Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-170 Venetoclax

Stand: Oktober 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Venetoclax [in Kombination mit Rituximab zur Therapie der vorbehandelten CLL]	
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	Beschlüsse vom 15. September 2016 und 16. März 2017 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Idelalisib Beschlüsse vom 21. Juli 2016 und 16. März 2017 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ibrutinib Beschluss vom 15. Juni 2017 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Venetoclax
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:	
Venetoclax L01XX52 Venclyxto®	Anwendungsgebiet: Venclyxto® in Kombination mit Rituximab ist indiziert zur Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine Vortherapie erhalten haben.
Zytostatische Wirkstoffe	
Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (CLL) […] (Stand: März 2016)
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Chronisch lymphatische Leukämie (CLL) nach Versagen der Standardtherapie (Chlorambucil/Prednison) (Stand: Januar 2015)
Fludarabin L01BB05 Bendarabin®	Therapie der chronischen-lymphatischen Leukämie (CLL) vom B-Zell-Typ bei Patienten mit ausreichender Knochenmarksreserve. (Stand: September 2014)
B-Zell-Rezeptor-Inhibitoren	
Ibrutinib L01XE27 Imbruvica®	IMBRUVICA als Einzelsubstanz oder in Kombination mit Bendamustin und Rituximab (BR) ist indiziert zur Behandlung erwachsener Patienten mit CLL, die mindestens eine vorangehende Therapie erhalten haben. (Stand: August 2016)
Idelalisib L01XX47 Zydelig®	Zydelig wird in Kombination mit einem monoklonalen anti-CD20-Antikörper (Rituximab oder Ofatumumab) zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) angewendet: - die mindestens eine vorangehende Therapie erhalten haben (siehe Abschnitt 4.4) (Stand: Oktober 2016)
Venetoclax L01XX52 Venclyxto®	Venclyxto wird als Monotherapie bei Erwachsenen zur Behandlung einer CLL ohne Vorliegen einer 17p-Deletion oder TP53-Mutation angewendet, bei denen sowohl unter einer Chemo-Immuntherapie als auch unter einem Inhibitor des B-Zell-Rezeptor-Signalwegs ein Therapieversagen auftrat. (Stand: Dezember 2016)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Anti-CD-20-Antikörper	
Ofatumumab L01XC10 Arzerra®	Refraktäre CLL: Arzerra ist angezeigt für die Behandlung von Patienten mit CLL, die refraktär auf Fludarabin und Alemtuzumab sind. Für weitere Informationen siehe Abschnitt 5.1. (Stand: Mai 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. Für weitere Informationen siehe Abschnitt 5.1. (Stand: September 2016)
Glucocorticoide	
Prednisolon H02AB06 Dermosolon®	Hämatologie/Onkologie: Chronisch lymphatische Leukämie (DS e) (Stand: August 2016)
Prednison H02AB07 Cutason®	Hämatologie/Onkologie: Chronisch lymphatische Leukämie (Stand: Februar 2015)
Weitere Arzneimittel mit Zulassung für Non-Hodgkin-Lymphome	
Bendamustin L01AA09 Levact®	Monotherapie bei indolenten Non-Hodgkin-Lymphomen bei Patienten mit Progression während oder innerhalb von 6 Monaten nach Behandlung mit Rituximab oder mit einer Rituximab-haltigen Therapie. (Stand: Januar 2016)
Cytarabin L01BC01 ARA-cell®	ARA-cell® 100 mg/ml wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: - refraktären Non-Hodgkin-Lymphomen (Stand: Mai 2015)
Doxorubicin L01DB01 Adrimedac®	Non-Hodgkin-Lymphom (Stand: September 2013)
Trofosfamid L01AA07 Ixoten®	Dieses Arzneimittel ist ein Zytostatikum. Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet. (Stand: Januar 2015)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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 (Stand: März 2016)
Vincristin L01CA02 Vincristinsulfat-Teva®	Vincristinsulfat-Teva® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen (Stand: März 2016)

Quellen: AMIS-Datenbank, Fachinformationen

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation chronische lymphatische Leukämie durchgeführt. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP, WHO. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgende Organisationen gesucht: CCO, DGHO, ESMO, NCCN, NCI. Die Recherche umfasste den Zeitraum vom 01.12.2011 bis 14.12.2016. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 07.03.2017 abgeschlossen.

Die Recherche ergab 333 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 20 Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden.

Indikation:

Zur Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine Vortherapie erhalten haben.

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
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
NCCN	National Comprehensive Cancer Network
NCI	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
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization
FluC-R	fludarabine plus cyclophosphamide plus rituximab
FluCM-R	fludarabine plus cyclophosphamide plus mitoxantrone plus rituximab
Flu-Cam	fludarabine plus alemtuzumab

IQWiG Berichte/G-BA Beschlüsse

Gemeinsamer Bundesausschuss (G-BA), 2017 [7]. 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 – Idelalisib (chronische lymphatische Leukämie; neues Anwendungsgebiet: in Kombination mit Ofatumumab) vom 16. März 2017	**Neues Anwendungsgebiet (Änderung der Zulassung vom 19. September 2016):** Idelalisib in Kombination mit Ofatumumab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL): • die mindestens eine vorangehende Therapie erhalten haben, oder • als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, für die keine anderen Therapien geeignet sind. *1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie (hier nur Ergebnisse für relevante Populationen dargestellt)* 1) Patienten, die mindestens eine vorangehende Therapie erhalten haben 1a) Patienten mit rezidivierender oder refraktärer CLL, für die eine Chemotherapie angezeigt ist: **Zweckmäßige Vergleichstherapie:** Eine patientenindividuelle, optimierte Chemotherapie nach Maßgabe des Arztes unter Beachtung des Zulassungsstatus, bevorzugt in Kombination mit Rituximab sofern angezeigt. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2017 [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 (neues	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 25. August 2016):** IMBRUVICA® als Einzelsubstanz oder in Kombination mit Bendamustin und Rituximab (BR) ist indiziert zur Behandlung erwachsener Patienten mit CLL, die mindestens eine vorangehende Therapie erhalten haben. **Hinweis:** Über den Zusatznutzen von Ibrutinib als Einzelsubstanz zur Behandlung erwachsener Patienten mit CLL, die mindestens eine vorangehende Therapie erhalten haben, hat der G-BA bereits mit Beschluss vom 21. Juli 2016 entschieden. *1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie* **Zweckmäßige Vergleichstherapie:** Eine patientenindividuelle, optimierte Chemotherapie nach Maßgabe des Arztes unter Beachtung des Zulassungsstatus, bevorzugt in Kombination mit

