydney Southwest Area Health Service	*remission or minimal residual uptake were considered PET-negative, while partial remission, stable disease, and progressive disease were considered PET-positive"*	• Histologically proven grade 1, 2 and 3a FL • Newly diagnosed and previously untreated • Underwent PET scans at mid-treatment or following completionof initial treatment • Median age of 59 years			38.2 months for PET-pos. (p = 0.083) • 3-year OS for post-treatment PET- and PET+ patients were 96 and 60 % • 3-year PFS for post-treatment PET- and PET+ patients were 72 and 30 % • Mid-treatment PET was not predictive of PFS (mean PFS 78.5 vs. 51.0 months for PET-neg. vs. PET-pos., p = 0.35) • Mid-treatment PET was not predictive of OS (mean OS 89.9 vs. 76.6 months for PET-neg. vs. PET-pos., p = 0.92).	
[34]	Retrospective study of FOLL05	N=142	FDG-PET in initial staging Vs.	**Patients Characteristics:** • **Patients with FL** • 18-75 years old	Not reported	Identification of nodal areas, FLIPI score, staging, extranodal sites	• PET identified a higher number of nodal areas in 32% (46 of 142) of	R: FOLL05 trial was randomized, but not for PET

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	phase III trial		Conventional staging **Intervention for FOLL05 trial:** Arm A: R-CVP Arm B: R-CHOP Arm C: R-FM	Ann Arbor stage II–IV			patients and more extranodal (EN) sites CT scan. • FLIPI score increased in 18% (26 of 142) and decreased in 6% (9 of 142) of patients. • Fifteen (11%) patients were up-staged with PET, while only five (1%) were down-staged. Moreover, 15 (62%) of the 24 patients previously classified as stage II were classified by PET as having stage III–IV62% (15 of 24) of cases with limited disease were upstaged with PET	B: N/A I: N/A F: Italian Ministry of Health national grant RF-CRB-2008 1146343 of the 'Bando Ricerca Finalizzata 2008' assigned to Rionero in Vulture, Italy
[35] FOLL05	phase III, randomized trial	N= 202	PET: Post-induction (defined as PET scan	Eligibility Criteria: • PI-PET scan carried out within 3 months from the	Median follow-up of 34 months	PET results Primary endpoint: PFS	• PET was defined as positive in 49 (24%) patients	R: yes, but not for PET B: N/A I: N/A

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	(randomized for treatment, not for PET)		carried out within 3 months post induction) Interventions: R-CVP, R-CHOP or R-FM	end of induction immunochemotherapy • 18-75 years • Ann Arbor stage II to IV • FL Patient Characteristics: Median age 55 years		Secondary endpoints: • response rates • DFS • OS	• the 3-year PFS was 66% and 35%, respectively, for patients with negative and positive PET (P < 0.001) • PET (HR= 2.57, 95% CI 1.52–4.34, P < 0.001) was independent of conventional response, FLIPI and treatment arm Conventional response assessment with CT scan was modified by PET (15% (22/145) CR after CT, and PR after PET & 53% (30/57)were PR after CT, and CR after PET	F: Italian Ministry of Health national grant RF-CRB-2008-1146343 of the 'Bando Ricerca Finalizzata 2008' assigned to Rionero in Vulture, Italy M: N/A
[36] FOLL05	Subset analysis of FOLL05	N=41 for analysis (PET and BCL/IGH)	aim of the present study was to analyze the	study pts should also have had data available on end of treatment PET, performed up to three	53 months	primary endpoint was PFS	**5yrs PFS:** 62% (95% CI 45 to 75) End of treatment **PET+** was associated	R: yes, but not for PET B: N/A; PET was centrally reviewed

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	(phase III, randomized trial)		prognostic role of combined PET and BCL2/IGH analysis, performed at the end of treatment Positive scans (PET+) were defined by residual FDG uptake ≥ score 4 **Interventions:** R-CVP, R-CHOP or R-FM FOLL05 study included MRD evaluation at the end of treatment among planned study procedures	months after the last dose of induction rituximab (+/- chemotherapy) and have been assessed for the BCL2/IGH at diagnosis and at the EOT within 2 months from last dose			to a **poorer PFS** (HR 3.61, 95%CI 1.15-11.4, P=0.028), while the end of treatment positive molecular status showed a trend towards a shorter PFS (HR 2.54, 95%CI 0.96-6.72, P=0.060) stratified analysis combining the information on PET and MRD, the 3-yr PFS were 78%, 50% and 27% in PET/MRD -/-, PET/MRD -/+ and PET+ groups, respectively (P=0.015 for all groups, and P=0.067 between PET/MRD -/- and PET/MRD -/+ stratified pts into 2 groups (PET-/MRD- vs. PET+ or MRD+), and the achievement of both PET and MRD	by three independent nuclear medicine physicians applying the Deauville scale I: N/A F: Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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			Regarding MRD analysis, patients underwent bone marrow (BM) aspirate for qualitative and quantitative assessment of the BCL2/IGH fusion gene				negativity was associated to a better outcome (HR 3.42, 95%CI 1.31-8.95, P=.012), with a 5-yr PFS of 75% (95% CI 54 to 87%) and 35% (95% CI 11 to 60%) for PET/MDR -/- and PET+, respectively	
[37]	Retrospective study	N=50 FL: N=unclear	One arm WB MRI incl. DWI + 18F-FDG PET/CT	Inclusion criteria: • Histologically confirmed malignant lymphoma • age >18 years Exclusion criteria: • pacemakers • claustrophobia	Mean follow-up time: 36.76+-15.5 months	• quantitative parameters in WB DWI (mean ADC) and 18FFDG PET/CT (SUVmax and mean SUV [SUVmean]) • prognostic value of these parameters	• All patients: ADC DWI: 829+-359, SUVmaxDWI: 15+-10, SUVmeanDWI: 5.6+-2.3, SUVmax: 15.9+-10, SUVmean: 5.8+-2.5 • Aggressive NHL: ADC DWI: 822+-266, SUVmaxDWI: 18.5+-11.3, SUVmeanDWI: 6.2+-2.7, SUVmax: 19.4+-11.1, SUVmean: 5.2+-1.5	R: N/A B: N/A I: N/A F: Swedish Cancer Society M: small size of patient cohort, N of FL unclear

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[38]	Prospective study	N= 122 **Patient Recruitment Time:** January 2005 - January 2008	BMB and CT Vs. PET/CT scanning	**Patients Characteristics:** • NHL (101) and HL (21) (• 11 FL pts initial FDG-PET scan done	Not reported	Changes in staging through PET/CT Sensitivity Specificity	• FL: 0 patients upstaged through PET(CT • Compared with conventional CT, PET/CT upstaged 21 (17%) cases • Maximum FDG uptake of >10 standardized uptake value (SUV) seems to significantly correlate with an aggressive B-cell lineage (odds ratio 2.47, 95% confidence interval 2.23–2.70 • In HL, PET scan and marrow results agreed in 19 of the cases (90%), being concordantly negative in 18 cases and concordantly positive in one, giving a negative	R: N/A B: N/A I: N/A F: not reported

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							predictive value (NPV) of 100%, sensitivity of 100% and specificity of 90%	
[39]	Retrospective, single-center study	N=64 FL: All	BMB and F18-FDG PET/CT	• patients older than 18 years • FL diagnosed on biopsy of a nodal or extranodal lesion • BMB and F18-FDG PET/CT results were available. Exclusion criteria: • patients with known concomitant malignancy • more than 14 weeks had passed betweenBMBand FDG-PET/CT	N/A	• Sensitivity • Specifity • Diagnostic accuracy • SUV (mean) • SUV (max)	• On receiver operator curve analysis, BM-SUVmean>2.7 had a PPV of 100% for BM involvement (sensitivity of 68%), while BM-SUVmean<1.7 had an NPV of 100% (specificity of 73%) • Reducing the threshold to 2.5 had a PPV of 93% (13/14) and a sensitivity of 81% (13 of 16 cases). SUVmean lower than 1.7 had an NPV of 100% and specificity of 73% for cases without BMI • PPV: 48,5% • NPV: 100%	R: No B: Partial (outcome assessor unaware of BMB status) I: No F: N/A M: Only diagnostic accuracy

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[40]	Retrospective study	N=5712 All FL	CT-alone: N=3222 PET or PET/CT: N=2490	Inclusion criteria: • Patients with a histologically confirmed first primary diagnosis of FL Exclusion criteria: • Age at diagnosis less than 66 years • Subsequent diagnosis of cancer within 6 months of the diagnosis of FL • Date of initiation of therapy more than 45 days before date of diagnosis • Missing census tract information/incomplete claims history • No CT scan available (within 6 months of diagnosis and before start of treatment)	median duration of follow-up was 4.70 years	• receipt of PET • scans (PET or PET/CT scans) for initial staging • all-cause survival • lymphoma-specific survival	• 44% of the patients in this cohort underwent PET staging (increased sharply during study period up to 60%) • 2430 patients (43%) died during follow-up (23% of that lymphoma-related) • PET was associated with improved lymphoma-related (HR 0.69, 95% CI: 0.58–0.82) and overall (HR 0.75, 95% CI: 0.68–0.83) survival	R: N/A B: N/A I: N/A F: National Cancer Institute M: retrospective
[41]	Retrospective	N= 160	**PET:**	Eligibility Criteria:	Median follow-	PET results PFS	• PET status correlated with conventional	R: not for PET/CT

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		(subgroup of PRIMA trial population) (242 PET scans) **Patient Recruitment Time:** December, 2004-April, 2007 at 40 sites	Post-induction, pts went on to RM or observation (independent of PET result) **Intervention:** Arm A: 6 cycle of R-CHOP+ eight induction doses of rituximab Arm B: 8 cycles of rituximab+R-CVP+ eight induction doses of rituximab	• Untreated high-tumor-burden FL (grade 1, 2, or 3a) • ≥ 18 years old • ECOG performance of ≤2 • adequate haematological function **Exclusion Criteria:** • Grade 3b or transformed into diffuse large B-cell lymphoma • CNS involvement • Life expectancy of less than 6 months • Previous history of cancer (apart from adequately treated non-melanoma skin cancer or in-situ cervical cancer)	up of 36 months	OS CR PR	response criteria (P < .001) • Patients remaining PET positive (post treatment) had a significantly (P < .001) inferior PFS at 42 months of 32.9% (95% CI, 17.2% to 49.5%) compared with 70.7% (95% CI, 59.3% to 79.4%) in those who became PET negative • HR for progression: 3.3 (95% CI 1.9-5.9) • Median PFS 20.5 months • "In the 104 randomly assigned pts, postinduction PET positivity remained a highly significant predictor of disease progression, with a 42-month PFS rate of	B: of investigator not reported I: yes F: Ofer Shpilberg, Roche; Emmanuel Gyan, Janssen-Cilag, Amgen, Celgene; Gilles Salles, Roche M: N/A

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				• Poor renal or hepatic function (unless due to lymphoma) • Previous history of allergy to murine products • HIV/ hepatitis B or C virus infection			38.3% in PET-positive versus 72.6% in PET-negative patients (HR, 2.8; P = 0.002" • OS: Postinduction PET-positive pts had a significantly inferior OS: 42-month rate of 78.5% (95% CI, 57.6% to 89.9%) compared with 96.5% (95% CI, 89.7% to 98.9%) for PETnegative pts (log-rank P=.0011;HR,7.0;95%CI, 1.8 to 27.0)	
[42] Secondary analysis of GALLIUM	Prognostic value within a randomised phase III trial	N=1202 patients of which 595 were included in the PET population (PET at	Prognostic value of end-of-indiction PET/CT response after first-line immunochemotherapy	• aged ≥18y • previously untreated CD20-positive FL (grades 1-3a) • advanced stage (III or IV or II with bulk) • ECOG performance status: 0-2		• PET/CT-PFS • CT-PFS • PET/CT-Complete response • CT-Complete response • CT-partial response	• overall response in the PET population was 539 (90·6%; 95% CI 88·0–92·8) of 595 The proportion of • patients achieving a PET complete response and	R: yes, but not for prognostic value of PET B: partly yes ("Scans were assessed by investigators and an IRC, comprising two radiologists who were masked to

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		baseline and end-of-treatment); 533 prospective analysis (IHP 2007), 508 retrospective analysis (Lugano 2014) regarding PFS	• CT and PET response was evaluated for pts achieving a partial response or complete response as per the International Harmonisation Project (IHP) 2007 response criteria • PET scans to assess metabolic response were also retrospectively assessed by the IRC only according to the more recent Lugano 2014	• The median age was 59 years and • 53.2% of patients were female		• PET/CT-Complete metabolic response • OS	complete metabolic response more than doubled compared with the proportion achieving CT complete response patients • Having a CT-based CR at end of induction, as assessed by the IRC, was significantly prognostic for PFS when comparing responders vs non-responders; but not for OS (2·5-year OS for patients who had a CR was 97·7% [95% CI 94·0–99·1] vs 93·5% [90·5–95·6] for those who did not; HR 0·5, 95% CI 0·3–1·2, p=0·124) • According to IRC-assessed IHP 2007	clinical outcome, and a third adjudicating radiologist whose role was to resolve any disagreements between the radiologists relating to the attributed response") I: no F: F Hoffmann-La Roche M: retrospective and prospective; 10 (2%) of 543 had disease progression before the end-of-induction therapy and were excluded from PFS analyses

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			response criteria CT scans every 6 months PET/CT done at baseline and end of induction (GALLIUM: first-line immunochem otherapy (CHOP) with G vs. R, then mono, CVP or bendamustine followed by maintenance antibody – results extracted in chapter 6; Marcus 2016)				response criteria, end-of-induction CR status on PET was prognostic for both PFS and OS (2·5-year OS for patients with CR 96·9% [95% CI 94·5–98·2] vs non-CR 90·6% [84·6–94·3]; HR 0·4, 95% CI 0·2–0·9, p=0·011)	

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[43]	Retrospective study	N=149 FL: n=57 (38,25%)	No study arms (retrospective study of one cohort)	• Diagnosis of lymphoma • All subtypes included • PET-CT within 1 month of the bone marrow biopsy at staging or relapse	N/A	• Sensitivity • Specifity • Accuracy	• FL: previously untreated: sensitivity of PET-CT was 67% (95% CI 0.45-0.84), specificity 85% (95% CI 0.68-0.95) and accuracy 77% (95% CI 0.64-0.87) • FL: 30 patients with relapsed disease: sensitivity of PET-CT was 73% (95% CI 0.39-0.94) and specificity 89% (95% CI 0.67-0.99)	R: N/A B: N/A I: N/A F: CT by Siemens, FDG by Zevacor Phamra M: Only diagnostic accuracy
[44]	Retrospective Review	N=251 FL: N=41 (16,4%)	Statistical arms: Arm 1: HL with autologous SCT (n=44) Arm 2: NHL with autologous SCT (n=100)	• patients with lymphoma • underwent allogeneic or autologous SCT at Memorial Sloan-Kettering between January 2005 and December 2009 • patients had post-transplantation FDG PET/CT examinations	Median: 42 months	• Disease-free survival • SUV(max)	• DFS of patients with FDG nodes <1.5 cm was significantly superior to that of patients with other FDG-avid lesions (P <.001), and in fact was comparable with patients without FDG-avid lesions (P=.59)	R: No B: No I: No F: Cure Career Catalyst Research Grant M: Retrospective

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			Arm 3: HL with allogeneic SCT (n=29) Arm 4: NHL with allogeneic SCT (n=78)				• SUV(max): In the 21 patients with suggestive FDG-avid nodes but without pathological proof of malignancy, the SUVmax of the most FDG-avid node ranged from 3.8 to 10.8, median 5.5	
[45]	Retrospective Study	N= 42 **Patient Staging Time:** June 1997 - June 2006	Comparison of staging through physical examination, CT and bone marrow examination and additional PET	**Patients Characteristics:** • Previously untreated, biopsy-proved early **stage follicular lymphoma** • Median age of 52 years Follicular Grade of I, II, IIIa and other	/	Changes of staging through PET	• PET findings changed the stage or management in 19 patients: 13 (31%) who were upstaged to Stage III–IV, altering ideal management from IFRT to systemic therapy, and 6 (14%) who had the involved field enlarged, including 4 upstaged from Stage I to II • Of these 19 cases, PET findings were considered true	R: N/A B: N/A I: N/A F: Authors state no conflict of interest

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							positive in 8 patients, indeterminate in 10, and false positive in only 1 patient	
[46]	retrospective cohort study based on prospective cohort study	N=1289 FL: All	Arm 1: PET+CT N=447 Arm 2: CT alone N=537 Propensity score matched patients: Arm 3: PET+CT N=361 Arm 4: CT alone N=361	• completed R-based induction therapy • Stage II–IV • FL without large cell histology at diagnosis • received initial therapy with R-monotherapy or R-chemotherapy, including R-CHOP (rituximab plus cyclo-phosphamide, doxorubicin, vincristine, and prednisone), R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone), rituximab plus fludarabine, and R-other chemotherapy • completed planned (not terminated early,	Mean: 7.6 years	• association between imaging response assessment and survival • OS	• OS: PET positive: 78%, PET negative: 88%, CT positive 78%, CT negative: 87%, • PFS: PET positive: 51%, PET negative: 65%, CT positive 54%, CT negative: 64%, • positive PET±CT and CT were prognostic of inferior OS (HR 1.78; 95% CI: 1.16–2.72 and HR 1.61, 95% CI: 1.13–2.29, respectively) and PFS (HR 1.63, 95% CI: 1.21–2.20 and HR 1.45, 95% CI: 1.12–1.89,	R: No B: No I: No (observational) F: Genentech Inc M: Retrospective

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				as reported by clinical sites) therapy • reported treatment end date (last dose date)				
[47]	Retrospective study	N= 45 **Patient Recruitment Time:** December 2002-January 2004	CT and PET were performed at diagnosis (before treatment), 1 month after the end of chemotherapy, and during the follow-up every 6 months for the first 2 years and trotmthen every 12 month remaining staging procedures included bone marrow	**Eligibility Criteria:** • previously untreated pts with FL were studied with PET and CT scans after chemotherapy induction • Histologic diagnosis of FL grade I/II • ECOG performance of <3 • Normal hepatic, renal, and cardiac function **Patient Characteristics:** Median age of 55 years	Median follow-up of 25 months	• Differences in CT +/- and PET+/ • PFS • CR PR	• After treatment, 4 of 5 patients (80%) who had CT-negative/PET-positive findings experienced relapse/progression, compared with only 1 of 22 patients (4.5%) in the CT-negative/PET-negative subset • Among the 18 patients with CT-positive findings, all 6 patients (100%) who had PET-positive findings experienced relapse or progression, compared with 1 of 12 patients (8.3%) who had PET-negative findings	R: N/A B: N/A I: N/A F: partially supported by BolognAIL M: N/A

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen/Outcome	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			biopsy, hematologic, and biochemical survey Induction treatment: Arm A: 6 cycles of FM Arm B: CHOP+rituximab				• The 2-PFS rates were 20% and 90% in the CT-negative/PET-positive and CT-positive/ PET-negative subsets, respectively (P = 0.0031) • During the follow-up, 2 patients, who presented a PET positivity with a negative CT scan, underwent a lymph node biopsy, which confirmed the presence of FL infiltration	

Konsultat

10.1.2. GRADE-Bewertung

10.1.2.1. PET/CT zur Prognoseabschätzung (Initialdiagnostik)

[15, 30]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low

10.1.2.2. PET/CT zur Stadieneinteilung

[40]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non RCT	PFS						Not reported

Konsu

10.1.2.3. PET/CT zur Therapiesteuerung und Prognoseabschätzung (während Therapie)

[13]

Interim:

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-1	-	-	-	⊕⊖⊖⊖ very low
	Non RCT	PFS	-	-1	-	-	-	⊕⊖⊖⊖ very low

Verschiedene Richtungen der Ergebnisse, nur 3 Studien berichten interim PFS und OS

End-of-treatment:

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low

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10.1.2.4. PET/CT nach Induktion – Prognoseabschätzung

[13, 16, 17, 41, 46]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low

10.1.2.5. PET/CT während der Therapie – Therapiesteuerung und Prognoseabschätzung

[13, 22, 25, 33]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-1	-	⊕⊖⊖⊖ very low
	Non RCT	PFS	-	-1	-	-1	-	⊕⊖⊖⊖ very low

OS: geringe Anzahl Patienten, Konfidenzintervalle sehr breit; PFS: zwei Studien berichten keinen Unterschied, eine berichtet einen Unterschied; Konfidenzintervalle sehr breit

Konsultationsfas

10.1.2.6. PET/CT zur Prognoseabschätzung nach Beendigung Rezidivtherapie

[29, 32, 44]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS						Not reported
	Non RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low

10.1.2.7. Prognostischer Wert des PET/CT vor autologer SCT

[21]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-2	-	⊕⊖⊖⊖ very low
	Non RCT	PFS	-	-	-	-2	-	⊕⊖⊖⊖ very low

Sehr geringe Patientenanzahl, sehr geringe Anzahl an Events

Konsu...

10.2. Kapitel 6 Therapie der frühen Stadien

10.2.1. Evidenztabellen

10.2.1.1. Einzelstudien

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[48]	prospective randomized study	N=65 Arm 1: N=32 Arm 2: N=33	Arm 1: Patients were treated with **radiotherapy**. Radiation fields included mantle, whole abdomen and pelvic field (**central lymphatic** irradiation). Those fields were irradiated with a microscopic dose of 30.6 Gy. This	Patients <75 years and treatment-naïve, stage I to III follicular lymphoma were randomized. Patients were randomized to either radiotherapy or triple drug chemotherapy	The median follow-up was 71 months.	Overall survival Recurrence-free survival PCR-Response Safety/toxicity	Overall survival (5-year OS) Arm 1: 94% Arm 2: 89% Recurrence-free survival (5-year RFS) Arm 1: 45% Arm 2: 54%	R: Yes. B: No information provided. I: No sufficient information provided. F: The study was spported by RO1 CA62518 from the National Cancer Institute and grant by the Leukemia and Lymphoma Society.

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			approach was followed by a boost to the gross disease (to a total of 39.6 Gy) Arm 2: Patients were treated with **triple chemotherapy regimen** (different treatment protocols: CHOD-Bleo + ESHAP, + NOPP). Patients received 4 cycles of each regimen and in total, 12 chemotherapy cycles . CHOD-Bleo: Cyclophospham					M: N=35 patients (53.8%) had stage III follicular lymphoma.

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			ide, doxorubicin, vincristine, dexamethasone, bleomycin, 4 cycles. ESHAP: Etoposide, methylprednisolone, cisplatin, ara-C, 4 cycles. NOPP: Mitoxantrone, vincristine, procarbazine, prednisolone, 4 cycles.					
[49]	Prospective, randomised, phase 3 non-inferiority study	N= 548 pts (621 sites randomly assigned)	• standard dose RT (24 Gy in 12 fractions) (n=299 sites) • low-dose RT (4 Gy in 2	**Eligibility Criteria:** • >18 yrs old • follicular lymphoma or marginal zone lymphoma	Median follow-up of 26 months	**Primary outcome:** • Time to local progression **Secondary endpoints:**	**Local progression:** • 21 in the 24 Gy group • 70 in the 4 Gy group	R: yes, "RT target sites were randomised (1:1) with minimisation stratified by histology (FL vs MZL)"

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			fractions) (n= 315 sites)	• having local radiotherapy for radical or palliative local control • had received no previous treatment for at least 1 month before **Patient Characteristics:** • Male+Female • Age: 66 y		• Overall survival • Response • Toxic effects • Quality of life (using the EQ-5D form at 7 timepoints and yearly thereafter)	**Time to local progression** with 4 Gy was not non-inferior to 24 Gy (HR 3.42, 95% CI 2.09–5.55, p<0.0001) **FL pts with curative intent time to local progression:** (134 pts with 16 events) HR: 6.37, 95% CI 1.44–28.18, p=0·0051) **OS:** HR was 0.84 (95% CI 0.52–1.36, p=0.47) **Response** (12 weeks after treatment): **Follicular lymphoma only:** **CR** 152 (67%) in 24 Gy vs. 116 (48%) in 4	B: unblinded I: yes F: Cancer Research UK M: not specific to first line treatment; not specific to early stages; FL, MZL and other histology types included; reasons for RT curative and palliative; "Because of the sometimes lengthy periods between diagnosis and randomisation, patients had often received other treatments"

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							Gy **PR** (>30%) 53 (23%)in 24 Gy vs. 78 (32%) in 4 Gy **Stable disease** (including <30% regression) 19 (8%) in 24 Gy vs. 40 (16%) in 4 Gy **Progression** 2 (<1%) in 24 Gy vs. 9 (4%) in 4 Gy **Toxicity:** • 8 (3%) of 282 pts in the 24 Gy group and 4 (1%) of 300 in the 4 Gy group had acute grade 3–4 toxic effects • 4 (1%) pts in the 24 Gy group and 4 (1%) pts in the 4 Gy group had late toxic effects	

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							• most common acute: pain at the site of irradiation (2 patients in the 4 Gy group, 1 patient in the 24 Gy group; all grade 3). • most common late effect was fatigue (two pts in the 4 Gy group, one pt in the 24 Gy group; all grade 3) **QoL:** only pts with a single randomisation (228 in the 24 Gy group and 239 in the 4 Gy group) were included in the analysis: We did not note any difference between the two treatments (p=0·92)	

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Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[50]	Multicenter, prospective, randomised-controlled trial	N= 998 (NHL-pts with 1001 randomised treatment allocations) **Indolent:** 1. Standard arm (n=181) 2. Lower dose arm (n= 180) **Aggressive:**	**Indolent NHL (n=361 sites)**: • 40–45 Gy in 20–23 fractions (Standard arm) • 24 Gy in 12 fractions (lower dose arm) **Aggressive NHL (predominantly DLBCL) (n=640 sites):** • 40–45 Gy in 20–23 fractions (Standard arm) • 30 Gy in 15 fractions (lower dose arm)	**Eligibility Criteria:** • ≥18 years old • With any histological subtype of NHL, first line or subsequent therapies (first presentation of early-stage disease predominated) **Patient Characteristics:** • Total Median age : 64 y (Indolent group: 64 y (standard arm), 62 (lower dose arm); aggressive group: 65 y (standard arm, lower dose arm)) • Male+Female	Median follow up of 5.6 years	**Primary endpoint:** • ORR, defined as CR or PR within the radiotherapy field **Secondary endpoint:** • Freedom from local progression (FFLP) (rate of within-radiation field progression) • Acute toxicity (1 months after treatment) • Late morbidity (6 months after tretamnet) • PFS • OS	Results indolent NHL: • ORR was 93% in standard and 92% in lower dose arm (p = 0.72) • rate of within-radiation field progression : HR = 1.09 (95% CI 0.76-1.56) (p=0.64) • FFLP: HR: 1.13 (95% CI 0.73-1.61; p=0.59) (HR>1 in favor of high dose) • 5year FFLP: 78.9% for high dose and 75.6% for low-dose • OS: HR: 0.96 (95% CI 0.66-1.41; p=0.84) • PFS: HR: 1.06 (95% CI 0.83-1.34; p=0.66)	R: yes, "Randomisation was stratified by centre and histological grade (indolent vs aggressive)." "It was permitted to randomise more than once for different disease sites but in fact this applied to only three patients." B: of patients not reported, investigators not blinded I: yes (except for ORR at one month and acute toxicity) F: Lymphoma Research Trust.

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		1. Standard arm (n=321) 2. Lower dose arm (n=319) 40 treatment centers in UK					• PFS: first line: (exploratory analysis) HR 0.74 (95% CI 0.50-1.10; p=0.13) • PFS only FL: 57% in the 126 known FL patients, no differences between high and low detected Results aggressive NHL: • ORR was 91% in both arms (p = 0.87) The moderate or severe acute and late toxicities were modest. Compared to the standard arms, there was a trend for lower rates of acute toxicity	M: only 60% of pts had stage I or II FL and no subgroups for early stages and only FL reported, MZL, MCL and DLBCL included; "trial population was heterogeneous in terms of histological diagnosis, indication for radiotherapy, and other treatment received"; 83% of pts received RT as or as part of first-line therapy

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							and late morbidity in the lower-dose arms especially for erythema (29% vs. 41%, p < 0.001).	
[51]	Long-term follow up of prospective single arm study	N=177 (stage I and II NHL) follicular small cleaved-cell and follicular mixed small cleaved-cell and large-cell nonHodgkin's lymphoma (NHL)	Radiotherapy: either to one side of the diaphragm (involved or extended field) Or to both sides (total lymphoid irradiation [TLI] Or subtotal lymphoid irradiation [STLI]) Radiation doses ranged from 35 to 50 Gy	Stage I = 73 (41%) Stage II = 104 (59%) Forty-five pts (25%) had staging laparotomy; 34 (19%) had extranodal involvement	Median 7.7 yrs (longest 31 yrs)	Survival Freedom from relapse	Survival: Year 5: 82% Year 10: 64% Year 15: 44% Year 20: 35% Relapse-free: Year 5: 55% Year 10: 44% Year 15: 40% Year 20: 37% sign. worse for older patients "Treatment on both sides (67% relapse-free) of the diaphragm was associated with a significantly lower relapse rate	R: N/A B: N/A I: not reported F: not reported M: very old trial

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							compared with treatment on one side only (36% relapse-free) (P = .001)" "Univariate analysis showed that youth and staging laparotomy were associated with sign better survival and that free from relapse was better following treatment on both sides of the diaphragm or laparotomy"	
[52]	Retrospective case series/ multicenter observational study	N=94 Arm 1: N=43 Arm 2: N=51	**Arm 1:** Patients were treated with 3D conformal radiation therapy (**involved-field technique**) and **rituximab**.	Patients were adults and had grade 1 to 3a, stage I or II follicular lymphoma. Patients were recruited from two different cohorts. Each of those cohorts represents a different treatment arm	The median follow up was 10.9 years. Arm 1: 8.6 years.	Progression-free survival Overall survival Treatment response • CRR	PFS (median) Arm 1: not reached. Arm 2: 10.2 months OS (median) Arm 1: not reached. Arm 2: not reached.	R: No. B: No. I: No sufficient information reported. F: No information provided.

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			Radiation therapy was taken out using anterior-posterior/posterior-anterior fields or a multibeam approach one month after the last dose of rituximab. Rituximab was administered with a dose of 375mg/m² on days 1, 8, 15 and 22 • **Arm 2**: Patients were treated with **2D-involved-field radiotherapy**	for this retrospective comparison.	Arm 2: 16.5 years.	Bone marrow molecular disease Secondary malignancies/FL transformation	Treatment response CRR: Arm 1: 97.6% Arm 2: 86.3% For 51 pts receiving RT alone at a median follow-up of 16.7 years (range: 1.8-22.9 years), the 10-year PFS and OS projections were 50.7% and 83.6% For 43 pts receiving R and RT (Rit-RT) at a median follow-up of 8.6 years (range: 1.8-14), the 10-year PFS and OS projections were 64.6% and 94.4%	M: Patients in arm 2 received a significantly higher median cumulative radiation dose (40 vs. 31 Gy, p<0.001)

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			and a median cumulative dose of 40 Gy. 5 patients were treated with 3D conformal radiation therapy.					
[53]	Prospecti ve case series	N=117 Arm 1: N=55 Arm 2: N=62	Arm 1: **Total** centric **lymphatic** irradiation (patients with mediastinal, hilar, periaortic, iliac or mesenterium involvement) **Extended-field** radiation (patients with peripherically located	Patients with stage I to IIIa follicular lymphoma. These patients were treated with different radiation techniques.	The median follow-up was 68 months.	Freedom from relapse Lymph node in-field recurrences Any lymph node recurrences Extranodal recurrences Overall survival	Probabilities of relapse at 7 years Stage I patients • arm 1: 17% • arm 2: 27% Stage II patients • arm 1: 56% • arm 2: 31% Probabilities of lymph node in-field recurrences at 7 years Stage I patients	R: N/A B: N/A I: not reported F: No information provided. M: Only patients with peripherally located lesions were part of arm 2. N=7 patients had radiation dose deviations.

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			follicular lymphoma) total dose of 26 Gy (2 Gy per fraction, 5 days per week + 10 Gy boost (fractioned to 2Gy per day) to enlarged lymph nodes)			Safety/toxicity	• arm 1: 17% • arm 2: 2% Stage II patients • arm 1: 40% • arm 2: 0% Probabilities of lymph node recurrences at 7 years Stage I patients • arm 1: 17% • arm 2: 20% Stage II patients • arm 1: 43% • arm 2: 20% Extranodal recurrences Data were not described according to	

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Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							the different radiation strategies. **Overall survival** **Survival data were not described according to the different radiation strategies.**	
[54]	National Cancer Data Base retrospective cohort study	N= 35,961 Group 1: N= 13,208 Group 2: N= 7,366 Group 3: N=11,307 Group 4: N=2,957	Group 1: observational treatment strategy Group 2: radiotherapy alone Group 3: chemotherapy alone • Group 4: radiotherapy	Patients with grade 1 or 2 follicular lymphoma. Patients with other than external-beam radiotherapy were excluded.	The median follow-up was 58 months for the entire cohort and 64 months for survivors.	Overall survival	Overall survival • median Total cohort: 149 months Patients with any radiotherapy: 179 months Observational strategy: 125 months • at 5 years Total cohort: 78%	R: No B: Not mentioned F: Not mentioned M: Missing information on treatment strategy of 1,123 patients (3%).

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			and chemotherapy				Patients with any radiotherapy: 86% Observational strategy: 74% • at 10 years Total cohort: 59% Patients with any radiotherapy: 68% Observational strategy: 52%	
[55, 56]	Prospective, single-arm multicenter phase II	N=85	**involved field radiation** (30/40 Gy) in combination with **R (8 cycles, 375mg/m2)** over 12 weeks • 4 weeks R 4 weeks break (radiation	Stage I-II (Ann Arbor) WHO grade 1/2 CD20+ nodal FL age <76 (median 55yrs) ECOG performance status 0-2 47 male /37 female	Median 66 months (visits until 30 months defined with protocol, extended follow-up	**Primary:** PFS **Secondary:** OS CR after 7 weeks (R monotherapy) and after 18 weeks Relapse rate Relapse pattern	**ITT: 2yr PFS: 85%** (90% CI 77-91) one sided p=0.026) (counting 2 deaths due to secondary tumors: 83%) PP: 2yr PFS: 86% (90% CI 77-91) one sided p=0.025	R: N/A B: no I: yes and per protocol set for sensitivity analysis F: trial is funded by Roche Pharma AG, Switzerland. Funding includes trial organization

Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			planning CT) 4 weeks R + involved field radiation	Exclusion of pts with bulky disease or prior treatment	by participating centers)	Relapse free survival Toxicity QoL MRD	PP: 5yr PFS: 75% **ITT: 2yr OS: 97%** (95% CI 90-99) PP: 5yr OS: 96% (95% CI 89-99) **ITT:** CR 51% (7weeks) CR 73% (18weeks) CR 85% (6 months) **AEs:** 529 in 95% (81/85) of pts (most common: gastrointestinal disorders) **SAEs:** 13pts (first 30 months) 17/76 recurrences in PP population (14 outside radiation field)	and monitoring by the KKS Heidelberg, the statistical analysis, data management and the supply of the study medication. There is no other funding of the trial. The authors have no financial relationship with Roche Pharma AG. The authors also participate in other scientific trials which are supported by Roche Pharma AG.

