Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2014-B-044, 2014-B-068-z und 2014-B-069-z Idelalisib

Stand: September 2014

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Idelalisib **[zur Behandlung der chronischen lymphatischen Leukämie nach mindestens einer Vortherapie]** **[zur Behandlung der chronischen lymphatischen Leukämie mit 17p-Deletion oder einer TP53-Mutation in der Erstlinie]**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• allogene Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Nicht angezeigt.*
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:	
Idelalisib	Anwendungsgebiet laut „Positive Opinion“: Zydelig wird in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) angewendet: - die mindestens eine Vortherapie erhalten haben, oder - als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder TP53-Mutation bei Patienten, die für eine Chemoimmuntherapie ungeeignet sind.
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)
Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (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: - Chronisch lymphatische Leukämie (CLL) nach Versagen der Standardtherapie (Chlorambucil/Prednison) (FI Endoxan®, 09-2013)
Fludarabin L01BB05 generisch	Behandlung der chronisch-lymphatischen B-Zell-Leukämie (CLL) bei Patienten mit ausreichenden Knochenmarksreserven (FI Bendarabin®, 01-2012)
Ofatumumab L01XC10 Arzerra®	Nicht vorbehandelte chronische lymphatische Leukämie (CLL): Arzerra in Kombination mit Chlorambucil oder Bendamustin ist angezeigt für die Behandlung von Patienten mit CLL, die noch keine vorangegangene Therapie hatten und die nicht für eine Fludarabin-basierte Therapie geeignet sind. Refraktäre CLL: Arzerra ist angezeigt für die Behandlung von Patienten mit CLL, die refraktär auf Fludarabin und Alemtuzumab sind. (FI Arzerra®, 06-2014)
Prednisolon H02AB06 generisch	Hämatologie/Onkologie Chronisch lymphatische Leukämie (FI Dermosolon®, 09-2009)
Prednison H02AB07 generisch	Hämatologie/Onkologie: Chronisch lymphatische Leukämie (FI Cutason®, 02-2013)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Rituximab L01XC02 MabThera®	MabThera ist in Kombination mit einer Chemotherapie für die Behandlung von nichtvorbehandelten Patienten und von Patienten mit rezidivierender/refraktärer chronischer lymphatischer Leukämie angezeigt. Für Patienten, die bereits mit monoklonalen Antikörpern einschließlich MabThera behandelt wurden oder für Patienten, die refraktär auf eine vorherige Behandlung mit MabThera in Kombination mit Chemotherapie sind, liegen nur begrenzte Daten zur Wirksamkeit und Sicherheit vor. (FI MabThera®, 06-2013)
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)
Trofosfamid 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)

Quellen: AMIS-Datenbank, Fachinformationen

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Idelalisib [zur Behandlung des refraktären follikulären 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 Übersicht „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
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): • Off-Label-Indikation für Fludarabin: Fludarabin in Kombination mit Cyclophosphamid, Mitoxantron und Rituximab (FCM-R) bei geeigneten Patienten mit niedrig oder intermediär malignen Non-Hodgkin-Lymphomen der B-Zellreihe (CD20 positive NHL, u.a. lymphozytisch, lymphoplasmozytisch, lymphoplasmazytoid, follikulär Grad 1 oder 2, Mantelzell-, Marginalzonen-, nicht multiples Myelom, nicht Haarzellleukämie) und Resistenz auf CHOP (mit oder ohne Rituximab).
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Idelalisib	Geplantes Anwendungsgebiet laut Beratungsanforderung/Zulassungsantrag: Zydelig® wird als Monotherapie zur Behandlung von erwachsenen Patienten mit follikulärem Lymphom (FL), das refraktär gegenüber zwei vorausgegangenen Therapielinien ist, angewendet.
Ibritumomab V10XX02 Zevalin®	[^{90}Y]-radiomarkiertes Zevalin ist indiziert als Konsolidierungstherapie nach Remissionsinduktion bei zuvor nicht therapierten Patienten mit follikulärem Lymphom. Der Nutzen von Zevalin nach Rituximabbehandlung in Kombination mit Chemotherapie ist nicht belegt. [^{90}Y]-radiomarkiertes Zevalin ist indiziert zur Behandlung von erwachsenen Patienten mit einem nach einer Behandlung mit Rituximab rezidivierenden oder refraktären CD20-positiven follikulären Non-Hodgkin-Lymphom (NHL) vom B-Zell-Typ (FI Zevalin®, 05-2013)
Interferon alfa-2a L03AB04 Roferon-A®	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: - Follikuläres Non-Hodgkin-Lymphom. (FI Roferon-A®, 07-2013)
Interferon alfa-2b L03AB05 IntronA®	Follikuläre Lymphome: Therapie follikulärer Lymphome mit großer Tumormasse zusätzlich zu geeigneter Kombinations-Chemotherapie zur Induktion wie CHOP-ähnliche Behandlungsschemata. (FI IntronA®, 11-2013)
Rituximab L01XC02 MabThera®	Follikuläres Lymphom: MabThera ist in Kombination mit einer Chemotherapie für die Erstbehandlung von Patienten mit follikulärem Lymphom im Stadium III – IV angezeigt. Eine MabThera Erhaltungstherapie ist angezeigt zur Behandlung von Patienten mit follikulärem Lymphom, die auf eine Induktionstherapie angesprochen haben. MabThera ist als Monotherapie für die Behandlung von Patientenmit follikulärem Lymphom im Stadium III – IV angezeigt, die gegen eine Chemotherapie resistent sind oder nach einer solchen einen zweiten oder neuerlichen Rückfall haben. (FI MabThera®, 06-2013)
Weitere Arzneimittel mit Zulassung für Non-Hodgkin-Lymphome	
Bendamustin L01AA09 Levact®	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)
Bleomycin L01DC01 generisch	Non-Hodgkin-Lymphome von intermediärem oder hohem Malignitätsgrad im Erwachsenenalter. Bleomycinsulfat wird bei diesen Erkrankungen üblicherweise in Kombination mit anderen Zytostatika verwendet. (FI Bleomedac®, 09-2012)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Chlorambucil L01AA02 Leukeran®	niedrig maligne Non-Hodgkin-Lymphome (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) (FI Endoxan®, 09-2013)
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)
Etoposid L01CB01 generisch	Lastet ist in Kombination mit anderen antineoplastisch wirksamen Präparaten bei der Behandlung folgender bösartiger Neubildungen angezeigt: Non-Hodgkin-Lymphome von intermediärem und hohem Malignitätsgrad nach Versagen (nicht vollständiges Ansprechen auf die Therapie bzw. Wiederauftreten der Erkrankung) von Standardtherapien. (FI Lastet®, 02-2014)
Ifosfamid L01AA06 generisch	Non-Hodgkin-Lymphome: Zur Kombinationschemotherapie bei Patienten mit hochmalignen Non-Hodgkin-Lymphomen, welche nicht oder nur unzureichend auf die Initialtherapie ansprechen. Zur Kombinationstherapie von Patienten mit rezidivierten Tumoren. (FI Holoxan®, 11-2008)
Methotrexat L01BA01 generisch	Non-Hodgkin-Lymphome: - im Erwachsenenalter: Zur Behandlung von Non-Hodgkin-Lymphomen von intermediärem oder hohem Malignitätsgrad in Kombination mit anderen zytostatischen Arzneimitteln (FI Bendatrexat, 02-2012)
Mitoxantron L01DB07 generisch	Intermediäre und hochmaligne Non-Hodgkin Lymphome (NHL) des Erwachsenen in der Kombinationstherapie. (FI Onkotrone, 08-2010)
Pixantron L01DB11 Pixuvri	Die Monotherapie mit Pixuvri ist indiziert bei erwachsenen Patienten mit mehrfach rezidivierten 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)
Prednisolon H02AB06 generisch	Hämatologie/Onkologie: Non-Hodgkin-Lymphome (FI Dermosolon®, 09-2009)
Prednison H02AB07 generisch	Hämatologie/Onkologie: Non-Hodgkin-Lymphome (FI Cutason®, 02-2013)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Trofosfamid 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)
Vindesin L01CA03 Eldisine®	Kombinationschemotherapie: aggressives Non-Hodgkin-Lymphom (Stadium I oder II). (FI Eldisine®, 07-2010)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2014-B-044 Idelalisib

Datum: 24.06.2014

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

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Indikation für die Recherche

Idealisib ist indiziert in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL), die sich zuvor mindestens einer Therapie unterzogen haben.

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, randomisierte kontrollierte Studien und Evidenz-basierten systematischen Leitlinien zur Indikation „**chronische lymphatische Leukämie**“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am **21.03.2014** 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. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: DGHO-Onkopedia, NCCN, ESMO, CCO. 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 **399** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen

vorgenommen. Insgesamt ergab dies 22 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
C	cyclophosphamide
CCIT	Conventional chemo-(immuno) therapy
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CHOP-R	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CoI	Conflicts of Interest
CPG	ClinicalPracticeGuideline
CR	Complete response
DAHTA	Deutsche Agentur für Health Technology Assessment
FCM	Fludarabine, Cyclophosphamide, Mitoxantrone
FCM-R	Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone
Flu	fludarabine
FluC	fludarabine with cyclophosphamide
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GITMO	Gruppo Italiano Trapianto di Midollo Osseo
GoR	Grade of Recommendation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
M	mitoxantrone
NGC	National Guideline Clearinghouse
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
PR	Partial response
QALE	quality-adjusted life expectancy
R	rituximab
RT-allo-HCT	Reduced-toxicity allogeneic hematopoietic cell transplantatio
SCT	Stem CellTransplantation
SIE	Italian Society of Hematology
SIES	Società Italiana di Ematologia Sperimentale
TRIP	Turn Research into Practice Database

Cochrane Reviews

Bauer et al. 2012: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia.	1. **Fragestellung**: Assessing the efficacy of chemotherapy plus rituximab compared to chemotherapy without further therapy
	2. Methodik **Population**: CLL, newly diagnosed or relapsed patients. Three trials included relapsed or refractory patients: 1) NCRI-CLL 201 [previously treated with ≥ 1 chemotherapeutic regimen, WHO performance status 0 to 2; FluCM-R vs. FluCM; (N = 52)]; 2) REACH [minimum 1 lone treatment of the CLL; FluC-R vs. FluCM; N = 552]); 3) (Gribben 2005 [Abstract data only! N=12] …, patients who were treated within these trials did not suffer from other severe health problems aside from CLL; therefore, it remains unclear whether patients with severe co-morbidities will benefit from this treatment option. **Intervention**: chemotherapy plus rituximab **Komparator**: chemotherapy without further therapy **Endpunkte**: OS, PFS, time to next treatment, AEs Für Vergleiche 1) additional rituximab versus additional alemtuzumab *[nicht mehr zugelassen]* in CLL patients (CLL2007FMP; Gribben 2005): keine ausreichenden Daten bzw. nur first-line Therapie) chemotherapy vs. monoclonal anti-CD20 antibody therapy: keine RCTs **Suchzeitraum** (Aktualität der Recherche): Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 12, 2011), MEDLINE (January 1990 to 4 January 2012), and EMBASE (1990 to 20 March 2009) **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 3 (n=1421) five of the seven identified trials could be included in one of the two performed meta-analyses (2 trials only published abstracts with preliminary results of rituximab versus alemtuzumab (Overall survival NOT reported) [CLL2007FMP; Gribben 2005: Foa 2010; Zagoskina 2011] → included in group of ongoing studies) Three trials included relapsed or refractory patients (Gribben 2005 [Abstract data only!]; NCRI-CLL 201; REACH): Four trials evaluated the anti-CD20 antibody in patients receiving first-line therapy (CALBG 9712; CLL2007FMP; GCLLSG CLL 8; Wierda 2011). **Qualität der eingeschlossenen Studien:** We judged the overall the quality of these trials as moderate to high. All trials were randomized and open-label studies. However, two trials were published as abstracts only, therefore we were unable to assess the potential risk of bias for these trials in detail.
	3. Ergebnisdarstellung 3 eingeschlossene Studien (*für rezidivierende CLL*), davon 1 Studie nur als Abstract (N=12): gesamt eingeschlossene Patienten N=604 (aus 2 Studien mit Vollpublikation):

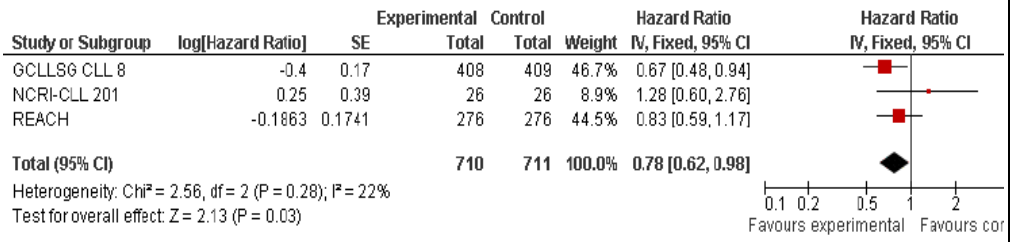
1) NCRI-CLL 201 [previously treated with ≥ 1 chemotherapeutic regimen, WHO performance status 0 to 2; FluCM-R vs. FluCM; (N = 52)];
2) REACH [minimum 1 lone treatment of the CLL; FluC-R vs. FluCM; N = 552])

NCRI-CLL 201 trial [u.a. Hillmen P et al. A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated chronic lymphocytic leukaemia. *British Journal of Haematology* 2011;**152**:570–8]:
Mean age: FluCM-R: 66 years (range 44 to 79 years), FluCM: 68 years (range 32 to 79 years)
Stage: FluCM-R: Binet A 15.4%, Binet B 42.3%, Binet C 38.5%; FluCM: Binet A 19.2%, Binet B 15.4%, Binet C 61.5%

REACH trial [u.a. Robak T et al: Rituximab plus fludarabine prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756 –1765]:
Mean age: FluC-R: 63 years (range: 35 to 83 years); FluCM: 62 years (range: 36 to 81 years)
Stage: Binet A: FluC-R 24 (9%); FluCM 31 (11%), Binet B: FluC-R 166 (60%); FluCM 160 (58%) Binet C: FluC-R 86 (31%); FluCM 85 (31%)

Ergebnisse zu:

- Overall Survival: not statistically significantly longer with rituximab than with chemotherapy alone in previously treated patients (2 trials, N=604) Hazard Ratio (Fixed, 95% CI) = 0.89 [0.65, 1.22] (page 68); s. unten Forest Plot subgrouped by different treatment regimens: FluC-R versus FluC (REACH trial, N=552) Hazard Ratio (Fixed, 95% CI) 0.83 [0.59, 1.17]; FluCM-R versus FluCM (NCRI-CLL 201 trial, N=52) Hazard Ratio (Fixed, 95% CI) 1.28 [0.60, 2.76]
  Anmerkung FBMed: steht im Gegensatz zu Ergebnisbeschreibung auf S. 16: OS für first und second-line zusammen (3 Studien): HR 0.78 (95%CI 0.62 to 0.98, P = 0.03; low heterogeneity I^2 of 22%) → Subgroups: „no statistical differences between the following subgroups:
  - *different anti-CD20 antibody treatment regimens (P = 0.22; first-line treatment: 1 trial, N = 817; previously treated: 2 trials, N = 604);*
  - *different treatment regimens (P = 0.18; FluC-R versus FluC: 2 trials, N = 1369; FluCM-R versus FluCM: 1 trial, N = 52)."*



- Time to next treatment: statistically significant difference favoring rituximab regarding: HR was 0.61 (95% CI 0.51 to 0.73; P < 0.00001; from the GCLLSG CLL 8 and REACH trials with 1369 participants.)
  Subgroups for time to next treatment, no statistical differences for: different anti-CD20 antibody treatment regimens (P = 0.60; first-line treatment: 1 trial, N = 817; previously treated: 1 trial, N = 552).
- Progression-free survival (PFS): statistically significant difference HR 0.75 [0.61, 0.94]; P < 0.012; (two trials NCRI-CLL 201; REACH with 604 previously

	treated participants Subgroup, no statistical differences for: different treatment regimens (P = 0.70; FluC-R versus FluC: 2 trials, N = 1369; FluCM-R versus FluCM: 1 trial, N = 52). - Total adverse events (AE) (WHO) grade 3-4 (NCRI-CLL 201; REACH, N = 598): no statistical differences, RR 1.08 [0.99, 1.18], P=0.068) - Serious adverse events (NCRICLL 201; REACH): No statistically significant differences (N = 598, RR 1.05 95% CI 0.89 to 1.23, P =0.57); ebenso in Subgruppe different treatment regimens (P = 0.92; FluC-R versus FluC: 1 trial, N = 546; FluCM-R versus FluCM: 1 trial, N = 52) - Number of patients discontinuing the study because of drug-related adverse events: kein signifikanter Unterschied: REACH trial 72 patients (26%) of the FC-R arm and 69 patients (25%) in the FluC arm discontinued treatment because of AEs. The NCRI-CLL 201 trial did not provide data with regard to this outcome.
	4. Fazit der Autoren: *This meta-analysis showed that patients receiving chemotherapy plus rituximab benefit in terms of OS as well as PFS compared to those with chemotherapy alone. Therefore, it supports the recommendation of rituximab in combination with FluC as an option for the first-line treatment as well as for the people with relapsed or refractory CLL. The available evidence regarding the other assessed comparisons was not sufficient to deduct final conclusions.* We are aware of 16 ongoing studies, including three trials comparing ofatumumab with or without additional chemotherapy versus no treatment. 5. *Anmerkung FBMed: mehr Information zu diesen ongoing studies siehe unten in Abschnitt "**Primärstudien**"*
Vidal et al. 2012: 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 lymphoma. We included both patients receiving bendamustine as first-line therapy and patients with relapsed or refractory disease receiving it as salvage therapy. Patients might have received high-dose chemotherapy following first-line or salvage therapy. We included patients of any age. **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 We included 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. Chemotherapy included: Adriamycin, cyclophosphamide, chlorambucil, fludarabine, mitoxantrone, vincristine, Steroids could be combined with any chemotherapeutic regimen

Endpunkte:
Primärer Endpunkt: Overall survival (OS); All-cause mortality (*Hinweis*: This outcome was added post-hoc to protocol due to the scarcity of OS data.
Sekundäre Endpunkte: 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

Suchzeitraum (Aktualität der Recherche): We electronically searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2012, Issue 2), MEDLINE (1966 to May 2012), EMBASE (1974 to November 2011), LILACS (1982 to May 2012), databases of ongoing trials (accessed 30 April 2012) and relevant conference proceedings. We searched references of identified trials and contacted the first author of each included trial.

Anzahl eingeschlossene Studien/Patienten: We included five trials randomising 1343 adult patients in the systematic review. varied in the type of lymphoid malignancy, bendamustine regimen and the comparator regimen. Two trials included only patients with CLL and compared bendamustine to chlorambucil, and to fludarabine. We did not conduct a meta-analysis due to the clinical heterogeneity among trials.

Qualität der eingeschlossenen Studien: The two trials regarding CLL/SLL Patients were of high quality.

3. Ergebnisdarstellung

Analyse der beiden Studien zu ausschließlich CLL/SLL Patienten (Endpunkt: All-cause mortality):

Knauf 2009:

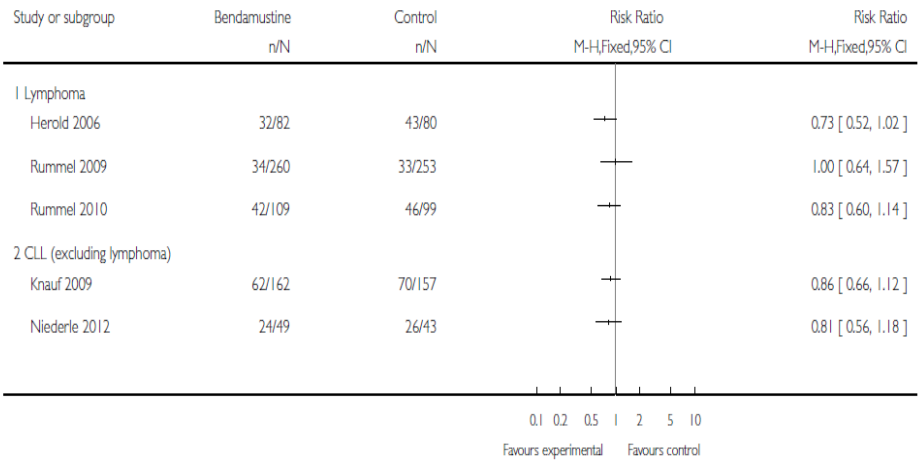
Knauf 2009

Methods	Allocation generation: adequate Allocation concealment: adequate Blinding: no ITT: yes Number of dropouts: 0 (all patients were included in the analysis, 7 patients did not start allocated therapy) Median follow-up: 35 months (range, 1 to 68)
Participants	319 randomised adult patients Type of lymphoma: CLL/SLL Stage: Binet B/C Previous treatment: no Mean age: 63 years, median 63 and 66 years WHO performance status: 303/311 patients < 2, 8/311 patients = 2
Interventions	Investigational intervention: IV bendamustine 100 mg/m^2 on days 1 to 2; every 4 weeks Comparator intervention: Oral chlorambucil 0.8 mg/kg on days 1 and 15; every 4 weeks
Outcomes	Primary endpoints: Overall response rate: CR or PR Progression-free survival Secondary endpoints: Time to progression Duration of remission Overall survival Adverse events, including infection rate

Niederle 2012:

Methods	Allocation generation: computer generated Allocation concealment: central Blinding: no Number of dropouts: 4 not eligible/96 Median follow-up: 36 months
Participants	92 randomised adult patients with relapsed chronic lymphocytic leukaemia requiring treatment after 1 previous systemic regimen Type of lymphoma: CLL/SLL Stage: Binet B/C Previous treatment: 1 line (refractory or relapse) Mean age: 68 years WHO Performance status: < 3
Interventions	Investigational: bendamustine 100 mg/m^2 iv, day 1 + 2, q4w Comparator: fludarabine 25 mg/m^2 iv, days 1 to 5, q4w
Outcomes	(Non-inferior) progression-free survival Overall survival

- Es zeigten sich in beiden Studien keine stat. signifikanten Unterschiede zwischen den Interventionen (siehe forest plot unten). Unter Berücksichtigung des Anwendungsgebietes ist lediglich die Studie von **Niederle 2012** relevant, da in der Studie von **Knauf 2009** unbehandelte CLL/SLL Patienten eingeschlossen waren.



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 requiring discontinuation of therapy were reported in one trial (**Knauf 2009**). Eighteen patients (11%) discontinuedbendamustine therapy and five (3%) discontinued chlorambucil (P = 0.005).

….while the risk of grade 3 or 4 adverse events was increased when bendamustine was compared to chlorambucil in patients with CLL (**Knauf 2009**),…

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 bendamustine group compared to chlorambucil (3%, 5 of 151 patients).