Anwendungsgebiet: chronische lymphatische Leukämie; in Kombination mit Bendamustin und Rituximab) vom 16. März 2017	Rituximab sofern angezeigt. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** a) Patienten mit mindestens zwei Vortherapien, für die Bendamustin in Kombination Rituximab die patientenindividuell optimierte Therapie darstellt Anhaltspunkt für einen beträchtlichen Zusatznutzen. b) Patienten mit einer Vortherapie und Patienten für die eine andere Therapie als Bendamustin in Kombination Rituximab die patientenindividuell optimierte Therapie darstellt Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2016 [4]. 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 vom 21. Juli 2016	**Zugelassenes Anwendungsgebiet (laut Zulassungen vom 21.10.2014 und 03.07.2015):** 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.[1] [1] Entspricht Anwendungsgebiet I des Beschlusses. *1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie (hier nur Ergebnisse für relevante Populationen dargestellt)* Anwendungsgebiet I: Chronische lymphatische Leukämie 1a) Patienten mit rezidivierender oder refraktärer CLL, für die eine Chemotherapie angezeigt ist **Zweckmäßige Vergleichstherapie:** Eine patientenindividuelle, optimierte Chemotherapie nach Maßgabe des Arztes unter Beachtung des Zulassungsstatus, bevorzugt in Kombination mit Rituximab sofern angezeigt. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2016 [5]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-	**Zugelassenes Anwendungsgebiet (laut Zulassung vom23. März 2016):** Zydelig wird in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) angewendet: • die mindestens eine vorangehende Therapie erhalten haben (siehe Abschnitt 4.4 der Fachinformation), oder • zur Fortsetzung der Therapie bei Patienten mit einer 17p-

Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Idelalisib vom 15. September 2016	Deletion oder einer TP53-Mutation, die für eine Chemoimmuntherapie ungeeignet waren und bei denen bereits eine Erstlinientherapie mit Zydelig initiiert wurde (siehe Abschnitt 4.4 der Fachinformation). Zydelig wird als Monotherapie zur Behandlung von erwachsenen Patienten mit follikulärem Lymphom (FL), das refraktär nach zwei vorausgegangenen Therapielinien ist, angewendet (siehe Abschnitt 4.4 der Fachinformation). [Hinweis: Der vorliegende Beschluss bezieht sich nur auf die Behandlung der chronischen lymphatischen Leukämie (CLL)] *1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie (hier nur Ergebnisse für relevante Populationen dargestellt)* <u>Anwendungsgebiet 1:</u> Zur Behandlung von Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben. • Teilpopulation 1a: Patienten mit rezidivierender oder refraktärer CLL, für die eine Chemotherapie angezeigt ist: **Zweckmäßige Vergleichstherapie:** Eine patientenindividuelle, optimierte Chemotherapie nach Maßgabe des Arztes unter Beachtung des Zulassungsstatus, bevorzugt in Kombination mit Rituximab sofern angezeigt **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.

Cochrane Reviews

Bauer K et al., 2012 [2]. Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia	1. Fragestellung The objective of this review is to assess and summarise the evidence for the treatment of patients with CLL with monoclonal anti-CD20 antibodies.
	2. Methodik Population: CLL, pre-treated and chemotherapy-naive patients Intervention: Anti-CD20 antibody (rituximab, ofatumumab) given alone or in combination with chemotherapy as primary treatment or maintenance treatment Komparator: 'Watchful waiting' and conventional therapies such as fludarabine or Clb monotherapy, fludarabine in combination with other chemotherapeutic agents, or other antibody therapy. Kombinationen: 1. Anti-leukaemic therapy plus anti-CD20 antibody versus anti-leukaemic therapy alone; anti-leukaemic therapy identical in both groups. 2. Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (antileukaemic therapy not identical in both groups). 3. Different dosages or times of anti-CD20 antibody (with or without identical chemotherapy in both arms). Endpunkte: primär: OS • sekundär: PFS, time to next treatment, treatment-related mortality (TRM), complete response rate (CRR), overall response rate (ORR), minimal residual disease (MRD), adverse events (AE), number of patients discontinuing the study because of drug-related AEs Suchzeitraum: 1990 – 2012 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7/1 763 Qualitätsbewertung der Studien: Cochrane Risk of Bias Tool Heterogeneity: Because of the small number of studies in each analysis (two), the quantification of heterogeneity was not reliable, since the Cis were very wide. In meta-analyses with more trials, we would have assessed heterogeneity of treatment effects between trials… We explored potential causes of heterogeneity by sensitivity and subgroup analyses. Sensitivity analysis: We did not perform any sensitivity analysis,

	because all these trials showed no differences regarding publication form (full-text publications/abstracts), type of results (preliminary results/mature results) or quality issues.
	3. Ergebnisdarstellung (Three trials included relapsed or refractory patients (Gribben 2005; NCRI-CLL 201; REACH) Risk of Bias: Gribben 2005 – unclear; NCRI-CLL 201 und REACH – low - 3 eingeschlossene Studien (für rezidivierende CLL), davon 1 Studie nur als Abstract (n = 12): gesamt eingeschlossene Patienten n = 604 (aus 2 Studien mit Vollpublikation): - NCRI-CLL 201 [previously treated with ≥ 1 chemotherapeutic regimen, WHO performance status 0 to 2; FluCM-R vs. FluCM; (n = 52)]; - REACH [minimum 1 lone treatment of the CLL; FluC-R vs. FluCM; n = 552]) Ergebnisse für die Subgruppenanalyse "zuvor behandelt vs. therapienaiv" unterscheiden sich nicht von Gesamtgruppenergebnissen.
	4. Anmerkungen/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.

