

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: September 2014

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

Ibrutinib [zur Behandlung des Mantelzell-Lymphoms]

Kriterien gemäß 5. Kapitel § 6 Verfo

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.

Siehe Tabelle „II. Zugelassene Arzneimittel im Anwendungsgebiet“

Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.

- Allogene Stammzelltransplantation
- Strahlentherapie
- Autologe Stammzelltransplantation

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen

- Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Stand: 3. Dezember 2013):
 - o Off-Label-Indikation für Fludarabin: Kombinationstherapie bei niedrig oder intermediär malignen Non-Hodgkin-Lymphomen der B-Zellreihe
- Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Pixantron vom 16. Mai 2013
 - o Ein Zusatznutzen ist nicht belegt
- Änderung der Richtlinie Methoden Krankenhausbehandlung: Positronenemissionstomographie (PET); PET/Computertomographie (CT) bei malignen Lymphomen vom 21. Oktober 2011

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: IMBRUVICA® ist indiziert zur Behandlung erwachsener Patienten mit rezidiviertem oder refraktärem Mantelzell-Lymphom (MCL).
Temsirolimus L01XE09 Torisel®	<u>Mantelzell-Lymphom</u> Torisel ist angezeigt zur Behandlung von erwachsenen Patienten mit rezidiviertem und/oder refraktärem Mantelzell-Lymphom (mantle cell lymphoma, MCL), (siehe Abschnitt 5.1). (FI Torisel®, 11-2012)
Weitere Arzneimittel mit Zulassung für Non-Hodgkin-Lymphome	
Cytarabin L01BC01 generisch	ARA-cell® 100 mg/ml wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: - refraktären Non-Hodgkin-Lymphomen (FI ARA-cell®, 04-2012)
Doxorubicin L01DB01 generisch	Non-Hodgkin-Lymphom (FI Doxorubicin Accord, 05-2013)
Trofosamid L01AA07 Ixoten®	Dieses Arzneimittel ist ein Zytostatikum. Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet. (FI Ixoten®, 07-2013)
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 (FI Vinblastinsulfat Teva®, 10-2011)
Vincristin L01CA02 generisch	Vincristinsulfat-Teva® wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen (FI Vincristinsulfat-Teva®, 09-2011)
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. (FI Levact®, 12-2010)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (CLL), niedrig maligne Non-Hodgkin-Lymphome, Waldenström Makroglobulinämie. (FI Leukeran®, 04-2012)
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Non-Hodgkin-Lymphome (in Abhängigkeit vom histologischen Typ und vom Krankheitsstadium auch als Monotherapie) - Chronisch lymphatische Leukämie (CLL) nach Versagen der Standardtherapie (Chlorambucil/Prednison) (FI Endoxan®, 09-2013)
Lomustin L01AD02 Cecenu®	Als Bestandteil von Chemotherapieprogrammen der zweiten Linie in der Therapie des Brustkrebses (Mammakarzinom), der Hauttumoren (maligne Melanome), der Tumoren der lymphatischen Organe (Non-Hodgkin-Lymphome und Tumoren des Verdauungstraktes (gastro-intestinale Karzinome). (FI Cecenu®, 09-2012)
Prednisolon H02AB06 generisch	Hämatologie/Onkologie Non-Hodgkin-Lymphome, chronisch lymphatische Leukämie, Morbus Waldenström (FI Dermosolon®, 09-2009)
Prednison H02AB07 generisch	Hämatologie/Onkologie: Non-Hodgkin-Lymphome, Chronisch lymphatische Leukämie, Morbus Waldenström (FI Cutason®, 02-2013)
Pixantron L01DB11 Pixuvri®	Die Monotherapie mit Pixuvri ist indiziert bei erwachsenen Patienten mit mehrfach rezidierten oder therapierefraktären aggressiven Non-Hodgkin-B-Zell-Lymphomen (NHL). Der Nutzen der Pixantron-Behandlung ist nicht erwiesen bei Anwendung als Fünft- und Mehrlinientherapie bei Patienten, die refraktär gegen die vorausgegangene Therapie waren. (FI Pixuvri®, 05-2012)

Quellen: AMIS-Datenbank, Fachinformationen



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

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Indikation für die Recherche bei Wirkstoff (evtl. Markenname): Ibrutinib

Anwendungsgebiet: indiziert zur Behandlung erwachsener Patienten mit rezidiviertem oder refraktärem Mantelzell-Lymphom (MCL)

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 evidenzbasierten systematischen Leitlinien zur Indikation „erwachsene Patienten mit rezidivierten oder refraktärem Mantelzell-Lymphom (MCL)“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 09.09.2014 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC, Clinical Evidence. Aufgrund der onkologischen Indikation wurde zusätzlich in

folgenden Datenbanken bzw. Internetseiten folgender Organisationen gesucht: DGHO-Onkopedia, NCCN, ESMO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 887 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 12 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CHOP-R	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CoI	Conflicts of Interest
DAHTA	Deutsche Agentur für Health Technology Assessment
DGHO-Onkopedia	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
ESMO	European Society for Medical Oncology
FCM	Fludarabine, Cyclophosphamide, Mitoxantrone
FCM-R	Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone
FL	follicular lymphoma
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendation
HR	Hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
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
OS	Overall survival
PFS	Progression-free survival
RR	Risk ratio
SCT	Stem Cell Transplantation
TRIP	Turn Research into Practice Database
CRD	Centre for Reviews and Dissemination (York)
REM	Random effects model
SR	Systematic review
hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone

IQWiG Berichte/G-BA Beschlüsse

Für die Fragestellung wurden keine IQWiG Berichte/G-BA Beschlüsse identifiziert.

Cochrane Reviews

Für die Fragestellung wurden keine Cochrane Reviews identifiziert.

Systematische Reviews

Njue A, et al. 2014 [1] Clinical Efficacy and Safety in Relapsed/Refractory Mantle Cell Lymphoma: A Systematic Literature Review	1. Fragestellung We therefore undertook to systematically evaluate published information on the efficacy and safety of treatments used in patients with relapsed/refractory Mantle cell lymphoma (R/R MCL).
	2. Methodik Population: patients with R/R MCL, 18 years or older, ineligible to receive high-dose chemotherapy with/or stem cell transplant (autologous or allogeneic) Intervention: chemotherapy Komparator: not previously stated Endpunkt: not previously stated Suchzeitraum: from January 1, 1997, to August 2, 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 59 MCL studies, 6 comparative, 5 RCTs/291 (two published in abstract form) Qualitätsbewertung der Studien: based on guidance in the NICE "Single Technology Appraisal specification for manufacturer/sponsor submission of evidence 2009", adapted from the CRD guidance for undertaking reviews in health care, parameters: randomization, masking of patients and clinicians, concealment of treatment allocation, similarities between treatment groups at baseline, documentation of dropouts, intent-to-treat (ITT) analysis
	3. Ergebnisdarstellung (siehe auch Abbildung 1 im Anhang dieser Synopse) <ul style="list-style-type: none">• only 5 of the 59 MCL studies RCTs, no treatment appeared in more than 1 study → meta-analysis not feasible• only phase III studies with medications approved for Germany

reported here
Forstpointer R, et al. 2004:

- FCM-R regimen significantly prolonged survival: median OS not reached vs. FCM = 11 months ($p = 0,0042$); median follow-up, 18 months)

Hess G, et al. 2009 und NCT00117598 (OPTIMAL):

- led to approval of temsirolimus by the EMA
- approved dose of temsirolimus is 175/75 mg
- ORR in temsirolimus 175/75 mg group significantly greater than in investigator's choice group (22.2% vs. 1.9%; $p = 0,0019$), but 175/25 mg group was not (5.6%; $p = 0,6179$)
- PFS significantly longer in temsirolimus 175/75 mg or temsirolimus 175/25 mg than in investigator's choice of therapy (median 4,8 months; 3,7 months; 1,8 months, respectively; $p < 0,0001$ for both temsirolimus groups vs. investigator's choice therapy)
- study was not powered to detect a difference between groups in OS
- median durations of response (3,6 months with temsirolimus 175/25 mg; 7,1 months with temsirolimus 175/75 mg)

comparing across comparative studies

- PFS of temsirolimus 175/75 mg monotherapy appeared to be less than the PFS reported for R-FCM combination regimen

Hematologic Toxicities: Comparative and Noncomparative Studies

- Grade 3/4 hematologic adverse events reported in $\geq 10\%$ of patients
- incidence of Grade 3/4 thrombocytopenia significantly greater in temsirolimus 175/75 mg group than in the investigator's choice group ($p = 0,020$)
- incidence of Grade 3/4 leukopenia significantly greater in the investigator's choice group ($p = 0,014$)
- main Grade 3/4 hematologic events among noncomparative studies: thrombocytopenia, neutropenia
- thrombocytopenia reported in all studies

4. Anmerkungen/Fazit der Autoren

The small number of RCTs in R/R MCL precludes identifying an optimal treatment. Small sample sizes, infrequent reporting of OS and PFS, and limited information on patient characteristics made a comparison of results difficult. High-quality comparative studies of novel therapies that have the potential to demonstrate OS advantages in R/R MCL are needed.

