Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-02-01-D-212 Ibrutinib

Stand: Mai 2015

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

Ibrutinib

zur Behandlung erwachsener Patienten mit Morbus Waldenström (MW), die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinien-Therapie bei Patienten, die für eine Chemo-Immuntherapie nicht geeignet sind

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	➔ Siehe Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Plasmapherese - Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegt ein Beschluss des G-BA vom 17.02.2011 zur Änderung von Anlage VI der AM-RL zu Fludarabin vor. <u>Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation):</u> Fludarabin in Kombination mit Cyclophosphamid, Mitoxantron und Rituximab (R-FCM) bei geeigneten Patienten mit niedrig oder intermediär malignen Non-Hodgkin-Lymphomen der B-Zellreihe (CD20 positive NHL, u.a. lymphozytisch, lymphoplasmazytisch, lymphoplasmazytoid, follikulär Grad 1 oder 2, Mantelzell, Marginalzonen, nicht multiples Myelom, nicht Haarzellleukämie) und Resistenz auf CHOP (mit oder ohne Rituximab).
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ibrutinib L01XE27 IMBRUVICA®	Anwendungsgebiet laut Dossier: Behandlung erwachsener Patienten mit Morbus Waldenström (MW), die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinien-Therapie bei Patienten, die für eine Chemo-Immuntherapie nicht geeignet sind
Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (CLL), niedrig maligne Non-Hodgkin-Lymphome, Waldenström Makroglobulinämie
Prednison H02AB07 Cutason®	Hämatologie/Onkologie: – Akute lymphoblastische Leukämie (DS: e), Morbus Hodgkin (DS: e), Non-Hodgkin-Lymphome (DS: e), Chronisch lymphatische Leukämie (DS: e), Morbus Waldenström (DS: e), Multiples Myelom (DS: e), Hyperkalzämie bei malignen Grunderkrankungen (DS: c bis a)
Prednisolon H02AB06 Dermosolon®	Hämatologie/Onkologie – akute lymphoblastische Leukämie (DS: e) Morbus Hodgkin (DS: e) Non-Hodgkin-Lymphome (DS: e) chronisch lymphatische Leukämie (DS: e) Morbus Waldenström (DS: e) multiples Myelom (DS: e) Hyperkalzämie bei malignen Grunderkrankungen (DS: c bis a)
Für (niedrig-maligne) Non-Hodgkin-Lymphome zugelassene Wirkstoffe	
Fludarabin L01BB05 Fludarabinmedac®	Behandlung der chronisch-lymphatischen B-Zell-Leukämie (CLL) bei Patienten mit ausreichend Knochenmarkreserven. <u>Beschluss des G-BA vom 17.02.2011 zur Änderung von Anlage VI der AM-RL (Off-Label-Indikation):</u> Fludarabin in Kombination mit Cyclophosphamid, Mitoxantron und Rituximab (R-FCM) bei geeigneten Patienten mit niedrig oder intermediär malignen Non-Hodgkin-Lymphomen der B-Zellreihe (CD20 positive NHL, u.a. lymphozytisch, lymphoplasmozytisch, lympho-plasmazytoid, follikulär Grad 1 oder 2, Mantelzell, Marginalzonen, nicht multiples Myelom, nicht Haarzellleukämie) und Resistenz auf CHOP (mit oder ohne Rituximab).
Bendamustin L01AA09 Levact®	Primärtherapie bei chronisch-lymphatischer Leukämie (Binet-Stadium B oder C) bei Patienten, bei denen eine Fludarabin-Kombinations-Chemotherapie ungeeignet ist. Monotherapie bei indolenten Non-Hodgkin-Lymphomen bei Patienten mit Progression während oder innerhalb von 6 Monaten nach Behandlung mit Rituximab oder mit einer Rituximab-haltigen Therapie. Primärtherapie bei multiplem Myelom (Stadium II nach Durie-Salmon mit Progression oder Stadium III) in Kombination mit Prednison, bei Patienten, die älter als 65 Jahre und nicht für eine autologe Stammzellen-Transplantation (HDT/ASCT) geeignet sind und die bereits bei Diagnosestellung eine klinische Neuropathie aufweisen, wodurch eine Behandlung mit Thalidomid oder Bortezomib ausgeschlossen ist.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Cyclophosphamid L01AA01 Endoxan®	- Remissionsinduktion und Konsolidierungstherapie bei akuter lymphatischer Leukämie - Remissionsinduktion bei Morbus Hodgkin - Non-Hodgkin-Lymphome (in Abhängigkeit vom histologischen Typ und vom Krankheitsstadium auch als Monotherapie) - Chronisch lymphatische Leukämie (CLL) nach Versagen der Standardtherapie (Chlorambucil/Prednison) - Remissionsinduktion bei Plasmozytom (auch in Kombination mit Prednison) - …
Vincristin L01CA02 Vincristinsulfat-Teva®	Entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - akuter lymphatischer Leukämie - malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen - multiplem Myelom - soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom, kleinzelligem Bronchialkarzinom - Ewing-Sarkom, embryonalem Rhabdomyosarkom, primitiven neuroektodermalen Tumoren (Medullablastom und Neuroblastom), Wilms-Tumor und Retinoblastom - idiopathischer thrombozytopenischer Purpura (ITP). Patienten mit einer echten ITP, die gegenüber Splenektomie und einer kurzzeitigen Behandlung mit Adrenokortikoiden therapierefraktär ist, sprechen vielleicht auf Vincristin an. Als Primärtherapie für diese Erkrankung wird dieses Arzneimittel jedoch nicht empfohlen.
Trofosfamid L01AA07 Ixoten®	Dieses Arzneimittel ist ein Zytostatikum. Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet.
Vinblastin L01CA01 Vinblastinsulfat-Teva®	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: – maligne Non-Hodgkin-Lymphome – Morbus Hodgkin – fortgeschrittenes Hodenkarzinom – rezidivierendes oder metastasierendes Mammakarzinom (wenn eine Behandlung mit Anthracyclinen nicht erfolgreich war) – Langerhans-Zell-Histiozystosis (Histiozystosis X)
Nimustin-HCl L01AD06 Acnu®	Maligne Gliome, Hirnmetastasen bei zugrundeliegenden kleinzelligen Bronchialkarzinomen als Primärtumor. Kleinzelliges Bronchial- CA. Kolorektalekarzinome. Lokalisiertes, nicht reserzierbares Magen-CA. Chron myeloische Leukämie. Morbus Hodgkin. Non-Hodgkin-Lymphome.
Mitoxantron L01DB07 Strimax®	Mitoxantron ist indiziert zur der Behandlung des metastasierenden Mammakarzinoms, des Non-Hodgkin-Lymphoms und bei akuter nicht-lymphatischer Leukämie.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Teniposid L01CB02 VM 26®	Dieses Arzneimittel ist als Monosubstanz und in Kombination mit anderen antineoplastisch wirksamen Substanzen bei der Behandlung folgender Tumoren wirksam: - Morbus Hodgkin; - Non-Hodgkin-Lymphome (Lymphosarkom, Retikulumzell-Sarkom); - Hirntumoren (malignes Gliom, Astrozytom, Ependymom); - Harnblasenkarzinom.
Cytarabin L01BC01 ARA-cell®	ARA-cell® 100 mg/ml wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: • refraktären Non-Hodgkin-Lymphomen • refraktärer akuter nichtlymphatischer Leukämie • refraktärer akuter lymphoblastischer Leukämie • Rezidiven akuter Leukämien • Leukämien mit besonderem Risiko: – sekundäre Leukämien nach vorausgegangener Chemotherapie und/oder Bestrahlung – manifeste Leukämie nach Transformation von Präleukämien • Konsolidierung der Remission akuter nichtlymphatischer Leukämie bei Patienten unter 60 Jahren
Asparaginase L01XX02 Asparaginase medac®	Asparaginase 5000 (10000) E medac ist als Bestandteil einer antineoplastischen Kombinationstherapie der akuten lymphatischen Leukämie (ALL) im Kindes- und Erwachsenenalter sowie bei Non-Hodgkin-Lymphomen im Kindesalter angezeigt
Methotrexat Methotrexat 15 Injektionslösung medac®	Non-Hodgkin-Lymphome – im Erwachsenenalter Zur Behandlung von Non-Hodgkin-Lymphomen von intermediärem oder hohem Malignitätsgrad in Kombination mit anderen zytostatischen Arzneimitteln – im Kindesalter in Kombination mit anderen zytostatischen Arzneimitteln