Systematische Reviews

Pan-Canadian Oncology Drug Review (pCODR), 2016 [15]. Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma	1. Fragestellung To evaluate the effectiveness of ibrutinib for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with or without del(17)p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog.
	2. Methodik Population: Patients with CLL or SLL with or without del(17)p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog • Subgroup analyses: Age (≥ 65) Intervention: Ibrutinib 420 mg/d Komparator: Chemotherapy (chlorambucil, cyclophosphamide), stem cell transplants, EGFR·TKI inhibitors, monoclonal antibodies (ofatumumab, rituximab, obinutuzumab, alemtuzumab), Alkalating agents (bendamustine) Endpunkte: OS, PFS, Response rate, Quality of Life,·Grade 3 or 4 adverse events (including febrile neutropenia and thrombocytopenia and severe infection and lymphocytosis), Withdrawal due to AE's, fatigue Suchzeitraum: bis September 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 1/391 Qualitätsbewertung der Studien: SIGN-50 Checklists applied as a minimum standard, additional limitations and sources of bias identified by the pCODR Review Team
	3. Ergebnisdarstellung **Literature Search Results** Of the 11 potentially relevant reports identified, 1 study was included in the pCODR systematic review[5] and 10 studies were excluded. Studies were excluded because they were not randomized trials, reviews, or abstracts where full publication was available. 5. Byrd JC, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. New England Journal of Medicine. 2014;371(3):213-23. • Studienbeschreibung (siehe Anhang) **Ongoing Clinical Trials (n = 4)** • one Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

	Janssen Research & Development, LLC. A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma [online]. NCT01611090. In: ClinicalTrials.gov. 03.03.2017. [Zugriff: 13.03.2017] URL: https://clinicaltrials.gov/ct2/show/NCT01611090. • one study of Ibrutinib Versus Ibrutinib + Rituximab (i vs iR) in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL) M.D. Anderson Cancer Center. Ibrutinib Versus Ibrutinib + Rituximab (i vs iR) in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL) [online]. NCT02007044. In: ClinicalTrials.gov. 05.10.2016. [Zugriff: 13.03.2017] URL: https://clinicaltrials.gov/ct2/show/NCT02007044. • one Study of PCI-32765 (Ibrutinib) Versus Rituximab in Relapsed or Refractory Chronic Leukemia/Lymphoma Janssen Research & Development, LLC. A Study of PCI-32765 (Ibrutinib) Versus Rituximab in Relapsed or Refractory Chronic Leukemia/Lymphoma [online]. NCT01973387. In: ClinicalTrials.gov. 05.01.2017. [Zugriff: 13.03.2017] URL: https://www.clinicaltrials.gov/ct2/show/NCT01973387. • one Phase 3 Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (RESONATE™) 38. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01578707, A Phase 3 Study of Ibrutinib (PCI-32765) Versus Ofatumumab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia (RESONATE™); 2012 Apr 11[Last updated 2014 March 7; cited 2014 December 2]. Avaliable from: http://clinicaltrials.gov/show/NCT01578707.
	4. Anmerkungen/Fazit der Autoren In conclusion the Clinical Guidance Panel (CGP) felt that treatment with ibrutinib offered net clinical benefit to patients with relapsed and refractory CLL who were ineligible for treatment with purine analogues. The panel based this conclusion on the results of a single, well-conducted randomized comparative trial that enrolled a large number of patients. Evidence in favour of this conclusion includes a substantial number of durable responses among patients in the experimental arm of the RESONATE trial (progression-free survival not reached at 9.4 months with ibrutinib vs. 8.1 months with ofatumumab, HR for progression or death 0.22 (95%CI: 0.15-0.32, p<0.001)). Benefit was seen in all subgroups of patients with CLL, including those with chromosome 17p deletion, bulky disease, advanced stage and disease that was refractory to purine analogues. Adverse events were manageable and generally familiar to physicians who treat this condition. In reaching this conclusion the panel was unable to comment on the optimal timing of ibrutinib in relation to other available treatments. The panel felt re-treatment with ibrutinib is likely not an issue given the short survival in this relapsed/refractory setting, furthermore administration is until relapse or intolerance to ibrutinib. To the panel's knowledge, there are no trials assessing re-treatment with ibrutinib. The panel noted that ofatumumab is currently only available through its manufacturer's compassionate access program in Canada and that second-line treatments for CLL are generally more toxic and less effective than this agent. As a result it was felt that ibrutinib would offer greater

	improvements in quality of life and clinical benefit in the Canadian context.
Grössmann N, 2016 [8]. Venetoclax (Venclexta?) for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with chromosome 17p deletion	1. Fragestellung <u>Clinical effectiveness</u> What is the expected beneficial effect of venetoclax on mortality? How does venetoclax affect progression (or recurrence) of CLL? How does venetoclax affect symptoms and findings (severity, frequency) of CLL? What is the effect of venetoclax on patients' body functions? What is the effect of venetoclax on generic health-related quality of life? What is the effect of venetoclax on disease-specific quality of life? <u>Safety</u> How safe is venetoclax in relation to no intervention? Are the harms related to dosage or frequency of applying venetoclax? What are the susceptible patient groups that are more likely to be harmed through the use of venetoclax?
	2. Methodik Population: relapsed/refractory CLL Intervention: Venetoclax Komparator: k.A. Endpunkte: (siehe Fragestellungen) Suchdatum: am 4. August 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 2/k.A. Qualitätsbewertung der Studien: assessed using a modified Downs and Black instrument[23] [23] Dow ns SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology and Community Health. 1998;52(6):377-84.
	3. Ergebnisdarstellung Overall, 270 references were identified. Included in this report are: • 1 phase II study, assessing venetoclax in relapsed or refractory CLL patients harbouring a 17p deletion [20, 21] • 1 phase I study, assessing venetoclax in patients with relapsed or re-fractory CLL or small lymphocytic lymphoma [22]. [20] Stilgenbauer S, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia w ith 17p deletion: a multicentre, open-label, phase 2 study. The Lancet Oncology. 2016;17(6):768-78. [21] Stilgenbauer S, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia w ith 17p deletion: a multicentre, open-label, phase 2 study - Supplementary appendix. The Lancet Oncology. 2016;17(6):768-78.