5. Hinweise durch FB Med

- *work supported by Sanofi*
- *Disclosure: authors are employees of RTI Health Solutions*

	<p><i>and provided consulting services to Sanofi, are/were employees of Sanofi, provided consulting services to Sanofi and are supported by a Career Development Award from the Lymphoma Research Foundation</i></p>
<p>Gao G, et al. 2010 [2] A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma</p>	<p>1. Fragestellung We performed this study to ... investigate the effects and toxicities of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma.</p> <hr/> <p>2. Methodik</p> <p>Population: patients older than 18 years, histologically proven B-cell non-Hodgkin's lymphoma, regardless of stage of disease and previous therapy received Intervention: R-chemo Komparator: same chemotherapy alone Endpunkt: overall survival, secondary (progression free survival, event-free survival, time to treatment failure, time to progression, adverse events)</p> <p>Suchzeitraum: 1966 - 2008 Anzahl eingeschlossene Studien/Patienten (Gesamt): 12/4 996</p> <p>Qualitätsbewertung der Studien: using the Jadad composite scale with internal validity parameters: randomization, masking of patients and clinicians, concealment of allocation, documentation of dropouts and withdrawals, intent-to-treat analysis</p> <p>Heterogenität: tested, p-value less than 0,1 defined as heterogenous, than REM applied, sensitivity analyses performed</p> <p>Publication bias: funnel plot generated or a linear regression test performed</p> <hr/> <p>3. Ergebnisdarstellung</p> <p>Eine von 12 Studien untersuchte Effekte bei Menschen mit R/R MCL: Forstpointer R, et al. 2004 (siehe auch Extraktion aus Njue A, et al. 2014).</p> <ul style="list-style-type: none"> • Jadad score: 3 (of 5) points – ITT analysis performed, adequate allocation concealment, 13 % dropouts, • clinical stage III/IV <p>Zwei von 12 Studien untersuchten Effekte in der Erstlinie bei Menschen mit MCL: Herold M, et al. 2004; Lenz G, et al. 2005.</p> <p>OS (11 Studien, n = 4 933)</p> <ul style="list-style-type: none"> • only a trend toward improving OS in the subgroup of patients with MCL who had received R-chemo • n = 260, too small to yield statistical significance (RR 1,16;

	<p>95 % CI 1,00 – 1,36; p = 0,06) disease control (11 Studien, n = 4 903)</p> <ul style="list-style-type: none"> • only a trend toward improving OS in the subgroup of patients only a trend toward improving disease control in the subgroup of patients with MCL who had received R-chemo • n = 212, too small to yield statistical significance (RR 1,82; 95 % CI 0,99 – 3,34; p = 0,05) <p>adverse events</p> <ul style="list-style-type: none"> • not uniformly described • most often reported grade 3 and 4 adverse events were hematologic toxicity (i.e., leukocytopenia, thrombocytopenia, or granulocytopenia), fever, and infection • fever or leukocytopenia statistically significantly higher in R-chemo than in chemotherapy alone: OR 4,18; 95 % CI 1,55 – 11,28; p < 0,001 and OR 1,32; 95 % CI 1,10 – 1,58; p = 0,003, respectively) • no difference with respect to the risk of treat-related deaths <p>4. Anmerkungen/Fazit der Autoren There is a clear need for more prospective randomized trials for patients with relapsed or refractory mantle cell lymphoma. ... R-chemo is superior to chemotherapy alone in patients with B-cell non-Hodgkin's lymphoma, especially for diffuse large B-cell lymphoma and follicular lymphoma.</p> <p>5. Hinweise durch FB Med</p> <ul style="list-style-type: none"> • <i>work supported by Scientific Research Foundation of Huashan Hospital, Fudan University, Shanghai, China</i> • <i>The authors indicated no potential conflicts of interest.</i>
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Leitlinien

<p>Kouroukis T, et al. 2012 [3] Cancer Care Ontario (CCO)</p> <p>Stem Cell Transplantation in Lymphoma</p>	<p>Fragestellung</p> <p>What is the role of stem cell transplantation in the treatment of the various lymphomas?</p> <hr/> <p>Methodik: evidenz- und konsensbasierte LL</p> <p>Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur (update von 2009), informaler Konsensusprozess</p> <p>Suchzeitraum: 2006 through February (week three) 2011</p> <p>Weitere Kriterien für die Qualität einer LL:</p> <ul style="list-style-type: none"> • Bewertung der eingeschlossener Übersichtsarbeiten mit AMSTAR • Bewertung eingeschlossener Leitlinien mit AGREE 2 • Bewertung eingeschlossener RCTs nach Randomisierung, Verblindung, Berechnung von Power und Stichprobengröße,
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	<p>Dauer der Beobachtung, Bericht statistischer Analysemethoden, Bericht und Diskussion der Studienabbrüche, Bericht der finanziellen Untrestützung</p> <ul style="list-style-type: none"> • CCO Stem Cell Transplant Steering Committee provided feedback and helped to draft report <p>LoE: „we do not routinely use quality grading or rating systems to evaluate the quality of studies”, “overall quality of the evidence is evaluated in a more narrative fashion to present the reader with the information necessary for judging the quality of the included studies“</p> <p>GoR: „justification for each recommendation and the degree to which it is based on the evidence directly versus the opinion and consensus of the Working Group must be explicitly stated in the recommendation itself”</p> <p>Sonstige methodische Hinweise</p> <ul style="list-style-type: none"> • Contributing authors disclosed any potential conflicts of interest. • The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care. • berücksichtigte Quellen sind schwache Evidenz • CLL nicht Inhalt der LL
	<p>Freitext/Empfehlungen/Hinweise</p> <p>Mantle Cell Lymphoma (MCL)</p> <p><i>Recommendation:</i> Autologous stem cell transplantation is recommended for patients with MCL in first remission.</p> <p><i>Evidence:</i> This Recommendation was modified slightly from the 2009 Recommendation Report (5) that stated that autologous stem cell transplantation was an option for eligible patients only. This change was made based on Expert Panel consensus and in consideration of a paper on the topic published by Dreyling et al (9) (see Discussion section).</p> <p><i>Recommendation:</i> Select patients with MCL in first or second remission may be considered for allogeneic transplant. Autologous transplantation is also an option for chemo-sensitive patients with MCL in second remission.</p> <p><i>Evidence:</i> This Recommendation was brought forward from the 2009 Recommendation Report (5) and modified slightly to include allogeneic transplant for select patients in first remission based on consensus from the Expert Panel.</p> <p><i>Discussion:</i> The recommendation for autologous stem cell transplant for MCL at the time of first remission was strengthened from being an option to being recommended. This was based on two abstracts reports with longer follow-up than the original trial publication (9). Both abstracts suggest an overall survival benefit for MCL patients who received high-dose chemotherapy and autologous stem cell transplant following induction with CHOP-R type chemotherapy. It was also believed that in select patients with MCL with high-risk features, allogeneic transplantation in first remission might be considered on a case-by-case basis.</p> <p>5. Imrie K, Rumble RB, Crump M. Stem Cell Transplantation in Adults. Toronto: Cancer Care Ontario; 2009 [cited 2011 March 28, 2011]; Available from: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=35448.</p> <p>9. Dreyling MH, Hoster E, Van Hoof A, Metzner B, Gisselbrecht C, Pfreundschuh M, et al. Early Consolidation with Myeloablative Radiochemotherapy Followed by Autologous Stem Cell Transplantation in First Remission in Mantle Cell Lymphoma: Long Term Follow up of a Randomized Trial of the. ASH Annual Meeting Abstracts. 2008;112(11):769.</p>

