Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-04-01-D-222 Idelalisib

Stand: August 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Idelalisib [zur Behandlung der chronischen lymphatischen Leukämie)]	
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	Beschluss vom 5. Februar 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Obinutuzumab Beschluss vom 19. März 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Idelalisib Beschluss vom 16. April 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ibrutinib
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: Zydelig wird in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) angewendet: • die mindestens eine vorangehende Therapie erhalten haben, oder • als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, die für eine Chemoimmuntherapie ungeeignet sind. (FI Zydelig®, September 2014)
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®, November 2014)
Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (FI Leukeran®, Juli 2014)
Cyclophosphamid L01AA01 generisch	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®, Januar 2015)
Fludarabin L01BB05 generisch	Therapie der chronischen-lymphatischen Leukämie (CLL) vom B-Zell-Typ bei Patienten mit ausreichender Knochenmarksreserve. Die First-Line-Therapie mit Bendarabin 50 mg sollte nur bei Patienten mit fortgeschrittener Erkrankung begonnen werden, einhergehend mit krankheitsbedingten Symptomen oder dem Nachweis der fortgeschrittenen Erkrankung. (FI Bendarabin®, September 2014)
Ibrutinib L01XE27 IMBRUVICA®	IMBRUVICA ist indiziert zur Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinien-Therapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemo-Immuntherapie nicht geeignet sind. (FI IMBRUVICA®, Oktober 2014)
Obinutuzumab L01XC15 Gazyvaro™	Gazyvaro in Kombination mit Chlorambucil wird bei erwachsenen Patienten mit nicht vorbehandelter chronischer lymphatischer Leukämie (CLL) angewendet, die aufgrund von Begleiterkrankungen für eine Therapie mit einer vollständigen Dosis von Fludarabin nicht geeignet sind. (FI Gazyvaro™, Juli 2014)
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®, Juli 2014)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Prednisolon H02AB06 generisch	Hämatologie/Onkologie: Chronisch lymphatische Leukämie (FI Dermosolon®, August 2011)
Prednison H02AB07 generisch	Hämatologie/Onkologie: Chronisch lymphatische Leukämie (FI Cutason®, Februar 2015)
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®, Mai 2014)
Weitere Arzneimittel mit Zulassung für Non-Hodgkin-Lymphome	
Cytarabin L01BC01 generisch	Die Infusionslösung wird eingesetzt zur Hochdosistherapie bei: - refraktären (anderweitig therapieresistenten) Non-Hodgkin-Lymphomen (ARA-cell®, 03-2014)
Doxorubicin L01DB01 generisch	Non-Hodgkin-Lymphom (FI Adrimedac®, September 2013)
Trofosfamid L01AA07 Ixoten®	Dieses Arzneimittel ist ein Zytostatikum. Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet. (FI Ixoten®, Januar 2015)
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®, Februar 2014)
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®, September 2011)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Indikation für die Recherche bei Ibrutinib: 5

Berücksichtigte Wirkstoffe/Therapien: 5

Systematische Recherche: 6

- IQWiG Berichte/ G-BA Beschlüsse 7
- Cochrane Reviews 10
- Systematische Reviews 15
- Leitlinien 27
- Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren 41

Detaillierte Darstellung der Recherchestrategie: 46

Literatur: 48

Anhang: 51

Indikation für die Recherche bei Ibrutinib:

Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL)

- die mindestens eine vorangehende Therapie erhalten haben, oder

- zur Erstlinientherapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemoimmuntherapie ungeeignet sind.

Berücksichtigte Wirkstoffe/Therapien:

Siehe Unterlage zur Beratung in AG: Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „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 (CLL)“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 24.07.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, ESMO, NCI. 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 667 Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden 85 Quellen eingeschlossen. Insgesamt ergab dies 24 Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden.

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCI	U.S. National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PFS	Progression free survival
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2015 [5]. Arzneimittel-Richtlinie, Anlage VI: Off-Label-Use (früher: Anlage 9).Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use). Stand 05.05.2015	VI. Anwendung von Fludarabin bei anderen als in der Zulassung genannten niedrig bzw. intermediär malignen B - Non-Hodgkin-Lymphomen (B-NHL) als chronische lymphatische Leukämien (CLL) 1. Hinweise zur Anwendung von Fludarabin gemäß § 30 Absatz 2 AM-RL a) Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation): Fludarabin in Kombination mit Cyclophosphamid, Mitoxantron und Rituximab (R-FCM) bei geeigneten Patienten mit niedrig oder intermediär malignen Non-Hodgkin-Lymphomen der B-Zellreihe (CD20 positive NHL, u.a. lymphozytisch, lymphoplasmozytisch, lymphoplasmazytoid, follikulär Grad 1 oder 2, Mantelzell, Marginalzonen, nicht multiples Myelom, nicht Haarzellleukämie) und Resistenz auf CHOP (mit oder ohne Rituximab)
G-BA, 2015 [6]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ibrutinib Stand: 16. April 2015	**Zugelassene Anwendungsgebiete:** *Anwendungsgebiet 1:* – Ibrutinib (IMBRUVICA®) ist indiziert zur Behandlung erwachsener Patienten mit rezidiviertem oder refraktärem Mantelzell-Lymphom (MCL). *Anwendungsgebiet 2:* – IMBRUVICA® ist indiziert zur Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinien-Therapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemo-Immuntherapie nicht geeignet sind. <u>Ausmaß des Zusatznutzens:</u> *Anwendungsgebiet 2:* a) Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben – nicht quantifizierbar b) Erstlinien-Therapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemo-Immuntherapie nicht geeignet sind – nicht quantifizierbar Hinweise FB Med: – Ausmaß des Zusatznutzens nur für das Anwendungsgebiet 2 dargestellt
G-BA, 2015 [7]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII -	**Zugelassenes Anwendungsgebiet:** Idelalisib (Zydelig®) wird in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) angewendet: – die mindestens eine vorangehende Therapie erhalten haben, oder – als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, die für eine Chemoimmuntherapie ungeeignet

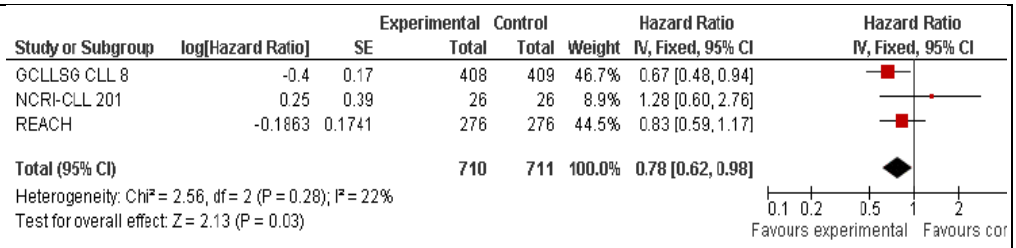
Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Idelalisib Stand: 19. März 2015	sind. Idelalisib (Zydelig®) wird als Monotherapie zur Behandlung von erwachsenen Patienten mit follikulärem Lymphom (FL), das refraktär gegenüber zwei vorausgegangenen Therapielinien ist, angewendet. <u>Ausmaß des Zusatznutzens:</u> *Anwendungsgebiet 1:* Zur Behandlung von Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben. *Teilpopulation 1a:* *Patienten mit rezidivierender CLL, für die eine Chemotherapie angezeigt ist* Zweckmäßige Vergleichstherapie: – Eine Chemotherapie in Kombination mit Rituximab nach Maßgabe des Arztes, unter Beachtung des Zulassungsstatus Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Chemotherapie in Kombination mit Rituximab: – Da erforderliche Nachweise nicht vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V). *Teilpopulation 1b:* *Patienten mit rezidivierender CLL, für die eine Chemotherapie nicht angezeigt ist* Zweckmäßige Vergleichstherapie: – Best-Supportive-Care Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: – Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen *Teilpopulation 1c:* *Patienten mit refraktärer CLL, für die eine Chemotherapie oder Therapie mit Ofatumumab angezeigt ist* Zweckmäßige Vergleichstherapie: – Eine patientenindividuelle, optimierte Therapie nach Maßgabe des Arztes, unter Beachtung des Zulassungsstatus Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer patientenindividuellen, optimierten Therapie: – Da erforderliche Nachweise nicht vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V). *Teilpopulation 1d:* *Patienten mit refraktärer CLL, für die eine Chemotherapie oder Therapie mit Ofatumumab nicht angezeigt ist* Zweckmäßige Vergleichstherapie: – Best-Supportive-Care

	Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: – Da erforderliche Nachweise nicht vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V). *Anwendungsgebiet 2:* Zur Erstlinientherapie der chronischen lymphatischen Leukämie (CLL) bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, die für eine Chemoimmuntherapie ungeeignet sind. Zweckmäßige Vergleichstherapie: – Best-Supportive-Care Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: – Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen **Hinweise FB Med:** – Ausmaß des Zusatznutzens nur für die Anwendungsgebiete 1 und 2 dargestellt (AWG 3: Behandlung von Patienten mit follikulärem Lymphom (FL))
G-BA, 2015 [8]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Obinutuzumab Stand: 05. Februar 2015	**Zugelassenes Anwendungsgebiet:** Obinutuzumab (GazyvaroTM) in Kombination mit Chlorambucil wird bei erwachsenen Patienten mit nicht vorbehandelter chronischer lymphatischer Leukämie (CLL) angewendet, die aufgrund von Begleiterkrankungen für eine Therapie mit einer vollständigen Dosis von Fludarabin nicht geeignet sind. <u>Ausmaß des Zusatznutzens:</u> – nicht quantifizierbar

Cochrane Reviews

Bauer K et al., 2012 [2]. 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 = 1 421) 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.
Vidal L et al., 2012 [24]. Bendamustine for patients with indolent B cell lymphoid	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

malignancies including chronic lymphocytic leukaemia.	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 1 343 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 und Niederle 2012: (siehe Anhang)** - Es zeigten sich in beiden Studien keine stat. signifikanten Unterschiede zwischen den Interventionen (siehe forest plot im Anhang). 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

Police RL et al., 2015 [21].