[22] Roberts AW, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. The New England journal of medicine. 2016;374(4):311-22. Epub 2015/12/08.

7.1 Clinical efficacy and safety – phase II study

- M13-982: open-label, single-arm phase II study, 107 relapsed/refractory CLL patients, daily dose of 400 mg,
- median follow-up duration: 12.1 months
- median age of 67 years and ECOG performance status of 0–2
- primary outcome: proportion of patients who achieved an overall response

7.1.1 Clinical efficacy

- median OS had not been reached, estimated 12-month OS: 86.7%
- median PFS had not been reached, estimated 12-month PFS: 72.0%
- QoL data will be investigated in a safety expansion cohort

7.1.2 Safety

- most common grade 3–4 AEs: neutropenia, infection, anaemia, and thrombocytopenia
- dose reductions due to AEs (neutropenia, infection, etc.)
- tumour lysis syndrome and embryo-foetal harm

7.2 Clinical efficacy and safety – further studies

- M12-175: efficacy, safety and pharmacokinetic profile of venetoclax in relapsed/refractory CLL
- 79% of patients showed a response to venetoclax

9 Ongoing research

- 3 phase III studies are ongoing, investigating venetoclax in patients with CLL

NCT02756611: An open-label, single-arm, phase IIIb multicentre study evaluating the efficacy of venetoclax (ABT-199) in re-lapsed/refractory subjects with chronic lymphocytic leukaemia (CLL) including those with the 17p deletion or TP53 mutation or those who have received prior treatment with a B-cell receptor in-hibitor. Estimated study completion date is August 2020.

NCT02005471: A multicentre, phase III, open-label randomised study in relapsed/refractory patients with chronic lymphocytic leu-kaemia to evaluate the benefit of GDC-0199 (ABT-199) plus ritux-imab compared with bendamustine plus rituximab. Estimated study completion date is September 2020.

NCT02242942: An open-label, multicentre, randomised phase III study is designed to compare the efficacy and safety of a combined regimen of obinutuzumab and GDC-0199 versus obinutuzumab + chlorambucil (GClb) in patients with chronic lymphocytic leukae-mia (CLL) and coexisting medical conditions. Estimated study completion date is November 2018.

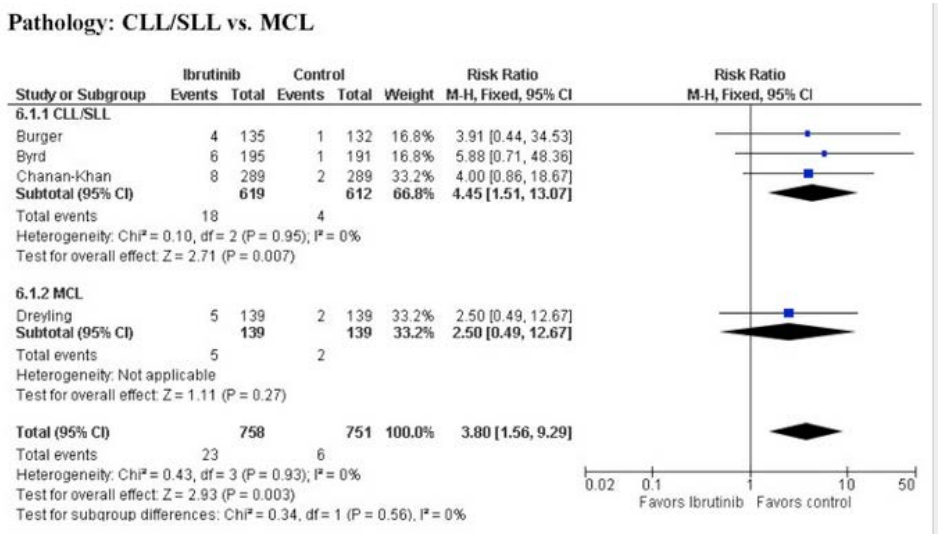
- numerous ongoing phase I and II trials in different treatment lines and regimens

4. Anmerkungen/Fazit der Autoren

- indication approved by the FDA, but not by the EMA

	• M13-982: OR-IRC was achieved in 85 patients • shorter duration of response in patients with del(17p) - mature data is needed • age was not representative of the actual patient population • most frequent grade 3–4 AEs: neutropenia, infection, anaemia, thrombocytopenia • QoL results are lacking • prophylaxis of tumour lysis syndrome • small sample size of patients who were previously treated with kinase inhibitors • limitations inherent to single-arm design and due to the sample size • potential of developing resistance • feasible treatment option for patients with relapsed/refractory CLL wit del(17p) deletion • BUT no RCT available, immature data, long-term effects missing, • no cost information available *5. Kommentar zum Review* • *Format ist „horizon scanning", aber mit systematischer Recherche, Auswahl und Bewertung der Literatur* • *Abschnitt „current treatment" in Tabelle „ergänzende Dokumente…" abgebildet (siehe unten)*
Yun S et al., 2016 [20]. Risk of Atrial Fibrillation and Bleeding Diathesis Associated With Ibrutinib Treatment: A Systematic Review and Pooled Analysis of Four Randomized Controlled Trials	1. Fragestellung We performed a systematic review and pooled analysis of 4 randomized controlled trials (RCT) to precisely estimate the risks of all-grade and serious Afib/Aflutter and all-grade and major bleeding in patients under ibrutinib treatment.
	2. Methodik Population: adult patients with CLL/SLL, MCL, or WM Intervention: ibrutinib-based regimen Komparator: chemotherapy, monoclonal antibody, or a combination Endpunkte: AE outcomes Suchzeitraum: up to May 15, 2016 Anzahl eingeschlossene Studien/Patienten (Gesamt): 4/1 518 Qualitätsbewertung der Studien: using Cochrane Collaboration's tool Heterogeneity: Cochrane's Q statistic, I2 statistic, treatment effects calculated using fixed-effects model, assuming low I2 statistics, publication bias: assessed by funnel plot method
	3. Ergebnisdarstellung