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Indikation für die Recherche bei Ibrutinib:

IMBRUVICA® zur Behandlung erwachsener Patienten mit Morbus Waldenström

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Morbus Waldenström“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***26.03.2015*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), arztbibliothek.de (ÄZQ),

AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **140** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **34** Quellen eingeschlossen. Insgesamt ergab dies **5** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

Acronym	Beschreibung
2-CDA	2-chlorodeoxyadenosine
ABVD	adriamycin + bleomycin + vinblastine + dacarbazine
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase (test)
ALL	acute lymphoblastic leukemia
ALT	alanine transaminase (test)
AML	acute myeloid leukemia
ATCL	adult T-cell lymphoma
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCNU	carmustine
BEACOPP	bleomycin + etoposide + adriamycin + cyclophosphamide + vincristine + procarbazine + prednisone
BEAM	BCNU + etoposide + cytarabine + melphalan
BL	Burkitt lymphoma
BMT	bone marrow transplant
B-R	Bendamustine-rituximab
CALGB	Cancer and Leukemia Group B
CAP	cyclophosphamide , doxorubicin prednisone
CAP	cyclophosphamide + adriamycin + prednisone
CBV	cyclophosphamide + BCNU + etoposide
CCO	Cancer Care Ontario
CEC	cyclophosphamide + lomustine + vindesine + melphalan + prednisone + epidoxirubicin + vincristine + procarbazine + vinblastine + bleomycin
CEPP	cyclophosphamide + etoposide + procarbazine + prednisone
ChlVPP	chlorambucil + vinblastine + procarbazine + prednisone
CHOEP	cyclophosphamide + adriamycin + vincristine + etoposide + prednisone
CHOP	cyclophosphamide + adriamycin + vincristine + prednisone
CLL	chronic lymphocytic leukemia
CMED	cyclophosphamide + etoposide + methotrexate + dexamethasone + leucovorin + G-CSF
CNS	central nervous system
CODOX-M	cyclophosphamide + vincristine + adriamycin + methotrexate
COPP	cyclophosphamide + vincristine + procarbazine + prednisone
CR	Complete Response
CR	complete remission
CS	clinical stage
CSF	cerebrospinal fluid

CT	computed tomography scan
CTCL	cutaneous T-cell lymphoma
CVAD	cyclophosphamide + vincristine + adriamycin + dexamethasone
CVP	cyclophosphamide + vincristine + prednisone
DAHTA	Deutsche Agentur für Health Technology Assessment
DGHO-Onkopedia	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
DHAP	dexamethasone + cytarabine + cisplatin
DICE	dexamethasone + ifosfamide + cisplatin + etoposide + mesna
DICEP	dexamethasone + cyclophosphamide + etoposide + cisplatin + mesna + Septra
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide
EBER	Epstein-Barr virus encoded ribonucleic acid
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ENS	extracapsular neoplastic spread
ENT	ear, nose, and throat
ESHAP	etoposide + methylprednisolone + cytarabine + cisplatin
ESMO	European Society for Medical Oncology
ESR	erythrocyte sedimentation rate
FB Med	Fachberatung Medizin
FC	fludarabine + cyclophosphamide
FEV1	forced expiratory volume in one second
FISH	fluorescent *in situ* hybridization
FLIPI	Follicular Lymphoma International Prognostic Index
FND	fludarabine + mitoxantrone + dexamethasone
G-BA	Gemeinsamer Bundesausschuss
G-CSF	granulocyte-colony stimulating factor
GDP	gemcitabine + dexamethasone + cisplatin
GHSG	German Hodgkin Study Group
GIN	Guidelines International Network
GMALL	German multicentre adult acute lymphoblastic leukemia protocol
H&E	hematoxylin and eosin stain
HAART	highly active antiretroviral therapy
HAMA	human anti-mouse antibodies
Hb	Hämoglobin
HDCT	high dose chemotherapy
HL	Hodgkin lymphoma
HP-Pac	lansoprazole + clarithromycin + amoxicillin
HR	Hazard Ratio
HSCT	hematopoietic stem cell transplantation
HVS	hyperviscosity syndrome
ICE	ifosfamide + carboplatin + etoposide
IELSG	International Extranodal Lymphoma Study Group
IFRT	involved field radiation therapy
IgM	Lymphomzellen Immunglobulin M
IMRT	intensity-modulated radiation therapy
IPI/IPS	International Prognostic Index/Score
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	intravenous
IVAC	ifosfamide + mesna + etoposide + cytarabine
IVE	ifosfamide + vincristine + etoposide

KPS	Karnofsky Performance Status Scale
LDH	lactate dehydrogenase test
LPL	lymphoplasmozytischen Lymphomen
LPL	lymphoplasmacytic lymphoma
LVEF	left ventricular ejection fraction
MACOP-B	methotrexate + adriamycin + cyclophosphamide + vincristine + bleomycin + prednisone
MALT	mucosa-associated lymphoid tissue
MDS	myelodysplastic syndrome
MDS/AML	Myelodysplastische Syndrome /Akute myeloische Leukämie
MEP	mitomycin C + etoposide + cisplatin
mg	milligram
mSMART	Mayo Stratification of macroglobulinemia and Risk-Adapted Therapy
MTD	maximum transthoracic diameter
MTX	methotrexate
MUGA	multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NHL	non-Hodgkin lymphoma
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
NK	natural killer
NLPHD	nodular lymphocyte predominant Hodgkin disease
OS	overall survival
PCNSL	primary central nervous system lymphoma
PCP	*Pneumocystis jiroveci* pneumonia
PEBC	Program in Evidence-Based Care
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
POMP	mercaptopurine + vincristine + methotrexate + prednisone
PR	partial response
PTCL	peripheral T-cell lymphoma
PTLD	post-transplant lymphoproliferative disorder
PUVA	psoralen + ultraviolet A radiation
R	rituximab
R-CHOP	Rituximab-Cyclophosphamid, Hydroxydaunorubicin (Doxorubicin) Vincristin (Oncovin®), Predniso(lo)n
R-CHOP	rituximab + cyclophosphamide + adriamycin + vincristine + prednisone
RCT	Randomized Controlled Trial
R-CVP	rituximab + cyclophosphamide + vincristine + prednisone
R-FCM	fludarabine + cyclophosphamide + mitoxantrone + rituximab
RIT	radioimmunoconjugate therapy
RR	Relative Risk
RR	response rate
RT	radiotherapy
SBFT	small bowel follow-through (test)
SCT	Stem cell therapy
SCT	stem cell transplant
SD	stable disease
SLL	small lymphocytic lymphoma
SOT	solid organ transplant