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Referenz	Design	Studien-größe	(verglichene) Interventionen / (ggf. Dosierung)	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							QoL: (QLQ-C30 questionnaire): “no substantial influence” MRD: clonal marker in 36% of pts at diagnosis, all but 1 pts experienced molecular treatment response	

Konsultation

10.2.2. GRADE-Bewertung

10.2.2.1. GRADE-Bewertung: Strahlentherapie (RT) vs. Watch and Wait (W&W)

[54]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non RCT	PFS						Not reported
	Non RCT	QoL						Not reported
	Non RCT	Safety						Not reported

Konsultation

10.2.2.2. GRADE-Bewertung: Radiotherapie vs. Radiotherapie + Systemtherapie

[57]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-1	-	-	-1	-	⊕⊕⊖⊖ low
	RCT	PFS	-1	-	-	-1	-	⊕⊕⊖⊖ low
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-2	-	⊕⊕⊖⊖ low

OS: Kaplan-Meier-Kurven zeigen in Interventionsarm unerklärten loss-to-follow-up, keine Konfidenzintervalle gegeben, geringe Anzahl an Events; PFS: bei 10 Jahren signifikant mit breiten Konfidenzinterval, zu anderen Zeitpunkten nicht; Kaplan-Meier-Kurven zeigen in Interventionsarm unerklärten loss-to-follow-up; Safety: keine Analyse, geringe Anzahl Events

10.2.2.3. GRADE-Bewertung: Radioimmuntherapie (RT+R)

[52, 55]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-	-	⊕⊕⊖⊖

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Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								low
	Non RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non RCT	QoL	-	-	-	-1	-	⊕⊖⊖⊖ very low
	Non RCT	Safety	-	-	-	-	-	⊕⊕⊖⊖ low

QoL: nur in einer Studie berichtet, insgesamt wenige Patienten, keine Zahlen gegeben, in Abbildung teilweise breite Streuung

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10.2.2.4. GRADE-Bewertung: Strahlentherapie (RT) total lymphatisch vs. extended field

[53]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS						Not reported
	Non RCT	PFS						Not reported
	Non RCT	QoL						Not reported
	Non RCT	Safety						Not reported

[51]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non RCT	PFS	-	-	-	-	-1	⊕⊖⊖⊖ very low
	Non RCT	QoL						Not reported
	Non RCT	Safety						Not reported

OS: „Survival“ und statt PFS: „Relapse-free survival“ als Endpunkt bewertet; Studie sehr alt, dafür langes follow-up;

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10.2.2.5. GRADE-Bewertung: Strahlentherapie (RT) Dosis

[50] 40-45 Gy in 20-23 Teilen vs. 24 Gy in 12 Teilen

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-1	-1	-	⊕⊕⊖⊖ low
	RCT	PFS	-	-	-1	-1	-	⊕⊕⊖⊖ low
	RCT	QoL						Not reported
	RCT	Safety	-	-	-1	-1	-	⊕⊕⊖⊖ low

OS, PFS, Safety: Patientenpopulation sehr heterogen (nicht nur Erstlinientherapie eingeschlossen, nicht nur FL-Patienten; keine Subgruppen berichtet), Konfidenzintervalle sehr breit

Konsultation

[49] 24 Gy in 12 Teilen vs. 4 Gy in 2 Teilen

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-1	-1	-	⊕⊕⊖⊖ low
	RCT	PFS	-	-	-	-2	-	⊕⊕⊖⊖ low
	RCT	QoL			-1	-1	-	⊕⊕⊖⊖ low
	RCT	Safety	-	-	-1	-1	-	⊕⊕⊖⊖ low

For PFS: „time to local progression"-assessment; Patientenpopulation sehr heterogen bezüglich Einschlusskriterien (nicht spezifisch zu Erstlinientherapie, nicht spezifisch FL-Patienten); sehr breite Konfidenzintervalle, oder Ergebnisse nicht ausreichend berichtet

Konsultation

10.3. Kapitel 7 Zeitpunkt und Wahl der Erstlinientherapie in fortgeschrittenen Stadien III und IV

10.3.1. Evidenztabellen

10.3.1.1. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
[58]	Only RCT Eligibility criteria: • Age >=18 • Histologic confirmation of FL • Advanced disease (stage III+IV)	Arm A: Anthracycline-containing regimens (ACR) Arm B: non-ACR	Primary outcome: • OS Secondary outcome: • PFS • CR • ORR • RD • Relapse • Disease control • QoL AEs	N of included studies= 8 N of included pts.=2636 **Characteristics of included pts.:** • Low-grade NHL • Initial, untreated indolent NHL • No prior chemotherapy **OS** (3 studies; 464 pts.): HR: 0.99 (95% CI 0.77 to 1.29) (I2=0%) All cause mortality (2 studies; 539 pts.) • At 3 years: A vs. B.: RR 0.92 (95%CI 0.67 to 1.26) • At 5 years: A vs. B.: RR 0.95 (95% CI 0.77 to 1.18 **CR** (all trials): A vs. B: RR 1.05 (95% CI 0.94 to 1.18) (I2=0.46%) (after adjusting for causing trial: RR 1.11; 95% CI 0.99 to 1.25; I2=0%)	SR 1a Follow-up: between 3-5 y Randomization: Yes Blinding: No ITT: N/A Financial support: No external funding received	• Federico 2013 (*Journal of Clinical Oncology)* • Jones 1983 *(Cancer)* • Kimby 1994 (*Annals of Oncology)* • Lepage 1990 (*Hematological Oncology)* • Peterson 2003 (*Journal of Clinical Oncology)* • Taylor 2006 *(Leukemia & Lymphoma)* • Unterhalt 1996 *(Leukemia)* Zinzani 2000 *(Journal of Clinical Oncology)*

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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				ORR (3 trials; 616 pts.): RR 1.06 (95% CI 1.00 to 1.12; I2=12% **Disease control:** A vs. B.: HR 0.65 (95% CI 0.52 to 0.81; I2=0.14)		
[59]	Nb of included studies for FL: 3 Nb. of FL pts. not explicitly reported	"efficacy and safety of chlorambucil in treatment of B-cell malignancies"	No outcomes prioritized Efficacy data (PFS, ORR , CRR, PRR, OS) and safety data extracted	"For patients with FL {…} immediate prescription of CLB alone was not advantageous in comparison with delayed use of CLB in terms of OS" Time to second chemotherapy longer in the observation group (66 months) than in intermediate CLB group (43 months) (p=0.01) For pts. with FL, suitable for chemotherapy: · CRR: CHOP group (18%) vs. MCP group (14%) (not statistically significant; p=0.066) · ORR: CHOP group (86%) vs. MCP group (77%) (Statistically significant; p=0.0094) · "A statistical difference was observed in favor of the CHOP regimen (91%) in comparison with the MCP regimen (82%) (p1⁄40.026) in terms of ORR only for the FL subgroups"	Narrative SR 3a Follow-up: not applicable Randomization: yes, only RCTs included Blinding: not applicable ITT: not applicable Financial support: not reported	• Herold 2007 *(J Clin Oncol)* • Nickening 2006 *(Cancer)* • Ardeshna 2003 *(Lancet)* • (the ones with FL pts)
[60]	Only FL Only first line	Chemo+R Vs.	• OS • PFS	**OS:** For all four trials there was an increased likelihood of survival if receiving R-chemotherapy. For R-CVP	**Health Technology Assessment (HTA) for clinical effectiveness**	• Marcus 2005, 2008 *(Blood)*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Only stages III and IV Only RCT	Chemo (Chemo: CVP, CHOP, MCP, CHVPi)	• Response rates • Cost-effectiveness QoL	compared with CVP, there was 36% increased survival benefit, for R-CHOP compared with CHOP there was a 42% increased survival benefit, for R-MCP compared with MCP a 60% increased survival benefit and for RCHVPi compared with CHVPi there was a 31% survival benefit (all but the latter sign.) **PFS:** median PFS was significantly prolonged in OSHO-39 trial. PFS was not reported in the other three trials. **AE:** The most common AEs observed in the four trials were related to the blood and bone marrow, including leucocytopenia, neutropenia and granulocytopeniaFatigue, neutropenia and back pain were the most common severe AEs and occurred at a slightly higher frequency in patients receiving R-CVP. Adverse events of any grade were reported as more frequent in the R-MCP arm than in the MCP	**and cost-effectiveness of R** **ITT**: partly **Randomization:** yes **Blinding:** no **Follow-up:** 4-5 yrs **Financial support:** not clearly stated, conflicts of interests of authors reported as “none” **Methodological flaws:** “Given resource constraints and data limitations, it was not possible to calculate the standard errors (SEs) and confidence intervals (CIs) to give an indication of the uncertainty in the data.” “It is noted that the median age of patients within the trials (52–61 years) is considerably younger than that seen in clinical practice, where over 70% are aged > 60 years at diagnosis and clinical advice suggests	• Hiddemann 2005 *(Blood)* (Buske 2008) • Herold 2007 *(Journal of Clinical Oncology)* Salles 2008 *(Blood)*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
					that the ECOG performance status is better than that seen in UK clinical practice."	
[61] Journal : Clinical lymphoma, myeloma & leukemia	Database and Conference : 1. Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library Issue 2011, The Cochrane Collaboration, Oxford, UK) 2. MEDLINE (January 1996 to June 2011) 3. Conference proceedings of American Society of Hematology (2004-2011) and American Society of	Treatment with induction chemotherapy, followed by RIT consolidation with either 131I-tositumomab or 90Y-ibritumomab tiuxetan	OR 2 year OS 5 year OS 2 year PFS 5 year PFS	1. Included study : 8 studies (6 were phase II trial and 2 were nonblinded phase III trial) 2. Financing: Funding for this study was received from Dr Flowers' Georgia Cancer Coalition Distinguished Scholars Award and Spectrum. 3. Patient Characteristics : 783 patients Median age from 49 to 57 years 97.2% of patients had stage III/IV disease, with 73% to 100% patients having grade 1/2 disease 4. Result: CR= 82.7% with I2= 94.2 and Cochran Q test P value of < 0.0001, indicating a high degree of heterogeneity OR was 96.2% with I2 =71.2 and the Cochran Q test P =0.002, which indicates moderate heterogeneity 2-year PFS was 76.8% with I2 = 65.4 and the Cochran Q test P =0.005, which indicates moderate heterogeneity.	1. Study quality: Blinding : not mentioned ITT : not mentioned 2. Bias : Egger Test found significant evidence of bias for the CR rate, OR rate, and 2-year PFS. The Begg and Mazumadar Rank Correlation Test found evidence of publication bias for only 2-year OS; and Duval and Tweedie Trim and Fill Test extrapolated the probable absence of at least one study for every measure. 3. Heterogenicity: moderate-to-high heterogeneity in the estimates of CR rate, OR rate, and 2- and 5-year	1. Hainsworth et al,2009 *(Clin Lymphoma Myeloma)* 2. Jacobs et al, 2008 *(Clin Cancer Res)* 3. Leonard et al, 2005 *(J Clin Oncol)* 4. Link et al, 2010 *(J Clin Oncol)* 5. Morschhauser et al, 2008 *(J Clin Oncol)* 6. Press et al, 2006 *(J Clin Oncol)* 7. Press et al, 2011a *(ASH Annual Meeting Abstracts)* 8. Zinzani et al, 2008 *(Lancet Oncol)*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Clinical Oncology Inclusion Criteria for the studies : 1. phase II or III clinical trials 2. patients with untreated FL 3. treatment with induction chemotherapy, with or without immunotherapy, followed by any RIT consolidation			2-year OS was 94.2% with I2 =0, which indicated low heterogeneity 5-year PFS was 57.6% (Figure 3C) with I2=66.5 and the Cochran Q test P =0 .018, which indicates moderate heterogeneity 5-year OS was 90.1% with I2 = 49.32 and a P value of 0.116, which fell within the range of low heterogeneity 5. Trial type : 7 were multicenter trials	PFS. Low heterogenecity in both 2- and 5-year OS.	
[62, 63]	Only RCT Eligibility criteria: • Age: >=18	Arm A: chemotherapy + Rituximab Arm B: chemotherapy	• OS • Disease control • Overall response • Toxicity	N of included studies= 7 (5 with FL) N of included pts.= 1943 (1480 with FL) **Results for FL pts:** **OS:** HR for mortality 0.63; 95% CI 0.51 to 0.79 (better overall survival in the Rchemo group than in chemotherapy-alone group)	SR 1a Follow-up: between 18-39 months Randomization: yes Blinding: yes in 6/7 studies	• Forstpointner 2004 *(Blood Journal)* (mantle cell and FL) • Herold 2004 *(ASH Annual Meeting Abstract)* • Hiddeman 2005 *(Blood Journal)* • Forstpointner 2004 *(Blood)*

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	• Histologic confirmation of FL or mantle cell lymphoma			**Disease Control:** R-chemo statistically significantly superior to chemotherapy alone: Peto Odds-Ratio: 0.58 (95% CI 0.50 to 0.68) **Toxicity:** not given for FL pts seperately	ITT: yes in 6/7 studies Financial support: authors' association with the Hoffmann-LaRoche AG., external support received from the German Federal Ministry for Education and Research	• Herold 2004 *(ASH Abstract)* • Lenz 2005 *(Journal of Clinical Oncology)* • Marcus 2005 *(Blood Journal)* • Rivas Vera 2005 *(ASH Abstracts)* Van Oers 2006 *(Blood Journal)*
[64]	Number of included studies: 3 or 2, (FL frontline only)	R-CHOP vs. R-CVP as frontline treatments Arm A: R-CHOP (n=223) Arm B: R-CVP (n=162)	Primary outcome: Response rates (PR, CR, PR+CR)	CR: A: 44 pts. (19.7%); B: 66 pts. (41.3%) (p<0.001) PR: A: 170 pts. (76.2%); B: 65 pts. (40.6%) (p<0.001) CR+PR: A: 214 pts. (96%); B: 131 pts. (81.9%) (p<0.001)	SR 4 with questionable methodology Follow-up: not reported Randomization: included studies randomized but not for here analyzed comparison Blinding: not reported ITT: only 1/4 Financial support: Funding and sources of support not reported; The authors declare that they have no competing interests. Methodological flaws: inconsistent in terms of how many studies are	• Hiddemann 2005 • Domingo 2001 *8Haematologica)* • Marcus 2005 *(Blood)* •

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
					included only frontline analysis (2 to 4 mentioned in different sections of the paper); statistical analysis not feasible this way since different studies compared with each other instead of different study-arms; no reliable conclusions can be drawn	

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10.3.1.2. Einzelstudien

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
(Ardeshna 2003)	RCT	N=309 Recruited between 1982 and 1990	Immediate systemic therapy with oral chlorambucil (10mg/day) (n=158) Vs. Observation until disease progression (n=151) In both arms: RT to symptomatic nodes allowed	Asymptomatic, advanced stages (III+IV), low grade non-HL	16 yrs	OS Cause-specific survival	median **overall survival** for oral chlorambucil 5.9yrs [range 0–17·8] and for observation 6.7yrs [0·5–18·9], p=0·84; hazard ratio 1·026 [95% CI 0·798–1·319) median **cause-specific survival** 9yrs [0–17·8] for oral chlorambucil and for observation 9.1yrs [0·67–18·9] years, respectively p=0·44; hazard ratio 1·125 [95% CI 0·835–1·517])).	R: yes I: yes B: not reported F: Lymphoma Research Trust funded this trial; Conflict of interests: non declared M: recruitment time and study period long ago
(Ardeshna 2014)	RCT	N=463 Recruited between 2004-2009 (UK, Australia, New Zealand,	Planned: Arm A: watch and wait (n=187) Arm B: R induction (4 weekly infusions of375 mg/m2 R) (n=84)	Eligibility criteria: • Pts. aged >= 18 years • Low-tumor-burden follicular lymphoma (grades 1, 2, and 3a) **stage II, III, or IV** • Asymptomatic (no B symptoms or severe pruritus)	46-50 months	• QoL • Time to start of treatment • OS • PFS	**Time to start of new treatment:** 78% (95% CI 69–87) of pts in the R induction group did not need treatment at 3 years, which was sign. more than in the watchful waiting group (HR 0·35, 95% CI 0·22–0·56; p<0·0001)	R: yes I: yes B: no, open label F: trial sponsor (University College London); declaration of interest: Authors received honoraria from Roche, Amgen, Celegene, Novartis, AstraZeneca and so on; furthermore Authors received funding for being

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		Turkey, Poland)	Arm C: R induction + R maintenance (12 infusions given at 2-monthly intervals for 2 yrs) (n=192) Carried out: as a two-arm study: w&w vs. R induction and R maintenance	• ECOG performance status of 0-1 Characteristics of included pts.: Median age: A: 60 years (range 28 to 82); B: 60 years (range 33-86); C: 60 years (range 27-87) Male sex: A: 79 pts. (42%); B: 34 pts. (40%); 99 pts. (52%)			Pts in the R induction group did not show improvements in their **QoL** compared with the w&w group. There was a sign. improvement in the Mental Adjustment to Cancer scale score from baseline to month 7 in the R maintenance group (p=0·0001) that did not occur in the watchful waiting group (p=0·19) 18 serious **AEs** reported in the R groups (four in the rituximab induction group and 14 in the maintenance rituximab group) **Time to start of new treatment w&w vs. maintenance**: sign difference in the time to start of new treatment, with 46% (95% CI 39–53) of pts in the w&w group not	advisory board members, speakers or data managers or travel and accommodations; Roche provided Rituximab free of charge, Authors also received funding from National Institute for Health Research Biomedical Center at University College London Hospitals M: planned 3 arm trial went on to be a 2 arm trial for most of the analysis

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							needing treatment at 3 years compared with 88% (83–92) in the R maintenance group (hazard ratio [HR] 0·21, 95% CI 0·14–0·31; p<0·0001) **3-year PFS** was 36% (95% CI 29–43) in the w&w group and 82% (77–88) in the R maintenance group (HR 0·23, 95% CI 0·16–0·32; p<0·0001) **3-year OS** was 94% (95% CI 90–98) for the w&w group and 97% (94–99) for the R maintenance group, with **no difference** between the two groups (HR 0·73, 95% CI 0·34–1·54;p=0·40)	
[65]	RCT	N=193 Newly diagnose d FL pts with low	Arm 1: no initial treatment (N=66) (watch&wait)	Previously untreated pts with small-cell or mixed-cell follicular NHL confirmed by nodal biopsy < 70 years old	Median 45 months	• ORR/CR • Freedom from treatment (FFT) • FFT failure (FFTF)	ORR/CR evaluated for treatment arms 2&3, no sign. differences Progression: Median time to progression:	R: yes I: yes B: no F: not reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		tumor burden Recruitment: October 1986 to May 1995	Arm2: prednimustine 200mg/m2/d for 5 days per month for 18 months (N=63) Arm 3: interferon-alfa 5 MU/d for 3 months then 5 MU three times per week for 15 months (N=63)	Ann Abor stages II, III, IV		• OS • Progression Toxicity/Safety	Arm 1: 23 months Arm 2: 40 months Arm 3: 32 months Early progression (<1 year): Arm 1: 21 Arm 2: 7 Arm 3: 13 • No further analysis OS at 5 years: Arm 1: 78% Arm 2: 70% Arm 3: 84% Median OS: not reached Major cause of death: progression Toxicity: no analysis “toxicity of prednimustine was mild”; “Side effects of interferon alfa, such as fever, chills, and asthenia, were commonly observed. For 10 patients in arm 3, treatment with interferon alfa was withdrawn in the	M: old study

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							absence of lymphoma progression"	
(Colombat 2012)	Prospective cohort study	N=49	One arm Outpatient weekly treatment with R	• 18–75 years of age • a histologically confirmed diagnosis of FL according to the Revised European American Lymphoma classification • stage II–IV of the Ann Arbor classification, with at least one measurable site and low tumor burden according to the GELF criteria	Median: 83.9 months	• clinical response 1 month after the end of rituximab treatment • PFS • OS • bcl-2 status	• clinical response rate at day 78 was 74% with 13 complete responses (CR)/unconfirmed complete responses (CRu) and 23 partial responses (PR) • median PFS: 23.5 months [95% CI 13.6–36.7] • median response duration for the responders after 3 months (n = 36) was 28.7 months	• R: N/A • B: N/A • I: No (per protocol) • F: Roche • M: No comparator

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							(95% CI 14.9–54.4) • median PFS for patients still bcl-2 positive in blood at day 50 (12.5 months) was significantly shorter than the median PFS of 36.7 months for patients who responded and became bcl-2 negative after rituximab treatment with (P = 0.019)	
[66]	Randomized Phase II trial	N =59	Arm A: N=29 500 mg ofatumumab IV on day 1 + CHOP every three weeks of each cycle, 6 cycles in total. Arm B: N = 30 1000 mg ofatumumab IV on day 1 + CHOP every three weeks of	Eligible patients: ≥18 years old, had previously untreated grade 1–3 FL (according to WHO) **stage III/IV or bulky stage II**; • ECOG performance status was 0-2.	Median follow-up was 12.6 months.	Primary: • ORR Secondary: • CRR • PFS • OS • PET response • Safety • Pharmacokinetics	ORR: Arm A: 90% Arm B: 100% CRR: Arm A: 24% Arm B: 38% PFS and OS could not be assessed, due to the short follow-up period. AEs had not been separately reported for	R: Yes. I: No sufficient information provided. B: No, study was an open-label trial F: The study was cosponsored by Genmab A/S and GlaxoSmithKline. Editorial support was funded by GlaxoSmithKline.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			each cycle, 6 cycles in total. Patients received acetaminophen 1000 mg and cetirizine 10 mg (or equivalent) before each dose of study drug; all patients received glucocorticoid (prednisolone 100 mg or equivalent) before doses 1 and 2.				each arm. In total, 35 grade 3 or 4 AEs have been documented. Neutropenia (N=13) and leucopenia (N=17) were the most common AEs.	
[67-70] (SABRINA)	2 stage, randomised, open-lable, phase III trial	113 centers in 30 countries N=410	Intravenous 375 mg/m2 R Vs. subcutaneous 1400 mg R Boths plus chemotherapy (6-8 cycles CHOP or 8	• Aged 18 and older • Untreated grade 1,2,3a FL • CD20+ • ECOG 0-2 • Life expectancy of 6 months or more	Median 37 months	• OR (CR, CRu, PR) • EFS • OS • PFS • Pharmacokinetic non-inferiority • SAE and AEs	• OR (after induction) =84.9% (95% CI 79.2-89.5) intravenous vs. 84.4% (95% CI 78.7-89.1) subcutaneous • Frequency of AEs similar in both groups (95% intravenous and 96% subcutaneous)	R: yes, stratified by selected chemotherapy, FLIPI and region I: yes B: NR F: SABRINA trial was sponsored by F Hoff mann-La Roche.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			cycles CVP) every 3 weeks druing induction, followed by R maintenance every 8 weeks	• One or more symptoms requiring treatment			• PFS: (HR 0.84; 95% CI 0.57-1.23) • EFS: (HR 0.91; 95% CI 0.64-1.31) • OS: (HR 0.81; 95% CI 0.42-1.57) • OR (after maintenance)= 78.1% (95% CI 71.3-83.9) intravenous vs. 77.9% (95% CI 71.0-83.9) subcutaneous	
[71]	Retrospective study	N=849	Arm A: watch and wait (n=286) (Arm B: "pts. treated upfront" (n=563))	Eligibility criteria: A: • Newly diagnosed FL grade 1-3A • Ann Arbor stage III-IVA • Watch and wait phase B: • Pts. with stage III-IVA FL • treated upfront during the same period • "Matched background population: ten age- and	Median follow-up (using reverse Kaplan-Meier censoring method: 56.5 months)	OS PFS	A: PFS: • 3-year: 48% (95% CI 43-54) • 5-year: 35% (95% CI 29-42) • 10-year: 29% (95% CI 23-38) OS: • 3-year: 92% (95% CI 89-95)	R: not applicable I: not reported B: not reported F: H. Kopps Foundation, Hasselbalch & Lykkegaard Andersen Foundation, Kong Christian den Tiendes Foundation, and the Danish Research Agency

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				sex-matched persons for pt. in A" Characteristics of included pts. (in A): • Median age (range): 62 years (31-88) Male: female ratio: 0.9			• 5-year: 83% (95% CI 78-89) • 10-year: 65% (95% CI 54-78) Cumulative risk of dying from lymphoma within 10 years of diagnosis: 13% (95% CI 7-20) "A and B had similar OS during the first 50 months after diagnosis (P = 0.7), but A had increased risk of death after 50 months (P < 0.001)"	
[36, 72-78] [79]FOLL 05	RCT	N=534	Arm A: Rituximab, cyclophosphamide, vincristine, prednisone (R-CVP) (n=178; eligible for ITT analysis: 168) Arm B: Rituximab, cyclophospha	Eligibility criteria: • Patients between age 18 to 75 • Histologically confirmed diagnosis of grade 1, 2, or 3a FL • Ann Arbor stage **II to IV** disease • ECOG status of 0 to 2	Median follow-up: • 34 months (range 1 to 90)	Primary outcome: • TTF • OS • ORR • PFS AEs	At median follow-up of 34 months 3-year TTF: • A: 46% • B: 64% • C: 61% 8-Year PFS:	R: Yes" Eligible patients were randomly assigned according to a central procedure stratified by Follicular Lymphoma International Prognostic Index (FLIPI) score (0 to 2 v 3 to 5)" I: Yes "Study end points were evaluated according to the intention-to-treat principle" B: No, Open-label design

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			mide, doxorubicin, vincristine, prednisone (R-CHOP) (n=178; eligible for ITT analysis: 165) Arm C: Rituximab, fludarabine, mitoxantrone (FM) (n=178; eligible for ITT analysis: 171)	• Characteristics of included patients: • Median age: A: 56 years (range 31-75; 32% over 60 years old); B: 56 years (range 33-75; 34% over 60 years old); C: 54 years (range 30-75 years; 34% over 60 years old) Male sex: A: 52%; B: 50%; C: 55%			B vs A: HR for R-CHOP vs. R-CVP: 0.73 (95% CI, 0.54 to 0.98; P = .037) C vs A: HR for R-FM vs CVP 0.67 (95% CI, 0.50 to 0.91; P = .009) 8-year OS: 83% (95% CI, 79% to 87%), with no significant differences among study arms 3-year OS: • A: 98% • B: 95% • C: 93% ORR: • A: 88% • B: 93% • C: 91% • (p=0.247) “Patients treated with R-FM had a higher rate of g III-IV neutropenia (64% vs 28% R-CVP, p<0.001; and vs 50% R-	F: Sources of funding not reported

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							CHOP, p=0.015). During follow-up second malignancies were registered as late events in 23 patients (2%, 3% and 8% in R-CVP, R-CHOP and R-FM, respectively)." At median follow-up of 56 months: 5-year TTF: • A: 43% • B: 56% • C: 56% 5-Year PFS: • A: 62% • B: 60% • C: 47% (overall p=0.011) "27 second malignancies were recorded in all treatment arms: four in R–CVP, 9 in R–CHOP and 14 in R–FM	

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							(p=0.062; R-CVP vs R-CHOP, p=0.169; R-CVP vs R-FM, p=0.018)"	
[80-82] BRIGHT	RCT	N=447	Arm A: Bendamustine + rituximab (BR) (n=224) Arm B: standard rituximab-chemotherapy regimen (R-CHOP or R-CVP) (n=223)	Eligibility criteria: • Age >=18 • CD20-positive indolent NHL (not specific to FL) • Bidimensional measurable disease • Treatment naïve with a need for treatmen Characteristics of included pts.: • Median age (range): A: 60 (28-84); B: 58 (25-86) • Male sex: A: 61% ;B: 59% **Predominantly stage IV**	Follow-up for TTE outcomes: A: 65.0 months ; B: 64.1 months	Primary outcome: • CRR Secondary outcomes: • ORR • PFS • EFS • Time to treatment failure • Median duration of response • OS • QoL (measured by EORTC QLQ-C30)	CR-rate ratio: 1.27; 95% CI: 0.87-1.84; P 5 .0569) No other subgroup results for only FL reported! CR: • A: 67 pts. (31%; (95% CI 25.3-38.2) • B: 52 pts. (25%; 95% CI 19.5-31.7) • CR ratio: 1.26 PR: • A: 139 pts. (65%) • B: 135 pts. (66%) OR • A: 206 pts. (97%; 95% CI 93.3-98.7)	R: Yes "patients were then randomized to open-label treatment with either BR or the standard therapy at a 1:1 ratio" I: Not reported B: No, Open-label design IRC assessed CR F: Frazer, PA.; Funding for editorial, design, and production support was provided by Teva Branded Pharmaceutical Products R&D, Inc.

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						• Safety and tolerability	• B: 187 pts. (91%; 95% CI 86.0-94.4) 5-year PFS: • A: 65.5% (95% CI 58.5–71.6) • B: 55.8% (95% CI 48.4–62.5) OS: • A: 81.7% (95% CI 75.7–86.3) • B: 85% (95% CI 79.3-89.3) HRs: • PFS: 0.61 (95% CI 0.45-0.85; p=0.0025) • EFS: 0.63 (95% CI 0.46-0.84; p=0.0020) • DOR: 0.66 (95% CI 0.47-0.92; p=0.0143) • OS: 1.15 (95% CI 0.72-1.84; p=0.5461) “Incidences of vomiting and drug-hypersensitivity	

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							reactions were significantly higher in patients treated with BR ($P < .05$), and incidences of peripheral neuropathy/paresthesia and alopecia were significantly higher in patients treated with standard-therapy regimens ($P < .05$)" physician-reported AEs differed somewhat from patient-reported QOL QoL: BR showed improvements in Cognitive Functioning, Physical Functioning, Social Functioning, GHS BR showed reduction in dyspnea, constipation, fatigue (at some but not all time points assessed) Standard therapy showed less nausea/	

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							vomiting at one time point assessed	
[83]	Randomized phase trial	N=81 pts	Induction therapy: Arm 1: 4-6 cycles of obinutuzumab (1000mg IV on days 1 and 8 of the first and on day 1 of each subsequent cycle) +bendamustine every 4 weeks Vs. Arm 2: 6-8 cycles of obinutuzumab (1000mg IV on days 1 and 8 of the first and on day 1 of each	• aged ≥18y • CD20+ FL • with no prior systemic therapy • ≥1 bi-dimensionally measurable lesion (>1.5 cm at its largest dimension by CT • life expectancy >12 weeks • ECOG performance status: 0-2 • no disease transformation based on lymph node biopsy or re-biopsy within 5 months of the start of treatment (most patients (91%) had **Ann Arbor stage III-IV** disease, had an intermediate/high FLIPI	2 years	**Primary:** • Safety **Secondary:** • ORR • CRR • PFS • Pharmacokinetics of study drug • B-Cell depletion and recovery Safety of maintenance therapy	Safety • Adverse events 37% of patients in arm 1 and 55% of patients in arm 2 suffered from at least one grade 3 or 4 hematological adverse event. The most common AE was neutropenia. ORR: Total: 94% Arm 1: 93% Arm 2: 95% CRR: • after completion of induction phase Total: 36% Arm 1: 37%	R: Yes. I: Safety and efficacy analysis included all patients with at least one dose of study drugs. B: No, study was an open-label trial F: The study was funded and sponsored by Hoffmann-La Roche M: Reporting bias → No report on event-free survival (preliminary defined as relevant outcome in the study protocol)

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			subsequent cycle) +CHOP every 3 weeks Pts with end-of-treatment response: eligible for obinutuzumab **maintenance** every 3 months for 2 years or until progression	score (82%), and had extra-nodal involvement (67%); 43% had bulky disease)			Arm 2: 35% •after 30 months Total: 61% Arm 1: 63% Arm 2: 58% PFS: • 3-year PFS rate Arm 1: 90% Arm 2: 84%	
[84, 85] *2012 (HD2000)	Randomized	N=126 All patients FL	CHOP + 1 dose R vs. CHOP + 3 doses R vs. CHOP + 6 doses R (every group 6 cycles of CHOP)	Advanced stage FL (IIIa + IV) Previously untreated CD20+	60 months	• Molecular remission (primary) • Clinical remission • EFS • OS • toxicity	• Molecular Remission: "Results … strongly biased, … the duration of molecular remission could be answered" • PR: 97% (arm B,C, 86% in arm A) • Five-year EFS: 45% in arm A, 60% in arm B and 65% in arm C, no difference between the three arms (P=0.35) • Five-year OS: 72% in ar m A, 82% in arm B, and 80% in arm C, with no	R: yes I: Yes B: not reported F: N/A M: No comparator; dose-finding-study

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							significant difference between the three arms (P=0.46) • AE: most common: leucopoenia (70% of allCHOP cycles); no difference in infectious (P 5 0.67) and allergic(P 5 0.70) complications	
[86] East German Study group Hematology and Oncology Study	Randomized	n=358; FL: N=201 MCP+R n=105 MCP n=96	MCP + R Vs. MCP alone Each: 8x28-day cycles CR or partial remission: Interferon maintenance until relapse	• Advanced stages (III & IV) indolent or mantle cell lymphoma; 56% of pts FL • Here previous results from only FL pts! • Previously untreated • CD20+ • 18-75 yrs • Grade 1&2 only • General performance status of < =2 • In need of therapy	6 years (Herold 2011)	• OS • OR • CR • EFS • PFS • AE	• OS: MCP + R 87%, MCP 74% (4 years) • OR: MCP + R 92% vs. MCP 75% • CR: MCP + R 50%, MCP 25% • EFS: MCP + R: 34 vs. MCP: 57 patients have experienced a treatment failure event (median EFS not reached in MCP+R group vs. 26 months) • PFS: MCP + R 71%, MCP 40% • AE: reported more frequently in theR-MCP armthan in the MCP	R: yes I: yes B: not reported F: conflict of interest disclosure provided for all authors, mostly honoraria and research funds from Roche and Novartis stated

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							arm (99% v 86% of patients)	
[87] (GLSG)	prospective, randomized, open-label multicenter phase 3	N=427 CHOP+R: N=223 CHOP: N=205	CHOP+R Vs. CHOP	• Advanced stages FL • Requirement for therapeutiv interventions	3 yrs	• ORR • OS • RR for treatment failure • Time to treatment failure • Duration of remission • AE	• CR: CHOP: 17% vs. CHOP+R: 20% • ORR: CHOP: 90% (85-94) vs. CHOP+R 97% (93-98) • OS: At 2 years 95% for those treated with R-CHOP and 90% for those treated with CHOP • Time to treatment failure: RR 0.354 (60 and older) (CHOP+R) • Duration of Remission: 16 months (CHOP+R) vs 10 months (CHOP); P<0,38) • AE: Grades 3 and 4 granulocytopenia occurred after 63% of R-CHOP cycles compared	R: yes I: yes B: no F: DKH, BMBF

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							with 53% of CHOP cycles	
[88, 89] Nordic lymphoma	Phase III, randomized	N=313	R (N=156) Vs. R plus 5 weeks of Interferon (N=157) Each 4 weekly infusions of R, responders eligible for another cycle (N=120 in R; N=124 in R+IFN)	• 87 % had not received any previous lymphoma therapy • Symptomatic indolent B-cell lymphomas (FL, MZL, SLL, NOS) • Advanced stages • CD20+ • Requiring therapy because of symptomatic or progressive disease Aged >18	61 months	• CR • Cru • PR • Median time to treatment failure (TTF) OS	• CR/CRu/OR after cycle 1: 59% in pts with R+IFN and 54% in R only (p=0.34) • CR/CRu/OR after cycle 2: 82% for R+IFN vs. 74% R alone (p=0.116) • Median TTF: 28.0 months R+IFN vs 21.5 months Ralson (p=0.302) • At 5 years, 33% of pts were still failure-free, with no difference between the randomization arms • **FL Subgroup (N0257):** no sign. diff in TTF • OS:13% in R and 11% in R+IFN (p=0.496), no treatment related death reported	R: yes, for induction I: yes B: not reported F: The study was supported by research grants from F.Hoffman-La Roche Ltd in collaboration with the NordicLymphoma Group (NLG) and was also supported in part by research funding from the Nordic Cancer Union (NCU) and a joint grant from Karolinska Institutet and Stockholm County Council. Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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							• **FL OS**: 87% R vs 90% in R+IFN Hematologic toxicity of grade 3 or 4 was neutropenia and thrombocytopenia, each occurring in 3% of patients in the R+ IFN group, compared to <1% (neutropenia) or none (thrombocytopenia) in the R only group	
[90]	Randomized open label	N=322 Enrolled between 2000-2002	I. CVP Dose 750 mg/m2 cyclophosphamide intravenously (i.v.) on day 1; 1.4 mg/m2 vincristine, up to a maximal dose of 2 mg i.v., on day 1; and 40 mg/m2 prednisone per day, orally, on days 1–5; n = 159.	Inclusion criteria: Pts 18 yrs or older with untreated CD20-positive FL; stage III or IV disease; need for therapy Median age: 52yrs male: 174; female: 148	53 months	• OR • CR • PR • OS • TTF • TTP • DFS • AEs	**TTF:** sign. prolonged in pts receiving R-CVP (27months; 95% CI: 6-9) compared with those who received CVP alone (7months; 95% CI: 6-9) (P < 0.0001) **OS:** improvement after treatment with R-CVP (83%; 95%CI 77-89) versus CVP (77%; 95% CI 70-83) alone (P=0.029) **incidence of AE:**	R: yes B: no I: yes F; many authors received honoraria from pharmaceutical industries, are consultants and advisory board members or received research funding

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			II. Rituximab + CVP Dose 375 mg/m2 rituximab i.v. on day 1 of eight therapy cycles; n = 162. Patients in both groups were treated every 21 days for a maximum of 8 cycles.				similar in the R-CVP and CVP groups; higher incidence of grade 3/4 neutropenia during treatment with R-CVP (24%) compared with CVP (14%), this did not translate into a higher rate of infections; no treatment-related deaths Statistically sign. And clinically relevant improvements in all other time-to-event variables—including TTP (P<.0001), response duration (P<.0001), and time to next antilymphoma treatment or death (P <. 0001) were demonstrated in pts treated with R-CVP compared with those who received CVP alone.	

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[91-93]	RCT	N=1202 patients with follicular lymphoma	Arm 1: N=601 Obinutuzumab (1000mg IV on days 1, 8 and 15 of the frist and on day 1 of each subsequent cycle, 6 to 8 cycles in total) + chemotherapy (either CHOP, CVP or bendamustine) Arm 2: Rituximab (375mg/m2 IV on day 1 of each cycle, 6 to 8 cycles in total) + chemotherapy (either CHOP, CVP or bendamustine) (Chemo: CHOP (33.1% of pts), CVP (9.8% of	• aged ≥18y • previously untreated FL (grades 1-3a) • **advanced stage (III or IV or II with bulk)** • ECOG performance status: 0-2 • The median age was 59 years and 53.2% of patients were female)	Median follow-up was 34,5 months.	**Primary:** • PFS **Secondary:** • ORR • Duration of response • OS • Event-free survival • Disease-free survival • time to new antilymphoma treatment • Safety • Pharmacokinetics and pharmacodynamics • Minimal-residual disease • Transformation rate to diffuse	PFS: HR: 0.66, 95% CI: 0.51 to 0.85, p=0.001, favoring arm 1. ORR: Arm 1: 88.5% Arm 2: 86.9% CRR: Arm 1: 19.5% Arm 2: 23.8% OS: HR: 0.75, 95% CI: 0.49 to 1.17, p=0.21. EFS: HR: 0.65, 95% CI: 0.51 to 0.83, p<0.001. New antilymphoma treatment: HR: 0.68, 95% CI: 0.51 to 0.91, p=0.009. Safety	R: Yes. I: Efficacy analyses included all randomized patients and safety results were analyzed in the subgroup of patients with at least on dose of study drugs. B: No, study was an open-label trial. F: The study was sponsored and funded by Hoffmann-La Roche

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			pts), or bendamustine (B) 57.1% of pts - allocated according to center) Pts with a CR or PR at the end of induction received study antibody every 2 months for 2 years or until withdrawal from trial as **maintenance** therapy			large-cell lymphoma	-Grade 3 to 5 AEs (induction phase) Arm 1: 60% Arm 2: 56.3% -Patients with at least one SAE (induction phase) Arm 1: 27.9% Arm 2: 24.1%	
[94]	Prospective observational study	N=1754	Arm A: Watchful waiting (n=386) Arm B: Rituximab monotherapy (n=296) Arm C: Rituximab +	"The National LymphoCare Study is a prospective, multi-centre, observational study collecting data on over 2700 previously untreated patients with FL newly diagnosed from 2004 to 2007 at 265 sites in the United States (US)	Median follow-up: 8.1 years	• **OS** **PFS**	HRs (multivariate analysis) C vs. A: • OS: 0.96 (95% CI 0.74-1.24; p=0.77) • Confirmed/ suspected transformation: 0.67 (95% CI 0.49-0.91; p=0.01)	R: no I: N/A B: N/A F: This work was supported by Genentech Inc./F. Hoffmann-La Roche Ltd. Support for editorial assistance was funded by Genentech Inc. M: non randomized calculating hazard ratios: comparable?

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			chemotherapy (n=1072)	Eligibility criteria: • Pts. aged >=18 years • Diagnosed with FL within 6 months of enrolment • No prior history of lymphoma • **FL stage II-IV** • Characteristics of included pts: • Age <=50: A: 87 pts. (23%); B: 47 pts. (16%); C: 270 pts. (25%) • Age 51-60: A: 99 pts. (26%); B: 53 pts. (18%); C: 287 pts. (27%) • Age 61-70: A: 100 pts. (26%); B: 66 pts. (22%); C: 274 pts. (26%) Age >=70: A: 100 pts. (26%); B: 130 pts. (44%); C: 536 pts. (50%)			• PFS from diagnosis: 0.44 (95% CI 0.38-0.52, p<0.0001) • TTNT: 0.37 (95%CI 0.31–0.45; p<0.0001) • Time to first chemotherapy: NA • PFS after second-line therapy: 0.71 (0.58-0.87; p=0.001) • PFS from first active-lymphoma treatment: 0.98 (0.70-1.38; p=0.91) B vs. A: • OS: 0.90 (95% CI 0.66-1.23; p=0.51) • Confirmed/ suspected transformation: 1.01 (95% CI 0.69-1.48); p=0.95) • PFS from diagnosis: 0.70 (95% CI 0.57-0.86, p=0.001)	

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							• TTNT: 0.70 (95%CI 0.57–0.87; p=0.001) • Time to first chemotherapy: 0.71 (95% CI 0.54-0.93; p=0.01) • PFS after second-line therapy: 1.01 (0.79-1.29; p=0.93) • PFS from first active-lymphoma treatment: 0.84 (0.60-1.16; p=0.28) "Although time to new treatment and progression-free survival following first- and second-line therapy were improved with chemoimmunotherapy, and time to chemotherapy was improved with rituximab monotherapy, there were no differences in overall survival between watchful waiting and	

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							chemoim- munotherapy or rituximab monotherapy"	
[95-98] SWOG S0016	RCT	N = 532	Arm A: CHOP-R (n = 267) 6 cycles of CHOP every 21 days with 6 doses of rituximab Arm B: CHOP-RIT (n = 265) 6 cycles of CHOP every 21 days **followed by consolidation** with tositumomab/iodine I-131 tositumomab radioimmunotherapy	• Patients: • >18y • **advanced-stage (bulky stage II, III, or IV)** evaluable FL of any grade (1, 2, or 3) • **had not received previous therapy** • expressing CD20 • performance status 0-2	median follow-up 4.9 years	• CR • Cru • PR 200 and 365 days after therapy initiation and every 6 months until deaths or signs of FL recurrence: • Remission • Survival status • AE	• Objective remissions were documented in 84 % of pts in both groups • CR detected in 40 % (Arm A) / 45% (Arm B) / P=.30 After follow up: • 2yPFS: 80% (Arm B) • 5yPFS: 66% (Arm B) • 2yPFS: 76% (Arm A) • 5yPFS: 60% (arm A) • two-sided P=.11; one-sided P=.05 • 2yOS: 93% (Arm B) • 5yOS: 86% (Arm B) • 2yOS: 97% (Arm A) • 5yOS: 92% (Arm A) • P=.08	Randomly assigned, but not for consolidation ITT and Blinding are not reported Some Authors are employee at pharmaceutical industries and/or received honoraria of those

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							"AE were similar on the two arms and appeared dominated by the effects of CHOP chemotherapy rather than the immunotherapeutic components" Kelly 2015: Although statistical significance was not reached [...] serum vitamin D might be the first potentially modifiable factor to be associated with FL survival.	
[99, 100]	RCT	N=549 (514 assessed)	A: Bendamustine + rituximab (n=261) B: CHOP-R (n=253)	Eligibility criteria: • Pts. aged >=18 • WHO performance status of 2 or less • stage III or IV disease • Histologically confirmed diagnosis of mantle-cell lymphoma or indolent non-Hodgkin lymphoma, including	Median follow-up: 45 months (range 29-57)	Primary outcome: • PFS Secondary outcomes: • ORR • CRR • Acute or late toxic effects • OS	At median follow-up of 45 months (all pts, FL pts 54%): PFS: HR for A vs. B: 0.58 (95% CI 0.44-0.74; p<0.001) Median PFS: • A: 69.5 months • B: 31.2 months	R: Yes "Patients were stratified by histological lymphoma subtype, then randomly assigned according to a prespecified randomization list" I: No "Analysis was per protocol." B: No, Open-label design F: Funding was received from Roche Pharma AG, Ribosepharm/Mundipharma GmbH

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				• Follicular (FL) (grade 1 and 2) • Lymphoplasmatic • Small lymphocytic • Marginal-zone lymphoma Characteristics of included pts. • Median age: A: 64 years (range 34-83); B: 63 years (range 31-82) • Nb. of pts. with follicular lymphoma: A: 139 pts. (53%); B: 140 (55%)		• Time to next antilymphoma treatment EFS	**PFS in pts. with FL:** HR for A vs. B: 0.61 (95% CI 0.42-0.87; p=0.0072) ORR: • A: 242 pts. (93%) • B: 231 pts. (91%) CRR • A: 104 pts. (40%) • B: 76 pts. (30%) (p=0.021) "Patients in the bendamustine plus rituximab group had fewer toxic effects than did those in the R-CHOP group": SAEs: • A: 49 pts. (19%) • B: 74 pts. (29%) "Overall survival did not differ between the treatment arms, with 43 and 45 deaths in the B-R and CHOP-R arms, respectively."	