	➔ Studie von Knauf 2009 aber zu unvorbehandelten CLL Patienten!!!
	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 evaluatethe effect of bendamustine on quality of life.*

Systematische Reviews

Keating 2010 [5]: Rituximab A Review of its Use in Chronic Lymphocytic Leukaemia, Low-Grade or Follicular Lymphoma and Diffuse Large B-Cell Lymphoma.	1. Fragestellung This article reviews the use of intravenous rituximab in the treatment of chronic lymphocytic leukaemia (CLL), low-grade or follicular lymphoma, and diffuse large B-cell lymphoma.
	2. Methodik Population: patients with chronic lymphocytic leukaemia, low-grade or follicular lymphoma or diffuse large B-cell lymphoma Intervention: Monotherapy rituximab or combination therapy Komparator: chemotherapy alone (cyclophosphamide, doxorubicin, vincristine and prednisone [CHOP] Endpunkte: primary: progression free survival Suchzeitraum (Aktualität der Recherche): 06/2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (n=k.A.)
	3. Ergebnisdarstellung **Chronic Lymphocytic Leukaemia (CLL): 1 trial (**results of the randomized, open-label, multicentre, phase III "REACH trial**)** *Patients with Relapsed or Refractory Disease - Rituximab, Fludarabine plus Cyclophosphamide versus Fludarabine plus Cyclophosphamide* - No significant between-group difference in overall survival was seen after a median duration of 25 months' follow-up, although it should be noted that at this timepoint <10% of patients had died. - Progression-free survival (primary endpoint): In patients with previously treated CLL, PFS was prolonged to a significantly greater extent with rituximab plus fludarabine and cyclophosphamide than with fludarabine plus cyclophosphamide (table II), (HR 0.65; 95% CI 0.51, 0.82) - In addition, the median time to new treatment was significantly longer in patients receiving rituximab plus fludarabine and cyclophosphamide than in those receiving fludarabine plus cyclophosphamide (HR 0.65; 95% CI 0.49,

	0.86) *Patients with Relapsed or Refractory Disease – 10 <u>Noncomparative</u> Trials* - Combination therapy with rituximab, oxaliplatin, fludarabine and cytarabine was associated with overall response rates of 33% and 63% in patients with relapsed or refractory CLL; the chemotherapy regimens differed slightly between these trials, with a higher oxaliplatin dose (30 mg/m2) and a lower cytarabine dose (0.5 g/m2) administered in the later trial than in the earlier trial. - In other trials, overall response rates were 77% with rituximab plus bendamustine (primary endpoint),75% with rituximab plus pentostatin and cyclophosphamide and 94% with rituximab plus pentostatin, cyclophosphamide and mitoxantrone - combination therapy with rituximab and high-dose methylprednisolone was associated with overall response rates of 78–93% in patients with relapsed or refractory CLL. - The median overall survival duration was 20 months, with median progression-free survival durations of 7 months and »1 year and a median time to progression of 15 months
	4. Fazit der Autoren: *In conclusion, rituximab remains a valuable therapy in patients with CLL, low-grade or follicular lymphoma and diffuse large B-cell lymphoma and, in a variety of treatment settings, represents the standard of care.* 5. Anmerkung durch FBMed: - Keine Qualitätsbewertung der Primärstudien!
Kharfan-Dabaja et al. 2012: Comparing efficacy of reduced-toxicity allogeneic hematopoietic cell transplantation with conventional chemo-(immuno) therapy in patients with relapsed or refractory CLL: a Markov decision analysis	1. Fragestellung: In the absence of randomized trial-based evidence on the comparative efficacy of RT-allo-HCT and CCIT for relapsed/refractory CLL, we examined these competing treatment options in a Markov decision model informed by systematic review (SR) and meta-analysis of available evidence.
	2. Methodik Population: Patients with relapsed/refractory CLL Intervention: Reduced-toxicity allogeneic hematopoietic cell transplantation (RT-allo-HCT) Komparator: Conventional chemo-(immuno) therapy (CCIT) Endpunkt: quality-adjusted life expectancy (QALE), treatment-related mortality, overall response rate (ORR) (CR and PR response), stable disease or progressive disease, progression from responsive disease, and survival. Suchzeitraum (Aktualität der Recherche): For studies evaluating the role of chemotherapy, immunotherapy (limited to therapeutic monoclonal antibodies) or chemo-immunotherapy combinations and for studies evaluating the role of RT-allo-HCT, a systematic and comprehensive literature search was performed using MEDLINE databases from 1966 to 31 December 2010 and supplemented by a hand search of references. **A Markov decision model was used.** Anzahl eingeschlossene Studien/Patienten (Gesamt): • For studies evaluating the role of chemotherapy, immunotherapy (limited to therapeutic monoclonal antibodies) or chemo-immunotherapy combinations:

	The final number of studies evaluated was 33. • For studies evaluating the role of RT-allo-HCT: 10 studies met inclusion criteria.
	3. Ergebnisdarstellung • Cohort analysis demonstrated superior outcome for RT-allo-HCT, with a 10-month overall life expectancy (and 6-month quality-adjusted life expectancy (QALE)) advantage over CCIT. Although the model was sensitive to changes in base-case assumptions and transition probabilities, RT-allo-HCT provided superior overall life expectancy through a range of values supported by the meta-analysis. • QALE was superior for RT-allo-HCT compared with CCIT. This conclusion was sensitive to change in the anticipated state utility associated with the post-allogeneic HCT state; however, RT-allo-HCT remained the optimal strategy for values supported by existing literature.
	4. Fazit der Autoren: *This analysis provides a quantitative comparison of outcomes between RT-allo-HCT and CCIT for relapsed/refractory CLL in the absence of randomized comparative trials. Confirmation of these findings requires a prospective randomized trial, which compares the most effective RT-allo-HCT and CCIT regimens for relapsed/refractory CLL.* 5. Anmerkungen FBMed: • Laut Review existieren keine vergleichende RCTs.
Lepretre et al. 2012: The value of rituximab for the treatment of fludarabine-refractory chronic lymphocytic leukemia: a systematic review and qualitative analysis of the literature.	1. Fragestellung: The aim of the present review is to evaluate the efficacy and safety of rituximab, administered alone or in combination, in patients refractory to fludarabine, as there are no randomized controlled trials (RCTs) in this setting.
	2. Methodik Population: Patients with fludarabine-refractory chronic lymphocytic leukemia Definition of fludarabine-refractory: 'failure to achieve partial response (PR) or complete response (CR) to a fludarabine-containing regimen, or relapse within 6 months of the last treatment. Intervention: Rituximab Monotherapy or in combination with different agents Komparator: Siehe Ergebnisteil Endpunkt: overall survival (OS), event-free survival, response to treatment (overall response [OR], CR, PR and nodular partial response [nPR]), stable disease (SD), progressive disease (PD), progression free survival (PFS) and therapy-related morbidity and mortality Suchzeitraum (Aktualität der Recherche): Systematic searches that had previously been undertaken for a previous review were updated to September 2011. Medline, Embase and The Cochrane Library were searched to identify studies of any treatment for patients with refractory CLL.

	Anzahl eingeschlossene Studien/Patienten (Gesamt): Siehe Ergebnisteil
	3. Ergebnisdarstellung **<u>Allgemein</u>**: Thirteen studies (reported in 17 publications) either included only, or mostly, fludarabine-refractory patients or considered a mixed population but reported stratified data for fludarabine-refractory patients for at least one efficacy outcome. **<u>Response/Remission:</u>** **Rituximab in combination with methylprednisolone:** Two studies evaluated rituximab in combination with methylprednisolone. Castro *et al.* included 14 patients with fludarabine-refractory CLL. Dungarwalla *et al.* also included 14 heavily pretreated patients with CLL, and 13 (93%) had previously received fludarabine. The median number of previous treatments was 2 (range: 1 – 4 for patients with fludarabine-refractory CLL and 2 – 5 for heavily pretreated patients [18]) in both cases. The efficacy outcomes reported by Castro *et al.* were CR, PR, nPR, PD, OR and PFS. The number of patients showing CR, PR and nPR was five (36%), six (43%) and two (14%), respectively; PD was reported in one (7%) patient and OR was reported in 13 patients (93%). Median time to progression was 15 months (range: 3.2 – 23.0 months). Dungarwalla et al. reported CR, PR, nPR, PD and OR, as well as OS and PFS. The number of patients with CR, PR and nPR was two (14%), 10 (71%) and one (7%), respectively. An OR was reported in 13 (93%) patients. Median OS was 20 months and median PFS was reported as 7 months. **FCR and CFAR combination studies:** Wierda et al. and Badoux et al. evaluated FCR in 177 and 280 patients with relapsed/refractory CLL, respectively. The median number of previous treatments was 2 (range: 1 – 10). These two publications report results from the same trial: Wierda et al. presented interim results and Badoux et al. reported the final results after the inclusion of over 100 additional patients. The trial is part of the group of trials performed at the M. D. Anderson Cancer Center, Houston, Texas. Wierda et al. presented data on 145 (82%) patients previously exposed to fludarabine. Of these, 37 (21%) were fludarabine-refractory. Results for 33 fludarabine-refractory patients were reported. Four fludarabine-refractory patients were part of the FC patient group, for which outcomes were not reported in a stratified manner. The efficacy outcomes CR, PR, nPR and OR were used. CR, PR and nPR were observed in 2/33 (6%), 3/33 (9%) and 14/33 (42%) patients, respectively, while the number of patients achieving OR was 19/33 (58%). Badoux et al. included 53 (19%) fludarabine-refractory patients. The reported efficacy outcomes were CR, OR and OS. CR was reported in 4/53 (8%) patients and OR in 30/53 (57%) patients. Median

	OS was 37 months. Keating et al. also evaluated FCR (n= 33), but results are presented with results for CFAR-treated patients (n= 9). The efficacy outcomes reported were CR, PR and OR. The number of patients achieving CR was 12 (29%), PR was 14 (33%), nPR was nine (21%) and OR was 35 (83%). Median time to progression was 45 months, median time to treatment failure was 20 months and median OS was 44 months. All patients in this study were fludarabine-refractory. **Rituximab in patients previously treated with FCR:** Wierda et al. (rituximab in combination with fludarabine and cyclophosphamide) included 43 patients previously treated with FCR. CR and PR were achieved by 19% and 37% of patients, respectively. **<u>Overall Survival:</u>** Increasing patient survival is without doubt one of the main goals of treatment. OS was considered in six publications. The 6-month survival rate reported by Tsimberidou *et al.* was 89%. Median OS was 37 months for FCR, 20 months for rituximab with methylprednisolone. **<u>Safety:</u>** Two trials considered rituximab in combination with methylprednisolone. Death rates were 29% and 57%, respectively. Interestingly, while infections were the most important adverse event in one trial, affecting 50% of patients, they affected only 7% of patients in the other trial, which reported fluid retention in most patients and 29% of grade 3 or 4 neutropenia or thrombocytopenia. One trial (interim results in Wierda et al., final results in Badoux et al.) used rituximab in combination with fludarabine and cyclophosphamide. Myelosuppression led to discontinuation in 26% and 23% of patients, respectively. Infection was responsible for 6% and 12% of discontinuations, respectively. Grade 3 or 4 neutropenia was also an important adverse event, affecting 62% and 56% of treatment courses, respectively. Wierda et al. reported major infections in 16% of patients, while 16% were affected by pneumonia or sepsis according to Badoux et al.
	4. Fazit der Autoren: *This systematic review has identified the available published information in this setting. The resulting information, although of moderate quality and without direct comparative evidence, suggests that regimens containing rituximab are a viable treatment option in the refractory CLL setting.* 5. Anmerkungen durch FBMed: • Most studies were uncontrolled studies. No comparison to other treatment regimens for refractory CLL can be made. • Numbers of fludarabine-refractory patients available for inclusion in the

	trials were low, impacting on the significance of the results.
Nightingale G, 2011: Ofatumumab: A Novel Anti-CD20 Monoclonal Antibody for Treatment of Refractory Chronic Lymphocytic Leukemia.	1. **Fragestellung:** To present the current clinical evidence on ofatumumab for use in refractory chronic lymphocytic leukemia (CLL).
	2. **Methodik** Population: Refractory chronic lymphocytic leukemia (CLL). Intervention: Ofatumumab Komparator: Nicht vorab definiert Endpunkt: Nicht vorab definiert Suchzeitraum (Aktualität der Recherche): 1966 - May 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): Siehe Ergebnisteil
	3. **Ergebnisdarstellung** ***a. Anzahl und Charakterisierung der eingeschlossenen Studien / Patienten*** • Zulassungsstudie: Cross-study analyses were performed on data from patients, including 162 patients with CLL, who received multiple infusions of ofatumumab as a single agent at doses ranging from 100 to 2000 mg. • The safety and efficacy of ofatumumab were analyzed in an open-label, Phase 1/2, multicenter, dose-escalating study in the US and Europe that included 33 patients with relapsed or refractory CLL. (Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a Phase 1-2 study. Blood 2008;111:1094-100). • In this study, ofatumumab was administered intravenously weekly for 4 consecutive weeks (300 mg week 1 and 1000 mg weeks 2-4), then as 1000 mg monthly on months 2-6, followed by 1000 mg once every 2 months for months 7-24. (Badoux X, O'Brien S, Wierda WG, et al. Combination of ofatumumab and lenalidomide in patients with relapsed chronic lymphocytic leukemia: results of a Phase II trial (abstract 2464). ASH Annual Meeting Proceedings Part 2. 2010.) • A Phase 2, international, randomized, parallel-group study evaluated 2 doses of ofatumumab combined with standard frontline therapy consisting of fludarabine and cyclophosphamide in previously untreated patients with CLL. Patients received standard fludarabine (25 mg/m2 intravenously on day 1) plus cyclophosphamide (250 mg/m2 intravenously on days 1-3) in combination with ofatumumab 300 mg for the first dose, followed by either 500 mg (group A) or 1000 mg (group B) every 4 weeks for 6 cycles to evaluate the efficacy and tolerability of this chemoimmunotherapy regimen. The primary endpoint was the complete response rate from the start of treatment until 3 months following the last infusion. Safety evaluations included adverse events and deaths. The median age of patients was 56 years. (Wierda WG, Kipps TJ, Durig J, et al. Ofatumumab combined with fludarabine and cyclophosphamide (O -FC) shows high activity in patients with previously untreated chronic lymphocytic leukemia (CLL): results from a randomized, multi-center, international, two-dose, parallel group, phase II trial (abstract 207). Blood 2009;114:90.)

	• Hagenbeek and colleagues published the first clinical report of activity of ofatumumab in patients with non-Hodgkin lymphoma. This Phase 1/2 trial included 40 patients with relapsed or refractory grade 1 or 2 CD -20–positive follicular lymphoma who were treated with 4 weekly intravenous infusions of ofatumumab 300, 500, 700, or 1000 mg. (Hagenbeek A, Gadeberg O, Johnson P, et al. First clinical use of ofatumumab,a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. Blood 2008;111:5486-95) ***b. Daten-Synthese*** • A Phase 1/2 trial has established the safety and tolerability of single-agent ofatumumab at an initial dose of 300 mg intravenously on week 1, followed by 2000 mg once weekly for 7 doses (weeks 2-8), followed by 2000 mg once every 4 weeks for 4 doses (weeks 9-12), for a total of 12 doses. The final analysis of a pivotal international multicenter trial has shown promising activity in patients with CLL refractory to fludarabine and alemtuzumab, demonstrating overall response rates of 44-51%, with prolonged progression-free and overall survival. Ofatumumab activity has also been shown in a variety of other malignant and nonmalignant conditions, including non-Hodgkin lymphoma, rheumatoid arthritis, and multiple sclerosis. The most common adverse effect is grade 1 and 2 infusion reactions. Other adverse effects include infection, neutropenia, anemia, rash, fever, and diarrhea.
	4. Fazit der Autoren: *Clinical evidence suggests that ofatumumab is an effective agent in patients with CLL refractory to fludarabine and alemtuzumab. Data are awaited comparing ofatumumab to other salvage regimens. Until results of head-to-head trials are conducted comparing ofatumumab to existing regimens, it cannot be said whether ofatumumab is more efficacious or tolerable than currently available therapies.* 5. Anmerkungen durch FB Med • kein einheitliches Wording zu Beginn eines Ergebnisberichts für einen Endpunkt • keine einheitliche vergleichende Darstellung der eingeschlossenen Studien-(Populationen) und -Ergebnisse • keine Einschätzung der Studienqualität der eingeschlossenen Primärstudien es wurden auch Studienergebnisse aus Abstracts (z.B. von Kongressbänden) eingeschlossen

Leitlinien

British Committee for Standards in Haematology (BCSH), 2012: Guidelines on the diagnosis, investigation and management of Chronic Lymphocytic	**Fragestellung** The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia.
	Methodik ***Grundlage der Leitlinie*** review of the literature using Medline/Pubmed The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology. The guideline was then reviewed by a

Leukaemia.	sounding board of approximately 50 UK haematologists, the BCSH (British Committee for Standards in Haematology) and the British Society for Haematology Committee and comments incorporated where appropriate. ***Suchzeitraum*** bis August 2011 (Update der Version von 2004) ***LOE and GOR*** gemäß GRADE
	Empfehlungen ***Management of Relapsed CLL with no TP53 abnormality*** Recommendation (GRADE B2) • Patients relapsing **at least 2 years after FC, FCR or similar regimens** who have not acquired a *TP53* abnormality, remain fit enough for fludarabine-based treatment and in whom there is a clinical indication for treatment, should receive FCR. Further studies are required to evaluate the role of bendamustine in combination with an anti CD20 antibody in fit patients with relapsed disease. *Evidenzbasis: There are no phase III studies of patients relapsing after FC or FCR. A non randomised phase II study of FCR in 284 patients with relapsed CLL showed a higher CR rate and longer PFS and OS than seen in a historical cohort treated with FC. 78/284 patients received prior therapy with regimens that included fludarabine and an alkylating agent. 13% and 9% were refractory to fludarabine and chlorambucil respectively. The ORR was 73% with 42% CR + nPR. PFS was 19 months The CR + nodular PR (nPR) rate for fludarabine responsive cases was 46% compared to 8% for fludarabine refractory cases (Badoux et al, 2011;O'Brien et al, 2001)* *A non randomised phase II study of bendamustine and rituximab has shown response rates of 60% and 45% for relapsed or fludarabine-refractory patients respectively, with an event free survival of 14.7 months. Only 2/14 patients with a 17p deletion responded. (Fischer et al, 2008;Iannitto et al, 2011).* ***Relapse after or refractory to chlorambucil*** Recommendation (GRADE B2) • Patients relapsing after chlorambucil can be retreated with chlorambucil • Entry into trials which include bendamustine or chlorambucil and an anti-CD20 antibody is strongly recommended. • In the absence of a suitable trial, BR should be considered for patients refractory to chlorambucil. • The minority of patients relapsing after chlorambucil who are fit enough to receive fludarabine-based therapy should be considered for FCR. • Other options for patients who are refractory to chlorambucil and unable to tolerate myelosuppressive therapy include high dose steroids, alone or in combination with rituximab, and alemtuzumab. *Evidenzbasis: Most patients who relapse after chlorambucil will respond to retreatment with chlorambucil. The phase II trials of BR discussed in the previous section included elderly patients and the acceptable toxicity indicated that this regimen may be suitable for relapsed or refractory patients unfit for FCR. The REACH study randomised patients relapsing predominantly after single agent alkylating or purine analogue therapy to FC v FCR and showed an improved ORR, CR and PFS in the FCR arm (basierend auf: Robak et al, 2010).*

Management of High-risk CLL

Treatment of relapsed / refractory disease

Evidenzbasis: The outcome of fludarabine-refractory patients treated with chemotherapy is poor with a median OS of approximately 8 months. Alemtuzumab alone results in an ORR of about 30-35%. Combining alemtuzumab with high-dose steroids results in an improved ORR but the PFS and OS are nevertheless unsatisfactory. Regimens that include fludarabine and alemtuzumab have activity in patients refractory to either agent alone but responses are not durable and the risk of infectious complications is high (basierend auf: Badoux et al, 2011;Elter et al, 2005).

As with the initial treatment of high risk disease, the duration of remission following alemtuzumab - containing regimens is short and consolidation therapy such as allogeneic transplantation (see below) is recommended in suitable patients. For patients for whom allogeneic transplantation is not an option, re-treatment with alemtuzumab should be considered in those patients who relapse ***more than12 months after initial treatment*** *(basierend auf: Fiegl et al, 2011).*

Treatment options for patients who fail or relapse ***early*** *after alemtuzumab-based therapy are limited. Active agents include ofatumumab, lenalidomide (basierend auf: Ferrajoli et al, 2008) and high-dose steroids with or without rituximab (basierend auf: Pileckyte et al 2011). Steroids given at conventional dose can provide useful short-term disease control and improve CLL-related symptoms.*

The choice of therapy depends on patient fitness, previous treatment and drug availability.

In the registration study, ofatumumab achieved an ORR of 58% in patients refractory to both fludarabine and alemtuzumab (double refractory) and 47% in patients with bulky, fludarabine-refractory CLL for whom alemtuzumab was considered inappropriate. The median PFS was approximately 6 months for both groups (basierend auf: Wierda et al, 2010). The effectiveness of ofatumumab was not influenced by bulky lymphadenopathy, prior rituximab exposure or refractoriness to R-FC. The ORR was lower (14%) among patients with a 17p deletion in the bulky fludarabine-refractory group, but 41% in double refractory 17p deleted disease.

Role of radiotherapy

- *Evidenzbasis*: Radiotherapy should be considered for patients for whom chemo-immunotherapy has been ineffective or is contra-indicated and can provide effective palliation in cases with symptomatic bulky lymphadenopathy. Low doses of external beam radiotherapy (2 x 2Gy) can be highly effective in this situation and a higher dose (30 Gy in 2-3 Gy fractions) may be required in patients with transformed aggressive disease or those known to have a *TP53* abnormality (Lowry *et al*, 2011).

Recommendations (GRADE B1/2):

- The management of high-risk CLL is controversial and poses considerable therapeutic challenges. Accordingly, early input from a centre with a specialist interest in CLL is strongly recommended.
- Treatment for high-risk CLL should ideally be delivered as part of a clinical trial. Outside of trials, alemtuzumab in combination with pulsed high dose glucocorticoid is the treatment of choice. Meticulous attention should be paid to antimicrobial prophylaxis and supportive care.
- The use of alemtuzumab in combination with drugs other than steroids should be confined to clinical trials
- Since subcutaneous alemtuzumab injection is associated with comparable efficacy and less toxicity in CLL, this has become the preferred route of

	administration • Ofatumumab is the treatment of choice for patients with high-risk CLL who fail alemtuzumab. Other options include high-dose or conventional-dose glucocorticoids, lenalidomide or radiotherapy. ***The Role of allogeneic transplantation***. • Allogeneic stem-cell transplantation should be considered as consolidation therapy for all fit patients with high-risk CLL and should ideally be performed in the setting of a secure remission. Suitable patients should be discussed with a transplant centre at the earliest opportunity (GRADE B1). • There is no consensus on the value of screening potential allograft donors for MBL. It would seem sensible to exclude donors with early CLL or clinical MBL (GRADE C2). ***Consolidation / Maintenance therapy*** • Currently consolidation and maintenance immunotherapy therapy should only be offered in clinical trials as the clinical benefit versus the risk of morbidity is still uncertain (GRADE B2). • In the absence of an overall survival gain or evidence of improved quality of life, autografting is not recommended as part of standard care in CLL (GRADE A1). *Evidenzbasis: Preliminary data suggest that consolidation therapy with rituximab may prolong PFS (Bosch et al, 2010; Del Poeta G. et al, 2008;Hainsworth et al, 2003). The role of anti CD20 antibody therapy and lenolidamide as maintenance/consolidation therapy are currently being evaluated in clinical trials.* ***Treatment of small lymphocytic lymphoma*** • SLL should be managed in the same manner as CLL (GRADE B2). *Evidenzbasis: Treatment of small lymphocytic lymphoma Data on the optimal treatment of SLL is limited and patients are often included in studies which include other low grade B cell lymphomas rather than CLL. However, the biological similarities between SLL and CLL are so close that a similar response to treatment could be expected. This is supported by a single centre retrospective study of CLL and SLL which also showed a better outcome for both disorders when treated with regimens that included a nucleoside analogue and rituximab (Tsimberidou et al, 2007). Indications for, and choices of treatment are the same as for CLL. Rare patients in whom SLL is diagnosed following biopsy of an enlarged lymph node in the absence of detectable disease at any other site, may be offered local radiotherapy with curative intent.*
Imrie K, et al. 2012: Cancer Care Ontario (CCO): Rituximab in Lymphoma and Chronic Lymphocytic Leukemia. Evidenced-based Series 6-8 Version 2.2005 (in review). Toronto (ON): Cancer Care	**Fragestellung** **Chronic Lymphocytic Leukemia** 1. What beneficial outcomes are associated with the use of rituximab for the treatment of patients with chronic lymphocytic leukemia (CLL)? Outcomes of interest are overall survival, disease control (as assessed by measures such as progression-free survival, event-free survival, time-to-treatment failure, or response duration), and response rate. 2. What is the toxicity associated with the use of rituximab? 3. Which patients are more or less likely to benefit from treatment with rituximab?
	Methodik: evidenz- und konsensbasierte LL Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur

Ontario, 2012	(update von 1999 und 2006), informaler Konsensusprozess (zuletzt 2006), External Review by Ontario Clinicians Suchzeitraum (letzte Aktualisierung): March 2006 to March 2012 Weitere Kriterien für die Qualität einer LL: • Qualität der eingeschlossenen Studien beschrieben 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" 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" Sonstige methodische Hinweise • Die Gruppe (Hematology Disease Site Group) hält eine Aktualisierung der Empfehlungen von 2006 aufgrund der neuen Literatur für notwendig. • CONFLICT OF INTEREST: The members of the Hematology DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. The lead author and citation and evidence reviewer (KI) of this topic was a co-investigator in one trial included in this report (10) and is involved with an ongoing trial on rituximab. Three other DSG members reported research involvement with trials on this topic, of which one member was involved with one trial in this report (10). In addition, three of the above DSG members, including the lead author, reported involvement with the pharmaceutical company that manufactures rituximab, including research funding, membership on boards of directors or advisory committees, provision of consultancy, or honoraria. • Funding: The Program in Evidence-based care is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.
	Recommendations: Chronic Lymphocytic Leukemia There is insufficient evidence at this time to support or refute the use of single-agent rituximab or a rituximab-containing chemotherapy regimen in patients with CLL. **Key Evidence: Chronic Lymphocytic Leukemia** No randomized controlled trials were located. **New (relevant) Evidence: Chronic lymphocytic leukemia** 18. Hillmen P, Cohen DR, Cocks K, Pettitt A, Sayala HA, Rawstron AC, et al. A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated chronic lymphocytic leukaemia. British Journal of Haematology. 2011;152(5):570-8. - In conclusion, the addition of rituximab to FCM improves the response rates in relapsed CLL, resulting in more complete remissions and without additional safety concerns. Efficacy and safety should be fully tested in a randomized Phase III trial. 49. Zhao L, Xi Y-M, Guo M, Chao R, Jin R-R. Efectiveness and safety of FCR regimen for chronic lymphocytic leukemia: A systematic review. Chinese Journal of Evidence-Based Medicine. 2011;11(11):1321-6.