	• 4 RCTs met inclusion criteria for pooled analysis • 2 studies included patients with refractory/relapsing CLL/SLL (n = 969) 2. Byrd JC, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014; 371:213-23. 4. Chanan-Khan AAA, et al. Ibrutinib combined with bendamustine and rituximab (BR) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): first results from a randomized, double-blind, placebo-controlled, phase III study. J Clin Oncol 2015; 33(suppl), abstract LBA7005. • Byrd, et al. was open-labeled, did not report relevant information on random sequence generation, excluded patients requiring anticoagulation • Chanan-Khan, et al. was double blind, random sequence generation was performed adequately, only reported as abstract • patients treated with ibrutinib or ibrutinib, bendamustine, and rituximab, and controls received either ofatumumab or bendamustine and rituximab • median age ranged 64 to 67 years • around 32% of patients were female • risk stratification performed following Rai stage in CLL/SLL • one study excluded del(17p) patients • Ibrutinib dose was 420 mg/day in both studies • median duration of ibrutinib exposure was around 8,6 month • both studies were multi-center trials, baseline demographic characteristics were well balanced between experimental and control arms in both studies, although there was variation • funnel plot symmetry supports the same direction of intervention effect in all studies included **Analysis of RRs of Afib and Bleeding** Ibrutinib treatment with a significantly higher incidence of • serious Afib/Aflutter (3.03% vs. 0.80%, RR = 3.80, 95% confidence interval [CI] = 1.56-9.29, P = .003), • all-grade Afib/Aflutter (8.18% vs. 0.93%, RR = 8.81, 95% CI = 2.70-28.75, P = .0003), • all-grade bleeding (4.85% vs. 1.55%, RR = 2.93, 95% CI = 1.14-7.52, P = .03) compared to control treatments. • between-treatment difference in major bleeding rates was not statistically significant The risk of these adverse events was not different between subgroups on

	the basis of pathology, treatment setting, dose, and duration of ibrutinib exposure. 
	4. Anmerkungen/Fazit der Autoren The risks of Afib/Aflutter and all-grade bleeding were significantly higher in the ibrutinib group. These results indicate the need for vigilant monitoring while the patient is receiving ibrutinib therapy, and careful assessment of the risks and benefits of anticoagulation is required. *5. Kommentar zum Review* • *supported in part by predoctoral fellowships to N.D.V. from the Mayo Foundation for Education and Research and by a Bressler Alpert Society research grant to S.Y. from University of Arizona* • *authors have stated that they have no conflict of interest* • *in Population CLL/SLL (siehe Subgruppenanalyse vs. MCL) sind auch Therapienaive enthalten (Burger, et al.)*
Pan-Canadian Oncology Drug Review (pCODR), 2015 [16]. Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia	1. Fragestellung To evaluate the effectiveness and safety of idelalisib in combination with rituximab in the treatment of patients with relapsed chronic lymphocytic leukemia (CLL).
	2. Methodik Population: Patients with relapsed chronic lymphocytic leukemia • -Subgroup analyses in patients with cytogenic abnormalities and in patients with other prior treatments • Which line of treatment/sequencing is most beneficial with Idelalisib/rituximab • single agent idelalisib Intervention: Idelalisib 150 mg plus Rituximab 375 mg/m2 followed by

	500mg/m2 Komparator: Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions) • Placebo • Idelalisib • Chlorambucil plus an anti-CD20 monoclonal antibody • Rituximab • Obinutuzumab • Ofatumumab • Fludarabine plus rituximab (FR) • Bendamustine plus rituximab (BR) • Fludarabine, Cyclophosphamide and rituximab (FCR) • Ibrutinib • Alemtuzumab • Cyclophosphamide/prednisone • Cyclophosphamide/vincristine/prednisone (CVP) Endpunkte: Response rate, Overall survival, Progression free survival, Adverse events including fatigue, enlarged lymph nodes, infections, severe diarrhea/colitis, hepatotoxicity, intestinal perforations, pneumonitis, Quality of life Suchzeitraum: bis Juli 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 1/220 Qualitätsbewertung der Studien: SIGN-50 Checklists applied as a minimum standard, additional limitations and sources of bias identified by the pCODR Review Team
	3. Ergebnisdarstellung **Literature Search Results** Of the 45 potentially relevant reports identified, 4 studies, representing one unique trial were included in the pCODR systematic review[2,5,6,22] and 45 studies were excluded. Studies were excluded because they were review, cellular research, meta-analysis, RCT protocol, guideline, could not locate the study, and economic analysis. 2. Furman RR, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. New England Journal of Medicine. 2014;370(11):997-1007. 5. Coutre SE, et al. Second interim analysis of a phase 3 study of idelalisib (ZYDELIG) plus Rituximab for relapsed CLL. Journal of Clinical Oncology. 2014;32(5s):abstract 7012. 6. Sharman JP, et al. Second interim analysis of a phase 3 study of idelalisib (ZYDELIG) plus Rituximab for relapsed chronic lymphocytic leukemia (CLL): Efficacy analysis in patient subpopulations