Randomized Controlled Trials in Relapsed/Refractory Chronic Lymphocytic Leukemia: A Systematic Review and Meta-Analysis

1. Fragestellung

This systematic literature review with meta-analysis was conducted on the clinical efficacy and safety of interventions used in the treatment of chronic lymphocytic leukemia (CLL). We were particularly interested in whether there were treatments (chemotherapy or chemoimmunotherapy) that had better efficacy and safety than others and should be recommended as a standard against which to test drugs in development.

2. Methodik

Population: patients with relapsed/refractory chronic lymphocytic leukemia

Definitions of Relapsed or Refractory Disease in Select Studies in CLL

Reference	Definition of Relapsed or Refractory Disease
Elter, 2011	Based on the NCIWG 1996 criteria, with evidence of progressive disease that required treatment after 1 previous treatment for CLL
Faderl, 2006	Based on the NCIWG 1996 criteria; patients who had received at least 1 course of treatment with a purine analogue and who either experienced recurrence during or within 6 months, or were intolerant
Hillmen, 2011	Not clearly defined; methods state patients were previously treated with at least 1 therapy and now required therapy
O'Brien, 2009	Definition adapted from the literature: patient was refractory if they failed to achieve at least a partial response or if disease recurred within 6 months of treatment
Robak, 2010	Not defined
Wendtner, 2011	Not defined

Vergleich: siehe Ergebnisdarstellung

Endpunkte: *Primary efficacy outcomes*: objective response rate, progression-free survival, and overall survival. *Safety end points*: Grade 3/4 toxicities, serious adverse events, withdrawals because of toxicity, and deaths due to toxicity.

Suchzeitraum (Aktualität der Recherche): 01/1997 bis 08/2012

Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 RCTs (range: n=22-552)

Qualitätsbewertung der Studien: Assessment of the methodological quality of the included RCTs was based on guidance in the National Institute for Health and Care Excellence Single Technology Appraisal specification for manufacturer/sponsor submission of evidence 2009

and adapted from the Centre for Reviews and Dissemination guidance for undertaking reviews in health care.

3. Ergebnisdarstellung

Efficacy of Randomized Trials in CLL:

Reference	ORR, %[a]	Median Duration of Response, Months	Median PFS, Estimated PFS Rate, Months	Median OS Estimated OS Rate
Elter, 2011	Fludarabine with alemtuzumab, 82% Fludarabine, 75% P = NS	NR for either treatment group	Fludarabine with alemtuzumab: 23.7 Fludarabine: 16.5 P = .0003	Fludarabine with alemtuzumab, NR Fludarabine, 52.9 months P = .021
Faderl, 2006[b]	NR for either treatment group	NR for either treatment group	NR for either treatment group	NR for either treatment group
Hillmen, 2011	FCM, 58% FCM-R, 65% NR	NR for either treatment group	NR for either treatment group	NR for either treatment group
O'Brien, 2009	NR for either treatment group	Outcome not measured in months in follow-up study	NR for either treatment group	FC, 31 Oblimersen with FC, 27.3 months (ITT population) NS
Robak, 2010	FC, 58% FC-R, 70% P = .0034	FC, 27.7 FC-R, 39.6 P = .025	FC, 20.6 FC-R, 30.6 P < .001	FC, 52 months FC-R, NR P = NS
Wendtner, 2011	38%	NR for either treatment group	NR for either treatment group	NR for either treatment group

Abbreviations: FC = fludarabine and cyclophosphamide; FCM = fludarabine, cyclophosphamide, and mitoxantrone; FCM-R = fludarabine, cyclophosphamide, mitoxantrone, and rituximab; FC-R = fludarabine and cyclophosphamide, with rituximab; ITT = intention-to-treat; NS = not significant; OS = overall survival; PFS = progression-free survival.
[a]ORR as defined by Cheson et al, 1996.
[b]Study terminated early because of lack of objective response to treatment.

*Safety of Randomized Trials in CLL: s*iehe Anhang Evidenzsynopse

4. Fazit der Autoren

In the 6 studies, the most commonly investigated therapies were fludarabine and rituximab, both of which are currently recommended by ESMO for treatment of R/R CLL. Other drugs and combination regimens have not been as successful, in some instances perhaps

	because trials evaluating these treatments have been terminated early because of lack of patient enrollment. However, ongoing phase III clinical trials in patients with indolent NHL indicate an increased interest in studying the R/R CLL population and a need for developing novel effective and well-tolerated therapies to treat these patients. Additional well designed RCTs are needed to rigorously understand the efficacy and safety of more recently developed therapies in the R/R CLL population and the remaining medical unmet needs for this patient population. *5. Hinweise FBMed:* – *Definitionen der eingeschlossenen Patienten (relapsed/refractory) siehe Methodikteil* – *work supported by funding from Sanofi aventis* – *authors are employes of Sanofi*
Hua Q, Zhu Y, Liu H. 2015 [10]. Severe and fatal adverse events risk associated with rituximab addition to B-cell non-Hodgkin's lymphoma (B-NHL) chemotherapy: a meta-analysis	1. Fragestellung: Rituximab is a monoclonal antibody targetting the CD20 antigen with the ability to increase overall remission (OR) in B-cell non-Hodgkin's lymphoma (B-NHL). A systematic review and meta-analysis were conducted to determine the risk of the most clinically relevant severe and fatal adverse events (AEs) associated with the use of rituximab in the treatment of B-NHL.
	2. Methodik Population: B-NHL Intervention: chemotherapy in combination with rituximab or chemotherapy alone Komparator: k.A. Endpunkte: relevant severe and fatal AEs related with rituximab Suchzeitraum (Aktualität der Recherche): published over the last 10 years Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 RCTs/n = 3 363 i. Qualitätsbewertung der Studien: Jadad-Score
	3. Ergebnisdarstellung • one trial with CLL: Robak T, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010;28:1756–65. • phase III study (study quality 3) • six randomly assigned patients (FC, n = 4; R-FC, n = 2) did not receive study treatment

	• most fatal AEs (in both arms): infections Summary RR • no statistically significant rituximab-associated increased risk in 13 severe adverse events: infection, fever, anaemia, thrombocytopaenia, granulocytopenia, liver toxicity, cardiac toxicity, neurologic toxicity, lung toxicity, mucositis, nausea/vomiting, diarrhoea, alopecia o except leukocytopenia (36.4% versus 31%; RR = 1.13; 95%CI, 1.01–1.27; P = 0.03) i. incidences of fatal AEs: difference between rituximab group and control group (RR = 1.45; 95% CI, 1.04–2.02; P = 0.03)
	4. Fazit der Autoren: This meta-analysis indicates that there was no proof of statistically higher incidence of most SAEs in rituximab containing group compared with chemotherapy alone. However, fatal infections were more frequently observed in patients who received rituximab. Considering the low-incidence infection induced death during the treatment period, the effects of rituximab on infections need further investigation. *5. Anmerkungen FB Med:* • *Publikationsbias überprüft und als unwahrscheinlich bewertet* • *Funding None.* • *None of the authors declare any conflicts of interest.*
Kharfan-Dabaja MA et al. 2012 [12]. 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) Endpunkte: 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. Qualitätsbewertung der Studien: k.A.
	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.* - *The authors declare no conflict of interest.*
Lepretre S et al., 2012 [13]. 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 Qualitätsbewertung der Studien: RCT quality was assessed by two independent reviewers according to recommended methods [10]. In the absence of recommended methods for appraising non-RCTs, these were reviewed for reporting quality and completeness. [10] Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.
	3. Ergebnisdarstellung Allgemein: 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. *Response/Remission:* 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. *Overall Survival:* 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. *Safety:* 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.* - *Studienqualität bei der Bewertung und Synthese nicht berücksichtigt* - *The study sponsor, F. Hoffman-La Roche Ltd (Roche), provided assistance with literature searching and identification of studies in fludarabine-refractory patients. The manuscript was written by Dr. Lepretre, with some third-party editorial assistance provided by an independent medical writing agency funded by Roche.*
Hadjinicolaou AV et al. 2012 [9]. Non-infectious pulmonary toxicity of rituximab: a systematic review	1. Fragestellung Rituximab (RTX), a B-cell depleting mAb, has been reported to cause pulmonary toxicity in many patients. As the use of this biologic is increasing, we have undertaken a systematic review of the literature to gauge the nature and extent of non-infection-related RTX-induced lung disease.
	2. Methodik Population: reported cases of RTX-associated interstitial lung disease (RTX-ILD) Intervention: rituximab Komparator: k.A. Endpunkte: epidemiological, clinical, radiological, histopathological, laboratory and management data Suchzeitraum (Aktualität der Recherche): up to June 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 61/n = 121 Qualitätsbewertung der Studien: k.A.
	3. Ergebnisdarstellung • 121 cases of potential RTX-ILD identified from 21 clinical studies/trials, 30 case reports, 10 case series • most common indication for RTX: diffuse large B-cell lymphoma • 6 cases of chronic lymphocytic leukaemia • RTX-ILD occurred more frequently in male patients and was