	• 1 ongoing study from clinicaltrials.gov: Combination Chemotherapy With or Without Rituximab in Treating Patients With Previously Treated Chronic Lymphocytic Leukemia (Protocol ID: NCT00337246) – study completed
Mauro FR et al., 2011: SIE, SIES, GITMO updated clinical recommendations for the management of chronic lymphocytic leukemia	Italian Society of Hematology (SIE), SIES Società Italiana di Ematologia Sperimentale (SIES) and GITMO (Gruppo Italiano Trapianto di Midollo Osseo) Fragestellung/Zielsetzung: By using GRADE system we updated the guidelines for management of CLL issued in 2006 from SIE, SIES and GITMO group.
	Methodik A 3-member Advisory Council (AC) with expertise in clinical epidemiology, hematology, critical appraisal and research synthesis oversaw the process. An expert panel (EP) was selected according to the conceptual framework elements of the NIH Consensus Development Program **Grundlage der Leitlinie** Using a modified Delphi process, the list of produced statements was circulated electronically to all participants through 2 iterations. Participants voted on which statements they felt warranted discussion, and provided comments on the wording of the statements which were progressively finalized. Final adjudication of the recommendation (s) was made through the three face-to-face meetings held in Bologna, Italy. Recommendations were both classified into four mutually exclusive categories: do it, probably do it, probably don't do it, don't do it, according to GRADE suggestions, and were also provided in conversational form following the comments derived from the discussion of the EP. **Suchzeitraum** 2006 bis 3/2011 **LoE und GoR** In areas covered by the evidence, the production of recommendations was performed according GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.
	Empfehlungen ***Issue 5:*** Consolidation therapy (consensus-based recommendations) • The panel agreed that at present a consolidation/maintenance treatment approach in CLL patients should be undertaken only in the setting of controlled clinical trials. Evidenzbasis: Only one randomized controlled trial tackled the key question of appropriateness of a consolidation therapy in CLL. Patients in CR or PR after fludarabine or FC first-line treatment were randomized to receive alemtuzumab or only clinical observation. The primary endpoint was the PFS. The trial was prematurely stopped after the enrolment of the first 21 patients because of a severe infection rate in the alemtuzumab group. However, the PFS at month 36 after randomization was 81.8% for patients in the alemtuzumab arm vs. 20.6% in the observation arm. On the basis of these results and data derived from a non RCT the EP deemed that at present there was no evidence that patients in CR or PR may benefit from a consolidation treatment and provided the following recommendations.

Clinical questions and strength and direction of the recommendations formulated by the panel using GRADE system on the issue of second-line therapy.

Clinical question	Recommendation
1. Should R-FC be preferred to FC in previously treated CLL patients?	Use it, weak positive
2. Should oblimersen plus fludarabine and cyclophosphamide be preferred to fludarabine and cyclophosphamide in previously treated CLL patients?	Probably don't use it, weak negative
3. Is allo-SCT better than conventional therapy in previously treated CLL patients	No recommendations
4. Should alemtuzumab be preferred to fludarabine-based treatments in refractory patients, patients with early relapse, patients with del [17p] and/or p53 mutations?	Use it, weak positive

Issue 6: therapy of refractory or relapsed patients (evidence-based recommendations)

- In patients requiring a second-line treatment, del [17p] and/or p53 mutations should be checked.
- In patients with no del [17p] and/or p53 mutations and relapsed after 24 months, the same front-line therapy including rituximab can be considered.
- In patients with del [17p] and/or p53 mutations, in patients refractory or relapsed within 24 months from a fludarabine-based treatment, alemtuzumab containing regimens, or experimental treatment approaches within controlled trials should be given.
- Furthermore, in poor prognosis younger patients with adequate fitness status and no significant co-morbidities, a treatment approach including an allogeneic SCT, from either a sibling or wellmatched unrelated donor, should be offered after an appropriate cytoreductive treatment.

Evidenzbasis: **Chemoimmunotherapy**
Robak et al. randomized 552 patients (≤70 years: 83% of patients) who had received one prior line of therapy. Eligible patients were required to be sensitive (55% of patients) or refractory (27% of patients) to prior alkylating agents but had to be sensitive to fludarabine (prior responses ≥6 months; 17% of patients). A prior treatment with interferon, rituximab, other monoclonal antibodies, alkylators/nucleoside analogues combinations or transplantation was not allowed. Patients treated with FCR showed a significantly higher PFS than patients treated with FC (median PFS, FCR vs. FC: 30.6 vs. 20.6 months). The CR rate was also in favour of the FCR group. The AEs rate leading to dose modification or treatment interruption were 39% for the FCR group and 51% for the FC group. The evidence was graded as strong and the EP decided that the benefit of using FCR rather than FC in patients relapsed or refractory after single agent therapy overcome the risks.

In order to analyze the effect of the prior therapy on the response to FCR, Badoux et al. explored the efficacy of FCR given to 284 patients beyond first relapse. The overall RR in patients who were previously exposed to a single agent such as rituximab, fludarabine, alkylating agents were 92%, 90%, 78%, respectively, while the response rate of patients previously exposed to fludarabine combined with an alkylating agent was 73%. Patients refractory to fludarabine and those who had received more than three prior therapies, experienced short PFS.
Engert et al. presented at the 2010 ASH meeting the results of a multicentre randomized study including 335 relapsed or refractory patients after one prior regimen that included fludarabine in only 15% of the cases. Patients were randomized to receive fludarabine as single agent or fludarabine and alemtuzumab

	(FluCam) combination. Patients treated with FluCam showed a better outcome in terms of CR rate (12.5% vs. 4%) and PFS (24 vs. 18 months) with a similar infection rate. *Abbildung aus LL ''Evidence-based guidelines for the therapy of CLL''* **Guidelines** / **ESMO [48]** / **NCCN [49]** / **SIE, SIES, GITMO (present guidelines)** **Relapsed refractory patients** ESMO [48]: First-line therapy if relapse or progression occurs at least 12 months after the initial therapy and 24 months after immunochemotherapy. Alemtuzumab-containing regimen followed by allogeneic SCT in physically fit patients if the relapse occurs within 12 months after monotherapy or 24 months after immunochemotherapy, or if the disease does not respond to first line monotherapy. FCR for patients relapsed or refractory to first-line therapy with an alkylating agent. Alemtuzuman- or bendamustine-containing regimen in physically nonfit patients without del (17p). Alemtuzumab in physically non-fit patients with del (17p) NCCN [49]: Retreat as in first line therapy until short response in patients with long response to first line therapy (>3 years) Chemoimmunotherapy with reduced dose FCR, reduced dose PCR, bendamustine ± rituximab, HD methylprednisolone + rituximab in patients with short response <2 years for age ≥70 years (alternative: chlorambucil ± prednisone (if used first-line); ofatumumab; alemtuzumab ± rituximab; dose dense rituximab.) In patients with short response <2 years for age <70 years or older patients without significant co-morbidities and without del(11q) or del (17p): chemoimmunotherapy (FCR, PCR, BR, fludarabine + alemtuzumab; CHOP; HyperCVAD; dose adjusted EPOCH; OFAR). In alternative ofatumumab; alemtuzumab ± rituximab; HDMP + rituximab SIE, SIES, GITMO (present guidelines): In patients with no del [17p] and/or p53 mutations, and relapsed after 24 months, the same front-line therapy including rituximab can be considered. In patients with del [17p] and/or p53 mutations, in patients refractory or relapsed within 24 months from a fludarabine-based treatment, alemtuzumab containing regimens, or experimental treatment approaches within controlled trials should be given. Furthermore, in poor prognosis younger patients with adequate fitness status and no significant co-morbidities, a treatment approach including an allogeneic SCT, either from a sibling or well-matched unrelated donor, should be offered after an appropriate cytoreductive treatment.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE 2010: Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine *and alemtuzumab. NICE technology appraisal guidance 202.*	**Ergebnis:** • Ofatumumab is not recommended for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab. • People currently receiving ofatumumab for the treatment of chronic lymphocytic leukaemia that is refractory to fludarabine and alemtuzumab should have the option to continue treatment until they and their clinician consider it appropriate to stop. **Datenbasis:** The manufacturer's submission compared ofatumumab with best supportive care. The main source of evidence on clinical effectiveness was the Hx-CD20-406 study. This was a prospective uncontrolled trial that included 154 patients with chronic lymphocytic leukaemia, all of whom received ofatumumab, and 59 of whom had disease that was refractory to both fludarabine and alemtuzumab (that is, double-refractory chronic lymphocytic leukaemia). It also included 79 patients with chronic lymphocytic leukaemia that was refractory to fludarabine but for whom alemtuzumab was unsuitable because of bulky disease, and 16 patients who were not classified into either of these two groups. The evidence reported in the manufacturer's submission and considered in the appraisal was from the group of patients with double-refractory chronic lymphocytic leukaemia (that is, 59 patients from the total of 154 treated patients). **Weitere Quellen:** The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of ofatumumab, having considered evidence on the nature of chronic lymphocytic leukaemia and the value placed on the benefits of ofatumumab by people with the condition, those who represent them, and clinical specialists. It also

	took into account the effective use of NHS resources.
NICE 2010: Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia. NICE technology appraisal guidance 193.	**Ergebnis:** 1.1 Rituximab in combination with fludarabine and cyclophosphamide is recommended as a treatment option for people with relapsed or refractory chronic lymphocytic leukaemia except when the condition: • is refractory to fludarabine (that is, it has not responded to fludarabine or has relapsed within 6 months of treatment) or • has previously been treated with rituximab, unless: − in the context of a clinical trial, at a dose lower than the dose currently licensed for chronic lymphocytic leukaemia or − in the context of a clinical trial, in combination with chemotherapy other than fludarabine and cyclophosphamide. 1.2 Rituximab in combination with fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia that has previously been treated with rituximab, unless rituximab has been given as specified in section 1.1. 1.3 Rituximab in combination with chemotherapy other than fludarabine and cyclophosphamide is recommended only in the context of research for people with relapsed or refractory chronic lymphocytic leukaemia. 1.4 People with chronic lymphocytic leukaemia that is refractory to fludarabine (as defined in section 1.1), who are currently receiving rituximab in combination with fludarabine and cyclophosphamide should have the option to continue treatment until they and their clinicians consider it appropriate to stop. 1.5 People with chronic lymphocytic leukaemia that has previously been treated with rituximab other than as specified in section 1.1, who are currently receiving rituximab in combination with fludarabine and cyclophosphamide and people who are currently receiving rituximab in combination with other chemotherapy regimens that is not in the context of research, should have the option to continue treatment until they and their clinicians consider it appropriate to stop. **Datenbasis:** The manufacturer's submission compared the combination of rituximab plus fludarabine and cyclophosphamide with the combination of fludarabine plus cyclophosphamide. This comparison was based on the REACH trial, a phase III, multicentre, open-label, randomised controlled trial in people with previously treated chronic lymphocytic leukaemia. People were enrolled if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, a life expectancy greater than 6 months and if they had previously received treatment with chlorambucil monotherapy with or without prednisolone, fludarabine monotherapy (or other nucleoside analogue), or an alkylator-containing combination therapy (such as cyclophosphamide plus doxorubicin, vincristine and prednisolone, or cyclophosphamide plus vincristine and prednisolone). People were excluded from the trial if they had previously received treatment with interferon, rituximab or another monoclonal antibody, or fludarabine and cyclophosphamide, either concurrently or sequentially. People were also excluded if they had chronic lymphocytic leukaemia that was refractory to fludarabine (defined as not achieving at least a partial response for a minimum duration of 6 months). A total of 552 people were randomised to receive either rituximab plus fludarabine and

	cyclophosphamide or fludarabine and cyclophosphamide alone. The median age of people in the trial was 63 years and 67% were men. Most people (90%) had Binet stage B or C disease. **Weiteres / Experteneinschätzung:** The Appraisal Committee discussed current standard clinical management of relapsed or refractory chronic lymphocytic leukaemia. The Committee heard from clinical specialists that the most frequently used first-line treatments are: fludarabine plus cyclophosphamide with or without rituximab; and chlorambucil for people unable to have fludarabine because they have a poor performance status. However, for relapsed or refractory chronic lymphocytic leukaemia there is no single standard treatment option. The choice of treatment depends on a number of factors, including the presence of genetic abnormalities such as del(17p) mutation, previous treatments the person has received, whether a response was achieved from previous treatments, and if so, the duration of response. Clinical specialists noted that for these reasons, they considered it important to have a range of treatment options available.

Primärstudien

ÜBERSICHT

Table 1. Bases for approval of CLL drugs

Drug	Initial approval	Basis for approval
Alemtuzumab	May 7, 2001 (accelerated approval)	ORR in three single-arm studies in previously treated patients ($n = 149$); ORR was 21%–33%; median duration of response was 7–11 mo(s)
	September 19, 2007 (regular approval)	Improved PFS vs. chlorambucil in a randomized, active-controlled study ($n = 297$); HR favoring alemtuzumab was 0.58 [95% CI 0.43, 0.77 ($p <$ .0001, stratified log-rank test)]
Bendamustine	March 20, 2008 (regular approval)	Improved PFS vs. chlorambucil in a randomized, active-controlled study ($n = 301$); HR favoring bendamustine was 0.27 [95% CI 0.17, 0.43 ($p <$ .0001, stratified log-rank test)]
Ofatumumab	October 26 2009 (accelerated approval)	ORR of 42% in a single-arm study in patients refractory to fludarabine and alemtuzumab, most of whom also received alkylating agent drugs; median duration of response was 6.5 mo(s)

Abbreviations: CLL, chronic lymphocytic leukemia; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival.

Hinweise auf Zulassungstudien bei FDA (Aus: Casak SJ et al: U.S. Food and drug administration approval: rituximab in combination with fludarabine and cyclophosphamide for the treatment of patients with chronic lymphocytic leukemia. Oncologist 2011; 16: 97-104)

Chemoimmunotherapie

- *Anmerkung FBMed: narrative review mit Expert Opinion*
  "using PubMed (www.clinicaltrials. gov (till August 2012)), and recent American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Hematology association (EHA), International workshop on CLL (iwCLL) abstracts, using the primary search terms 'anti-CD20 monoclonal antibody' with/without CLL. Articles were chosen on the basis of relevance of anti-CD20 mAbs to CLL therapy"] (Quelle: Jain P, O'Brien S. Anti-CD20 monoclonal antibodies in chronic lymphocytic leukemia. Expert Opin Biol Ther 2013; 13 (2): 169-82.

Table 3. CIT with rituximab in relapsed/refractory CLL trials.

Protocols used	Number of patients	Median no. of prior treatments	Fludarabine refractory (%)	ORR (%)	CR (%)	Median remission duration (months)	Phase
BR [74]	78	2	22	59	9	14.7	II
FCR [75]	284	2	54	74	30	21	II
FCR vs FC [73]	276 vs 276	1	0	70 vs 58	24 vs 13	31 vs 21	III
R-HDM [116]	14	2	14	93	36	15	II

BR: Bendamustine with rituximab; CIT: Chemoimmunotherapy; CLL: Chronic lymphocytic leukemia; CR: Complete response; FCR: Fludarabine, cyclophosphamide and rituximab; ORR: Overall response rate.

Rituximab oder Ofatumumab:

- Der Cochrane Review von Bauer et al. 2012 (Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia) verweist auf "16 ongoing studies, including three trials comparing ofatumumab with or without additional chemotherapy versus no treatment."

- Lt. Recherche in Trialregister “clinicaltrials.gov” (durchgeführt am 20.3.2014) sind von oben genannten Studien 12 Studien noch laufend mit geplanten Patientenrekrutierungen bis mindestens ins Jahr 2016, davon 3 Studien mit relapsed/refractory CLL, 1 Studie mit first- und second-line Behandlung und 8 Studien mit unbehandelten CLL Patienten (first-line Setting).
  4 „abgeschlossene“ Studien:
  - 2 Studie mit unbehandelten CLL Patienten (first-line Setting) [Foa 2010, NCT00275054: „status unknown“],
  - 1 Studie bei Patienten in Remission nach first-line Therapie [Zagoskina 2011, nur Abstract]
  - 1 Studie mit nicht mehr zugelassenem Alemtuzumab (terminated – lack of accrural)

Bendamustin: in Dtl. nur zugelassen zur Primärtherapie

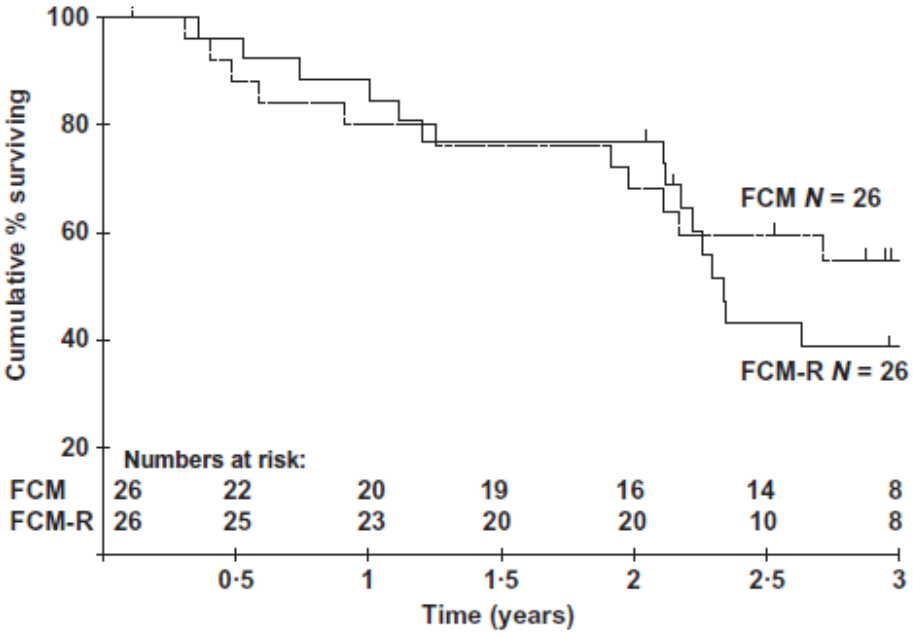
- *lediglich zur Info*: 1 Studie [Niederle et al, 2012, N=92] mit Vergleich Bendamustine vs. purine analogue (Fludarabine) bei Patienten unter second-line Behandlung mit nicht signifikantem Ergebnis bei Gesamtmortalität: RR=0,81 [95% K.I. 0,56-1,18] (lt. Cochrane Review von Vidal et al. 2012 [Bendamustine for patients with indolent B cell lymphoid malignancies including chronic lymphocytic leukaemia])

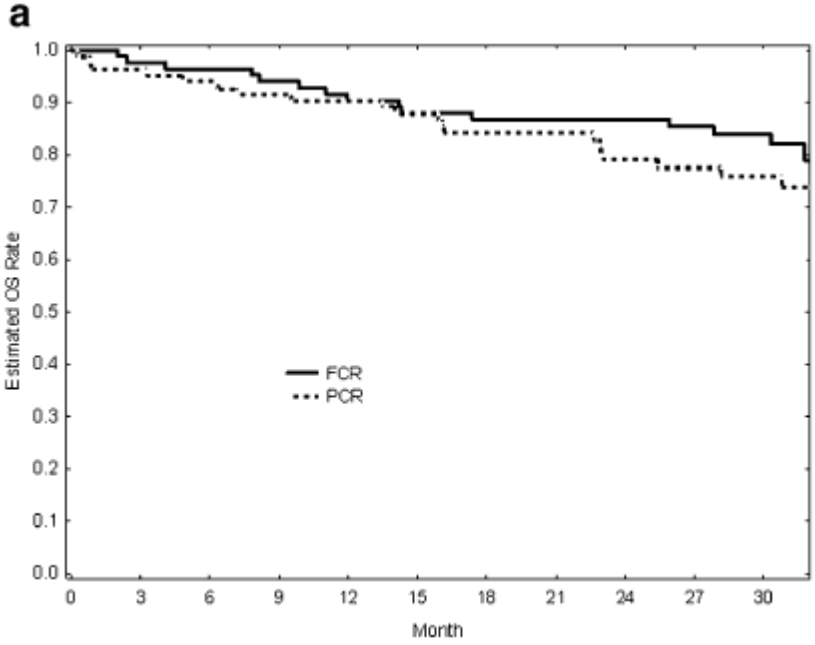
- *Zulassungsstudie, lediglich zur Info*: Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia: Knauf WU[1], et al: J Clin Oncol. 2009 Sep 10;27(26):4378-84. doi: 10.1200/JCO.2008.20.8389. Epub 2009 Aug 3.