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[101] GELA-GOELAMS FL 2000	Randomized Comparison unclear? Paralell Design	n=358 all FL CHVP+R n=175 CHVP: n=183	6xCHVP + 6 Infusions of Interferon + R Vs. 12xCHVP + Interferon Each over 18 months	• **Age:** 18-75 • First line • High tumor burden • ARBOR stage II, III, IV	Median 8.3 yrs (Bachy 2013)	• EFS • 5y OS • AE	• 8-year EFS rates were 27.9% (95%CI) (CHVP+I) 21.1-34.6%) and 44.1% (CHVP+I+R) (95%CI: 36.7-51.7%) • OS at eight years was 69.8% (95%CI: 63.1-76.6%) and 78.6% (95%CI: 72.5-84.7%) in CHVP+I and R-CHVP+I arms • AE: 23 (6.4%) secondary malignancies occurred: 14 (7.6%) in the CHVP+I and 9 (5.1%) in the R-CHVP+I group	R: yes I: yes B: Open label M: are study arms comparable? And results interpretable like this?
[102]	retrospective	N=348 (FL pts diagnosed between 2000 and 2012)	W&w (n=101) Vs. Immediate treatment (n=247)	Median age 57 yrs (19-85) Inclusion criteria: • Patients who were newly diagnosed with FL grades 1 to 3a Exclusion criteria:	Median: 75 months (range: 7–169)	• OS • TTF • Cumulative risk of transformation	• TTF: median TTF were 92 months (95 % CI, 60.1–NA) in the WW cohort vs. 77 months (95%CI, 65.1–107.6) in the immediate treatment	R: no B: N/A I: N/A F: National Cancer Center Research and Development Fund, Japan Agency for Medical Research and Development (AMED). M: Retrospective analysis

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				• presence of a histological transforming component such as diffuse large B cell lymphoma (DLBCL) at the time of the initial diagnosis enrolled in new agent clinical trials			cohort, which were not significantly different (P = 0.272) • OS: difference in OS rates between the WW cohort and the immediate treatment cohort was not significant (P = 0.294) • cumulative incidence rates of transformation at 5 and 10 years were 4.4 % (95 % CI, 1.0–11.8) and 4.4 % (95 % CI, 1.0–11.8) in the WW cohort and 3.6 % (95%CI, 1.7–6.7) and 7.6 % (95 % CI, 4.2–12.1) in the immediate treatment cohort, respectively	

Konsu

10.3.2. GRADE-Bewertung

10.3.2.1. GRADE-Bewertung Antikörper vs. kein Antikörper

10.3.2.1.1. GRADE-Bewertung: Chemo + Rituximab vs. Chemo

[86, 87, 90, 101]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS/Mortalität	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL						Not reported
	RCT	Safety	-	-1	-	-1	-	⊕⊕⊖⊖ low

OS nicht in allen Studien als HRs berichtet: breite Konfidenzintervalle, die die schmalere CIs haben: nicht signifikant; wenige Events insgesamt; PFS: nur von einer Studie konkret berichtet, andere EFS; Safety: teilweise verschiedene Richtungen, breite Konfidenzintervalle

Konsultation

10.3.2.1.2. GRADE-Bewertung: Chemo+Obinutuzumab vs. Chemo+Rituximab

[91, 92]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-	-	⊕⊕⊕⊕ high

OS: breites Konfidenzintervall

10.3.2.1.3. GRADE-Bewertung: Dosisvergleich 500mg Ofanutumumab vs. 1000 mg Ofanutumumab

[66]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS						Not reported
	RCT	PFS						Not reported
	RCT	QoL						Not reported

Konsultation

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	Safety						Not reported

10.3.2.1.4. GRADE-Bewertung: Rituximab subkutan vs. Intravenös

[67-70]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	QoL						Not reported
	RCT	Safety	-1	-	-	-		⊕⊕⊕⊖ moderate

OS, PFS: breites Konfidenzintervall und nur eine Studie; Safety: nur eine Studie

Konsu

10.3.2.2. GRADE-Bewertung: Watch and wait vs. Induktion

[65, 94, 103-105]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT+Non-RCT	OS	-	-1	-	-1	-	⊕⊕⊖⊖ low
	RCT+Non-RCT	PFS	-	-1	-	-	-	⊕⊕⊕⊖ moderate
	RCT	QoL	-1	-	-	-1	-	⊕⊕⊖⊖ low
	RCT	Safety	-1	-	-	-1	-	⊕⊕⊖⊖ low

OS: viele verschiedene Studienmodelle mit verschiedenen Vergleichsarmen, breite Konfidenzintervalle, keine klare Richtung; PFS: in einer randomisierten und in einer nicht-randomisierten Studie berichtet; QoL, Safety: nur in 1 RCT berichtet, keine Berichte zu Grad 1 und 2 AEs, keine Analyse

Konsultation

10.3.2.3. GRADE-Bewertung Chemotherapie-Vergleiche

10.3.2.3.1. GRADE-Bewertung: Bendamustine vs. CHOP/CVP

[82, 83, 100]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-1	-1	-	⊕⊕⊖⊖ low
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL	-	-	-1	-1	-	⊕⊕⊖⊖ low
	RCT	Safety	-	-	-	-1	-	⊕⊕⊕⊖ moderate

OS: breite Konfidenzintervalle, Grigg 2016 berichtet kein OS, Flinn 2014 nicht spezifisch zu FL; QoL: nur von einer Studie berichtet, diese nicht spezifisch zu FL; Safety: keine Analyse

Konsultation

10.3.2.3.2. GRADE-Bewertung: CVP vs. CHOP

[79]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-1	+1	⊕⊕⊕⊕ high
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-1	-	⊕⊕⊕⊖ moderate

nur eine Studie vorhanden; PFS: langer Nachbeobachtungszeitraum und signifikanter Effekt

Konsultat

10.4. Kapitel 8 Systemische Postinduktions-Therapien in der Erstlinientherapie

10.4.1. Evidenztabellen

10.4.1.1. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
[106]	• Objectives : effects of IFN in maintenance therapy • CENTRAL (Issue 4, 2008), CHMG trial register, MEDLINE (1966-2008), DARE (1990-2008), SCOPUS (December 2008), Current Contents : Clinical Medicine and Life Science (1975-2008) • RCTs of FL (or at least >70% FL) • N=8 • N=1563 pts	• Interferon-alpha (IFN) vs no intervention or placebo (5RCTs) • or • IFN plus chemo vs chemo alone (3RCTs) • IFN alfa-2b in six RCTs / IFN alfa-2a in 2 RCTs Heterogenous in terms of diagnosis of FL	• OS • PFS • AE/Toxicity • Overall response • Adherence and coping with therpay, expressed as number of pts lost to follow up • QoL • Cost-effectiveness and costs per	**OS**: no difference in the risk for all-cause mortality between interferon and placebo or no intervention (HR 0.90; 95% CI 0.61 to 1.34) ; statistical evidence of heterogeneity (P = 0.03, I2 = 63%). **OS**: IFN vs all comparators (fixed effects HR 0.79, 95% CI 0.67 to 0.94, I2 = 52%), but adjusted for heterogeneity: (random effects HR 0.82, 95% CI 0.63 to 1.08) with marginally significant statistical heterogeneity between the trials (P=0.04, I2 = 52%) **OS** : IFN vs placebo/no intervention (HR 0.90, 95% CI 0.61 to 1.34) **OS:** IFN plus chemo vs chemo alone (HR 0.68, 95% CI 0.52 to 0.90) no heterogeneity (P = 0.39, I2 = 0%) **PFS:** IFN vs placebo/no intervention (HR 0.74;95% CI 0.61 to 0.91); no significant heterogeneity (P = 0.97, I2 = 0%)	SR&MA 1a randomization: ja ITT: in 4 of 8 RCTs Allocation Concealment: reported by one RCT Median follow up: not reported Financial Funding: no industrial funding Blinding: not reported All studies well balanced in terms of baseline characteristics	• Aviles 1996 Leukemia and Lymphoma • Aviles 2004 Leukemia and Lymphoma • Fisher 2000 Journal of Clinical Oncology • Heganebeek 1998 Journal of Clinical Oncology • Neri 2001 Journal of Hematotherapy and Stem Cell Research • Rohantiner 2001 British Journal of Cancer • Smalley 2001 Leukemia • Solal-Celigny 1998 Journal of Clinical Oncology

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	RCTs with induction or upfront therapy with IFN excluded		quality adjusted life year	**PFS:** IFN plus chemo vs chemo alone (HR 0.56; 95%CI 0.45 to 0.71) moderate heterogeneity among studies (P = 0.13, I2 = 51%) **PFS:** IFN vs all comparators: (HR 0.66, 95% CI 0.57 to 0.77) using the fixed-effects model; was no statistical heterogeneity between trials (P=0.20, I2 = 31%). **Toxicity and loss to follow up**: sign. higher in IFN **Overall response**: no significant difference in response to treatment for patients given interferon-alpha and patients not treated (RR = 1.12; 95% CI 0.95 to 1.33); evidence of heterogeneity (P = 0.02, I2=75%) **Lost to follow-up:** (4RCTs) greater risk to drop out in patients treated with interferon (RR=5.63; 95% CI 1.06 to 29.94); significant heterogeneity between trials (P = CHVP chemotherapy plus interferon-alpha provided an average gain of 7.8 quality-adjusted months as compared with chemotherapy alone 0.06, I2 = 59%) **QoL:** CHVP chemotherapy plus		

Kor

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				interferon-alpha provided an average gain of 7.8 quality-adjusted months as compared with chemotherapy alone		
[107] ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Search according to ESMO standards, not further explained	Recommendation on **consolidation/ maintenance in first line therapy**: Myeloablative consolidation + ASCT		• Rituximab maintenance for 2 years improves PFS (59% vs 43% after 6 years, P < 0.0001, a shorter maintenance period results in inferior benefit (I, B) • RIT consolidation also prolongs PFS after chemotherapy, but its benefit seems to be inferior in comparison with rituximab maintenance for 2 years (II, B) Myeloablative consolidation followed by ASCT prolongs PFS after chemotherapy, but its benefit after a R-containing induction is minor and no OS has been observed. Therefore, such an approach is not recommended in first-line therapy of responding patients (I, D)	• Clinicial practice guideline developed in accordance with the ESMO standard operating procedure • LoE and grades of recommendation given (adapted from the Infectious Diseases Society of America-United States Public Health Grading System COI: Authors received funding from several	• Salles 2013 Blood • Taverna 2013 Blood • Morschauser 2013 J Clin Oncol • Lopez-Guillermo 2013 Blood • Hiddemann 2013 Blood

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
					industrial companies such as Celegne, Janssen, Mundipharma, GileadPfizer, Roche; Authors in advisory boards for Bayer, Celegene, Gilead, Janssen, Pfizer, Roche, AstraZeneca; some received research support from Celegende, Janssen, Munidpharma, Pfizer, Roche	
[108] CME Information: Follicular lymphoma: 2015 update on diagnosis and management	First line and relapse	/	Maintenance R Maintenance Radioimmuntherapy Maintenance HDT+ASCT	**Rituximab:** **First line:** • A prospective study compared observation to R alone or R followed by maintenance in previously untreated FL. No difference in OS or incidence of histologic transformation was seen (A) • The important issues of time to second therapy, cost, toxicity, and future responses	• No commercial support has been accepted related to the development or publication of this activity • Authors claim no financial conflicts of interest No clear recommendations given, only relevant studies and their results listed	• Ardeshna 2014 Lancet Oncology • Ardeshna 2010 Blood • Kahl 2014 J Clin Oncol • (D)SAKK trial Martinelli 2010 J Clin Oncol • Salles 2011 Lancet • Vitolo 2013 J Clin Oncol • Morschhauser 2013 J Clin Oncol

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				to rituximab are not yet addressed (B) • A trial in a similar patient population randomized patients following four doses of weekly R to either observation and retreatment at progression, or R maintenance for 2 years. No difference in time to treatment failure, histologic transformation, or OS was seen, but more R was administered to the maintenance arm. There was a difference in time to cytotoxic therapy, in favor of the maintenance R receiving patients (C) • At a median follow-up of 36 months from randomization, pts assigned to R maintenance had a		• Press 2013 J Clin Oncol • (I) Al Khabori 2012 J Natl Cancer Inst

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				higher rates of PFS (75 vs. 58%). A higher percentage of patients in CR/CRu at 24 months (72 vs. 52%) 2 years post randomization. There was a significantly higher percentage of patients with grade III/IV AEs and infections in the R maintenance • group. At this time, OS is the same in both groups. (E) • abbreviated maintenance R: R maintenance did not have a statistically • significant PFS benefit. Therefore, the role for maintenance with regimens besides CHOP-R or CVP-R remains uncertain (F) **First line & relapsed:**		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				• At a median follow-up of 35 months, patients who received the prolonged R maintenance had a two fold increase in EFS (23 vs. 12 months). Now with longer follow-up 35% of responders remain in remission at eight years with 45% of newly diagnosed patients in this study in remission at eight years with the additional maintenance R (D) **RIT:** • As consolidaton: At 8 years, both the PR and CR patients who received Yi90-ibritumomab tiuxetan had significantly longer median PFS with improvement of about 36 months.(G)		

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				In contrast to this study a randomized trial of CHOP plus rituximab to CHOP followed by 131I tositumomab did not see any differences in PFS between the two arms (H) **HDT+ASCT:** • majority of these studies have demonstrated a significant • improvement in PFS, but no impact on OS. One reason for the lack of impact on OS has been the excess number of second malignancies (I)		
[109] NICE reports results of PRIMA study	N=1 (N of pts. 1018) Multicenter-open-label, phase 3 RCT	Intervention : Rituximab Control : Observation only	Primary outcome: PFS Secondary outcomes: EFS	PFS (Median follow-up: 38 Months): Intervention: Median time-to-event not reached Control: Median PFS : 48.36 months	Evidence Review (based on single study and Cost-effectiveness analysis) RCT	PRIMA

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Pts. with advanced follicular non Hodgkins lymphoma		Time-to-next antilymohoma treatment ORR	(HR 0.55, 95% CI 0.44-0.68 ; p<0.0001) Median follow-up for secondary outcomes : 36 months EFS Intervention: Median not reached Control: Median 45.4 (HR 0.59 (0.48-0.72) OS : Insufficient events Time-to-next antilymphoma treatment : Intervention : Median not reached Control : Median not reached (HR : 0.60, 95% CI 0.47-0.76, p<0.0001)	Blinding and ITT not reported Judgement by « Evidence Review Group » (ERG) : « Longer follow-up with more events would be required before informed decisions could be made regarding the clinical effectiveness of RTX as a first-line maintenance therapy compared with observation. » « The ERG considered it impossible to draw firm conclusions regarding the clinical or cost effectiveness of the intervention as the dataset was as yet too immature «	
[110] Canadian evidence-based guideline for the first-line treatment of follicular lymphoma	**Fist line**	Systematic literature search and giving recommendations on this basis	Relevant here: Question 4: In which patients should additional treatment be considered after first-line induction?	"*Recommendation (Level of Evidence: Category 1).* Given the improved response with R-maintenance versus observation in 2 randomized trials, **maintenance R is recommended after first-line treatment of FL.** Note: There is currently insufficient evidence to determine the optimal frequency and duration of	• Giving recommendations based on profound methodology • The authors have stated that they have	• Maintenance R: • Vitolo 2013 J Clin Oncol • Salles 2011 Lancet • Van Oers 2010 J Clin Oncol

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				maintenance rituximab after first-line treatment of FL." *"Recommendation (Level of Evidence: Category 1).* We do not recommend HDT followed by ASCT as part of front-line treatment of FL given the lack of a survival benefit and the potential toxicity of this approach. Note: There is no evidence to support the use of RIT after first-line treatment of FL."	no conflicts of interest • financial support of Lymphoma Canada	• Hochster 2009 J Clin Oncol • Forstpointer 2006 Blood • • Consolidation HDT+ASCT: • Morschhauser 2013 J Clin Oncol • Morschhauser 2008 J Clin Oncol • Ladetto 2008 Blood • Tarella 2013 Blood

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
			Consolidation HDT+ASCT			
[111] British Society for Hematology	MEDLINE EMBASE 1980-2010 First line and relapsed	R IFN HDT+ASCT		*Recommendation first line R*: "R maintenance after successful induction therapy prolongs PFS and is recommended in patients responding to first-line R-based chemotherapy (Strong, Moderate)." IFN: Ten trials examined the role of IFN either as an adjunct to induction therapy or as maintenance. In a MA (Rohatiner et al, 2005) a modest improvement in OS and remission duration were seen HDT+ASCT: "has no role in first line therapy for FL (which has no evidence of histological transformation) outside the setting of a clinical trial (Strong, Moderate)"	• GRADE for assessing LoE • Financial support of authors: Travel support and honoraria from Roche; advisory board work Roche, research support Genentech; but non declared a	• Ardeshna 2010 ASH-Abstract • Salles 2008 Blood • Ghielmini 2004 Blood • Hochster 2005 Blood • Salles 2011 Lancet • Lenz 2004 • Deconinck 2005 • Sebban 2006

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
					conflict of interest	• Lenz 2004
[112]	• prospective trials enrolling patients with FL and MCL (5% of those were CLL/SLL pts treated in FL studies) • n=1009 pts receiving MR • only full texts (RCTs and Non-RCTs) • FL or mantle cell lymphoma • Only studies reporting 3/4 AEs • Only studies using R alone or R with Chemo as induction • Only if MR was delivered up to 24 months	• comparative schedule-related toxicities with maintenance rituximab in FL and MCL • trying to find the least toxic schedule • R maintenance R in induction	Grade 3/4 AEs	• 10 trials met inclusion criteria with 9 reporting Aes • 4 front-lin • 4 relapse • 1 study enrolled boths lines • Induction regimens and MR schedules varied amongst studies • **Only front line (>80 % FL pts (and MCL) : 151 AEs of 625 pts I2=93,4%** Overall results : • Total of 24% of pts receiving MR developed grade 3/4 Aes (85% CI : 14-36) ; high degree of hetergeneity among studies (χ 2 = 9 9.6, p = 0.0001, I 2 = 92.0%) • Grade 3/4 AEs summarized by schedule: pts receiving MR every 6 months as 4 weekly infusions for 2 y had fewer grade ¾ AEs compared with those receiving MR as single infusions every 2 months (10% vs. 28%; p= 0.035)	• SR & MA 2a • For potential conflict of interests a link is given, which does not work, so no declaration if potential COIs given Random effects models	• Hainsworth 2005 Journal of Clinical Oncology **(Minnie Pearl Cancer Research Network)** • Hainsworth 2002 Journal of Clinical Oncology • Ghielmini 2005 Journal of Clinical Oncology + Ghielmini 2005 Annals of Oncology (**SAKK** swiss group for Clnical Cancer Research) • Martinelli 2010 Journal of Clinical Oncology (**SAKK**) • Forstpointner 2006 Blood (**GLSG** German Low Grade Lymphoma Study Group) • Van Oers 2010 Journal of Clinical Oncology + van Oers 2006 Blood (**EORTC 20981**) • Kenkre 2011 Leukemia and Lymphoma (**Wisconsin Oncology Network**) • Salles 2011 The Lancet (**PRIMA**)

Kon

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Search: MEDLINE, CENTRAL, Google Scholar for articles published between 1997-2012			• Toxicities were lower for pts R alone vs R+chemo in induction (12% vs 35% ; p= 0.031) No sign. differneces in toxicities between pts in front line vs. Relapsed setting (24% vs 30%, p=0.1)		• Raty 2012 Leukemia and Lymphoma (**Finnish Lymphoma Group**) • Tomas 2011 Leukemia and Lymphoma (**LNHF-03** - Spanish Cooperative Trial)
[113] Madrid	Search in: PubMed Is knowledge ESMO, NCCN, Annual Clinical Updates in Hematology Malignancies of the AJH consulted	R IFN RIT HIT+ASCT		• Only first line recommendations: • Regarding maintenance therapy, the results from the Primary Rituximab and Maintenance (PRIMA) phase III trial have demonstrated that maintenance therapy results in longer PFS, although there is no impact in OS • as first line in patients that need treatment, a combination of chemotherapy with R induction followed by 2 years of R	• The authors declare that they have no conflict of interest • Not systematic • LoE not explained	• Vidal 2009 J Natl Cancer Inst • Provencio 2014 Leu Lymphoma • Montoto 2013 Haematologica

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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
				maintenance is the best option [I, B • A meta-analysis suggested the use of IFN maintenance therapy as part of first-line treatment [II, B]; however, due to poor toxicity profile front of R has made the latter preferred in this setting • RIT consolidation prolongs PFS after chemotherapy, although its benefit following R combinations has not been established as a first-line treatment. It can be an option for patients who are unable to tolerate standard chemotherapy (elderly or unfit patients) or in high-risk patients achieving a PR or CR		

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				after induction therapy • HIT+ASCT in first line has not shown improvement and is not recommended as first-line therapy, this strategy shouldbe used only in clinical trials		
[114]	8 phase III trials with « low-grade » or specifically FL pts for IPD analysis N=1922 (majority stage IV) Median age : 52 (17-91)	In 6 RCTs IFN was part of initial therapy, in 4 RCTs IFN only as maintenenace therapy Chemotherapy : less intensive (CVP) – more intensive (anthracycline or mitoxantrone-based) Interferon : individual dose equal to or less than 5x 106 (ie, 2x106 units/m2 or 3x106 units per dose). vs cumulative doses doses, given 3x weekly, translate	CR/partial response Survival times Duration of remission	**Results specific to maintenance:** no sign. improvement in survival in studies in which IFN was given only as maintenance (2P = 0.20; data not shown) “a survival benefit was seen when IFN was given with chemotherapy rather than as maintenance therapy (P=0.004)” **Overall (not maintenance specific) results:** Response: addition of IFN to initial chemotherapy did not significantly influence response rate overall (2P = .41); estimated difference in percentage response rate was-2%(ie, in favor of the no IFN group; 95% CI,-6%to 3%); though there was considerable heterogeneity between studies (2P = .005)	• SR&MA • 1a • Blinding : not reported • ITT : not reported • Median follow up : not reported • Research funding: A.Z.S. • Rohatiner, Schering-Plough; P. Solal-Celigny, Schering- Plough Some of included trials are very old	• Chisesi 1987 J Investing New Drugs • Peterson 1997 Proc Am Soc Clin Oncol • Solal-Celigny 1993 N Engl J Med • Solal-Celigny 1998 J Clin Oncol • Smalley 1992 N Engl J Med • Andersen 1993 N Engl J Med • Smalley 2001 Leukemia • Arranz 1998 J Clin Oncol • Hagenbeek 1998 J Clin Oncol • Unterhalt 1996 Blood

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		into a monthly dose of 36x106 units		**Survival:** use of IFN-_2 at any point in treatment appeared to prolong survival (2P = .004) ; significant heterogeneity between studies (2P = .003) Considering the individual dose of IFN for patients receiving 5x106 units or more per dose, there was a highly significant increase in survival (2P = .000002; 5- and 10-year survival differences being 15% [95% CI, 9% to 21%] and 20% [95% CI, 12% to 28%], respectively) Conversely, for patients receiving less than 5 x 106 units per dose, there was no effect on survival (2P=.75) **Remission**: prolonged remission duration when all ten studies were considered (2P = .000001; 5- and 10-year remission duration differences being 11% [95% CI, 7% to 15%] and 10% [95% CI, 6% to 13%], respectively)		• Aviles 1996 Leuk Lymphoma • Fisher 2000 J Clin Oncol • Rohatiner 2001 Br J Cancer
[61]	Included studies: N= 8 Included pts:	RIT with either 90Y-ibritumomab tiuxetan or 131I-tositumomab as a possible	• Response rates (OR, CR) • PFS • OS	pts in studies: • age ranged from 49 to 57 years • 41% to 61% male subjects	SR+MA 1a	• Hainsworth (2009) Clin Lymphoma Myeloma • Jacobs (2008) Clin Cancer Res

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	N=783 Eligible studies: • phase II/III clinical trials • assessed RIT consolidation • at least 30 pts **untreated FL** • induction chemotherapy, with or without immunotherapy**, followed by any RIT consolidation** • CENTRAL and MEDLINE libraries, and conference abstracts	consolidation therapy for patients with previously untreated FL (induction chemotherapy regimens, dosing, and number of cycles varied across studies)	MA: pooled estimates of CR, OR, 2-year OS, 5-year OS, 2-year PFS, and 5-year OS were computed when there was sufficient reporting of these measures 5-year OS	• 97.2% of patients had **stage III/IV disease** • 19% to 44% of patients had abnormal LDH values • 25% to 50% had bulky lymph nodes • 73% to 100% patients having grade 1/2 disease among those studies reporting histology Results: • pooled estimate for **CR** was 82.7% with I2 =94.2 and the Cochran Q test P value of <.0001(high degree of heterogeneity) • pooled estimate for **OR** was 96.2% with I2= 71.2 and the Cochran Q test P < .002(moderate heterogeneity) • pooled estimate for **2-year PFS** was 76.8% with I2=65.4 and the Cochran Q test P< .005 (moderate heterogeneity) • pooled estimate for **2-year OS** was 94.2% with I2 = 0 (low heterogeneity) • pooled estimate **for 5-year PFS** was 57.6% with I2 = 66.5 and the	8 studies (n 783) were included in the metaanalyses. Follow-up: 5-8y **Randomization: not all** Blinding: not all ITT: N/A Financial support: N/A	• Leonard (2005) J Clin Oncol • Link (2010) J Clin Oncol • Morschhauser (2008) J Clin Oncol • Press (2006) J Clin Oncol • Press (2011) ASH Annual Meeting Abstracts • Zinzani (2008) Lancet Oncol

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				Cochran Q test P = .018 (moderate heterogeneity) • pooled estimate of **5-year OS** was 90.1% with I2 = 49.32 and a P value of .116 (low heterogeneity) CR rate improved after RIT compared with the CR rate before RIT in every study different test found different results on publication bias CR rates after RIT ranged from 69.0% to 96.5%, 2-year PFS ranged from 64.8% to 86.1%, and 5-year PFS ranged from 47.0% to 67.3%. The pooled estimates of the CR rate and OR rate were 82.7% (95% CI, 67.4%-91.7%) and 96.2% (95% CI, 90.4%-98.6%), respectively. The pooled estimates for 5-year PFS and OS were 57.6% (95% CI, • 47.8%-66.9%) and 90.1% (95% CI, 83.9%-94.1%), respectively.		
[115]	studies: N= 5 pts: N=1093	Arm A: HDT with ASCT Arm B: chemotherapy	Primary outcomes • Overall survival (OS) was evaluated as the	Overall quality of included RCTs: moderate **PFS:** in previously untreated FL patients in the HDT + ASCT arm sign.	SR+MA 1a All trials were open-label, unmasked trials (risk for	• Schouten 2000 Annals of Oncology + *Schouten 2003 Journal of Clnical Oncology + Stade

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	Randomised controlled trials comparing chemotherapy or immuno-chemotherapy with HDT followed by ASCT in adults with previously **untreated or relapsed** FL. (Adult male and female patients (≥ 18 years of age) with a confirmed diagnosis of FL). Searched CENTRAL, MEDLINE, and EMBASE January 1985-September 2011 for RCTs.	and immuno-chemotherapy.	primary efficacy Endpoint Secondary outcomes • Progress-ion-free survival (PFS) • Response rate (RR) • Qualitiy of life (Qol) • Treatment-related mortality (TRM) • Adverse events • Secondary malignancies	increased (HR = 0.42 (95% CI 0.33 to 0.54; P < 0.00001). **OS:** in previously untreated FL pts: no sign advantage (HR = 0.97; 95% 0.76 to 1.24; P = 0.81) **ORR:** previously untreated: no sign difference; Risk Ratio: Risk Ratio =1.13 [0.96, 1.34] **CRR:** (prev. untreated) Risk Ratio: 1.11 [0.64, 1.92] **TRM:** (prev. untreated) no sign difference (RR = 1.28; 95% CI 0.25 to 6.61; P = 0.77) **QoL:** no RCTs assessed this **secondary malignancies:** (prev. untreated) acute myeloid leukaemia/myelodysplastic syndromes: no sign. difference (RR = 2.87; 95% CI 0.7 to 11.75;P = 0.14) **solid cancer:** no sign difference (RR = 1.20; 95% CI 0.25 to 5.77; P = 0.82)	detection and performance bias). The risk of selection bias and attrition bias was low in the single trial reporting on relapsed patients. The study was supported by internal sources from the University hospital of Cologne, Germany.	1994 Onkologie **(CUP trial)** • Sebban 2003 Blood Journal + Sebban 2003 + Sebban 2003 Blood Journal + *Sebban 2006 Blood Journal **(GELA/GELF-94)** • Ladetto 2002 Blood Journal+ *Ladetto 2008 Blood Journal + Ladetto 2003 Bone Marrow Transplantation+ Ladetto 2006 Leukemia **(GIT MO/IIL)** • Lenz 2004 Blood Journal + Lenz 2004 Journal of Clinical Oncology + *Nickening 2007 Annals of Oncology Nickening 2006 Cancer **(GLGS)** • Deconinck 2005 Annals of Oncology + Deconinck 2003 Blood Journal +

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
						Deconinck 2005 Blood Journal + *Gyan 2009 Blood Journal **(GOELAMS 064)**
[116, 117]	N= 5 (N of pts. : 1056) RCTs Patients with histologically confirmed **B-cell follicular lymphoma** CENTRAL MEDLINE EMBASE LILACS Clinical trials in haematological malignancies	Intervention : Rituximab maintenance therapy Control : Observation, treatment at relapse, or other maintenance treatment	Primary outcome : • OS Secondary outcome: • EFS • PFS • Response duration • QoL • Bcl-2 conversion rate AEs	OS : I vs. C : HR 0.60, 95% CI 0.45-0.79 (p=0.0003) (5 trials; 985 pts.) EFS : I vs. C : HR 0.46, 95% CI 0.37-0.57 (p<0.00001) (3 trials; 589 pts.) PFS : I vs. C : HR 0.53, 95% CI 0.42-0.66 (p<0.00001) (3 trials; 454 pts.) Higher rate of grade 3 or 4 AEs in Intervention group (RR 1.52 , 95% CI 1.00-2.30)	SR+MA 1a Only RCTs included None of the trials were blinded ITT in 2 of the included trials	• 10 SR / 9 MA Ardeshna 2010 Blood Journal - ASH Abstract) • Forstpointner 2006 Blood Journal (**GLSG**) • Hainsworth 2007 Journal of Clinical Oncology (**Phase II Trial of the Minnie Pearl Cancer Research Network**) • Hochster 2007 + 2009 Journal of Clinical Oncology (**ECOG 1496/ECOG/CALGB**) • Ghielmini 2004 Blood Journal + Martinelli • 2010 Journal of Clinical Oncology (**SAKK 35/98**) • Pettengell 2010 Journal of Clinical Oncology • Salles 2010 Blood Journal (**GELA-GOELAMS FL2000**)

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	Not specific to first or second line					• Van Oers 2010 Journal of Clinical Oncology + van Oers 2006 Blood (**EORTC 20981**) Witzens-Harig 2009 Annals of Hematology + Witzens-Harig 2006 Blood Journal
[118]	• N=2315 ; **treatment naive and relapsed FL** pts ; media nage 57 years ; majority advanced stages • Only RCT • Search up to 2014 • 11 eligible trials performed between 1998 and 2009 7 of 11 eligible trials (those 7 were willing to work together on individual patient data anlysis – the results of the	MR vs. No MR (control group was observed without R-treatment and did not receive R at progression while on study, but R was allowed when treatment was indicated) MR : 4 weekly infusions every 6 months ; single infusion every 2-3months Duration : 4 months to 2 years Induction regimen before MR : with (74%) or without R	Primary : • OS Secondary : • PFS • Toxicity Subgroup analysis	• **OS first line only : Pts N=1561 HR of MR vs no MR = 0.92 ; 95% CI of MR vs no MR : 0.70–1.20** • No patient or disease characteristics associated with survival beneift with MR • MR benefical effect on OS compared with observation for all types of patients – not shown in one particular subgroup in which the patient had already received R in induction and received first line therapy • effect of MR was not statistically significantly different with R-CVP/CVP or R-CHOP/CHOP • HR of MR effect for the 233 patients who received fludarabine-based induction was 1.97 with a wide CI • OS 10 eligible trials (not only IPD): 0.79, 95% CI 0.66-0.94, 2786 patients (1 trial didn't report OS)	1a Individual patient data (IPD) meta-analysis ITT ✓ Allocation concealment ✓ Random allocation ✓ Baseline balanced ✓ Blinding X Heterogeneity I2 test :19% for IPD, 0% fpr summary data, total 0% We analysed data in two ways: (a) using a two-stage analysis and (b) using a multivariate model Publication bias :	• Ghielmini 2004 Blood Journal (**SAKK**) ; n=151 • Pettengell 2013 Journal of Clinical Oncology (lymphoma working party of the European group for blood and marrow transplantation) ; n=280 • Salles 2011 The Lancet (**PRIMA**) ; n=1030 • Vitolo 2013 Journal of Clinical Oncology (**FIL**); n=202 • Witzens-Harig 2015 British Journal of Haematology (**HD2002**); n=41 • Hochster 2009 Journal of Clinical Oncology (**ECOG1496**); n= 279 • Van Oers 2010 Journal of Clinical Oncology (**EORTC**); n=334

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	other 4 were also used for sensitivity analysis)	(62% CHOP ; 23% CVP, 15% Fluradabin-based)		median OS time : 12years in MR vs. 11.5 years in observation group • PFS : improved with MR compared to observation (HR 0.57, 95% CI 0.51-0.64, p < 0.0001, 2305 patients) • AE : higher with MR, specially grade ¾ infections(HR 1.27, 95% CI 1.12-1.45) ; rate of any AE grade 1-4 in MR group was 52% and in the no MR group 40%, Median follow-up : 6years		• Ardeshna 2014 (no IPD) • Forstpointer 2016 (no IPD) • Hainsworth 2005 (no IPD) Ardeshna (no IPD, no OS data, not in analysis)
[119]	N=4 (N of included pts.: 941) Included studies : • RCTS reporting on OS, EFS and/or secondary tumor rate • Pts. with FL in first-line setting	Intensified therapy (IT) + ASCT Vs. Conventional therapy	Primary Outcome: Secondary outcomes: • Secondary tumor rate	**Follow-up: 51 months-9 years** **OS:** no sign benefit from IT+ASCT (random-effects summary HR=0.95 [0.70, 1.30] (p = 0.75)) **EFS:** sign advantage of IT+ASCT as first-line treatment (random-effects summary HR=0.59 [0.44, 0.79] (p<0.001)) **Secondary tumor rate:** no difference (random-effects summary relative risk ratio=0.95 [0.70, 1.30] (p = 0.75))	SR+MA 1a Included RCTs only None of the included trials was (double) blinded ITT : 3 of the 4 included trials	• Lenz 2004 Blood • Sebban 2006 Blood • Ladetto 2008 Blood • Gyan 2009 Blood

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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
[120] Italien	Search In 2011 limited to English language edited after 2005	1.In patients with at least partial response after firstline chemoimmunotherapy, is maintenance with R better than watchful waiting? 2.In patients candidates to frontline chemoimmunotherapy, high-dose chemoimmunotherapy with ASC support is better than standard chemoimmunotherapy? 3.In patients who achieved partial response after first-line chemoimmuno-therapy, is consolidation with RI-conjugates an option?		*Only first line recommendations:* 1.Maintenance therapy with R is recommended in patients who reach at least a partial response at the end of first-line therapy (quality of evidence, high; strength of recommendation, strong). 2.Upfront high-dose chemoimmunotherapy with ASC support cannot be recommended (quality of evidence, low; strength of recommendation, strong) 3.Ibritumomab tiuxetan proved to prolong PFS in pts achieving PR after first-line chemoimmuno-therapy. However, the lack of comparison between ibritumomab tiuxetan and R maintenance does not allow to produce recommendations on RIT in this setting (quality of evidence, low; strength of recommendation, weak). The panel claimed to be important to have a randomized study evaluating the role of RIT versus R maintenance in pts who achieved a response after first-line chemoimmunotherapy.	• GRADE for LoE (evidence tables and quality of evidence tables prepared) =evidence-based-recommendations • Consensus-based recommendations • Update of revised guideline for management of FL from SIE, SIES and GITMO group	• Ladetto 2008 Blood • Salles 2011 Lancet • Morschhauser 2008 J Clin Oncol