STNI	subtotal nodal irradiation
TBI	total body irradiation
TBuC	thiotepa + busulfan + cyclophosphamide
TRIP	Turn Research into Practice Database
TRM	Transplant-related mortality
TSH	thyroid stimulating hormone
TTP	Time to progression
UGI	upper gastrointestinal series (test)
VIPD	etoposide + ifosfamide + cisplatin + dexamethasone
WHO	World Health Organisation
WM	Waldenströms Macroglobulinämie / Waldenström's macroglobulinemia

IQWiG Berichte/ G-BA Beschlüsse

Es liegen keine relevanten IQWiG Berichte / G-BA Beschlüsse vor.

Cochrane Reviews

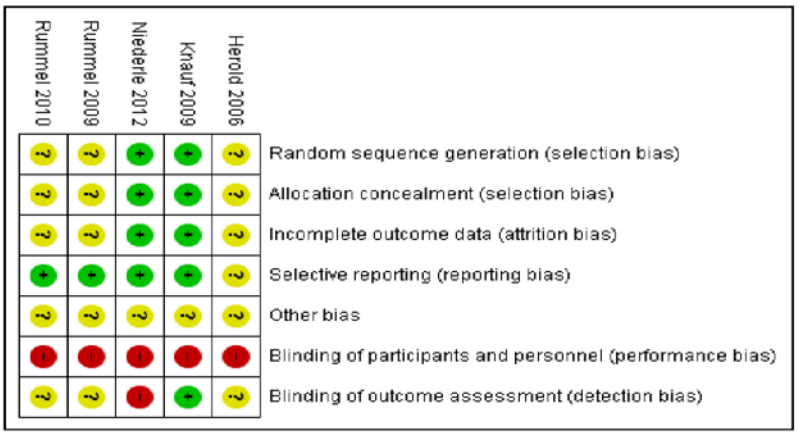
Vidal et al. 2012: [5] Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia.	1. **Fragestellung**: To evaluate the efficacy of bendamustine therapy for patients with indolent B cell lymphoid malignancies including CLL.
	2. Methodik Population: Patients with histologically confirmed indolent B cell lymphoid malignancies, i.e. SLL/CLL, follicular lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, marginal zone lym- phoma. Both, patients receiving bendamustine as first-line therapy and patients with relapsed or refractory disease receiving it as salvage therapy were included. Patients might have received high-dose chemotherapy following first-line or salvage therapy. Intervention: Bendamustine as a single agent or in combination with chemotherapy and immunotherapy Komparator: • Observation or steroids alone • Chemotherapy • Chemotherapy in combination with immunotherapy (i.e. rituximab) or radio-immunotherapy Trials in which bendamustine was combined with immunotherapy or radio-immunotherapy only if bendamustine was compared to chemotherapy combined with the same immunotherapy or radio-immunotherapy were included. Chemotherapy included: • Adriamycin, cyclophosphamide, chlorambucil, fludarabine, mitoxantrone, vincristine • Steroids could be combined with any chemotherapeutic regimen Endpunkte: **Primary outcomes**: Overall survival (OS) (all-cause mortality. This outcome was added post-hoc to protocol due to the scarcity of OS data) **Secondary outcomes:** Progression-free survival (PFS), Complete response (CR), Overall response (partial and complete response), Quality of life, Treatment-related mortality, Adverse events requiring discontinuation of therapy, Grade 3/4 adverse events, Infection-

related adverse events
Note: Subgroup analysis and investigation of heterogeneity were made e.g. for Type of lymphoma (SLL/CLL, FL, MCL, lymphoplasmacytic lymphoma)

Suchzeitraum (Aktualität der Recherche):
Systematische Literaturrecherche bis Mai 2012.

Anzahl eingeschlossene Studien/Patienten (Gesamt):
5 studies with N=1294 patients.

Studienqualität:
Cochrane Risk of Bias Tool



3. Ergebnisdarstellung

nur die Intervention (Bendamustin-Gabe) einer Studie (**RCT von Rummel et al. 2010**) entspricht der deutschen Zulassung von Bendamustin (***vgl. Anlage 1***)

In general:
All five eligible trials included adult patients with indolent B cell lymphoid malignancies requiring chemotherapy. Three trials (Herold 2006; Rummel 2009; Rummel 2010) included patients with follicular lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma and other indolent lymphomas.
Three trials (Herold 2006; Knauf 2009; Rummel 2009) included previously untreated patients and two trials included previously treated patients (Niederle 2012; Rummel 2010).
Bendamustine was compared to an alkylating agent-containing protocol in three trials (Herold 2006; Knauf 2009; Rummel 2009). Bendamustine was compared to the combination of cyclo-phosphamide, doxorubicin, vincristine and prednisone (CHOP) (Rummel 2009), to cyclophosphamide (as part of the COP reg- imen) (Herold 2006) and to chlorambucil (Knauf 2009). Ben- damustine was compared to a purine analogue (fludarabine) in two trials (Niederle

	2012; Rummel 2010). The different comparators may be responsible for the statistical heterogeneity in secondary outcomes. Bendamustine was not compared to placebo, no treatment or steroids in any of the included trials. We amended the protocol and did not pool results due to the high clinical heterogeneity as well as statistical heterogeneity of the patients in terms of disease (non-Hodgkin's lymphoma, CLL) and disease status (untreated, previously treated), interventions (different bendamustine-containing protocols) and the various comparator protocols. **Overall survival:** • All three showed a non-statistically significant improvement in survival in the bendamustine group as indirectly estimated. Two trials did not provide any data on overall survival. • Four trials showed a non-significant im- provement in all-cause mortality in the bendamustine group and one trial showed no difference between groups. • Data were not reported according to the type of lymphoma (SLL/ CLL, FL, MCL, lymphoplasmacytic lymphoma, MZL), thus we could not perform a subgroup analysis according to the type of lymphoproliferative malignancy. **Progression-free survival (PFS):** • Three of the four trials (1132 patients) that reported on PFS of patients with indolent B cell lymphoid malignancies demonstrated an improved PFS with bendamustine compared to control (Knauf 2009; Rummel 2009; Rummel 2010). One trial (Niederle 2012) demonstrated a non-statistically significant improvement of PFS with bendamustine. No meta-analysis was done. The estimated hazard ratios (HR) of disease progression or death were HR 0.28, 95% CI 0.19 to 0.42 (Knauf 2009, 319 patients); HR 0.91, 95% CI 0.50 to 1.64 (Niederle 2012, 92 patients); HR 0.58, 95% CI 0.43 to 0.77 (Rummel 2009, 513 patients); HR 0.51, 95% CI 0.37 to 0.71 (Rummel 2010, 208 patients). **Complete and overall response:** • Four trials reported on CR rates (Herold 2006; Knauf 2009; Rummel 2009; Rummel 2010). We did not pool the results of complete and overall response rate due to high statistical hetero- geneity (I^2 of heterogeneity = 88% and 97%, respectively). Bendamustine had no statistically significantly effect on CR rate as compared to cyclophosphamide (RR 1.10, 95% CI 0.60 to 2.00, Herold 2006; RR more than 1 is in favour of bendamustine) and increased the RR of CR rate in three trials: compared to chloram- bucil (RR 16.15, 95% CI 5.14 to 50.72, Knauf 2009); compared to CHOP (RR 1.30, 95% CI