AUFLISTUNG EINZELNER STUDIEN

Lt. Recherche (durchgeführt am 21.3.2014)

Casak SJ,. U.S. Food and drug administration approval: **rituximab in combination with fludarabine and cyclophosphamide** for the treatment of patients with chronic lymphocytic leukemia. Oncologist 2011; 16 (1): 97-104.	[*Anmerkung FBMed: Fragestellung der Publikation: results of two multinational, randomized trials in CLL patients comparing rituximab combined with fludarabine and cyclophosphamide versusFC were reviewed.]; Autoren sind aus FDA office* BO17072 [entspricht "REACH" trial im Cochrane Review von Baer et al. 2012], "An Open-Label, Multicenter, **Randomized, Comparative** Phase 3 Study to Evaluate the Efficacy and Safety of FCR versus FC Alone in Previously Treated Patients with CD20 Positive CLL" [Robak T, Dmoszynska A, Solal-Seligny P et al. Rituximab plus fludarabine prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756 –1765.]. **Study design** (Study BO17072 = REACH trial): open-label, **randomized (1:1) trial (N= 552)** comparing the efficacy of FCR (N= 276) to FC (N= 276). Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, BO17072 (previously treated) is an industry-sponsored, international trial conducted in Europe, Australia, New Zealand, Canada, and a single center in the United States that recruited 552 patients, and data in the clinical study report and datasets for this study included data from enrollment of the first patient, in July 2003, until data cutoff for the complete report analysis on July 23, 2008. The last patient was enrolled in August 2007. Patients who received one prior chemotherapy regimen. Patients previously exposed to fludarabine were required to be fludarabine-sensitive (i.e. have achieved a partial response (PR) or complete response (CR) lasting at least 6 months). **Results:** Overall survival: At the time of data cutoffs for the PFS analyses, the majority of patients were alive. Therefore, median survival times could not be estimated and no definitive conclusions can be made regarding the treatment effect of rituximab, when combined with FC chemotherapy, on survival. Progression free survival: primary efficacy analysis, based on 285 IRC [independent review committee]-determined PFS events (clinical data cutoff July 23, 2008) demonstrated a statistically significant difference in PFS that favored the FCR arm. The HR for PFS (FCR versus FC) was 0.76 (95% CI: 0.60, 0.96; *p*-value = .0218, log-rank test).The median PFS was 26.7 and 21.7 months for the FCR and FC arms, respectively. The analysis of PFS based on investigator-determined events is consistent with and supportive of the IRC [independent review committee] determined results.
Hillmen P,. A randomized phase II trial of **fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab** in previously treated chronic lymphocytic leukaemia. Br J Haematol 2011; 152 (5): 570-8.	**Trial design** [entspricht NCRI-CLL 201 trial aus Cochrane Review] multi-centre, **randomized, controlled**, open, two-stage, parallel group, Phase II trial assessing FCM and FCM-R for patients with CLL requiring therapy, who had received at least one prior therapy. Patients had CLL requiring therapy, previous treatment with at least one chemotherapeutic regimen, a World Health Organization (WHO) performance status (PS) of 0, 1, or 2 and a life expectancy of at least 12 weeks. → N = 52 patients were randomized **Intervention/Komparator:** randomized to fludarabine with cyclophosphamide plus mitoxantrone alone (FCM) or with simultaneous rituximab (FCM-R) on a 1:1 basis. **Primary endpoint** was ORR, defined as complete(CR) or partial remission (PR) by the International Workshop on CLL (IWCLL) Criteria (Hallek et al, 2008). Secondary endpoints were the proportion of patients with undetectable MRD, OS, PFS

	and toxicity. **Results**: The efficacy endpoints of response at 2 months posttreatment on all patients randomized to both stages of the trial are summarized in Table II. ORRs were 58% (95% CI: 40%, 77%) and 65% (95%CI: 44%, 83%) in the FCM and FCM-R arms respectively. Overall Survival:  Fig 2. Kaplan–Meier curve demonstrating the overall survival from randomization by treatment group, after 38 months median follow-up time for survivors. 29 of the 52 patients have died in total. **Safety**: Forty-one Serious Adverse Events (SAEs) were reported from 27(52%) patients (Table III). Nineteen of the events were from 13 (50%) patients who received FCM, and 22 were from 14 (54%) patients who received FCM-R.
Reynolds A Phase III trial of **fludarabine, cyclophosphamide, and rituximab vs. pentostatin**, **cyclophosphamide, and rituximab** in B-cell chronic lymphocytic leukemia. Invest New Drugs 2012; 30 (3): 1232-40.	**Study design** Phase III, open label, **randomized multicenter, community-based study**. **Patients** (N=177) Progressive, histologically confirmed, CD20+, B-cell CLL. Patients may have received 1 prior course of chemotherapy, including rituximab or fludarabine; prior radiation was not allowed. Other inclusion criteria included ECOG 0–2 (Patients were excluded if received >1 prior treatment regimen, received any prior radiation or pentostatin) **Intervention/Komparator:** randomized centrally into FCR (fludarabine plus C+R, N=88) or PCR (pentostatin (P), cyclophosphamide (C), and rituximab (R) , N=89); **Outcomes**: OS, PFS, response and toxicity Toxicities and adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 [16]. **Results**: • median OS for FCR and PCR has not been reached after 32 months. 12-month OS was 90.4% and 90.5% and 24-month OS was 86.7% and 79.1% for the FCR and

	PCR groups, respectively. • median PFS has not been reached for either group. 12-month PFS was 85.9% and 83.8% and 24-month PFS was 72.0% and 62.9% for the FCR and PCR groups Overall Survival:  *Anmerkung FBMed: moderate bis geringe Studienqualität (bspw. Randomisierung und Concealment nicht beschrieben, Fallzahlschätzung basiert nicht auf hier interessierenden Endpunkten, sondern auf Endpunkt „infection“ und würde 2x128 Patienten erfordern, die nicht erreicht/eingeschlossen wurden)*
Badoux XC,. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood 2011; 117 (11): 3016-24.	**study design** open-label, <u>single arm, non-comparative</u>, phase 2 trial **Patienten**: 284 previously treated patients (WHO/Eastern Cooperative Oncology Group [ECOG] performance status ≤ 3) were enrolled from December 1999 through April 2008. **Intervention**: fludarabine (F) 25 mg/m2 and cyclophosphamide (C) 250 mg/m2 on days 2-4 for course 1 and days 1-3 for courses 2-6. Rituximab (R) was administered on day 1 at 375 mg/m2 for course 1 and 500 mg/m2 for courses 2-6. **Results**: • **Overall survival:** Among 284 patients, 192 (68%) have died with a median follow-up time for all patients of 43 months (range, 0-122 months). estimated median survival time for all patients was 46.7 months (95% CI, 41.2-53.4 months • **Progression-free survival:** The estimated median PFS was 20.9 months (95% confidence interval [CI], 18.8-27.6 months) for the whole cohort of patients (n = 284).
Cortelezzi A, Bendamustine in combination with Ofatumumab in relapsed or refractory chronic lymphocytic leukemia: a GIMEMA Multicenter Phase II Trial. Leukemia 2014; 28 (3): 642-8.	**Studiendesign:** phase II, <u>non-comparative</u>, open-label, single-stage, multicenter study at 14 centers in Italy (GIMEMA CLL0809 Protocol, ClinicalTrials.gov Identifier: NCT01244451). **Patients**: relapsed and/or refractory CLL **Intervention**: Bendamustine and Ofatumumab (bendamustine (70 mg/m2) for 2 consecutive days every 28 days and ofatumumab (300mg on day 1 and 1000mg on day 8 at the first cycle and 1000mg on day 1 at the subsequent cycles), up to six cycles.) **Primary objective:** ORR (including CR, CR with incomplete marrow recovery, minimal residual disease (MRD)-negative CR (cytometric and molecular) or partial remission

	(PR)), (BendOfa) association in patients with refractory or relapsed CLL. Secondary objectives: CR, CR with incomplete marrow recovery, MRD-negative CR (cytometric and molecular), PR, safety, PFS, OS **Statistical analyses** The primary end point was the ORR. On the basis of a historical ORR rate of 70% with FCR in relapsed/refractory CLL,14 the desirable ORR rate was 85%. The sample size estimation was performed according to the A'Hern singlestage design with type I error of 0.05, to conclude the efficacy of an uninteresting regimen (response rate o70%), and a type II error of 0.20, implying the rejection of an active regimen (response rate >85%). **Results**: N=49 Patients: After a median follow-up of 23.6 months (range 1.3–33.3), OS was 83.6% (95% CI, 73.0–95.7%)
Cramer P,. Second-line therapies of patients initially treated with fludarabine and cyclophosphamide or fludarabine, cyclophosphamide and rituximab for chronic lymphocytic leukemia within the CLL8 protocol of the German CLL Study Group. Leuk Lymphoma 2013; 54 (8): 1821-2.	NUR updated BEOBACHTUNGSDATEN aus ursprünglichen behandlungs-naiven Studiengruppe, KEINE EIGENSTÄNDIGE RCT MIT SECOND-LINE PATIENTEN: Updated results of the CLL8 trial with 817 treatment naive patients with CLL in good physical fitness; randomized within the CLL8 trial and received up to six courses of FC without or with rituximab (FCR). **Results**: • Until July 2010, 232 patients were treated for relapse, among them 91 of 408 (22%) initially treated with FCR and 141 of 409 (35%) initially treated with FC. Forty-seven of 232 patients (20.3%) required second-line therapy within 6 months, 66 patients (28.5%) required treatment 6 – 24 months after initial treatment, 97 patients (41.8%) were treated within 24 – 48 months and 22 patients (9.5%) were treated > 48 months after initial therapy. • Drugs most frequently used for second-line treatment were rituximab (52% of all second-line therapies), fludarabine (21%), bendamustine (21%) and alemtuzumab (12%). Some 49.8% of all second-line therapies were chemoimmunotherapies. • The combination of cyclophosphamide, doxorubicin, vincristine, prednisolone and rituximab (R-CHOP) was the most common treatment (35 patients, 15% of all second-line therapies), followed by FCR (32 patients, 13.8%) and bendamustine/ rituximab (BR) (27 patients, 11.6%), and single agent alemtuzumab (20 patients) or bendamustine (17 patients). • Other prevalent second-line therapies were CHOP and FC (11 patients, respectively) and chlorambucil (nine patients) as well as rituximab monotherapy (seven patients); nine patients underwent stem cell transplants (four allogeneic, one autologous, four unknown). Patients initially treated with FC received mainly R-CHOP (25 of 141 patients, 17.7%), FCR (21/141 patients, 14.9%) and BR (15/141 patients, 10.6%), whereas patients initially treated with FCR received mainly BR (12/91 patients, 13.2%), FCR and single-agent alemtuzumab (11/91 patients, 12.1%, respectively) or R-CHOP (10/91 patients, 11.0%). In patients who required second-line treatment within the first 2 years after initial therapy, R-CHOP (28 of 113 patients, 24.8%), alemtuzumab (12/113 patients, 10.6%), CHOP and BR (10/113 patients, 8.9%, respectively) were the most common therapies. Patients with a late relapse and start of second-line treatment > 24 months after FC/FCR received mainly FCR (16 of 119 patients, 13.5%), BR (13/119 patients, 10.9%) or bendamustine (9/119 patients, 7.6%).
Delgado J, Rituximab-based chemoimmunotherapy prolongs survival of patients with chronic lymphocytic leukemia independently of the time of administration. Clin	FALLSERIE: All patients consecutively treated for CLL at our institution from January 1980 to December 2010, independently of whether they had been included in trials, were classified into 3 different groups: (1) those treated with alkylating agents (e.g. chlorambucil, cyclophosphamide) but never received PA nor rituximab (AA) (n = 211); (2) those who had received PA at some point in their clinical course, but not rituximab (PA) (n = 159); and (3) those who had received both PA and rituximab (PAþR) (n = 114). **Results**: After a median follow-up of 7.3 years (range, 0.3-21 years) for the entire group, including

Lymphoma Myeloma Leuk 2014; 14 (1): 73-9.	survivors and non-survivors, 148 of 273 (54%) patients remain alive. At 8 years, the projected OS of the PAþR group was 88% (95% confidence interval [CI], 82%-94%) compared with 68% (60%-76%) for the PA group (P < .001). This survival advantage was observed in patients with Binet stage B disease at the time of front-line therapy (88% vs. 65%; P = .001), but not in patients with stage A (86% vs. 83%; P = .275) or stage C disease (91% vs. 60%; P = .179). Moreover, the projected 8-year OS of patients aged 60 years or younger at the time of treatment was 91% (97%-85%) and 73% (63%-83%) for those treated with PAþR and PA, respectively (P ¼ .004), and older patients showed an 8-year OS of 69% (43%-95%) and 61% (49%-73%), respectively (P = .366). Causes of death were equally distributed among groups (P = .283), with the only caveat being that there was a higher proportion of patients from the PA group whose cause of death was unknown (P = .068). When the OS of patients treated with
Fischer K, Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011; 29 (26): 3559-66.	***Study Design*** prospective, multicenter, nonrandomized, single arm phase II **Intervention**: All patients (78 patients at 32 centers in Germany) to receive bendamustine 70mg/m2 on days 1 and 2 combined with rituximab 375 mg/m2 on day 0 for the first course and 500 mg/m2 on day 1 for all subsequent courses primary end point is ORR **Results**: In the ITT population, the ORR was 59.0% (95% CI, 47.3% to 70.0%; n_46), with a CR rate of 9.0% (n=7), two nodular partial responses, and a partial response rate of 47.4% (n=37).
Visco C, . The **combination of rituximab, bendamustine**, **and cytarabine** for heavily pretreated relapsed/refractory cytogenetically high-risk patients with chronic lymphocytic leukemia. Am J Hematol 2013; 88 (4): 289-93.	**Study design:** four-center, single arm, open-label, prospective study [pilot trial] **Patients** (N=13!): cohort of relapsed or refractory patients with B-CLL, previously treated, enrolled between February 2010 and September 2012. **Intervention**: R-BAC regimen consisted of rituximab (375 mg/ m2, Day 1 of first cycle, then 500 mg/m2 for subsequent cycles), bendamustine (70 mg/m2, Days 1–2, given as a 1-hr infusion) and cytarabine (800 mg/m2, Day 1–3, given as a 2-hr infusion starting 2 hr after bendamustine). **Endpoints**: • Primary end-point: the response rate. • Secondary end-points: PFS, overall survival (OS) **Results:** After a median follow-up for survivors of 17 months (range 2–34), eight patients (62%) were alive and disease-free. Median PFS was 16 months while median OS was not reached (1-year OS: 75 +- 13%, CI: 5%)
Wierda WG, , et al. **Ofatumumab** as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1749-1755.	**Study design:** single arm, prospective trial (N=138, in interim analysis), pivotal study (registered at Clinical Trials.gov (NCT00349349) All patients were to receive 8 weekly, then 4 monthly, intravenous infusions of ofatumumab (dose 1, 300 mg; doses 2-12, 2000 mg). **Endpoints**: • Primary end point: ORR • Secondary endpoints: PFS, OS, and safety **Results**:

	Weitere posthoc analysis of the pivotal study: s. unten (Wierda et al, 2011) In the interim analysis of the pivotal international trial in patients with fludarabine- and alemtuzumab-refractory (FA-ref; n_59)CLLor fludarabine-refractoryCLLwith bulky (_5 cm lymph nodes) lymphadenopathy (BF-ref; n_79), the overall response rate (ORR) with ofatumumab was 58% and 47% in the FA-ref and BF-ref groups, respectively.11 Median PFS and OS were 5.7 months and 13.7 months for the FA-ref group, and 5.9 months and 15.4 months for the BF-ref group, respectively. **Abstract:** ***Objective:*** New treatments are needed for patients with fludarabine- and alemtuzumab-refractory (FA-ref) chronic lymphocytic leukemia (CLL) or patients with fludarabine-refractory CLL with bulky (> 5 cm) lymphadenopathy (BF-ref) who are less suitable for alemtuzumab treatment; these groups have poor outcomes with available salvage regimens. Ofatumumab (HuMax-CD20) is a human monoclonal antibody targeting a distinct small-loop epitope on the CD20 molecule. We conducted an international clinical study to evaluate the efficacy and safety of ofatumumab in patients with FA-ref and BF-ref CLL. ***Patients and methods:*** Patients received eight weekly infusions of ofatumumab followed by four monthly infusions during a 24-week period (dose 1 = 300 mg; doses 2 to 12 = 2,000 mg); response by an independent review committee (1996 National Cancer Institute Working Group criteria) was assessed every 4 weeks until week 24 and then every 3 months until month 24. ***Results:*** This planned interim analysis included 138 treated patients with FA-ref (n = 59) and BF-ref (n = 79) CLL. The overall response rates (primary end point) were 58% [corrected] and 47% in the FA-ref and BF-ref groups, respectively. Complete resolution of constitutional symptoms and improved performance status occurred in 57% and 48% of patients, respectively. Median progression-free survival and overall survival times were 5.7 and 13.7 months in the FA-ref group, respectively, and 5.9 and 15.4 months in the BF-ref group, respectively. The most common adverse events during treatment were infusion reactions and infections, which were primarily, grade 1 or 2 events. Hematologic events during treatment included anemia and neutropenia. ***Conclusion:*** Ofatumumab is an active, well-tolerated treatment providing clear clinical improvements for fludarabine-refractory patients with very poor-prognosis CLL.
Wierda et al: Ofatumumab is active in patients with fludarabine-refractory CLL irrespective of prior rituximab: results from the phase 2 international study. Blood 2011; 118 (19): 5126-9.	**Study design:** single arm, prospective trial; hier: posthoc analysis of the pivotal study (siehe oben: Wierda WG, Kipps TJ, Mayer J, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. *J Clin Oncol.* 2010;28(10):1749-1755., registered at Clinical Trials.gov (NCT00349349)) **Objective**: to potentially gain perspective into whether prior exposure and refractoriness to rituximab correlated with ofatumumab treatment outcomes. All patients were to receive 8 weekly, then 4 monthly, intravenous infusions of ofatumumab (dose 1, 300 mg; doses 2-12, 2000 mg). Final enrollment (n _ 206) for this analysis included all patients from the interim analysis (n = 138) and an additional 68 patients (36 FA-ref; 32 BF-ref). Median follow-up was 25.8 months. The prior rituximab subgroup had a higher proportion of patients with poorer Eastern Cooperative Oncology Group Performance Status (1 or 2 vs 0; *P* =.027) and was more heavily pretreated (median prior treatments 5 vs 4; *P* =.001) compared with the rituximab naive subgroup. **Enpoints:** • Primary end point: ORR

	• Secondary endpoints: PFS, OS, and safety **Results**: Among 206 patients (FA-ref, n_95; BF-ref, n_111), 117 received prior rituximab monotherapy or rituximab-containing therapy and 89 were rituximab-naive. Slightly longer median progression-free survival (mPFS) after ofatumumab for rituximab-naive patients compared with patients previously treated with rituximab (5.6 vs 5.3 months, respectively, *P* = .04), and no difference in ORR or median overall survival (OS). Of patients with prior rituximab exposure, type of last rituximab containing therapy (e.g. monotherapy or combination regimen), refractoriness to last rituximab regimen, and time to progression from the last rituximab regimen did not appear to impact ORR, mPFS, or mOS with ofatumumab treatment

Übersicht zu Studien zu Ofatumumab

[Anmerkung FBMed: non-systematic narrative review]
(aus: Gupta IV, Jewell RC. Ofatumumab, the first human anti-CD20 monoclonal antibody for the treatment of B cell hematologic malignancies. Ann N Y Acad Sci 2012; 1263 43-56.):

Table 1. Clinical trials of ofatumumab in CLL

GlaxoSmithKline, GenMab, and NCT study numbers	Phase	Therapy	Setting	Status[a]	Efficacy	Safety
N/A Hx-CD20-402 NCT00093314[28]	I/II	Ofatumumab monotherapy	Relapsed/refractory CLL	Completed	ORR[b] = 50% ($N = 26$) 62% of pts responding within four weeks mPFS = 106 days	MTD not reached ($N = 33$) 97% of pts received all planned infusions 92% of pts with grade 1/2 AEs 56% of AEs were infusion-related events 51% of pts with infections
OMB111773 Hx-CD20-406 NCT00349349[30]	IIA	Ofatumumab monotherapy	Relapsed/refractory CLL who failed fludarabine and alemtuzumab	Active, not recruiting	ORR[c] = 51% (FA-ref, $n = 95$); 44% (BF-ref, $n = 111$) mDOR = 5.7 mo (FA-ref); 6.0 mo (BF-ref) mPFS = 5.5 mo (both groups) mOS = 14.2 mo (FA-ref); 17.4 mo (BF-ref)	50% of pts received all planned infusions Infusion-related reactions: 63% (both groups) Grade 3/4 infections: 24% (both groups)
OMB111827 Hx-CD20-416 NCT00802737[54]	IV	Ofatumumab monotherapy retreatment and maintenance	Patients with CLL who progressed following response or stable disease after ofatumumab treatment in Hx-CD20-406	Active, not recruiting	N/A	N/A
OMB112517 N/A NCT01039376 PROLONG[55]	IIIA	Ofatumumab maintenance versus observation	Patients with relapsed CLL who have responded after second- or third-line therapy	Recruiting	N/A	N/A
OMB114242 N/A NCT01313689[56]	IIIA	Ofatumumab monotherapy versus physician's choice	Patients with bulky fludarabine-refractory CLL who underwent at least 2 prior therapies	Recruiting	N/A	N/A

Continued

Table 1. *Continued*

GlaxoSmithKline, GenMab, and NCT study numbers	Phase	Therapy	Setting	Status[a]	Efficacy	Safety
OMB111774 Hx-CD20-407 NCT00410163 BIFROST[56]	IIA	O-FC	Previously untreated CLL	Active, not recruiting	CR[d] = 32% (500-mg group); 50% (1,000-mg group); 41% (both groups) ORR = 77% (500-mg group); 73% (1,000-mg group); 75% (both groups) mPFS and mOS = not reached	All infusion-related reactions were grade 1/2 48% grade 3/4 neutropenia Infections: 38% (all grades), 8% (grade 3/4) 41% nausea (all grades) Thrombocytopenia: 26% (all grades), 15% (grade 3/4) 13% grade 3/4 anemia
OMB115991 N/A NCT01520922[57]	II	Ofatumumab + bendamustine	Untreated or relapsed CLL	Recruiting	N/A	N/A
OMB110911 N/A NCT00748189 COMPLEMENT 1[58]	IIIA	Ofatumumab + chlorambucil versus chlorambucil monotherapy	Untreated CLL	Active, not recruiting	N/A	N/A
OMB110913 N/A NCT00824265 COMPLEMENT 2[59]	IIIA	O-FC versus FC	Relapsed CLL	Active, not recruiting	N/A	N/A

[a]As per www.clinicaltrials.gov.
[b]Assessed up to week 19.
[c]Assessed up to week 24.
[d]Assessed up to three months after last infusion.
AE, adverse event; BF-ref, bulky lymphadenopathy fludarabine-refractory; CLL, chronic lymphoid leukemia; CR, complete response; FA-ref, fludarabine- and alemtuzumab-refractory; mDOR, median duration of response; mo, months; mOS, median overall survival; mPFS, median progression-free survival; MTD, maximum-tolerated dose; N/A, data not yet available; NCT, National Clinical Trial; O-FC, ofatumumab + fludarabine + cyclophosphamide; ORR, overall response rate; pts, patients.

Detaillierte Darstellung der Recherchestrategie:

Cochrane (Database of Systematic Reviews, DARE, Technology Assessments) am 27.02.2014

Suchschritt	Suchfrage	Trefferzahl
#1	MeSH descriptor: [Leukemia, B-Cell] explode all trees	228
#2	b-cell:ti,ab,kw or chronic*:ti,ab,kw (Word variations have been searched)	60578
#3	lymphocytic:ti,ab,kw or lymphoid:ti,ab,kw (Word variations have been searched)	1533
#4	leukaemia*:ti,ab,kw or leukemia*:ti,ab,kw (Word variations have been searched)	6570
#5	#2 and #3 and #4	546
#6	lymphoma*:ti,ab,kw (Word variations have been searched)	4893
#7	#4 or #6	10167
#8	chronic*:ti,ab,kw and b-cell:ti,ab,kw (Word variations have been searched)	339
#9	#7 and #8	278
#10	CLL:ti,ab,kw (Word variations have been searched)	327
#11	small next cell:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	49
#12	small:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	28
#13	well next differentiated:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	8
#14	SLL:ti,ab,kw (Word variations have been searched)	23
#15	#1 or #5 or #9 or #10 or #11 or #12 or #13 or #14 from 2009 to 2014	46

MEDLINE (PubMed) am 27.02.2014

Suchschritt	Suchfrage	Trefferzahl
#1	Search "leukemia, b cell"[MeSH Terms]	12447
#2	Search (b-cell[Title/Abstract]) OR chronic*[Title/Abstract]	903047
#3	Search (lymphocytic[Title/Abstract]) OR lymphoid[Title/Abstract]	102041
#4	Search (leukaemia*[Title/Abstract]) OR leukemia*[Title/Abstract]	195005
#5	Search (#2 AND #3 AND #4)	18399
#6	Search lymphoma*[Title/Abstract]	128371
#7	Search (#4 OR #6)	301338
#8	Search (chronic*[Title/Abstract]) AND b-cell[Title/Abstract]	9737
#9	Search (#7 AND #8)	7123
#10	Search CLL[Title/Abstract]	10109
#11	Search (small-cell[Title/Abstract]) AND lymphoma*[Title/Abstract]	1850
#12	Search ((small[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	1830
#13	Search ((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	200
#14	Search SLL[Title/Abstract]	579
#16	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	27335
#22	Search ((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR	167284

	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]))))	
#25	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) Filters: Systematic Reviews; Meta-Analysis; Technical Report	248
#26	Search (#16 AND #22)	158
#27	Search (#25 OR #26)	316
#28	Search (#25 OR #26) Filters: published in the last 5 years	142

MEDLINE (PubMed) nach Leitlinien am 27.02.2014

Suchschritt	Suchfrage	Trefferzahl
#1	Search "leukemia, b cell"[MeSH Terms]	12447
#2	Search (b-cell[Title/Abstract]) OR chronic*[Title/Abstract]	903047
#3	Search (lymphocytic[Title/Abstract]) OR lymphoid[Title/Abstract]	102041
#4	Search (leukaemia*[Title/Abstract]) OR leukemia*[Title/Abstract]	195005
#5	Search (#2 AND #3 AND #4)	18399
#6	Search lymphoma*[Title/Abstract]	128371
#7	Search (#4 OR #6)	301338
#8	Search (chronic*[Title/Abstract]) AND b-cell[Title/Abstract]	9737
#9	Search (#7 AND #8)	7123
#10	Search CLL[Title/Abstract]	10109
#11	Search (small-cell[Title/Abstract]) AND lymphoma*[Title/Abstract]	1850
#12	Search ((small[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	1830
#13	Search ((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	200
#14	Search SLL[Title/Abstract]	579
#16	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	27335
#17	Search (non-hodgkin*[Title]) AND lymphoma*[Title]	13590
#18	Search (#16 OR #17)	39854
#19	Search ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]	69915
#20	Search (#18 AND #19)	110
#21	Search (#18 AND #19) Filters: published in the last 5 years	34