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10.4.1.2. Einzelstudien

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[121] E1496	Phase III	311	Observational strategy: N=155 Rituximab: N=158	Patients with stage III or IV small lymphocytic, follicular small cleaved, follicular mixed small cleaved and large cell lymphoma had been included. 73% of patients had follicular lymphoma. Patients received either CVP (cyclophosphamide, prednisone, vincristine) or CF (cyclophosphamide, fludarabine) as induction therapy. Patients on CVP with other than progressive disease were randomized to either maintenance therapy with rituximab or observational strategy.	The median follow-up was 11.5 years.	PFS OS Treatment response Prognostic factors for OS and PFS	**Subgroup results for FL-pts:** Median **PFS** for follicular lymphoma patients: Arm 1: 1.3 years Arm 2: 4.6 years ➔ HR: 0.46, 95% CI: 0.34 to 0.63, p<0.0001 Median **OS** for follicular lymphoma patients: Arm 1: not reached Arm 2: 13.5 years HR: 0.91, 95% CI: 0.59 to 1.42, p<0.69	R: Yes, patients were randomized for either induction and maintenance therapy. B: Not reported I: Comparisons based on the ITT principles. F: The study was supported in part by the Public Health Service (grants CA180794, CA180820, CA180826, CA180790, CA180816, CA180799, and CA180821) and the National Cancer Institute (National Institutes of Health, US Department of Health and Human Services). Methodological issues: Only 73% of

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
								patients had follicular lymphoma
[122]	RCT	N=349	Arm A: Mitumprotimut-T/ GM-CSF (n=174) Arm B: Placebo / GM-CSF (n=175) (after Rituximab)	Eligibility criteria: • Histologically confirmed CD20+ follicular lymphoma (**treatment naïve or relapsed/ refractory**), WHO grade 1 to 3 • Pts. Aged >=18 • ECOG performance status of 0 to 1 Characteristics of included pts.: • Median age: 54 years; A: 55.8 years (range 22-86); B: 53.0 years (range 21-81) • Treatment naïve: 79%; A: 79%; B: 79% • Stage III/IV disease: 86%	Not reported (Pts. assessment and enrollment between July 2004 and January 2006 – Assessment of PD/ efficacy analysis in March 2008)	Primary (efficacy) endpoint: • TTP (measured from date from date of assignment to the date of first documentation of PD) Secondary endpoints: • ORR • RRI (pts. with SD or a PR after rituximab whose response subsequently improved to a PR or CR) • Duration of response • Safety	PD (as of March 2008) • 215 assigned pts. (62%) • A: 113 pts. • B: 102 pts. Median TTP • A: 9.0 months (95% CI 6.2 to 12.5) • B: 12.6 months (95% CI 10.7 to 20.8) • A:B HR: 1.384 (95% CI 1.053 to 1.819, p= 0.19) **Median TTP in treatment naïve pts.** • A: 11.9 months (95% CI 8.4 to 17.1) • B: 17.2 months (95% CI 11.0 to 25.0) • A:B HR: 1.196 (95% CI 1.053 to 1.819, p=0.258)	R: "Random assignment occurred regardless of successful production of mitumprotimut-T and was performed centrally on a 1:1 schedule using balanced blocks of four, with stratification by prior treatment (treatment-naive v relapsed/refractory disease) and response to rituximab therapy (CR/PR v SD)." B: "To ensure the integrity of treatment blinding, study drug and placebo prepared at Favrille were sent to an independent distributor that shipped the

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							Median TTP of pts. achieving CR or PR (n=205): • A: 18.8 months (95% CI 12.5 to 27.2) • B: 25.4 months (95% CI 21.0 to undetermined) • A:B HR: 1.352 (p=0.142) Median TTP of pts. achieving SD after rituximab (n=144): • A: 6.4 months (95% CI 4.5 to 73) • B: 6.3 months (95% CI 5.8 to 8.8) • A:B HR: 1.412 (p=0.68) "Toxicity was similar in the two arms; 76% of adverse events were mild or moderate, and 94% of patients had injection site reactions."	appropriate vials to clinical sites." I: "The intent-to-treat population consisted of all randomly assigned patients." Supported and sponsored by Favrille, Inc.
[123-132] FIT *Morschhauser 2013	RCT	N=409 (consolidation, n = 207;	Arm A: Consolidation with RIT: 90Y-ibritumomab tiuxetan	• Pts in remission **after first line treatment**	Median of 7.3 yrs	Primary: • PFS • PFS stratified	**median PFS: 4.1yrs Arm A vs. 1.1yrs Arm B**; HR, 0.47; 95% CI, 0.37 to 0.60;	randomized I: Yes B: NR

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		control, n = 202)	Arm B: No further treatment (control)	• CD20+histologically confirmed grade 1 or 2 FL • **Stage III or IV FL** • Achieved CR, CRu or PR after first-line induction treatment • ≥18 y old WHO performance status 0-2		by response (PR or CR/CRu) Secondary: • PFS based on type of first-line induction regimen • Improvement in CR, conversion rate • OS Safety	for CR: 48% vs 32% for control (HR, 0.61; P= 0.008) for PR: 33% vs 10% (HR, 0.38; P =0.001) There was no significant difference in OS between treatment groups (HR, 0.82; 95% CI, 0.50 to 1.37; P .45) Consolidation with RIT sign. prolongs PFS after 3.5yrs: 36.5 v 13.3 months in control arm; [HR] = 0.465, P < .0001) (regardless of PR or CR/CRu status after induction) Safety: • Most common toxicity with RIT: hematologic toxicities and grade 3 o4 infections in 8% of pts • number of second malignancies that occurred after treatment in the 90Y-ibritumomab and control groups was not statistically different • median time from registration/random	Some authors are employees in pharmaceutical companies and receive honoraria and/or research funding from those (Bayer Schering Pharma)

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							assignment to second malignancy was 58 months (range, 4 to 92 months	
[133] RESORT E4402	RCT	N= 289	Maintenance rituximab (MR) – R every 3 months until treatment failure Vs Re-treatment rituximab (RR) (pts eligible for re-treatment at each disease progression until treatment failure)	All patients (previously untreated) with biopsy-proven grade 1 or 2 FL **MR arm** N = 146 Age: 59 (25.2-86.1) FL histology: Grade 1(97), Grade 2 (42), Grade 3a (2), Non classifiable (5) **RR arm** N = 143 Age: 59.7 (26-86.2) FL histology: Grade 1(101), Grade 2 (33), Grade 3a (3), Non classifiable (6)	4.5 yrs	**Primary:** Time to treatment failure **Secondary:** OS Toxicity Health related QoL	• **OS** No difference between arms • **Health related QOL** No detectable difference between arms • **Toxicity (Grade 3-5)** RR: n = 12 MR: n = 22	R: YES, for randomization if responding to Rituximab B: N/A I: No F: Genentech, Roche
[134]	RCT	N=287	(All pts. received chemotherapy with CVP every 21 days for 8 cycles; pts.	Eligibility criteria: • Pts. Aged >=18 • Untreated FL requiring therapy	Median follow-up: 58 months	Primary endpoint: • PFS Secondary endpoints:	"There was no difference in PFS between pts. receiving A versus B" • A:B HR: 0.98 (95% CI 0.72 to 1.33, p= 0.89)	R: "Those achieving sustained partial or complete remission (n = 287 [44%]) were randomly assigned at a ratio of 2:1 to

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			were restaged 4 to 8 weeks after the end of chemotherapy (n=513); Pts. achieving PR of CR where assigned at a ratio of 2:1 to:) Arm A: MyVax (pts. specific recombinant Id coupled to KLH + GM-CSF) (n=192; n=9 did not receive intended therapy) Arm B: Control immunotherapy (KLH + GM-CSF) (n=95; n=1 did not receive intended therapy)	• Ann Arbor Stage III or IV disease • WHO histologic grade 1, 2, 3 • ECOG performance status <3 • FL confirmed by central pathologic review Characteristics of included pts.: • Median age: A: 50 years (range 22-80); B: 50 years (range 25-80) • Male sex: A: 44.8%; B: 46.3%		• SALT (sub-sequent anti-lymphoma therapy)-free survival • IRs	"There was no significant difference in the time to SALT between the two trial arms" • A:B HR: 0.85 (95% CI 0.6 to 1.19, p=0.36) "In the A , anti-Id IRs were observed in 41% of patients, with a median PFS of 40 months, significantly exceeding the median PFS observed in patients without such Id-induced IRs and in those receiving control immunotherapy"	receive one injection per month for 7 months of MyVax or control immunotherapy" B: "To maintain blinding, a specific vaccine was manufactured for all randomly assigned patients, including those assigned to control immunotherapy" I: "(the randomized population) was evaluable for clinical outcome on an intent-to-treat (ITT) basis." Study sponsor not reported, funding not reported, financial support by one of the (financially conflicted) authors

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[135]	RCT Protocol/ Interim Report	N=167	(Pts. are initially treated with combination a chemotherapy (PACE) regimen until they experience their best response (n=148); pts. who exibit a CR or unconfirmed CR (n= 126) are randomized to:) Arm A: Tumor specific vaccination (Id-KLH vaccine plus GM-CSF) Arm B: nonspecific vaccination arm (KLH plus GM-CSF)	Eligibility criteria: • Previously untreated • Tissue diagnosis of FCC lymphoma (grade 1, 2, 3a with surface IgM or IgG • Monoclonal heavy and light chain as determined by flow cytometry • Karnovsky status >=70% • Life expectancy >1 year Characteristics of included pts	Not applicable	Primary objective • Impact of Id vaccine on DFS in pts. who have exhibited a CRR	Current CRR: 85%	R & B: "The double-blinded randomization is performed in a 2:1 ratio in favor of the specific vaccination arm." I: "This calculation is based on an assumption of intent-to-treat analysis […]."
[136]	RCT, multicentre, open-label,	N=154 aged ≥18 y; histologi	• Subcutaneous (sc) vs intravenous (iv)	• baseline demographics and disease characteristics were similar	total of 38 pts in the sc arm and	• Demonstrate noninferior R sc	• Ctrough, sc/Ctrough, iv ratios were 1.24 and 1.12, respectively, for q2m and q3m, and lower limits of the	R: ✓ B: X I: not reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
	noninferiority	cally confirmed CD20+ grade 1, 2, or 3a FL **(first line or relapsed (no subgroups reported)** all pts had responded to a R induction regimen and had at least one dose of R iv maintenance therapy.	R as maintenance 1400mg fixed dose sc or 375 mg/m2 iv of each cycle of their remaining maintenance cycles (ever 2-3months for 2 years)	• median age: 59.0 years in the sc arm; 57.5 years in the iv arm prior to study entry complete response (confirmed) was 53% in the sc arm and 58% in the iv arm; partial response was 40% in the sc arm and 38% in the iv arm	33 pts in the iv arm were ongoing in the treatment period of the study, and 22 sc and 24 iv pts were ongoing in the follow-up period	compared with iv • Peripheral blood B-cell depletion • Safety (administration related reactions ARR) AUC of R	two-sided 90% CI (1.02 and 0.86, respectively) exceeded the protocol-specified noninferiority limit (Ctrough, sc/Ctrough, iv ratio of 0.8) • Ctrough values were higher in the sc arm for both dosing regimens • CD19+ B lymphocytes remained depleted throughout the study for both arms • geometric mean AUC_T, sc/AUC_T, iv ratio was 1.35 for both q2m and q3m, and the lower limit of the two-sided 90% CI was 1.23 • 13 patients in the sc arm had withdrawn (seven for progressive disease [PD], four for adverse events [AEs], one at the investigator's discretion, one for ineligibility) and 17 patients in the iv arm had withdrawn (10 for PD, four for AEs, three for ineligibility)	F: not reported

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							AEs: incidence and intensity well balanced between treatment arms	
[137] CALGB8691	Multicentre, randomized, phase III trial	First line, only FL, stage III & IV N=581, of these 436 eligible Recruitment between 1986 and 1991	Daily oral cyclophosphamide (**CPA** – 100mg/m2) **plus IFN-a2** (2x106 IU/m2) (N=288) vs **CPA alone** (3 times a week) (N=293) **Second randomization:** (of responding pts) **IFNA-a2 maintenance** (2x106 IU/m2 3 times a week) (N=99; eligible 70) vs	5 pts withdrew consent after randomization prior any therapy Another 95 pts ineligible after randomization Median age: 55yrs Performance status 0= 67%, 1=30% 2% DLBCL	Median Follow-up: 11.5yrs	• Initial response assessment after 12 weeks (via CT) CR and PR • Time to progression • Duration of CR • OS • Toxicity EFS	**Maintenance Outcomes:** Maintenance duration 23 months (range 1 week to 9.5y; half of all pts at least 2y) No difference in OS and between maintenance groups **EFS**: CPA-obersvation: 2.4 y [95% CI: 1.6, 4.6] CPA+IFN-observation: 3.3 years [95% CI: 1.6, 7.5] CPA-IFN: 3.9 years [95% CI: 2.2, 6.7] CPA+IFN-IFN: 3.7 years [95% CI:2.3, 5.5] **subset analysis** comparing outcomes of patients achieving a CR versus a PR following induction, maintenance IFN-a2 improved EFS of the patients with PR, but not OS pts with PR randomized to observation – inferior to all other; median EFS Pr-pts-observation: 1.8 years (95% CI	R: yes (induction and again for maintenance) B: not reported I: yes F: The research for CALGB 8691 was supported, in part, by grants from the National Cancer Institute (CA31946) to the Cancer and Leukemia Group B (Richard L. Schilsky, MD, Chairman) and to the CALGB Statistical Center (Stephen George, PhD, CA33601).

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			observation (N=105; eligible 84)				1.3, 2.6) vs. 3.9 years (95% CI 2.6, 5.2) p<0.002 **Overall results**: **Median EFS**: for CPA induction alone: 2.5yrs (95% CI 2.2; 3.0) compared to 2.4 yrs (95% CI 2.1; 3.1) combination **Median OS:** for CPA induction alone: 9 yrs (95% CI 7.7; 10.2) compared to 8.4 yrs (95% CI 7.5; 11.1) combination **Toxicity** : Grade 3 or greater leucopenia, thrombocytopenia, granulocytopenia, and neurologic CNS toxicities were significantly higher in the CPA plus IFN-a2 arm (p<0.001), as were hepatic toxicities, fever without infection, and other toxicities (p<0.01). Pts with partial response and observation had the worst outcome • Authors Conclusion: low dose IFN-a1 in combination with CPA in first line FL does not	

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							sign. improve the response rate, duration of response, EFS or OS	
[138, 139] SAKK 35/03	Phase III RCT	N=270 (FL)	Short term maintenance Vs Long term maintenance "The short-term maintenance therapy consisted of four rituximab infusions (375 mg/m2) administered intravenously every 2 months, whereas the long-term maintenance therapy consisted of rituximab infusions (375 mg/m2) every 2 months for a	**Short term arm:** • N=82 • Median age: 55 (34-81) Disease status: • **55 untreated**, • **27 relapsed/progressed** (nor subgroups reported) **Long term arm**: • N= 83 • Median age: 57(25-81) Disease status: • **58 untreated** • **24 relapsed/progressed** • 1 stable	Median: 6.4 yrs	Primary: EFS Secondary: PFS, OS & toxicity	• **EFS** **Short term arm** yrs(95% CI, 2.1 to 5.3) **Long term arm** yrs (95% CI, 3.5 to N/A) (P = 0.14) • **PFS** **Short term arm** (95% CI, 2.1 to 5.9) **Long term arm** 7.4 (95% CI, 5.1 to N/A) (log-rank test, P = 0.04) • **OS** No significant difference • **AE** Short term arm: 50% Long term arm: 76% (P< 0.001) • **Toxicity** Short term arm: 0 Long term arm: 3 (P = 0.25)	R: YES B: No I: No F: Supported by a scientific grant from Oncosuisse (OCS 01468-02-2004); the Swiss State Secretariat for Education, Researchand Innovation (SERI)

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			maximum of 5 years or until relapse or progression or unacceptable toxicity occurred"					
[98, 140] SWOG-S0016	RCT	N = 532	Arm A: CHOP-R (n = 267) 6 cycles of CHOP every 21 days with 6 doses of rituximab Arm B: CHOP-RIT (n = 265) 6 cycles of CHOP every 21 days followed by consolidation with tositumomab/iodine I-131 tositumomab	Patients: • >18y • advanced-stage (bulky stage II, III, or IV) evaluable FL of any grade (1, 2, or 3) • had not received previous therapy • expressing CD20 performance status 0-2	median follow-up 4.9 years	• CR • Cru • PR 200 and 365 days after therapy initiation and every 6 months until deaths or signs of FL recurrence: • Remission • Survival status AE	• Objective remissions were documented in 84 % of pts in both groups • CR detected in 40 % (Arm A) / 45% (Arm B) / P=.30 After follow up: • 2yPFS: 80% (Arm B) • 5yPFS: 66% (Arm B) • 2yPFS: 76% (Arm A) • 5yPFS: 60% (arm A) • two-sided P=.11; one-sided P=.05 • 2yOS: 93% (Arm B) • 5yOS: 86% (Arm B) • 2yOS: 97% (Arm A) • 5yOS: 92% (Arm A)	Randomly assigned, but not for consolidation ITT and Blinding are not reported Some Authors are employee at pharmaceutical industries and/or received honoraria of those

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			radioimmunotherapy				• P=.08 "AE were similar on the two arms and appeared dominated by the effects of CHOP chemotherapy rather than the immunotherapeutic components" • Kelly 2015: Although statistical significance was not reached […] serum vitamin D might be the first potentially modifiable factor to be associated with FL survival.	

Konsultation

10.4.2. GRADE-Bewertung

10.4.2.1. GRADE-Bewertung: Interferon-alfa vs. kein Interferon-alfa/Plazebo

[106, 114]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-1	-	-	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL	-1	-	-	-2	-	⊕⊖⊖⊖ very low
	RCT	Safety	-	-1	-	-1	-	⊕⊕⊖⊖ low

OS: beide Meta-Analysen zeigen statistisch signifikante Heterogenität der Studien; PFS: der in 4 RCTS hohes Risiko für ‚loss to follow-up', nur 4 RCTs ITT; QoL beruht nur auf 2 Studien; keine Analyse, Safety: teilweise statistische Heterogenität; wenige Studien berichten Ereignisse in vergleichbarer Weise;

10.4.2.2. GRADE-Bewertung: Erhaltung mit Rituximab vs. keine Erhaltung

[118]

Konsultat

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-1	-	-	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-1	-	-	⊕⊕⊕⊖ moderate
	RCT	QoL						Not reported
	RCT	Safety	-	-1	-1	-	-	⊕⊕⊖⊖ low

OS: Ergebnisse der Studien heterogen (verschiedene Richtungen); PFS und Safety: nur für gesamte Gruppe (nicht für Patienten der Erstlinientherapie separat) berichtet; Safety: HR-Angabe gilt nur für Grad 3 und 4 Infektionen, viele unerwünschte Ereignisse wurden nicht berichtet

10.4.2.3. GRADE-Bewertung: Vakzinierung

[108, 134]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS						Not reported
	RCT	PFS	-	-1	-	-1	-	⊕⊕⊖⊖ low
	RCT	QoL						Not reported

Konsultationsfassung

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	Safety	-1	-	-	-2	-	⊕⊖⊖⊖ very low

PFS: verschiedene Richtungen, breite Konfidenzintervalle; Safety: keine Analyse, nur in einer Studie berichtet

10.4.2.4. GRADE-Bewertung: Dauer Rituximab kurz vs. lang

[138]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-1	-	-	-1	-	⊕⊕⊖⊖ low
	RCT	PFS	-1	-	-	-	-	⊕⊕⊕⊖ moderate
	RCT	QoL						Not reported
	RCT	Safety	-1	-	-	-	-	⊕⊕⊕⊖ moderate

OS und Safety: keine Zahlen oder Konfidenzintervalle gegeben, keine Subgruppenergebnisse für nur Patienten der Erstlinientherapie berichtet; OS, PFS und Safety: nur eine Studie mit relativ wenig Teilnehmern

Konsultationsfassung

10.4.2.5. GRADE-Bewertung: Autologe Stammzelltransplantation (ASCT) vs. keine Erhaltung

[115]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL						Not reported
	RCT	Safety	-1	-	-	-1	-	⊕⊕⊖⊖ low

OS: breites Konfidenzintervall; Safety: nur wenige Studien haben unerwünschte Ereignisse berichtet, selten die gleichen, keine statistische Analyse und damit keine eindeutige Aussage möglich

10.4.2.6. GRADE-Bewertung: Radioimmuntherapie vs. keine Radioimmuntherapie

[125]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-1	-	-	-1	-	⊕⊕⊖⊖ low

Konsultation

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	PFS	-1	-	-	-	-	⊕⊕⊕⊖ moderate
	RCT	QoL						Not reported
	RCT	Safety	-1	-	-	-1	-	⊕⊕⊖⊖ low

OS, PFS, Safety: nur eine Studie; OS: sehr breites Konfidenzintervall; Safety: keine Analyse

10.5. Kapitel 11 Therapie des Rezidivs

10.5.1. Evidenztabellen

10.5.1.1. Systematische Übersichtsarbeiten

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
[112]	prospective trials enrolling patients with FL and MCL (5% of those were CLL/SLL pts treated in FL studies)	• comparative schedule-related toxicities with maintenance rituximab in FL and MCL	• Grade 3/4 AEs	• 10 trials met inclusion criteria with 9 reporting Aes • **4 front-lin** • 4 relapse • 1 study enrolled boths lines	• SR & MA 2a • For potential conflict of interests a link is given, which does not work, so no declaration if potential COIs given Random effects models	• Hainsworth 2005 Journal of Clinical Oncology (**Minnie Pearl Cancer Research Network)**

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	n=1009 pts receiving MR only full texts **(RCTs and Non-RCTs)** FL or mantle cell lymphoma Only studies reporting 3/4 AEs Only studies using R alone or R with Chemo as induction Only if MR was delivered up to 24 months Search: MEDLINE, CENTRAL, Google Scholar for articles published between 1997-2012	• trying to find the least toxic schedule • R maintenance R in induction		• Induction regimens and MR schedules varied amongst studies Overall results : • Total of 24% of pts receiving MR developed grade 3/4 Aes (85% CI : 14-36) ; high degree of hetergeneity among studies (χ 2 = 9 9.6, p = 0.0001, I 2 = 92.0%) • Grade 3/4 AEs summarized by schedule: pts receiving MR every 6 months as 4 weekly infusions for 2 y had fewer grade ¾ AEs compared with those receiving MR as single infusions every 2 months (10% vs. 28%; p= 0.035) • Toxicities were lower for pts R alone vs R+chemo in induction (12% vs 35% ; p= 0.031) No sign. differneces in toxicities between pts in front line vs. Relapsed setting (24% vs 30%, p=0.1)		• Hainsworth 2002 Journal of Clinical Oncology • Ghielmini 2005 Journal of Clinical Oncology + Ghielmini 2005 Annals of Oncology **(SAKK** swiss group for Clnical Cancer Research) • Martinelli 2010 Journal of Clinical Oncology **(SAKK)** • Forstpointner 2006 Blood (**GLSG** German Low Grade Lymphoma Study Group) • Van Oers 2010 Journal of Clinical Oncology + van Oers 2006 Blood (**EORTC 20981**) • Kenkre 2011 Leukemia and Lymphoma (**Wisconsin Oncology Network**)

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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
						• Salles 2011 The Lancet (**PRIMA**) • Raty 2012 Leukemia and Lymphoma (**Finnish Lymphoma Group**) • Tomas 2011 Leukemia and Lymphoma (**LNHF-03** - Spanish Cooperative Trial)
[141]	PubMed, Medline, National Center of Biotechnology Information Website at the National Library of medicine of the National Institutes of Health searched in Juni 2008 1990-2009 + manual search of reference lists of reviews and included articles was conducted	Hematopoetic stem cell transplantation (SCT): 1-line ASCT vs. non-ASCT treatment +/- R Salvage ASCT vs. non-ASCT therapy +/- R Autologous SCT vs. Allogenic SCT 1-line vs. salvage ASCT (timing of transplantation)	PFS OS CR 3y TRM EFS/DFS/RFS Acute myelogenous leukemia Myelodysplastic sysndrome	Treatment recommendations: ASCT is recommended as salvage therapy based on pre-rituximab data, with a significant improvement in OS and PFS ASCT is not recommended as first-line treatment for most patients because of no significant improvement in OS ASCT is recommended for transformed follicular lymphoma patients reduced intensity conditioning before allogeneic SCT appears to be an acceptable alternative to myeloablative regimens	Systematic evidence based Review with expert panel (each has published studies using SCT and other therapies) giving consensus treatment recommendations based on existing literature Only U.S. based experts Levels of evidence (1++ - 4) and grades of recommendations (A-D) judged after Harbour 2001 Financial disclosure: Major funding for this study was provided by the National Marrow Donor Program. The American Society for	• Gyan 2009 Blood • Horning 2001 Blood • Sebban 2008 J Clin Oncol • Schouten 2003 J Clin Oncol • Brice 2000 Ann Oncol • Rohatiner 2007 J Clin Oncol • Van Besien 2003Blood • Bierman 2003J Clin Oncol • Hosing 2003 Ann Oncol • Stein 1999 Bone Marrow Transplant • Ingram 2008 Br J Heamatol • Seyfarth 2001 Ann Oncol • Tarella 2008 J Clin Incol • Hoerr 2004 J Clin Oncol • Kang 2007 Bone marrow Transplant • Williams 1996 J Clin Oncol • Gopal 2003 Blood

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	FL > 15y	R vs. no R prior to ASCT Purged vs. unpurged Autologous Bone Marrow Transplant High-Dose Therapies prior to ASCT Myeloablative vs. reduced intensity allogenic SCT Prognostic Factors Chemo+IFN vs. Autologous peripheral blood stem cell transplantation + IFN maintenance ASCT vs. reduced-intensity conditioning allogenic SCT Myeloablative conditioning vs. RIC allogenic SCT		An human leukocyte antigen (HLA)-matched unrelated donor appears to be as effective an HLA-matched related donor for reduced intensity conditioning allogeneic SCT • There are insufficient data to make a recommendation on the use of ASCT after R-based salvage therapy	Blood and Marrow Transplantation and Drs. Hahn and McCarthy are indebted to the members of the Follicular Lymphoma Review Expert Panel and the ASBMT Evidence- Based Review Steering Committee, who voluntarily and enthusiastically participated in this endeavor. The authors of this review and the American Society for Blood and Marrow Transplantation thank the National Marrow Donor Program, and especially Jeffrey Chell, MD, and Michael Boo, for their support of this project. The authors kcknowledge Dr. C. Fred Le- Maistre for pioneering and supporting this effort and Alan Leahigh and Dianne O'Rourke for their invaluable administrative assistance. The authors are grateful to all the patients who participated in the clinical trials that led to the	• Gutierrez-Delgado 2001 Bone Marrow Transplant • Weaver 1998 Bone Marrow Transplant

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
					evidence upon which this review is based.	
[142]	**Study type :** RCTs **Data bases** : Medline via PubMed, Embase, Cochrane Library and conference proceedings from ASCO, EHA, ASH and ESMO, Clinicaltrials.gov **Time period :** 1997 to 2012 **Exclusion criteria :** • inclusion of NHL other than follicular lymphoma • inclusion of patients with autologous stem cell transplant	Trials included in meta-analysis compared the following treatment strategies : a) **rituximab monotherapy;** b)**rituximab+bortezomib;** c) **obinutuzumab;** d)**rituximab+sargramostim;** e)**rituximab+ dulanermin;** f)**dulanermin monotherapy).**	• Response rates (ORR, CRR, PR) • Duration of response • PFS • OS • Safety (AEs, SAEs)	N=10 RCTs with R/R FL pts, 4 RCTs with R/R FL pts included in MA **Overall response rate :** a) rituximab monotherapy:R R: 1.28, 95% CI: 1.11 to 1.47) b) rituximab+bortezomib vs. obinutuzumab: RR: 1.14; 95% CI: 0.76 to 1.72 c) rituximab+bortezomib vs. rituximab+sargramostim: RR: 1.25, 95% CI: 0.44 to 2.01 d) rituximab+sargramostim vs. obinutuzumab: RR: 0.92, 95% CI: 0.50 to 1.65 **Overall survival** : not reported in any of the 4 RCTs included in MA **PFS**: only reported seperately for each trial due to different intervention settings **Safety:** **AEs** rituximab+sargramostim vs. rituximab+bortezomib: RR: 0.898, 95% CI: 0.794 to 1.017	SR&MA, 1a Methodological issues : Outcomes selected for extraction had slightly different definitions across studies Different definitions were used for tumor response criteria and response was measured at different intervals. Missing definitions of relapsed or refractory disease in several trials. Comparison of only a few different regimens. Inclusion of Congress Abstracts	• Coiffier 2011 Lancet Oncol • Rothman 2011 Presented at the 16th congress of the European hematology association, (accessed 8 December 2013). • Coiffier 2010 Presented at the ASH Annual Meeting, Orlando, FL • Ghielmini 2004 Blood • Leonard 2012 Presented at the ASCO annual meeting,Chicago, IL • Van Oers 2006 Blood • Van Oers 2010 J Clin Oncol • Witzig 2002 J Clin Oncol

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	without any further information on short-term outcome after standard chemotherapy **Inclusion criteria :** • patients with **relapsed or refractory indolent NHL**			**SAEs:** rituximab+sargramostim vs. rituximab+bortezomib: RR, 0.842, 95% CI : 0.274 to 2.586		• Gomez Almaguer 2012 Presented at the 17th congress EHA • NCT00268983. Comparison of rituximab versus tositumomab and iodine I 131 tositumomab (accessed 8 December 2012.). • NCT00308087. Comparison study of rituximab plus sargramostim to rituximab (accessed 8 December 2012). • NCT00400764. A study of dulanermin in combination with rituximab (accessed 8 December 2012). • Goy 2012 Presented at the 17th congress of the EHA
[115]	Study design: RCTs	High-dose chemotherapy + autologous	OS PFS	One trial (N=70 patients) reported on patients with relapsed follicular lymphoma.	SR+MA 1a	• Schouten 2000 Annals of Oncology + Schouten 2003

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Data bases: Medline, EMBASE, Cochrane Library and conference proceedings (ASH, ASCO, EBMT) Time period: January 1985 to September 2011 Exclusion criteria: • uncontrolled trials Inclusion criteria: • RCTS, either published or unpublished • adult patients with follicular lymphoma (either previously untreated or relapsed)	hematopoietic stem cell transplantation vs. chemotherapy and/or immunotherapy	Response rate QoL TRM AEs Secondary malignancies	Treatment prior to ASCT was CHOP and total body irradiation for patients with relapsed follicular lymphoma and was compared to CHOP (CUP trial). Median-follow up was 69 months. PFS: HR = 0.30; 95% CI 0.15 to 0.61 OS: HR = 0.40; 95% CI 0.18 to 0.89) • No report on TRM, adverse events or secondary malignancies.	All trials were open-label, unmasked trials (risk for detection and performance bias). The risk of selection bias and attrition bias was low in the single trial reporting on relapsed patients. The study was supported by internal sources from the University hospital of Cologne, Germany.	Journal of Clnical Oncology + Stade 1994 Onkologie (CUP trial) • Sebban 2003 Blood Journal + Sebban 2003 + Sebban 2003 Blood Journal + Sebban 2006 Blood Journal (GELA/GELF-94) • Ladetto 2002 Blood Journal+ *Ladetto 2008 Blood Journal + Ladetto 2003 Bone Marrow Transplantation+ Ladetto 2006 Leukemia • (GIT MO/IIL) • Lenz 2004 Blood Journal + Lenz 2004 Journal of Clinical Oncology + Nickening 2007 Annals of Oncology Nickening 2006 Cancer (GLGS) • Deconinck 2005 Annals of Oncology

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	no restrictions were made on chemo- or immunotherapeuticals					+ Deconinck 2003 Blood Journal + Deconinck 2005 Blood Journal + Gyan 2009 Blood Journal (GOELAMS 064)
[116]	N= 5 (N of pts. : 1056) RCTs Patients with histologically confirmed **B-cell follicular lymphoma** CENTRAL MEDLINE EMBASE LILACS Clinical trials in haematological malignancies **Not specific to first or second line**	Intervention : Rituximab maintenance therapy Control : Observation, treatment at relapse, or other maintenance treatment	Primary outcome : OS • Secondary outcome : EFS PFS Response duration QoL Bcl-2 conversion rate AEs	OS : I vs. C : HR 0.60, 95% CI 0.45-0.79 (p=0.0003) (5 trials; 985 pts.) EFS : I vs. C : HR 0.46, 95% CI 0.37-0.57 (p<0.00001) (3 trials; 589 pts.) PFS : I vs. C : HR 0.53, 95% CI 0.42-0.66 (p<0.00001) (3 trials; 454 pts.) Higher rate of grade 3 or 4 AEs in Intervention group (RR 1.52 , 95% CI 1.00-2.30)	SR+MA 1a Only RCTs included None of the trials were blinded ITT in 2 of the included trials	• 10 SR / 9 MA Ardeshna 2010 Blood Journal - *ASH Abstract*) • Forstpointner 2006 Blood Journal (**GLSG**) • Hainsworth 2007 Journal of Clinical Oncology (Phase II Trial of the Minnie Pearl Cancer Research Network) • Hochster 2007 + 2009 Journal of Clinical Oncology - **ECOG 1496/ECOG/CALGB**) • Ghielmini 2004 Blood Journal + Martinelli 2010

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
						Journal of Clinical Oncology (**SAKK 35/98**) • Pettengell 2010 Journal of Clinical Oncology • Salles 2010 Blood Journal (**GELA-GOELAMS FL2000**) • Van Oers 2010 Journal of Clinical Oncology + van Oers 2006 Blood (**EORTC 20981**) • Witzens-Harig 2009 Annals of Hematology + Witzens-Harig 2006 Blood Journal
[117] Update von Vidal 2009	N=9 trials N=2586 patients (only FL) Patients were eligible for trial entry if they had at least partial response or at least stable			**OS :** **Relapsed/refractory FL pts :** (Chemotherapy regimen and the schedule of rituximab maintenance had no statistically significant effect on outcome) I vs. C : HR for death = 0.72, 95% CI = 0.57-0.91		• Ardeshna 2010 Blood (first line) • Forstpointer 2006 Blood (relapse) • Hainsworth 2005 J Clin Oncol (relapse) • Hochster 2007+2009 J Clin Oncol (first line)

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	disease after induction therapy			**All patients** : I vs. C : HR of death = 0.76, 95% CI =0.62-0.92 **Patients in first-line setting** : no survival benefit (HR for death : 0.86, 95% CI = 0.60-1.25) **PFS :** HR of disease progression or death from 9 trials (2550 pts) = 0.54, 95% CI = 0.48-0.60 (effect consistent in boths pts groups) **Relapse/refractory** : HR of disease progression or death = 0.60, 95% CI = 0.49 - 0.72) Valid for different chemotherapy regimes **QoL**: (2 trials) "rituximab maintenance did not impair the quality of life" AE		• Martinelli 2010 J Clin Oncol (first line and relapse) (vorher Ghielmini 2004) • Pettengell 2010 J Clin Oncol (relapse) • Salles 2010 Blood (first line) • Van Oers 2010 J Clin Oncol (relapse) • Witzens-Harig 2009 Ann Hematol (first line and relapse)
[118]	N=2315 ; **treatment naive and relapsed FL** pts ; media nage 57 years ; majority advanced stages Only RCT	MR vs. No MR (control group was observed without R-treatment and did not receive R at progression while on study, but R was allowed when	Primary : • OS Secondary : • PFS • Toxicity • Subgroup analysis	• **OS >2line only : (N=753) HR = 0.70, 95% CI 0.54- 0.91** • No patient or disease characteristics associated with survival beneift with MR • MR benefical effect on OS compared with observation for all types of	1a Individual patient data (IPD) meta-analysis ITT ✓ Allocation concealment ✓ Random allocation ✓ Baseline balanced ✓	• Ghielmini 2004 Blood Journal (**SAKK**) ; n=151 (entspricht später Martinelli 2010) • Pettengell 2013 Journal of Clinical Oncology (lymphoma working

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Search up to 2014 11 eligible trials performed between 1998 and 2009 7 of 11 eligible trials (those 7 were willing to work together on individual patient data anlysis – the results of the other 4 were also used for sensitivity analysis)	treatment was indicated) MR : 4 weekly infusions every 6 months ; single infusion every 2-3months Duration : 4 months to 2 years Induction regimen before MR : with (74%) or without R (62% CHOP ; 23% CVP, 15% Fluradabin-based)		patients – not shown in one particular subgroup in which the patient had already received R in induction and received first line therapy • effect of MR was not statistically significantly different with R-CVP/CVP or R-CHOP/CHOP • HR of MR effect for the 233 patients who received fludarabine-based induction was 1.97 with a wide CI • OS 10 eligible trials (not only IPD): **0.79, 95% CI 0.66-0.94, 2786 patients** (1 trial didn't report OS) median OS time : 12years in MR vs. 11.5 years in observation group • **PFS** : improved with MR compared to observation **(HR 0.57, 95% CI 0.51-0.64, p < 0.0001, 2305 patients)** • AE : higher with MR, specially grade ¾ infections(HR 1.27, 95% CI 1.12-1.45) ; rate of any AE grade 1-4 in MR group was 52% and in the no MR group 40%, Median follow-up : 6years	Blinding X Heterogeneity I2 test :19% for IPD, 0% fpr summary data, total 0% We analysed data in two ways: (a) using a two-stage analysis and (b) using a multivariate model Publication bias	party of the European group for blood and marrow transplantation) ; n=280 • Salles 2011 The Lancet (**PRIMA**) ; n=1030 • Vitolo 2013 Journal of Clinical Oncology **(FIL);** n=202 • Witzens-Harig 2015 British Journal of Haematology (**HD2002**); n=41 • Hochster 2009 Journal of Clinical Oncology **(ECOG1496**); n= 279 • Van Oers 2010 Journal of Clinical Oncology (**EORTC**); n=334 • Ardeshna 2014 (no IPD)

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Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
						• Forstpointer 2016 (no IPD) • Hainsworth 2005 (no IPD) • Ardeshna (no IPD, no OS data, not in analysis)
[143]	Study type : RCTs and controlled trials Data bases : Medline via Ovid, Embase via Ovid, Cochrane Library and Science citation index.. Identification of ongoing or unpublished clinical trials. Time period: Medline (1966 to September 2000), EMBASE (1980 to September 2000), Cochrane	Rituximab 375mg/m2 (once weekly, 4 doses in total) vs. any comparator (observational therapy, placebo or other treatment).	• Survival • Treatment response • Adverse events • Quality of life	N=4 studies were included in SR. Study population consisted of 387 patients. All studies included were prospective case series. Median follow-up ranged from 0 to 18 months. Survival: Not reported in any case series included. Treatment response: • Overall response rate: 39 to 48% • Complete response rate: 3 to 6% • Partial response rate: 35 to 43%	SR 2a Authors did not perform a meta-analysis. Authors did not identify any RCT. No report on relevant outcomes such as survival and QoL in the original case series included. Detection bias was evident in original case series.	• Davis 1999 J Clin Oncol • Foran 2000 Br J Haematol • Ghielmini 2000 Ann Oncol • McLaughlin 1999 Semin Oncol • McLaughlin 1998 J Clin Oncol

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Library (2000), Sciences citation index (1981 to 2000) Exclusion criteria: Case series with less than 10 patients. Inclusion criteria: patients with relapsed or refractory stage III or IV indolent follicular lymphoma			Time to progression: Median: 8.1 to 13 months. QoL: Not reported in any case series included.		
[144]	**Study type** : RCTs, retrospective or prospective cohort studies with control groups **Data bases :** Medline via PubMed, Embase and Cochrane Library	Weekly vs. biweekly administered bortezomib in patients with indolent NHL.	• Treatment response AE	N=6 trials were eligible for systematic review. **Overall response rate:** OR: 1691, 95%CI: 1.02 to 2.80, p<0.001, favoring biweekly bortezomib. Adverse events: no significant differences. No detailed ORs provided. • Neuropathy • Fatigue	SR, 2a **Methodological issues :** • **inclusion of indolent NHL other than follicular lymphoma** • language bias : only studies published in English were eligible. • publication bias : “Begg'test showed low risk of publication bias of studies.”	• Ribrag 2013 Eur J Cancer • de Vos 2009 J Clin Oncol • Gerecitano 2009 Br J Haematol • O'Connor 2005 J Clin Oncol • Agathocleous 2010 Br J Haematol

Referenz/ Studientyp	Untersuchte Studien	(verglichene) Interventionen/ (ggf. Dosierung)	untersuchte Endpunkte	Ergebnisse	methodische Bemerkungen / Evidenzklasse (SIGN/ CEBM Oxford)	Literaturbelege/ eingeschlossene Publikationen
	Time period : Inception of each database to 2016 **Exclusion criteria:** Language other than English **Inclusion criteria :** comparison of bortezomib to other treatment regimens in patients with indolent NHL			• Diarrhea • Nausea	• only 3 out of 6 trials were RCTs **Funding source** : This work was partly supported by National Natural Science Foundation (No. 812 70598, No. 31340009, No. 81100335), Natural Science Foundations of Shandong Province (No. ZR2011HQ009, No. vc R2012HZ003), Technology Development Projects of Shandong Province (No. 2010 GSF10250), National Public Health Grand Research Foundation (No. 201202017), Program of Shandong Medical Leading Talent and Taishan Scholar Foundation of Shandong Province.	