<p>MacEachern J, et al. 2013 [4]</p> <p>Cancer Care Ontario (CCO)</p>	<p>Fragestellung</p> <p>1. What are the relative efficacy and other benefits of fludarabine compared with alternative options when treating patients with advanced-stage follicular and other low grade lymphoma and Waldenstrom's Macroglobulinemia? Outcomes of interest include overall survival, progression-free survival, quality of life, and economic evaluations.</p> <p>2. What are the toxicities of fludarabine?</p>
<p>Treatment with Fludarabine for Patients with follicular and other low grade non-Hodgkin's Lymphoma and Waldenstrom's Macroglobulinemia</p>	<p>Methodik: evidenz- und konsensbasierte LL</p> <p>Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur (update von 2001), informaler Konsensusprozess, External Review by Ontario Clinicians</p> <p>Suchzeitraum (letzte Aktualisierung): January 2000 to December 31, 2012</p> <p>Weitere Kriterien für die Qualität einer LL:</p> <ul style="list-style-type: none"> • Qualität der eingeschlossenen Studien beschrieben <p>LoE: „we do not routinely use quality grading or rating systems to evaluate the quality of studies”, “overall quality of the evidence is evaluated in a more narrative fashion to present the reader with the information necessary for judging the quality of the included studies“</p> <p>GoR: „justification for each recommendation and the degree to which it is based on the evidence directly versus the opinion and consensus of the Working Group must be explicitly stated in the recommendation itself“</p> <p>Sonstige methodische Hinweise</p> <ul style="list-style-type: none"> • Die Gruppe (Hematology Disease Site Group) hält eine Aktualisierung der Empfehlungen von 2001 aufgrund der neuen Literatur für nicht notwendig (siehe unten). • Members of the Hematology DSG disclosed potential conflict of interest information. • The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.
	<p>Freitext/Empfehlungen/Hinweise</p> <p>Recommendations</p> <p><u>Previously Treated Patients with Stage III-IV Low Grade Lymphoma</u></p> <p>Fludarabine is an acceptable option for patients requiring treatment following disease progression after first-line therapy. Other therapies such as chlorambucil with or without prednisone; cyclophosphamide, vincristine, and prednisone; cyclophosphamide, doxorubicin, vincristine, and prednisone; or rituximab may be appropriate alternatives. Choice of treatment should be determined by patient preferences, clinical judgement, and drug availability and should take into account factors such as the route of administration, the risk of infection, and outcomes of</p>

interest.

IV.RESULTS

Klasa et al reported in abstract form (6) preliminary results of a randomized trial comparing fludarabine with CVP in 91 patients with low grade lymphoma who had previously received one to four treatment regimens. Patients were required to have had a response to all previous treatment courses; the dose of cyclophosphamide in patients allocated to CVP was 750 mg/m² given intravenously. Patients receiving fludarabine had a superior two-year progression-free survival (32% vs. 14%; p=0.028). The trial also assessed the time interval to requiring subsequent therapy (two-year treatment-free survival) and found this time was longer in the fludarabine group (41% vs. 20%; p=0.034). No difference in two-year survival was detected (70% vs. 75%; p=0.738). Patients receiving CVP experienced more nausea, vomiting, neurotoxicity, and alopecia. Patients receiving fludarabine experienced more infections; there were three treatment-related deaths in the fludarabine group but none attributed to treatment toxicity in patients receiving CVP. Quality-of-life outcomes assessed in this study were reported in a separate abstract (11), with superior social function observed in patients receiving fludarabine; no difference in other domains was detected. The authors attributed the improvement in social function to the lower incidence of nausea, vomiting, and alopecia in patients receiving fludarabine.

V. INTERPRETIVE SUMMARY

One RCT compared fludarabine to a well-described standard therapy in a sufficient number of patients to assess progression-free survival and toxicity and to estimate overall survival (6).

The trial comparing fludarabine with CVP in previously treated patients (6) demonstrated superior progression-free and treatment-free survival in patients receiving fludarabine. No survival difference was detected. A quality-of-life assessment detected superior social function with no differences in other quality-of-life domains (11). These results were considered to be sufficient to recommend fludarabine as an acceptable treatment option for these patients. More complete reporting of results in article form, including a description of the baseline features of the patients, may allow for a better assessment of the time point at which fludarabine should be considered the preferred treatment option.

6. Klasa R, Meyer R, Shustik C, Sawka C, Smith A, Grenier JF, et al. Fludarabine versus CVP in previously treated patients with progressive low grade non-Hodgkin's lymphomas (Ig-NHL) [abstract]. *Proc Am Soc Clin Oncol* 1999;9a. Abstract 28.

11. Bérubé S, Meyer RM, Klasa R, Shustik C. Quality of life of patients with low grade non-Hodgkin's lymphoma treated with fludarabine or cyclophosphamide, vincristine and prednisone. *Proceedings of First Int. Soc. For Pharmacoeconomics and Outcomes Research* 1999.

Literature Search and New Evidence (siehe auch Tabelle 1 im Anhang dieser Synopse)

	<p>4. Forstpointner R, Dreyling M, Repp R, Hermann S, Hanel A, Metzner B, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. <i>Blood</i>. 2004;104(10):3064-71.</p> <p>15. Dreyling M, Forstpointner R, Gramatzki M, Bock H, Hanel M, Seymour J, et al. Rituximab maintenance improves progression-free and overall survival rates after combined immuno-chemotherapy (R-FCM) in patients with relapsed follicular and mantle cell lymphoma: Final results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). <i>ASCO Meeting Abstracts</i>. 2006;24(18_suppl):7502.</p> <p>16. Dreyling MH, Forstpointner R, Ludwig W-D, Gramatzki M, Boeck H-P, Haenel M, et al. Combined immuno-chemotherapy (R-FCM) results in superior remission rates and overall survival in recurrent follicular and mantle cell lymphoma: Follow-up of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). <i>ASCO Meeting Abstracts</i>. 2005;23(16_suppl):6528.</p> <p>29. Rummel MJ, Kaiser U, Balsler C, Stauch MB, Brugger W, Welslau M, et al. Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab In Patients with Relapsed Follicular, Indolent and Mantle Cell Lymphomas - Final Results of the Randomized Phase III Study NHL 2-2003 on Behalf of the StiL (Study Group Indolent Lymphomas, Germany). <i>ASH Annual Meeting Abstracts</i>. 2010;116(21):856. – Conclusions of the authos: These data confirm the efficacy of bendamustine plus rituximab in patiens with relapsed FL, indolent or mantle cell lymphomas, and, in this setting, demonstrate a superior PFS benefit for this regimen in comparison with fludarabine plus rituximab. (siehe https://ash.confex.com/ash/2010/webprogram/Paper26917.html)</p> <p>Impact on Guidelines and Its Recommendations</p> <ul style="list-style-type: none"> • The new data supports existing recommendations
<p>Caballero D, et al. 2013 [5]</p> <p>GEL/TAMO Spanish Cooperative Group</p> <p>Clinical practice guidelines for diagnosis, treatment, and follow-up of</p>	<p>Fragestellung</p> <p>In view of this situation, the Spanish Group of Lymphomas/Autologous Bone Marrow Transplantation has conducted a series of reviews on different aspects of MCL, namely its diagnosis, prognosis, first-line and salvage treatment (both in young and elderly patients), new targeted therapies, and detection of minimal residual disease.</p> <hr/> <p>Methodik: evidenzbasierte LL</p> <p>Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur</p> <p>Suchzeitraum (letzte Aktualisierung): bis Januar 2011</p>