	most common during the fifth and sixth decades of life • in most cases RTX part of combination chemotherapy, but in 30 (24.7%) cases it was monotherapy • mean and median number of cycles of RTX before disease onset: 4 (cases following the first cycle or as late as the 12th cycle also identified) • mean time of onset from last RTX infusion until symptom development or relevant abnormal radiological change: 30 days (range 0 - 158 days) • abnormal radiological findings similar in all patients: with diffuse bilateral lung infiltrates apparent on chest radiographs and/or thoracic CT • hypoxaemia seen in all cases • pulmonary function tests uniformly abnormal with a characteristic diffusion capacity deficit and restrictive ventilatory pattern • RTX-ILD fatal in 18 cases
	4. Fazit der Autoren ILD is a rare but potentially fatal complication of RTX therapy. This diagnosis should be considered in any patient who develops respiratory symptoms or new radiographic changes while receiving this biologic agent. *5. Anmerkungen durch FBMed:* - *research in the authors' laboratories is funded by the National Institute for Health Research (NIHR), Cambridge Biomedical Research Centre, Wellcome Trust, Medical Research Council (MRC), Addenbrooke's Charity Trust, Asthma-UK, Biotechnology and Biological Sciences Research Council (BBSRC), Intensive Care Society and Papworth Hospital, National Health Service (NHS) Foundation Trust R&D Department.* - *A.J.K.O¨ . has received support from (including attendance at conferences), undertakes clinical trials and acts as a consultant to Roche, Chugai, Schering-Plough/MSD, Abbott, Wyeth, BMS, GSK, MerckSorono and UCB* - *All other authors have declared no conflicts of interest.*
CLL Trialists' Collaborative Group (CLLTCG), 2012 [3]. Systematic review of purine analog treatment for chronic lymphocytic leukemia: lessons for future trials.	1. Fragestellung With the completion and publication of the additional trials, it was agreed that the collaborative group would address this question using individual patient data (IPD), and also investigate combination treatments that included purine analogs. Antibody therapies were excluded as the trials were too recent and data were not yet available. Use of IPD would allow examination of differences in the timings of response evaluations and the use of a more uniform definition of PFS.
	2. Methodik Population: patients with untreated CLL (Subgroup analyses were pre-planned by sex, age (<60, 60-69, ≥70 years), stage, IGHV (mutated or unmutated), 17p13 deletion or not, and by year of

	follow up.) Intervention: at least one treatment arm including a purine analog with the exception of those involving an antibody therapy, such as rituximab or alemtuzumab Komparator: k.A. Endpunkte: good response (complete or nodular partial), any response, PFS and overall survival Suchzeitraum (Aktualität der Recherche): k.A. Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 (n = k.A.) Qualitätsbewertung der Studien: k.A.
	3. Ergebnisdarstellung • 16 trials found, addressing seven comparisons • Median follow up: from 2 to 12 years • male patients: 63-74% of study subjects • most male and female patients under 70 years of age • a small subset of trials able to supply data on 17p13 deletion **PFS** *single agent purine analog* • 8 trials (n = 2 753 patients): odds ratio = 0.71; 95% confidence interval=0.63-0.79), heterogeneity substantial *addition of cyclophosphamide* • 3 trials (n = 1 403 patients): odds ratio = 0.54; 0.47-0.62 *addition of other drugs to purine analog* • fewer data available, none showed clear benefit • 2 trials (n = 544 patients) suggested cladribine improved PFS compared to fludarabine (odds ratio = 0.77; 0.63-0.95) **OS** • no differences for any comparisons **subgroups** • no significant differences between treatment effects on response, PFS or OS in subgroups by 17p13 deletion for any of the comparisons • trend or heterogeneity test P>0.1
	4. Fazit der Autoren In conclusion, purine analogs, particularly combined with cyclophosphamide, significantly improve progression free survival but not survival. Some groups, such as the elderly, may not see the same benefits and maximizing doses may be important for all treatments, including chlorambucil. Longer follow up, consistent definitions and detailed reporting of trials should be encouraged.

	5. Anmerkungen durch FBMed: - *work supported by Cancer Research UK and Medical Research Council. Funders were not involved in the design, analysis or reporting*
Keating GM 2010 [11]. 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.) Qualitätsbewertung der Studien: 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:* - *The preparation of this review was not supported by any external funding.* - *During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.*

Leitlinien

Prica A et al., 2015 [22]. **Cancer Care Ontario, Toronto (CAN)** Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline, vers. 3	**Fragestellung** Target Population: Chronic Lymphocytic Leukemia • Adult patients with CLL at any stage. Research Questions: Chronic Lymphocytic Leukemia 1. What beneficial outcomes are associated with the use of rituximab for the treatment of patients with CLL? Outcomes of interest are OS, disease control (as assessed by measures such as PFS, EFS, TTF, or RD), 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 (update von 1999 und 2006), bei homogener Datenlage Metaanalysen durchgeführt, informaler Konsensusprozess („considered judgement of benefits and harms“) führt zu Empfehlungsvorschlägen, external Review by Ontario Clinicians nad other experts, • updated through an annual assessment and subsequent review process. • Suchzeitraum (letzte Aktualisierung): Oktober 2013 LoE/GoR: über Beschreibungen und Formulierung *Sonstige methodische Hinweise* - *CONFLICT OF INTEREST: Information regarding conflict of interest declarations can be found in Section 4, Appendix 7A.* - *Funding: The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.* *detaillierte Angaben zur Qualität und Eigenschaften sowie Ergebnissen der eingeschlossen Studien in Evidenztabellen aufbereitet*
	Freitext/Empfehlungen/Hinweise **Recommendation 3** *Chronic lymphocytic leukemia/small lymphocytic lymphoma* <u>Previously Untreated Patients</u> a. Patients with previously untreated CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab. b. In patients with previously untreated CLL/SLL who are appropriate

candidates for chlorambucil chemotherapy, the addition of rituximab can be considered.

Patients with Relapsed/Refractory Disease

c. Patients with relapsed or refractory CLL/SLL, who are appropriate candidates for fludarabine-based chemotherapy, should receive this treatment in combination with rituximab.

Summary of Key Evidence for Recommendation 3

- two systematic reviews [54,55] included patients with fludarabine-resistant CLL – Anmerkung FB Med: beide oben extrahiert

Quellen:

54. Lepretre S, Jager U, Janssens A, Leblond V, Nikitin E, Robak T, et al. The value of rituximab for the treatment of fludarabine-refractory chronic lymphocytic leukemia: a systematic review and qualitative analysis of the literature. Leuk Lymphoma. 2012;53(5):820-9.

55. Bauer K, Rancea M, Roloff V, Elter T, Hallek M, Engert A, et al. Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia. Cochrane Database of Syst Rev. 2012(11).

- review by Lepretre et al [54] included randomized and nonrandomized trials
- AMSTAR tool applied: review by Bauer et al [55] was of best quality
- Working Group decided not to use any of the existing systematic reviews of summary data because of differences in questions, population, or provincial context

Previously Untreated Patients

Four randomized controlled trials [40-43], represented by 12 publications, were included. This body of evidence indicates a benefit in terms of PFS with the use of rituximab in addition to fludarabine-based chemotherapy and cyclophosphamide, when compared with chemotherapy alone. Grade 3 or 4 neutropenia and leukocytopenia have been reported [42], however these counts were significantly less than those seen with other monoclonal antibodies [41].

Quellen:

40. Woyach JA, Ruppert AS, Heerema NA, Peterson BL, Gribben JG, Morrison VA, et al. Chemoimmunotherapy with fludarabine and rituximab produces extended overall survival and progression-free survival in chronic lymphocytic leukemia: long-term follow-up of CALGB study 9712. J Clin Oncol. 2011;29(10):1349-55.

41. Lepretre S, Aurran T, Mahe B, Cazin B, Tournilhac O, Maisonneuve H, et al. Excess mortality after treatment with fludarabine and cyclophosphamide in combination with alemtuzumab in previously untreated patients with chronic lymphocytic leukemia in a randomized phase 3 trial. Blood. 2012;119(22):5104-10.

42. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164-74.

43. Goede V, Fischer K, Humphrey K, Asikanius E, Busch R, Engelke A, et al. Obinutuzumab (GA101) plus chlorambucil (Clb) or rituximab (R) plus Clb versus Clb alone in patients with chronic lymphocytic leukemia (CLL) and preexisting medical conditions (comorbidities): Final stage 1 results of the CLL11 (BO21004) phase III trial. ASCO Meeting Abstracts; June 17, 2013. p. Abstract 7004.

General Characteristics of Included Studies

- sample size: 104 to 817 patients with CLL

	• rituximab given concurrently or sequentially vs. fludarabine [40], • rituximab-fludarabine-cyclophosphamide combination vs. other monoclonal antibodies [41] • rituximab-fludarabine-cyclophosphamide vs. chemotherapy alone [42], • rituximab-chlorambucile vs. chlorambucile alone vs. chlorambucile combined with obinutuzumab [43], • Three studies [41-43] had PFS, and one study [40] had complete remission as primary outcome. Other outcomes reported included OS and measures of response, as well as toxicities (AE). Quality of Included Studies: • three studies reported as full-text publications [40-42] • one as a conference abstract [43] • CALGB Study 9712 [40] not been designed for between-arm comparison • overall quality of the studies was high, although all were open label *Patients with Relapsed/Refractory Disease* Two studies [44,45], represented by six publications, were included. This body of evidence indicates a benefit for PFS, FFS, and response with the use of rituximab in addition to fludarabine-based chemotherapy when compared with chemotherapy alone. The included studies did not detect any statistically significant between-group difference in grade 3 or 4 adverse events. Quellen: 44. 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. Br J Haematol. 2011;152(5):570-8. 45. Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1756-65. General Characteristics of Included Studies • sample size: 52 patients in phase II study [44], 552 in the other [45] • rituximab in combination with fludarabine-based chemotherapy vs. chemotherapy alone • PFS [45], overall response [44] as primary outcomes • other outcomes reported: OS, QOL Quality of Included Studies • two studies reported as full-text publications • NCRI CLL201 trial [44]: phase II study with a smaller sample • BO17072 study [45]: open-label trial, at moderate risk of bias (no report on random sequence generation and allocation concealement; no blinded patients, clinicians or outcome assessors; intention-to-treat analysis conducted without report on all outcomes stated in methods section)