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10.5.1.2. Einzelstudien

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[145, 146]	RCT	Planned: N=500	Arm 1: **Lenalidomide** 20mg PO on days 1 to 21 of every 28-day cycle during cycles 1 through 12 and **rituximab** 375mg/m2 IV every week in cycle 1 on days 1, 8, 15, and 22 and on day 1 of every 28-day cycle during cycles 3, 5, 7, 9, and 11, followed by a maintenance period (lasting 18 Cycles) that includes Lenalidomide 10 mg PO QD on Days 1 to 21 of every 28-day cycle during	Patients with relapsed/refractory indolent NHL including follicular lymphoma, marginal zone lymphoma and mantle-cell lymphoma.	-	• Progression-free survival • Treatment response • Safety	-	R: Yes. B: No, open label trial. **No results provided, yet. Study is still recruiting and enrolling patients.** Study is currently sponsored by Celgene.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			cycles 13 to 30 and rituximab 375 mg/m2 IV on Day 1 of every 28-day cycle during cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29 followed by a maintenance period (up to Progressive Disease) disease progresses Arm 2: **Lenalidomide** 20 mg PO QD on days 1 to 21 of every 28-day cycle during cycles 1 to 12 and **rituximab** 375 mg/m2 IV every week in cycle 1 on days 1, 8, 15, and 22 and on day 1 of					

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			every 28-day cycle during cycles 3, 5, 7, 9, and 11, followed by a **maintenance** period for 18 Cycles that includes: rituximab 375 mg/m2 IV on day 1 of every 28-day cycle during cycles 13, 15, 17, 19, 21, 23, 25, 27, and 29.					
[147]	Phase 2 trial	N=45	Patients received **bortezomib** 1.3mg/m2 IV on days 1, 4, 8 and 11 (21 day cycle, total of 6 cycles) and **rituximab** 375mg/m2 IV on day 1 of the 3rd to 6th cycle.	Patients with relapsed/refractory follicular lymphoma, who undergone one to three prior anti-cancer therapies.	The median follow-up was 52 months.	• Treatment response (ORR, CRR, duration of remission) • Progression-free survival • Overall survival • Safety	Treatment response: -ORR: 64% -CRR: 47% Median duration of remission: 50 months 5-year duration of remission: 49% Median PFS: 22months 5-year PFS: 34%	R: No. B: No. I: Safety analysis based on the ITT principles. The study was supported in part by the Associazione Angela

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			Patients further received two additional doses of rituximab after completion of the last cycle.				Median OS: not reached 5-year OS: 70%	Serra per la Ricerca sul Cancro, Modena, Italy, and by research funding from Johnson & Johnson/Janssen-Cilag S.p.A.
[148]	Phase 2 trial	N=66 **Of these, 14 patients had follicular lympho ma.**	Patients were treated with idelalisib and entospletinib. Patients underwent dose escalation of idelalisib from 100 to 150mg twice daily and of entospletinib from 200 to 800mg twice daily every 2 or 4 weeks.	Patients had relapsed or refractory NHL or CLL.	Median exposure to the treatmen t was 10 weeks.	• Treatment response • Safety	Treatment response (only FL patients) -ORR: 36%	R: No. B: No, study was an open-label trial. I: No information provided. The study was supported by Gilead Sciences Inc.. The study was terminated early because of treatment emergent pneumonitis in 18%of patients Only 14/66 patients had follicular lymphoma.

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[149]	Phase 2 trial	N=40	Patients were daily treated with **ibrutinib** 560mg	Patients with relapsed/refractory follicular lymphoma and at least one prior chemotherapy.	Median follow-up was 25.5 months.	• Progression-free survival • Treatment response (ORR, CRR, duration of response) • Time to treatment failure • Safety • Overall survival • Mutation analyses • Metabolic analyses	Median PFS: 14.0 months ORR: 25% CRR: 37.5% Median duration of response: 13.9 months Median time to treatment failure: 10 months. Median OS: not reached. 2-year OS: 79% 42.5% of patients experiencing at least one grade 3-4 AE. Grade 3-4 neutropenia (10%), lymphopenia (7.5%), anemia (7.5%), infection (7.5%), and diarrhea (5%) each occurred in more than 1 patient	R: No. B: No, study was an open-label trial. I: All patients with at least one dose of study drug were included in efficacy and safety analyses. The study was sponsored by the National Cancer Institute.
[150]	Phase 2 trial	N=72 Of these, 31 patients had follicular lymphoma	Patients received **mocetinosat** three times a week (28 day cycle, until disease progression or discontinuation)	Patients with relapsed/refractory follicular lymphoma or diffuse large B-cell lymphoma. Patients with follicular were required to have	Not reported.	• Treatment response (ORR, CRR, PRR, duration of response, time to response) • Progression-free survival	Results are extracted from the subgroup of patients with follicular lymphoma. ORR:11.5% Duration of response: 4.4 to 22.7 months (range).	R: No. B: No. I: Efficacy population consisted of all patients, who received at least 8 doses of study drug during one cycle.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			. The starting doses varied from 70 to 110 mg and the escalated dose was either 135 or 110 mg.	had at least three prior therapies.		• Overall survival • Safety	Time to response: 3.7 to 7.9 months (range). Median PFS: 3.7 months. Median OS: not reached.	Safety was calculated including all patients with a single dose of study drug. The study was supported by Mirati Therapeutics Inc.. 31/72 of the patients included had follicular lymphoma.
[151]	Phase 2 trial	N=55 Of these, 23 patients had follicular lymphoma.	Patients received **everolimus** 10mg PO daily (28-day cycle, at least six cycles).	Patients with relapsed or refractory lymphoma.	The median follow-up was 5.1 years (all patients).	• Treatment response (ORR, duration of response) • Progression-free survival • Overall survival	Treatment response (only patients with FL): -ORR: 61% Median PFS (all patients): 7.2 months Median OS (all patients): 29.4 months.	R: No. B: No. I: Efficacy analysis based on ITT principles. F: No funding source reported. 23/55 of the patients included had follicular lymphoma.
[152]	Retrospective study registry	N=2359 Arm 1: N=1973	Arm 1: BEAM Arm 2: Z-BEAM Arm 3: R-BEAM	Patients with follicular lymphoma who underwent a first autologous hematopoietic stem cell	Median follow-up was 19 months.	Overall survival Event-free survival Non-relapse mortality	Cumulative incidence or relapse -at 2 years BEAM: 32%	R: No. B: No information provided.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		Arm 2: N=207 Arm 3: N=179		transplantation after BEAM chemotherapy with either +/- 90Yttrium-ibritumomab tiuxetan (Z-BEAM) or +/- rituximab (R-BEAM).		• Incidence of relapse	Z- BEAM: 34% R- BEAM: 32% BEAM vs. Z-BEAM: HR: 1.02, 95% CI: 0.78 to 1.33 BEAM vs. R-BEAM: HR: 0.92, 95% CI: 0.68 to 1.23 NRM -at 12 months. BEAM: 3% Z- BEAM: 3% R- BEAM: 3% BEAM vs. Z-BEAM: HR: 0.88, 95% CI: 0.4 to 1.94 BEAM vs. R-BEAM: HR: 1.24, 95% CI: 0.57 to 2.72 OS -at 2 years: BEAM: 82% Z- BEAM: 86%	I: No information provided. The study funded by grant from Sepropharm.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							R- BEAM: 88% P=0.463 BEAM vs. Z-BEAM: HR: 0.93, 95% CI: 0.64 to 1.35 BEAM vs. R-BEAM: HR: 0.78, 95% CI: 0.51 to 1.2 EFS -at 2 years: BEAM: 63% Z- BEAM: 62% R- BEAM: 63% P=0.978 BEAM vs. Z-BEAM: HR: 0.93, 95% CI: 0.71 to 1.23 BEAM vs. R-BEAM: HR: 1.1, 95% CI: 0.84 to 1.41	
[153]	RCT	N=37	Arm 1: **INF alpha**-2b, 3 MU three days per week for 18 months.	221 patients with different lymphomas. Of these, 37 patients had follicular lymphoma.		• Overall survival • Event-free survival	No detailed results reported.	R: Yes. B: Not reported.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			Arm 2: Observational strategy.					All patients were included in ITT analysis. The study was sponsored by Schering Plough. Only abstract extraction was possible. No separate results for patients with follicular lymphoma reported.
[154]	Retrospective analysis of data from the CIBMTR and NLCS	N=349 Arm 1: N=175 Arm 2: N=174	Arm 1: Patients were treated with ASCT Arm 2: Patients were not treated with ASCT	Patients with follicular lymphoma, who relapsed within the first 2 years after first-line therapy. First-line therapy included rituximab. Patients were divided into autologous hematopoietic stem cell transplantation (ASCT) group (Arm 1) and alternative treatment (Arm 2).	Not reported	Overall survival	5-year OS: Arm 1: 60% Arm 2: 67% P=0.16 Subgroup: patients with early treatment failure receiving autoHCT soon after treatment failure (≤1year of ETF; n=123) had higher five year OS than those without autoHCT (73% vs 60%, p=0.05)	R: No. B: No. I: No information provided. F: No information provided.

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							early use of autoHCT was associated with significantly reduced mortality (HR=0.63, 95%CI:0.42-0.94,p=0.02)	
[155]	Phase 1b/2 trial	N=60 in phase 2. Arm 1: N=11 Arm 2: N=23 Arm 3: N=26	Arm 1: **Dulanermin** 8mg/kg IV on days 1-5 of a 21 day cycle (4 cycles in total). Arm 2: **Rituximab** 375mg/m2 IV weekly for eight courses. Arm 3: **Dulanermin** 8mg/kg IV on days 1-5 of a 21 day cycle (4 cycles in total) + rituximab 375mg/m2 IV weekly for eight courses.	Patients with follicular lymphoma (stage 1-3a) for phase 2.	Not reported.	• Treatment response • OS • PFS • Safety	N=60 FL pts Objective responses: Arm 1: 9.1% Arm 2: 63.6% Arm 3: 64% Median OS: could not be calculated (low number of events) Median PFS	R: Yes. B: No, open label trial. Safety analysis based on ITT principle. The study was sponsored by Genentech Inc. and collaborated by Amgen. "The Sponsor terminated the study on 5 May 2010, prior to the completion of the 36-month follow-up (FU) period, based on the primary analysis results. All patients were off-study or in survival FU (the treatment period was completed)."

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[156, 157]	RCT	N=676 Arm 1: N=336 Arm 2: N=340	Arm 1: **Bortezomib** 1.6mg/m2 on days 1,8,15, and 22 of a 35-day cycle + 4 doses of **rituximab** 375mg/m2 once a week on days 1,8,15, and 22 of cycle 1 and in combination with a single dose of rituximab on day 1 of cycles 2 to 5. Arm 2: **Rituximab** 375mg/m2 once a week on days 1,8,15, and 22 of cycle 1 and in combination with a single dose of	Patients with relapsed/refractory follicular lymphoma. The patients' lymphomas were either rituximab-naïve or rituximab-sensitive.	Median follow-up was 33.9 months.	Progression-free survival Treatment response (ORR, CRR, PRR) Overall survival Safety • Health status	Median PFS: Arm 1: 12.8 months Arm 2: 11 months HR: 0.82, 95% CI: 0.68 to 0.99, P=0.039 Median time to progression Arm 1: 13.3 months Arm 2: 11.3 months HR: 0.81, 95% CI: 0.67 to 0.98, P=0.027 Median time to next treatment Arm 1: 23 months Arm 2: 17.7 months HR: 0.80, 95% CI: 0.66 to 0.97, P=0.024 Median overall survival Arm 1: not reached. Arm 2: not reached. HR: 0.97, 95% CI: 0.71 to 1.33, p=0.854 Treatment response: ORR Arm 1: 63% Arm 2: 49% Odds ratio: 0.57, 95% CI: 0.42 to 0.78	R: Yes. B: No, open label trial. Efficacy analysis based in part (PFS) on the ITT principle. The study was funded by Johnson&Johnson and Millennium Pharmaceuticals Inc.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			rituximab on day 1 of cycles 2 to 5.					
[158]	Retrospective case series	N=79	Patients received **idelalisib** 150mg b.d.	Patients with relapsed/refractory follicular lymphoma.	The median follow-up was 6.1 months	• Treatment response (ORR, CRR) • Progression-free survival • Overall survival	ORR: 57% CRR: 15% Median PFS: 7.1 months. Median OS: not reached.	R: No. B: No. I: No information provided. F: The authors stated that there was no relevant funding source.
[159] GLSG	RCT	N=147 (N=105 patients had follicular lymphoma)	Induction therapy was either R-FCM or FCM regimen. Dosages were as follows: rituximab 375 mg/m2 IV daily, fludarabine 25 mg/m2 IV on days 1 to 3, cyclophosphamide 200 mg/m2 IV on days 1 to 3 and	Patients with relapsed or refractory indolent NHL including follicular lymphoma and mantle cell lymphoma.	Median follow-up: 26 months	Response rates (OR, CR, PR) (Overall survival, Treatment response, Safety – results in table 1.4 “Rituximab maintenance”)	**FL-pts only:** **ORR:** 95% versus 71% (P =0.01) **CR**: 41% vs. 23% **PR:** 54% vs. 48% Pts with initial therapy with R-FCM: significant prolongation of response duration by R maintenance compared with that by observation only was observed, with the median not being reached in this evaluation, compared with an estimated median of 26	R: Yes. B: No, open-label trial. All patients were included in ITT analysis. This work was supported in part by a grant by Deutsche Krebshilfe (T14/96/Hi 1, project no. 70-2208-Hi 2) and by the Competence Network Malignant Lymphoma

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			mitoxantrone 8 mg/m2 IV on day 1. Treatment cycles were repeated every 4 weeks for a total of 4 cycles. (for maintenance see table 1.4)				months, respectively (P = 0.035) (further results in table 1.4 Rituximab maintenance)	supported by the German Ministry for Research and Technology. "A number of patients (195) were randomized for R-maintenance versus no further treatment, and randomization was stopped in May 2005 after the respective statistical test showed a significant advantage for the R-maintenance arm."
[160]	RCT	-	Arm 1: **BR-CHOP+Ibrutinib or R-CHOP+Ibrutinib**: 560 mg (4*140 mg) ibrutinib PO once daily, continuously starting on cycle 1, day 1 +	Patients with relapsed/refractory indolent NHL including follicular lymphoma and marginal zone lymphoma. All patients had at least one prior therapy with a CD20 antibody and chemotherapy.	-	• Progression-free survival • Overall survival • Overall response rate • Complete response rate • Duration of response	No results provided, yet.	The SELENE trial is still enrolling patients. The authors have not published any preliminary results. R: Yes. B: Yes, double blinded trial.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			Bendamustine 90mg/m2 IV on days 1 to 2 of cycles 1 to 6. + rituximab 375 mg/m2 IV on day 1 of cycles 1 to 6. CHOP: (Cyclophosphamide 750 mg/m2 administered intravenously on day 1 of cycles 1 to 6, doxorubicin 50 mg/m2 administered intravenously on day 1 of cycles 1 to 6, vincristine 1.4 mg/m2 (maximum total 2 mg) administered intravenously on day 1 of			• Safety		I: Not reported. Study is sponsored by Janssen Research & Development, LLC

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			Cycles 1 to 6, prednisone 100 mg administered orally on says 1 to 5 of Cycles 1 to 6) Drug: Placebo **Placebo (4 capsules) matched to ibrutinib** administered orally once daily, continuously starting on Cycle 1, Day 1. Arm 2: **BR-CHOP+Placebo or R-CHOP+Placebo: Bendamustine** 90mg/m2 IV on days 1 to 2 of cycles 1 to 6. + rituximab 375					

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			mg/m2 IV on day 1 of cycles 1 to 6. CHOP: (Cyclophosphamide 750 mg/m2 administered intravenously on day 1 of cycles 1 to 6, doxorubicin 50 mg/m2 administered intravenously on day 1 of cycles 1 to 6, vincristine 1.4 mg/m2 (maximum total 2 mg) administered intravenously on day 1 of Cycles 1 to 6, prednisone 100 mg administered orally on says 1					

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			to 5 of Cycles 1 to 6) + Placebo Placebo (4 capsules) matched to ibrutinib administered orally once daily, continuously starting on cycle 1, day 1.					
[122]	RCT	N=349	Arm A: Mitumprotimut-T/ GM-CSF (n=174) Arm B: Placebo / GM-CSF (n=175) (after Rituximab)	Eligibility criteria: • Histologically confirmed CD20+ follicular lymphoma (**treatment naïve or relapsed/ refractory**), WHO grade 1 to 3 • Pts. Aged >=18 • ECOG performance status of 0 to 1 Characteristics of included pts.:	Not reported (Pts. assessment and enrollment between July 2004 and January 2006 – Assessment of	Primary (efficacy) endpoint: • TTP (measured from date from date of assignment to the date of first documentation of PD) Secondary endpoints: • ORR	PD (as of March 2008) • 215 assigned pts. (62%) • A: 113 pts. • B: 102 pts. Median TTP • A: 9.0 months (95% CI 6.2 to 12.5) • B: 12.6 months (95% CI 10.7 to 20.8) • A:B HR: 1.384 (95% CI 1.053 to 1.819, p= 0.19)	R: "Random assignment occurred regardless of successful production of mitumprotimut-T and was performed centrally on a 1:1 schedule using balanced blocks of four, with stratification by prior treatment (treatment-naive v relapsed/refractory disease) and response

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				• Median age: 54 years; A: 55.8 years (range 22-86); B: 53.0 years (range 21-81) • Treatment naïve: 79%; A: 79%; B: 79% Stage III/IV disease: 86%	PD/ efficacy analysis in March 2008)	• RRI (pts. with SD or a PR after rituximab whose response subsequently improved to a PR or CR) • Duration of response • Safety •	**Median TTP in treatment naïve pts.** • A: 11.9 months (95% CI 8.4 to 17.1) • B: 17.2 months (95% CI 11.0 to 25.0) • A:B HR: 1.196 (95% CI 1.053 to 1.819, p=0.258) Median TTP of pts. achieving CR or PR (n=205): • A: 18.8 months (95% CI 12.5 to 27.2) • B: 25.4 months (95% CI 21.0 to undetermined) • A:B HR: 1.352 (p=0.142) Median TTP of pts. achieving SD after rituximab (n=144): • A: 6.4 months (95% CI 4.5 to 73) • B: 6.3 months (95% CI 5.8 to 8.8) • A:B HR: 1.412 (p=0.68)	to rituximab therapy (CR/PR v SD)." B: "To ensure the integrity of treatment blinding, study drug and placebo prepared at Favrille were sent to an independent distributor that shipped the appropriate vials to clinical sites." I: "The intent-to-treat population consisted of all randomly assigned patients." Supported and sponsored by Favrille, Inc.

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							"Toxicity was similar in the two arms; 76% of adverse events were mild or moderate, and 94% of patients had injection site reactions."	
[161]	Single-arm trial	N=72 (with follicular lymphoma); correspond to 58% of participants	**Idealisib** 150mg twice a day	Histologic types included follicular lymphoma grade 1, 2, or 3a; small lymphocytic lymphoma; splenic, nodal, or extranodal marginal-zone lymphoma; or lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia. All patients had at least two prior systemic therapies for indolent non- Hodgkin's lymphoma with rituximab and alkylating agent.	Median follow-up: 9.7 months	• ORR (CR &PR) • Time to response • Duration of response • PFS • OS • AE • SAE	ORR only FL (58% of patients): 0.54 (0.42-0.66) Overall ORR: 0.57 (0.48-0.66) Overall AE*: 103 Overall SAE*: 68 *FL not reported separately	R: No B: No, open label trial. I: No information provided. F: Sponsored by Gilead Sciences
[162]	Phase II DAWN study	N=110	Ibrutinib for a median duration of 7.0 months (range, 1 to 37 months)	Chemo-immuntherapy (with CD20 AB) relapsed/refractory >18 yrs, grad 1,2,3a nontransformed FL	27.7 months	• ORR (independent review committee-assessed –CR+PR) • Exploratory analyses of T-cell	ORR: 20.9% (95% CI 13.7-29.7%) "which did not meet the 18% lower-bound threshold for the primary end point"	R: no B: no

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			at a mean daily dose of 539 mg (standard deviation, 40.6 mg) until progression	Two or more prior lines of therapy (median 3 prior lines) Meian age 61.5yrs		subsets in peripheral blood and cytokines/chemokines	CR: 11% (95% CI 5.8-18.3%) Median duration of response: 19.4 months Median PFS: 4.6 months (95% CI 2.8-5.5 months) 30-months PFS: 11% (95% CI 0.05-0.18%) Median OS: not reached after 27.7 months 12-months OS: 78% (95% CI 0.69–0.85%) 30-months OS: 61% (95% CI 0.51-0.70) Lymphoma symptoms resolved in 67% (Symptom resolution lasted a median of 10.4 months (95% CI, 6.5 months to not estimable) AEs: 107 pts (97%) Most common AEs: diarrhea, fatigue, cough, muscle spasms SAE: 48.2% (53 pts), most common: pneumonia and	F: Supported by Janssen Research & Development.

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							pyrexia; 8 pts dired during study, 3 because of AEs	
[163]	Phase 2 trial	N=81 Of these, 72 patients had follicular lymphoma.	Patients received **Inotuzumab ozogamicin** 1.8mg/m2 (28 days cycle, total of 6 cycles).	Patients with relapsed/refractory indolent NHL including follicular lymphoma, mantle-cell lymphoma or small lymphocytic lymphoma. All of these patients had at least 2 prior anti-cancer therapies.	All patients were followed-up for 2 years.	• Treatment response (ORR, CRR, duration of response) • Progression-free survival • Overall survival • Safety	The following results were taken from the subgroup of patients with follicular lymphoma. Treatment response: ORR: 71% CRR: 38% Median PFS: 14.7 months Median OS: not reached. most common all-causality treatment-emergent AEs included thrombocytopenia [74% (Grade ≥3, 56%)], neutropenia [56% (36%)], nausea [48% (5%)]; fatigue [48% (2%)], increased AST [43% (2%)], leucopenia [36% (12%)] and lymphopenia [35% (14%)	R: No. B: No. I: No information provided. The study was supported by Pfizer Inc.. 72/81 patients had follicular lymphoma.
[164, 165]	Phase 2 trial	N=60 patients Arm 1: N=29	Arm 1: **Rituximab** 375mg/m2 IV every week for 4 weeks and	All patients had follicular lymphoma and 1 or 2 prior chemotherapies. Previous treatment with rituximab was permitted,	Median follow-up: 34 months	• Progression-free survival • Response rate	Progression-free survival: HR: 0.40; 95% CI, 0.10-0.71; P= 0.007)	R: Yes. B: Not reported.

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		Arm 2: N=31	**bevacizumab** 10mg/kg IV on days 3 and 15. Patients with stable disease or treatment response continued therapy with 4 additional doses of rituximab (month 3, 5, 7 and 9) and 16 dosages of bevacizumab (every 2 weeks). Arm 2: **Rituximab** 375mg/m2 IV every week for 4 weeks. Patients with stable disease or treatment response continued therapy with 4 additional	but patients with previous bevacizumab treatment were excluded.		• Overall survival • Toxicity	Median PFS: Arm 1: 20.7 months Arm 2: 10.4 months Overall response rate: Arm 1: 48%, 95% CI: 29 to 67 Arm 2: 42%, 95% CI: 25 to 61 P=0.80 Overall survival: HR: 0.40; 95% CI, 0.15-1.05; P= 0.055 Median survival: Arm 1: Not reached. Arm 2: 48 months. Toxicity: Patients requiring hospitalization: Arm 1: 14% Arm 2: 3% HR, 0.40; 95% CI, 0.15-1.05; P= .055	All patients were included in ITT analysis Study was supported in part by grant from Genentech, Inc. The trial was prematurely closed because of slow accrual. Initially, 90 participants were planned to be randomized.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			doses of rituximab (month 3, 5, 7 and 9)					
[166]	Retrospective case series	N=30 reduced-intensity conditioning RIC: N=17 myeloablative condi-tioning MAC: N=13	RIC: a) Fludarabine either 125–180 mg/m2 plus busulfan 16 mg/kg oral or 6.4 mg/kg intravenous with or without low-dose TBI (2–4 Gy) or b) Fludarabine 125–180 mg/m2 and melphalan 140 mg/m2 intravenous with or without low-dose TBI (2–4 Gy) or	Patients with relapsed/refractory follicular lymphoma, who underwent allogeneic stem cell transplantation. All patients had a chemotherapy including rituximab prior to allogeneic stem cell transplantation. Patients were then treated by either myeloablative conditioning therapy (MAC) or reduced-intensity conditioning therapy (RIC)	Median follow-up was 21.4 months (all patients) and 57.1 months for survivors.	• Graft versus host disease • Progression-free survival • Overall survival	2-year PFS: 46.7% 2-year OS: -RIC: 47.1% -MAC: 46.2%	R: No. B: No I: No information provided. The study was supported, in part, by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology in Japan (23390254 & 24659462 to T.M.).

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			c) other regimens. MAC: a) Busulfan 12.8mg/kg and cyclophosphamide 120mg/kg b) Busulfan 16mg/kg and melphalan 200mg/m2 IV c) Total body radiation (12Gy9 and cyclophosphamide 120mg/kg d) Etoposide or thiopeta + either total body radiation or cyclophosphamide					
[167]	RCT	N=46	Arm 1: **Bendamustine** 120mg/m2 IV	Patients with relapsed or refractory, indolent B-cell	Not reported.	• Accomplishment rate of chemotherapy	ORR: Arm 1: 83% Arm 2: 77%	R: Yes.

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		Arm 1: N=24 Arm 2: N=22	on days 1 and 15 every 4 weeks (maximum of 7 cycles). Arm 2: **Bendamustine** 120mg/m2 IV on days 1 and 2 every 3 weeks (maximum of 7 cycles).	NHL or mantle cell lymphoma. Prior therapy with bendamustine was not permitted.		• Treatment response (CRR, ORR) • Progression-free survival • Overall survival • Safety	CRR: Arm 1: 46% Arm 2: 50% Median PFS: Arm 1: 21 months Arm 2: 15.5 months 15-month OS rate: Arm 1: 89.2% Arm 2: 88.9%	B: No sufficient information provided. All patients were included in ITT analysis F: No funding source reported. The study was terminated after the provisional duration of the study protocol.
[168]	Retrospective analysis	N=162 Arm 1: N=113 Arm 2: N=49	Patients were divided into two groups: 1) patients with progressive disease within the first 24 months (POD24) after first-line therapy: Arm 1. 2) patients without POD24: Arm 2.	Patients with relapsed/refractory follicular lymphoma, who have been previously randomized in the GLSG1996 (MCP versus CHOP) and the GLSG2000 trial (CHOP versus R-CHOP) for first-line treatment. Patients had not received ASCT.	Median follow-up was 9.4 years.	Progression-free survival • Overall survival	**PFS:** Arm 1: 35% Arm 2: 53% P=0.04 **OS:** Arm 1: 60% Arm 2: 83% P=0.02 Among patients with Arm 1: **PFS** (ASCT vs. rituximab): HR: 0.36, 95% CI 0.22 to 0.59, p<0.0001	R: No. B: No. I: Analysis was carried out according to the ITT principles. F: No information provided.

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			Patients in both arms were treated with ASCT, rituximab or a combination of both.				**OS** (ASCT vs. rituximab): HR: 0.50, 95% CI: 0.3 to 0.83, p=0.006	
[169]	Retrospective case series	N=518 Auto-HCT: N=250 Allo-HCT: N=268	Patients underwent either a) First autologous hematopoietic stem cell transplantation (Auto-HCT) b) First reduced intensity/nonmyeloablative conditioning allogeneic hematopoietic stem cell transplantation. (Allo-HCT)	Patients with relapsed/refractory grade 1 or 2 follicular lymphoma undergoing first autologous hematopoietic stem cell transplantation (Auto-HCT) Or first reduced intensity/nonmyeloablative conditioning allogeneic hematopoietic stem cell transplantation. (Allo-HCT)	Median follow-up was 61 months.	• Non-relapse mortality • Disease progression • Progression-free survival • Overall survival • Secondary malignancies	Non-relapse mortality At 5-years: • Auto-HCT: 5% • Allo-HCT: 26% • P<0.001 Probability of disease progression: At 5-years: • Auto-HCT: 54% • Allo-HCT: 20% • P<0.001 5-year PFS: • Auto-HCT: 41% • Allo-HCT: 58%	R: No. B: No. I: No. F: „The CIBMTR is supported by Public Health Service grant/cooperative agreement U24-CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a grant/cooperative agreement 5U10HL069294 from

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							• P<0.001 5-year OS • Auto-HCT: 74% • Allo-HCT: 65% P=0.05 GVHD incidence • at day 100: 28% • at 5 years: 60% Secondary malignancies: at 5 years: • Auto-HCT: 5% • Allo-HCT: 8% • P=0.22	NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); 2 grants N00014-13-1-0039 and N00014-14-1-0028 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals; Allos Therapeutics, Inc.; *Amgen, Inc.; anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; *Blue Cross and Blue Shield Association; *Celgene Corporation; Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Fresenius-Biotech North America, Inc.;

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								*Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.;*Gentium SpA; Genzyme Corporation; laxoSmithKline; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Jeff Gordon Children's Foundation; Kiadis Pharma; The Leukemia & Lymphoma Society; Medac GmbH; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; *Milliman USA, Inc.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.;

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								Otsuka America Pharmaceutical, Inc.; Perkin Elmer, Inc.; *Remedy Informatics; *Sanofi US; Seattle Genetics; Sigma-Tau harmaceuticals; Soligenix, Inc.; St. Baldrick's Foundation; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; *Tarix Pharmaceuticals; *TerumoBCT; *Teva Neuroscience, Inc.; *THERAKOS, Inc.; University of Minnesota; University of Utah; and *Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the

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								Department of the Navy, the Department of Defense, Health Resources and Services Administration or any other agency of the US Government.“
[170]	Retrospective case series	N=197 Auto-HCT: N=136 Allo-HCT: N=61	Patients underwent either a) First autologous hematopoietic stem cell transplantation (Auto-HCT) b) First reduced intensity/nonmyeloablative conditioning allogeneic hematopoietic stem cell transplantation. (Allo-HCT)	Patients with relapsed/refractory grade 3 follicular lymphoma undergoing first autologous hematopoietic stem cell transplantation (Auto-HCT) Or first reduced intensity/nonmyeloablative conditioning allogeneic hematopoietic stem cell transplantation. (Allo-HCT)	Median follow-up was 57 months (auto-HCT) and 59 months (allo-HCT).	• Non-relapse mortality • Disease progression • Progression-free survival • Overall survival • Secondary malignancies	Non-relapse mortality At 5-years: -Auto-HCT: 4% -Allo-HCT: 27% P<0.001 Probability of disease progression: At 5-years: -Auto-HCT: 61% -Allo-HCT: 20% P<0.001 5-year PFS: -Auto-HCT: 41% -Allo-HCT: 58%	R: No. B: No. I: No. F: „The CIBMTR is supported by Public Health Service grant/ cooperative agreement U24-CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a grant/cooperative agreement

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							P<0.001 5-year OS -Auto-HCT: 59% -Allo-HCT: 54% P=0.70 GVHD incidence -at day 100: 25% -at 5 years: 55% Secondary malignancies: -at 5 years: -Auto-HCT: 9% -Allo-HCT: 8% P=0.53	5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); 2 grants N00014-13-1-0039 and N00014-14-1-0028 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals; Allos Therapeutics, Inc.; *Amgen, Inc.; anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; *Blue Cross and Blue Shield Association; *Celgene Corporation; Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Fresenius-Biotech

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								North America, Inc.; *Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.;*Gentium SpA; Genzyme Corporation; GlaxoSmithKline; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Jeff Gordon Children's Foundation; Kiadis Pharma; The Leukemia & Lymphoma Society; Medac GmbH; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; *Milliman USA, Inc.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Osiris

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								Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Perkin Elmer, Inc.; *Remedy Informatics; *Sanofi US; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; St. Baldrick's Foundation; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; *Tarix Pharmaceuticals; *TerumoBCT; *Teva Neuroscience, Inc.; *THERAKOS, Inc.; University of Minnesota; University of Utah; and *Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the

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								Department of the Navy, the Department of Defense, Health Resources and Services Administration or any other agency of the US Government.“
[171]	Phase 2 trial	N=62	Patients were treated by allogeneic hematopoietic stem cell transplantation on day 0. Condition regimen was as follows: Rituximab 375 mg/m2 on day -13, rituximab 1000 mg/m2 on days -6, +1, and +8, fludarabine 30 mg/m2 on days -5 to -3 Cyclophospham	Patients with follicular lymphoma who underwent prior chemotherapy or autologous hematopoietic stem cell transplantation. Patients in first or subsequent partial remission or second/subsequent complete remission were enrolled.	Median follow-up was 47 months.	• Progression-free survival • Overall survival • Disease progression • Treatment response • Safety • Quality of life	• 2-year PFS: 73% • 2-year OS: 84% • 3-year OS: 82% • Cumulative incidence of progression/relapse: -at 3 years: 13% • Cumulative incidence of GVHD: at 100 days: 27% • Non-relapse mortality: at 3 years: 16% • 50 patients experienced at least 1 grade 3 to 5 toxicity during the first 2 years SF-36 instrument showed no statistically significant	R: No. B: No. F: The study was supported by the National Heart, Lung and Blood Institute and the National Cancer Institute through the National Institutes of Health Grant U10HL069294; Eastern Cooperative Oncology Group grants CA180820, CA180853, and CA 180799; and Southwest Oncology Group NCTN grant U10 CA180888.

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			ide 750 mg/m2 on days -5, -4, -3 GVHD prophylaxis included tacrolimus and methotrexate				difference in SF-36 score between the baseline and 2-year time points except that the raw SF-36 "health transition" item did show improvement from a mean score of 3 at baseline to 2 at 2 years	
[172]	Retrospective case series	N=175 CHVP-I: 105 R-CHVP-I: N= 70	CHVP-I vs. R-CHVP-I ASCT vs. non-transplanted	**Patients with relapsed/refractory follicular lymphoma** after induction and consolidation therapy with either CHVP-I oder R-CHVP-I. Moreover, patients were analyzed according to treatment with or without autologous hematopoietic stem cell transplantation (ASCT). CHVP-I: Cyclophosphamide, doxorubicin, etoposide, prednisolone + interferon-alpha2a over 18 months. R.CHVP-I: Rituximab (6 infusions) + cyclophosphamide,	Median follow-up was 31 months	• Overall survival • Event-free survival	Patients with and without ASCT, Rituximab naive **EFS** at 3 years ASCT: 73% (95%CI 56-84%) No-ASCT: 39% (95%CI 29-50%) P=0.002 **OS** at 3 years: ASCT: 92% (95%CI 78-97%) No-ASCT: 63% (95%CI 51-72%) P=0.0003	R: Patients were initially randomized, but not for the current trial B: No information provided. I: No information provided. F: No information provided.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
				doxorubicin, etoposide, prednisolone + interferon-alpha2a over 18 months.				
[173, 174]	RCT	/	Arm1: **Rituximab** 375mg/m2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) on Day 1 of every 28 day cycle from Cycles 2 to 5 and lenalidomide 20mg PO on Days 1 to 21 every 28 days up to 12 cycles Arm2: **Rituximab** 375mg/m2 IV every week in Cycle 1 (Days 1, 8, 15 and 22) on Day 1 of	All participants suffered from relapsed/refractory indolent NHL including follicular lymphoma or marginal zone lymphoma.	/	Progression-free survival Complete response rate Overall survival Overall response rate Safety Time to next treatment	/	The AUGMENT trial is still enrolling patients. The authors have not published any preliminary results. R: Yes. B: Yes. I: Not reported. Study is currently sponsored by Celgene.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			every 28 day cycle from Cycles 2 to 5 and placebo PO on Days 1 to 21 every 28 days up to 12 cycles					
[175] CALGB	RCT	N=91	Arm A: Lenalidomide Arm B: Lenalidomide+Rituximab	median age was 63 yrs (range, 34 to 89 years) Overall median TTP since last rituximab dose in this population with relapsed, nonrefractory FL was 1.4 years (range, 0.5 to 9.5 years); the median TTPs were 1.6 and 1.3 years in the lenalidomide-alone and LR arms, respectively	2.5 yrs	ORR, CR Safety TTP	full treatment course was completed in 36% of pts in Arm A and 63% of pts in Arm B, with the difference caused by more progressions or nonresponders in the Arm A. Safety: Arm A vs Arm B: grade 3 to 4 AEs occurred in 58% and 53% of patients, with 9% and 11% of patients experiencing grade 4 toxicity, respectively; grade 3 to 4 AE included neutropenia (16% v 20%, respectively), fatigue (9% v 13%, respectively), and thrombosis (16% [n = 7] v 4% [n = 2], respectively; P =0.157). ORR was 53% Arm A (20% CR) and 76% Arm B (39% CR)	R: yes B: N/A I: N/A F: Potential conflicts of interests of authors disclosed, some received research fundings from Genentech

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							OS was similar in the two arms and was 4.5 years for Arm A and not reached in Arm B (P=0.149)	
[176]	Phase 1 trial	N=81 Of these, 10 patients had follicular lymphoma	**Nivolumab** 1 or 3 mg/kg IV at weeks 1 and 4 and then every 2 weeks for a total of 2 years.	Patients with relapsed/refractory Hodgkin lymphoma, NHL or multiple myeloma. Patients with autologous or allogeneic SCT were excluded.	Median follow-up was 91.4 weeks for patients with FL.	• Safety • Genetic alteration of PD-L1 and PD-L2 • Treatment response (ORR, CRR, duration of response) • Progression-free survival	Adverse events were not separately reported for patients with follicular lymphoma. Treatment response (FL patients) -ORR: 40% -CRR: 10% Median PFS: not reached.	R: No. B: No. I: Safety and biomarker analyses based on ITT principles. The study was sponsored by Bristol-Myers Squibb. Only 10/81 patients had follicular lymphoma.
[177]	Retrospective case series	N=44 Auto-HCT: N=22 Allo-HCT: N=22	Patients underwent either a) First autologous hematopoietic stem cell transplantation (Auto-HCT) Or	Patients with relapsed/refractory follicular lymphoma who underwent first autologous hematopoietic stem cell transplantation (Auto-HCT)	Median follow-up was 60 months.	• Event-free survival • Overall survival	**EFS** -at 3 years: Auto-HCT: 64% Allo-HCT: 81% **OS** -at 3 years: Auto-HCT: 70%	R: No B: Not reported. I: Not reported. F: None reported.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			b) First allogeneic hematopoietic stem cell transplantation. (Allo-HCT)	first allogeneic hematopoietic stem cell transplantation. (Allo-HCT)			• Allo-HCT: 81%	
[178]	Retrospective case series	N=60 **First-line ASCT: N=18** **Second-line ASCT: N=34** **≥Third-line ASCT: N=8**	First-line ASCT Second-line ASCT ≥Third-line ASCT	Patients with high-dose chemotherapy for treatment of follicular lymphoma. All patients were subsequently treated with autologous hematopoietic stem cell transplantation.	Median follow-up was 5.7 years after ASCT.	• Overall survival • Progression-free survival • Freedom from progression • Minimal-residual disease • Non-relapse mortality Secondary malignancies	**Median OS**: not reached. **10-year OS**: 53% (total) • First line ASCT: 79% • Second line ASCT: 41% • ≥Third-line ASCT: 47% P=0.067 **Median PFS**: 68 months. **10-year PFS**: 40% (total) • First line ASCT: 57% • Second line ASCT: 35% ≥Third-line ASCT: 17%	R: No. B: No information provided. I: No information provided. F: No information provided.