	1.02 to 1.64, Rummel 2009); com- pared to fludarabine (RR 2.38, 95% CI 1.44 to 3.96, Rummel 2010). Overall response rate was improved with bendamustine when compared to chlorambucil (RR 2.22, 95% CI 1.72 to 2.88, Knauf 2009) and fludarabine (RR 1.59, 95% CI 1.29 to 1.95, Rummel 2010), and was not affected compared to cyclophospha- mide (RR 0.86, 95% CI 0.71 to 1.05, Herold 2006) and CHOP (RR 1.00, 95% CI 0.96 to 1.05, Rummel 2009). The high chance of heterogeneity makes these results difficult to interpret and may be explained by the intensity of the comparator chemotherapy. **Quality of life:** • The effect of bendamustine on quality of life was reported in one trial in which it was compared with chlorambucil (Knauf 2009). After completion of the study treatment no differences were demonstrated with respect to physical, social, emotional and cognitive functioning, and self-assessment of global health status **Adverse events:** • Treatment-related mortality was reported in one trial (Herold 2006) in two patients of 82 treated with bendamustine and none of 80 patients in the comparator treatment group. Adverse events requiring discontinuation of therapy were reported in one trial (Knauf 2009). • Eighteen patients (11%) discontinued bendamustine therapy and five (3%) discontinued chlorambucil (p = 0.005). • Data regarding grade 3 to 4 adverse events were reported in three trials (Knauf 2009; Rummel 2009; Rummel 2010). Due to the high statistical heterogeneity we did not pool the results of the three trials. • Two trials reported infection-related adverse events (Knauf 2009; Rummel 2009). In one trial (Knauf 2009) the rate of grade 3 or 4 infection was higher (8%, 13 of 161 patients) in the bendamus- tine group compared to chlorambucil (3%, 5 of 151 patients). In another trial that rate was decreased with bendamustine therapy (95 of 260 patients) compared to CHOP (121 of 253 patients) (Rummel 2009).
	4. Fazit der Autoren: As none of the currently available chemotherapeutic protocols for induction therapy in indolent B cell lymphoid malignancies confer a survival benefit and due to the improved progression-free survival in each of the included trials, and a similar rate of grade 3 or 4 adverse events, bendamustine may be considered for the treatment of patients with indolent B cell lymphoid malignancies. However, the unclear effect on survival and the higher rate of adverse events

	compared to chlorambucil in patients with CLL/SLL does not support the use of bendamustine for these patients. The effect of bendamustine combined with rituximab should be evaluated in randomised clinical trials with more homogenous populations and outcomes for specific subgroups of patients by type of lymphoma should be reported. Any future trial should evaluate the effect of bendamustine on quality of life. 5. <u>Anmerkungen:</u> ***der Autoren:*** • Due to the clinical heterogeneity and the small number of trials and patients, it is impossible to draw clear conclusions based on the results. • Trials were diverse in the type of included patients: the type of lymphoma, the treatment line, the type of bendamustine-containing protocol and the type of comparator regimen. • No reports on subgroups of patients according to type of lymphoma were avail- able in the included trials. • In none of the trials were the patients and caregivers blinded to allocated treatment. ***der FBMed:*** nur die Intervention (Bendamustin-Gabe) einer Studie (**RCT von Rummel et al. 2010**; *vgl. Studienmerkmale in **Anlage 1***) entspricht der deutschen Zulassung von Bendamustin [*Monotherapie bei indolenten NHL bei Patienten mit Progression während oder innerhalb von 6 Monaten nach Behandlung mit Rituximab-haltiger Therapie*]

Systematische Reviews

Rourke et al., 2010: [4] Review of clinical trials conducted in Waldenstrom macroglobulinemia and recommendations for reporting clinical trial response in these patients.	1. **Fragestellung**: Review of clinical trials conducted in Waldenstrom macroglobulinemia
	2. Methodik ***Population***: Patients with WM ***Intervention/Komparator:*** Different pharmacological treatment options ***Endpunkte***: Progressionsfreies Überleben, Zeit bis zur Progression, Ereignisfreies Überleben, Dauer des Ansprechens ***Suchzeitraum (Aktualität der Recherche)***: Systematische Literaturrecherche in PubMed, Medline, Cochrane. Kein Suchzeitraum angegeben. ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** A total of 44 clinical trials were found in this search. Of these, 11 were performed in patients with untreated WM, 14 in patients with relapsed or refractory WM, 17 in both upfront and relapsed or refractory WM, and two studies did not provide this information.
	3. Ergebnisdarstellung <u>In general:</u> Single agents tested in WM included alkylating agents such as chlorambucil, nucleoside analogs such as fludarabine and cladribine, and monoclonal anti-CD20 antibody rituximab. • *Chlorambucil*: There were two large clinical trials using chlorambucil in WM. One was a phase 3 and one a retrospective review of 167 patients. In beiden Studien wurde Chlorambucil allerdings als ,,upfront'' Therapie gegeben und sind daher nicht relevant für die Population von Interesse. • Studien zu ,,relapsed/refractory'' Patienten untersuchten folgende, nicht in Deutschland zugelassene Wirkstoffe: Cladribine, Fludarabine, Rituximab, Bortezomib, Thalidomide, Atacicept, Perifosine, Everolimus, PR-171
	4. Anmerkungen/Fazit der Autoren ---
Colosia A et al. 2014: [2] Clinical Efficacy and Safety in	1. **Fragestellung**: This review was designed to systematically collect and review information on the clinical efficacy and safety of current non-ASCT treatments for R/R DLBCL and to perform a meta-analysis if possible. Because we anticipated a paucity of randomized controlled trials

Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Systematic Literature Review	(RCTs), we also planned to determine the types of regimens being evaluated in single-arm studies and their individual efficacy.
	2. Methodik ***Population***: R/R DLBCL who were not eligible to receive high-dose therapy (HDT) with stem cell transplantation (SCT) (autologous or allogeneic). ***Intervention/Komparator:*** Nicht spezifiziert ***Endpunkt****e*: Nicht spezifiziert ***Suchzeitraum (Aktualität der Recherche)***: 1997 – 8/2012 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 4 RCT (5 Publikationen) 3 vergleichende, nicht randomisierte Studien 48 einarmige Studien ***Qualitätsberwertung der Studien:*** Quality assessment for RCTs was performed based on guidance in the National Institute for Health and Care Excellence “Single Technology Appraisal (STA) Specification for Manufacturer/ Sponsor Submission of Evidence 2009”19 and adapted from the Centre for Reviews and Dissemination’s guidance for undertaking reviews in health care.
	3. Ergebnisse **RCTs:** The treatment groups in all 4 trials were similar at baseline. One of the studies reported being a single-blind study with no further explanation, but given the nature of the disease and treatments, presumably the assessor was blinded. Two other studies gave no information regarding blinding. The fourth study was reported in conference abstracts, and no details were given about blinding. Information on dropout rates was presented in 2 of the RCTs but not in the other 2 RCTs.