	Justification for Recommendation 3 Rituximab is effective in extending life and prolonging PFS and EFS in previously untreated patients, when administered in combination with fludarabine-based chemotherapy, and in extending PFS when added to chlorambucil. Rituximab is also effective in extending PFS in the relapsed setting when added to fludarabine-based chemotherapy, and this consistent benefit formed the basis for the recommendation in this setting. **Qualifying Statements for Recommendation 3** Rituximab should be administered at a dose of 375 mg/m2 given at the beginning of the first cycle, followed by a dose of 500 mg/ m2 given at the beginning of each subsequent treatment cycle of chemotherapy as this was the treatment dose and schedule used in the included studies.
Follows GA et al., 2015 [4]. **British Society for Haematology** Interim statement from the BCSH CLL Guidelines Panel	**Fragestellung** The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia. Considering the significant developments in the treatment of CLL in the last 18 months, the BCSH Guidelines group have asked the CLL Guidelines Panel to provide an interim update for the BCSH guidelines website. This interim statement has not been peer-reviewed, but it is anticipated that a definitive rewriting of the CLL Guidelines will be completed before the end of 2015.
	Methodik *(Angaben zur Methodik aus der Version von 2012)* Grundlage der Leitlinie: This guideline replaces the previous BCSH guideline on chronic lymphocytic leukaemia published in 2004 and should be read in conjunction with the IWCLL guidance published in 2008. 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 *Sonstige methodische Hinweise (zur Version von 2015)* • *Conflicts of interest statements provided in appendix 2*

	Freitext/Empfehlungen/Hinweise **Initial treatment of patients with TP53 disruption** Treatment of TP53-disrupted patients with standard chemotherapy is associated with significantly worse outcomes in terms of disease response, duration of response and overall survival compared with patients who do not have TP53 disruption. … The combination of alemtuzumab +/- steroids appears to deliver a better overall response rate and PFS compared with patients treated with standard chemotherapy, although this has not been tested prospectively with a randomised trial. Although the majority of TP53-disrupted patients have been treated at relapse, similar high levels of response have been observed in the few patients with TP53-disrupted CLL treated as first line. The response rates and duration of remissions have been strikingly good compared with historical controls, and this has led to the current licensing of these drugs, which includes treatment of first –line CLL in patients who are shown to have TP53 disruption. **Recommendation** Treatment with either idelalisib + rituximab or ibrutinib is the treatment of choice for first line therapy for patients with TP53 disruption (GRADE B1) If either idelalisib + rituximab or ibrutinib are not available then treatment with alemtuzumab +/- corticosteroids remains preferable to chemotherapy (GRADE B1) Quellen: Zenz T, Eichhorst B, Busch R et al.,TP53 mutation and survival in chronic lymphocytic leukemia.J Clin Oncol. 2010 Oct 10;28(29):4473-9. doi: 10.1200/JCO.2009.27.8762. Epub 2010 Aug 9. Furman RR, Sharman JP, Coutre SE et al., Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.N Engl J Med. 2014 Mar 13;370(11):997-1007. doi: 10.1056/NEJMoa1315226. Epub 2014 Jan 22 O'Brien S, Jones JA et al., Efficacy and Safety of Ibrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Leukemia with 17p Deletion: Results from the Phase II RESONATE™-17 Trial Abstract 327, ASH 2014 RELAPSE THERAPY **Recommendation** Idelalisib + rituximab or ibrutinib is the treatment of choice for patients with relapsed CLL who meet specific criteria – see appendix 1 (GRADE A1) Patients with relapsed CLL who do not meet the treatment criteria for either idelalisib + rituximab or ibrutinib should be treated with chemotherapy+/- rituximab, most likely Bendamustine and Rituximab (BR) or Fludarabine, Cyclophosphamide, and Rituximab (FCR) although the quality of data to support this choice is limited. Chlorambucil (CBL) is an option where a more palliative approach is required (GRADE B2)

Quellen:

Furman RR, Sharman JP, Coutre SE et al., Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.N Engl J Med. 2014 Mar 13;370(11):997-1007. doi: 10.1056/NEJMoa1315226. Epub 2014 Jan 22

Byrd JC, Brown JR, O'Brien S et al., RESONATE Investigators.Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.N Engl J Med. 2014 Jul 17;371(3):213-23. doi: 10.1056/NEJMoa1400376. Epub 2014 May 31.

Dreger P, Schetelig J, Andersen N et al., European Research Initiative on CLL (ERIC) and the European Society for Blood and Marrow Transplantation (EBMT).Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents? Blood. 2014 Dec 18;124(26):3841-9. doi: 10.1182/blood-2014-07-586826. Epub 2014 Oct 9. Review.

Brown JR, Hillmen P, O'Brien S et al., Updated Efficacy Including Genetic and Clinical Subgroup Analysis and Overall Safety in the Phase 3 RESONATETM Trial of Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Abstract 3331, ASH 2014

Appendix 1

Idelalisib + rituximab inclusion criteria from Furman et al NEJM 2014

1. CLL that had progressed within 24 months after their last treatment

2. Previous treatment must have included either a CD20 antibody–based regimen or at least two previous cytotoxic regimens.

3. Not able to receive cytotoxic agents for one or more of the following reasons:

    a. severe neutropenia or thrombocytopenia caused by cumulative myelotoxicity from previous therapies,

    b. an estimated creatinine clearance of less than 60 ml per minute,

    c. a score on the Cumulative Illness Rating Scale (CIRS) of more than 6 for coexisting illnesses not related to CLL.

    d. 17p deletion or mutation (added by CDF)

Ibrutinib inclusion criteria from Byrd et al NEJM 2014

1. Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog–based therapy, defined by at least one of the following criteria:

    a. Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analog–based therapy and anti-CD20–containing chemoimmunotherapy regimen after at least two cycles.

    b. Age ≥70 years, or age ≥65 and the presence of comorbidities (Cumulative Illness Rating Scale [CIRS] ≥6 or creatinine clearance <70 ml/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analog–based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent–based (or purine analog–based) anti-CD20 antibody–containing chemoimmunotherapy

	regimen. CIRS score can be determined using a web-based tool. c. History of purine analog–associated autoimmune anemia or autoimmune thrombocytopenia. d. Fluorescent hybridization showing del17p in ≥20% of cells (either at diagnosis or at any time before study entry) either alone or in combination with other cytogenetic abnormalities, provided the patient has received at least one prior therapy.
NCCN, 2015 [15]. Non-Hodgkin's Lymphomas	Leitlinie der National Comprehensive Cancer Network (NCCN)
	Methodik Grundlage der Leitlinie: – Update 2015 – Suchzeitraum 08/2013 – 12/2014 – Recherche in Pubmed nach ‚key literature', search term: chronic lymphocytic leukemia, Richter syndrome, and histologic transformation,Auswahl der Literatur unklar LoE: depends on – *extent* of data (e.g., number of trials, size of trials, clinical observations only) – *consistency* of data (e.g., similar or conflicting results across available studies or observations), – *quality* of data based on trial design and how the results/observations were derived (e.g., RCTs, non-RCTs, meta-analyses or systematic reviews, clinical case reports, case series) 2 categories: high level of evidence and lower level of evidence; Bewertung der Studien und Einteilung in LoE unklar *NCCN Categories of Evidence and Consensus:* Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. *All recommendations are category 2A unless otherwise noted.*
	Empfehlungen - Siehe Anhang
Alberta	**Fragestellung**

Provincial Hematology Tumour Team, 2014 [1]. Chronic lymphocytic leukemia (Vers. 3).	What are the recommended treatment strategies for adult patients in Alberta with newly diagnosed, relapsed, or refractory CLL? What are the recommended follow-up and supportive care practices for adult patients in Alberta with CLL? Target population: The following guidelines apply to adults over 18 years of age. Different principles apply to pediatric patients.
	Methodik Grundlage der Leitlinie: - Repräsentatives Gremium, systematische Literatursuche, -auswahl und –bewertung und Erstellung von Evidenztabellen (mit methodischer Unterstützung „kowledge management specialist“), Konsensusverfahren (nicht als formalisiert beschrieben) ***Update:*** This guideline was originally developed in May, 2010 and subsequently revised in March, 2013 and again in October, 2014. ***Suchzeitraum:*** bis 2014 ***LOE and GOR*** The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members will be explicitly stated in the guideline recommendations. Similar to the ASCO methodology for formulating guideline recommendations, GURU does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.[3] 3. American Society of Clinical Oncology. Guideline Procedures Manual, Expert Panel Version 4.0. January 2011. *Available at:* http://www.asco.org/ASCOv2/Practice+%26+Guidelines/Guidelines/Development+Process *Accessed: January 10, 2013*
	Empfehlungen <u>Diagnosis and Prognosis:</u> - FISH cytogenetic analysis for del(17p) should be performed at the time when patients are started on first line treatment. FISH analysis for del(17p) should be repeated at the time of second or third line therapy if patients are potential candidates for allogeneic stem cell transplantation or alemtuzumab. FISH analysis is not recommended at diagnosis in patients who do not require therapy, outside of clinical trials. *<u>First-Line Treatment Options:</u>* - The majority of patients with early-stage CLL are managed initially with watchful waiting. The decision to initiate treatment should be based upon symptoms, advanced disease (bulky adenopathy/ splenomegaly