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[179]	Single-arm trial	N=72 with follicular lymphoma	Idelalisib 150mg twice daily.	Patients with relapsed indolent NHL including small lymphocytic lymphoma, marginal zone lymphoma, lymphoplasmocytic lymphoma or follicular lymphoma. All patients had a previous treatment with rituximab and alkylating agent.	Median follow-up was 8.1 months.	• Treatment response (ORR, CRR, PRR)	ORR: 54%, 95% CI: 42 to 66% CRR: 8% PRR: 46%	R: No B: No, open label trial. I: No information provided. F: No information provided.
[180]	Consensus project EBMT	Due to lack of RCTs – expert panel consensus meeting	/	/	/	Statements on hematopoietic stem cell tansplantation in FL in Europe	8 statements, agreement reached: HDT-ASCR is not an appropriate treatment option to consolidate first remission in patients with FL responding to immuno-chemotherapy, outside the setting of clinical trials. In patients in first relapse with chemo-sensitive disease HDT-ASCR is an appropriate treatment option to consolidate remission. Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse	Expert panel consensus decisions The participants rated every statement using a 9-point scale from 1-3 (‘disagree’: 1, trongly; 2, disagree; 3, moderately) to 7-9 (‘agree’: 7, moderately; 8, agree; 9, strongly); scores of 4-6 corresponded to ‘neither agree nor disagree’

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							in patients with a short response duration (<3 years) after immuno-chemotherapy. Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients with high-risk FLIPI at relapse. Remission consolidation with HDT-ASCR is an appropriate treatment option in 1st relapse in patients previously treated with rituximab. (only partial consensus) Remission consolidation with HDT-ASCR is an appropriate treatment option in patients in second or subsequent relapses with chemo-sensitive disease. Allogeneic transplantation should be considered in patients with relapse after HDT-ASCR. Reduced-intensity/ non-myeloablative conditioning regimens are generally more	

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							appropriate in patients receiving an allogeneic transplant. In FL, the available biological and genetic risk factors are not sufficient to guide treatment decisions. Treatment decisions including the indication for HDT-ASCR and allogeneic transplantation are mainly guided by the clinical course.	
[181]	Phase 2 trial	N=121 Arm 1: N=63 Arm 2: 58	Arm 1: **Rituximab** 375 mg/m2 IV on day 1 of each cycle + **pinatuzumab** 2.4mg/kg IV on day 2 of the first 2 cycles and on day 1 one the following cycles. Arm 2: **rituximab** 375 mg/m2 IV on day 1 of each	Patients with refractory NHL including follicular lymphoma and diffuse large B cell lymphoma.	Follow-up was insufficient for patients with follicular lymphoma.	• Safety • Treatment response (CRR, ORR, PRR) • Duration of reponse • Proportion of patients with anti-treatment antibodies • Overall survival • Progression-free survival	Progression-free survival: Not provided due to insufficient follow-up. Overall response rate: Arm 1: 62% Arm 2: 70% Complete response rate: Arm 1: 10% Arm 2: 40%	R: Yes. B: No, open label trial. I: Not reported. Study was sponsored by Genentech, Inc. The follow-up period was insufficient for patients with follicular lymphoma. The authors did not provide data for every preliminary defined outcome.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			cycle + **polatuzumab** 2.4mg/kg IV on day 2 of the first 2 cycles and on day 1 one the following cycles.					
[182]	Retrospective case series	N=171 Arm 1: N=117 Arm 2: N=54	Arm 1: Auto-BEAM Patients underwent autologous hematopoietic stem cell transplantation Arm 2: Allo-BEAM Patients underwent allogeneic hematopoietic stem cell transplantation	Patients with chemosensitive follicular lymphoma following salvage treatment . Patients underwent BEAM chemotherapy and either autologous or allogeneic hematopoietic stem cell transplantation	Median follow-up was 6.5 years. Arm 1: 5.5 years Arm 2: 7.7 years	• Overall survival • Disease-free survival • Cumulative incidence of relapse • Transplantation-related mortality • Secondary malignancies • Non.-relapse mortality	Overall survival (p=0.506) -at 2 years Auto-BEAM: 78.7% Allo-BEAM: 68.5% -at 5 years Auto-BEAM: 62.9% Allo-BEAM: 66.6% -at 10 years Auto-BEAM: 48.3% Allo-BEAM: 64.4% Disease-free survival (p=0.785) -at 2 years Auto-BEAM: 64.1%	R: No. B: No. I: No information provided. F: No information provided.

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							Allo-BEAM: 57.4% -at 5 years Auto-BEAM: 49.9% Allo-BEAM: 53.4% -at 10 years Auto-BEAM: 34.7% Allo-BEAM: 48.1% CIR (p=0.042) -at 2 years Auto-BEAM: 30.9% Allo-BEAM: 24.2% -at 10 years Auto-BEAM: 55.1% Allo-BEAM: 31.4% TRM (p<0.001) Auto-BEAM: 2% Allo-BEAM: 24%	
[183]	RCT	N=280	Arm 1: **Rituximab** 375mg/m2 IV	• Patients with rituximab-naive, but chemosensitive relapsed	Median follow-	Progression-free survival	**Progression-free survival at 10 years:**	R: Yes. B: No, open label trial.

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		Arm 1: N=69 Arm 2: 72 Arm 3: 69 Arm 4: 70	every week for 4 weeks. **Maintenance** therapy consisted of **rituximab** every 2 months (total: 4 doses). Arm 2: **Rituximab** 375mg/m2 IV every week for 4 weeks. **No maintenance therapy.** Arm 3: **No further treatment. Maintenance therapy consisted of rituximab every 2 months (total: 4 doses).** Arm 4: **No further treatment. No**	follicular lymphoma in complete or very good partial remission.	up: 8.3 years.	Overall survival Response rate Safety • Molecular remission rate	Purging: 48.6% No purging: 42% HR: 0.80; 95% CI: 0.58 to 1.11 P=0.18 **Overall survival at 10 years**: Purging: 66.1% No purging: 74.5% **Safety:** "Early or late toxicities did not differ significantly across the treatment groups." • Comparison between purging (arm 1+2) and no purging arms (arm 3+4).	All patients were included in ITT analysis Study was supported by grant from Roche. The trial was prematurely closed because of slow accrual. Initially, 480 participants were planned to be randomized. Details of response rate were not reported in detail.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			maintenance therapy. 2x2 trial. Induction therapy was cyclophosphamid IV on day 0 or standard induction chemotherapy regimen. Each patient received daily G-CSF subcutaneously. PBCS were collected from all patients and all received BEAM high dose chemotherapy within first 4 weeks.					
[184]	Retrospective case series	N=9	All patients received a single dose of 90Yttrium-ibritumomab tiuxetan (either	All patients were relapsed Patients with grade 1 or 2 follicular lymphoma previously treated with	Median follow-up after consolidation therapy	• Treatment response • Progression-free survival	**Treatment response after FCR** • CR: N=7 • PR: N=2	R: No. B: No. I: Not reported.

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			11..1 to 14,8 MBq/kg) as consolidation therapy three months after the last FCR course. FCR: Fludarabine 25mg/m2 on day 1 to 3, cyclophosphamide 1000mg/m2 on day 1 and rituximab 375mg/m2 on day 4 of each cycle (4 cycles in total).	fludarabine,cyclophosphamide and rituximab. All patients showed complete or partial response to FCR.	was 88 months.	• Overall survival • Safety	**Treatment response after consolidation therapy** • CR: N=9 **Median PFS**: not reached,. • 7.5 years PFS: 67% **Median OS**: not reached. • 7.5 years OS: 67% **Safety**: Grade 3 or 4 neutropenia occurred in 8/9 patients treated with FCR andin 9/9 patients assessable after 90Y-RIT	F: No information provided.
[185]	Phase 2 trial.	N= 24 Of these, 5 patients had follicular lymphoma.	All patients were treated with **rituximab** 375mg/m2 IV on day 1, **cladibrine** 4mg/m2 IV on days 1 to 5 and **bortezomib** 1.3	Patients with relapsed/refractory mantle-cell lymphoma, follicular lymphoma, marginal zone lymphoma, lymphoplasmocytic lymphoma, small lymphocytic lymphoma.	Median follow-up was 38.5 months	• Treatment response (ORR, CRR) • Time to progression • Progression-free survival	ORR (only patients with FL): 80% The following results represent the subgroup of patients with lymphoma other than mantle cell lymphoma: Median PFS: not reached.	R: No. B: No, study was an open-label trial. I: No information provided. F: No funding source reported. Bortezomib

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			mg/m2 IV on days 1 and 4. (Total numbers of 6 cycles, 28 days per cycle).	Patients with mantle-cell lymphoma, marginal-zone lymphoma or lymphoplasmocytic lymphoma could be treatment-naïve.		• Overall survival • Safety	2-year PFS: 54%. 2-year OS: 69%.	was supplied Millennium Pharmaceuticals. Only 5 patients had follicular lymphoma.
[186]	RCT	N=15 Arm 1: N=9 Arm 2: N=6	Arm 1: **Tositumumab and Iodine I 131** Tositumumab: dosimettric dose: tosituzumab 450mg IV followed by 35mg tosituzumab IV + 5mCi of I 131. The dosimetric dose was followed by tosituzumab 450mg IV followed by 35mg tosituzumab IV + the patient	Patients with recurrent follicular lymphoma with 1 or 2 prior chemotherapy regimens. Patients had either one prior course on rituximab or were rituximab-naïve.	Median follow-up was 62 months for arm 2 and 91.5 months for arm 1	• Event-free survival • Treatment response (investigator-assessed response rate, duration of reponse) • Progression-free survival • Overall survival • Safety	Treatment response **CR:** Arm 1: N=6 Arm 2: N=1 **PR:** Arm 1: N=2 Arm 2: N=3 **Duration of response (median)** Arm 1: not reached. Arm 2: 7.3 months. **PFS (median)** Arm 1: not reached. Arm 2: 9 months. **OS (median):** Arm 1: not reached. Arm 2: not reached. All patients experienced at least one AE. For rituximab, pyrexia (n = 3) and infusion-related	R: Yes. B: No, open label trial. End point analysis based on ITT principles. The study was sponsored by GlaxoSmithKline. The study was prematurely terminated due to lack of feasibility.

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			specific activity of I 131 (=therapeutic dose). 7 to 14 days after dosimetric dose. Arm 2: **rituximab** 375mg/m2 IV once weekly for 4 weeks.				reactions (n = 3) were the most common AEs. The most common AEs for TST/I-131 TST were headache (n = 5), nausea (n = 5), thrombocytopenia (n = 5), leukopenia (n = 4), lymphopenia (n = 4), vomiting (n = 4), white blood cell (WBC) count < 2000 cells/mm^3 (n = 4) and cough (n = 4)	
[187] GAUDI	Phase 1b study	N=56 Arm 1: N=28 Arm 2: N=28	Arm 1: **Obinutuzumab + CHOP**, N=28 obinutuzumab 1600mg/800mg or 400mg/400mg IV on days 1 and 8 of each cycle (starting dose/subsequent dose + doxorubicin, 50 mg/m2	Patients with relapsed/refractory CD20+ follicular NHL after one or two prior chemo-immunotherapies. Patients in the CHOP arm were not allowed to have had a prior treatment with anthracyclines. • Patients in the FC arm were not allowed to have had a prior treatment with fludarabine or purine analogues.	Not reported.	Safety (AEs, SAEs) Treatment response (ORR, CRR, PRR) Progression-free survival Event-free survival • Pharmacodynamics and pharmacokinetics of obinutuzumab	Safety: “G-CHOP (68%) and G-FC cohorts (71%) had similar incidences of grade 3/4 AEs, with no relevant differences between arms in each cohort.” “Serious AEs (SAEs) were reported in 29% and 25% of patients in the G-CHOP and G-FC cohorts, respectively. There were no relevant differences in specific infections between arms in each cohort. No treatment-related deaths were reported.”	R: Yes. B: No, open label trial. Efficacy and safety analysis based on an ITT-population. Study was sponsored by Hoffmann-La Roche. 50% of patients in each arm received the 1600mg/800mg dose of obinutuzumab and 50% were treated with

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			intravenously on day 1; vincristine, 1.4 mg/m2 capped at 2 mg intravenously on day 1; cyclophosphamide 750 mg/m2 intravenously on day 1; prednisone, 100 mg per day orally on days 1 to 5. Arm 2: **Obinutuzumab** + FC, N=28 Either obinutuzumab 1600mg/800mg or 400mg/400mg IV on days 1 and 8 of each cycle (starting dose/subsequent dose) +				Treatment response: ORR Arm 1: • 1600/800: 100% • 400/400: 93% Arm 2: • 1600/800: 86% • 400/400: 100%	the 400mg/400mg dose. Reporting bias (no report on PFS or EFS data).

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			fludarabine, 25 mg/m2 per day intravenously on days 1 to 3; cyclophosphamide, 250 mg/m2 intravenously on days 1 to 3.					
[188, 189]	Phase 2 trial	N=87 Arm 1: N=50 Arm 2: N=37	Arm 1: 1.5mg/m2 **bortezomib** IV biweekly on days 1, 4, 8, and 11(21 days cycles, 8 cycles in total) Arm 2: 1.6mg/m2 **bortezomib** IV weekly on days 1, 8, 15, and 22 (35 days cycles, 6 cycles in total)	Patients with previously treated, relapsed/refractory follicular lymphoma.	Arm 1: 36 months Arm 2: 38 months	Treatment response (ORR, CRR, PRR) Progression-free survival Overall survival Safety • Tolerability of study drug	ORR: Arm 1: 32% Arm 2: 23% CRR: Arm 1: 8% Arm 2: 14% Safety: Serious adverse events: Arm 1: 19 Arm 2: 19	R: Yes. B: No, open label trial. Efficacy and safety analysis based on an ITT-population. Study was supported in part by research funding from Johnson&Johnson. “As planned by the statistical design, an interim analysis was done to assess treatment efficacy in both arms when 15 patients were evaluable for efficacy on week 14 (5 courses in arm A and

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
								3 courses in arm B). At this time, arm B was closed since only 2/13 patients reached a response that was lower than the minimal response rate designed by the protocol to pursue inclusions (at least 5/15 responses). Six out of 37 patients included in arm B (bortezomib 1.6 mg/m2) that remained on therapy at the time of interim analysis switched to arm A (bortezomib 1.5 mg/m2)"
[190, 191]	Retrospective case series	N=183	Patients underwent reduced-intensity allogeneic stem cell transplantation	Patients with follicular lymphoma, who relapsed after autologous stem cell transplantation.	Median follow-up was 58.8 months.	• Non-relapse mortality • Disease progression • Progression-free survival	NRM (cumulative incidence) • at 100 days: 11.9% • At 2 years: 27.4% Disease progression Median time to progression: 5.6 months	R: No B: No I: No F: No.

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						• Overall survival	PFS • at 2 years: 61.8% • at 5 years: 47.7% OS • at 2 years: 63.3% at 5 years: 51.1%	
[192]	Retrospective case series	N=510	Group 1: **Alkylating agent** (AA) Group 2: **Anthracycline**-containing agent (AC) Group 3: Nucleoside analogues containing agent (NA)	Patients with relapsed follicular lymphoma after a single-agent chemotherapy regimen with or without rituximab. Patients refractory to first-line chemotherapy were not eligible Study group investigated the effect of agent from the first-line therapy on the outcome of salvage therapy for relapsed follicular lymphoma.	Median follow-up was 42 months.	• Time to next treatment	Patients alive without need for third-line treatment: AA: 23% AC: 42% NA: 32%	R: No. B: No. I: No information provided. F: No information provided. Insufficient report on outcomes, for some outcomes, all groups were only analyzed together.
[193, 194]	RCT	N=230	Arm 1: **Rituximab** 375mg/m2 IV	Patients with relapsed/refractory indolent NHL lymphoma	Median follow-	• Progression-free survival • Overall survival	Progression-free survival (median): Arm 1: 34.2 months	R: Yes. B: No, open label trial.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
NHL 2 2003		Arm 1: N=116 Arm 2: N=114	on day 1 of each cycle + **bendamustine** 90mg/m2 on day 1 and 2 of each cycle (4-week cycles, total of 6 cycles). Arm 2: **Rituximab** 375mg/m2 IV on day 1 of each cycle + **fludarabine** 25mg/m2 on day 1, 2 and 3 of each cycle (4-week cycles, total of 6 cycles).	including follicular lymphoma (N=111), lymphoplasmacytic lymphoma (Waldenstrom's macro globulinaemia), small lymphocytic lymphoma, nodular and generalised marginal zone lymphoma, or mantle-cell lymphoma .	up: 96 months	• Treatment response • Safety	Arm 2: 11.7 months HR: 0.54, 95% CI: 0.38 to 0.72, P<0.0001 (Patients with follicular lymphoma: HR: 0.56, 95% CI: 0.34 to 0.87) 1-year PFS Arm 1: 0.76 Arm 2: 0.48 P<0.0001 Overall survival (median): Arm 1: 109.7 months Arm 2: 49.1 months HR: 0.64, 95% CI: 0.45 to 0.91, P<0.012 Treatment response ORR Arm 1: 82% Arm 2: 51% P<0.0001 CRR Arm 1: 40% Arm 2: 17% P=0.0002	Efficacy and safety analysis based on ITT principle. Study was funded by Roche Pharma AG, Ribosepharm GmbH, Mundipharma GmbH and Studiengruppe indolente Lymphome.

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[136] BP22333	RCT, multicentre, open-label, noninferiority	N=154 aged ≥18 y; histologically confirmed CD20+ grade 1, 2, or 3a FL **(first line or relapsed (no subgroups reported))** all pts had responded to a R induction regimen and had at least one dose of R iv maintena	Subcutaneous (sc) vs intravenous (iv) **R as maintenance** 1400mg fixed dose sc or 375 mg/m2 iv of each cycle of their remaining maintenance cycles (ever 2-3months for 2 years)	• baseline demographics and disease characteristics were similar • median age: 59.0 years in the sc arm; 57.5 years in the iv arm prior to study entry complete response (confirmed) was 53% in the sc arm and 58% in the iv arm; partial response was 40% in the sc arm and 38% in the iv arm	total of 38 pts in the sc arm and 33 pts in the iv arm were ongoing in the treatment period of the study, and 22 sc and 24 iv pts were ongoing in the follow-up period	• Demonstrate noninferior R sc compared with iv • Peripheral blood B-cell depletion • Safety (administration related reactions ARR) • AUC of R	• $C_{trough,\ sc}/C_{trough,\ iv}$ ratios were 1.24 and 1.12, respectively, for q2m and q3m, and lower limits of the two-sided 90% CI (1.02 and 0.86, respectively) exceeded the protocol-specified noninferiority limit ($C_{trough,\ sc}/C_{trough,\ iv}$ ratio of 0.8) • C_{trough} values were higher in the sc arm for both dosing regimens • CD19+ B lymphocytes remained depleted throughout the study for both arms • geometric mean AUC_T, sc/AUC_T, iv ratio was 1.35 for both q2m and q3m, and the lower limit of the two-sided 90% CI was 1.23 • 13 patients in the sc arm had withdrawn (seven for progressive disease [PD], four for adverse events [AEs], one at the investigator's discretion, one for ineligibility) and 17 patients in the iv arm	R: ✓ B: X I: not reported F: not reported

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		nce therapy.					had withdrawn (10 for PD, four for AEs, three for ineligibility) AEs: incidence and intensity well balanced between treatment arms	
[195]	Phase II study	N=18 Arm 1: N=22 Arm 2: N=18	Arm 1: **obinutuzumab** 1600mg/800mg IV on days 1 and 8 of the first cycle and day 1 of each subsequent cycle (starting dose/subsequent dose) Arm 2: **obinutuzumab** 400mg/400mg IV on days 1 and 8 of the first cycle and day 1 of each subsequent cycle (starting dose/subsequent dose)	Patients with relapsed/refractory indolent NHL. (Follicular lymphoma was the predominant diagnosis (85%).	Median follow-up was 33.7 months.	Treatment response (ORR, CRR) Progression-free survival Safety Pharmacokinetics	ORR (Only patients with follicular lymphoma): Arm 1: 50% Arm 2: 21% CRR: Arm 1: 90% Arm 2: 0% Median PFS: Arm 1: 11.9 months Arm 2: 6 months	R: Yes. B: No, open label trial. Efficacy and safety analysis based on an ITT-population. Study was sponsored by Hoffmann-La Roche.

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
[196]	Single-arm trial	N=72	**Idelalisib** 150mg twice daily.	Patients with relapsed or refractory follicular lymphoma. Patients had at least 2 prior chemotherapies with rituximab and alkylating agents.		• Treatment response • Progression-free survival • Overall survival • Safety	ORR: 55.6%, 95%CI: 43.4 to 67.3 CRR: 13.9% PRR: 41.7% Median PFS: 11 months, 95%CI: 8 to 14 1-year PFS: 43% Median OS: not reached. Estimated 2-year OS: 69.8% The most common treatment-emergent AEs (TEAEs) were diarrhea (51.4%), cough (31.9%), pyrexia (29.2%), fatigue (27.8%), and nausea (27.8%)	R: No. B: No, open label trial I: No information provided. The study was supported by Gilead Sciences.
[197]	RCT	N= 149* Arm 1: N= 74 Arm 2: N= 75 *Only patients with	Arm 1: **Obinutuzumab** 1000mg IV on days 1, 8, 15 and 22. Patients with treatment response entered	• Patients with relapsed indolent NHL including follicular lymphoma, mantle-cell lymphoma, lymphoplasmacytic lymphoma and small lymphocytic lymphoma. All patients had a previous treatment with rituximab	Median follow-up was 32 months.	Treatment response (ORR) Progression-free survival Safety Pharmacokinetics • Pharmacodynamics	Treatment response ORR Arm 1: 44.6% Arm 2: 33.3% P=0.08 CRR	R: Yes. B: No, open label trial. Safety analysis based on the ITT principles. Only patients with follicular lymphoma were included in efficacy analysis.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		follicular lymphoma	**maintencance regimen with 1000mg obinutuzumab** IV every two months. Arm 2: **Rituximab** 375mg/m2 IV on days 1, 8, 15 and 22. Patients with treatment response entered **maintencance regimen with rituximab** 375mg/m2 every two months.				Arm 1: 12.2% Arm 2: 5.3% P=0.07 Median PFS Arm 1: 17.6 months Arm 2: 25.4 months • HR: 0.93, 95% CI: 0.6 to 1.44	The study was sponsored by Hoffmann-La Roche.
[197]	RCT	N= 149* Arm 1: N= 74 Arm 2: N= 75	Arm 1: **Obinutuzumab** 1000mg IV on days 1, 8, 15 and 22. Patients with treatment	Patients with relapsed indolent NHL including follicular lymphoma, mantle-cell lymphoma, lymphoplasmacytic lymphoma and small lymphocytic lymphoma. All	Median follow-up was 32 months.	Treatment response (ORR) Progression-free survival Safety	Treatment response ORR Arm 1: 44.6% Arm 2: 33.3% P=0.08	R: Yes, for induction, not for maintenance B: No, open label trial. Safety analysis based on the ITT principles. Only patients with

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		*Only patients with follicular lymphoma	response entered **maintencance regimen with 1000mg obinutuzumab** IV every two months. Arm 2: **Rituximab** 375mg/m2 IV on days 1, 8, 15 and 22. Patients with treatment response entered **maintencance regimen with rituximab** 375mg/m2 every two months.	patients had a previous treatment with rituximab		Pharmacokinetics Pharmacodynamics	CRR Arm 1: 12.2% Arm 2: 5.3% P=0.07 Median PFS Arm 1: 17.6 months Arm 2: 25.4 months HR: 0.93, 95% CI: 0.6 to 1.44 Safety: "No new safety signals were observed for obinutuzumab, and the incidence of AEs was balanced between arms, with the exception of infusion-related reactions and cough, which were higher in the obinutuzumab arm"	follicular lymphoma were included in efficacy analysis. The study was sponsored by Hoffmann-La Roche.
[198-200] GADOLIN	RCT	N=396 Arm 1: N=194 Arm 2: N=202	Arm 1: **Obinutuzumab** 1000mg IV on days 1, 8 and 15 on first cycle and day 1 of	• Patients with indolent NHL (**follicular lymphoma (>80%)**, small small lymphocytic lymphoma, marginal zone lymphoma,	Median follow-up: 31.8 months	PFS OS Treatment response (ORR, CRR, PRR,	**Median PFS:** Arm 1: 25.8 Arm 2: 14.1 months **HR: 0.57; 95% CI, 0.44 to 0.73; P , .001**	R: Yes, for induction not for maintenance, B: No, open label trial.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			each subsequent cycle (total of 6 cycles) + **bendamustine** 90mg/m2 IV on day 1 and days 2 of each cycle. Patients without evidence for disease progression received **obinutuzumab as maintenance** therapy after induction therapy. Arm 2: **Bendamustine** 90mg/m2 IV on day 1 and days 2 of each cycle.	Waldenström macroglobulinaemia) refractory to rituximab and a maximum of 4 prior chemotherapies.		duration and time to best reponse) Disease-free survival Event-free survival Safety Health-related QoL Pharmacokinetics • Minimal-residual disease	Investigator-assessed **median PFS:** Arm 1: 29.2 months Arm 2: 14 months **HR: 0.52, 95% CI: 0.39 to 0.70, P<0.0001** **PFS in FL only subgroup** Arm 1 vs. Arm 2: (HR): 0.49 (95% CI, 0.35-0.68) **Median overall survival** Arm 1: not estimated. Arm 2: not estimated. **HR, 0.67; 95% CI, 0.47 to 0.96; P = .027** **Median disease-free survival** Arm 1: not estimated. Arm 2: 13.2 months **HR: 0.09, 95% CI: 0.02 to 0.40** **Median event-free survival** Arm 1: 26.8 months Arm 2: 13.7 months **HR: 0.57, 95% CI: 0.43 to 0.76, P=0.0001** **Treatment response**	Efficacy analysis based on an ITT-population. Study was sponsored by Genentech Inc., funded by Hoffmann-La Roche and Roche Pharma AG was the collaborator. The study was stopped after a pre-planned interim analysis because the primary end-point had been met.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							ORR Arm 1: 69% Arm 2: 63% P=0.31 CRR Arm 1: 11% Arm 2: 12% P=0.71 Health-related QoL: “The delayed time to worsening and greater proportion of patients reporting meaningful improvement in HRQoL in the G-B arm suggest that benefit in PFS is not at the expense of an increase in treatment-related toxicity that could lead to reduced HRQoL” FACT-Lym trial outcome index ≥6-point worsening from baseline in a the ITT population: HR: 0,83 (95% CI 0.60-1.13) • Safety: Grade 3 to 5 AEs were reported by 148 (72.5%) and 133v(65.5%) patients in the G-	

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							B and B monotherapy arms, respectively, most commonly neutropenia (G-B, 34.8%; B monotherapy, 27.1%), thrombocytopenia (10.8% and 15.8%), anemia (7.4% and 10.8%), and infusion-related reactions (9.3% and 3.4%).	
[138, 139] SAKK 35/03	Phase III RCT	N=270 (FL)	**Short term maintenance R** Vs **Long term maintenance R**	**Short term arm:** N=82 Median age: 55 (34-81) Disease status: **55 untreated,** **27 relapsed/progressed** (nor subgroups reported) **Long term arm:** N= 83 Median age: 57(25-81) Disease status: **58 untreated** **24 relapsed/progressed** 1 stable •	Median: 6.4 yrs	Primary: EFS Secondary: PFS, OS & toxicity •	• **EFS** **Short term arm** 3.4 yrs(95% CI, 2.1 to 5.3) **Long term arm** 5.3 yrs (95% CI, 3.5 to N/A) (P = 0.14) • **PFS** **Short term arm** 3.5 (95% CI, 2.1 to 5.9) **Long term arm** 7.4 (95% CI, 5.1 to N/A) (P = 0.04) • **OS** No significant difference • **AE** Short term arm: 50% Long term arm: 76% (P< 0.001)	R: YES B: No I: No F: Supported by a scientific grant from Oncosuisse (OCS 01468-02-2004); the Swiss State Secretariat for Education, Researchand Innovation (SERI)

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Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
							• **Toxicity** Short term arm: 0 Long term arm: 3 (P = 0.25)	
[201]	rospective multicenter trial	N=30 Auto-HCT: N=22 Allo-HCT: N=8	Patients were either treated with: a) Autologous hematopoietic stem cell transplantation (Auto-HCT) b) Allogeneic hematopoietic stem cell transplantation. (Allo-HCT) All patients received rituximab 375 mg/m2 IV on days 1 and 8 and cyclophosphamide 4000	Patients with grade I or II, chemotherapy-sensitive follicular lymphoma in first or subsequent relapse.	Median follow-up was 36 months.	• Treatment response • Progression-free survival • Overall survival • Toxicity • GVHD	**PFS** -at 3 years: Auto-HCT: 62.7% Allo-HCT: 85.7% **OS** -at 3 years: Auto-HCT: 73.3% Allo-HCT: 100% **Complete response rate** Auto-HCT: 60% Allo-HCT: 57% **Partial response rate** Auto-HCT: 35% Allo-HCT: 43% **GVHD incidence** -at 3 years:	R: No. B: Not reported I: No information provided The study was supported by the National Heart, Lung, and Blood Institute and the National Cancer Institute through National Institutes of Health Grant U01-8L069294 The trial was early terminated because of slow accrual.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			mg/m2 IV on day 2 within 6 weeks after. Patients assigned to the autologous HCT arm received filgrastim 10 mg/kg/day s.c. as a single daily dose or divided daily doses starting 2 days after cyclophosphamide.				Auto-HCT: 15.4% • Allo-HCT: 14.3%	
[202, 203] EORTC 20981	RCT	N=465 Arm 1: N=231 Arm 2: N=234	Arm 1: CHOP Arm 2: R-CHOP Afterwards: Maintenance treatment was started a median of 7	Patients with grade 1-3 follicular lymphoma, Ann Arbor stage III or IV at initial diagnosis and relapse or refractory follicular lymphoma after one or two non-anthracycline chemotherapies.	Median follow-up was 39.4 months	• **ORR** • **CR** • **PR** • **PFS** • **OS** • **Safety**	**OR**: 72.3% and 85.1% after CHOP and R-CHOP (P<0.001) **CR**: 15.6% in patients receiving CHOP and 29.5% in patients treated with R-CHOP (P<0.001) **PR**: 56.7% in the CHOP arm and 55.6% in the R-CHOP arm (nonsignificant)	R: Yes. B: No, open-label trial. All patients were included in ITT analysis. The trial was supported by grant

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			weeks after the end of the last induction cycle (see table 1.4)	474 patients were randomized to receive either R-CHOP or CHOP chemotherapy regimen as induction treatment. Of those, all patients with CR or PR were eligible for maintenance observation.			**Median PFS**: 20.2 months in the CHOP group vs 33.1 months in the R-CHOP group (P =0.001) HR: 0.65 **OS:** (3yrs from randomization): 71.9% in the CHOP arm and 82.5% in the R-CHOP arm (P=0.096, log-rank test; HR: 0.74) **Safety**: Grade 3-4 neutropenia was the most frequent AE: 48.2% grade 3-4 in the CHOP arm and 54.7% in the R-CHOP arm (NS). More pts on R-CHOP experienced grade 3-4 allergy (CHOP, 0 patients; R-CHOP, 8) and skin reactions (CHOP, 17 patients; R-CHOP, 31)	2U10 CA11488-28 (through 5U10 CA11488-35) from the National Cancer Institute (Bethesda, MD). The research project was supported by the Queen Wilhelmina Fund (The Netherlands).
[202, 203] EORTC 20981	RCT	N=334 Arm 1: N=167 Arm 2: N=167	Arm 1: Rituximab 375mg/m2 IV once every 3 months for 2 years or until disease progression.	Patients with grade 1-3 follicular lymphoma, Ann Arbor stage III or IV at initial diagnosis and relapse or refractory follicular lymphoma after one or two non-anthracycline chemotherapies.	Median follow-up was 6 years.	• **Progression-free survival** • **Overall survival** • **Safety**	**Maintenance Results: Median Progression-free survival:** Arm 1: 3.7 years Arm 2: 1.3 years HR: 0.55, P<0.0001 **5-year overall survival:** Arm 1: 74.3% Arm 2: 64.7%	R: Yes. B: No, open-label trial. All patients were included in ITT analysis. The trial was supported by grant

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			Arm 2: Observational strategy.	474 patients were randomized to receive either R-CHOP or CHOP chemotherapy regimen as induction treatment. Of those, all patients with CR or PR were eligible for maintenance observation.			HR: 0.70, 95% CI: 0.48 to 1.03, P=0.07 **Safety:** Neutropenia (grade 3/ 4): Arm 1: 11.5% Arm 2: 6% Grade 3/ 4 infections Arm 1: 9.7% Arm 2: 2.4% P=0.01	2U10 CA11488-28 (through 5U10 CA11488-35) from the National Cancer Institute (Bethesda, MD). The research project was supported by the Queen Wilhelmina Fund (The Netherlands).
[204]	Phase 2 trial	N=81 Arm 1: N=41 Arm 2: N=40	Arm 1: 1.3mg/m2 **bortezomib** IV biweekly on days 1, 4, 8, and 11(21 days cycles)+ 375mg/m2 **rituximab** IV weekly for 4 weeks. Arm 2: 1.6mg/m2 **bortezomib** IV biweekly on days 1, 8, 15, and 22 (35 days	Patients with relapsed/refractory indolent NHL including follicular lymphoma and mantle cell lymphoma.	Median follow-up was 4.1 months (Arm 1) vs. 7.2 months (Arm 2)	• Treatment response (ORR) • Time to progression • Duration of response • Safety	ORR: Arm 1: 49% Arm 2: 43% CRR: Arm 1: 14% Arm 2: 10% Median PFS: Arm 1: 5 months Arm 2: 10 months	R: Yes. B: Not reported. Efficacy and safety analysis based the ITT principle. Study was supported by Millennium Pharmaceuticals and Johnson and Johnson Pharmaceutical Research & Development LLC.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			cycles) + 375mg/m2 **rituximab** IV weekly for 4 weeks.					
[205]	RCT	N=143 Arm 1 N=73 Arm 2 N=70	Arm 1: 90Y ibritumomab tiuxetan Arm2:Rituximab	Patient characteristics were well balanced. There were no statistically significant differences between treatment groups at baseline. median of two prior regimens 75-83% FL	Max 4 years	• ORR • Duration of response • TTP • CR • CCR • PR • Time to next anticancer therapy • QoL • SAE • AE	**ORR:** Arm 1: 80% Arm 2: 56% p=0.002 **TTP** (only FL): Arm 1: 12.6 months Arm 2: 10.2 months p=0.62 **QoL**: not reported **SAE:** Arm 1: 5pts Arm 2:1pts **AEs**: "similar between the treatment groups during the treatment period (P = .36"	R: yes B: pts not, assessors yes I: yes Ft:not reported M: outcomes preplanned and not reported
[206]	Retrospective case series	N=46	All patients underwent reducedintensity Conditioning allogeneinic	Patients with relapsed/refractory follicular lymphoma who underwent first allogeneic hematopoietic	Median follow-up was 3.7 years	• Disease progression • Overall survival	**Disease progression:** N=6 -median time to progression: 8.2 months	R: No B: Not reported. I: Not reported.

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
			hematopoietic stem cell transplantation (Allo-HCT). Conditioning regimens included ⩽8 Gy in fractionated doses of TBI, busulfan dose o9 mg/kg (or intravenous equivalent) and Mel dose ⩽140 mg/m2	stem cell transplantation. (Allo-HCT).		• Progression-free survival • Non-related mortality • GVHD	**OS:** -at 5 years: 71.6% **PFS** -at 5 years: 62.5% Non-related mortality incidence -at 100 days: 10.9% -at 5 years: 22.7% • GVHD grade II-IV incidence: 34.8%	F: None reported.
[207]	Single-arm phase II study	N=72 Of these, 24 patients had follicular lymphoma. We did only extract data for patients	Patients received **buparlisib** 100mg daily during a 28 days cycle.	Patients with relapsed/refractory NHL including follicular lymphoma, diffuse large B-cell lymphoma or mantle-cell lymphoma.	Median follow-up was 3.7 months for PFS and the median follow-up was 12.1 months for OS.	• Treatment response • (Overall response rate, duration of response) • Progression-free survival • Overall survival • Safety • Tolerability	ORR: 25% Disease control rate: 87.5% Median time to treatment response: 3.5 months Median duration of response: 11 months. Median PFS: 9.8 months. Median OS: not reached.	R: No. B: No, open label trial. I: population included all patients with at least one dose of the study drug. This study was sponsored by Novartis Pharmaceuticals Corporation

Referenz	Design	Studien-größe	Studienarme	Patientencharakteristika	Follow-up	Zielgrößen	Hauptergebnis	Randomisierung (R) Blinding (B) ITT (I) Finanzierung (F) methodische Einschränkungen (M)
		with follicular lymphoma.						

Konsultationfassung

10.5.2. GRADE-Bewertung

10.5.2.1. GRADE-Bewertung: Chemo-Immuntherapie (nur RCT, je Chemo einzelne Bewertung)

Gesamtbewertung Chemo-Immuntherapie im Rezidiv – unabhängig vom Antikörper (Rituximab oder Obinutuzumab) und Chemotherapie (CHOP oder Bendamustin)

[187, 202, 208]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	Safety	-	-	-	-2	-	⊕⊕⊖⊖ low

OS: bei einer Studie kein Konfidenzintervall berichtet; QoL: breites Konfidenzintervall (für nur FL-Patienten); Safety: keine quantitative Analyse, wo eine durchgeführt wurde keine Konfidenzintervalle gegeben

10.5.2.1.1. CHOP+Rituximab vs. CHOP

[202]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖

Konsultation

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								moderate
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-1	-	⊕⊕⊕⊖ moderate

OS: keine Konfidenzintervalle gegeben; Safety: keine HR mit Konfidenzintervallen gegeben

10.5.2.1.2. FCM+Rituximab vs. FCM

[159]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS						Not reported
	RCT	PFS						Not reported
	RCT	QoL						Not reported
	RCT	Safety						Not reported

Studie bezieht sich nicht exklusiv auf FL-Patienten, Subgruppenergebnisse für die hier relevanten Endpunkte werden teilweise für nach der Erhaltungstherapie berichtet, dort auch GRADE bewertet. Hier nur Ansprechraten berichtet.