Table 2 Comparative Studies Involving Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Efficacy Data

Reference	No. of Patients[a]	ORR (%)[b]	Duration of Response, mo	Median PFS	Median OS
RCTs					
Aribi et al, 2010[21]	96 with DLBCL: ESHAP, n = 48 GDP, n = 48	ESHAP, 55 GDP, 63 *P* = .01	NR	NR 3-year PFS, %[c] (95% CI): ESHAP, 10.9 (8.2-13.7) GDP, 20.5 (16.3-24) *P* = .0003	NR 3-year OS, %[d] (95% CI): ESHAP, 11.8 (8.9-14.6) GDP, 20.5 (16.5-24.5) *P* = .001
Aviles et al, 2010[22]	100 with DLBCL: ESHAP, n = 53 R-ESHAP, n = 47	ORR (95% CI) ESHAP, 62 (55-69) R-ESHAP, 60 (50-69)	NR	5-year PFS, %[e] (95% CI): ESHAP, 51 (43-60) R-ESHAP, 50 (42-58) *P* = .6 (NS)	5-year OS, %[f] (95% CI): ESHAP, 31 (24-38) R-ESHAP, 26 (21-39) *P* = .8 (NS)
Gisselbrecht et al, 2010[13]	388 with DLBCL: R-ICE, n = 197 R-DHAP, n = 191	R-ICE, 63.5%[g] R-DHAP, 62.8%[g]	NR	NR 3-year PFS, all patients[h] R-ICE, 31% R-DHAP, 42% *P* = .4	NR 3-year OS, all patients[h] R-ICE, 47% R-DHAP, 51% *P* = .4
Morschhauser et al, 2011[23] and Cartron et al, 2010[24]	40 Low-dose obinutuzumab, 10 with DLBCL High-dose obinutuzumab, 15 with DLBCL	Low-dose obinutuzumab, 30 High-dose obinutuzumab, 27	3 responders in low-dose group: 6.3, 8.6, 9.8 5 responders in high-dose group: 3.1, 3.1+, 5.8, 16.5+, 19.5	Low-dose, 1.9 mo (range, 0.3-15.7 mo) High-dose, 2.7 mo (range, 0.2-22.3 mo)	NR

Abbreviations:
ASCT = autologous stem cell transplantation;
CHOP = cyclophosphamide, doxorubicin, vincristine (Oncovin), prednisone;
CI = confidence interval; C -MEP= carboplatin, mitoxantrone,
etoposide, prednisone;
DLBCL = diffuse large B-cell lymphoma;
ESHAP = etoposide, cisplatin, methylprednisolone (solumedrol), cytarabine (Ara-C);
GDP = gemcitabine, cisplatin, dexamethasone;
H-I/H =
high-intermediate/high;
ICE =ifosfamide, carboplatin, etoposide;
L/L-I = low/low-intermediate;
MEP = mitoxantrone, etoposide, prednisone;
NR = not reported; NS = not significant;
ORR = objective; response rate; OS =overall survival; PFS= progression-free survival;
RCT= randomized controlled trial;
R-DHAP= rituximab plus dexamethasone, cytarabine [Ara-C], cisplatin;
R-ESHAP= rituximab plus etoposide, cisplatin, methylprednisolone (solumedrol), cytarabine (Ara-C);
R-ICE= rituximab plus ifosfamide, carboplatin, etoposide; sAAIPI = second-line age-adjusted International Prognostic Index.
[a]Number of patients with relapsed/refractory (R/R) DLBCL. For RCTs, the number of patients presented is the number randomized.
[b]Cheson criteria.
[c]Progression-free survival was defined as survival without recurrence (no relapse or signs of progression after treatment).
[d]The Aribi et alarticle presents 2 sets of 3-year OS and PFS outcomes. The outcomes shown in the table of this report were taken from the text in the Results section of the article. The alternative
outcomes were presented in Table 2 of the article but were not called "3-year" outcomes; however, these were the numbers summarized in the Discussion section as 3-year outcomes.
[e]PFS was defined as the time from study entry until disease progression.
[f]Overall survival was defined as the time from start of treatment to death regardless of cause.
[g]Overall response rates were determined after salvage chemotherapy and before ASCT.

[h]Of the 398 patients in this study, 211 underwent ASCT; survival outcomes include patients who did and those who did not undergo ASCT.

Keine der eingeschlossenen Studien schließt Patienten mit Morbus Waldenström ein, obwohl danach gesucht wurde

5. Fazit der Autoren

The evidence gathered in this systematic review suggests that there is a paucity of high-quality comparative evidence regarding treatments used for R/R DLBCL. Response rates reported in the comparative and noncomparative studies for R/R DLBCL varied widely. Although data from the comparative studies could not be evaluated collectively because of a lack of common comparators, the single-arm studies also could not be assessed directly in relation to each other through meta-analysis because the sparse patient data

	provided precludes adjustment for differences in potentially prognostic patient characteristics. A visual assessment of outcomes from single-arm trials suggests that monotherapies are typically associated with fewer responses and shorter PFS than multidrug regimens and that regimens with more than 2 drugs may be more effective than 2-drug regimens. Another impression is that rituximab contributes little additional effect to regimens with more than 2 drugs. This interpretation is consistent with outcomes from the single comparative study of ESHAP with or without rituximab. However, the few studies with survival outcomes and the single-arm nature of most of the studies in this review do not allow definitive conclusions regarding the role of rituximab in R/R DLBCL. Nonetheless, rituximab is commonly used in the R/R setting in combination with chemotherapy or as a single agent. **6. Anmerkungen der FBMed:** Keine der eingeschlossenen Studien schließt Patienten mit Morbus Waldenström ein

Leitlinien

Alberta Provincial Hematology Tumour Team, 2014. [1] Lymphoma. Clinical Practice Guideline. LYHE-002, Version 8	**Fragestellung** • What are the diagnostic criteria for the most common lymphomas? • What are the staging and re-staging procedures for Hodgkin and non-Hodgkin lymphomas? • What are the recommended treatment and management options for Hodgkin and non-Hodgkin lymphomas? • What are the recommended follow-up procedures for patients with malignant Hodgkin and non-Hodgkin lymphoma?
	Methodik ***Grundlage der Leitlinie*** This updated guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team. Members of this team include hematologists, medical oncologists, radiation oncologists, surgical oncologists, nurses, nurse-practitioners, hematopathologists, and pharmacists. Updated evidence was selected and reviewed by members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. • systematische Recherche • transparente Ergebnisdarstellung • Empfehlungen sind mit Literaturstellen verknüpft • Formaler Konsensusprozess nicht beschrieben ***Suchzeitraum*** 1950 – 10/2011, Update der Version von 2009 ***Population***: adults over 18 years of age ***LoE und GoR*** nicht angegeben (binäre Empfehlungen basierend auf Literatur) ***Sonstige methodische Hinweise*** Leitlinie hat limitierte methodische Qualität (keine Beschreibung des Konsensprozesses, keine Angaben zur Literaturbewertung, kein LoE/GoR)
	3. Ergebnisse ***Indolent Lymphomas (Excluding Follicular Histology)*** Indolent lymphomas should generally be treated similarly to follicular grade 1-2 lymphomas.