MEDLINE (PubMed) nach RCTs am 21.03.2014

Suchschritt	Suchfrage	Trefferzahl
#10	Search ritux*[Title/Abstract]	10543
#11	Search rituximab[Supplementary Concept]	7895
#12	Search mabt*[Title/Abstract]	160
#13	Search zytux[Title/Abstract]	0
#14	Search ofatumumab[Supplementary Concept]	95
#15	Search ofatumumab*[Title/Abstract]	176
#16	Search idec*[Title/Abstract]	280
#17	Search arzerr*[Title/Abstract]	5
#18	Search humax*[Title/Abstract]	22
#19	Search gazyva[Title/Abstract]	1
#20	Search obinutuzumab*[Title/Abstract]	41
#21	Search obinutuzumab[Supplementary Concept]	29
#22	Search afutuzumab*[Title/Abstract]	1
#23	Search ga101[Title/Abstract]	36
#24	Search RO5072759[Title/Abstract]	1
#25	Search RO 5072759[Title/Abstract]	0
#26	Search ga 101[Title/Abstract]	11
#27	Search (monoclonal*[Title/Abstract]) AND antibod*[Title/Abstract]	173212
#28	"antibodies, monoclonal"[MeSH Terms]	175503
#29	Search (#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 OR #26 OR #27 OR #28)	253560
#30	Search "leukemia, b cell"[MeSH Terms]	12491
#39	Search (b-cell[Title/Abstract]) OR chronic*[Title/Abstract]	906836
#40	Search (lymphocytic[Title/Abstract]) OR lymphoid[Title/Abstract]	102334
#41	Search (leukaemia*[Title/Abstract]) OR leukemia*[Title/Abstract]	195566
#42	Search (#39 AND #40 AND #41)	18471
#43	Search lymphoma*[Title/Abstract]	128813
#44	Search (#41 OR #43)	302279
#45	Search (chronic*[Title/Abstract]) AND b-cell[Title/Abstract]	9783
#46	Search (#44 AND #45)	7157
#47	Search CLL[Title/Abstract]	10148
#48	Search (small-cell[Title/Abstract]) AND lymphoma*[Title/Abstract]	1858
#49	Search ((small[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	1837
#50	Search ((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	200
#51	Search SLL[Title/Abstract]	582
#52	Search (#30 OR #42 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51)	27442
#53	Search randomized controlled trial[Publication Type]	361456
#54	Search controlled clinical trial[Publication Type]	87042
#55	Search (randomized[Title/Abstract]) OR randomised[Title/Abstract]	370016
#56	Search placebo[Title/Abstract]	155865
#57	Search randomly[Title/Abstract]	211037
#58	Search trial[Title/Abstract]	354971
#59	Search groups[Title/Abstract]	1365446
#60	Search "Clinical Trials as Topic"[Mesh:NoExp]	166637

#61	Search (#53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60)	2119398
#62	Search (#29 AND #52)	1178
#68	Search (#61 AND #62)	568
#69	Search (#61 AND #62) Filters: Publication date from 2011/01/01 to 2014/12/31	135

Cochrane Trials Register am 21.03.2014

Suchschritt	Suchfrage	Trefferzahl
#1	(ritux* or mabt* or zytux or ofatumumab* or idec* or arzerr* or humax* or gazyva or obinutuzumab* or afutuzumab* or ga101 or RO5072759 or RO next 5072759 or ga next 101):ti,ab,kw (Word variations have been searched)	933
#2	monoclonal*:ti,ab,kw and antibod*:ti,ab,kw (Word variations have been searched)	5941
#3	MeSH descriptor: [Antibodies, Monoclonal] explode all trees	4688
#4	#1 or #2 or #3	6581
#5	MeSH descriptor: [Leukemia, B-Cell] explode all trees	228
#6	b-cell:ti,ab,kw or chronic*:ti,ab,kw (Word variations have been searched)	60581
#7	lymphocytic:ti,ab,kw or lymphoid:ti,ab,kw (Word variations have been searched)	1533
#8	leukaemia*:ti,ab,kw or leukemia*:ti,ab,kw (Word variations have been searched)	6570
#9	#6 and #7 and #8	546
#10	lymphoma*:ti,ab,kw (Word variations have been searched)	4893
#11	#8 or #10	10167
#12	chronic*:ti,ab,kw and b-cell:ti,ab,kw (Word variations have been searched)	339
#13	#11 and #12	278
#14	CLL:ti,ab,kw (Word variations have been searched)	327
#15	small next cell:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	49
#16	small:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	28
#17	well next differentiated:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	8
#18	SLL:ti,ab,kw (Word variations have been searched)	23
#19	#5 or #9 or #13 or #14 or #15 or #16 or #17 or #18	722
#20	#4 and #19	119
#21	#4 and #19: Publication Date from 2011 to 2014	33

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Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2014-B-068-z Idelalisib

Datum: 25.08.2014

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Inhalt

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Berücksichtigte Wirkstoffe/Therapien: 2

Systematische Recherche: 2

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Indikation für die Recherche

Idealisib wird in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation angewendet, die ungeeignet für eine Chemoimmuntherapie sind.

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 „**chronische lymphatische Leukämie**“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am **27.02.2014** 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), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **250** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **21** Quellen eingeschlossen. Insgesamt ergab dies **7** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

AC	Advisory Council
AE	adverse events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BCSH	British Committee for Standards in Haematology
C	cyclophosphamide
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CHOP-R	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
Clb	Chlorambucil
CLL	chronic lymphocytic leukaemia
CR	Complete response
CRR	complete response rate
DAHTA	Deutsche Agentur für Health Technology Assessment
EBMT	European Group for Blood and Marrow Transplant
EP	expert panel
FCM	Fludarabine, Cyclophosphamide, Mitoxantrone
FCM-R	Rituximab, Fludarabine, Cyclophosphamide, Mitoxantrone
Flu	fludarabine
FluC	fludarabine with cyclophosphamide
FluCam	Fludarabine and alemtuzumab in combination
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GITMO	Gruppo Italiano Trapianto di Midollo Osseo
GoR	Grade of Recommendation
Gy	Gray
HDMP	High-dose-methylprednisolone
HR	Hazard Ratio
HSCT	Hematopoietic stem cell transplantation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
M	mitoxantrone
MBL	Monoklonale B Lymphozytose
MRD	minimal residual disease
NGC	National Guideline Clearinghouse
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
ORR	overall response rate
OS	Overall survival
OS	Overall survival
PFS	Progression free survival
PR	Partial response
R	rituximab
RIC	reduced intensity conditioning
RT-allo-HCT	Reduced-toxicity allogeneic hematopoietic cell transplantatio
SCT	Stem CellTransplantation
SIE	Italian Society of Hematology
SIES	Società Italiana di Ematologia Sperimentale
TRIP	Turn Research into Practice Database
TRM	treatment-related mortality
UK	United Kingdom

Cochrane Reviews

Bauer et al. 2012: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia.	1. Fragestellung: The objective of this reviewis to assess and summarise the evidence for the treatment of patients with CLL with monoclonal anti-CD20 antibodies.
	2. Methodik Population: Patients with histologically confirmed B-cell CLL. Both pre-treated and chemotherapy-naive patients were included. If trial populations would have been mixed (i.e. patient groups with different haematological malignancies), data from the CLL subgroups would have been used. If subgroup data for CLL patients would not have been provided (after contacting the authors of the trial), the trial would have been excluded if less than 80% of patients had CLL. Intervention / Komparator: All randomised trials of anti-CD20 antibody given alone or in combination with chemotherapy as primary treatment or maintenance treatment in untreated as well as refractory or relapsed patients. Different treatment approaches for the control group including 'watchful waiting' and conventional therapies such as fludarabine or Clb monotherapy, fludarabine in combination with other chemotherapeutic agents, or other antibody therapy were considered. 1. Anti-leukaemic therapy plus anti-CD20 antibody versus anti-leukaemic therapy alone; anti-leukaemic therapy identical in both groups. 2. Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (antileukaemic therapy not identical in both groups). *Hinweis*: No trial regarding the comparison of anti-CD20 antibody versus anti-leukaemic therapy was identified. Endpunkte: • Primärer Endpunkt: OS • Sekundäre Endpunkte: PFS; time to next treatment; treatment-related mortality (TRM); complete response rate (CRR); overall response rate (ORR); minimal residual disease (MRD); adverse events (AE); number of patients discontinuing the study because of drug-related AEs Suchzeitraum (Aktualität der Recherche): Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 12, 2011), MEDLINE (from January 1990 to 4 January 2012), and EMBASE (from 1990 to 20 March 2009) as well as conference proceedings (American Society of Hematology, American Society of Clinical Oncology, European Hematology Association and European Society of Medical Oncology) for randomised controlled trials (RCTs) were searched. Anzahl eingeschlossene Studien/Patienten (Gesamt): Only five could be included in the two separate meta-analyses. Qualität der Studien: The overall the quality of these trials was judged as moderate to high. All trials were randomised and open-label studies. However, two trials were published as abstracts only, therefore it was impossible to assess the potential risk of bias for these trials in detail.
	3. Ergebnisdarstellung

Allgemein:

Four trials evaluated the anti-CD20 antibody in patients receiving first-line therapy (CALBG 9712; CLL2007FMP; GCLLSG CLL 8; Wierda 2011).

Three trials evaluated rituximab versus no further therapy and observation (GCLLSG CLL 8; NCRI-CLL 201; REACH).

Two trials (CLL2007FMP; Gribben 2005) assessed the role of rituximab versus alemtuzumab. One trial compared the effects of rituximab 500 mg with rituximab 1000 mg (Wierda 2011). The other trial assessed two schedules: rituximab and fludarabine plus rituximab (Flu-R) maintenance compared to fludarabine alone plus rituximab maintenance (CALBG 9712).

- GCLLSG CLL 8- Studie: Patients recruited (N (total) = 817); Studienarme: FluC-R (N = 408; 4 did not receive study drugs, 20 without response assessment, 7 lost to follow-up) / FluC (N = 409; 13 did not receive study drugs, 38 without response assessment, 20 lost to follow-up)
- CALBG 9712- Studie: Patients recruited (N (total)= 104); Randomisation: Arm 1 (sequential): 6 monthly courses of fludarabine alone followed 2 months later by rituximab consolidation therapy versus arm 2 (concurrent): 6 monthly courses of Flu-R followed 2 months later by 4 weekly doses of rituximab for consolidation therapy
- CLL2007FMP- Studie: Patients recruited (N (total)= 165); Randomisation: 6 courses of FluC--R versus 6 courses of FluC-Cam
- Wierda 2011- Studie: Patients recruited (N(total)= 61); Randomisation: arm 1 FCO500: (fludarabine plus cyclophosphamide plus ofatumumab) (500 mg) versus arm 2 FCO1000 (fludarabine plus cyclophosphamide plus ofatumumab) (1000 mg)

Comparison 1: Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups)

OS:

- Analyse: subgrouped by different anti-CD20 antibody treatment regimens → first-line treatment (basierend auf der GCLLSG CLL 8 Studie): HR: 0.67 [95%KI: 0.48, 0.94] zum Vorteil der Kombinationstherapie (Anti-leukaemic therapy plus anti-CD20 antibody)

PFS:

- Analyse: subgrouped by prognostic factor: → del17p (basierend auf der GCLLSG CLL 8 Studie): HR: 0.47 [95%KI: 0.24, 0.92] zum Vorteil der Kombinationstherapie (Anti-leukaemic therapy plus anti-CD20 antibody)
- Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line treatment (basierend auf der GCLLSG CLL 8 Studie): HR: 0.56 [95%KI: 0.46, 0.68] zum Vorteil der Kombinationstherapie (Anti-leukaemic therapy plus anti-CD20 antibody)

Time to next treatment:

- Analyse: subgrouped by different anti-CD20 antibody treatment regimens. →

	first-line treatment (basierend auf der GCLLSG CLL 8 Studie): HR: 0.59 [95%KI: 0.47, 0.74] zum Vorteil der Kombinationstherapie (Anti-leukaemic therapy plus anti-CD20 antibody) **ORR:** • Analyse: subgrouped by prognostic factor: → del17p (basierend auf der GCLLSG CLL 8 Studie): HR: 1.98 [95%KI: 1.11, 3.52] zum Vorteil der Kombinationstherapie (Anti-leukaemic therapy plus anti-CD20 antibody) • Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line treatment (basierend auf der GCLLSG CLL 8 Studie): HR: 1.13 [95%KI: 1.06, 1.19] zum Vorteil der Kombinationstherapie (Anti-leukaemic therapy plus anti-CD20 antibody) **CRR:** • Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line treatment (basierend auf der GCLLSG CLL 8 Studie): HR: 2.05 [95%KI: 1.65, 2.54] zum Vorteil der Kombinationstherapie (Anti-leukaemic therapy plus anti-CD20 antibody) **Treatment-related-mortality:** • Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line treatment (basierend auf der GCLLSG CLL 8 Studie): HR: 0.80 [95%KI: 0.32, 2.01] **Grade 3/4 AEs:** • Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line treatment (basierend auf der GCLLSG CLL 8 Studie): HR: 1.22 [95%KI: 1.11, 1.33] zum Vorteil der Kontrolltherapie (Anti-leukaemic therapy alone) **Comparison 2: Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (anti-leukaemic therapy not identical in both groups)** **ORR:** • Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line therapy (basierend auf der CLL2007FMP Studie): HR: 1.03 [95%KI: 0.91, 1.16] **CRR:** • Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line therapy (basierend auf der CLL2007FMP Studie): HR: 1.27 [95%KI: 0.98, 1.65] **Treatment-related mortality:** • Analyse: subgrouped by different anti-CD20 antibody treatment regimens. → first-line therapy (basierend auf der CLL2007FMP Studie: HR: 0.11 [95%KI: 0.01, 2.01]
	1. Fazit der Autoren: *This meta-analysis showed that patients receiving chemotherapy plus rituximab benefit in terms of OS as well as PFS compared to those with chemotherapy alone. Therefore, it supports the recommendation of*

	rituximab in combination with FluC as an option for the first-line treatment as well as for the people with relapsed or refractory CLL. The available evidence regarding the other assessed comparisons was not sufficient to deduct final conclusions. We are aware of 16 ongoing studies, including three trials comparing ofatumumab with or without additional chemotherapy versus no treatment.

Leitlinien

British Committee for Standards in Haematology (BCSH), 2012: Guidelines on the diagnosis, investigation and management of Chronic Lymphocytic Leukaemia.	Fragestellung The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia.
	Methodik ***Grundlage der Leitlinie*** review of the literature using Medline/Pubmed The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH (British Committee for Standards in Haematology) and the British Society for Haematology Committee and comments incorporated where appropriate. ***Suchzeitraum*** bis August 2011 (Update der Version von 2004) ***LOE and GOR*** gemäß GRADE
	Management of High-risk CLL *Hinweis*: Previously untreated or relapsed patients with a TP53 abnormality who require therapy and those who relapse within 2 years of, or are refractory to purine analogue based therapy regardless of biomarker results, are considered to have 'high risk' CLL. These patient groups have a poor outcome when treated conventionally and should be considered for alternative therapies. ***Initial treatment:*** *Evidenzbasis:* There have been no randomised studies specifically for patients with high risk CLL (*TP53* defect and/or failing fludarabine combination therapy within 2 years). The results of phase II and III studies using either FC, FCR, or alemtuzumab with or without high dose steroids which included previously untreated patients with a *TP53* abnormality are shown *in Table 12 (siehe unten).*

Studie	Regimen	Patienten (N)	CR (%)	OR (%)	Median PFS (Monate)	OS (%)
Hallek et al 2010	FC	29	4	45	0(2yrs)	41 at 2yrs
	FCR	22	19	71	11	N/A
Hillmen et al 2007	A	11		64	11	N/A
Pettitt et al. 2012	A + HDMP	17	37	100	18.3	38.9 (median)
Stilgenbauer et al. 2011	A + Dex	30	20	97	16.9	N/A

FCR and alemtuzumab are associated with similar response rates and PFS. However, combination therapy with alemtuzumab and pulsed high-dose glucocorticoids achieves response rates and PFS superior to those achieved with FCR or alemtuzumab alone. Consequently, alemtuzumab plus pulsed methylprednisolone or dexamethasone should be regarded as the induction

regimen of choice. This regimen is associated with a significant risk of infection and meticulous attention should be paid to antimicrobial prophylaxis and supportive care. Routine antimicrobial prophylaxis with oral co-trimoxazole, aciclovir and itraconazole and monitoring for CMV reactivation is recommended.
Since the duration of remission following alemtuzumab containing regimens is relatively short, consolidation with allogeneic transplantation is recommended in suitable patients.

Role of radiotherapy:
Evidenzbasis: Radiotherapy should be considered for patients for whom chemo-immunotherapy has been ineffective or is contra-indicated and can provide effective palliation in cases with symptomatic bulky lymphadenopathy. Low doses of external beam radiotherapy (2 x 2Gy) can be highly effective in this situation and a higher dose (30 Gy in 2-3 Gy fractions) may be required in patients with transformed aggressive disease or those known to have a TP53 abnormality (Lowry et al, 2011).

Recommendations (GRADE B1/2)

- The management of high-risk CLL is controversial and poses considerable therapeutic challenges. Accordingly, early input from a centre with a specialist interest in CLL is strongly recommended.
- Treatment for high-risk CLL should ideally be delivered as part of a clinical trial. Outside of trials, alemtuzumab in combination with pulsed high dose glucocorticoid is the treatment of choice. Meticulous attention should be paid to antimicrobial prophylaxis and supportive care.
- The use of alemtuzumab in combination with drugs other than steroids should be confined to clinical trials
- Since subcutaneous alemtuzumab injection is associated with comparable efficacy and less toxicity in CLL, this has become the preferred route of administration
- Ofatumumab is the treatment of choice for patients with high-risk CLL who fail alemtuzumab. Other options include high-dose or conventional-dose glucocorticoids, lenalidomide or radiotherapy.

The Role of allogeneic transplantation
Evidenzbasis: Allogeneic stem-cell transplantation provides the best opportunity of achieving long-term disease-free survival for patients with high-risk CLL, including those with TP53 abnormalities. An EBMT retrospective study of 44 transplants performed between 1995 and 2006 for 17p deleted CLL showed that about one third of patients achieved long-term remission (Schetelig et al, 2008). In the GCLLSG CLL3X trial, the 4-year EFS was 42% and was similar for all genetic subtypes (Dreger et al, 2010), indicating that 17p deletion loses its adverse prognostic significance in this therapeutic context.
A comparison of registry data suggests that reduced intensity conditioning (RIC) transplants may be superior to myeloablative transplants – the reduction in disease control using a reduced intensity approach is more than compensated for by the reduction in TRM. Recent data from the EBMT suggest that the outcomes following transplants from fully matched unrelated donors are identical to those following transplants from sibling donors and will increase the donor pool (Michallet et al, 2010). Analysis of prospective trials of allografting in CLL suggests that not being in remission has greater adverse prognostic significance than the number of lines of prior therapy (Delgado et al, 2009). Data from the Seattle also clearly identify the poorer outlook for both overall survival, EFS and NRM in patients with co-morbidities (Sorror et al, 2008).

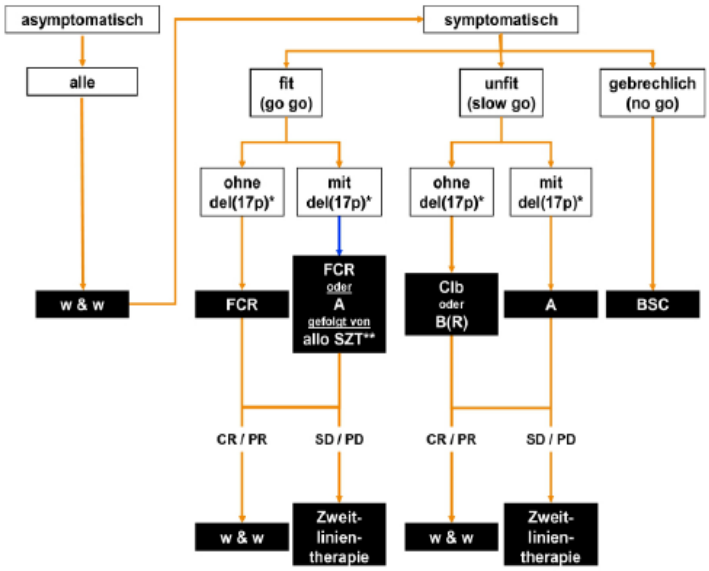
	Recommendations • Allogeneic stem-cell transplantation should be considered as consolidation therapy for all fit patients with high-risk CLL and should ideally be performed in the setting of a secure remission. Suitable patients should be discussed with a transplant centre at the earliest opportunity ***(GRADE B1).*** • There is no consensus on the value of screening potential allograft donors for MBL. It would seem sensible to exclude donors with early CLL or clinical MBL ***(GRADE C2)***
Mauro FR et al., 2011: SIE, SIES, GITMO updated clinical recommendations for the management of chronic lymphocytic leukemia	Italian Society of Hematology (SIE), SIES Società Italiana di Ematologia Sperimentale (SIES) and GITMO (Gruppo Italiano Trapianto di Midollo Osseo) Fragestellung/Zielsetzung: By using GRADE system we updated the guidelines for management of CLL issued in 2006 from SIE, SIES and GITMO group.
	Methodik A 3-member Advisory Council (AC) with expertise in clinical epidemiology, hematology, critical appraisal and research synthesis oversaw the process. An expert panel (EP) was selected according to the conceptual framework elements of the NIH Consensus Development Program **Grundlage der Leitlinie** Using a modified Delphi process, the list of produced statements was circulated electronically to all participants through 2 iterations. Participants voted on which statements they felt warranted discussion, and provided comments on the wording of the statements which were progressively finalized. Final adjudication of the recommendation (s) was made through the three face-to-face meetings held in Bologna, Italy. Recommendations were both classified into four mutually exclusive categories: do it, probably do it, probably don't do it, don't do it, according to GRADE suggestions, and were also provided in conversational form following the comments derived from the discussion of the EP. **Suchzeitraum** 2006 bis 3/2011 **LoE und GoR** In areas covered by the evidence, the production of recommendations was performed according GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.

	Front-line treatment options for patients with deletion 17p- and/or p53 mutations • Treatment options for patients with deletion17p- and/or p53 mutations were separately discussed. In the study by Hillmen et al., previously untreated patients with deletion 17p- showed a better OR rate with alemtuzumab than with chlorambucil (64 vs. 20%). In a study by Stilgenbauer et al. presented in an abstract form at the 2010 ASH meeting, 25 previously untreated patients with del [17p] showed a very high OR rate (96%) with 24% CR rate after a front-line treatment including alemtuzumab and dexamethasone. In a study by the GIMEMA group presented in an abstract form at the same meeting, fludarabine and alemtuzumab combination (FluCam) was investigated in 43 younger patients with an adverse biologic profile. The CR rate for the 9 patients with del [17p] included in this study was 46%. The available evidence about front-line treatments for CLL patients was analyzed according to the GRADE methodology, integrated by the information derived from phase II trials and by the clinical judgments of the EP and produced the following recommendations. **Recommendations** • Younger CLL patients and selected older patients with a good performance status, no clinically significant co-morbidities and with no deletion 17p-and/or p53 mutations should receive FCR regimen. • Patients not eligible for FCR regimen should be treated with a less toxic regimen in order to pursue a control of the diseases and a good quality of life, while preserving overall survival. Chlorambucil, bendamustine, fludarabine, cladribine, as single agents, fludarabine or cladribine associated with cyclophosphamide have been tested in RCTs and there is evidence of the efficacy and safety of use. The lack of RCTs, the small sample size or the poor directness of the existing evidence, do not allow to grade alternative treatment options that have demonstrated efficacy and safety such as fludarabine and rituximab schedule, modified FCR regimens (FCR lite, FCR according to Sloan Kettering), pentostatin including regimen (PCR), chlorambucil or bendamustine combined with rituximab. • In patients with del [17p] and/or p53 mutations and active disease the EP agreed that the use of alemtuzumab-based treatments should be preferred. In younger patients with del [17p] and/or p53 mutations, adequate fitness status and no significant co-morbidities, the strategy approach should include an allogeneic SCT.
Chronic lymphocytic leukemia, 2011: ESMO Clinical	Fragestellung/Zielsetzung: Empfehlungen zur Therapie des CLL.
	Methodik Keine allgemeinen Angaben zur Methodik - ist jedem einzelnen Treffer zu entnehmen.