<p>patients with mantle cell lymphoma</p>	<p>Weitere Kriterien für die Qualität einer LL:</p> <ul style="list-style-type: none"> • Konsensusprozesse nicht beschrieben • Zusammensetzung der LL-Gruppe nicht beschrieben <p>LoE/GoR: levels of evidence and grades of recommendation assigned to each recommendation given according to the definitions established by the US Preventive Services Task Force (siehe Abbildung 2 im Anhang dieser Synopse)</p> <p><i>Sonstige methodische Hinweise</i></p> <ul style="list-style-type: none"> • <i>Information zu “Col” und “funding” liegen nicht vor</i> 												
	<p>Freitext/Empfehlungen/Hinweise</p> <p>Salvage therapy for young patients with MCL</p> <table border="1" data-bbox="435 707 1401 1178"> <thead> <tr> <th data-bbox="435 707 1241 763">Recommendation</th> <th data-bbox="1241 707 1318 763">LoE</th> <th data-bbox="1318 707 1401 763">GoR</th> </tr> </thead> <tbody> <tr> <td data-bbox="435 763 1241 943">None of the available conventional chemotherapy regimens has been proven to be more beneficial than any other. Therefore, we cannot recommend any particular regimen for young patients with relapsed MCL.</td> <td data-bbox="1241 763 1318 943">II-1</td> <td data-bbox="1318 763 1401 943">B</td> </tr> <tr> <td data-bbox="435 943 1241 1043">Autologous SCT is, in general, not recommended as salvage treatment in young patients with relapsed MCL.</td> <td data-bbox="1241 943 1318 1043">II-2</td> <td data-bbox="1318 943 1401 1043">C</td> </tr> <tr> <td data-bbox="435 1043 1241 1178">Young patients with donor availability and chemosensitive disease should be treated with nonablative or reduced intensity allogeneic SCT after the first relapse.</td> <td data-bbox="1241 1043 1318 1178">II-3</td> <td data-bbox="1318 1043 1401 1178">B</td> </tr> </tbody> </table> <p><u>Freitext:</u></p> <p>Randomized, phase III data are available only from two trials by Forstpointner et al. [63, 91], in which the addition of rituximab to a combination of fludarabine, cyclophosphamide, and mitoxantrone (RFCM) was compared to FCM alone in patients with relapsed and refractory follicular lymphoma or MCL.</p> <p>63. Forstpointner R, et al (2004) The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. <i>Blood</i> 104(10):3064–3071</p> <p>91. Forstpointner R, et al (2006) Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). <i>Blood</i> 108(13):4003–4008</p> <ul style="list-style-type: none"> • results of first trial showed that compared to FCM alone, R-FCM increased number of CR (0 vs. 29 %, respectively) • improved, though not significantly, the ORR (46 vs. 58 %; p=0.282) in 48 patients with relapsed MCL • no significant differences observed regarding PFS (p=0.388) • median OS significantly higher in patients treated with R-FCM 	Recommendation	LoE	GoR	None of the available conventional chemotherapy regimens has been proven to be more beneficial than any other. Therefore, we cannot recommend any particular regimen for young patients with relapsed MCL.	II-1	B	Autologous SCT is, in general, not recommended as salvage treatment in young patients with relapsed MCL.	II-2	C	Young patients with donor availability and chemosensitive disease should be treated with nonablative or reduced intensity allogeneic SCT after the first relapse.	II-3	B
Recommendation	LoE	GoR											
None of the available conventional chemotherapy regimens has been proven to be more beneficial than any other. Therefore, we cannot recommend any particular regimen for young patients with relapsed MCL.	II-1	B											
Autologous SCT is, in general, not recommended as salvage treatment in young patients with relapsed MCL.	II-2	C											
Young patients with donor availability and chemosensitive disease should be treated with nonablative or reduced intensity allogeneic SCT after the first relapse.	II-3	B											

compared to FCM alone (not reached vs. 11 months; p=0.004)

- randomization stopped at 147 patients because of significant advantage of R-FCM over FCM observed in overall study population, and all patients enrolled subsequently received R-FCM

Finally, a phase III study compared bendamustine plus rituximab vs. fludarabine plus rituximab in patients with relapsed/refractory follicular, indolent, or MCL [99].

99. Rummel MJ, et al. (2010) Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas. Final results of the Randomized Phase III Study NHL 2–2003 on Behalf of the StiL (Study Group Indolent Lymphomas, Germany). Blood 116 (21 ASH Annual Meeting Abstracts):856

- results confirmed efficacy of combination of bendamustine plus rituximab over fludarabine plus rituximab, producing a significantly better PFS (30 vs. 11 months; p<0.001), ORR (83.5 vs. 52.5 %; p<0.001), and a higher CR rate (38.5 vs. 16.2 %; p<0.001)

Salvage therapy for elderly patients with MCL

Recommendation	LoE	GoR
The combinations PDG or DG, R-GemOx, GMR, R-B and R-BAD could be considered treatment options in patients with refractory or relapsed MCL.	II-B	B
Maintenance therapy with rituximab could be considered an option in elderly patients (or younger than 60 years but not eligible for intensive high-dose chemotherapy) with refractory or relapsed MCL.	I	A
Temsirolimus can be used as a single agent in the treatment of patients with relapsed or refractory MCL.	I	B
The combination of temsirolimus with rituximab could be a therapeutic option for patients with relapsed or refractory MCL.	II-1	B
Bortezomib could be used as a single agent in the treatment of relapsed or refractory MCL.	II-1	B
The combination of bortezomib with RCHOP or R-Hyper-CVAD, lternating with R-M/A, could be considered a therapeutic option for the first-line treatment of patients with MCL.	II-1	C

Freitext:

In an unplanned sub-analysis of a phase III trial that showed the superiority of bendamustine plus rituximab over fludarabine plus rituximab in terms of PFS, ORR, and CR rate, maintenance therapy with rituximab significantly prolonged OS and PFS in a small group of patients [99].

In another study, rituximab maintenance was employed after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone [91]. In this study, rituximab increased the duration of the response and improved PFS without increasing toxicity in patients with

	<p>refractory or recurring MCL. Thus, these results appear to confirm the favorable role of rituximab in maintenance therapy.</p> <p>New targeted therapies for the treatment of patients with MCL</p> <p>Based on these encouraging results, Hess et al. conducted a multicenter phase III study, which led to the approval of temsirolimus by the EMA in patients with relapsed or refractory MCL [134].</p> <p>134. Hess G, et al (2009) Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol 27(23):3822–3829</p> <ul style="list-style-type: none"> • 162 patients with relapsed or refractory MCL (median previous treatments, 3; range, 2–7; 32 % post autologous SCT) • randomly assigned (1:1:1) to receive one of two temsirolimus schedules (175 mg weekly for 3 weeks followed by either 75 or 25 mg weekly) or the investigator's choice monotherapy from available approved options • most common drugs in control arm: gemcitabine (42 %), fludarabine (27 %) • patients treated with temsirolimus 175/75 mg had significantly longer PFS than those treated with investigator's choice therapy (4.8 vs. 1.9 months, $p < 0.001$) • those treated with temsirolimus 175/25 mg showed a trend towards longer PFS ($p = 0.0618$) • ORR was significantly higher in the 175/75 mg group compared with the investigator's choice group (22 vs. 2 %; $p = 0.0019$) • Median OS for the temsirolimus 175/75 mg group and the investigator's choice group was 12.8 and 9.7 months, respectively ($p = 0.3519$) • thrombocytopenia, asthenia, and diarrhea occurred with a significantly higher incidence in the temsirolimus groups than in the investigator's choice group ($p \leq 0.04$) • leukopenia occurred with a significantly higher incidence in the investigator's choice group ($p \leq 0.04$) <p>In a later post hoc study, patients included in this randomized phase III trial were retrospectively classified as low, intermediate, or high risk using the simplified MIPI, and outcomes were re-analyzed [145].</p> <p>145. Hess G, Kang L, Moran PJ (2011) Effect of prognostic risk classification on temsirolimus efficacy and safety outcomes in patients with relapsed/refractory mantle cell lymphoma. Blood 2011 (21 ASH annual meeting abstracts):2708</p> <ul style="list-style-type: none"> • temsirolimus 175/75 mg was effective across all patient risk categories, with greatest benefit observed in the low-risk group
<p>McKay P, et al. 2012 [6] British Committee for Standards in</p>	<p>Fragestellung</p> <p>The objective of this guideline is to provide healthcare professionals with clear guidance on the investigation and management of patients with mantle cell lymphoma.</p>

<p>Heamatology (BSCH)</p> <p>Guidelines for the investigation and management of mantle cell lymphoma</p>	<p>Methodik: evidenz- und konsensbasierte LL</p> <p>Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur, guideline group: UK based medical experts and patients representatives, GRADE system used</p> <p>Suchzeitraum (letzte Aktualisierung): 1980 bis 2011</p> <p>Weitere Kriterien für die Qualität einer LL:</p> <ul style="list-style-type: none"> kein formaler Konsensusprozess beschrieben <p>Strength of Recommendations:</p> <p>Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.</p> <p>Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade two recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.</p> <p>Quality of Evidence</p> <p>The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.</p> <p>(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from RCTs without important limitations.</p> <p>(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from RCTs with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).</p> <p>(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.</p> <p><i>Sonstige methodische Hinweise</i></p> <ul style="list-style-type: none"> "Col" declared funding by British Committee for Standards in Heamatology (BSCH) <p>Freitext/Empfehlungen/Hinweise</p> <p><u>Management, second-line and beyond</u></p>
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Empfehlungen:

- There is no gold-standard therapy for relapsed MCL. The choice of therapy at relapse will be determined by patient age, performance status, bone marrow reserve and initial therapy. (Strong, Moderate)
- Hyper CVAD is not recommended at relapse due to high induction mortality. (Strong, Moderate)
- Rituximab may be considered for inclusion in therapy at relapse. (Strong, Moderate)
- Bortezomib may be considered for inclusion in therapy at relapse. (Strong, Moderate)
- Combination chemotherapy may be considered for inclusion in therapy at relapse. (Strong, Weak)
- Temsirolimus is licensed in Europe and is a possible option for treatment of relapsed MCL. (Weak, Moderate)
- Flavopiridol and enzastaurin are not recommended for treatment of relapsed MCL on the basis of inadequate response. (Strong, Moderate)

Freitext:

There is only one randomized study exploring the use of rituximab in combination with chemotherapy in the relapsed setting.