	with Del(17p) and other adverse prognostic factors. Blood. 2014;124(21):(abstract). 22. Ghia P, et al. Health-related quality of Life (HRQL) impact of idelalisb (IDELA) in patients (pts) with relapsed chronic lymphocytic leukemia (CLL):Phase 3 results. Journal of Clinical Oncology. 2014;32(5s):abstract 7099. • Studienbeschreibung (siehe Anhang) **Ongoing Clinical Trials** Nine ongoing clinical trials were found by searching Clinicaltrials.gov. There were three ongoing randomized studies of idelalisib in previously treated patients. Two combined idelalisib with another agent and one compared two different doses of idelalisib. There were six studies of idelalisib in untreated patients. One study investigated single agent idelalisib and the other five examined it in combination with other agents. 67. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01539291, A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia ; 2012 Feb 12[Last updated 2015 June 8; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01539291. 68. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01569295, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia ; 2012 Mar 27[Last updated 2015 May 1; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01569295. 69. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01090414, An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects With Hematologic Malignancies; 2010 Mar 17[Last updated 2015 July 1; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01090414. 70. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01203930, A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of Idelalisib Alone and in Combination With Rituximab in Elderly Subjects With Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; 2010 Sept 15[Last updated 2015 Mar; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01203930. 71. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01659021, A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia ; 2012 Aug 3[Last updated 2015 Apr 30; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01659021. 72. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT02135133, A Phase II Study of Idelalisib (GS1101, CAL101) + Ofatumumab in Previously Untreated Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Leukemia (SLL); 2014 Apr 24[Last updated 2015 Apr 13; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT02135133. 73. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01980888, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia; 2013 Nov 5[Last updated 2015 Mar; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01980888. 74. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01980875, A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Obinutuzumab Compared to Chlorambucil in Combination With Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia; 2013 Nov 5[Last updated 2015 Jun 8; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01980875. 75. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT02044822, A Phase 2, Single Arm Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Rituximab in Patients With Previously Untreated Chronic Lymphocytic Leukemia With 17p Deletion; 2014 Jan 22[Last updated 2015 May 27; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT02044822.
	4. Anmerkungen/Fazit der Autoren The Clinical Guidance Panel concluded that there may be net overall

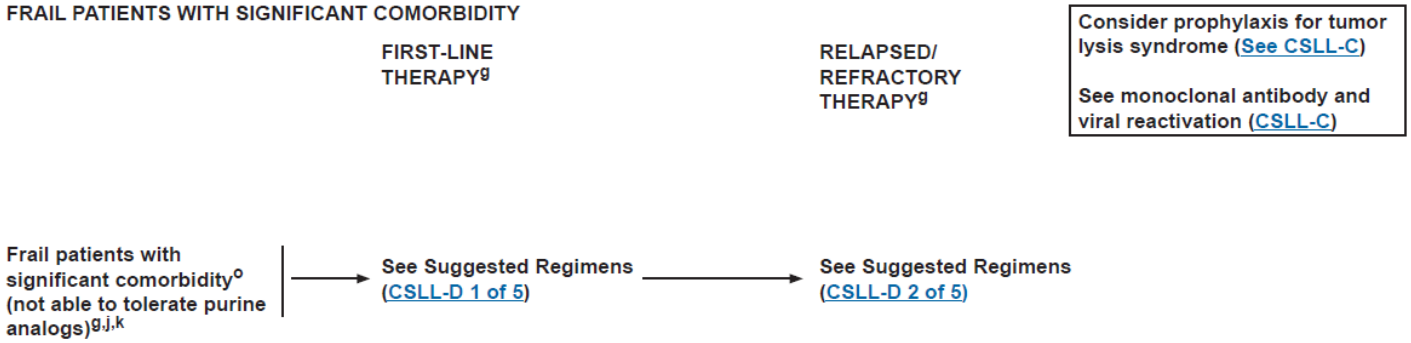
	clinical benefit to the use of idelalisib in the treatment of CLL, where duration of response to a previous regimen is less than two years, and when tolerance of cytotoxic chemotherapy would be expected to result in excessive toxicity due to poor renal function, residual neutropenia or thrombocytopenia from prior therapy, or the presence of multiple comorbidities. This recommendation is based on a single double blind placebo controlled trial that was of high quality, and demonstrated improvement in progression free survival and overall survival, as well as response rate and quality of life. These benefits were seen in older and younger patients, and in pre-defined subset analyses of patients with poor risk genetic features (p53 gene abnormalities and unmutated immunoglobulin variable region genes). The toxicity of idelalisib in this patient population was manageable, with few grade >3 toxicity or treatment discontinuation due to adverse events; side effects appear manageable with dose reduction after treatment interruption. The Clinical Guidance Panel also considered that from a clinical perspective: • Single agent rituximab is not a common treatment of choice in this patient population in Canada; this is due to variable but generally restricted funding of rituximab in most provinces, as well as data that suggest efficacy is quite limited in CLL when rituximab is used alone. As noted by PAG, rituximab is given at higher doses and more frequently than current Canadian treatment protocols with rituximab. • The follow-up of the GS US 312-0116 study was short at the time of reporting and the extent by which the results are influenced by the ability to cross over to idelalisib in the control arm is not known. • Idelalisib has an acceptable toxicity profile, especially important in the patient population in the phase III trial who had limited therapeutic options because of comorbidities and organ function. Idelalisib does have the potential to cause significant toxicities (pneumonitis, hepatitis, colitis) that may not be encountered currently available agent used as palliative treatment of patients with relapsed and refractory CLL. • Comparative data with ibrutinib, ofatumumab (a fully human CD20 antibody approved for the treatment of CLL as a single agent), rituximab-chlorambucil or chlorambucil are not available, and represent an area where additional research is needed. Idelalisib may be preferred to ibrutinib in patients who require anticoagulation with vitamin K antagonists or have experienced recent stroke or significant bleeding, for whom ibrutinib is contraindicated. • Data on the sequencing of BTK inhibitors such as ibrutinib and PI3kinase inhibitors such as idelalisib in the treatment of CLL are not yet available. • Similar response to idelalisib was seen regardless of cytogenic abnormalities, number of previous lines of therapies, and use of other anti-

	CD20 agents such as obinutuzumab or ofatumumab.