10.5.2.1.3. CHOP+Obinutuzumab vs. FC+Obinutuzumab

[187]

Konsultationsfas-

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS						Not reported
	RCT	PFS						Not reported
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-2	-	⊕⊕⊖⊖ low

Safety: sehr geringe Anzahl an Patienten, keine quantitative Analyse; Reporting Bias: PFS war eigentlich Endpunkt, wurde aber hier nicht berichtet

10.5.2.1.4. Bendamustine+Obinutuzumab vs. Bendamustine

[208]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	PFS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	QoL	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	Safety	-	-	-	-1	-	⊕⊕⊕⊖ moderate

QoL: breites Konfidenzintervall (für nur FL-Patienten); Safety: keine quantitative Analyse

Konsultationsfassung

10.5.2.1.5. Obinutuzumab vs. Rituximab

[197]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS						Not reported
	RCT	PFS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-1	-	⊕⊕⊕⊖ moderate

PFS, Safety: breites Konfidenzintervall, geringe Anzahl an Patienten

10.5.2.1.6. Lenalidomide vs. Lenalidomide+Rituximab

[175]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-2	-	⊕⊕⊖⊖ low
	RCT	PFS						Not reported
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-1	-	⊕⊕⊕⊖ moderate

OS, Safety: nur eine Studie mit geringer Patientenzahl, keine Analyse in Zahlen berichtet

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10.5.2.1.7. Rituximab Monotherapie

[142] Studien aus Metaanalyse

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS						Not reported
	RCT	PFS						Not reported
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-1	-	⊕⊕⊕⊖ moderate

10.5.2.2. GRADE-Bewertung: Erhaltungstherapie im Rezidiv

10.5.2.2.1. Erhaltung Rituximab vs. Observation

[117, 118]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-	-	⊕⊕⊕⊕ high
	RCT	PFS	-	-	-1	-	-	⊕⊕⊕⊖ moderate
	RCT	QoL	-2	-	-	-1	-	⊕⊖⊖⊖ very low
	RCT	Safety	-	-	-1	-	-	⊕⊕⊕⊖

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								moderate

Safety; PFS: nicht nur rezidivierte FL-Patienten betrachtet (auch Erstlinientherapie-Patienten miteingeschlossen); QoL: nur 2 Studien berichten QoL, sehr wenige Patienten eingeschlossen

10.5.2.2.2. Erhaltung Rituximab vs. keine Erhaltung, mit ASCT

[183]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-1	-1	⊕⊕⊖⊖ low

Sehr wenige Patienten je Arm; geplante Rekrutierungsanzahl wurde nicht erreicht, nicht verblindet; Safety: keine Zahlen gegeben

10.5.2.2.3. Erhaltung Obinutuzumab vs. Observation

[208] hier non-RCT, weil für Erhaltung nicht erneut randomisiert wurde

Konsultationsfassung

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	PFS	-	-	-	-1	-	⊕⊖⊖⊖ very low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety	-	-	-	-1	-	⊕⊖⊖⊖ very low

QoL: breites Konfidenzintervall (für nur FL-Patienten); Safety: keine quantitative Analyse

10.5.2.3. GRADE-Bewertung: Radiotherapie (RCT und non-RCT) / Radioimmuntherapie

10.5.2.3.1. Tositumumab und Iodine I 131 vs. Rituximab

[186]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-2	-	⊕⊕⊖⊖ low
	RCT	PFS	-	-	-	-2	-	⊕⊕⊖⊖ low
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-2	-	⊕⊕⊖⊖

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								low

OS, PFS, Safety: nur eine Studie und sehr geringe Patientenzahl, keine quantitativen Analyseergebnisse gegeben (keine HR, Konfidenzintervalle, P-Werte)

10.5.2.3.2. 90Y ibritumomab tiuxetan vs. Rituximab

[205]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-	-	Not reported
	RCT	PFS	-	-	-	-2	-	⊕⊕⊖⊖ low
	RCT	QoL	-	-	-	-	-	Not reported
	RCT	Safety	-	-	-1	-1	-	⊕⊕⊖⊖ low

PFS: es wurde TPP berichtet, allerdings wurden von 55 FL Patienten 24 zensiert und stehen nicht zur Auswrrtung zur Verfügung; Insgesamt sehr geringe Patientenzahl; Safety: nicht für nur FL Patienten berichtet; QoL sollte erhoben werden und wurde dann nicht berichtet

10.5.2.3.3. Konsolidierung mit 90Yttrium-ibritumomab tiuxetan (Zevalin) (nach FCR)

[184]

Konsultationsfassung

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-2	-	⊕⊖⊖⊖ very low
	Non-RCT	PFS	-	-	-	-2	-	⊕⊖⊖⊖ very low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety	-	-	-	-2	-	⊕⊖⊖⊖ very low

Nur eine Studie mit extrem geringer Patientenzahl

10.5.2.4. GRADE-Bewertung: Transplantation

10.5.2.4.1. HDT + autologe SCT vs. Chemo

[115]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	PFS	-	-	-	-1	-	⊕⊕⊕⊖ moderate
	RCT	QoL						Not reported

Konsultationsfas

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	Safety						Not reported

OS, PFS: geringe Patientenzahl

10.5.2.4.2. Autologe SCT

[154, 168, 172, 178]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety						Not reported

10.5.2.4.3. Allogene SCT

[171, 190, 191, 206]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-	-	⊕⊕⊖⊖

Konsultationsfassung

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								low
	Non-RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	QoL	-	-	-	-1	-	⊕⊖⊖⊖ very low
	Non-RCT	Safety	-	-	-	-	-	⊕⊕⊖⊖ low

QoL: nur von einer Studie berichtet

10.5.2.4.4. Autologe vs. Allogene Transplantation

[169, 170, 177, 182, 201]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety	-	-	-	-1	-	⊕⊖⊖⊖ very low

Konsultationsfassung

Safety: nur von einer Studie berichtet

10.5.2.4.5. Transplantation bei Patienten, die innerhalb von 2 Jahren nach Primärtherapieabschluss ein Rezidiv aufwiesen vs. Transplantation bei Patienten, die nach 2 Jahren nach Primärtherapieabschluss ein Rezidiv aufwiesen

10.5.2.5. GRADE-Bewertung: neue Substanzen

10.5.2.5.1. GRADE-Bewertung: Rituximab+Bevacizumab vs. Rituximab

[164, 165]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	RCT	OS	-	-	-	-2	-	⊕⊕⊖⊖ low
	RCT	PFS	-	-	-	-2	-	⊕⊕⊖⊖ low
	RCT	QoL						Not reported
	RCT	Safety	-	-	-	-2	-	⊕⊕⊖⊖ low

OS, PFS, Safety: geringe Anzahl Ereignisse und Studienteilnehmer

10.5.2.5.2. GRADE-Bewertung: Buparlisib

[207]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-1	-1	-	⊕⊖⊖⊖

Konsultation

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								very low
	Non-RCT	PFS	-	-	-1	-1	-	⊕⊖⊖⊖ very low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety	-	-	-1	-1	-	⊕⊖⊖⊖ very low

OS, PFS, Safety: keine Subgruppe mit nur FL Patienten berichtet, auch MCL und DLBCL Patienten eingeschlossen, sehr geringe Anzahl an Studienteilnehmern

10.5.2.5.3. GRADE-Bewertung: Entospletinib und Idelalisib

[148]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS						Not reported
	Non-RCT	PFS						Not reported
	Non-RCT	QoL						Not reported
	Non-RCT	Safety						Not reported

10.5.2.5.4. GRADE-Bewertung: Everolimus

[151]

Konsultationsfassung

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-1	-1	-	⊕⊖⊖⊖ very low
	Non-RCT	PFS	-	-	-1	-1	-	⊕⊖⊖⊖ very low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety						Not reported

OS, PFS: nur ca. 50% FL-Patienten, sehr geringe Patientenanzahl insgesamt

10.5.2.5.5. GRADE-Bewertung: Ibrutinib

[149, 162]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety	-	-	-	-	-	⊕⊕⊖⊖ low

Konsfass

10.5.2.5.6. GRADE-Bewertung: Idelalisib Monotherapie

[158, 161, 196]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	PFS	-	-	-	-	-	⊕⊕⊖⊖ low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety	-	-	-	-1	-	⊕⊖⊖⊖ very low

Safety: nur von einer Studie berichtet, in einer anderen keine FL-Subgruppe berichtet, insgesamt geringe Patientenzahl

10.5.2.5.7. GRADE-Bewertung: Inotuzumab ozoganmicin

[163]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS	-	-	-	-1	-	⊕⊖⊖⊖ very low
	Non-RCT	PFS	-	-	-	-1	-	⊕⊖⊖⊖ very low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety	-	-	-	-1	-	⊕⊖⊖⊖

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
								very low

OS, PFS, Safety: geringe Patientenanzahl

10.5.2.5.8. GRADE-Bewertung: Nivolumab

[176]

Schlüsselfrage	Design	Endpunkt	Verzerrungs-risiko	Inkonsistenz	Indirektheit	Impräzision	Weitere Überlegungen	Gesamtqualität
	Non-RCT	OS						Not reported
	Non-RCT	PFS	-	-	-	-2	-	⊕⊖⊖⊖ very low
	Non-RCT	QoL						Not reported
	Non-RCT	Safety						Not reported

PFS: nur 10 FL Patienten

10.6. Abkürzungen aus Evidenztabellen

90YIT: 90Y-ibritumomab-tiuxetan

ASCT: Autologous stem-cell therapy

ATT: Alternating Triple Therapy

Konsultation

AE: Adverse Event

BMB: Bone Marrow Biopsy

CHOP: Cyclophosphamid, Hydroxydaunorubicin (Doxorubicin), Vincristin, Predniso(lo)n

CHVP: cyclophosphamide, lowdose doxorubicin, teniposide, prednisone

CI: Confidence Intervals

CIBMTR: Center for International Blood and Marrow Transplant Research

CLI: Central Lymphatic Iradition

COI: conflict of interest

CPA: cyclophosphasphamide

CR: Complete Remission

CRR: complete response rate

CRu: unconfirmed Complete Response

CVP: Cyclophosphamid, Vincristine, Prednisone

DFS: Disease Free Survival

DLBCL: Diffuse Large B-Cell Lymphoma

ECOG: Eastern Cooperative Oncology Group

EFS: Event-free survival

FCCL: Follicle centre cell lymphoma

FDG: Fluordesoxyglucose

Konsultationfassung

FFLP: Freedom from local progression

FL: Follicular Lymphoma

FLIPI: Follicular Lymphoma International Prognostic Index

G: Obinutuzumab

GVHR: Graft-versus-Host-Reaction

HD: Hodgkin's Disease

HDT: High dose therapy

HR: Hazard Ratio

HT: Histological transformation

IFN: Interferon

IFRT: Involved Field Radiotherapy

iNHL: indolent Non-Hodgkin Lymphoma

IPD: individual patient data

IRR: infusion-related reaction

IT: Intensified Therapy

ITT: Intention To Treat

LDH: Lactate Dehydrogenase

MA: Meta Analysis

MR: Molecular Response

Konsultationfassung

MRD: Minimal Residual Disease

MRI: magnetic resonance imaging

MZL: Marginal Zone Lymphoma

N/n: Number

N/A: Not applicable

NLCS: National LymphoCare Study

NPV: Negative predictive value

NR: Not reported

OFA: Ofamtumumab

ORR: Overall Response Rate

OS: Overall Survival

PBSCT: peripheral stem cell transplantation/support

PCR: Polymerase Chain Reaction

PD: Progressive disease

PFS: Progression Free Survival

PP: per protocol

PPV: Positive predictive value

PR: Partial Remission

Pts: Patients

Konsultationfassung

QoL: Quality of life

R: Rituximab

RCT: Randomized Controlled Trial

RFS: Relapse Free Survival

RIT: Radio Immun Therapy

RR: Relative Risk

R/R: relapsed/refractory

RT: Randomized Trial

SCT: stem cell transplantation

SD: Stable disease

SR: Systematic Review

SUV: Standardized Uptake Value

SWOG: Southwest Oncology Group

TMTV: Total Metabolic Tumor Volume

TRM: Treatment related mortality

TTF: Time to Treatment Failure

TTP: Time to Progression

VCAP: cyclophosphamide, high-dose doxorubicin, prednisone, vincristine

WB MRI: Whole-body Magnetic resonance imaging

Konsultationfassung

Y/yrs: Years

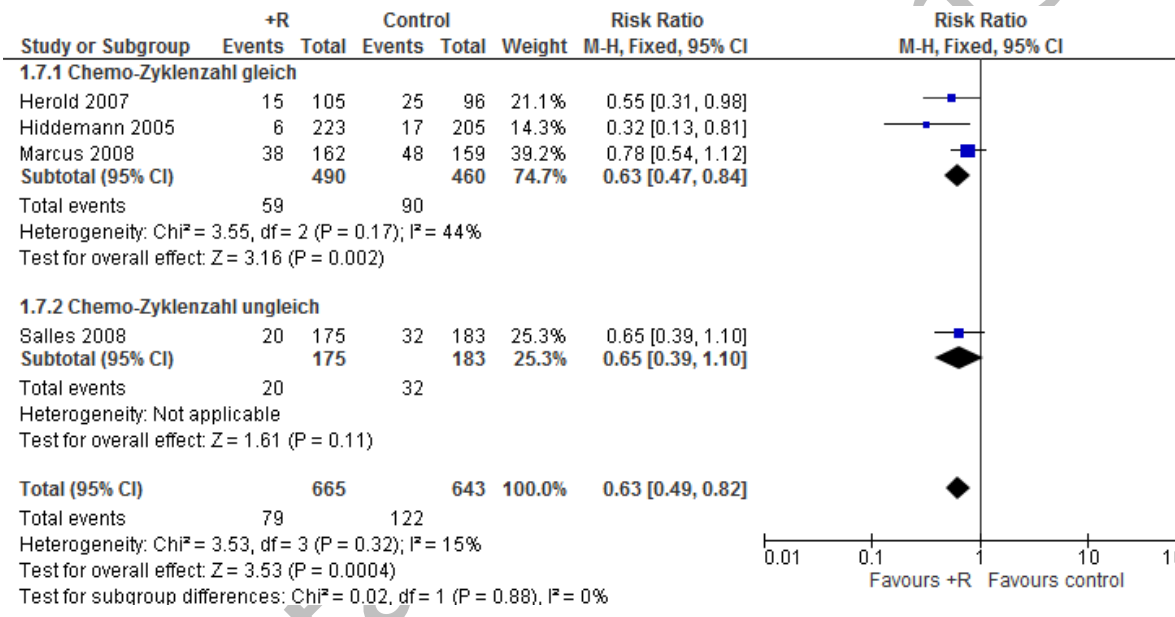
WHO: World Health

Konsultationfassung

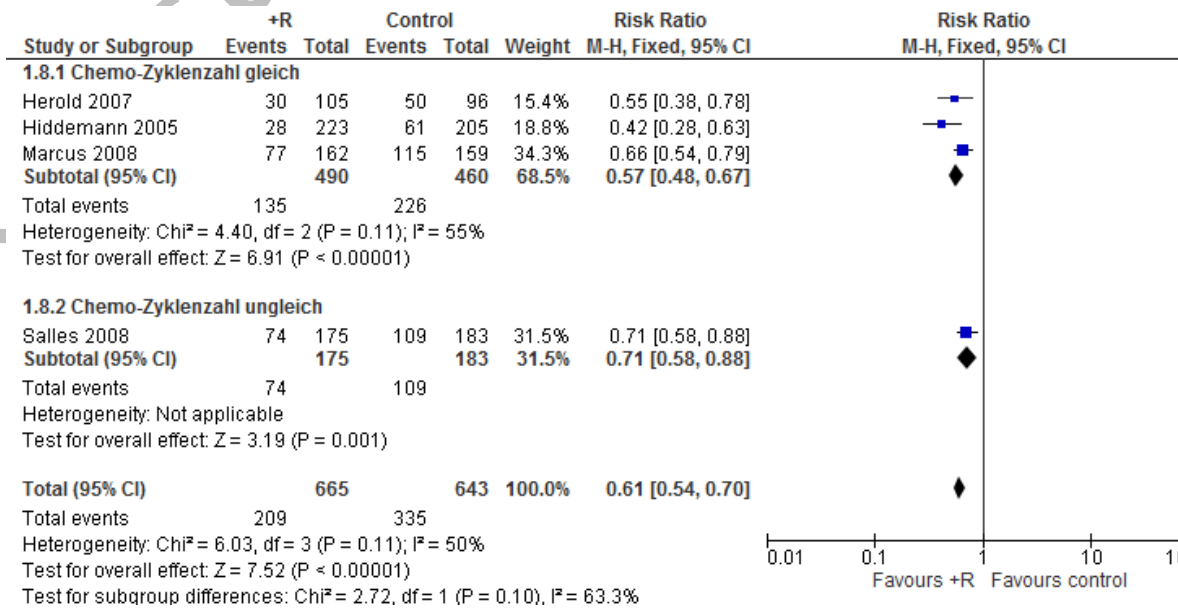
11. Meta-Analysen

11.1. Kapitel 6 - Therapie fortgeschrittener Stadien

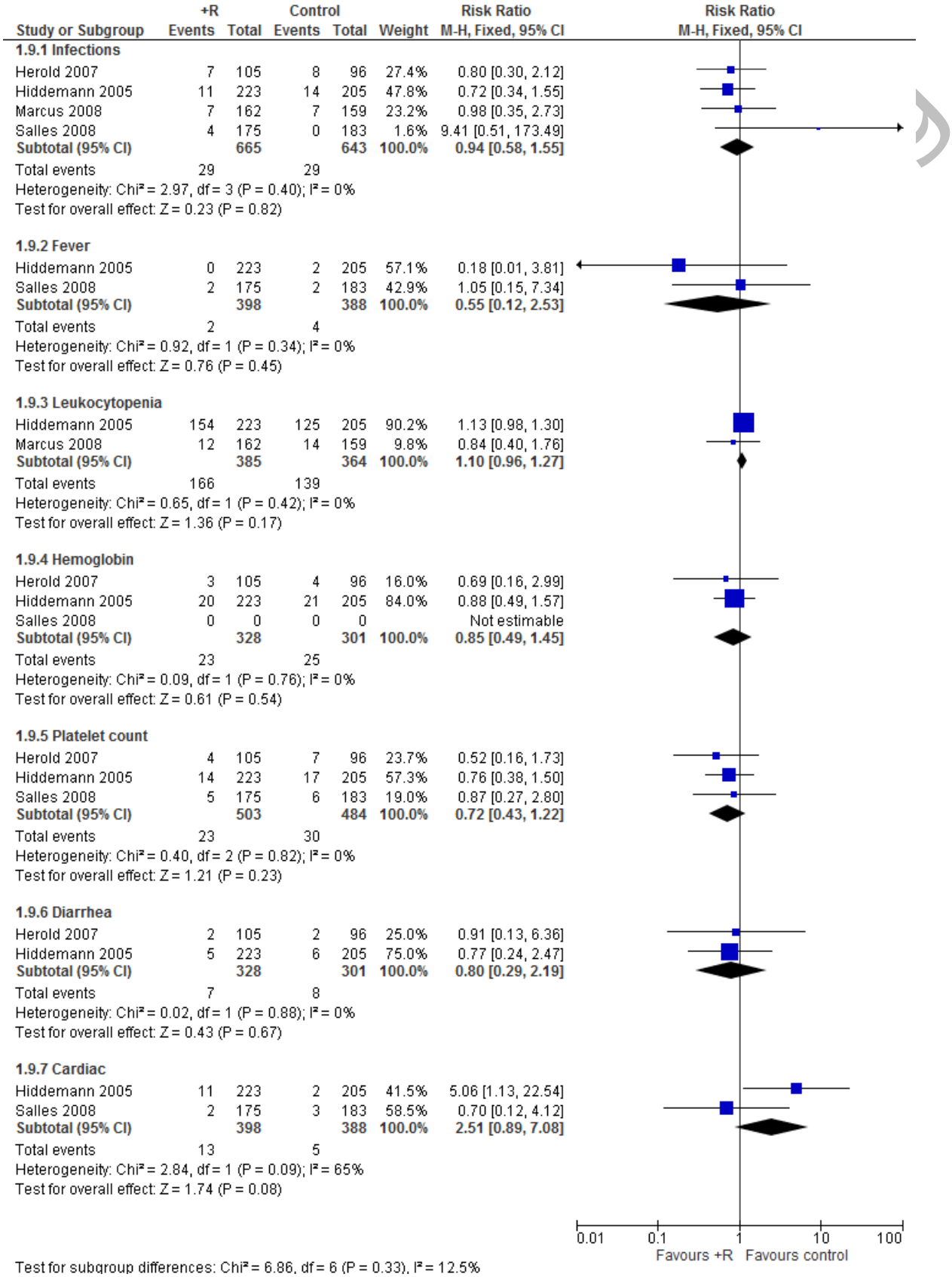
11.1.1. Mortality:



11.1.2. Disease Control:



11.1.3. Adverse Events (Grade 3 and 4 only):



12. Abbildungsverzeichnis

Abbildung 1: Schema zur Darstellung der Kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades. 29

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Konsultationfassung

14. Anlagen

14.1. Gliederung S3 Leitlinie follikuläres Lymphom

Epidemiologie, Risikofaktoren

Initiale Diagnostik, Stadieneinteilung und Verlaufsbeurteilung

Aufklärung des Patienten und Therapieplanung

Therapie des frühen Stadiums

Therapie des fortgeschrittenen Stadiums

Erhaltungstherapie

Subgruppen

Rezidiv

Therapie des Rezidivs

Nachsorge und Rehabilitation

Supportivmaßnahmen, Palliativmedizin und komplementäre Verfahren

Forschungsziele

14.2. Themen und Fragestellungen

Epidemiologie, Risikofaktoren

Epidemiologie

Risikofaktoren für die Entwicklung eines Follikulären Lymphoms

Initiale Diagnostik, Stadieneinteilung und Verlaufsbeurteilung

Typische Symptome

Was sind die typischen Symptome eines Follikulären Lymphoms?

Wie ist das Vorgehen beim Auftreten von typischen Symptomen?

Die histologische Diagnostik

Bedeutung von Lymphknotenbiopsie / Corebiopsie / Feinnadelaspiration

Welche diagnostische Methode (Histologie, Zytologie, Durchflusszytometrie) soll zur Diagnosestellung genutzt werden?

Soll die histologische Diagnose durch Biopsie eines ganzen Lymphknotens / Corebiopsie / Feinnadelaspiration gestellt werden?

Referenzpathologie notwendig?

Soll bei histologischer Diagnose eines Follikulären Lymphoms eine Beurteilung durch einen Referenzpathologen durchgeführt werden?

Konsultationfassung

Anforderung an die Diagnostik

Zeitpunkt

Zeitrahmen

Verlauf

Soll nach histologischer Diagnose eines Follikulären Lymphoms die weitere Diagnostik in einem bestimmten (welchem?) Zeitrahmen erfolgen?

Soll die gesamte Diagnostik bei ED oder vor Therapieeinleitung durchgeführt werden?

Soll bestimmte Diagnostik vor Therapieeinleitung erneut durchgeführt werden?

Soll bestimmte Diagnostik unter Therapie / unter keiner Therapie in bestimmten Abständen erneut durchgeführt werden?

Welche bildgebenden Untersuchungen sollen durchgeführt werden?

Welche bildgebenden Untersuchungen sollen nach histologischer Diagnose eines Follikulären Lymphoms durchgeführt werden?

Knochenmarkspunktion

Soll nach histologischer Diagnose eines Follikulären Lymphoms aus einem Lymphknoten / extranodal Befall eine Knochenmarkspunktion erfolgen?

Extranodaler Befall

Sollen klinisch verdächtige extranodale Befälle oder Organbefälle mit den adäquaten / welchen? Methoden abgeklärt werden?

Ergänzende Maßnahmen

-Weitere Untersuchungen

Sollen weitere (Labor etc.) Untersuchungen vor Therapiebeginn durchgeführt werden?

-Organtoxizitätsuntersuchungen

Sollen Organfunktions-Untersuchungen vor Therapiebeginn durchgeführt werden?

Welche Organfunktions-Untersuchungen sollen vor Therapiebeginn durchgeführt werden?

-Komorbiditäten / Funktionelle Untersuchungen

Soll die Schwere der Begleiterkrankungen definiert werden?

Wie soll die Schwere der Begleiterkrankungen definiert werden

Sollen funktionelle Untersuchungen vor Therapiebeginn durchgeführt werden?

Welche funktionellen Untersuchungen sollen vor Therapiebeginn durchgeführt werden?

Bei welchen Patienten sollen funktionelle Untersuchungen vor Therapiebeginn durchgeführt werden?

Prognostische / prädiktive Faktoren

Welche prognostischen / prädiktiven Faktoren sind bekannt?

Welche prognostischen / prädiktiven Faktoren sind belegt?

Konsultationfassung

Welche prognostischen / prädiktiven Faktoren sollen erhoben werden?

Prognostische Relevanz in Initial- und Verlaufsdiagnostik von PET/CT, CT und MRD

Welche prognostische Relevanz bezüglich PFS /OS haben PET CT, CT und MRD in Initial- und Verlaufsdiagnostik? Systematische Recherche

Stadieneinteilung

Basierend auf welcher Klassifikation soll eine Stadieneinteilung erfolgen?

Psycho-Onkologie

Soll jedem Patienten mit Follikulärem Lymphom die Möglichkeit eines psychoonkologischen Gesprächs orts- und zeitnah angeboten werden?

Sollen / welche Messinstrumente sollen herangezogen werden?

Sollen Psycho-onkologische Behandlungsmaßnahmen in das therapeutische Gesamtkonzept integriert werden?

Fertiliätsprotektive Maßnahmen

Soll auf Möglichkeiten der fertilitätserhaltenden Maßnahmen hingewiesen werden?

Soll eine Aussage zur Therapiespezifischen Sterilitätswahrscheinlichkeit getroffen werden?

Welche fertilitätserhaltenden Maßnahmen werden empfohlen?

Aufklärung des Patienten und Therapieplanung

Aufklärung und Diagnosemitteilung

Therapieplanung

Therapie des frühen Stadiums

Watch and Wait

Alleinige Strahlentherapie

Antikörper Therapie

Wie sollen Patienten in einem frühen Stadium behandelt werden? Systematische Recherche

Therapie des fortgeschrittenen Stadiums

Therapie Indikation

Tumorlast und Symptomatische Erkrankung

Wie ist die Therapiepflichtigkeit definiert?

Watch and Wait

Induktionstherapie

Konsultationfassung

Wie sollen Patienten in einem fortgeschrittenen Stadium behandelt werden? Systematische Recherche

Erhaltungstherapie

Erhaltungstherapie nach der Firstline Therapie (R / Interferon / R + I)

Radio-Immuntherapie

Konsolidierung mit autologer Stammzelltransplantation

Soll nach einer Induktionstherapie eine Erhaltungstherapie erfolgen? Systematische Recherche

Subgruppen

Therapieempfehlungen Follikuläres Lymphom in situ

Wie sollen Patienten mit einem in-situ Follikulären Lymphom behandelt werden?

Therapieempfehlungen Follikuläres Lymphom Grad 3a

Wie sollen Patienten mit einem Follikulären Lymphom Grad 3a behandelt werden?

Therapieempfehlungen Follikuläres Lymphom Grad 3b

Wie sollen Patienten mit einem Follikulären Lymphom Grad 3b behandelt werden?

Therapieempfehlungen extranodales Follikuläres Lymphom

Wie sollen Patienten mit einem extranodalen Follikulären Lymphom behandelt werden?

Therapieempfehlungen intestinales Follikuläres Lymphom

Wie sollen Patienten mit einem intestinalen Follikulären Lymphom behandelt werden?

Therapieempfehlungen cutanes Follikuläres Lymphom

Wie sollen Patienten mit einem cutanen Follikulären Lymphom behandelt werden?

Therapieempfehlungen pädiatrisches Follikuläres Lymphom

Wie sollen Patienten mit einem pädiatrischen Follikulären Lymphom behandelt werden?

Therapieempfehlungen transformiertes Follikuläres Lymphom

Wie sollen Patienten mit einem transformierten Follikulären Lymphom behandelt werden?

Therapieempfehlungen stark begleiterkrankte Patienten

Wie sollen Patienten mit einem Follikulären Lymphome, die stark begleiterkrankt sind, behandelt werden?

Wie sollen Patienten mit einem Follikulären Lymphom, mit funktionellen Einschränkungen, behandelt werden?

Konsultationfassung

Rezidiv

Diagnostik des Rezidiv, analog zu Kapitel 2

Die histologische Diagnostik

Anforderung an die Diagnostik

Knochenmarkspunktion

Extranodaler Befall

Ergänzende Maßnahmen

-Weitere Untersuchungen

-Organtoxizitätsuntersuchungen

-Komorbiditäten / Funktionelle Untersuchungen

Prognostische / prädiktive Faktoren

Stadieneinteilung

Therapie Indikation

Therapie des Rezidivs

Therapie des Rezidivs

-Neue Substanzen

-(Chemo)-Immuntherapie

-Strahlentherapie

-Autologe Transplantation

-Allogene Transplantation

Wie sollen Patienten mit einem Therapiebedürftigen Rezidiv behandelt werden? Systematische Recherche

Erhaltungstherapie

Soll eine Erhaltungstherapie nach Rezidivtherapie durchgeführt werden? Systematische Recherche

Nachsorge und Rehabilitation

Nachsorge

Nachsorge zur Rezidivfrüherkennung

Routinemäßige Nachsorge:

-Allgemein

Soll eine regelmäßige Nachsorge durchgeführt werden?

Konsultationfassung

In welchen Abständen soll eine Nachsorge durchgeführt werden?

Welche Maßnahmen soll eine Nachsorgeuntersuchung umfassen?

-Stellenwert des CT / PET CT / Sonographie / Körperliche Untersuchung hinsichtlich Rezidiv Detektion

Wie ist der Stellenwert des CT / PET CT / Sonographie / Körperliche Untersuchung hinsichtlich Rezidiv Detektion? Systematische Recherche

Strahlenbelastung und Sekundärneoplasien durch routinemäßige CT / PET CT

Wie hoch ist die Strahlenbelastung durch regelmäßige routinemäßige CT / PET CT ?

Rezidiv-Verdacht

Wie soll bei einem klinischen Rezidiv-Verdacht vorgegangen werden?

Früherkennung für Sekundärneoplasien

Wie soll bezüglich Früherkennung für Sekundärneoplasien vorgegangen werden?

Spätfolgen und Organtoxizität

Wie soll bezüglich Früherkennung für Spätfolgen und Organtoxizität vorgegangen werden?

Rehabilitation

Soll Patienten (m/w) nach erfolgter Therapie eine onkologische Rehabilitation (Anschlussheilbehandlung oder allgemeines Heilverfahren) angeboten werden und gibt es spezifische Patientengruppen die einer anderen Rehabilitationsform bedürfen?

Supportivmaßnahmen, Palliativmedizin und komplementäre Verfahren

Supportivtherapie

Soll eine prophylaktische/supportive Behandlung häufiger unerwünschter therapiebedingter Wirkungen durchgeführt werden?

Gibt es spezifischen Empfehlungen zu medizinischen Intervention nach Therapie (zB Impfung)?

Gibt es Angebote zur spezifischen Patientenschulung?

Gibt es Angebote zur spezifischen Angehörigen Betreuung?

Palliativtherapie

Soll der Arzt den Patienten aktiv auf palliativmedizinische Maßnahmen/palliativmedizinische Versorgungsangebote ansprechen? Frage: Soll der Arzt dem Patienten aktiv palliativmedizinische Maßnahmen/palliativmedizinische Versorgungsangebote empfehlen (welche)?

Komplementäre Verfahren

Soll der Arzt den Patienten aktiv auf komplementärmedizinische Maßnahmen bzw.

alternative Heilmethoden ansprechen?

Konsultationfassung

Soll der Arzt dem Patienten aktiv komplementärmedizinische Maßnahmen bzw. alternative Heilmethoden empfehlen (welche)?

Forschungsziele

Sollen in der Arbeitsgruppe erarbeitet werden

Konsultationfassung

14.3. Dokumentation Anwesenheiten

Leitliniensteuergruppenmeeting 15.06.2016		
Herfarth	Klaus	Prof. Dr. med.
Herold	Michael	Prof. Dr. med.
Hiddemann	Wolfgang	Prof. Dr. med.
Klapper	Wolfram	Prof. Dr. med.
Skoetz	Nicole	PD Dr. med.
Unterhalt	Michael	Dr. rer. nat.
Zoellner	Anna	Dr. med.

Leitliniensteuergruppenmeeting 17.11.2016 in München		
Dreyling	Martin	Prof. Dr. med.
Herfarth	Klaus	Prof. Dr. med.
Herold	Michael	Prof. Dr. med.
Hiddemann	Wolfgang	Prof. Dr. med.
Holtkamp	Ulrike	Dr. med.
Klapper	Wolfram	Prof. Dr. med.
Sandherr	Michael	PD Dr. med.
Skoetz	Nicole	PD Dr. med.
Unterhalt	Michael	Dr. rer. nat.
Zoellner	Anna	Dr. med.

Kick-Off Meeting 08.02.2017 in München		
Baumann	Walter	Dr.
Buske	Christian	Prof. Dr.
Dietrich	Christoph Frank	Prof. Dr.
Dreger	Peter	Prof. Dr.
Dreyling	Martin	Prof. Dr. med.
Dührsen	Ulrich	Prof. Dr.
Fend	Falko	Prof. Dr.
Goede	Valentin	PD Dr.
Görg	Christian	Prof. Dr.
Hackenberg	Ulrich	Dr.
Herfarth	Klaus	Prof. Dr. med.
Herold	Michael	Prof. Dr. med.
Heußner	Pia	Dr.
Hiddemann	Wolfgang	Prof. Dr. med.
Holtkamp	Ulrike	Dr.
Horneber	Markus	Dr.

Kick-Off Meeting 08.02.2017 in München		
Hoster	Eva	PD Dr.
Hübel	Kai	Prof. Dr.
Klapper	Wolfram	Prof. Dr. med.
Möller	Peter	Prof. Dr.
Nieters	Alexandra	PD Dr.
Nipken	Lars H.	Dr.
Pfluger	Thomas	Prof. Dr.
Rosenbruch	Johannes	Dr.
Rummeny	Ernst	Univ.-Prof. Dr.
Sandherr	Michael	PD Dr.
Schmidberger	Heinz	Prof. Dr.
Schmidt	Christian	Dr.
Scholz	Christian	PD Dr.
Schüring	Andreas	PD Dr.
Skoetz	Nicole	PD Dr.
Unterhalt	Michael	Dr. rer. nat.
Viardot	Andreas	PD Dr.
von Tresckow	Bastian	PD Dr.
Weigert	Oliver	Dr.
Wick	Manfred	Dr.
Zoellner	Anna	Dr. med.

Autorentreffen 30.06.2017 in München		
Buske	Christian	Prof. Dr.
Dreyling	Martin	Prof. Dr.
Dührsen	Ulrich	Prof. Dr.
Hellwig	Dirk	Prof. Dr. Dipl. Phys.
Herfarth	Klaus	Prof. Dr.
Herold	Michael	Prof. Dr.
Heß	Georg	Prof. Dr.
Hiddemann	Wolfgang	Prof. Dr.
Holtkamp	Ulrike	Dr.
Horneber	Markus	Dr.
Hoster	Eva	PD Dr.
Hübel	Kai	Prof. Dr.
Jakob	Tina	
Klapper	Wolfram	Prof. Dr.
Köhn	Michael	Prof. Dr.
Möller	Peter	Prof. Dr.

Autorentreffen 30.06.2017 in München		
Christiane	Pott	PD Dr.
Pfluger	Thomas	Prof. Dr.
Scholz	Christian	PD Dr.
Skoetz	Nicole	PD Dr.
Trümper	Lorenz	Prof. Dr.
Unterhalt	Michael	Dr. rer. nat.
Viardot	Andreas	PD Dr.
Weigert	Oliver	Dr.
Zoellner	Anna	Dr. med.

Leitliniensteuergruppen-Kapitelleiter Meeting 02.05.2018 in München		
Herfarth	Klaus	Prof. Dr.
Herold	Michael	Prof. Dr.
Hiddemann	Wolfgang	Prof. Dr.
Holtkamp	Ulrike	Dr.
Horneber	Markus	Dr.
Hübel	Kai	Prof. Dr.
Klapper	Wolfram	Prof. Dr.
Nieters	Alexandra	PD Dr.
Sandherr	Michael	PD Dr.
Unterhalt	Michael	Dr. rer. nat.
Weigert	Oliver	Dr.
Zoellner	Anna	Dr. med.

Leitliniensteuergruppen-Kapitelleiter Meeting 03.05.2018 in München		
Buske	Christian	Prof. Dr.
Dreyling	Martin	Prof. Dr.
Herfarth	Klaus	Prof. Dr.
Herold	Michael	Prof. Dr.
Hiddemann	Wolfgang	Prof. Dr.
Hübel	Kai	Prof. Dr.
Jakob	Tina	
Klapper	Wolfram	Prof. Dr.
Skoetz	Nicole	PD Dr.
Unterhalt	Michael	Dr. rer. nat.
Weigert	Oliver	Dr.
Zoellner	Anna	Dr. med.

Erste Konsensus Konferenz 16.11.2018 in München		
Baumann	Walter	Dr.
Dührsen	Ulrich	Prof. Dr.
Fend	Falko	Prof. Dr.
Follmann	Markus	Dr. MPH MSc
Göbel	Rainer	
Goede	Valentin	PD Dr.
Hellwig	Dirk	Prof. Dr. Dipl. Phys.
Herfarth	Klaus	Prof. Dr.
Herold	Michael	Prof. Dr.
Heußner	Pia	PD Dr.
Hiddemann	Wolfgang	Prof. Dr.
Hilgenfeld	Eva	Dr.
Holtkamp	Ulrike	Dr.
Horneber	Markus	Dr.
Hübel	Kai	Prof. Dr.
Jakob	Tina	
Klapper	Wolfram	Prof. Dr.
Köhn	Frank-Michael	Prof. Dr.
Langer	Thomas	
Mansmann	Ulrich	Prof. Dr.
Micke	Oliver	Prof. Dr.
Nipken	Lars	Dr.
Nothacker	Monika	Dr.
Pfluger	Thomas	Prof. Dr.
Rosenbruch	Johannes	Dr.
Rummeny	Ernst	Prof. Dr.
Sandherr	Michael	PD Dr.
Schmidberger	Heinz	Prof. Dr.
Scholz	Christian	PD Dr.
Skoetz	Nicole	PD Dr.
Unterhalt	Michael	Dr. rer. nat.
Viardot	Andreas	PD Dr.
Wick	Manfred	Dr.
Zoellner	Anna	Dr.

Zweite Konsensus Konferenz 22.02.2019 in München		
Buske	Christian	Prof. Dr.
Dietrich	Christoph Frank	Prof. Dr.
Dreyling	Martin	Prof. Dr.