Forstpointner, R, et al. (2004) The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*, 104, 3064–3071

- evaluated use of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without antibody
- only 48 evaluable patients with MCL
- whilst no statistically significant difference in response between arms, significant survival benefit following the addition of rituximab (OS not reached vs. 11 months $p = 0,0042$)
- addition of mitoxantrone to FC (FCM) lead to an ORR of 46% (0% CR)
- subsequent addition of rituximab improved quality of responses; 58% ORR with 29% CR

The registration study involved a randomization between two dosing schedules of temsirolimus (175 mg/week for 3 weeks and then 75 mg or 25 mg/week) versus investigator choice single agent therapy.

Hess, G, et al. (2009a) Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *Journal of Clinical Oncology*, 27, 3822–3829.

- 162 relapsed/refractory disease patients randomized
- those treated with higher dose of temsirolimus had significantly longer PFS than the investigator choice arm and a higher objective

	<p>response rate (22% vs. 2%)</p> <ul style="list-style-type: none"> • lower dose arm showed a trend towards longer PFS • median OS for the HD temsirolimus group and investigator choice arms: 12, 8 and 9, 7 months respectively <p>Temsirolimus requires continuous therapy, with quick progressions reported on cessation of the drug. In spite of this, as the only drug licensed in Europe for the treatment of relapse, it is included in this guideline as a possible treatment option.</p> <p>Bendamustine is widely used in MCL.</p> <p>Rummel, MJ, et al. (2005) Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and lowgrade non-Hodgkin's lymphoma. <i>Journal of Clinical Oncology</i>, 23, 3383–3389.</p> <ul style="list-style-type: none"> • Bendamustine with rituximab (16 patients) • 81% ORR • 31% CR • PFS of 20,4 months
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Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

<p>NIHR Horizon Scanning Centre, 2013 [7] Idelalisib for indolent non-Hodgkin's lymphoma</p>	<p>Target group Indolent non-Hodgkin's lymphoma: patients relapsed or refractory to standard treatments.</p> <p>Existing comparators and treatments For relapsed disease, options include rituximab in combination with chemotherapy followed by rituximab maintenance therapy (unless high dose therapy is considered a suitable option). Regimens commonly used include:</p> <ul style="list-style-type: none"> • Bendamustine in combination with rituximab, • cyclophosphamide, vincristine and prednisolone in combination with rituximab, • cyclophosphamide, doxorubicin, vincristine and prednisolone in combination with rituximab or • Fludarabine, cyclophosphamide and rituximab (FCR). • Single agent rituximab or chlorambucil with rituximab can be given to older patients in whom the above regimens are not considered appropriate.
<p>NIHR Horizon Scanning Centre (NIHR HSC). 2013 [8] Ibrutinib for relapsed or refractory mantle cell lymphoma</p>	<p>Target group Mantle cell lymphoma (MCL): relapsed or refractory</p> <p>Existing comparators and treatments For patients with relapsed MCL, there is no gold standard treatment. The following options may be considered (Quelle: McKay P, et al. Guidelines for the investigation and management of mantle cell lymphoma. <i>British Journal of Haematology</i>. 2012;159(4):405-26):</p> <ul style="list-style-type: none"> • Rituximab, • Bortezomib, • Temsirolimus, • Combination chemotherapy or • Allogeneic stem cell transplantation in younger, fit patients.

	<p>Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) is not widely used in the UK as it is considered too toxic for most patients and is not recommended by guidelines for use at relapse due to high induction mortality. Also, guidelines do not recommended the use of flavopiridol and enzastaurin for relapsed patients due to inadequate response rates.</p>
<p>NIHR Horizon Scanning Centre (NIHR HSC). 2014 [9] Obinutuzumab in combination with bendamustine for rituximab-refractory indolent non-Hodgkin's lymphoma ? second line</p>	<p>Target group Non-Hodgkin's lymphoma: rituximab-refractory; indolent – second line; in combination with bendamustine.</p> <p>Current treatment options Current UK practice for patients who are refractory to rituximab is to treat with single agent bendamustine, and if this has failed, a combination such as fludarabine and cyclophosphamide may be used if this hasn't previously been attempted. In general however, treatment options are very limited and prognosis is poor.</p>
<p>ECRI Institute for Agency for Healthcare Research and Quality (AHRQ), 2014 [10] Healthcare Horizon Scanning System - Potential High-Impact Interventions - Priority Area 02: Cancer</p>	<p>Ibrutinib for Treatment of Non-Hodgkin's Lymphomas</p> <p><u>Key Facts:</u> B-cell non-Hodgkin's lymphomas such as chronic lymphocytic leukemia and mantle cell lymphoma often respond well to first-line therapy; however, patients with these diseases frequently experience recurrence. In this situation, available therapies have limited or no efficacy. Additionally, certain molecularly defined subtypes, such as chronic lymphocytic leukemia harboring a deletion in the short arm of chromosome 17, have poor response to standard therapies. New agents to treat these conditions are highly desired. Recent research has identified the non-receptor tyrosine kinase Btk as a potential target in treating B-cell malignancies. Researchers have identified two potential roles for Btk in the biology of B-cell malignancies: (1) Btk promotes malignant B-cell proliferation and survival and (2) Btk promotes malignant B-cell homing to and retention in lymph nodes. Ibrutinib (Imbruvica™) is an oral, first-in-class inhibitor of Btk that is under study for treating a wide range of B-cell malignancies. In single-arm phase II studies in patients with mantle cell lymphoma or chronic lymphocytic leukemia, ibrutinib demonstrated substantial activity with reported response rates between 66% and 71%. FDA granted ibrutinib breakthrough therapy designation for several indications with high unmet needs including chronic lymphocytic leukemia harboring a chromosome 17 deletion and relapsed/refractory mantle cell lymphoma. FDA approved the drug for mantle cell lymphoma in November 2013. The recommended dosage on the labeling is 560 mg taken orally once daily (four 140 mg capsules once daily). A separate new drug application has been submitted for the chronic lymphocytic leukemia indication and is under FDA review. The company stated that the list price of ibrutinib would be about \$10,900 (about \$91 per capsule) per patient, per month, or about \$130,000 per year.</p> <p><u>Key Expert Comments:</u> Overall, experts opined that a significant need exists for novel treatments for chronic lymphocytic leukemia and mantle cell lymphoma and that the response rates observed in initial trials of ibrutinib indicated that it has significant potential to improve patient outcomes. Although reviewers suggested that further study was needed to confirm this early promise (particularly studies comparing ibrutinib to alternative treatments), the relatively benign side-effect profile of the drug and its potential to be used in treating several B-cell malignancies place ibrutinib at the high end of the high-impact-potential range. At the time of expert commenting, the pricing of the drug was not known.</p> <p><u>Potential for High Impact:</u> High</p>