Leitlinien

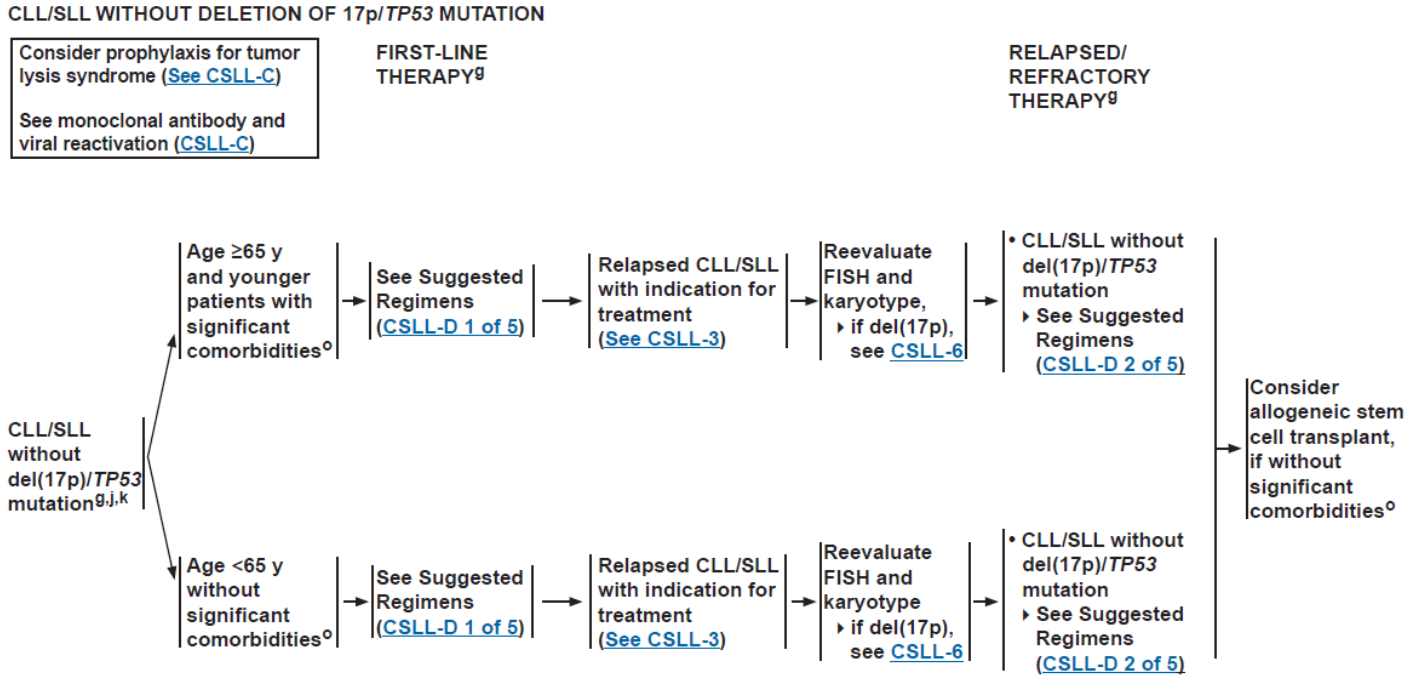
National Comprehensive Cancer Network (NCCN), 2017 [12]. Chronic lymphocytic leukemia/ small lymphocytic lymphoma: Version 2.2017	Fragestellung • Update of the NCCN Guidelines for CLL/SLL Version 1.2017
	Methodik Grundlage der Leitlinie: Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - Diskussion der Literatur und Empfehlungen im Expertenpanel - eigenes Graduierungssystem (siehe unten) - industriefinanziert Literatursuche (Update): in PubMed zwischen 07/2015 und 10/2016 GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert. **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.**

Freitext/Empfehlungen/Hinweise



[g]See Supportive Care for Patients with CLL/SLL (CSLL-C).
[j]Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[k]Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
[o]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.

Abbildung 1: CSLL-4



[g]See Supportive Care for Patients with CLL/SLL (CSLL-C).
[j]Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[k]Given incurability with conventional therapy, consider a clinical trial as first line of treatment.
[o]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.

Abbildung 2: CSLL-5

SUGGESTED TREATMENT REGIMENS[a,b]
(in order of preference)

CLL/SLL without del(17p)/*TP53* mutation

Relapsed/Refractory Therapy

- Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities
  - Ibrutinib[c] (category 1)
  - Idelalisib + rituximab[c,h] (category 1)
  - Idelalisib[c]
  - Venetoclax[i,j] ± rituximab
  - Chemoimmunotherapy
    - ◊ Bendamustine ± rituximab
    - ◊ Reduced-dose FCR[e,f]
    - ◊ Reduced-dose PCR
    - ◊ High-dose methylprednisolone (HDMP) + rituximab
    - ◊ Rituximab + chlorambucil
    - ◊ Ibrutinib,[c] bendamustine, rituximab (category 3)
    - ◊ Idelalisib,[c] bendamustine, rituximab (category 3)
  - Ofatumumab
  - Obinutuzumab
  - Lenalidomide[k] ± rituximab
  - Alemtuzumab[l] ± rituximab
  - Dose-dense rituximab (category 2B)

Relapsed/Refractory Therapy

- Age <65 y without significant comorbidities
  - Ibrutinib[c] (category 1)
  - Idelalisib + rituximab[c,h] (category 1)
  - Idelalisib[c]
  - Venetoclax[i,j] ± rituximab
  - Chemoimmunotherapy
    - ◊ FCR[e,f]
    - ◊ FC + ofatumumab
    - ◊ PCR
    - ◊ Bendamustine ± rituximab
    - ◊ RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
    - ◊ OFAR[e] (oxaliplatin, fludarabine,[f] cytarabine, rituximab)
    - ◊ Ibrutinib,[c] bendamustine, rituximab (category 2B)
    - ◊ Idelalisib,[c] bendamustine, rituximab (category 2B)
  - Ofatumumab
  - Obinutuzumab
  - Lenalidomide[k] ± rituximab
  - Alemtuzumab[l] ± rituximab
  - HDMP + rituximab