(vgl. unten)

Table 6. Treatment of indolent lymphomas.(125)

Stage	Treatment
Limited	IFRT (24Gy/12 - 30Gy/20)
Advanced	**Asymptomatic**: observation until treatment indication **Symptomatic:** • majority should receive B-R, then rituximab maintenance • alternatives in special situations include IFRT, fludarabine, or chlorambucil

Recurrent CD20+ indolent B-cell lymphomas should be considered for rituximab therapy alone (375mg/m2 weekly x 4) or rituximab plus chemotherapy (B-R, R-fludarabine, R-FC, R-FND, R-CVP), or chemotherapy alone (chlorambucil, fludarabine, etoposide, CEPP, GDP, FND, PEC, or MEP). Patients less than 70 years of age without serious co-morbid disease, and who respond to salvage therapy could be considered for high dose chemotherapy and autologous or allogeneic stem cell transplantation.

General treatment guidelines for LPL/WM.*(1 Studie)* The usual indications for starting patients with LPL/WM on active therapy consist of clinical evidence of adverse effects of the paraprotein (HVS with neurological or ocular disturbance, peripheral neuropathy, amyloidosis, symptomatic cryoglobulinemia), symptomatic anemia (Hb<100g/L), platelets <100, progression to high-grade lymphoma, significant adenopathy or organomegaly, or constitutional symptoms.

• *Plasmapheresis:* 1-2 procedures, exchanging 1-1.5 calculated plasma volumes, are advised for the treatment of HVS in WM, followed by chemotherapy to prevent paraprotein re-accumulation. In patients who are drug-resistant, plasmapheresis may be indicated for long-term management. Although there are few studies that consider the role of plasma exchange in the treatment of cryoglobulinemia, there is a clear rationale for its use. The treatment room should be warm and blood warmers used in the cell separator circuit to prevent precipitation during the procedure.

• *Chemotherapy:* The most common initial chemotherapy for LPL is B-R followed by rituximab maintenance, similar to other indolent B-cell lymphomas. Alkylating agent-based therapy or purine analogues are also reasonable for the initial and subsequent treatment of WM, especially for older patients with significant co-morbid illnesses. There is no consensus on the duration of treatment with cladribine or fludarabine, or on which purine analogue is superior. While fludarabine is more active than CAP as salvage therapy, neither of these therapies has been shown to offer survival benefit over another. Rituximab is active in the treatment of WM but associated with the risk of transient exacerbation of clinical effects of the disease and should be used with caution in patients with symptoms of hyperviscosity and/or IgM levels >40 g/L. A prospective randomized controlled trial demonstrated superior response rates and progression-

free survival rates with R-CHOP compared to CHOP alone for LPL. In retrospective studies, purine analogue therapy is associated with higher rates of prolonged cytopenias, infections, secondary MDS/AML, and transformation to large cell lymphoma when compared to therapy with alkylating agents. Autologous SCT is used with increasing frequency for LPL, and as such, purine analogue therapy and chlorambucil should be avoided as initial therapy for transplant-eligible patients to prevent stem cell damage and decrease the risk of blood mobilization failure in the future.

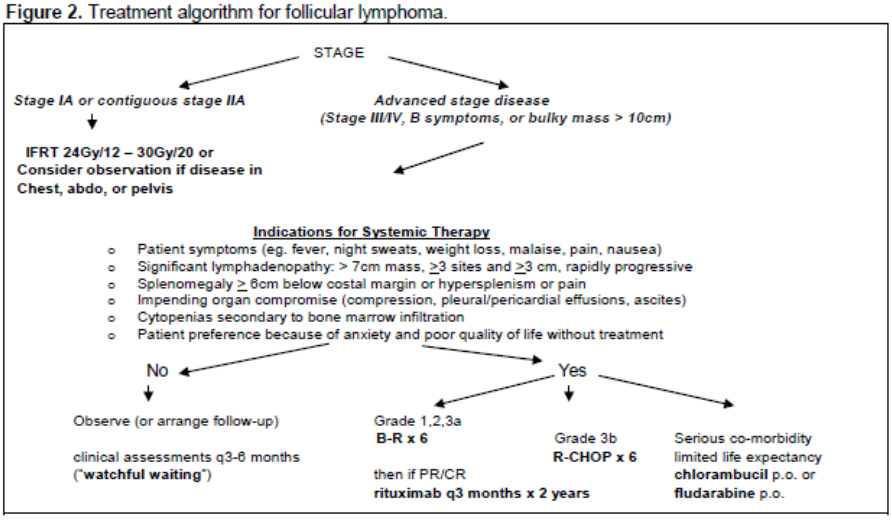
- Thalidomide is of potential use in the treatment of patients who have previously received alkylating agents, purine analogues and antibody therapy. Other agents are currently only recommended in the context of clinical trials.
- High-dose therapy supported by autologous SCT has a role in the management of selected patients with WM who have chemosensitive primary induction failure or relapsed disease (preferably first relapse). Autologous stem cell collection is often not possible for patients who have received more than 4 months of prior chlorambucil or purine analogue (fludarabine or 2-CDA) therapy. As with other indolent lymphomas, allogeneic SCT should be considered at second relapse, before the disease develops absolute chemoresistance.

Follicular Lymphoma

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

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

Figure 2. Treatment algorithm for follicular lymphoma.



For newly diagnosed patients with peripheral stage IA or contiguous non-bulky stage IIA follicular lymphoma, even if the patient is asymptomatic.

Initial therapy of advanced stage disease (stage III/IV, B symptoms, or bulky stage I/II).

Indications for systemic therapy (usually stage III/IV or bulky stage I/II) include:

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

For patients who do not have any of the above indications for therapy, the recommended approach is to observe with (or arrange) follow-up clinical assessments every 3-6 months ("watchful waiting").

For grades 1,2,3a follicular lymphoma who have an indication for therapy, the recommended therapy involves 6 cycles of B-R (bendamustine-rituximab) chemotherapy, followed in responding patients by 2 years of maintenance rituximab (375mg/m_2 IV single dose every 3 months for total of eight doses). In patients with previously untreated indolent lymphoma, B-R can be considered as a prefered first-line treatment approach to R-CHOP because of increased progression-free survival and fewer side-effects. Patients who have limited life-expectancy from serious co-morbid illness, or who do not want intravenous therapy, may be treated with oral chlorambucil or fludarabine monotherapy.