Practice Guidelines for diagnosis, treatment and follow-up	**Treatment of advanced, active disease** • An improved survival has been demonstrated following firstline chemoimmunotherapy with FCR in physically fit patients with CLL [I, A]. Therefore, in this patient group (physically active, no major health problems, normal renal function) FCR is the standard first-line therapy. Combinations based on other purine analogs such as cladribine or pentostatin have shown similar activity, but it is uncertain whether they can replace fludarabine in the FCR regimen [II, B]. • In patients with relevant co-morbidity, chlorambucil [II, B] seems to be the standard therapy [16]. Alternatives are dosereduced purine analog-based therapies [FC, PCR (pentostatin, cyclophosphamide and rituximab] [III, B] or bendamustine [II, B]. • Patients showing a chromosomal defect del(17p) or p53 mutation frequently do not respond to conventional chemotherapy with fludarabine or FC. Even after FCR therapy, progression-free survival of these patients remains short. Therefore, physically fit (and young) patients should be offered an effective initial regimen, of which alemtuzumab is currently the most widely explored, followed by an allogeneic stem cell transplantation within clinical trials [III, B].
ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)	Fragestellung/Zielsetzung: Empfehlungen zur Therapie zu verschiedensten Subgruppen des NHL.
	Methodik Keine allgemeinen Angaben zur Methodik - ist jedem einzelnen Treffer zu entnehmen.
	Can a risk-adapted therapy be based on biological risk factors? **Recommendations:** • Even though many biological markers have been associated with prognosis, none of them have been clearly shown to be sufficiently predictive to be used for treatment decisions, except for del(11q), del (17p) and TP53 mutation. *Level of evidence: I Strength of recommendation: A* • In patients with del(11q), chemoimmunotherapy with FCR has been shown to result in a longer PFS than other regimens (e.g. fludarabine and cyclophosphamide). *Level of evidence: I Strength of recommendation: A* • For patients with del(17p)/TP53 mutation, alemtuzumab along with corticosteroids is an alternative to FCR for remission induction, and allo-SCT should be considered for consolidation in eligible patients once they achieve response. *Level of evidence: III Strength of recommendation: B* Evidenzbasis für die Empfehlungen: *Recurrent genomic aberrations such as del(11q) and del(17p) and mutations of TP53 also help in defining biological and clinical subgroups.* *Currently, the only biological parameters useful to guide treatment are deletion del (11q), del(17p) and TP53 mutation. Patients with del(11q) usually have short PFS with traditional alkylator-based chemotherapy, which however can be overcome by chemoimmunotherapy, such as fludarabine, cyclophosphamide and rituximab (FCR). On the other hand, remission rates, PFS and OS of patients with del(17p) or TP53 mutation are poor. This applies to chemotherapy alone, chemoimmunotherapy and immunomodulators. There are no clinical trials comparing alemtuzumab or allo-SCT against standard first-line treatment (i.e. FCR), and therefore, no firm recommendation can be given as to the best treatment approach for these patients. Based on single-arm phase II studies, it is considered*

	that alemtuzumab, particularly when combined with corticosteroids, can be effective. Allo-SCT is however the only treatment actually active in that setting. Based on these data, alemtuzumab and allo-SCT are considered valid therapies for CLL with del(17p)/TP53 mutation. It is highly recommended that patients with del(17p) or TP53 mutation are offered allo-SCT early, before resistance to therapy or disease transformation occurs.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

DGHO, 2012: Chronische Lymphatische Leukämie (CLL)	• Patienten mit Nachweis einer 17p13 Deletion bzw. einer p53 Mutation haben eine niedrigere Ansprechrate und kürzeres Progressionsfreies sowie Gesamt-Überleben nach Chemotherapie (Chlorambucil, Fludarabin-haltige Schemata, Bendamustin, auch in Kombination mit Rituximab). Bei Patienten ohne relevante Komorbidität mit therapiepflichtiger CLL und Deletion 17p13 sollten alternative Therapieansätze (z.B. Alemtuzumab mit nachfolgender konsolidierender allogener Blutstammzelltransplantation), wenn möglich im Rahmen klinischer Studien, angestrebt werden, da damit ein langfristiges krankheitsfreies Überleben erreicht werden kann. *Abbildung 2: Erstlinientherapie der CLL*  *Legende: palliativer Therapieansatz; kurativer Therapieansatz;* ** zur Methodik siehe Kapitel 4.1.2. Diagnostik; ** allo SZT bei Patienten, die hierfür geeignet sind;* *A - Alemtuzumab, allo SZT - allogene Stammzelltransplantation, B - Bendamustin, BSC - Best Supportive Care, C - Cyclophosphamid, Clb - Chlorambucil, C - Cyclophosphamid, CR - komplette Remission, F - Fludarabin, P - Prednison, PD - Progress, PR - partielle Remission, R - Rituximab, SD - stabile Erkrankung, w & w - abwartendes Verhalten;*

NCCN, 2014: NCCN clinical practice guidelines in oncology. Non-Hodgkin's Lymphoma. Version 1.2014	**All recommendations are category 2A:** • No standard treatment exists for patients with del(17p), as outcome remain poor with currently available treatment regimens. Therfore, enrollment in an appropriate trial is particularly recommended for patients with del (17p). • In the absence of clinical trials in the patient's local area, suggested first-line therapie options include FCR or FR, HDMP plus ritumximab, or alemtuzuumab with or without rituximab. • Patients who have achieved CR or PR to first-line therapy should be condidered for allogeneic HSCT, if they are eligible. • Patients with CR or PR following transplant can either be observed or enrolled in clinical trials. Alternativerly, patients with PR could also be treated with chemoimmunotherapy. • Patients with no response to first-line therapy, patients who respond to first-line therapy but are not eligible for allogenic HSCT and for those with no response to transplant should be enrolled in clinical trials or be treated with secon-line therapy for relapsed or refractory disease. • The NCCN guidelines have included chemoimmunotherapy regimens, monotherapy with ofatunumba, lenaldomide with or without rituximab as options.

Detaillierte Darstellung der Recherchestrategie:

Cochrane (Database of Systematic Reviews, DARE, Technology Assessments) am 27.02.2014

Suchschritt	Suchfrage
#1	MeSH descriptor: [Leukemia, B-Cell] explode all trees
#2	b-cell:ti,ab,kw or chronic*:ti,ab,kw (Word variations have been searched)
#3	lymphocytic:ti,ab,kw or lymphoid:ti,ab,kw (Word variations have been searched)
#4	leukaemia*:ti,ab,kw or leukemia*:ti,ab,kw (Word variations have been searched)
#5	#2 and #3 and #4
#6	lymphoma*:ti,ab,kw (Word variations have been searched)
#7	#4 or #6
#8	chronic*:ti,ab,kw and b-cell:ti,ab,kw (Word variations have been searched)
#9	#7 and #8
#10	CLL:ti,ab,kw (Word variations have been searched)
#11	small next cell:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)
#12	small:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)
#13	well next differentiated:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)
#14	SLL:ti,ab,kw (Word variations have been searched)
#15	#1 or #5 or #9 or #10 or #11 or #12 or #13 or #14 from 2009 to 2014

MEDLINE (PubMed) am 27.02.2014

Suchschritt	Suchfrage
#1	Search "leukemia, b cell"[MeSH Terms]
#2	Search (b-cell[Title/Abstract]) OR chronic*[Title/Abstract]
#3	Search (lymphocytic[Title/Abstract]) OR lymphoid[Title/Abstract]
#4	Search (leukaemia*[Title/Abstract]) OR leukemia*[Title/Abstract]
#5	Search (#2 AND #3 AND #4)
#6	Search lymphoma*[Title/Abstract]
#7	Search (#4 OR #6)
#8	Search (chronic*[Title/Abstract]) AND b-cell[Title/Abstract]
#9	Search (#7 AND #8)
#10	Search CLL[Title/Abstract]
#11	Search (small-cell[Title/Abstract]) AND lymphoma*[Title/Abstract]
#12	Search ((small[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]
#13	Search ((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]
#14	Search SLL[Title/Abstract]
#16	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#22	Search ((((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]))))
#25	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) Filters: Systematic Reviews; Meta-Analysis; Technical Report
#26	Search (#16 AND #22)
#27	Search (#25 OR #26)
#28	Search (#25 OR #26) Filters: published in the last 5 years

MEDLINE (PubMed) nach Leitlinien am 27.02.2014

Suchschritt	Suchfrage
#1	Search "leukemia, b cell"[MeSH Terms]
#2	Search (b-cell[Title/Abstract]) OR chronic*[Title/Abstract]
#3	Search (lymphocytic[Title/Abstract]) OR lymphoid[Title/Abstract]
#4	Search (leukaemia*[Title/Abstract]) OR leukemia*[Title/Abstract]
#5	Search (#2 AND #3 AND #4)
#6	Search lymphoma*[Title/Abstract]
#7	Search (#4 OR #6)
#8	Search (chronic*[Title/Abstract]) AND b-cell[Title/Abstract]
#9	Search (#7 AND #8)
#10	Search CLL[Title/Abstract]
#11	Search (small-cell[Title/Abstract]) AND lymphoma*[Title/Abstract]
#12	Search ((small[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]
#13	Search ((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]
#14	Search SLL[Title/Abstract]
#16	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#17	Search (non-hodgkin*[Title]) AND lymphoma*[Title]
#18	Search (#16 OR #17)
#19	Search ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
#20	Search (#18 AND #19)
#21	Search (#18 AND #19) Filters: published in the last 5 years

Literatur:

Bauer K, Rancea M, Roloff V, Elter T, Hallek M, Engert A, Skoetz N. Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia. Cochrane Database of Systematic Reviews 2012; (11): CD008079.

British Committee for Standards in Haematology. Guidelines on the diagnosis, investigation and management of Chronic Lymphocytic Leukaemia. Stand: Juli 2012. http://www.bcshguidelines.com/documents/Revised_CLL_guideline_july_13.pdf, Zugriff am 26.02.2014.

DGHO Onkopedia. Chronische Lymphatische Leukämie (CLL). Stand: Januar 2012. http://www.dgho-onkopedia.de/de/onkopedia/leitlinien/cll, Zugriff am 27.02.2014.

Eichhorst B, Dreyling M, Robak T, Montserrat E, Hallek M. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2011; 22 (Suppl 6): vi50-vi54.

Ghielmini M, Vitolo U, Kimby E, Montoto S, Walewski J, Pfreundschuh M, Federico M, Hoskin P, McNamara C, Caligaris-Cappio F, Stilgenbauer S, Marcus R, Trneny M, Dreger P, Montserrat E, Dreyling M. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol 2013; 24 (3): 561-76.

Mauro FR, Bandini G, Barosi G, Billio A, Brugiatelli M, Cuneo A, Lauria F, Liso V, Marchetti M, Meloni G, Montillo M, Zinzani P, Tura S. SIE, SIES, GITMO updated clinical recommendations for the management of chronic lymphocytic leukemia. Leuk Res 2012; 36 (4): 459-66.

National Comprehensive Cancer Network (NCCN). Non-Hodgkin's Lymphomas. Version 1.2014. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site, Zugriff am 27.02.2014.

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2014-B-069-z Idelalisib

Datum: 08.09.2014

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

Inhalt

Indikation für die Recherche bei Wirkstoff (evtl. Markenname): 2

Berücksichtigte Wirkstoffe/Therapien: 2

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Anhang: 36

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

“Idelalisib wird als Monotherapie zur Behandlung von erwachsenen Patienten mit follikulärem Lymphom (FL), das refraktär gegenüber zwei vorausgegangenen Therapielinien ist, angewendet.“

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 wurden zwei systematische Literaturrecherchen nach systematischen Reviews, Metaanalysen, HTA-Berichten und Leitlinien zur Indikation „refraktäres Non-Hodgkin Lymphom“ sowie „chronische lymphatische Leukämie“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherchen am 03.03.2014 beziehungsweise 27.02.2014 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 Recherchen ergaben 782 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 16 Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden. Aus der Handsuche wurde eine Primärstudie extrahiert.

Abkürzungen

ASCT	autologous stem cell transplantation
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
CCR	complete clinical response
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CHOP-R	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CoI	Conflicts of Interest
CPG	ClinicalPracticeGuideline
CR	complete response
CRu	complete response unconfirmed
CTC	common toxicity criteria
DAHTA	Deutsche Agentur für Health Technology Assessment
DGHO-Onkopedia	*Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*
EFS	Event-free survival
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
HDT	High-dose therapy
HR	Hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
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
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PR	partial response
RD	remission duration
RR	risk ratio
SCT	Stem Cell Transplantation
TRIP	Turn Research into Practice Database
TRM	treatment-related mortality
TTP	time to progression

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2011 [1] **Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI - Off-Label-Use: Anwendung von Fludarabin bei anderen als in der Zulassung genannten niedrig bzw. intermediär malignen B-NHL als CLL**	**Fazit:** Der Unterausschuss „Arzneimittel“ hat die Bewertung der Expertengruppe … überprüft und die Plausibilität festgestellt. Die Expertengruppe kommt zu folgendem Fazit: *„Ein zulassungsüberschreitender Einsatz („off label use“) von intravenösem Fludarabin ist bei geeigneten Patienten mit niedrig oder intermediär malignen Lymphomen der B-Zellreihe begründet, wenn folgende Voraussetzungen erfüllt sind:* *- die Lymphomerkrankung ist refraktär auf CHOP (mit oder ohne Rituximab) oder* *- bei Patienten, die für CHOP nicht geeignet sind, ist das Lymphom refraktär auf mindestens eines der folgenden Alkylanzienhaltigen Standardtherapien Chlorambucil, Bendamustin, CVP (=COP) (jeweils mit oder ohne Rituximab), siehe Abschnitt 5.* *Für den zulassungsüberschreitenden Einsatz werden folgende Therapieschemata empfohlen:* *- Fludarabin-Monotherapie oder,* *- FC (Fludarabin, Cyclophosphamid), beide bei Resistenz der Lymphomerkrankung auf Alkylanzienhaltige Therapien (mit oder ohne Rituximab) bei Patienten, die für CHOP nicht geeignet sind und* *- FCM (Fludarabin, Cyclophosphamid, Mitoxantron) bei Resistenz der Lymphomerkrankung auf CHOP (mit oder ohne Rituximab), insbesondere bei Patienten mit follikulären NHL oder Mantelzell-NHL.* *Zur Verstärkung der Wirksamkeit wird bei allen 3 Therapiesschemata bei CD20-positiven NHL die Kombination mit Rituximab empfohlen, jeweils 375 mg/m2 vor Kursbeginn.“*

Cochrane Reviews

Schaaf et al. 2012 [2] High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults	1. Fragestellung: To compare the effectiveness of HDT with ASCT to chemotherapy or immuno-chemotherapy in patients with newly diagnosed or relapsed FL.
	2. Methodik **Population:** Adult male and female patients (≥ 18 years of age) with a confirmed diagnosis of FL. **Intervention:** HDT with ASCT **Komparator:** Chemotherapy and immuno-chemotherapy We considered any chemotherapeutic and immunochemotherapeutic regimen for comparison. **Endpunkt:** • Primary enpoint: OS • Secondary endpoint: PFS; RR; Qol; Treatment-related mortality (TRM); Adverse events; secondary malignancies **Suchzeitraum:** We searched CENTRAL, MEDLINE, and EMBASE as well as conference proceedings from January 1985 to September 2011 for RCTs. **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 5 RCTs/1 093 patients; four trials in previously untreated patients, **one trial in relapsed patients**
	3. Ergebnisdarstellung: For patients with relapsed FL (CUP trial): • There is some evidence (one trial, n = 70) that HDT + ASCT is advantageous in terms of PFS and OS (PFS: HR = 0.30; 95% CI 0.15 to 0.61; OS: HR = 0.40; 95% CI 0.18 to 0.89). For this trial, no results were reported for TRM, adverse events or secondary cancers. <u>Qualität der Studie:</u> • quality of CUP trial judged to be moderate • reported as randomised and judged to be open-label (usually trials evaluating stem cell transplantation are not blinded) • protocol amended in March 1996 to enable centres that felt uncomfortable treating relapsed patients without HDT and ASCT to provide this regimen to all patients, after March 1996, patients were randomised to purged versus unpurged stem cells only.
	4. Anmerkungen/Fazit der Autoren:

	... There is evidence that HDT + ASCT is advantageous in patients with relapsed FL. *Hinweise FBMed:* • *nur OS patientenrelevant, hier kein signifikanter Effektivitätsvorteil* • *Unterschied zwischen „relapsed" und „refraktär" ist zu berücksichtigen*
Itchaki G, et al. 2013 [3] Anthracycline-containing regimens for treatment of follicular lymphoma in adults	1. Fragestellung: To compare the efficacy of Anthracycline-containing regimens (ACRs) to other chemotherapy regimens, in the treatment of FL.
	2. Methodik **Population:** adult patients (≥ 18 years of age) with a historically confirmed diagnosis of FL **Intervention:** ACR, regardless of additional agents, with or without radiotherapy (considered Anthracyclines included doxorubicin (adriamycin), daunorubicin, idarubicin, epirubicin, mitoxantrone, pixantrone) **Komparator:** non-ACR, as a single agent or multiple agents, regardless of dose **Endpunkt:** • Primary enpoint: OS (time from entry to study until death of any cause, assessed among all patients), all-cause mortality at three, five and 10 years • Secondary endpoint: PFS; CR; ORR; RD, relapse; disease control; Qol; Adverse events **Suchzeitraum:** until April 2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 RCTs/2 636 patients
	3. Ergebnisdarstellung • All trials included patients with initial, untreated indolent NHL. • two trials examined refractory patients, but did not specify the number of FL patients included (Pott 1994, Santoro 2006) • one ongoing study retrieved: NCT00551239, "Fludarabine and rituximab with or without pixantrone in treating patients with relapsed or refractory indolent non-Hodgkin lymphoma", RCT, single blind (outcomes assessor), ongoing but not recruiting
	4. Anmerkungen/Fazit der Autoren: The use of anthracyclines in patients with FL has no demonstrable

	benefit on overall survival, although it may have been mitigated by the more intense regimens given in the control arms of three of five trials. ACR improved disease control, as measured by PFS and RD with an increased risk for side effects, notably cardiotoxicity. The current evidence on the added value of ACR in the management of FL is limited. Further studies involving immunotherapy during induction and maintenance may change conclusion. *Hinweise FBMed:* • *Auswertungen für Zweit- und Drittlinientherapie nicht möglich*

Systematische Reviews

Keating GM. 2010 [4] Rituximab: a review of its use in chronic lymphocytic leukaemia, low-grade or follicular lymphoma and diffuse large B-cell lymphoma	1. Fragestellung This article reviews the use of intravenous rituximab in the treatment of chronic lymphocytic leukaemia (CLL), low-grade or follicular lymphoma, and diffuse large B-cell lymphoma.
	2. Methodik **Population:** patients with chronic lymphocytic leukaemia, low-grade or follicular lymphoma or diffuse large B-cell lymphoma **Intervention:** Rituximab **Komparator:** not previously stated **Endpunkt**: not previously stated **Suchzeitraum:** searches last updated 22 June 2010 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7/k.A. **Qualitätsbewertung der Studien:** based mainly on methods section of the trials, when available, large, well controlled trials with appropriate statistical methodology preferred
	3. Ergebnisdarstellung <u>4.2 Low-Grade or Follicular B-Cell Lymphoma - 4.2.2 Patients with Relapsed or Refractory Disease</u> • efficacy of rituximab monotherapy in patients with relapsed or refractory CD20-positive low-grade or FL examined in noncomparative multicentre trials **62.** Feuring-Buske M, Kneba M, Unterhalt M, et al. IDECC2B8 (rituximab) anti-CD20 antibody treatment in relapsed advanced-stage follicular lymphomas: results of a phase-II study of the German Low-Grade Lymphoma Study Group. Ann Hematol 2000 Sep; 79 (9): 493-500 **63.** Maloney DG, Grillo-Lo´ pez AJ, White CA, et al. IDECC2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997 Sep 15; 90 (6): 2188-95 **64.** Davis TA, Grillo-Lo´ pez AJ, White CA, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. J Clin Oncol 2000 Sep; 18 (17): 3135-43 **65.** Davis TA, White CA, Grillo-Lo´ pez AJ, et al. Single-agent monoclonal antibody efficacy in bulky non-Hodgkin's lymphoma: results of a phase II trial of rituximab. J Clin Oncol 1999 Jun; 17 (6): 1851-7 **66.** Piro LD, White CA, Grillo-Lo´ pez AJ, et al. Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma. Ann Oncol 1999; 10 (6): 655-61 **67.** McLaughlin P, Grillo-Lo´ pez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998 Aug; 16 (8): 2825-33 **77.** Foran JM, Gupta RK, Cunningham D, et al. A UK multicenter phase II study of rituximab (chimaeric anti-CD20 monoclonal antibody) in patients with follicular lymphoma, with PCR

	monitoring of molecular response. Br J Haematol 2000 Apr; 109 (1): 81-8 included patients: • aged ≥ 18 years [62,64,65], low-grade or FL [62-67] or only FL [77], all [62] or majority [63-66] with stage III or IV disease, required therapy (e.g. 'B' symptoms, bulky disease, progressive disease and/or impaired haematopoiesis), Karnofsky index of ≥ 60% [62], performance status of 0–2 (assessed using ECOG [77], WHO [63-66] or Zubrod [67] criteria), expected survival duration of ≥ 3 [63] or ≥ 4 [64-66] months intervention: • intravenous rituximab 375 mg/m2 once weekly for 4 [62-65,67,77] or 8 [66] weeks methodology aspects: • median duration of followup was 173 days [62], 11.8 months [67] or 1.5 years [77], analyses usually conducted in ITT population [63-67], in one study results reported in subgroup of evaluable patients with follicular lymphoma [62] baseline characteristics: • median patient age was 50–58 years [62-67,77] 34–63% male [62-67,77], received a median of two [62,63], three [65,67,77] or four [64] prior treatments results: • monotherapy with rituximab demonstrated efficacy in patients with relapsed or refractory low grade or follicular lymphoma
	4. Anmerkungen/Fazit der Autoren Thus, rituximab remains a valuable therapy in patients with CLL, low-grade or follicular lymphoma and diffuse large B-cell lymphoma and, in a variety of treatment settings, represents the standard of care. Hinweise durch FB Med • *not supported by any external funding. during peer review process, manufacturer of the agent under review was offered an opportunity to comment on this article, changes resulting from comments received made on the basis of scientific and editorial merit* • *relapsed/refractory zusammen bewertet*

Leitlinien

Zinzani PL, et al. 2013 [5] **SIE, SIES, GITMO** Revised guidelines for the management of follicular lymphoma	Fragestellung … In patients relapsing after first line chemoimmunotherapy and requiring treatment, is rituximab and chemotherapy reinduction superior to chemotherapy alone? In patients relapsing after first-line chemoimmunotherapy and achieving a response to reinduction rituximab and chemotherapy, is rituximab maintenance better than observation? Which role for autologous HSCT? Which role for allogeneic HSCT? Which role for radioimmunoconjugates?
	Methodik: evidenz- und konsensbasierte LL Grundlage der Leitlinie: systematische Literatursuche und Bewertung (anhand vom GRADE-Schema), Empfehlungen durch formale Konsensusmethoden verabschiedet (nominaler Gruppenprozess) Suchzeitraum: bis Juli 2011 Weitere Kriterien für die Qualität einer Leitlinie: • Empfehlungen durch Hintergrundtexte mit Quellenangaben verknüpft LoE/GoR: GRADE *Sonstige methodische Hinweise:* • *The SIE administered all aspects of the meetings. The funding sources had no role in identifying statements, abstracting data, synthesizing results, grading evidence, or preparing the manuscript or in the decision to submit the manuscript for publication.* • *relapsed/refractory zusammen bewertet*
	Freitext/Empfehlungen/Hinweise <u>Issue 6: Relapsed/refractory patients (evidence-based recommendations)</u> In fit patients relapsing after first-line chemoimmunotherapy and requiring treatment, rituximab should be added to chemotherapy as reinduction, provided there is no evidence of resistance to rituximab (quality of evidence, low; strength of recommendation, weak). **47.** Van Oers M, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial. Blood 2006;108:32953301.