	or cytopenias), or evidence for rapid disease progression (e.g. lymphocyte count doubling within 6 months). - Patient fitness and co-morbidities should be considered to determine whether aggressive treatments can be tolerated. In physically fit CLL patients who are able to tolerate more aggressive treatment, the combination of fludarabine + cyclophosphamide + rituximab (FCR) is recommended. The potential for toxicity of this regimen suggests that patients who have some comorbidities may benefit from less aggressive treatments such as rituximab + bendamustine (BR), rituximab + fludarabine (FR) or chlorambucil + rituximab (CLB-R). - In frail patients with significant co-morbidities and competing causes of death, less toxic treatment options are warranted. In such cases, or if a patient declines intravenous treatment, oral chlorambucil is recommended as first choice, followed by oral fludarabine monotherapy as an alternative treatment. Whenever possible, all patients should receive an anti-CD20 monoclonal antibody with first line therapy based on evidence of a PFS and OS advantage. - Patients whose CLL possesses del(17p) usually do not respond to standard chemotherapy options for CLL. In such cases, alemtuzumab, early use of allogeneic stem cell transplantation or clinical trials including novel agents should be considered as reasonable options. *<u>Second-Line Treatment Options:</u>* - In fit patients, FCR is an effective regimen for rituximab naïve patients. Re-treatment with FCR is a reasonable treatment option for patients experiencing a long remission (more than two years) after initial FCR treatment. 53. Robak T, et al. Rituximab, fludarabine, and cyclophosphamide prolongs progression-free survival in relapsed or refractory chronic lymphocytic leukemia (CLL) compared with FC alone: final results from the international randomized phase III **REACH** trial. Blood ASH Annual Meeting Abstract 2008;112(11):Abstract LBA-1. - The combination of fludarabine and low-dose alemtuzumab (FluCam) is a safe and effective therapy for relapsed/refractory CLL and has been demonstrated to improve PFS and OS compared to monotherapy with fludarabine. 54. Elter T, et al. Fludarabine plus alemtuzumab versus fludarabine alone in patients with previously treated chronic lymphocytic leukaemia: a randomised phase 3 trial. Lancet Oncol 2011 Dec;12(13):1204-1213 - In frail patients, fludarabine or chlorambucil are reasonable second-line treatment options. If the initial remission is greater than 1 year, re-treatment with the initial chemotherapy agent is recommended. If the initial remission is shorter than 1 year, treatment with a different second-line agent is indicated. 26. Rai KR, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic

	leukemia. N Engl J Med 2000 Dec 14;343(24):1750-1757 27. Eichhorst BF, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009 Oct 15;114(16):3382-3391 28. Keating MJ, et al. Early results of a chemoimmunotherapy regimen of fludarabine, cyclophosphamide, and rituximab as initial therapy for chronic lymphocytic leukemia. J Clin Oncol 2005 Jun 20;23(18):4079-4088 29. Keating MJ, et al. Fludarabine: a new agent with major activity against chronic lymphocytic leukemia. Blood 1989 Jul;74(1):19-25 - Allogeneic stem cell transplantation should be considered for fit patients who are younger than 65 years of age and who have not responded to therapy, have progressive disease within 1 year of fludarabine treatment or within 2 years of fludarabine-based chemoimmunotherapy, or those whose CLL possesses del(17p) and require treatment. 13. Dreger P, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic *leukemia: the EBMT transplant consensus. Leukemia 2007 Jan;21(1):12-17* <u>*Follow-up and Supportive Care:*</u> - Patients with CLL often have compromised immune systems due to either the disease itself and/or the associated treatments. Antibiotic prophylaxis and regular vaccinations are recommended, depending on the type of treatments administered. PCP and anti-viral prophylaxis are strongly recommended for all patients receiving FCR or FluCam. Patients treated with alemtuzumab should also be screened for CMV reactivation with weekly CMV PCR. Primary prophylactic use of G-CSF is not recommended with FCR due to the risk of progressive neutropenia, dose reduction of cytotoxic agents (F +/- C) is preferred. - Special attention should be paid to the appearance of autoimmune cytopenias, such as autoimmune hemolytic anemia, immune thrombocytopenia purpura, and pure red-cell aplasia, which occur in up to 11 percent of patients with CLL. <u>Discussion - Assessing response to treatment</u> ... Patients experiencing treatment failure during or within six months of treatment are identified as having refractory disease. Those demonstrating PD more than six months after treatment has ended, who have previously achieved a CR or PR, are identified as having relapsed disease [4]. 4. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008 Jun 15;111(12):5446-5456
Mauro FR et al., 2012 [14]. SIE, SIES, GITMO updated clinical recommendations	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.

for the management of chronic lymphocytic leukemia	**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.
	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. *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. *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.

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

Clinical question	Recommendation
1. Should fludarabine monotherapy or fludarabine plus cyclophosphamide combination therapy be preferred to chlorambucil monotherapy in first- line therapy for previously untreated CLL patients?	Use it, weak positive
2. Should bendamustine be preferred to chlorambucil in first-line therapy for previously untreated CLL patients?	Use it, weak positive

3. Should alemtuzumab monotherapy be preferred to chlorambucil in first-line therapy for previously untreated CLL patients?	Probably don't use it, weak negative.
4. Should fludarabine-cyclophosphamide combination be preferred to fludarabine monotherapy in first- line therapy for previously untreated CLL patients?	Probably use it, weak positive
5. Should cladribine-cyclophosphamide combination therapy be preferred to cladribine monotherapy in first- line therapy for previously untreated CLL patients?	Probably don't use it, weak negative.
6. Should cladribine-cyclophosphamide combination therapy be preferred to fludarabine-cyclophosphamide therapy in first- line therapy for previously untreated CLL patients?	No recommendation
7. Should Rituximab be added to FC in first- line therapy for previously untreated CLL patients?	Use it, strong positive

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

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE 2010 [16]. Ofatumumab for the treatment of chronic lymphocytic leukaemia refractory to fludarabine and alemtuzumab (TA 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 [17] . Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia (TA193)	**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.
NICE, 2011 [18]. Bendamustine for the first-line treatment of chronic lymphocytic leukaemia (TA216)	**Guidance** 1.1 Oral fludarabine is recommended as second line therapy for B-cell chronic lymphocytic leukaemia (CLL) for patients who have either failed, or are intolerant of, first line chemotherapy, and who would otherwise have received combination chemotherapy of either: 1.1.1 cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) 1.1.2 cyclophosphamide, doxorubicin and prednisolone (CAP) or 1.1.3 cyclophosphamide, vincristine and prednisolone (CVP) 1.2 The oral formulation of fludarabine is preferred to the intravenous formulation on the basis of more favourable cost effectiveness. Intravenous fludarabine should only be used when oral fludarabine is contra-indicated.
NICE, 2015 [19]. Obinutuzumab in combination with chlorambucil for untreated chronic lymphocytic leukaemia (TA343)	**Guidance** 1.1 Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if: • bendamustine-based therapy is not suitable and • the company provides obinutuzumab with the discount agreed in the patient access scheme. 1.2 People whose treatment with obinutuzumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.
NICE, 2015 [20]. Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia (TA344)	**Guidance** 1.1 Ofatumumab in combination with chlorambucil is recommended as an option for untreated chronic lymphocytic leukaemia only if: • the person is ineligible for fludarabine-based therapy and • bendamustine is not suitable and • the company provides ofatumumab with the discount agreed in the patient access scheme. 1.2 People whose treatment with ofatumumab is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue ofatumumab until they and their NHS clinician consider it appropriate to stop.

Rothschedl E et al., 2014 [23]. Idelalisib (Zydelig(R)) in addition to rituximab for the treatment of relapsed chronic lymphocytic leukaemia	**5 Current treatment** • treatment options depend on patient characteristics such as age or comorbidities and tumour characteristics, regimen administered previously, duration of remission • relapsed disease: progressive disease after a period of six months or more after either a complete or partial remission had been achieved • refractory disease: no response to therapy, i.e. if they fail to achieve either a partial or complete remission with therapy, or if they develop a disease progression within six months of therapy <u>Second and subsequent line chemotherapy:</u> • fit patients: combination therapy with fludarabine, cyclophosphamide and rituximab (FCR) if patients can tolerate it or if they responded well (PFS > 24 months) to first-line FCR or • bendamustine and rituximab (well-established, but few RCTs) • frail patients: For older patients or those with comorbidities who are not considered well enough for intensive cytotoxic chemotherapy (e.g. FCR), there is no recognised standard treatment. Options include chlorambucil with rituximab (in patients previously untreated with chemotherapy), bendamustine (with or without rituximab) or dose-reduced FCR. <u>Biological therapy:</u> • Rituximab may be used in combination with chemother-apy agents. • Other anti-CD20 monoclonal antibodies, such as ofatu-mumab, may be considered; ofatumumab is currently be-ing used predominantly in patients who are refractory to rituximab and alemtuzumab. • Ibrutinib for CLL patients with 17p deletion which is as-sociated with poor responses to standard treatment of CLL (approved by the FDA for this indication in July 2014)[5]. • Allogeneic stem-cell transplantation should be considered for fit patients with high-risk CLL and should ideal-ly be performed in the setting of a remission. • Alemtuzumab and methylprednisolone for patients with high-risk disease (with early relapse or TP53 deletion/mutation) when tolerated, or alemtuzumab with or without corticosteroids as an option for fitter patients who have failed other conventional therapies. However, the drug was voluntarily withdrawn by the marketing au-thorisation holder in Europe in 2012 [17]. <u>Radiotherapy: rarely used, may be indicated for patients with enlarged lymph nodes/spleen or prior to bone marrow transplant [1].</u> **6 Evidence** • 384 references identified by systematic literature search in 4 databases, one phase III trial [18] included in this report • trial compared efficacy and safety of idelalisib + rituximab to placebo + rituximab in 220 patients • median PFS was 5.5 months in the placebo group and was not reached by the idelalisib group • improved rates of OS and overall response in the idelalisib group • serious adverse events occurred in 40% (idelalisib group) and 35% (placebo group) • study terminated after the first interim analysis due to significant