Zweite Konsensus Konferenz 22.02.2019 in München		
Dührsen	Ulrich	Prof. Dr.
Fend	Falko	Prof. Dr.
Follmann	Markus	Dr. MPH MSc
Göbel	Rainer	
Goede	Valentin	PD Dr.
Hellwig	Dirk	Prof. Dr. Dipl. Phys.
Herfarth	Klaus	Prof. Dr.
Herold	Michael	Prof. Dr.
Heyll	Axel	Prof. Dr.
Hiddemann	Wolfgang	Prof. Dr.
Holtkamp	Ulrike	Dr.
Horneber	Markus	Dr.
Hoster	Eva	Dr.
Hübel	Kai	Prof. Dr.
Jakob	Tina	
Köhn	Frank-Michael	Prof. Dr.
Langer	Thomas	Dipl. Soz. Wiss.
Micke	Oliver	Prof. Dr.
Mumm	Friederike	Dr
Nipken	Lars	Dr.
Nothacker	Monika	Dr.
Pott	Christiane	PD Dr.
Rosenbruch	Johannes	Dr.
Sandherr	Michael	PD Dr.
Schmidt	Christian	Dr.
Scholz	Christian	PD Dr.
Schüring	Andreas	PD Dr.
Skoetz	Nicole	PD Dr.
Trenker	Corinna	Dr.
Unterhalt	Michael	Dr. rer. nat.
Viardot	Andreas	PD Dr.
Weigert	Oliver	Dr.
Wick	Manfred	Dr.
Witzens-Harig	Mathias	Prof. Dr.
Zoellner	Anna	Dr.

ssung

14.4. Recherche nach internationalen Qualitätsindikatoren

14.4.1. Rechercheauftrag

Die Recherche wurde vom Bereich Infoplattform (Jessica Lobitz und Maike Schäfer) zwischen dem 21.04.2019 und 29.04.2019 durchgeführt.

Als Recherchevokabular wurden folgende Begriffe verwendet:

Population:

Erwachsene mit Follikulärem Lymphom (Non Hodgkin Lymphom) in allen Versorgungssettings (ambulant/stationär).

Non Hodgkin Lymphom, Non-hodgkin Lymphom, Nonhodgkin Lymphom, No hodgkin Lymphom

lymphoma, non hodgkin

non hodgkin* OR non-hodgkin* OR nonhodgkin* OR no hodgkin*

Intervention:

Qualitätsindikator; Qualitätsindikatoren

Quality Indicators, Health Care

quality indicator* OR performance indicator* OR health indicator* OR quality measure* OR performance measure* OR health measure*

Limits:

Bei der Suche erfolgte eine Einschränkung des Suchzeitraums (01.01.2009 bis 24.04.2019).

Weitere Einschränkungen bezüglich spezifischer Subgruppen innerhalb der Zielpopulation erfolgten nicht.

Die Suche wurde in folgenden Quellen durchgeführt:

- Literaturdatenbanken: Medline über https://www.ncbi.nlm.nih.gov/ & Cochrane über http://www.cochranelibrary.com/
- Webseiten von nationalen Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Webseiten von internationaler Agenturen im Bereich medizinische Qualitätssicherung/Qualitätsmessung/Qualitätsindikatoren
- Internetrecherche via www.google.de

Recherchestrategie und -vokabular richten sich nach den Möglichkeiten der jeweiligen Recherchequelle, wurden entsprechend modifiziert und unter 2 Recherchestrategien dargelegt.

Konsultationfassung

14.4.2. Recherchestrategien

14.4.2.1. Bibliographische Datenbanken

14.4.2.1.1. PubMed

Search	Query	Items found
#10	Search **(#3 AND #6)** Filters: **Publication date from 2009/01/01 to 2019/04/24; English; German**	147
#9	Search **(#3 AND #6)** Filters: **Publication date from 2009/01/01 to 2019/04/24; English**	146
#8	Search **(#3 AND #6)** Filters: **Publication date from 2009/01/01 to 2019/04/24**	150
#7	Search **(#3 AND #6)**	240
#6	Search **(#4 OR #5)**	257478
#5	Search **Quality Indicators, Health Care [MeSH Terms]**	19422
#4	Search **((quality[Title/Abstract] OR performance[Title/Abstract])) AND (indicator[Title/Abstract] OR indicators[Title/Abstract] OR measure[Title/Abstract] OR measures[Title/Abstract])**	245472
#3	Search **(#1 OR #2)**	
#2	Search **lymphoma, non hodgkin[MeSH Terms]**	97569
#1	Search **(non hodgkin*[Title/Abstract] OR non-hodgkin*[Title/Abstract] OR nonhodgkin*[Title/Abstract] OR no hodgkin*[Title/Abstract])**	36818

Recherchedatum: 24.04.2019

14.4.2.1.2. Cochrane

Search	Query	Items found
#1	Search **(non hodgkin* OR non-hodgkin* OR nonhodgkin* OR no hodgkin*ti,ab,kw** (Word variations have been searched)	4402
#2	Search **(quality OR performance OR health) AND (indicator* OR measure*) ti** (Word variations have been searched)	4536
#3	#1 AND #2	5
#5	#1 and #2; Publikation date from Jan 2009	5

Recherchedatum: 24.04.2019

Anzahl der Treffer in Cochrane nach Duplikatecheck: 5

14.4.2.2. Nationale Qualitätsindikatorenprojekte/-programme

Institution	Quelle	Treffer
AQUA-Institut	Internetseite zur Sektorenübergreifenden Qualitätssicherung über https://sqg.de/front_content.php?idcat=15&lang=1	0
	QISA – Qualitätsindikatorensystem für die ambulante http://www.aok-gesundheitspartner.de/bund/qisa/themen/index.html	0
GKV-Spitzenverband	Qualitätsindikatoren-Thesaurus über http://quinth.gkv-spitzenverband.de/content/suche.php	0
IQTiG	Suchfunktion auf https://iqtig.org	0

14.4.2.3. Internationale Qualitätsindikatorenprojekte/-programme

Institution	Quelle	Treffer
AHRQ (Agency for Health Research and Quality) Quality Indicators	über http://www.qualityindicators.ahrq.gov/	0
AMA (American Medical Association)	Über https://www.thepcpi.org/	0
ASCO (American Society of Clinical Oncology) Quality Oncology Practice Initiative	http://qopi.asco.org/index.html QOPI® Measures & Reporting Pathways - Spring 2017	0
CIHI (Canadian Institute for Health Information) Health Indicators	http://www.cihiconferences.ca/indicators/2012/definitions12_e.html	0
CQCO (Cancer Quality Council of Ontario) Cancer System Quality Index – set of indicators	http://www.csqi.on.ca/all_indicators/#.UlJ9iW25OH4	0
ISD Scotland Health Indicators	http://www.isdscotland.org/Health-Topics/Cancer/ http://www.healthcareimprovementscotland.org/our_work/cancer_care_improvement/cancer_qpis/quality_performance_indicators.aspx	6
JCAHO (Joint Commission on Accrediation of Healthcare Organizations)	http://www.jointcommission.org/accountability_measures.aspx	0
NHS (National Health Services) Indicators for Quality Improvement	https://digital.nhs.uk/ https://digital.nhs.uk/data-and-information	0
NQF (National Quality Forum) Performance Measures	http://www.qualityforum.org/QPS/	0
OECD Health Care Quality Indicators	http://www.oecd.org/health/health-systems/hcqi-cancer-care.htm	0

Institution	Quelle	Treffer
RAND Corporation Quality of Care Assessment Tools (QA Tools)	http://www.rand.org/health/surveys_tools/qatools.html	0
Oncoline (Niederlande)	http://oncoline.nl/index.php	0
KCE (Belgien)	https://kce.fgov.be/	0

14.4.2.4. Suchmaschine

Suchmaschine: www.google.de

Suchbegriffe deutsch: (non Hodgkin Lymphom OR non-hodgkin Lymphom OR nonhodgkin Lymphom OR no hodgkin Lymphom) AND (Qualitätsindikator OR Qualitätsindikatoren)

Suchbegriffe englisch: (non hodgkin* OR non-hodgkin* OR nonhodgkin* OR no hodgkin*) AND ((quality OR performance) AND (indicator OR indicators OR measure OR measures))

Recherchedatum: 24.04.2019

Anzahl der Treffer nach Screening: 0

14.4.3. Rechercheergebnisse

Ausschlussgründe:

A1: Doppelpublikation

A2: andere Entität

A3: kein Qualitätsindikator

A4: Publikationsart (z.B.: Letter, Editorial)

A5: Volltext nicht verfügbar

14.4.3.1. Bibliographische Datenbanken

Anzahl der Treffer nach Titel- und Abstractsichtung (Pubmed): 4

Treffer nach Volltextsichtung: 3

[1,2,3]

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
QI 1 - Diagnosis based on histological examination or an excision or wide incision biopsy **A Histologic examination** **B Excision or wide incision biopsy**	Ja [1,2,3] QI 1 2007: 82% 2011: 79%	**2.1** Zur Diagnosesicherung ***soll*** eine histologische und immunhistochemische Untersuchung einer Gewebebiopsie durchgeführt werden. Starker Konsens

Konsultationfassung

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
	QI 1A 2007: 97% 2011:97% QI 1B 2007: 82% 2011: 80%	**EK** **2.2** Zur Diagnosesicherung ***soll*** eine möglichst große Gewebebiopsie gewonnen werden, wobei ein ganzer exzidierter Lymphknoten einer Stanzbiopsie vorzuziehen ist. Starker Konsens **EK**
QI 2 - Patients staged according to Ann Arbor classification	Ja [1,2,3] 2007: 80% 2011: 81%	**2.31 (vorher 2.35)** Patienten mit einem follikulären Lymphom ***sollen*** nach der Ann Arbor Klassifikation in Stadien eingeteilt werden. Starker Konsens **EK**
QI 3 - Diagnosis for NHL based on morphology and immune phenotype **A Morphology** **B Immune phenotype** **C Molecular clonality only supplementary**	Ja [1,2,3] QI 3 2007: 99% 2011: 96% QI 3A 2007: 100% 2011: 100% QI 3B 2007: 99% 2011: 97% QI 3C 2007: 100% 2011: 99%	
QI 4 - Staging techniques should include CT scans of the neck, thorax, and abdomen, bone	Ja [1,2,3] QI 4: 2007: 26%	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
marrow aspirate, and bone marrow biopsy **A. CT scan of the neck** **B. CT scan of the thorax** **C. CT scan of the abdomen** **D. Bone marrow aspirate** **E. Bone marrow biopsy**	2011: 43% QI 4A 2007: 41% 2011: 46% QI 4B 2007: 84% 2011: 75% QI 4C 2007: 84% 2011: 77% QI 4D 2007: 68% 2011: 66% QI 4E 2007: 85% 2011: 78%	
QI 5 - Assessment of International Prognostic Index (IPI) for patients with aggressive NHL	Ja [1,2,3] 2007: 21% 2011: 43%	
QI 6 - Assessment of lactate dehydrogenase value	Ja [1,2,3] 2007: 93% 2011: 92%	
QI 7 - Examination of blood counts **A Leukocyte count** **B Leukocyte differentiation** **C Thrombocyte count** **D Hemoglobin**	Ja [1,2,3] QI 7: 2007: 90% 2011: 82% QI 7A	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
	2007: 99% 2011: 98% QI 7B 2007: 91% 2011: 83% QI 7C 2007: 99% 2011: 97% QI 7D 2007: 99% 2011: 98%	
QI 8 - Reporting of response to therapy using complete remission, partial remission, stable disease, progression, recurrence	Ja [1,2,3] 2007: 65% 2011: 92%	
QI 9 – All target lesions documented in radiology report before therapy **A. Location of lesions reported** **B. Size of lesions reported** **C. Size of lesions reported in mm**	Ja [1,2,3] QI 9: 2007: 64% 2011: 67% QI 9A 2007: 99% 2011: 100% QI 9B 2007: 74% 2011: 77% QI 9C 2007: 64%	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
	2011: 67%	
QI 10 – All target lesions documented in radiology report after therapy **A. Location of lesions reported** **B. Size of lesions reported** **C. Size of lesions reported in mm**	Ja [1,2,3] QI 10: 2007: 67% 2011: 58% QI 10A 2007: 98% 2011: 98% QI 10B 2007: 68% 2011: 70% QI 10C 2007: 68% 2011: 58%	
QI 11 - Evaluation after chemotherapy with CT scans (or PET), and for stage IV patients also with a bone marrow aspirate and biopsy **A. CT scan before therapy** **B. CT/PET scan after therapy** **C. Bone marrow aspirate evaluation** **D. Bone marrow biopsy evaluation**	Ja [1,2,3] QI 11A 2007: 94% 2011: 97% QI 11B 2007: 77% 2011: 89% QI 11C 2007: 46% 2011: 39% QI 11D 2007: 37% 2011: 45%	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
QI 14 - Sending and receiving of unfixed biopsy material	Ja [1,2,3] 2007: 41% 2011: 41%	
QI 15 - Integrated reporting of pathology techniques	Ja [1,2,3] 2007: 88% 2011: 89%	
QI 16 - Pathology report should be complete **A. Origin of tissue** **B. Tissue characteristics** **C. Biopsy method** **D. Receipt of material** **E. Frozen tissue**	Ja [1,2,3] QI 16 2007: 12% 2011: 14% QI 16A 2007: 91% 2011: 98% QI 16B 2007: 56% 2011: 52% QI 16C 2007: 77% 2011: 91% QI 16D 2007: 41% 2011: 34% QI 16E 2007: 27% 2011: 21%	
QI 17 - Patients discussed in multidisciplinary consultations	Ja [1,2,3] 2007: 23% 2011: 41%	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
QI 18 - Results of pathology known before the start of treatment	Ja [1,2,3] 2007: 73% 2011: 83%	
QI 19 - Diagnostic period of 4 weeks after first visit to the hospital	Ja [1,2,3] 2007: 56% 2011: 49%	
QI 20 - Start of therapy within 2 weeks after diagnostic period	Ja [1,2,3] 2007: 55% 2011: 54%	

14.4.3.2. Nationale Qualitätsindikatoren

Recherchedatum: 21.04.2019

Treffer: 0

14.4.3.3. Internationale Qualitätsindikatoren

Recherchedatum: 21.04.2019

Treffer: 1 und 1 mit Ergebnissen

14.4.3.3.1. ISD Scotland Health Indicators NHS Scotland

[4] ([5] – Ergebnisse)

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
QPI 1 - Radiological Staging Patients with lymphoma should be evaluated with appropriate imaging to detect the extent of disease and guide treatment decision making. (i) Patients with lymphoma undergoing treatment with curative intent who are evaluated with appropriate imaging. **Numerator:** Number of patients with lymphoma undergoing treatment with curative intent who undergo CT of chest, abdomen and pelvis or PET CT scanning prior to treatment.	Ja [5] (i) 2015/16: 94,5% (653/691) (ii) 2015/16: 81,6% (566/694)	

Konsultationsfassung

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Denominator: All patients with lymphoma undergoing treatment with curative intent. *Exclusions:* Patients who refuse investigation, Patients with primary cutaneous lymphoma. (ii) Patients with lymphoma undergoing treatment with curative intent who are evaluated with appropriate imaging within 2 weeks of radiology request **Numerator:** Number of patients with lymphoma undergoing treatment with curative intent who undergo CT of chest, abdomen and pelvis or PET CT scanning prior to treatment and within 2 weeks of radiology request. **Denominator:** All patients with lymphoma undergoing treatment with curative intent who undergo CT of chest, abdomen and pelvis or PET CT scanning prior to treatment. (iii) Patients with lymphoma undergoing treatment with curative intent who are evaluated with appropriate imaging where the report is available within 3 weeks of radiology request. **Numerator:** Number of patients with lymphoma undergoing treatment with curative intent who undergo CT of chest, abdomen and pelvis or PET CT scanning prior to treatment where the report is available within 3 weeks of radiology request. **Denominator:** All patients with lymphoma undergoing treatment with curative intent who undergo CT of chest, abdomen and pelvis or PET CT scanning prior to treatment.		
QPI 5 – Lymphoma MDT	Ja [5] 2015/16:	

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Patients with lymphoma should be discussed by a multidisciplinary team following diagnosis. **Numerator:** Number of patients with lymphoma discussed at the MDT within 8 weeks of diagnosis. **Denominator:** All patients with lymphoma. *Exclusions:* Patients who died before first treatment, Patients with primary cutaneous lymphoma.	78,4% (822/1.049)	
QPI 6 – Treatment for Follicular Lymphoma and Diffuse Large B-Cell Lymphoma Patients with symptomatic advanced* follicular lymphoma and Diffuse Large B Cell Lymphoma (DLBCL) should undergo treatment with anti-B cell monoclonal antibody therapy** in combination with chemotherapy. **Numerator:** Number of patients with follicular lymphoma and DLBCL who receive chemotherapy in combination with anti-B cell monoclonal antibody therapy. **Denominator:** All patients with follicular lymphoma and DLBCL who receive chemotherapy. *Exclusions:* Patients who refuse chemotherapy, Patients enrolled in clinical trials. *As it is difficult to accurately identify those patients with symptomatic advanced follicular lymphoma, the number of patients with follicular lymphoma undergoing chemotherapy is being utilised as a proxy measure for symptomatic advanced disease. ** At time of publication, rituximab is the only anti-B cell monoclonal antibody therapy approved by the Scottish Medicines Consortium (SMC) for first line treatment of lymphoma.	Ja [5] 2015/16: 98,4% (420/427)	**6.3** Patienten mit fortgeschrittenen Stadien III und IV, bei denen eine Behandlungsindikation besteht und bei denen keine Einschränkung der Behandlungsfähigkeit besteht, ***sollen*** initial mit der Kombination eines anti-CD 20 Antikörpers plus Chemotherapie behandelt werden. Starker Konsens **EG A**
QPI 11 – Hepatitis and HIV Status	Ja [5] 2015/16:	**9.8**

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
Virological testing for Human Immunodeficiency Virus (HIV), hepatitis B and C should be undertaken for patients undergoing systemic anti cancer therapy (SACT). **Numerator:** Number of patients with lymphoma undergoing SACT who have hepatitis B, C and HIV status checked prior to treatment. **Denominator:** All patients with lymphoma undergoing SACT.	95,0% (549/578)	Vor Einleitung einer systemischen Therapie soll eine Hepatitis B, C und HIV Serologie durchgeführt werden. Starker Konsens **EK**
QPI 13 – Maintenance Therapy for Follicular Lymphoma Patients with follicular lymphoma undergoing R-Chemotherapy* should receive maintenance treatment with anti-B cell monoclonal antibody therapy**. **Numerator:** Number of patients with follicular lymphoma who undergo treatment with R-Chemotherapy who receive maintenance treatment with anti-B cell monoclonal antibody therapy. **Denominator:** All patients with follicular lymphoma who undergo treatment with R-Chemotherapy. *Exclusions:* Patients enrolled in clinical trials. * R-Chemotherapy is a chemotherapy regimen that includes rituximab. Examples include but are not limited to R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone), R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone), and R-bendamustine (rituximab and bendamustine). ** At time of publication, rituximab is the only anti-B cell monoclonal antibody therapy approved by the Scottish Medicines Consortium (SMC) for first line maintenance treatment of lymphoma.	Nein	**7.1 (vorher 7.2)** Bei Ansprechen auf eine kombinierte Immunochemotherapie *soll* eine anti-CD20-Antikörper-Erhaltung über 2 Jahre in der Erstlinientherapie angeboten werden. Konsens **EG B**

Indikator	Ergebnisse vorhanden?	Starke Empfehlung der S3-LL
QPI 14 – Clinical Trial and Research Study Access All patients should be considered for participation in available clinical trials / research studies, wherever eligible. **Numerator:** Number of patients diagnosed with lymphoma consented for a clinical trial / research study. **Denominator:** All patients diagnosed with lymphoma.	Nein	

Konsultationfas

14.5. Ergebnisse der Interessenkonflikterklärungen

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Dr. Walter Baumann	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGSMP, DGHO, DNVF, DGMS	Versorgungsforschung in der Onkologie	Ruhestand Zuvor: Winho GmbH Köln bis 31.03.2018
Prof. Dr. Andreas Buck	Ja Eisai	Ja DGN	Nein	Nein	Ja Bayer	Nein	Ja DGN	Lymphome	Universitätsklinikum Würzburg
Prof. Dr. Christian Buske	Ja Janssen, Roche, Gilead, Hexal, Celltrion	Ja Janssen, Roche, Pfizer, Gilead, Hexal	Ja Janssen	Nein	Nein	Nein	Ja DGHO, ASH, EHA, ESMO, DGIM, ISEH	Lymphome	Universitätsklinikum Ulm
Prof. Dr. Christoph F. Dietrich	Ja JAZZ, Hitachi, Mindray	Ja Siemens, Bracco, Falk, Pentax, Novartis, Supersonic, Mindray, Hitachi	Nein	Nein	Nein	Nein	Ja EFSUMB	Im Tätigkeitsgebiet	Caritas-Krankenhaus Bad Mergentheim
Prof. Dr. Peter Dreger	Ja Riemser, Janssen, Gilead, Roche, Abbvie	Ja Riemser, Gilead/Kite, Sanofi	Ja Riemser	Nein	Nein	Nein	Ja DAG-KBT, EBMT, S3-Leitlinie CLL	HCT, CLL, Lymphome	Universitätsklinikum Heidelberg
Prof. Dr. Martin Dreyling	Ja Bayer, Roche, Celgene, Pfizer, Gilead, Janssen, Sandoz, Mundipharma	Ja Celgene, Gilead, Janssen, Pfizer, Roche, Bayer	Ja Celgene, Janssen, Roche, Mundipharma	Nein	Nein	Nein	Ja ASH, DGHO, ASCO, EHA, ESMO, GLSG DSHNHL, MCL net, LRF	Maligne Lymphome	Klinikum der Universität München

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Prof. Dr. Ulrich Dührsen	Nein	Ja Roche, Alexion, Abbvie, Update Hämatologie und Onkologie	BMBF, Deutsche Krebshilfe	Nein	Nein	Nein	Ja DGHO, Leitlinie aggressive Lymphome	Erkrankungen im blutbildenden System	Universitätsklinikum Essen
Prof. Dr. Falko Fend	Ja Janssen, Roche	Ja Roche	Ja DFG, Sander-Stiftung	Nein	Nein	Nein	Ja DGP, ESP, EAH	Pathologie & Pathophysiologie & molekulare Genetik maligner Lymphome	Universitätsklinikum Tübingen
PD Dr. Sebastian Fetscher	Ja IQWIG, EMA	Nein	Nein	Nein	Nein	Nein	Ja DGHO	Stammzelltransplantation	Sana Kliniken Lübeck
Rainer Göbel	Nein	Ja Tumorzentrum Berlin	Nein	Nein	Nein	Nein	Ja Dt. Leukämie- & Lymphom-Hilfe e.V., Leukämie- & Lymphomselbsthilfe Berlin e.V., Aplastische Anämie und PNH e.V.	Krebs und Arbeit, Krebs und Armut	Gemeinsames Krebsregister Leben nach Krebs! e.V. Zuvor: ASH Berlin, HWR Berlin, Biochrom GmbH, Dr. Mößler Laborsoftware
PD Dr. Valentin Goede	Ja Roche, Janssen, Gilead, Abbvie	Ja Roche, Janssen, Gilead	Nein	Nein	Nein	Nein	Ja DGHO, EHA, DGG, SIOG	Lymphome	St. Marien-Hospital Köln Zuvor: Universitätsklinikum Köln
Prof. Dr. Christian Görg	Nein	Nein	Nein	Nein	Nein	Nein	Ja DEGUM	Ultraschalldiagnostik	Universitätsklinikum Marburg
Sonja Hackenberg	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine	Klinikum der Universität München

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Ulrich Hackenberg	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGHO, ESMO, ASCO	Keine	Kompetenzzentrum Onkologie Zuvor: Universitätsklinikum Giessen
Prof. Dr. med. Dipl. Phys. Dirk Hellwig	Ja Sander-Stiftung, DKG e.V., Bayer. Landesärztekammer	Ja Siemens, Prof. Dr. Klünemann, GE Healthcare, RG Gesellschaft für Information und Organisation GmbH, Thieme-Verlag	Ja Universität des Saarlandes, Aragon Pharmaceuticals, Astra Zeneca, Biogen, GE Healthcare, Pfizer, Roche	Ja Patent auf Messtechnik der PET, Universitätsklinikum Regensburg	Nein	Nein	Ja BLAEK, DGN, BDN, BGN	Referenz-Nuklearmediziner für die DSHNHL, Schwerpunkt PET/CT	Universität und Universitätsklinikum Regensburg
Prof. Dr. Klaus Herfarth	Nein	Nein	Ja Roche	Nein	Nein	Nein	Ja DEGRO	Behandlung von Lymphomen mit Bestrahlung mit Ionen	Universitätsklinikum Heidelberg
Prof. Dr. Michael Herold	Ja Rentenversicherer, Roche	Ja Roche, KML	Ja Roche	Nein	Nein	Nein	Ja GLSG, GLA	Hämatologie/ Onkologie	Helios Klinikum Erfurt
Prof. Dr. Georg Heß	Ja Roche, Celgene, Janssen, Novartis, Morphosys	Ja Roche, Celgene, Janssen, Morphosys	Ja Roche, CTI, Celgene	Nein	Nein	Nein	Ja DGHO, GLA, GSLG, EMCL	Lymphome	Universitätsklinikum Mainz
Dr. Pia Heußner	Nein	Ja APOM, CPM, Elsevier-Verlag	Ja Dt. Krebshilfe	Nein	Nein	Nein	Ja PSO der DKG, DGHO	Entscheidungen am Lebensende	Klinikum Garmisch-Partenkirchen Zuvor: Klinikum der Universität München

Konsultationsfassung

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Prof. Dr. Axel Heyll	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGHO, DAG-KBT	Stammzell-transplantation	MDK Nordrhein
Prof. Dr. Wolfgang Hiddemann	Ja Roche, Gilead	Ja Roche	Ja Roche, Janssen, Gilead	Nein	Nein	Nein	Ja Kompetenznetzwerk maligne Lymphome	Lymphome, akute Leukämien	Klinikum der Universität München
Dr. Eva Hilgenfeld	Ja MDK	Ja MDS	Nein	Nein	Nein	Nein	Ja DGHO, ESMO	Keine	MDK Nordrhein Zuvor: Onkologische Praxis
Dr. Ulrike Hotkamp	Nein	Nein	Nein	Nein	Nein	Nein	Ja DGHO, DAG-KBT, GLA, Dt. Leukämie- und Lymphomhilfe e.V., Stiftung dt. Leukämie- und Lymphomhilfe	Keine	DLH e.V.
Dr. Markus Horneber	Nein	Ja Mundipharma, Roche, KOKON	Ja Dt. Krebshilfe	Nein	Nein	Nein	ASOR	Komplementärmedizin, Supportivtherapie, Kommunikation Arzt-Patienten-beziehung	Klinikum Nürnberg Zuvor: Praxis Dr. Grabowski, Nürnberg
PD Dr. Eva Hoster	Nein	Ja Celgene	Nein	Nein	Nein	Nein	Ja GMDS	Lymphome	Klinikum der Universität München
Prof. Dr. Kai Hübel	Ja Roche, Sanofi, Servier,	Ja Roche,Sanofi, Servier, cti	Nein	Nein	Nein	Nein	Ja DHGO, GLA	Lymphome, Stammzell-transplantation	Universitätsklinikum Köln

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
	Celgene, Hexal								
Tina Jakob	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Mitglied der Cochrane Haemato-logical Malignancies Group	Universitätsklinikum Köln Zuvor: Kliniken Essen-Mitte
Prof. Dr. Wolfram Klapper	Ja Roche, Takeda, Amgen, Regeneron	Nein	Ja Roche, Takeda, Amgen, Regeneron	Nein	Nein	Nein	Ja DGP	Indolente Lymphome	Universitätsklinikum Schleswig-Holstein
Prof. Dr. Sabine Kliesch	Ja AiCuris, Dr. Kade-Besins, Jenapharm	Ja Merck-Serono, Jenapharm, Dr. Kade-Besins, Ferring, Lilly, Boston-Scientific, Arbeitskreis Andrologie der DGU	Ja Dr. Kade-Besins, Galen-Pharma	Nein	Nein	Nein	Ja DGU, DGA, Dt. Krebsgesellschaft, Europäische Gesellschaft für Sexualmedizin	Fertilitäts-störungen beim Mann	Universitätsklinikum Münster
Prof. Dr. Frank-Michael Köhn	Nein	Ja Ferring, Lilly, Medical Tribune Verlags-gesellschaft, Akademie für Fort- und Weiterbildung der DGE	Ja PRA Health Sciences, Gilead	Nein	Nein	Nein	Ja Dt. Gesellschaft für Reproduk-tionsmedizin, DGA, DGD, Arbeitskreis Andrologie der Dt. Dermato-logischen Gesellschaft, Dt. Gesellschaft für Sexualmedizin	Klinische Andrologie	Selbstständig

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Prof. Dr. Nicolaus Martin Kröger	Ja Sozialgerichte, Novartis, Alexion, Sanofi, Neovii, JAZZ, Amgen	Ja Neovii, Novartis, Celgene	Ja Neovii, Riemser, Pierre Fabre, Novartis, Celgene	Nein	Nein	Nein	Ja DAG-KBT, DGHO, EBMT, EHA	Stammzell-trans-plantation	Universitätsklinikum Hamburg Eppendorf
Prof. Dr. Ulrich Mansmann	Ja Boehringer-Ingelheim, Roche	Nein	Ja Boehringer-Ingelheim	Nein	Nein	Nein	Ja GMDS, DFG	Prognostische Faktoren	Klinikum der Universität München
Prof. Dr. Georg Maschmeyer	Ja Gilead	Ja Gilead, Pfizer, BMS, Janssen-Cilag, Merck-Serono, Celgene, Boehringer-Ingelheim, Basileas	Nein	Nein	Nein	Nein	Ja DGHO, Dt. Krebsgesell-schaft, DAG-KBT, ASH, ESCMIO	Infektionen, Myelom, Leukämie, HNO	Klinikum Ernst von Bergmann gGmbH Potsdam
Metz, Melanie	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Keine	Klinikum der Universität München
Prof. Dr. Oliver Micke	Ja Clinigen Specialty Pharmaceuticals	Ja Merck-Serono	Nein	Nein	Nein	Nein	Ja DEGRO, BVDST, Dt. Krebsgesell-schaft, AG PRIO	Strahlen-therapie gutartiger Erkrankungen	Franziskus Hospital Bielefeld
Prof. Dr. Peter Möller	Nein	Nein	Nein	Nein	Nein	Nein	Ja KML, DGP	Maligne Lymphome	Universitätsklinikum Ulm
Dr. Monika Nothacker	Ja, IQWIG IQTIG	Ja, Vortrags-/oder Schulungstätigkeit ÄK Niedersachsen Berlin School of Public Health	Ja, DFG, DKG	Nein	Nein		Deutsche Krebsgesellschaft Deutsches Netzwerk evidenzbasierte	Leitlinien und leitinienba-sierte Qualitätsindikatoren	AWMF

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
		Berliner Urologische Gesellschaft DAG Selbsthilfe					Medizin: Sprecherin Fachbereich Leitlinien AWMF: Stellvertr. Leitung AWMF-IMWi		
PD Dr. rer. nat. Alexandra Nieters	Nein	Nein	BMBF	Nein	Nein	Ja Novartis	Ja Dt. Gesell. für Epidemiologie, Dt. Gesell. für Immunologie, European Society for Immunodeficiency	Epidemiologie	Universitätsklinikum Freiburg
Dr. Lars-Hendrik Nipken	Nein	Nein	Nein	Nein	Nein	Nein	Ja DKG, AIO, ASORS	Keine	Winkelwaldklinik Nordrach
Kerstin Paradies-Schödler	Ja Roche, Amgen	Ja Roche, Astra Zeneca	Nein	Nein	Nein	Nein	KOK	Keine	Amalie-Sieveking-Krankenhaus Hamburg Zuvor: Praxis Prof. Dr. Schmidt-Rhode
Prof. Dr. Thomas Pfluger	Nein	Nein	Nein	Nein	Nein	Nein	Ja DRG, EANM	Pädiatrische Nuklearmedizin	Klinikum der Universität München
Prof. Dr. Christiane Pott	Ja Roche	Nein	Ja Roche	Nein	Nein	Nein	Ja DGHO	Behandlung und Diagnostik von Lymphomen	Universitätsklinikum Schleswig-Holstein
Dr. Johannes Rosenbruch	Nein	Ja Hospiz- und Pallliativdienste, Christophorus	Nein	Nein	Nein	Nein	Ja Dt. Gesell. für Palliativmedizin,	Symptomkontrolle	Klinikum der Universität München

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		Akademie München					S3-LL Palliativmedizin		
Prof. Dr. Ernst Rummeny	Nein	Nein	Nein	Nein	Nein	Nein	Ja DRG	Onkologische Bildgebung	Klinikum Rechts der Isar der Technischen Universität München
PD Dr. Michael Sandherr	Ja Roche	Nein	Nein	Nein	Nein	Nein	Ja Bayr. Krebsgesellschaft	Keine	Praxis für Hämatologie und Onkologie, Weilheim
Prof. Dr. Heinz Schmidberger	Ja VARIAN	Ja Dt. Krebshilfe	Nein	Nein	Nein	Nein	Ja ARO, DEGRO, DKG, ESTRO, ASTRO, ASCO	Maligne Lymphome, GI-Tumore, Urogenital-Tumore	Universitätsklinikum Mainz
Dr. Christian Schmidt	Ja Celgene, Takeda, Hexal, Amgen	Ja Gilead, Celgene	Nein	Nein	Nein	Nein	Ja GLA, GSLG	Lymphome, Myelome, zelluläre Immuntherapie	Klinikum der Universität München
PD Dr. Christian Scholz	Ja Gilead, Janssen, Novartis, Roche, Amgen, BMS, Hexal	Ja Gilead, Janssen, Novartis, Roche, Sepropharm, Pfizer	Nein	Nein	Ja Astra Zeneca, BMS, Kite Pharma	Nein	Ja DGHO, ASH, ESO, Ostdt. Studiengesellschaft für Hämatologie und Onkologie, ASCO, GLSG	Lymphome	Vivantes Klinikum am Urban, Berlin Zuvor: Charité Universitätsmedizin Berlin
PD Dr. Andreas Schüring	Ja Novartis	Ja Intensivkurs NRW	Nein	Nein	Nein	Nein	Ja Netzwerk Fertiprotekt e.V., S2k-LL Fertilitätsprotektion	Reproduktionsmedizin inkl. Fertilitätsprotektion	Universitätsklinikum Münster

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
PD Dr. Nicole Skoetz	Ja Cochrane Library, Cochrane Scientific Committee	Ja Cochrane Workshops, Cochrane Reviews	Nein	Nein	Nein	Nein	Ja EbM-Netzwerk	Systemic Review, Metaanalysen	Universitätsklinikum Köln
Dr. Christoph Stoll	Nein	Ja Techniker Krankenkasse, Bayr. Krebsgesellschaft	Nein	Nein	Nein	Nein	Ja PRIO, DKG, DGHO, ESMO	Supportive Onkologie, Komplementärmedizin	Dt. Rentenversicherung Nordbayern, Klinik Herzoghöhe
Dr. Corinna Trenker	Nein	Nein	Nein	Nein	Nein	Nein	Ja DEGUM, DEGIM, GLA	Lymphome	Ûniversitätsklinikum Gießen und Marburg, Standort Marburg
Prof. Dr. Lorenz Trümper	Ja DFG	Nein	Ja BMBF	Nein	Nein	Nein	Ja DGHO, ASH, GLA	Lymphome	Universitätsklinikum Göttingen
Dr. rer. nat. Michael Unterhalt	Nein	Nein	Ja Roche, Janssen	Nein	Nein	Nein	Ja DGHO, GLA, GLSG	Lymphome	Klinikum der Universität München
PD Dr. Andreas Viardot	Ja Amgen, BMS, Pfizer, Roche, Kite, Gilead	Ja Roche, Pfizer, Amgen, BMS, Celgene	Nein	Nein	Nein	Nein	Ja GLA	Lymphome	Universitätsklinikum Ulm
PD Dr. Bastian von Tresckow	Ja Takeda, Novartis, MSD	Ja Takeda, Amgen, Celgene, Novartis	Ja Takeda, Novartis, MSD	Nein	Nein	Nein	Ja GSHG, GLA	Keine	Universitätsklinikum Köln
Dr. Oliver Weigert	Ja Roche, Incyte	Ja EHA, DGHO	Ja Roche, Novartis, DFG, Dt. Krebshilfe	Nein	Nein	Nein	Ja GLSG, GLA	Klinische und translationale Forschung beim Foll. Lymphom und Mantelzelllymphom	Klinikum der Universität München

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäftsanteilen, Aktien, Fonds [5]	Persönliche Beziehungen [6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitliniengruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
Dr. Manfred Wick	DGLN	DGLN	Nein	Nein	Nein	Nein	DGLN, DGKL	Liquordiagnostik, Eisenstoffwechsel, Hämatologie, Lymphome	Berentet, zuvor Klinikum der Universität München
Prof. Dr. Mathias Witzens-Härig	Ja Roche, BMS, Pfizer, Novartis	Ja Roche, Novartis, Pfizer, Janssen, Riemser	Ja Pfizer	Nein	Nein	Nein	Ja DGHO	Lymphome	Universitätsklinikum Heidelberg
Prof. Dr. Bernhard Wörmann	Nein	Nein	Nein	Nein	Nein	Nein	DGHO: Medizinischer Leiter	Koordination von Onkopedia Leitlinien	Charité Universitätsmedizin Berlin DGHO
Dr. Anna-Katharina Zoellner	Ja Hexal, Abbvie	Nein	Nein	Nein	Nein	Nein	Ja DGHO, GLA	Maligne Lymphome	Klinikum der Universität München
Dipl. Soz.Wiss. Thomas Langer	Nein	Ja AWMF (Vortrag zu CoI)	Nein	Nein	Nein	Nein	DNEbM	Leitlinien, Interessenkonflikt-management	Deutsche Krebsgesellschaft e.V.
Dr. Friederike Mumm	Nein	Ja Servier	Nein	Nein	Nein	Nein	Vorstand TZM AG Psychoonkologie DGHO, PSO, IPOS, Marburger Bund	PROs bei onkolog. Patienten, Kommunikation	Med. III, Klinikum der Universität München
Dr. Henning Adam	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Deutsche Krebsgesellschaft e.V., Gemeinsamer Bundesausschuss (G-BA)
PD Dr. Simone Wesselmann	Nein	Nein	Nein	Nein	Nein	Nein	Deutsche Krebs-gesellschaft e.V.	Qualitäts-sicherung in	Deutsche Krebsgesellschaft e.V.,

	Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit [1]	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften [2]	Finanzielle Zuwendungen (Drittmittel) [3]	Eigentümerinteresse (z. B. Patent, Urheberrecht, Verkaufslizenz) [4]	Besitz von Geschäfts-anteilen, Aktien, Fonds [5]	Persön-liche Beziehungen[6]	Mitgliedschaft Fachgesellschaften/Berufsverbände, andere Leitlinien-gruppen [7]	wissenschaftliche oder persönliche Interessen [8]	Gegenwärtiger Arbeitgeber, relevante frühere Arbeitgeber der letzten 3 Jahre
								onkolog. Versorgungs-strukturen Auswertung von Qualitätsindikatoren	
Marius Goldkuhle	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Evidenzbasierte Medizin, Methodik-forschung	Universitätsklinikum Köln
Dipl. Bibl. Ina Monsef	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Universitätsklinikum Köln

1 = Berater-bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z.B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

2 = Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

3 = Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung

4 = Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)

5 = Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft

6 = Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft

7 = Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung

8 = Politische, akademische (z.B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten

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