<p>Geiger-Gritsch S. Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA), 2010 [11] Bendamustine (Ribomustin/Treanda/ Levact) for indolent non- Hodgkin's Lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and multiple myeloma (Horizon Scanning in Oncology)</p>	<p>6 Evidence 3 phase III trials in indolent NHL: Kahl, et al. 2010 (MCL unklar, Zweitlinientherapie); Rummel, et al (ASH Meeting Abstract). 2009 (18,5 % MCL; Erstlinientherapie); Herold, et al. 2006 (siehe auch Extraktion aus Gao G, et al. 2010)</p> <p>9 Commentary</p> <ul style="list-style-type: none"> • heterogeneity of NHL and differences in treatment regimens (i.e. first- vs. second-line therapy, differing dosing regimens, differing combinations) make it difficult to conclusively judge the potential clinical benefit associated with bendamustine therapy • despite data indicating improvements in progression-free survival, overall response rate or overall remission rate, to date no trial has demonstrated increases in overall survival or quality of life (QoL) <p>Due to current reported data, its reasonable safety profile and its low costs, bendamustine can be seen as an additional therapeutic option for some patients with indolent NHL but further trials are needed. ... the optimal dose and schedule have to be defined and toxicities (mainly grade 3/4 haematological adverse events) have to be monitored when bendamustine is used.</p>
<p>Ndegwa S, Spry C. Canadian Agency for Drugs and Technologies in Health (CADTH). 2010 [12] Rituximab for non- hodgkin's lymphoma: a review of the clinical and cost-effectiveness and guidelines</p>	<p>Research Questions</p> <ol style="list-style-type: none"> 1. What is the clinical effectiveness and safety of rituximab for the treatment of patients with non-Hodgkin's lymphoma? <p>...</p> <ol style="list-style-type: none"> 3. What are the guidelines for the use of rituximab in non-Hodgkin's lymphoma? 4. What date is used for time zero in clinical trials evaluating survival following treatment for non-Hodgkin's lymphoma? Are there any guidelines for survival analysis when rituximab is used? <p>Methods Systematic literature search between 2003 and 2009</p> <p>Anzahl eingeschlossene Studien (Gesamt)</p> <ul style="list-style-type: none"> • 3 SRs, 5 RCTs, 9 economic evaluations, 7 evidence-based guidelines <p>Für MCL nur eingeschlossener SR von Gao, et al. 2009 relevant. Extraktion daraus findet sich weiter oben in dieser Synopse.</p> <ul style="list-style-type: none"> • dazu heist es: „Pooled results for mantle cell lymphoma, another subtype of B-cell non-Hodgkin's lymphoma, showed that improvements with rituximab in combination with chemotherapy were statistically significant for overall response when compared with chemotherapy alone.” • <i>Mantle cell lymphoma</i>: RR 1,22 (95 % CI 1,07 to 1,40; p = 0.004)

Primärstudien

Eine Suche nach Primärstudien wurde nicht in Auftrag gegeben.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Database of Systematic Reviews am 05.09.2014

Suchschritt	Suchfrage
1	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees
2	MeSH descriptor: [Waldenstrom Macroglobulinemia] explode all trees
3	MeSH descriptor: [Leukemia, Hairy Cell] explode all trees
4	MeSH descriptor: [Leukemia, Lymphoid] explode all trees
5	(waldenstrom* or waldenstroem*) and (macroglobulinemia* or macroglobulinaemia*):ti,ab,kw (Word variations have been searched)
6	(lymphoplasmacytic or lymphoplasmacytoid or lymphoplasmocytic or lymphoplasmocytoid or lpl) and lymphom*:ti,ab,kw (Word variations have been searched)
7	((non next hodgkin*) or nonhodgkin* or nhl or inhl) and lymphom*:ti,ab,kw (Word variations have been searched)
8	follicular lymphom*:ti,ab,kw (Word variations have been searched)
9	((small next lymphocytic) or sll) and lymphom*:ti,ab,kw (Word variations have been searched)
10	(b-cell or chronic*) and (lymphocytic or lymphoid) and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)
11	chronic* and b-cell and (lymphom* or leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)
12	(well next differentiated) and lymphocytic and lymphom*:ti,ab,kw (Word variations have been searched)
13	cll:ti,ab,kw (Word variations have been searched)
14	((marginal next zone) or "mucosa associated lymphoid tissue" or malt) and lymphom*:ti,ab,kw (Word variations have been searched)
15	burkitt* and (lymphom* or tumour* or leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)
16	sezary* and (syndrome* or lymphom* or erythroderma*):ti,ab,kw (Word variations have been searched)
17	(pagetoid next reticulos*) or (mycosis next fungoides) or (lymphomatoid next granulomatos*) or (lymphomatoid next papulos*) or "granulomatous slack skin" or (Woringer next Kolopp next disease*):ti,ab,kw (Word variations have been searched)
18	(b-cell or t-cell or nk-cell or (natural next killer) or (mantle next cell) or (mantle next zone) or (cleaved next cell) or (noncleaved next cell) or (large next cell) or (mixed next cell) or histiocytic or (primary next effusion) or (primary next cutaneous) or lymphoblastic or dlbcl or mcl) and lymphom*:ti,ab,kw (Word variations have been searched)
19	((hairy next cell) and (leukemia* or leukaemia*)) or (leukemic next reticuloendothelios*):ti,ab,kw (Word variations have been searched)
20	adult-t and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)
21	(large next granular) and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)

22	prolymphocytic and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)
23	lymphoblastic and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)
24	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 from 2009 to 2014
25	#24 Publication Year from 2009 to 2014

MEDLINE (PubMed) nach SR, HTA am 06.09.2014

Suchschritt	Suchfrage
1	("Lymphoma, Non-Hodgkin/drug therapy"[Mesh] OR "Lymphoma, Non-Hodgkin/radiotherapy"[Mesh] OR "Lymphoma, Non-Hodgkin/surgery"[Mesh] OR "Lymphoma, Non-Hodgkin/therapy"[Mesh])
2	("Waldenstrom Macroglobulinemia/drug therapy"[Mesh] OR "Waldenstrom Macroglobulinemia/radiotherapy"[Mesh] OR "Waldenstrom Macroglobulinemia/surgery"[Mesh] OR "Waldenstrom Macroglobulinemia/therapy"[Mesh])
3	("Leukemia, Hairy Cell/drug therapy"[Mesh] OR "Leukemia, Hairy Cell/radiotherapy"[Mesh] OR "Leukemia, Hairy Cell/surgery"[Mesh] OR "Leukemia, Hairy Cell/therapy"[Mesh])
4	("Leukemia, Lymphoid/drug therapy"[Mesh] OR "Leukemia, Lymphoid/radiotherapy"[Mesh] OR "Leukemia, Lymphoid/surgery"[Mesh] OR "Leukemia, Lymphoid/therapy"[Mesh])
5	((waldenstrom*[Title/Abstract] OR waldenstroem*[Title/Abstract])) AND ((macroglobulinemia*[Title/Abstract] OR macroglobulinaemia*[Title/Abstract])
6	(((((lymphoplasmacytic[Title/Abstract] OR lymphoplasmacytoid[Title/Abstract] OR lymphoplasmocytic[Title/Abstract] OR lymphoplasmocytoid[Title/Abstract] OR lpl[Title/Abstract])) AND lymphom*[Title/Abstract]
7	(((((non hodgkin*[Title/Abstract] OR nonhodgkin*[Title/Abstract] OR nhl[Title/Abstract] OR inhl[Title/Abstract])) AND lymphom*[Title/Abstract]
8	(follicular[Title/Abstract] AND lymphom*[Title/Abstract]
9	((small lymphocytic[Title/Abstract] OR slil[Title/Abstract])) AND lymphom*[Title/Abstract]
10	((((b cell[Title/Abstract] OR chronic*[Title/Abstract])) AND ((lymphocytic[Title/Abstract] OR lymphoid[Title/Abstract])) AND ((leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract])
11	((chronic*[Title/Abstract] AND b cell[Title/Abstract] AND (((lymphom*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract])
12	((well-differentiated[Title/Abstract] AND lymphocytic[Title/Abstract]) AND lymphom*[Title/Abstract]

Suchschritt	Suchfrage
13	cll[Title/Abstract]
14	((((marginal zone[Title/Abstract]) OR mucosa associated lymphoid tissue[Title/Abstract]) OR malt[Title/Abstract])) AND lymphom*[Title/Abstract]
15	(burkitt*[Title/Abstract]) AND (((lymphom*[Title/Abstract]) OR tumour*[Title/Abstract]) OR leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
16	(sezary*[Title/Abstract]) AND ((syndrome*[Title/Abstract]) OR lymphom*[Title/Abstract]) OR erythroderma*[Title/Abstract])
17	(((((pagetoid reticulos*[Title/Abstract]) OR mycosis fungoides[Title/Abstract]) OR lymphomatoid granulomatos*[Title/Abstract]) OR lymphomatoid papulos*[Title/Abstract]) OR granulomatous slack skin[Title/Abstract]) OR wronger kolopp disease*[Title/Abstract])
18	(((((((((((((((((b cell[Title/Abstract]) OR t cell[Title/Abstract]) OR nk cell[Title/Abstract]) OR natural killer[Title/Abstract]) OR mantle cell[Title/Abstract]) OR mantle zone[Title/Abstract]) OR cleaved cell[Title/Abstract]) OR noncleaved cell[Title/Abstract]) OR large cell[Title/Abstract]) OR mixed cell[Title/Abstract]) OR histiocytic[Title/Abstract]) OR primary effusion[Title/Abstract]) OR primary cutaneous[Title/Abstract]) OR lymphoblastic[Title/Abstract]) OR dlbcl[Title/Abstract]) OR mcl[Title/Abstract])) AND lymphom*[Title/Abstract]
19	(((((hairy cell[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract]))) OR leukemic reticuloendothelios*[Title/Abstract])
20	(adult t[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
21	(large granular[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
22	(prolymphocytic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
23	(lymphoblastic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
24	(((((((((((((((((#5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15) OR #16) OR #17) OR #18) OR #19) OR #20) OR #21) OR #22) OR #23
25	(((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract]
26	(#24) AND #25
27	((((#1) OR #2) OR #3) OR #4) OR #26
28	(#27) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])