	improved PFS **8 Ongoing research** In October 2014, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted; the following trials were identified: • NCT01539291 (EudraCT number: 2011-006293-72): a multicentre, 2-arm, double-blind, parallel-group extension study (phase III) aims to evaluate the effect of idelalisib on the onset, magnitude and duration of tumour control. It is a companion study for patients with CLL who participated in study GS-US-312-0116. Estimated study completion date is December 2015. • NCT02136511 (EudraCT number: 2013-005343-82): an expanded access study (idelalisib in combination with rituximab) for previ-ously treated patients with relapsed CLL. Ongoing phase III trials evaluating idelalisib combination therapies: • NCT01569295 (EudraCT number: 2011-006292-20): a phase III, randomised, double-blind, placebo-controlled study assessing the effect of idelalisib in combination with bendamustine and rituxi-mab for previously treated CLL. Estimated study completion date is December 2017. • NCT01659021 (EudraCT number: 2012-001236-65): this random-ised, controlled phase III study evaluates the efficacy and safety of idelalisib in combination with ofatumumab in previously treated patients with CLL. Estimated study completion date is November 2016. **9 Commentary** • approved by both the EMA and the FDA • long-term data on safety and efficacy are required • positive treatment effects also among “high risk” patients • a variety of comparators exist; ibrutinib has been approved for the same indication recently • for both agents: potential development of resistance? • optimal treatment needs to be chosen individually • feasible treatment option for patients with relapsed CLL who are ineligible for cytotoxic therapy In conclusion, combination therapy of idelalisib and rituximab offers a new treatment option for patients with relapsed CLL who are ineligible for cyto-toxic therapy; particularly for those with genetic factors including 17p dele-tion, TP53 mutation or unmutated IGHV. Nevertheless, further trials are needed to evaluate efficacy and safety in the long-term use of idelalisib, as well as the important issue of potential idelalisib resistance.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 24.07.2015**

#	Suchfrage
#1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees
#2	Chronic:ti,ab,kw or b-cell:ti,ab,kw
#3	lymphocytic:ti,ab,kw or lymphoid*:ti,ab,kw or lymphatic*:ti,ab,kw or lymphoblastic:ti,ab,kw
#4	leukemia*:ti,ab,kw and leukaemia*:ti,ab,kw
#5	#2 and #3 and #4
#6	chronic:ti,ab,kw and b-cell:ti,ab,kw
#7	#4 and #6
#8	lymphocytic:ti,ab,kw and lymphoma:ti,ab,kw
#9	Non-Hodgkin*:ti,ab,kw and lymphoma*:ti,ab,kw
#10	malignant:ti,ab,kw and lymphoma*:ti,ab,kw
#11	b-cell:ti,ab,kw and lymphoma*:ti,ab,kw
#12	b-cell malignancy:ti,ab,kw
#13	CLL:ti,ab,kw
#14	small-cell:ti,ab,kw and lymphoma*:ti,ab,kw
#15	small:ti,ab,kw and lymphocytic:ti,ab,kw and lymphoma*:ti,ab,kw
#16	SLL:ti,ab,kw
#17	#1 or #5 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18	#17 Publication Year from 2010 to 2015, in Cochrane Reviews (Reviews only), Other Reviews and Technology Assessments

Leitlinien in Medline (PubMed) am 24.07.2015

#	Suchfrage
#1	Search "leukemia, lymphocytic, chronic, b cell"[MeSH Terms]
#2	Search (b-cell[Title/Abstract]) OR chronic[Title/Abstract]
#3	Search (((lymphocytic[Title/Abstract]) OR lymphoid*[Title/Abstract]) OR lymphatic*[Title/Abstract]) OR lymphoblastic[Title/Abstract]
#4	Search (leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract]
#5	Search #2 AND #3 AND #4
#6	Search (chronic[Title/Abstract]) AND b-cell[Title/Abstract]
#7	Search #4 AND #6
#8	Search lymphocytic[Title/Abstract] AND lymphoma[Title/Abstract]
#9	Search Non-Hodgkin*[Title/Abstract] AND lymphoma*[Title/Abstract]
#10	Search malignant[Title/Abstract] AND lymphoma*[Title/Abstract]
#11	Search b-cell[Title/Abstract] AND lymphoma*[Title/Abstract]
#12	Search b-cell malignancy[Title/Abstract]
#13	Search CLL[Title/Abstract]
#14	Search small-cell[Title/Abstract] AND lymphoma*[Title/Abstract]
#15	Search small[Title/Abstract] AND lymphocytic[Title/Abstract] AND lymphoma*[Title/Abstract]
#16	Search SLL[Title/Abstract]
#17	Search #1 OR #5 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	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]
#19	Search #17 AND #18
#20	Search #17 AND #18 Filters: Publication date from 2010/07/01 to 2015/07/24

SR, HTAs in Medline (PubMed) am 24.07.2015

#	Suchfrage
#1	Search "leukemia, lymphocytic, chronic, b cell"[MeSH Terms]
#2	Search (b-cell[Title/Abstract]) OR chronic[Title/Abstract]
#3	Search (((lymphocytic[Title/Abstract]) OR lymphoid*[Title/Abstract]) OR lymphatic*[Title/Abstract]) OR lymphoblastic[Title/Abstract]
#4	Search (leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract]
#5	Search #2 AND #3 AND #4
#6	Search (chronic[Title/Abstract]) AND b-cell[Title/Abstract]
#7	Search #4 AND #6
#8	Search lymphocytic[Title/Abstract] AND lymphoma[Title/Abstract]
#9	Search Non-Hodgkin*[Title/Abstract] AND lymphoma*[Title/Abstract]
#10	Search malignant[Title/Abstract] AND lymphoma*[Title/Abstract]
#11	Search b-cell[Title/Abstract] AND lymphoma*[Title/Abstract]
#12	Search b-cell malignancy[Title/Abstract]
#13	Search CLL[Title/Abstract]
#14	Search small-cell[Title/Abstract] AND lymphoma*[Title/Abstract]
#15	Search small[Title/Abstract] AND lymphocytic[Title/Abstract] AND lymphoma*[Title/Abstract]
#16	Search SLL[Title/Abstract]
#17	Search #1 OR #5 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	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]))))
#19	Search "meta analysis"[Publication Type]
#20	Search "technical report"[Publication Type]
#21	Search #18 OR #19 OR #20
#22	Search #17 AND #21
#23	Search #17 AND #21 Filters: Publication date from 2010/07/01 to 2015/07/24

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Anhang:

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

Abbildung 1: aus Vidal L, et al., 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