	In patients relapsing after first-line chemoimmunotherapy and achieving a response to reinduction rituximab and chemotherapy, rituximab maintenance is recommended (quality of evidence, low; strength of recommendation, weak). **21.** Rambaldi A, Carlotti E, Oldani E, et al. Quantitative PCR of bone marrow BCL2/IgH1 cells at diagnosis predicts treatment response and long-term outcome in follicular non-Hodgkin lymphoma. Blood 2005;105:3428–3433. **47.** Van Oers M (siehe oben) **48.** Forstpointer R, Unterhalt M, Dreyling M, et al. Maintenance therapy leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophoshamide, and mitoxantrone (RFCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German low Grade Lymphoma Study Group (GLSG). Blood 2006;108:4003–4008. **49.** Hainsworth J, Litchy S, Shaffer D, et al. Maximizing therapeutic benefit of rituximab: Maintenance therapy versus re-treatment in patients with indolent non Hodgkin's lymphoma-A randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005;23:1088–1095. **50.** Ghielmini M, Schmitz S, Cogliatti S, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004;103:4416–4423. Autologous HSCT is recommended in young (<65-year old) fit patients relapsing within 12 months from the end of frontline chemoimmunotherapy and achieving a response to chemoimmunotherapy reinduction. Autologous HSCT is a therapeutic option in young (<65-year old) fit patients relapsing after at least 12 months from the end of frontline chemoimmunotherapy and achieving a response to chemoimmunotherapy reinduction. No sufficient evidence support universal rituximab maintenance in patients achieving a response after autologous HSCT. **37.** Ladetto M, De Marco F, Benedetti F, et al. Gruppo Italiano Trapianto di Midollo Osseo (GITMO); Intergruppo Italiano Linfomi (IIL). Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: The superior disease control of R-HDS does not translate into an overall survival advantage. Blood 2008;111:4004–4013. **52.** Sebban C, Brice P, Delarue R, et al. Impact of rituximab and/or high-dose therapy with autotransplant at time of relapse in patients with follicular lymphoma: A GELA study. J Clin Oncol 2008;26:3614–3620. **53.** Rohatiner A, Nadler L, Davies A, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: Long term follow-up. J Clin Oncol 2007;25:2554–2559. **54.** Tarella C, Zanni M, Magni M, et al. Rituximab improves the efficacy of highdose chemotherapy with autograft for high-risk follicular and diffuse large Bcell lymphoma: A multicenter Gruppo Italiano Terapie innovative nei linfomi survey. J Clin Oncol 2008;26:3166–3175. **55.** Arcaini L, Montanari F, Alessandrino EP, et al. Immunochemotherapy with in vivo purging and autotransplant induces long clinical and molecular remission in advanced relapsed and refractory follicular lymphoma. Ann Oncol 2008;19:1331–1335. **56.** Peters AC, Duan Q, Russell JA, et al. Durable event-free survival following autologous stem cell transplant for relapsed or refractory follicular lymphoma: Positive impact of recent rituximab exposure and low-risk follicular lymphoma international prognostic index score. Leuk Lymphoma 2011;52:2124–2129. **57.** Le Gouill S, De Guibert S, Planche L, et al. Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. GELA and GOELAMS. Haematologica 2011;96:1128–1135. **58.** Hoerr AL, Gao F, Hidalgo J, et al. Effects of pretransplantation treatment with rituximab on outcomes of autologous stem-cell transplantation for non-Hodgkin's lymphoma. J Clin Oncol 2004;22:45614566. **59.** Kang TY, Rybicki LA, Bolwell BJ, et al. Effect of prior rituximab on high-dose therapy and autologous stem cell transplantation in follicular lymphoma. Bone Marrow Transplant 2007;40:973978. **60.** Pettengell R, Schmitz N, Gisselbrecht C, et al. Randomized study of rituximab in patients with relapsed or resistant follicular lymphoma prior to high-dose therapy as in vivo purging and to maintain

	remission following highdose therapy. ASCO Annual Meeting 2010; Chicago, Abstract 8005. Young (<65-year old) fit patients who relapsed after or were refractory to a previous therapy including autologous SCT are candidates to allogeneic SCT. The availability of a compatible donor and the patient preference should be considered in making this decision. **61.** Khouri IF, McLaughlin P, Saliba RM, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. Blood 2008;111:5530–5536. **62.** Pin˜ana JL, Martino R, Gayoso J, et al. GELTAMO Group. Reduced intensity conditioning HLA identical sibling donor allogeneic stem cell transplantation for patients with follicular lymphoma: Long term follow-up from two prospective multicenter trials. Haematologica 2010;95:1176–1182. **63.** Thomson KJ, Morris EC, Milligan D, et al. T-cell depleted reduced-intensity transplantation followed by donor leukocyte infusions to promote graft-versus lymphoma activity results in excellent long-term survival in patients with multiply relapsed follicular lymphoma J Clin Oncol 2010;28:3695–3700. **64.** Avivi I, Montoto S, Canals C, et al. Matched unrelated donor stem cell transplant in 131 patients with follicular lymphoma: An analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Br J Haematol 2009;147:719–728. **65.** Hari P, Carreras J, Zhang MJ, et al. Allogeneic transplants in follicular lymphoma: Higher risk of disease progression after reduced-intensity compared to myeloablative conditioning. Biol Blood Marrow Transplant 2008;14:236–245. The panel argued that for relapsed/refractory patients, treatment with radioimmunoconjugates is a therapeutic option. This should apply for those patients non eligible to high-dose chemotherapy and HSCT. **66.** Witzig TE, Gordon LI, Cabanillas F, et al. Randomized controlled trial of yttrium-90-labelled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2002;20:2453–2463. **67.** Davies AJ, Rohatiner AZ, Howell S, et al. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. J Clin Oncol 2004;22:1469–1479. **68.** Gordon LI, Molina A, Witzig T, et al. Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20Þ B-cell lymphoma: Long-term followup of a phase 1/2 study. Blood 2004;103:4429–4431. **69.** Gregory SA, Leonard JP, Knox SJ, et al. The iodine 1–131 tositumab therapeutic regimen: Summary of safety in 995 patients with relapsed/refractory low grade (LG) and transformed LG non-Hodgkin's lymphoma. (abs.6732). J Clin Oncol 2004;22:615s.
Kouroukis T, et al. 2012 [6] **Cancer Care Ontario (CCO)** Stem Cell Transplantation in Lymphoma	Fragestellung What is the role of stem cell transplantation in the treatment of the various lymphomas?
	Methodik: evidenz- und konsensbasierte LL Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur (update von 2009), informaler Konsensusprozess Suchzeitraum: 2006 through February (week three) 2011 Weitere Kriterien für die Qualität einer LL: • Bewertung der eingeschlossener Übersichtsarbeiten mit AMSTAR • Bewertung eingeschlossener Leitlinien mit AGREE 2 • Bewertung eingeschlossener RCTs nach Randomisierung, Verblindung, Berechnung von Power und Stcihprobengröße, Dauer der Beobachtung, Bericht statistischer Analysemethoden, Bericht und Diskussion der Studienabbrüche, Bericht der

	finanziellen Untrestützung • CCO Stem Cell Transplant Steering Committee provided feedback and helped to draft report 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" 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" Sonstige methodische Hinweise • 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
	Freitext/Empfehlungen/Hinweise RECOMMENDATIONS AND KEY EVIDENCE <u>Follicular Lymphoma (FL)</u> Autologous or allogeneic transplantation are options for chemo-sensitive patients with poor prognosis FL refractory to or relapsed after primary therapy. Evidence: This recommendation is supported by evidence obtained from a systematic review (8), and a CPG (6). The systematic review (SR) (8) recommended autologous SCT as salvage treatment based on pre-rituximab data, as there was a demonstrated benefit in both OS and PFS. The CPG (6) stated that either autologous SCT or allogeneic SCT were acceptable options for second-line or subsequent treatment. Quellen: **6.** Zelenetz AD, Advani RH, Byrd JC, Czuczman MS, Damon LE, Duvic M, et al. Non-Hodgkin's lymphomas. J Natl Compr Canc Netw. 2008;6(4):356-421. – Leitlinie ohne systematische Literaturrecherche und -auswahl **8.** Oliansky DM, Gordon LI, King J, Laport G, Leonard JP, McLaughlin P, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. Biol Blood Marrow Transplant. 2010;16(4):443-68. – siehe Extraktion weiter unten in dieser Tabelle • keine laufenden Studien aufgelistet
Imrie K, et al.	Fragestellung

2012 [7] **Cancer Care Ontario (CCO)** Rituximab in Lymphoma and Chronic Lymphocytic Leukemia (in review)	**Lymphoma** 1. In patients with lymphoma of any type or stage, is rituximab used alone or in combination with chemotherapy more effective than non–rituximab-containing regimens for improving overall survival, disease control (as assessed by measures such as progression-free survival, event-free survival, time-to-treatment failure, or response duration), response rate, or quality of life? 2. What is the toxicity associated with the use of rituximab used alone or in combination with chemotherapy compared with non–rituximab-containing regimens? 3. Which patients with lymphoma are more or less likely to benefit from treatment with rituximab compared with those treated with non–rituximab-containing regimens?
	Methodik: evidenz- und konsensbasierte LL Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur (update von 1999 und 2006), informaler Konsensusprozess (zuletzt 2006), External Review by Ontario Clinicians Suchzeitraum (letzte Aktualisierung): March 2006 to March 2012 Weitere Kriterien für die Qualität einer LL: • Qualität der eingeschlossenen Studien beschrieben 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" 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" *Sonstige methodische Hinweise* • *Rituximab bei FL nur als Monotherapie in der Zweitlinie zugelassen* • *Die Gruppe (Hematology Disease Site Group) hält eine Aktualisierung der Empfehlungen von 2006 aufgrund der neuen Literatur für notwendig.* • *CONFLICT OF INTEREST: The members of the Hematology DSG disclosed potential conflicts of interest relating to the topic of this practice guideline. The lead author and citation and evidence reviewer (KI) of this topic was a co-investigator in one trial included in this report (10) and is involved with an ongoing trial on rituximab. Three other DSG members reported research involvement with trials on this topic, of which one member was involved with one trial in this report (10). In addition, three of the*

	above DSG members, including the lead author, reported involvement with the pharmaceutical company that manufactures rituximab, including research funding, membership on boards of directors or advisory committees, provision of consultancy, or honoraria. • *Funding: The Program in Evidence-based care is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.*
	Freitext/Empfehlungen/Hinweise **Recommendations: Lymphoma** … For **previously treated patients with follicular or other indolent B-cell–histology lymphoma** (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding SLL: • Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this **chemotherapy in combination with rituximab**. – CAVE: Rituximab in DL nur als Monotherapie in der Zweitlinie zugelassen • Patients who have previously received rituximab (including combination rituximab-chemotherapy, rituximab monotherapy, or maintenance rituximab) and **who have achieved a response of at least one year's duration to the last rituximab administration** and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab. **Key Evidence: Lymphoma (siehe auch: Anhang dieser Synopse)** A total of 22 randomized controlled trials were identified: 9 trials assessed patients with aggressive histology and 13 assessed patients with indolent histology. Three trials in aggressive histology were published in article form, as were seven trials in indolent histology; all remaining reports were preliminary publications in abstract form. The Hematology DSG was compelled by these data despite the limitation of their being primarily in abstract form. … In one trial comparing FCM to FCM-R in previously treated patients with indolent lymphomas, response rate, disease control (progression-free survival) and overall survival were superior in patients allocated to receive FCM-R. In another trial comparing CHOP to CHOP-R in patients with follicular lymphoma relapsed or resistant to a maximum of two non-anthracycline regimens, complete response and disease control (three-year progression-free survival) were superior in patients allocated to

	receive CHOP-R compared to patients that received CHOP alone. In both trials, patients responding to induction therapy underwent a second randomization to receive maintenance therapy with rituximab or observation. Disease control (response duration or progression-free survival) was superior in patients allocated to receive maintenance rituximab; overall survival was not reported in the abstract reports of these studies. … There were no trials that compared chemotherapy to the same chemotherapy plus rituximab in patients who had previously received rituximab and achieved a response duration of at least one year. Two randomized trials comparing chemotherapy plus rituximab to chemotherapy alone in patients previously treated with rituximab alone showed improvement in survival or progression-free survival. One randomized trial that compared maintenance rituximab to re-treatment with rituximab at disease progression following induction treatment with rituximab monotherapy, reported a response rate for re-treatment that was comparable to first-line treatment. No important additional hematologic or non-hematologic toxicities were observed when rituximab was combined with chemotherapy. **New (relevant) Evidence: Lymphoma** **9.** Ghielmini ME, Hsu Schmitz S, Martinelli G, Peccatori F, Hess U, Fey M, et al. Long-term follow-up of patients with follicular lymphoma (FL) receiving single agent rituximab at two different schedules in study SAKK 35/98. Journal of Clinical Oncology Conference. 2009;27(15 SUPPL. 1). – erst- und Zweitlinie • 1 ongoing study from clinicaltrials.gov: Single Agent Ofatumumab vs. Single Agent Rituximab in Follicular Lymphoma Relapsed After Rituximab-Containing Therapy (Protocol ID: NCT01200589)
Oliansky DM, et al. 2010 [8] **American Society for Blood and Marrow Transplantation (ASBMT)** The role of cytotoxic therapy with hematopoietic stem cell transplantation in	Fragestellung The goals of the current review are to assemble and critically evaluate evidence regarding the role of SCT in the therapy of follicular lymphoma (FL), make treatment recommendations based on the available evidence, and identify areas of needed research. Methodik: systematische Übersichtsarbeit mit informal konsentierten Empfehlungen Grundlage der Leitlinie: systematische Recherche und Auswahl der Literatur, Bewertung und Empfehlungsableitung durch Expertengremium Suchzeitraum: on June 10, 2008 Weitere Kriterien für die Qualität einer LL: • Empfehlungen mit Literaturstellen verknüpft • Starke Empfehlung basiert auf schwacher Evidenz (siehe Freitextangaben unten)

the treatment of follicular lymphoma: an evidence-based review	• Für 8 von 11 Fragen keine Empfehlung formuliert, Grund schlechte oder fehlende Evidenz LoE/GoR: siehe Anhang dieser Synopse *Sonstige methodische Hinweise* • *Major funding for this study was provided by the National Marrow Donor Program.* *CoI not stated*
	Freitext/Empfehlungen/Hinweise **Indication for SCT:** Autologous SCT versus nontransplantation therapy as salvage treatment without rituximab as part of induction and/or salvage therapy **Treatment Recommendation Grade:** A **Highest Level of Evidence:** 1- Reference (represents highest LoE used to make recommendation, not inclusive of all evidence in the review): 17. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP Trial. J Clin Oncol. 2003;21:3918-3927. **Treatment Recommendation:** Comments: Based on pre-rituximab data, there is a statistically significant improvement in OS and PFS using autologous SCT as salvage therapy.
Imrie K, et al. 2009 [9] **Cancer Care Ontario (CCO). Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group** Stem cell transplantation in adults	Fragestellung 1. What are the accepted indications for stem cell transplantation?
	Methodik Grundlage der Leitlinie: systematic review and environmental scan, recommendations based on clinical trial evidence, if clinical trial evidence absent, recommendations developed through the consensus Suchzeitraum: bis Woche 5 in 2008 Weitere Kriterien für die Qualität einer LL: • aggregierte Evidenz eingeschlossen • Übersicht über eingeschlossene RCTs der gefundenen Übersichtsarbeiten liegt vor • keine formalisierten Konsensusverfahren beschrieben • Verknüpfung von Quellen mit Empfehlungen eindeutig LoE/GoR: The Panel utilized the following factors in its deliberations: quality of available evidence, recency of publication, consistency in recommendations across published guidelines, and availability of alternative treatment options. Where existing evidence was weak or

guidelines differed in their recommendations, a consensus process was utilized to develop recommendations.

Sonstige methodische Hinweise:

- *Funding: The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.*
- *CoI: None declared (by KI, BR).*

Freitext/Empfehlungen/Hinweise

Indications

The following recommendations address the role of stem cell transplantation for the following indications:

…

Follicular Lymphoma (FL)

Autologous or allogeneic transplantation are options for selected patients with poor prognosis FL that progresses after second-line therapy.

…

Outcomes – Systematic Review of the Literature - Follicular lymphoma

Two papers were identified that reported on follicular lymphoma (2,53). One reported on autologous SCT procedures (53) and the other reported on SCT with either PBSCT or CBSCT (2). One paper was a review with an expert panel consensus (53) and the other was a special report of the EBMT (2). These papers are summarized in Table 22.

Table 22. Summary of papers pertaining to non-Hodgkin's lymphomas.

Follicular lymphoma				
ESMO Guidelines Task Force, 2003 (53) Sponsor: European Society for Medical Oncology	SCT	Autologous	Under investigation: Following initial treatment or RT or CT, the role of autologous SCT in this setting is still under investigation.	Review + Expert panel consensus
Ljungman P et al, 2006 (2) Sponsor: European Group for Blood & Marrow Transplantation	BMT/ PBSCT/ CBSCT	Autologous	Accepted indications: Autologous SCT is the standard treatment for early relapsing patients. In late relapsing patients, the advantages are less clear.	Special Report

				Under investigation: First-line therapy with autologous SCT remains investigational, but there may be a role for a subgroup of high-risk patients.	

Both papers report that first-line treatment with autologous SCT remains investigational (2,53), with one stating that there may be a role for a limited subgroup of high-risk patients (2). One of the papers reported that autologous SCT is the standard treatment for patients in early relapse, but the same paper noted that the advantages, if any, for patients in late relapse were less clear (2).

Discussion of evidence review

The role of SCT in follicular lymphoma is not as clear. Allogeneic SCT offers the potential for cure in this disease, and autologous SCT has been reported to be associated with improved disease control when compared to conventional chemotherapy in a limited number of controlled trials. Many patients can be expected to do well with conventional chemotherapy, particularly when combined with rituximab. For this reason, the Panel recommends that SCT (autologous or allogeneic) be reserved as an option for selected patients who have failed second-line therapy. It would be reasonable to extrapolate this strategy to the other indolent B-cell non-Hodgkin lymphomas.

References

2. Jungman P, Urbano-Ispizua A, Cavazzana-Calvo M, Demirer T, Dini G, Einsele H, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe. Bone Marrow Transplant. 2006 Mar;37(5):439-49.

53. ESMO Guidelines Task Force. ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of newly diagnosed follicular lymphadema. Ann Oncol. 2003;14:1163-4.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Geiger-Gritsch S (LBIHTA). 2010 [10] Bendamustine (Ribomustin/Treanda/ Levact) for indolent non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukaemia (CLL) and multiple myeloma	**5 Current treatment** The most common subtypes of indolent (slow growing) B-cell NHL include chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), follicular lymphoma and Marginal Zone lymphoma. Different therapeutic approaches exist in the treatment of these types of lymphoma and the following substances are used in different chemotherapy regimes: - Fludarabine - Chlorambucil - Cyclophosphamide - Vincristine - Mitoxantrone

	- Rituximab **6.1 Efficacy and safety - Phase III studies** [23] Kahl BS, Bartlett NL, Leonard JP, Chen L, Ganjoo K, Williams ME, et al. Bendamustine is effective therapy in patients with rituximabrefractory, indolent B-cell non-Hodgkin lymphoma: Results from a multicenter *study. Cancer. 2010;116(1):106-14.* **6.2 Efficacy and safety - further studies - Indolent NHL** In addition … we identified six non-randomized phase II clinical trials investigating bendamustine either in monotherapy or in different combination therapy regimes for patients with pre-treated relapsed or refractory indolent (low-grade) NHL. <u>Bendamustine Monotherapy</u> [25] Bremer K. High rates of long-lasting remissions after 5-day bendamustine chemotherapy cycles in pre-treated low-grade non-Hodgkin'slymphomas. Journal of Cancer Research and Clinical Oncology. 2002;128(11):603-9. [26] Friedberg JW, Cohen P, Chen L, Robinson KS, Forero-Torres A, La Casce AS, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: Results from a phase II multicenter, single-agent study. Journal of Clinical Oncology. 2008;26(2):204-10. <u>Bendamustine in combination with other cytotoxic agents or rituximab</u> [27] Kath R, Blumenstengel K, Fricke HJ, Peters HD, Hoffken K. Bendamustine, vincristine, prednisolone in relapsed and refractory low grade non-Hodgkin's lymphoma. Deutsche Medizinische Wochenschrift. 2001;126(8):198-202. [28] Weide R, Hess G, Koppler H, Heymanns J, Thomalla J, Aldaoud A, et al. High anti-lymphoma activity of bendamustine/mitoxantrone/rituximab in rituximab pretreated relapsed or refractory indolent lymphomas and mantle cell lymphomas. A multicenter phase II study of the German Low Grade Lymphoma Study Group (GLSG). Leukemia and Lymphoma. 2007;48(7):1299-306. [29] Rummel MJ, Al-Batran SE, Kim SZ, Welslau M, Hecker R, Kofahl-Krause D, et al. Bendamustine plus rituximab is effective and has a favorable toxicity profile in the treatment of mantle cell and low-grade non-Hodgkin's lymphoma. Journal of Clinical Oncology. 2005;23(15):3383-9. [30] Robinson KS, Williams ME, Van Der Jagt RH, Cohen P, Herst JA, Tulpule A, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. Journal of Clinical Oncology. 2008;26(27):4473-9. **8 Ongoing research** According to ClinicalTrials.gov (www.clinicaltrials.gov) … several clinical trials of bendamustine are currently being conducted in patients with different cancer diseases. <u>Indolent NHL</u> Four phase III trials are investigating the efficacy of bendamustine in patients with indolent NHL. The trials either use bendamustine monotherapy or bendamustine in combination with different antibodies: - One study (NCT00139841), sponsored by Cepahlon, was completed only recently in May 2010. It is a multicenter phase III nonrandomized study which investigated the safety and efficacy of Treanda ® (Bendamustine HCl) in patients with indolent Non-Hodgkin's Lymphoma (NHL) who are refractory to rituximab. The study started in 2005; primary endpoint was overall response rate. The results have not been published yet. - One study (NCT01077518), sponsored by GlaxoSmithKline and starting June 2010 will evaluate the safety and efficacy of ofatumumab (Arzerra®) and bendamustine combination therapy in patients with indolent B-cell NHL that did not respond to rituximab or a rituximab-containing regimen during or within 6 months of the last rituximab treatment. The study will last until 2022. Ofatumumab is a monoclonal antibody targeting CD20. - One study (NCT01059630), sponsored by Genentech, is an openlabel, randomized phase III trial investigating the efficacy and safety of GA101 combined with bendamustine compared to bendamustine alone in patients with rituximab-refractory, indolent Non-Hodgkin's lymphoma (NHL).