Suchschritt	Suchfrage
29	(((((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]))))
30	(#27) AND #29
31	(#28) OR #30
32	(#31) AND ("2014/02/01"[PDAT] : "2014/09/06"[PDAT])

MEDLINE (PubMed) nach Leitlinien am 06.09.2014

Suchschritt	Suchfrage
1	lymphoma, non hodgkin[MeSH Terms]
2	waldenstrom macroglobulinemia[MeSH Terms]
3	leukemia, hairy cell[MeSH Terms]
4	leukemia, lymphoid[MeSH Terms]
5	Lymphoma, mantle cell[Mesh Terms]
6	((((waldenstrom*[Title/Abstract] OR waldenstroem*[Title/Abstract])) AND ((macroglobulinemia*[Title/Abstract] OR macroglobulinaemia*[Title/Abstract]))
7	(((((lymphoplasmacytic[Title/Abstract] OR lymphoplasmacytoid[Title/Abstract] OR lymphoplasmacytic[Title/Abstract] OR lymphoplasmacytoid[Title/Abstract] OR lpl[Title/Abstract])) AND lymphom*[Title/Abstract]
8	(((((non hodgkin*[Title/Abstract] OR nonhodgkin*[Title/Abstract] OR nhl[Title/Abstract] OR inhl[Title/Abstract])) AND lymphom*[Title/Abstract]
9	(follicular[Title/Abstract] AND lymphom*[Title/Abstract]
10	((((small lymphocytic[Title/Abstract] OR slil[Title/Abstract])) AND lymphom*[Title/Abstract]
11	(((((b cell[Title/Abstract] OR chronic*[Title/Abstract])) AND ((lymphocytic[Title/Abstract] OR lymphoid[Title/Abstract])) AND ((leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract]))
12	((chronic*[Title/Abstract] AND b cell[Title/Abstract] AND (((lymphom*[Title/Abstract] OR leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract]))
13	((well-differentiated[Title/Abstract] AND lymphocytic[Title/Abstract] AND

Suchschritt	Suchfrage
	lymphom*[Title/Abstract]
14	cll[Title/Abstract]
15	(((marginal zone[Title/Abstract]) OR mucosa associated lymphoid tissue[Title/Abstract]) OR malt[Title/Abstract])) AND lymphom*[Title/Abstract]
16	(burkitt*[Title/Abstract]) AND (((lymphom*[Title/Abstract]) OR tumour*[Title/Abstract]) OR leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
17	(sezary*[Title/Abstract]) AND (((syndrome*[Title/Abstract]) OR lymphom*[Title/Abstract]) OR erythroderma*[Title/Abstract])
18	(((pagetoid reticulos*[Title/Abstract]) OR mycosis fungoides[Title/Abstract]) OR lymphomatoid granulomatos*[Title/Abstract]) OR lymphomatoid papulos*[Title/Abstract]) OR granulomatous slack skin[Title/Abstract]) OR woringer kolopp disease*[Title/Abstract]
19	((((((((((((((((b cell[Title/Abstract]) OR t cell[Title/Abstract]) OR nk cell[Title/Abstract]) OR natural killer[Title/Abstract]) OR mantle cell[Title/Abstract]) OR mantle zone[Title/Abstract]) OR cleaved cell[Title/Abstract]) OR noncleaved cell[Title/Abstract]) OR large cell[Title/Abstract]) OR mixed cell[Title/Abstract]) OR histiocytic[Title/Abstract]) OR primary effusion[Title/Abstract]) OR primary cutaneous[Title/Abstract]) OR lymphoblastic[Title/Abstract]) OR dlbcl[Title/Abstract]) OR mcl[Title/Abstract])) AND lymphom*[Title/Abstract]
20	(((hairy cell[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract]))) OR leukemic reticuloendothelios*[Title/Abstract]
21	(adult [Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
22	(large granular[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
23	(prolymphocytic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
24	(lymphoblastic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
25	(((cutaneous[Title]) OR malignant[Title])) AND lymphom*[Title]
26	((((((((((((((((((((((#1) OR #2) OR #3) OR #4) OR #5) OR #6) OR #7) OR #8) OR #9) OR #10) OR #11) OR #12) OR #13) OR #14) OR #15) OR #16) OR #17) OR #18) OR #19) OR #20) OR #21) OR #22) OR #23) OR #24) OR #25)
27	(((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
28	(#27) AND #26
29	#28 Filters: Publication date from 2014/02/01 to "2014/09/09

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1. **Njue A, Colosia 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 Mantle Cell Lymphoma: A Systematic Literature Review. *Clin Lymphoma Myeloma Leuk* 2014; [Epub ahead of print].
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5. **Caballero D, Campo E, Lopez-Guillermo A, Martin A, Arranz-Saez R, Gine E, Lopez A, Gonzalez-Barca E, Canales MA, Gonzalez-Diaz M, Orfao A.** Clinical practice guidelines for diagnosis, treatment, and follow-up of patients with mantle cell lymphoma. Recommendations from the GEL/TAMO Spanish Cooperative Group. *Ann Hematol* 2013; 92 (9): 1151-79.
6. **McKay P, Leach M, Jackson R, Cook G, Rule S.** Guidelines for the investigation and management of mantle cell lymphoma. *Br J Haematol* 2012; 159 (4): 405-26.
7. **NIHR Horizon Scanning Centre.** Idelalisib for indolent non-Hodgkin's lymphoma. Birmingham: NHSC, 2013
8. **NIHR Horizon Scanning Centre (NIHR HSC).** Ibrutinib for relapsed or refractory mantle cell lymphoma, Stand: September 2013. Birmingham: NHSC, 2013 www.hsc.nihr.ac.uk/files/downloads/2199/2482.1f175b58.UPDATEDNonconfidentialIbrutinibforrelapsedorrefractorymantlecelllymphomarevised11112013.pdf, Zugriff am 30.09.2014.
9. **NIHR Horizon Scanning Centre (NIHR HSC).** Obinutuzumab in combination with bendamustine for rituximab-refractory indolent non-Hodgkin's lymphoma ? second line. Birmingham: NHSC, 2014
10. **ECRI Institute.** AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions: Priority Area 02: Cancer. Rockville, MD: Agency for Healthcare Research and Quality, 2014 (Prepared by ECRI Institute under Contract No. HSA29020100006C.)
11. **Geiger-Gritsch S.** Bendamustine (Ribomustin/Treanda/ Levact) for indolent non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and multiple myeloma. Wien: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBIHTA), 2010 (DSD: Horizon Scanning in Oncology 10): <http://eprints.hta.lbg.ac.at/884/#>, Zugriff am 30.09.2014.
12. **Ndegwa S, Spry C.** Rituximab for non-hodgkin's lymphoma: a review of the clinical and cost-effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH), 2010

Anhang:

Table 2 Comparative Studies Involving Patients With Relapsed/Refractory Mantle Cell Lymphoma: Efficacy Data							
Reference	Inclusion Criteria	Number of Patients With R/R MCL, Treatment	ORR, % ^a	Median Duration of Response, Months	Median Duration of Follow-Up, Months	Median PFS, Months	Median OS, Months
Agathocleous et al, 2010 ²²	Patients with recurrent and/or refractory disease ^b	n = 19 randomized: bortezomib with rituximab ^c	58% (CR, 16%; PR, 42%) ^d	NR	NR	NR	NR
Forstpointner et al, 2004 ²³	Patients with nonresponse or relapse after at least 1 preceding chemotherapy and recurrence after ASCT	n = 48 randomized: ■ FCM (n = 24) ■ R-FCM (n = 24)	■ FCM: 46% (CR, 0%; PR, 46%) ■ R-FCM: 58% (CR, 29%; PR, 29%) P = .282 for FCM versus R-FCM	NR	■ 18 (range, 1-43)	■ FCM, 4 ■ R-FCM, 8 P = .3887	■ FCM, 11 ■ R-FCM, not reached P = .0042
ClinicalTrials.gov ²⁶	Patients who had received 2 to 7 previous therapies that might include HSCT (ie, induction + consolidation + maintenance)	n = 169 randomized: ■ Temozolimus 175/75 mg (n = 57) ^e ■ Temozolimus 175/25 mg (n = 56) ^f ■ Investigator's choice therapy (n = 56) ^g	ORR (95% CI) ■ Temozolimus 175/75 mg, 22.2% (11.1%-33.3%) ■ Temozolimus 175/25 mg, 5.6% (0%-11.7%) ■ Investigator's choice, 1.9% (0%-5.4%) P = .0019 for temozolimus 175/75 mg versus investigator's choice P = .6179 for temozolimus 175/25 mg versus investigator's choice	■ Temozolimus 175/75 mg, 7.1 ■ Temozolimus 175/25 mg, 3.6 ■ Investigator's choice, NA (unable to calculate: only 1 patient with a response)	NR	Median (95% CI) ■ Temozolimus 175/75 mg, 4.8 (2.9-7.0) ■ Temozolimus 175/25 mg, 3.7 (3.4-6.2) ■ Investigator's choice, 1.8 (1.6-2.0) P < .0001 for temozolimus 175/75 mg versus investigator's choice P < .0001 for temozolimus 175/25 mg versus investigator's choice	Median (95% CI) ■ Temozolimus 175/75 mg, 11.1 (8.2-18.0) ■ Temozolimus 175/25 mg, 8.8 (6.4-14.5) ■ Investigator's choice, 9.5 (5.3-15.1) P = .3053 for temozolimus 175/75 mg versus investigator's choice P = .9515 for temozolimus 175/25 mg versus investigator's choice
Rule et al, 2012 ²⁹	■ MCL refractory to, or relapse or progression after, first-line chemotherapy	■ CHOP (n = 23) ■ VCHOP (n = 23)	■ CHOP, 47.8% (CR, 21.7%; PR, 26.1%) ■ VCHOP, 82.6% (CR, 34.8%; PR, 47.8%)	NR	24.2	■ CHOP, 8.2 ■ VCHOP, 15.7 P = .07	■ CHOP, 16.4 ■ VCHOP, 36.1 P = .026 Estimated hazard ratio, CHOP versus VCHOP, 0.4
Robak et al, 2006 ³¹	Patients who had undergone treatment of at least 2 lines of chemotherapy, including 1 alkylating agent and prednisone	n = 9 treated ■ RC (n = 7) ■ RCC (n = 2)	Total (RC + RCC), 67% (CR, 22%): ■ RC, 44% (CR, 11%) ■ RCC, 22% (CR, 11%)	NR	NR	NR	NR

Abbildung 1: aus Njue A, et al. 2014



Tabelle 1: Ergebnisse der Aktualisierungsrecherche zu McEachern, et al. 2013

Interventions	Article Name	Population (n)	Outcomes	Brief results	References
4 courses of chemotherapy with 25 g/m ² fludarabine on days 1 to 3, 200 mg/m ² cyclophosphamide on days 1 to 3, and 8 mg/m ² mitoxantrone on day 1 (FCM), Vs. 4 courses of chemotherapy with 25 g/m ² fludarabine on days 1 to 3, 200 mg/m ² cyclophosphamide on days 1 to 3, and 8 mg/m ² mitoxantrone on day 1 (FCM), combined with rituximab (375 mg/m ² ; R-FCM)	The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group	n=147 Follicular lymphoma (FL) and mantle cell lymphoma (MCL)	PFS, OS	<ul style="list-style-type: none"> R-FCM arm was significantly superior concerning progression-free survival (PFS; p = .0381) and overall survival (OS; p = .0030). In FL PFS was significantly longer in the R-FCM arm (p = .0139) whereas in MCL a significantly longer OS was observed (p = .0042). There were no differences in clinically relevant side effects in both study arms. 	Forstpointner et al. (2004)
4 courses of chemotherapy with Fludarabine (25 mg/m ² /d days 1–3), Cyclophosphamide (200 mg/m ² /d days 1–3) and Mitoxantrone (8 mg/m ² /d day 1) (FCM) Vs. 4 courses of chemotherapy with Fludarabine (25 mg/m ² /d days 1–3), Cyclophosphamide (200 mg/m ² /d days 1–3) and Mitoxantrone (8 mg/m ² /d day 1) (FCM) ± Rituximab (375 mg/m ² /d day 0)	Rituximab maintenance improves progression-free and overall survival rates after combined immuno-chemotherapy (R-FCM) in patients with relapsed follicular and mantle cell lymphoma: Final results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG)	N=195 Patients with advanced stage relapsed or refractory FL and mantle cell lymphoma (MCL) were eligible	MPFS	<ul style="list-style-type: none"> median PFS after end of induction has not been reached in the R-maintenance arm in contrast to 17 months in patients with no further treatment (p = 0.001). This improvement was seen both in FL (n = 81; p = 0,035) and MCL (n = 47; p = 0,049) 	Dreyling M., et al. (2006)
Fludarabine containing regimen (FCM) was chosen for salvage therapy Vs. Fludarabine containing regimen (FCM) for salvage therapy followed by Rituximab maintenance	Combined immuno-chemotherapy (R-FCM) results in superior remission rates and overall survival in recurrent follicular and mantle cell lymphoma: Follow-up of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG)	N=244, 122 (50%) had follicular, 95 (39%) mantle cell and 24 (10%) with other indolent lymphomas	PFS, OS, remission rates	<ul style="list-style-type: none"> In 67 randomized patients with follicular lymphoma, progression-free survival (median: 3.9 vs. 1.7 years, p=0,029) and overall survival (74% at 4 years vs. median of 3.8 years, p=0,033) was significantly improved after combined immuno-chemotherapy. 55 patients subsequently designated to the combined 	Dreyling M., et al. (2005)

				<p>study arm (R-FCM) confirmed the superior remission rates (36%/96%), progression-free and overall survival</p> <ul style="list-style-type: none"> • Similarly, in 50 randomized MCL patients, R-FCM achieved higher overall survival (median: 2.5 vs 0.9 years, p=0.031). The improved overall survival was • confirmed by 45 patients subsequently designated to combined immunotherapy 	
<p>Rituximab 375 mg/m2 (day 1) plus bendamustine 90 mg/m2 (days 1+2) Vs. Rituximab 375 mg/m2 (day 1) plus fludarabine 25 mg/m2 (days 1–3) q 28 days for a maximum of 6 cycles. Prophylactic use of antibiotics or granulocyte-colony stimulating factor (G-CSF) was not generally recommended; however in cases of severe granulocytopenia, G-CSF use was permitted. The protocol was amended in 2006 to allow rituximab maintenance therapy (rituximab 375 mg/m2 q 3 months for up to 2 years) in both arms, following regulatory approvals in this setting.</p>	<p>Bendamustine Plus Rituximab Versus Fludarabine Plus Rituximab In Patients with Relapsed Follicular, Indolent and Mantle Cell Lymphomas - Final Results of the Randomized Phase III Study NHL 2-2003 on Behalf of the StiL (Study Group Indolent Lymphomas, Germany)</p>	<p>n=219 pts with relapsed FL, indolent or MCL in need of treatment Most pts had stage IV (71.6% B-R; 60.6% F-R) or stage III disease (21.1% B-R and 25.3% F-R, respectively)</p>	<p>PFS</p>	<ul style="list-style-type: none"> • Median PFS was significantly prolonged with B-R compared with F-R (30 vs 11 months; hazard ratio [HR] 0.51, 95 % confidence interval [CI] 0.34–0.67; p<0.0001) 	<p>Rummel M.J., et al. (2010)</p>
ONGOING CLINICAL TRIALS					
Intervention	Official title	Status	Protocol ID	Last updated	
<p>Bendamustine plus Rituximab Vs. Fludarabine plus Rituximab</p>	<p>Prospective Randomised Multicenter Study for Therapy Optimization of Recurrent, Progressive Low Grade Non-Hodgkin Lymphomas and Mantle Cell Lymphomas</p>	<p>completed</p>	<p>NCT01456351</p>	<p>February 11, 2013</p>	



Table 1 Definition of levels of evidence and grades of recommendation according to the USPSTF [4]

Levels of evidence	
Level I	Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1	Evidence obtained from well-designed controlled trials without randomization.
Level II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3:	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
Grades of recommendation	
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
C	The USPSTF recommends against routinely providing the service. There may be considerations that support providing the service in an individual patient. There is at least moderate certainty that the net benefit is small.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

*USPSTF US Preventive
Services Task Force*

Abbildung 2: aus Caballero, et al. 2013