Abbildung 2: aus Vidal L, et al., 2012

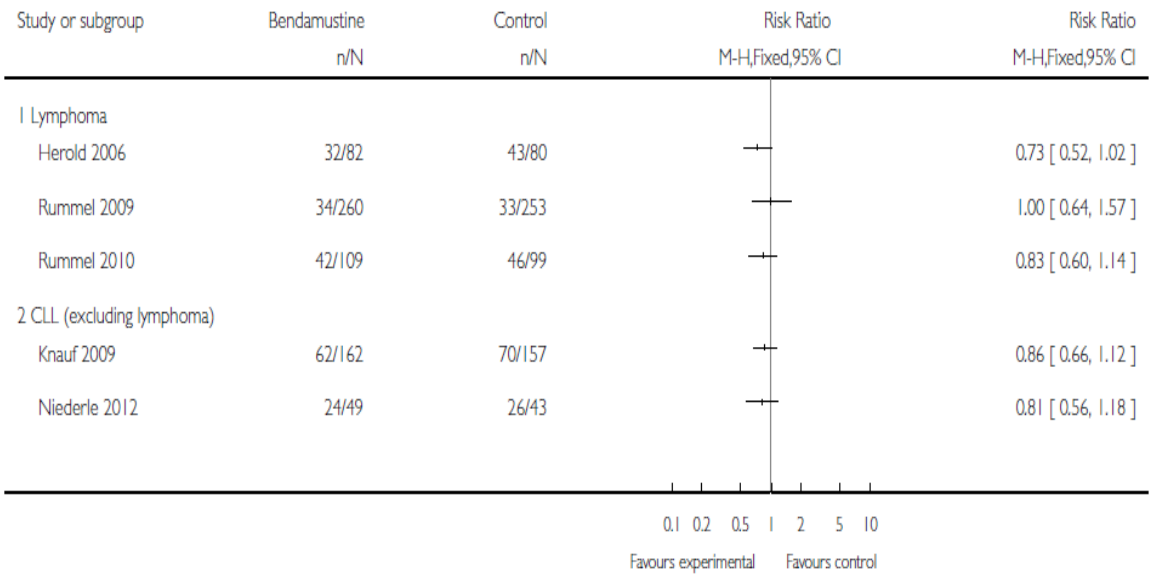


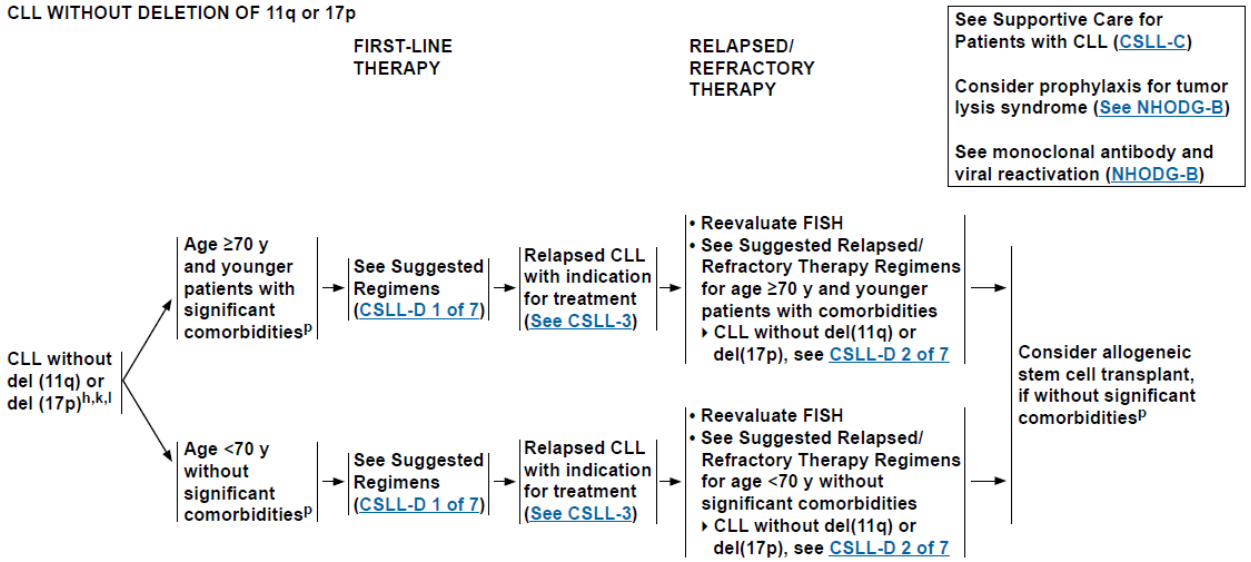
Abbildung 3: aus Vidal L, et al., 2012

Table 4 Summary of Safety Outcomes in Studies of Relapsed or Refractory Chronic Lymphocytic Leukemia

Reference, Trial Identifier, Study Phase	Treatment	Patients, n	Exposure: Median No. of Treatment Cycles	SAE or Death[a]	Grade 3/4 AEs	
					Overall, %	Specific Grade 3/4 AEs Reported in ≥ 5% of Patients
Eter et al, 2011[14] NCT00086580 **Phase III**	Fludarabine with alemtuzumab	164	6 (Range, 1-6)	SAE, 33% Death, 6% (n = 10)	67[b]	Infusion-related reaction, Grade 3: 5%
	Fludarabine	165	6 (Range, 1-6)	SAE, 25% Death, 7% (n = 12)	55[b]	—
Faderl et al, 2006[15] **Phase II**	Bortezomib	22	Range, 1-6	SAE, 27% Death, 0	50[b]	Grade 3: Anemia, neutropenia, thrombocytopenia, hemolytic anemia, dyspnea, peripheral neuropathy, aphasia, confusion, disease progression, hyponatremia, inappropriate secretion of antidiuretic hormone, muscle weakness not otherwise specified, peripheral sensory neuropathy, and pitting edema: 5% each; vomiting and abdominal pain: 9% each Grade 4: upper abdominal pain: 5%; neutropenia: 9%
Hillmen et al, 2011[16] **Phase 2**	FCM	26	Range, 1-6	SAE, 50% Death, n = 1	15.2 (Grade 3 only)/13.3[c]	Grade 3 or 4 neutropenia: n = 14
	FCM with rituximab	26	Range, 1-6	SAE, 54% Death, n = 3	15.6 (Grade 3 only)/8.0[c]	Grade 3 or 4 neutropenia: n = 14
O'Brien et al, 2009[17] **Phase 3 Five-year follow-up study**	FC with oblimersen	120	4 (Range, 1-6)	SAE, NA Death, 4% (n = 5)	NA	Grade 4: neutropenia, 7% Grades 3 and 4 nonhematologic (among AEs reported in ≥20% of patients): nausea, 7.8%; fatigue, 6.1%; vomiting, 6.1%; dyspnea, 5.2%
Robak et al, 2010[18] **REACH Phase III**	FC	272	Range, 1-6	SAE, 48% Death, 5% (n = 14)	74	Grade 3 or 4 AEs: neutropenia, 40%; febrile neutropenia, 12%; anemia, 13%; thrombocytopenia, 9%; pneumonia, 6%; pancytopenia, 5% Grade 3 or 4 hematologic toxicity during treatment (laboratory data): hemoglobin, 19%; platelets, 26%; neutrophils, 84%
	FC with rituximab	274	Range, 1-6	SAE, 50% Death, 7% (n = 19)	80	Grade 3 or 4 AEs: neutropenia, 42%; febrile neutropenia, 12%; anemia, 12%; thrombocytopenia, 11%; granulocytopenia, 7%; pneumonia, 5% Grade 3 or 4 hematologic toxicity during treatment (laboratory data): hemoglobin, 19%; platelets, 27%; neutrophils, 89%

Abbreviations: AE = adverse event; FC = fludarabine and cyclophosphamide; FCM = fludarabine, cyclophosphamide, and mitoxantrone; REACH = Rituximab in the Study of Relapsed Chronic Lymphocytic Leukemia; SAE = serious adverse event.
[a]Death at least possibly related to treatment.
[b]Grade ≥ 3.
[c]Grade 4.

Abbildung 4: aus Police RL, et al., 2015



[h] See Supportive Care for Patients with CLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[l] Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CSLL-5

Abbildung 5: aus NCCN, 2015

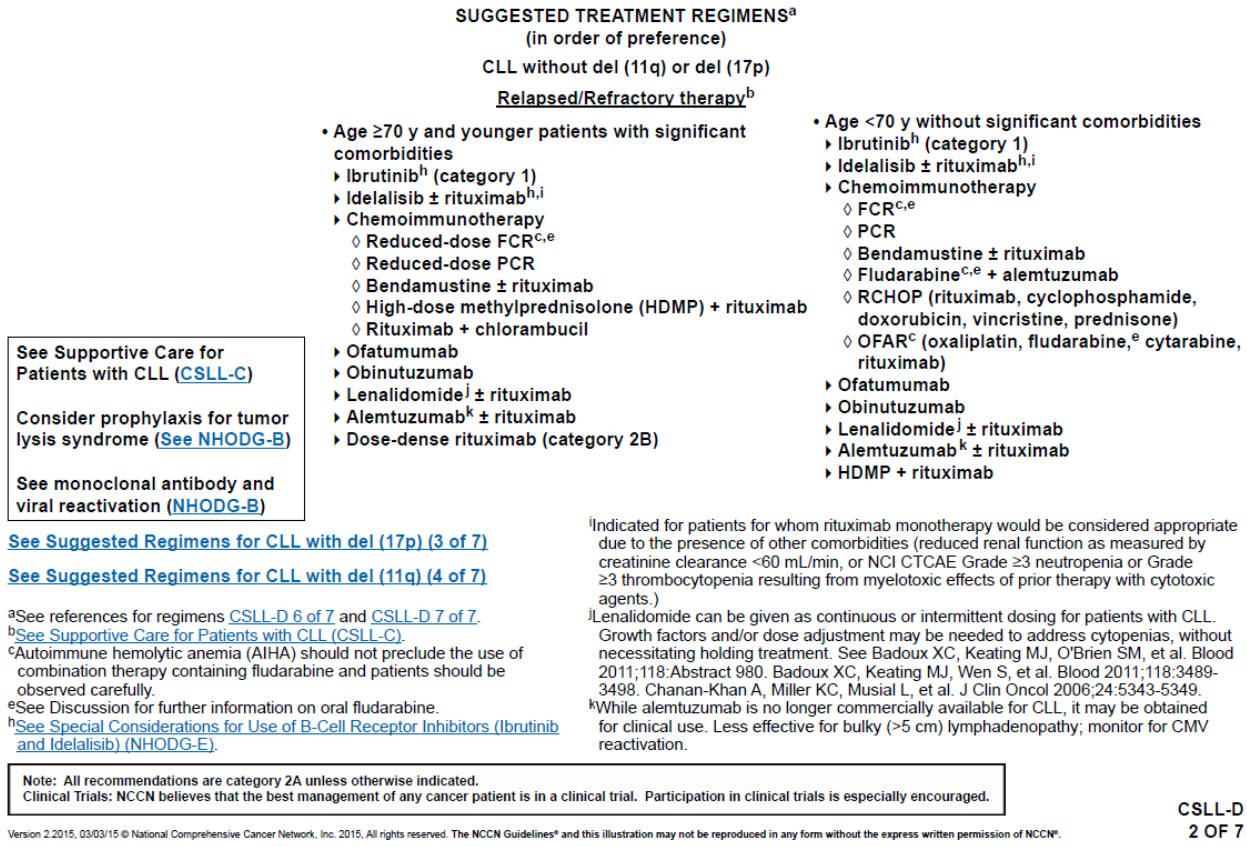
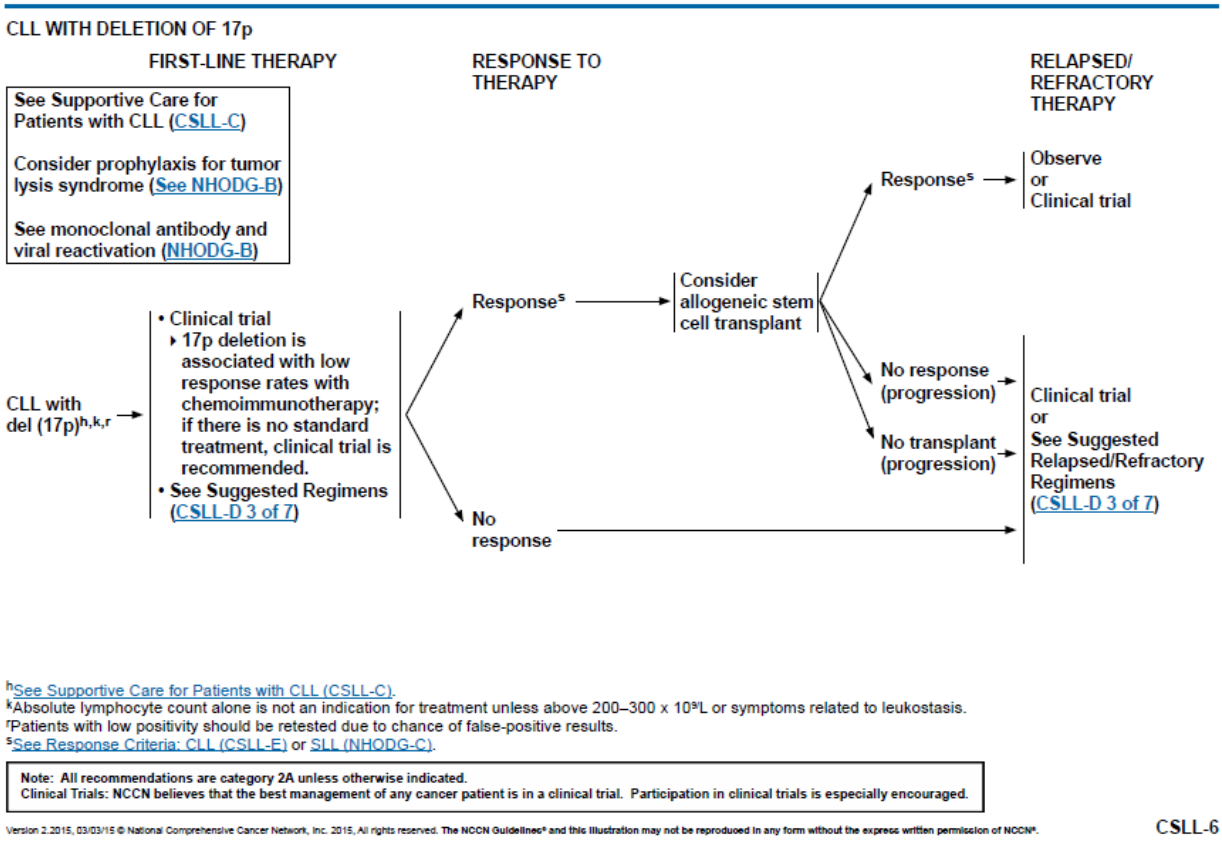