	RO5072759 (GA101) is the first humanized and glycoengineered monoclonal anti-CD20 antibody. The study lasts until 2015. **9 Commentary - Bendamustine in Patients with Indolent Non-Hodgkin's lymphomas (NHL)** Although several phase III as well as phase II studies which assessed bendamustine for the treatment of NHL were found, the heterogeneity of NHL and the 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). The NCCN guidelines 'Non-Hodgkin's Lymphomas' include bendamustine with or without rituximab as an option for second-line therapy for patients with relapsed or refractory NHL. This recommendation is only based on low-level evidence (2B recommendation) because only limited data are available for this indication. [35] Non-Hodgkin's lymphoma - NCCN Clinical Practice Guidelines in Oncology. [cited May 29, 2010]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf 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 results of these trials will help to better identify the role of bendamustine among treatment options for indolent NHL. In addition, 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.
Boland A, et al. 2009 [11] Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma	**Abstract** … The submitted clinical evidence included two randomized controlled trials [European Organisation for Research and Treatment of Cancer (EORTC) and German Low Grade Lymphoma Study Group‐Fludarabine, Cyclophosphamide and Mitoxantrone and (GLSG-FCM)] comparing the clinical effects of chemotherapy with or without rituximab in the induction of remission at first or second relapse and the clinical benefits of rituximab maintenance therapy versus the NHS' s current clinical practice of observation for follicular lymphoma (FL) patients. Both trials showed that in patients with relapsed FL the addition of rituximab to chemotherapy induction treatment increased overall response rates. Furthermore, rituximab maintenance therapy increased the median length of remission when compared with observation only. Safety data from the two trials showed that while the majority of patients reported some adverse events, the number of patients withdrawing from treatment in the EORTC trial was low, with rates not being reported for the GLSG-FCM trial. The most commonly reported adverse events were blood/bone marrow toxicity, skin rashes and allergies. … **Conclusions:** … In summary, the ERG agrees that the use of rituximab for the treatment of FL is probably costeffective, but cannot confidently recommend either or both single-use strategies over the dual-use strategy, based on the available data.
NIHR Horizon Scanning Centre (NIHR HSC). 2013 [12] Idelalisib for indolent	**Target Group** Indolent non-Hodgkin's lymphoma: patients relapsed or refractory to standard treatments. **Innovation and/or advantages**

non-Hodgkin's lymphoma	If licensed, idelalisib will offer an additional oral treatment option for patients with NHL that have relapsed or are refractory to standard treatments, including rituximab and an alkylating-agent containing chemotherapy regimen. **Existing comparators and treatments** Indolent lymphomas often grow slowly and there may be long periods where there is little or no change in the disease. For many people, regular check-ups are often the most appropriate option (known as active surveillance or watchful waiting), with appropriate interventions when symptoms develop. There may be multiple episodes of remission and relapse, and the nature of the disease can change at relapse, sometimes transforming to a more aggressive type. The aim of current management for people with NHL is to prolong survival, achieve the longest possible remission and improve quality of life. Treatment for localised indolent NHL usually consists of radiotherapy to the affected lymph nodes. However, expert opinion states that for patients who are refractory to standard treatment, therapeutic options are limited with little chance of disease control. 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: • R-B. • R-CVP. • R-CHOP. • 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.
National Institute for Health and Care Excellence (NICE). 2008 [13] Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma (review of technology appraisal guidance 37)	… 1.3 Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).
Ndegwa S, Spry C (CADTH). 2010 [14] Rituximab for non-hodgkin's lymphoma: a review of the clinical and cost- effectiveness and guidelines	**Research Question:** 1. What is the clinical effectiveness and safety of rituximab for the treatment of patients with non-Hodgkin's lymphoma? **Systematic reviews and meta-analyses** … Vidal et al. conducted a systematic review and meta-analysis to evaluate the clinical effect of maintenance treatment with rituximab during remission in patients with follicular lymphoma. ... However, a subgroup analysis showed that overall survival was statistically significantly improved in patients with relapsed or refractory follicular lymphoma (maintenance after two or more inductions) but not in patients with previously untreated follicular lymphoma (maintenance after first induction). … The authors concluded that rituximab maintenance therapy for up to two years should be used for patients with relapsed or refractory follicular lymphoma following successful induction of remission while considering the higher risk of infections. 10. Vidal L, Gafter-Gvili A, Leibovici L, Shpilberg O. Rituximab as maintenance therapy for patients with follicular lymphoma. Cochrane Database Syst Rev [Internet]. 2009 [cited 2009 Dec

	1];(2). Available from: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD006552/frame.html 44. Vidal L, Gafter-Gvili A, Leibovici L, Dreyling M, Ghielmini M, Hsu Schmitz SF, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials. J Natl Cancer Inst. 2009 Feb 18;101(4):248-55. **Limitations** • Trials included in the systematic reviews were heterogeneous with respect to patient population (type of lymphoma), previous therapy (previously untreated patients or patients with relapsed/refractory disease), induction regimens, and maintenance therapy schedules. … • Few trials evaluated the effectiveness of rituximab as second-line therapy in patients with relapsed or refractory diffuse large B-cell lymphoma or for maintenance therapy in patients with diffuse large B-cell lymphoma. … **Conclusions and implications for decision and policy making** In summary, there is clear evidence to support the addition of rituximab to chemotherapy in patients with … relapsed/refractory follicular lymphoma. Although trials have indicated higher rates of leukocytopenia and neutropenia when rituximab is used for induction therapy, this does not appear to lead to higher rates of infection or treatment-related deaths when compared to chemotherapy alone. … Based on the available evidence, current guidelines … also recommend rituximab for second-line treatment in patients with relapsed or refractory follicular lymphoma and as maintenance therapy for patients with follicular lymphoma. Further trials are needed to investigate the role of rituximab for second-line therapy in patients with relapsed or refractory diffuse large B-cell lymphoma or as maintenance therapy in patients with diffuse large B-cell lymphoma. … strengths and limitations of the available evidence, clinical experience, and institution-specific budgets should be considered when making policy decisions regarding the use of rituximab in patients with non-Hodgkin's lymphoma.
Ramos FG, et al (Andalusian Agency for Health Technology Assessment - AETSA). 2010 [15] Utility of 90Y-Ibritumomab Tiuxetan (Zevalin) in the treatment of adult patients with non-Hodgkin lymphoma (executive summary in english, full text in spanish)	**Objectives** To evaluate the utility of 90Y-Ibritumomab Tiuxetan in the treatment of patients with NHL, in terms of clinical use (improvement of the prognosis, increase of the period free of disease or increase in the survival time) and quality of life, compared with the conventional treatment or the therapy with MoAb only, using the scientific literature available. The identification of clinical trials in phase III is pursued. **Conclusions** There are few phase III clinical trials, and publications derived from them, which evaluate the utility of 90Y-Ibritumomab Tiuxetan as a therapeutic option in NHL patients. Radioimmunotherapy (RIT) with 90Y-Ibritumomab Tiuxetan prolongs the time to relapse and the global survival of patients with indolent NHL. However, the information available at the present time is insufficient to determine the risk/benefit ratio derived from the addition of 90Y-Ibritumomab Tiuxetan to the present standard chemotherapy-rituximab treatment. It would be advisable to wait for the trials currently underway to be completed to confirm the preliminary results obtained.
Pohar R, et al (Canadian Agency for Drugs and Technologies in Health - CADTH). 2009 [16] Radioimmunotherapies for non-hodgkin	**Research Questions** **1.** What is the clinical effectiveness of using radioimmunotherapies in the treatment of Non-Hodgkin lymphoma? **Conclusions and Implications for Decision- or Policy-Making** Based on the evidence, the use of 131I-tositumomab and 90Y-ibritumomab may be treatment options for patients with refractory or relapsed NHL. The guidelines recommended the use of these drugs in patients with NHL that is

lymphoma: systematic review of clinical effectiveness, cost-effectiveness, and guidelines (rapid review)	refractory to chemotherapy. … The evidence* suggests that the use of 90Y-ibritumomab [is] reserved for individuals with follicular NHL whose initial treatment fails to produce a response. * 9. Barosi G, et al. Management of nodal indolent (non marginalzone) non-Hodgkin's lymphomas: Practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. Haematologica 2005;90(9):1236-57. – LL (ausserhalb unseres Suchzeitraumes) 12. Cheung MC, et al (Members of the Hematology Disease Site Group of the Cancer Care Ontario Program in Evidence-Based Care). Yttrium 90 ibritumomab tiuxetan in lymphoma. Leuk Lymphoma 2006;47(6):967-77. – SR (ausserhalb unseres Suchzeitraumes) 15. Witzig TE, et al. Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. Cancer 2007;109(9):1804-10. – MA (ohne systematische Suche und Auswahl der Quellen) 16. Gordon LI, et al. Yttrium 90-labeled ibritumomab tiuxetan radioimmunotherapy produces high response rates and durable remissions in patients with previously treated B-cell lymphoma. Clin Lymphoma 2004;5(2):98-101. – Langzeitdaten zu sekundären Endpunkten der Studie von Witzig et al. 2002 (siehe Abschnitt Primärstudien) 19. Cheung M, et al (Hematology Disease Site Group). Ibritumomab Tiuxetan in Lymphoma: A Clinical Practice Guideline [Evidence-based Series #6-17: Section 1]. Toronto: Cancer Care Ontario; 2006 Jul 17. Available: http://www.cancercare.on.ca/pdf/pebc6-17f.pdf (accessed 2009 Aug 13). – LL (ausserhalb unseres Suchzeitraumes)

Primärstudien

Zur Fragestellung der Wirksamkeit von Radioimmuntherapie im oben genannten Anwendungsgebiet wurde eine Studie extrahiert. Die Arbeit ist in der Leitlinie „Zinzani PL, et al. 2013“ sowie dem HTA-Bericht „Ramos FG, et al. 2010“ eingeschlossen.

Witzig TE, et al. 2002 [17] Randomized Controlled Trial of Yttrium-90 –Labeled Ibritumomab Tiuxetan Radioimmunotherapy Versus Rituximab Immunotherapy for Patients With Relapsed or Refractory Low-Grade, Follicular, or Transformed B-Cell Non-Hodgkin's Lymphoma	**Methodik:** Studientyp: RCT (offen) Fallzahlen: Ibritumomab = 73, Ristuximab = 70 Endpunkte: primary – ORR; secondary – DR, TTP (in all patients and in responders); additional efficacy end points - CR CCR, Cru, PR, TTNT, quality of life (FACT-G) Beobachtungszeitraum: maximum of 4 years in patients with a clinical response (response duration assessed at 6,9 and 12 month) Dosierungszeitraum: 13 weeks Randomisierungsverfahren/Allocation Concealment: mentioned, but method not specified Vergleichbarkeit der Studiengruppen: no statistically significant differences between treatment groups at baseline Fallzahlplanung: not mentioned in the text Angaben zu potenziellen Interessenskonflikten: not mentioned **Results (ITT-Daten):** ORR • Ibritumomab group: 80% (95 % CI 68,1 – 87,7) • Rituximab group: 56% (95 % CI 43,4 – 67,4) • difference statistical significant (p = 0,002) • Ibritumomab group, patients with FL: 86% • Rituximab group, patients with FL: 55% • difference statistical significant (p = 0,001) CR • Ibritumomab group: 30% • Rituximab group: 16%

	• difference statistical significant (p = 0,040) duration of response • percentage differences in favour of the Ibritumomab group, with statistical significance only to 6 months (p = 0.046) • percentage differences in favour of the Ibritumomab group in patients with FL, with statistical significance to 6 and 9 months (p = 0,019 and 0,037 respectively) FACT-G survey (81 patients completed at baseline and week 12) • ibritumomab group (n = 45): mean FACT-G score improved significantly from 86,9 at baseline to 93,3 at week 12 (p = 0,001) • rituximab group (n = 36): mean FACT-G score also increased from 90,7 at baseline to 93,4 at week 12 (p = 0,185) **Anmerkungen FBMed:** • „Response“ als patientenrelevanter Endpunkt zu diskutieren • Hinweise auf Surrogatendpunkte fehlen im Text • etwa 79% haben FL • im Mittel/Median 2 Therapielinien vorausgegangen • Indiz für Bias: offenes Studiendesign

Detaillierte Darstellung der Recherchestrategie:

Cochrane Database of Systematic Reviews am 03.03.2014

Suchschritt	Suchfrage	Treffer
1	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees	1195
2	MeSH descriptor: [Waldenstrom Macroglobulinemia] explode all trees	15
3	MeSH descriptor: [Leukemia, Hairy Cell] explode all trees	36
4	MeSH descriptor: [Leukemia, Lymphoid] explode all trees	1217
5	(waldenstrom* or waldenstroem*) and (macroglobulinemia* or macroglobulinaemia*):ti,ab,kw (Word variations have been searched)	28
6	(lymphoplasmacytic or lymphoplasmacytoid or lymphoplasmocytic or lymphoplasmocytoid or lpl) and lymphom*:ti,ab,kw (Word variations have been searched)	17
7	((non next hodgkin*) or nonhodgkin* or nhl or inhl) and lymphom*:ti,ab,kw (Word variations have been searched)	1966
8	follicular lymphom*:ti,ab,kw (Word variations have been searched)	413
9	((small next lymphocytic) or sll) and lymphom*:ti,ab,kw (Word variations have been searched)	18
10	(b-cell or chronic*) and (lymphocytic or lymphoid) and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)	546
11	chronic* and b-cell and (lymphom* or leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)	278
12	(well next differentiated) and lymphocytic and lymphom*:ti,ab,kw (Word variations have been searched)	8
13	cll:ti,ab,kw (Word variations have been searched)	327
14	((marginal next zone) or "mucosa associated lymphoid tissue" or malt) and lymphom*:ti,ab,kw (Word variations have been searched)	52
15	burkitt* and (lymphom* or tumour* or leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)	81
16	sezary* and (syndrome* or lymphom* or erythroderma*):ti,ab,kw (Word variations have been searched)	12
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)	56
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)	1808
19	((hairy next cell) and (leukemia* or leukaemia*)) or (leukemic next reticuloendothelios*):ti,ab,kw (Word variations have been searched)	78
20	adult-t and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)	40
21	(large next granular) and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)	3

22	prolymphocytic and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)	10
23	lymphoblastic and (leukemia* or leukaemia*):ti,ab,kw (Word variations have been searched)	1509
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	851

Cochrane Database of Systematic Reviews am 27.02.2014

Suchschritt	Suchfrage	Treffer
#1	MeSH descriptor: [Leukemia, B-Cell] explode all trees	228
#2	b-cell:ti,ab,kw or chronic*:ti,ab,kw (Word variations have been searched)	60578
#3	lymphocytic:ti,ab,kw or lymphoid:ti,ab,kw (Word variations have been searched)	1533
#4	leukaemia*:ti,ab,kw or leukemia*:ti,ab,kw (Word variations have been searched)	6570
#5	#2 and #3 and #4	546
#6	lymphoma*:ti,ab,kw (Word variations have been searched)	4893
#7	#4 or #6	10167
#8	chronic*:ti,ab,kw and b-cell:ti,ab,kw (Word variations have been searched)	339
#9	#7 and #8	278
#10	CLL:ti,ab,kw (Word variations have been searched)	327
#11	small next cell:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	49
#12	small:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	28
#13	well next differentiated:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw (Word variations have been searched)	8
#14	SLL:ti,ab,kw (Word variations have been searched)	23
#15	#1 or #5 or #9 or #10 or #11 or #12 or #13 or #14 from 2009 to 2014	46

MEDLINE (PubMed) nach SR, HTA am 03.03.2014

Suchschritt	Suchfrage	Treffer
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])	30050
2	("Waldenstrom Macroglobulinemia/drug therapy"[Mesh] OR "Waldenstrom Macroglobulinemia/radiotherapy"[Mesh] OR "Waldenstrom Macroglobulinemia/surgery"[Mesh] OR "Waldenstrom Macroglobulinemia/therapy"[Mesh])	900
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])	1291
4	("Leukemia, Lymphoid/drug therapy"[Mesh] OR "Leukemia, Lymphoid/radiotherapy"[Mesh] OR "Leukemia,	23313

Suchschritt	Suchfrage	Treffer
	Lymphoid/surgery"[Mesh] OR "Leukemia, Lymphoid/therapy"[Mesh])	
5	(((waldenstrom*[Title/Abstract]) OR waldenstroem*[Title/Abstract])) AND ((macroglobulinemia*[Title/Abstract]) OR macroglobulinaemia*[Title/Abstract])	2417
6	((((((lymphoplasmacytic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract]) OR lymphoplasmocytic[Title/Abstract]) OR lymphoplasmocytoid[Title/Abstract]) OR lpl[Title/Abstract])) AND lymphom*[Title/Abstract]	1045
7	(((((non hodgkin*[Title/Abstract]) OR nonhodgkin*[Title/Abstract]) OR nhl[Title/Abstract]) OR inhl[Title/Abstract])) AND lymphom*[Title/Abstract]	30445
8	(follicular[Title/Abstract]) AND lymphom*[Title/Abstract]	7233
9	(((small lymphocytic[Title/Abstract]) OR sll[Title/Abstract])) AND lymphom*[Title/Abstract]	1146
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])	18406
11	((chronic*[Title/Abstract]) AND b cell[Title/Abstract]) AND (((lymphom*[Title/Abstract]) OR leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	7129
12	((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphom*[Title/Abstract]	200
13	cll[Title/Abstract]	10109
14	((((marginal zone[Title/Abstract]) OR mucosa associated lymphoid tissue[Title/Abstract]) OR malt[Title/Abstract])) AND lymphom*[Title/Abstract]	5658
15	(burkitt*[Title/Abstract]) AND ((((lymphom*[Title/Abstract]) OR tumour*[Title/Abstract]) OR leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	8102
16	(sezary*[Title/Abstract]) AND (((syndrome*[Title/Abstract]) OR lymphom*[Title/Abstract]) OR erythroderma*[Title/Abstract])	1739
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 woringer kolopp disease*[Title/Abstract]	5833
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]	54126
19	((((hairy cell[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract]))) OR leukemic reticuloendothelios*[Title/Abstract])	3508

Suchschritt	Suchfrage	Treffer
20	(adult t[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	4472
21	(large granular[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	799
22	(prolymphocytic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	1027
23	(lymphoblastic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	24615
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	128666
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]	8007711
26	(#24) AND #25	64516
27	((((#1) OR #2) OR #3) OR #4) OR #26	89007
28	(#27) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])	980
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])))	167459
30	(#27) AND #29	704
31	(#28) OR #30	1241
32	(#31) AND (“2009/03/01”[PDAT] : “2014/03/03”[PDAT])	600

MEDLINE (PubMed) nach SR, HTA am 27.02.2014

Suchschritt	Suchfrage	Treffer
#1	Search "leukemia, b cell"[MeSH Terms]	12447
#2	Search (b-cell[Title/Abstract]) OR chronic*[Title/Abstract]	903047
#3	Search (lymphocytic[Title/Abstract]) OR lymphoid[Title/Abstract]	102041
#4	Search (leukaemia*[Title/Abstract]) OR leukemia*[Title/Abstract]	195005
#5	Search (#2 AND #3 AND #4)	18399

#6	Search lymphoma*[Title/Abstract]	128371
#7	Search (#4 OR #6)	301338
#8	Search (chronic*[Title/Abstract]) AND b-cell[Title/Abstract]	9737
#9	Search (#7 AND #8)	7123
#10	Search CLL[Title/Abstract]	10109
#11	Search (small-cell[Title/Abstract]) AND lymphoma*[Title/Abstract]	1850
#12	Search ((small[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	1830
#13	Search ((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	200
#14	Search SLL[Title/Abstract]	579
#16	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	27335
#22	Search ((((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])))	167284
#25	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) Filters: Systematic Reviews; Meta-Analysis; Technical Report	248
#26	Search (#16 AND #22)	158
#27	Search (#25 OR #26)	316
#28	Search (#25 OR #26) Filters: published in the last 5 years	142

MEDLINE (PubMed) nach Leitlinien am 03.03.2014

Suchschritt	Suchfrage	Treffer
1	lymphoma, non hodgkin[MeSH Terms]	81282
2	waldenstrom macroglobulinemia[MeSH Terms]	4436
3	leukemia, hairy cell[MeSH Terms]	2990
4	leukemia, lymphoid[MeSH Terms]	59456
5	(((waldenstrom*[Title/Abstract]) OR waldenstroem*[Title/Abstract])) AND ((macroglobulinemia*[Title/Abstract]) OR macroglobulinaemia*[Title/Abstract])	2417
6	((((((lymphoplasmacytic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract]) OR lymphoplasmocytic[Title/Abstract]) OR lymphoplasmocytoid[Title/Abstract]) OR lpl[Title/Abstract])) AND	1045

Suchschritt	Suchfrage	Treffer
	lymphom*[Title/Abstract]	
7	(((((non hodgkin*[Title/Abstract]) OR nonhodgkin*[Title/Abstract]) OR nhl[Title/Abstract]) OR inhl[Title/Abstract])) AND lymphom*[Title/Abstract]	30445
8	(follicular[Title/Abstract]) AND lymphom*[Title/Abstract]	7233
9	(((small lymphocytic[Title/Abstract]) OR sll[Title/Abstract])) AND lymphom*[Title/Abstract]	1146
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])	18406
11	((chronic*[Title/Abstract]) AND b cell[Title/Abstract]) AND (((lymphom*[Title/Abstract]) OR leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	7129
12	((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphom*[Title/Abstract]	200
13	cll[Title/Abstract]	10109
14	((((marginal zone[Title/Abstract]) OR mucosa associated lymphoid tissue[Title/Abstract]) OR malt[Title/Abstract])) AND lymphom*[Title/Abstract]	5658
15	(burkitt*[Title/Abstract]) AND ((((lymphom*[Title/Abstract]) OR tumour*[Title/Abstract]) OR leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	8102
16	(sezary*[Title/Abstract]) AND (((syndrome*[Title/Abstract]) OR lymphom*[Title/Abstract]) OR erythroderma*[Title/Abstract])	1739
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 woringer kolopp disease*[Title/Abstract]	5833
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]	54126
19	((((hairy cell[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract]))) OR leukemic reticuloendothelios*[Title/Abstract])	3508
20	(adult t[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	4472
21	(large granular[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	799
22	(prolymphocytic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	1027
23	(lymphoblastic[Title/Abstract]) AND ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])	24615
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	128666

Suchschritt	Suchfrage	Treffer
	#18) OR #19) OR #20) OR #21) OR #22) OR #23	
25	((((#1) OR #2) OR #3) OR #4) OR #24	180186
26	(((cutaneous[Title]) OR malignant[Title])) AND lymphom*[Title]	11363
27	(#25) OR #26	183093
28	((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]	69961
29	(#27) AND #28	333
30	(#29) AND ("2009/03/01"[PDAT] : "2014/03/03"[PDAT])	120

MEDLINE (PubMed) nach Leitlinien am 27.02.2014

Suchschritt	Suchfrage	Treffer
#1	Search "leukemia, b cell"[MeSH Terms]	12447
#2	Search (b-cell[Title/Abstract]) OR chronic*[Title/Abstract]	903047
#3	Search (lymphocytic[Title/Abstract]) OR lymphoid[Title/Abstract]	102041
#4	Search (leukaemia*[Title/Abstract]) OR leukemia*[Title/Abstract]	195005
#5	Search (#2 AND #3 AND #4)	18399
#6	Search lymphoma*[Title/Abstract]	128371
#7	Search (#4 OR #6)	301338
#8	Search (chronic*[Title/Abstract]) AND b-cell[Title/Abstract]	9737
#9	Search (#7 AND #8)	7123
#10	Search CLL[Title/Abstract]	10109
#11	Search (small-cell[Title/Abstract]) AND lymphoma*[Title/Abstract]	1850
#12	Search ((small[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	1830
#13	Search ((well-differentiated[Title/Abstract]) AND lymphocytic[Title/Abstract]) AND lymphoma*[Title/Abstract]	200
#14	Search SLL[Title/Abstract]	579
#16	Search (#1 OR #5 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)	27335
#17	Search (non-hodgkin*[Title]) AND lymphoma*[Title]	13590
#18	Search (#16 OR #17)	39854
#19	Search ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]	69915
#20	Search (#18 AND #19)	110
#21	Search (#18 AND #19) Filters: published in the last 5 years	34

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Anhang:

Tabelle 1: “Table 2. Randomized controlled trials evaluating chemotherapy plus rituximab versus non-rituximab regimens in indolent histology lymphoma. “ aus Imrie K, et al. 2012 Cancer Care Ontario (CCO)

Second-line or later therapy								
Author, study	**N rand**	**Patients**	**Treatment[A]**	**Follow-up time of study**	**RR[B]**	**Disease control[B]**	**OS[B]**	**Comment**
Forstpointner (30), Full Dreyling (31), abst	147	Relapsed follicular and mantle Maintenance randomization described below (Dreyling 37)	FCM-R vs. FCM	Median 18 mo	79% vs. 58%; p=0.01 (CR+PR)	Median PFS, 16 vs. 10 mo; p=0.0381	Median, not reached vs. 24 mo (p=0.0030)	Eval: 128 pts; 10 pts had incomplete documentation, 9 pts withdrew after randomization prior to starting therapy Age 35-80 y
Van Oers (32), abst	461	Relapsed/ Resistant[Q] Follicular NHL (stg III or IV) Maintenance randomization described below (Van Oers 38)	CHOP-R vs. CHOP	NR	CR after induction: 30.4% vs. 18.1%; p=0.0004	3 y PFS 67.7% vs. 31.2%; p<0.0001	NS	Eval: 369 pts for induction response; 268 pts for maintenance

Note: abst=abstract; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP=cyclophosphamide, mitoxantrone, vincristine, prednisone; CR=complete response; CVP=cyclophosphamide, vincristine, prednisone; EFS=event-free survival; DFS=disease-free survival; est=estimated; eval=evaluable; FCM=fludarabine, cyclophosphamide, mitoxantrone; IFN-alpha=interferon-alpha; ITT=intention to treat; maint=maintenance; max=maximum; MCP=mitoxantrone, chlorambucil, prednisone; mo=month; N=number; NHL=non-Hodgkin's lymphoma; NR=not reported; NS=not significant; obs=observation; OS=overall survival; PFS=progression-free survival; PR=partial response; prelim=preliminary; pts=patients; rand=randomized; R=rituximab; RR=response rate; SD=stable disease; SLL=small lymphocytic lymphoma; stg=stage; TTF=time-to-treatment failure; vs.=versus; y=year.
[A]Treatment details are provided in Appendix 1.
[B]Data provided in order of intervention versus control.

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Table 1. Grading the Quality of Design and Strength of Evidence

	Levels of evidence
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-controlled or cohort studies. High-quality case-controlled or cohort studies with a very low risk of confounding, bias, or chance, and a high probability that the relationship is causal
2+	Well-conducted case controlled or cohort studies with a low risk of confounding, bias, or chance, and a moderate probability that the relationship is causal
2−	Case-controlled or cohort studies with a high risk of confounding, bias, or chance, and a significant risk that the relationship is not causal
3	Nonanalytic studies (eg, case reports, case series)
4	Expert opinion

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Abbildung 1: aus Oliansky DM, et al. 2010

Table 2. Grading the Strength of the Treatment Recommendation

Grades of Recommendation	
A	At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+

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Abbildung 2: aus Oliansky DM, et al. 2010