For grade 3b follicular lymphoma or DLBCL with areas of follicular lymphoma, R-CHOP should be used. Rituximab maintenance has not been proven effective following R-CHOP therapy for large B-cell

	lymphoma, and therefore is not recommended. ***Therapy of relapsed disease.*** Therapeutic recommendations for recurrent follicular lymphoma need to be individualized, and no one recommendation is suitable for all patients. Numerous factors need to be taken into consideration before recommending therapy for recurrent follicular lymphoma, including: • Patient Factors: Age, co-morbidity, symptoms, short vs. long-term goals, preservation of future options, reimbursement/ability to pay for expensive treatments, acceptance of risks/toxicities of treatment option relative to potential benefit (RR, PFS, OS). • Disease Factors: Stage, sites of involvement, grade, transformation, prior therapy, time from prior therapy (disease-free interval). For example, previously healthy patients younger than 65 years who relapse within 2 years of initial chemotherapy have a median life expectancy of <5 years, and are best managed with HDCT/ autologous SCT. HDCT/SCT maximizes the length of disease control for all patients less than 65 years, regardless of length of initial remission, and as such is a reasonable treatment option for those who accept potential risks/toxicities. Conversely, some patients may be best managed by repeating their initial treatment regimen if they achieved an initial remission greater than 2 years. Other patients should be changed to a second line standard-dose chemotherapy regimen (bendamustine, chlorambucil, CVP, fludarabine, etoposide, CEPP, GDP, FND, PEC, or MEP). For patients who have rituximab, it is reasonable to re-treat with rituximab (probably in the weekly x 4 dose schedule) alone or with chemotherapy as long as the patient attained at least a 6 month remission to prior rituximab-based therapy. Rituximab maintenance should only be used once in the course of a patient's disease (first remission or first relapse). Patients younger than 70 years without serious co-morbid disease, and who respond to salvage therapy should be considered for high dose chemotherapy and autologous (relapse 1-2) or allogeneic stem cell transplantation (relapse 2-3). Palliative, symptomatic care (possibly including palliative IFRT 4Gy/2 fractions) is usually the best option for patients who were refractory to their 2 most recent treatment regimens, those with CNS involvement, or those with an ECOG score of 3-4.
Owen RG et al., 2014: [3] Guidelines on the diagnosis and management of Waldenström macroglobulinaemia	British Committee for Standards in Haematology
	Methodik ***Grundlage der Leitlinie*** The guideline group was selected to be representative of UK experts in Waldenström macroglobulinaemia (WM). Recommendations are based on the systematic review of published English language literature up to July 2013 and including data presented in abstract form at the 2012 American

	Society of Hematology meeting. The writing group produced a draft guideline, which was reviewed and revised by members of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was further reviewed by a sounding board of approximately 50 UK haematologists and BCSH and the British Society for Haematology Committee and further consensus amendments were made. ***Suchzeitraum*** Bis Juli 2013 ***LoE und GoR*** GRADE ***Sonstige methodische Hinweise*** Prozess der Empfehlungsentwicklung nicht vollständig transparent
	3. Ergebnisse ***Summary of key recommendations*** ***Treatment at diagnosis*** 1 Patients with symptomatic WM should receive a rituximab-containing regimen (Grade A1). Appropriate regimens include dexamethasone + rituximab + cyclophosphamide (DRC), bendamustine + rituximab (BR), fludarabine + rituximab (FR), fludarabine + cyclophosphamide + rituximab (FCR) and cladribine + rituximab (Clad-R). The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for stem cell transplantation (SCT) (Grade B1). 2 Given the risk of IgM flare, careful monitoring of all patients receiving rituximab is required with monitoring of sequential IgM, clinical assessment for hyperviscosity (HVS) and monitoring of plasma viscosity (PV) if available (Grade A1). The introduction of rituximab should be deferred in patients considered at a higher risk of HVS, this being arbitrarily defined by an IgM M-protein >40 g/l and/or a PV >4 centipoise (cP) (Grade C1). 3 Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP-R) should not be used as primary therapy in WM (Grade B1). 4 Chlorambucil remains suitable therapy in elderly frail patients (Grade B1). 5 The use of bortezomib is not routinely recommended as primary therapy outside the context of a clinical trial (Grade B2).

	6 There is insufficient evidence to support the use of maintenance rituximab (Grade C2). ***Treatment at relapse*** 1 Repeat bone marrow aspirate and trephine assessment and CT scanning should be performed prior to the reintroduction of treatment (Grade B1). 2 Patients who remain asymptomatic despite serological evidence of progression can be observed until clinical symptoms occur (Grade A1). 3 Patients should receive a rituximab-containing regimen if CD20 expression is documented. Appropriate regimens include FR, FCR, Clad-R, BR and DRC. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for SCT (Grade B1). 4 Retreatment with primary therapy may be appropriate in some patients (Grade B1). 5 Bortezomib-containing regimens are suitable in the relapse setting. Weekly regimens are preferable, given the neurological toxicity associated with the biweekly schedules. Prophylaxis against herpes zoster reactivation is recommended (Grade B1). 6 Alemtuzumab is a potential option in refractory disease (Grade B1). Surveillance for cytomegalovirus (CMV) reactivation is recommended. ***Treatment for histological transformation*** 1 A diagnosis of transformation requires histological confirmation (Grade A1). 2 Patients who are suitable for intensive therapy should receive regimens currently employed for primary diffuse large B-cell lymphoma (DLBCL) (Grade B1). 3 Younger responding patients are candidates for a stem cell transplant (SCT) procedure and should be discussed with a transplant centre (Grade B2). ***Haemopoietic SCT*** 1 Autologous SCT is a feasible therapeutic option for relapsed WM in younger, fitter patients with aggressive disease [short progression-free survival (PFS), histological transformation] (Grade B2). 2 Allogeneic SCT may be considered in selected younger patients with relapsed WM and an aggressive clinical course (short PFS, histological transformation) (Grade B2).

	3 Autologous and allogeneic SCT should only be performed in the setting of chemosensitive disease with at least a partial response to reinduction therapy (Grade A1). ***Hyperviscosity syndrome*** 1 Plasma exchange is recommended for all patients with HVS irrespective of PV (Grade A1). 2 As per previous guidance 1–2 procedures, exchanging 1–1.5 calculated plasma volumes, is advised (Grade A1). 3 Plasma exchange may be indicated in certain asymptomatic individuals depending on the clinical circumstances, recorded plasma viscosities and co-morbidities (Grade C2). ***IgM-related neuropathy*** 1 Neurological examination should be performed in all patients with IgM paraproteins (Grade A1). 2 Collaborative working with a neurologist is encouraged. Anti-MAG serology and nerve conduction studies are recommended in patients with symptomatic peripheral neuropathy (Grade A1). 3 Chemotherapeutic intervention should be considered in patients with disabling or rapidly progressive anti-MAG neuropathy (Grade B1). 4 If chemotherapy is considered appropriate, a rituximabcontaining regimen is appropriate with the final choice of regimen being determined by factors such as performance status, co-morbidities and renal function (Grade B1). ***Cold haemagglutinin disease (CHAD) and cryoglobulinaemia*** 1 Rituximab-based therapy is recommended for patients with symptomatic CHAD. The addition of fludarabine should be considered for patients with adequate performance status and renal function (Grade B1). 2 Cryoglobulinaemia should be considered in patients with IgM monoclonal gammopathy and unexplained purpura, arthralgia, haematuria or peripheral neuropathy (Grade A1). 3 Patients with cryoglobulinaemia should be screened for HCV infection (Grade A1). 4 Patients with symptomatic cryoglobulinaemia may be treated with corticosteroids and rituximab (Grade B1). 5 Patients with symptomatic cryoglobulinaemia and overt WM can be treated with standard therapies (Grade B1).