Abbildung 6: aus NCCN, 2015



[h] See Supportive Care for Patients with CLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[r] Patients with low positivity should be retested due to chance of false-positive results.
[s] See Response Criteria: CLL (CSLL-E) or SLL (NHODG-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CSLL-6

Abbildung 7: aus NCCN, 2015

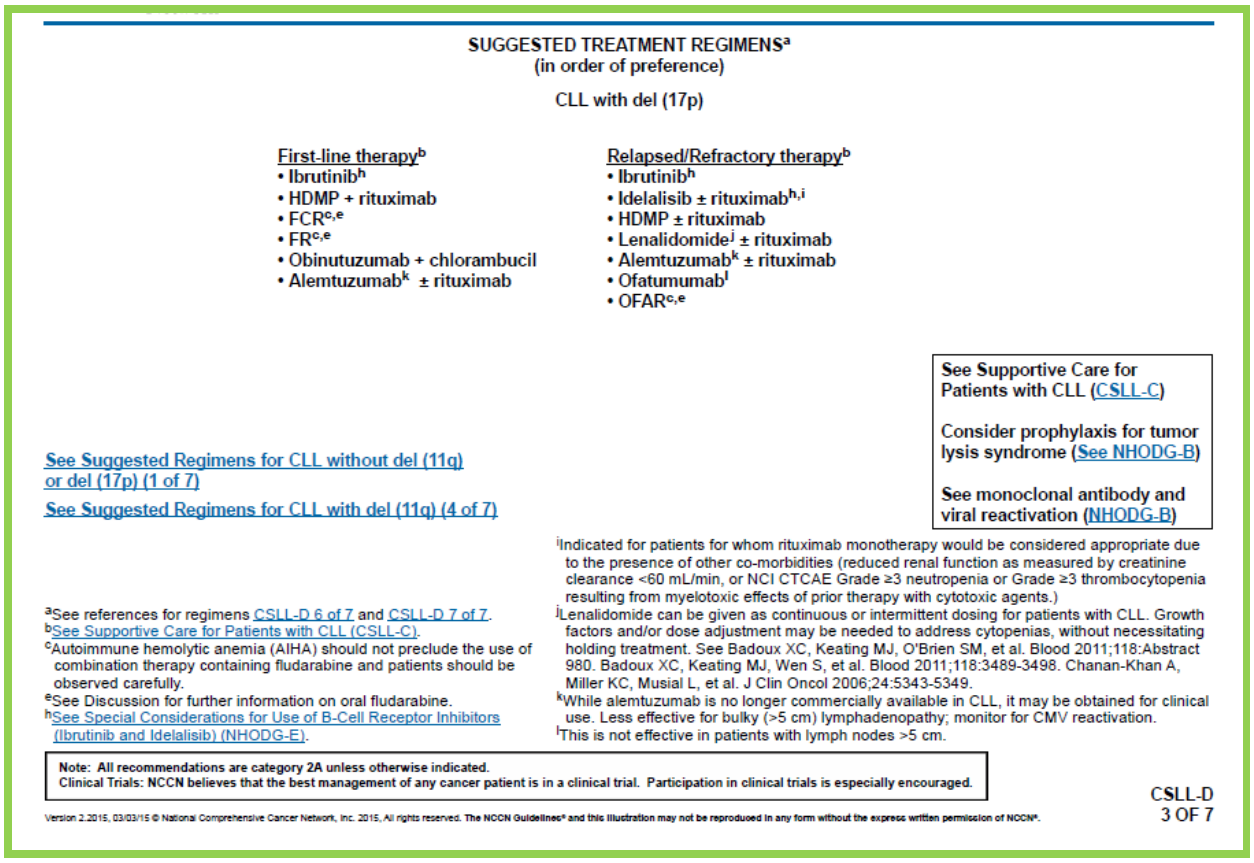


Abbildung 8: aus NCCN, 2015

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Alemtuzumab + rituximab

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Fludarabine + alemtuzumab

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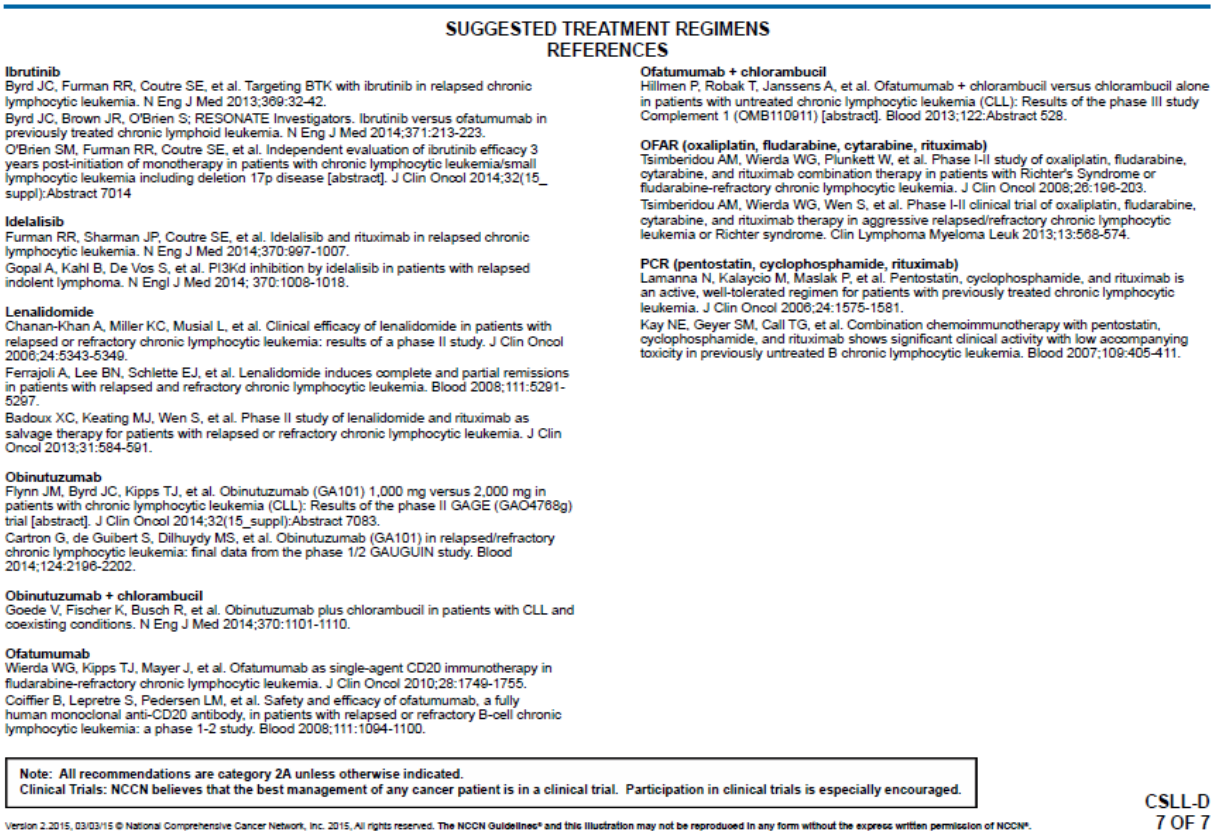
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Abbildung 9: aus NCCN, 2015: Suggested Treatment Regimens References (Teil 1)



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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CSLL-D
7 OF 7

Abbildung 10: aus NCCN, 2015: Suggested Treatment Regimens References (Teil 2)