	Supportive care 1 Antimicrobial prophylaxis should be considered for patients with hypogammaglobulinaemia who develop recurrent bacterial infections (Grade B1). 2 Immunoglobulin replacement therapy should be according to UK Department of Health clinical guidelines (Grade B1). 3 Anti-Pneumocystis jirovecii prophylaxis is recommended in patients requiring intensive and/or immunosuppressive treatment (Grade B1). 4 Anti-herpes simplex virus (HSV) and –herpes zoster virus (HZV) prophylaxis is recommended in patients requiring intensive, immunosuppressive or bortezomibbased therapy (Grade B1). 5 Pneumocystis and herpes prophylaxis is not routinely required in patients treated with alkylating agents or bendamustine (Grade B2). 6 The duration of anti-pneumocystis and herpes prophylaxis is controversial. Recommendations range from a minimum of 2 months post-therapy to awaiting a rise in CD4 count to 0_2 9 109/l (Grade C2). 7 Vaccination against Streptococcus pneumoniae (using a conjugate vaccine) and Haemophilus influenzae type B is encouraged at diagnosis although there is a lack of randomized trials to support vaccination. Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if S. pneumoniae and Haemophilus influenzae type b (HIB) antibody levels have fallen (Grade C1). 8 Annual vaccination against seasonal influenza including novel strains is recommended (Grade C1). 9 Live vaccines, such as polio, H. zoster and yellow fever, should be avoided (Grade A1). 10 Vaccinations should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy (Grade B1).

Anlage 1 – Studienmerkmale des RCT von Rummel et al. (2010) (Quelle: Vidal et al. 2012)

Rummel 2010		
Methods	Allocation generation: not reported Allocation concealment: not reported Blinding: no ITT: no Number of dropouts: 11/219 Median follow-up: 33 months	
Participants	219 randomised, 208 evaluable, adult patients Type of lymphoma: follicular lymphoma, mantle cell lymphoma, lymphoplasmacytic lymphoma, other indolent lymphoma Stage: 93% of patients allocated to bendamustine and 86% allocated to fludarabine stage III/IV Previous treatment: yes Mean age: 68 years (range 38 to 87 years)	
Interventions	Investigational intervention: Bendamustine 90 mg/m^2 on days 1 to 2, and rituximab 375 mg/m^2 on day 1; every 4 weeks, up to 6 cycles Comparator intervention: Fludarabine 25 mg/m^2 on days 1 to 3 and rituximab 375 mg/m^2 on day 1; every 4 weeks, up to 6 cycles	
Outcomes	Progression-free survival Overall survival	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"219 patients ... were randomized ...11 patients were not evaluable due to protocol violations, and were not followed further" Allocation of non-evaluable patients is not reported
Selective reporting (reporting bias)	Low risk	Analyses were done as stated in protocol
Other bias	Unclear risk	Published as an abstract
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded to allocated treatment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone
CLL: chronic lymphocytic leukaemia
CR: complete response
ITT: intention-to-treat
iv: intravenous
PR: partial response
SLL: small lymphocytic lymphoma

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 26.03.2015**

#	Suchfrage
1	MeSH descriptor: [Waldenstrom Macroglobulinemia] explode all trees
2	(waldenstrom* or waldenström* or waldenstroem* or primary) and (macroglobulinemia* or macroglobulinaemia*):ti,ab,kw (Word variations have been searched)
3	(lymphoplasmacytic or lymphoplasmocytic or lymphoplasmacytoid or lymphoplasmocytoid or lpl):ti,ab,kw (Word variations have been searched)
4	(plasmacytoid or plasmocytoid) and lymphocytic:ti,ab,kw (Word variations have been searched)
5	#3 or #4
6	lymphom*:ti,ab,kw (Word variations have been searched)
7	#5 and #6
8	MeSH descriptor: [Lymphoma, Non-Hodgkin] this term only
9	MeSH descriptor: [Lymphoma, B-Cell] this term only
10	(indolent or (b next cell)) and lymphom*:ti,ab,kw (Word variations have been searched)
11	#1 or #2 or #7 or #8 or #9 or #10
12	#1 or #2 or #7 or #8 or #9 or #10 Publication Year from 2010 to 2015, in Cochrane Reviews (Reviews only), Other Reviews and Technology Assessments

SR, HTAs in Medline (PubMed) am 26.03.2015

#	Suchfrage
1	waldenstrom macroglobulinemia[MeSH Terms]
2	((waldenstrom*[Title/Abstract]) OR waldenstroem*[Title/Abstract]) OR primary[Title/Abstract]
3	(macroglobulinemia*[Title/Abstract]) OR macroglobulinaemia*[Title/Abstract]
4	(#2) AND #3
5	((((lymphoplasmacytic[Title/Abstract]) OR lymphoplasmocytic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract]) OR lymphoplasmocytoid[Title/Abstract]) OR lpl[Title/Abstract]
6	(((plasmacytoid[Title/Abstract]) OR plasmocytoid[Title/Abstract])) AND lymphocytic[Title/Abstract]
7	(#5) OR #6
8	lymphom*[Title/Abstract]
9	(#7) AND #8
10	((#1) OR #4) OR #9
11	((#10) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]))
12	(#10) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract]

	OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
13	(#11) OR #12
14	((#13) AND ("2010/03/01"[PDAT] : "2015/03/26"[PDAT]))

Leitlinien in Medline (PubMed) am 26.03.2015

#	Suchfrage
1	waldenstrom macroglobulinemia[MeSH Terms]
2	((waldenstrom*[Title/Abstract]) OR waldenstroem*[Title/Abstract]) OR primary[Title/Abstract]
3	(macroglobulinemia*[Title/Abstract]) OR macroglobulinaemia*[Title/Abstract]
4	(#2) AND #3
5	((((lymphoplasmacytic[Title/Abstract]) OR lymphoplasmocytic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract]) OR lymphoplasmocytoid[Title/Abstract]) OR lpl[Title/Abstract]
6	(((plasmacytoid[Title/Abstract]) OR plasmocytoid[Title/Abstract])) AND lymphocytic[Title/Abstract]
7	(#5) OR #6
8	lymphom*[Title/Abstract]
9	(#7) AND #8
10	((#1) OR #4) OR #9
11	"Lymphoma, Non-Hodgkin"[Mesh:NoExp]
12	"Lymphoma, B-Cell"[Mesh:NoExp]
13	(((indolent[Title/Abstract]) OR b cell[Title/Abstract])) AND lymphom*[Title/Abstract]
14	((#11) OR #12) OR #13
15	(#10) OR #14
16	(#15) AND (((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title])
17	((#16) AND ("2010/03/01"[PDAT] : "2015/03/26"[PDAT]))

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1. **Alberta Provincial Hematology Tumour Team**. Lymphoma. Clinical Practice Guideline. LYHE-002, Version 8, Stand: Dezember 2014. Edmonton (Alberta): Alberta Health Services, Cancer Care 2014; http://www.albertahealthservices.ca/hp/if-hp-cancer-guide-lyhe002-lymphoma.pdf, Zugriff am 24.03.2015.

2. **Colosia A, Njue A, Trask PC, Olivares R, Khan S, Abbe A, Police R, Wang J, Ruiz Soto R, Kaye JA, Awan F**. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review. Clin Lymphoma Myeloma Leuk 2014; 14 (5): 343-55.

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5. **Vidal L, Gafter GA, Gurion R, Raanani P, Dreyling M, Shpilberg O**. Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia. Cochrane Database of Systematic Reviews 2012; (9): CD009045.