Post Second-line Maintenance Therapy
(for complete or partial response after relapsed or refractory therapy)

- Lenalidomide maintenance
- Ofatumumab maintenance (category 2B)

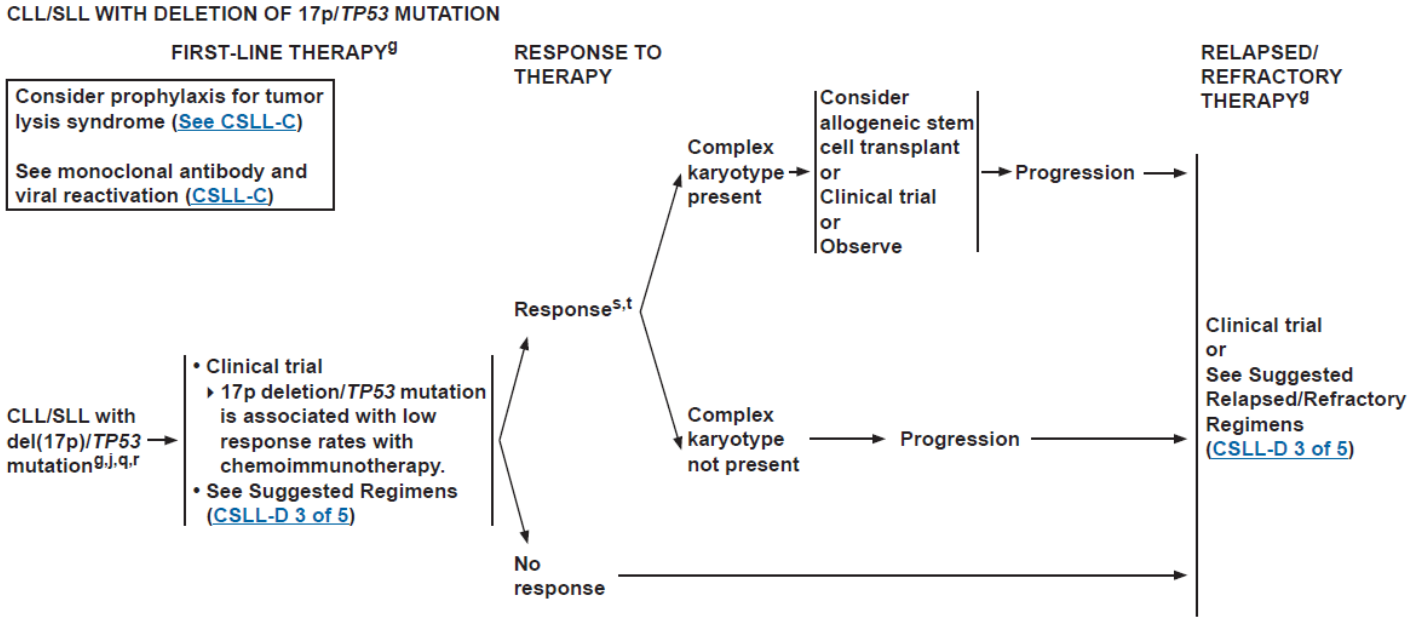
See Suggested Regimens for CLL/SLL with del(17p) (3 of 5)

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)

See monoclonal antibody and viral reactivation (See CSLL-C)

[a] See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[c] See Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib) (CSLL-F).
[e] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those where a history of fludarabine-associated AIHA is suspected.
[f] See Discussion for further information on oral fludarabine.
[h] Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[i] Particularly for patients deemed intolerant or refractory to ibrutinib or idelalisib.
[j] See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[k] Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[l] While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

Abbildung 3: CSLL-D 2 of 5



[g]See Supportive Care for Patients with CLL/SLL (CSLL-C).
[j]Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[q]Stimulated karyotype is useful to identify high-risk patients, particularly for Bruton's tyrosine kinase (BTK) inhibitor therapy.
[r]Patients with low positivity should be retested due to chance of false-positive results.
[s]See Response Criteria: CLL/SLL (CSLL-E).
[t]For patients with complex karyotype (≥3 abnormalities) in remission after BTK-inhibitor therapy, consider discussion of allogeneic transplant although data available do not support this as highly effective (Jaglowski et al. Br J Haematol 2012;159:82-87).

Abbildung 4: CSLL-6

SUGGESTED TREATMENT REGIMENS[a,b]
(in order of preference)

CLL/SLL with del(17p)/*TP53* mutation

First-line Therapy
- Ibrutinib[c]
- HDMP + rituximab
- Obinutuzumab + chlorambucil (category 3)
- Alemtuzumab[l] ± rituximab

Post First-line Maintenance Therapy
- Consider lenalidomide maintenance for high-risk patients (MRD $\geq 10^{-2}$ or $\geq 10^{-4}$ and $<10^{-2}$ with unmutated IGHV or del(17p)/TP53 mutation) after first-line therapy

Relapsed/Refractory Therapy
- Ibrutinib[c]
- Venetoclax[j] ± rituximab
- Idelalisib + rituximab[c,h]
- Idelalisib[c]
- HDMP + rituximab
- Lenalidomide[k] ± rituximab
- Alemtuzumab[l] ± rituximab
- Ofatumumab[m]
- OFAR[e,f]

Post Second-line Maintenance Therapy
(for complete or partial response after relapsed or refractory therapy)
- Lenalidomide maintenance
- Ofatumumab maintenance (category 2B)

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)

See monoclonal antibody and viral reactivation (See CSLL-C)

See Suggested Regimens for CLL/SLL without del(17p) (1 of 5)

[a]See references for regimens CSLL-D 4 of 5 and CSLL-D 5 of 5.
[b]See Supportive Care for Patients with CLL/SLL (CSLL-C).
[c]See Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib) (CSLL-F).
[e]Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine; however, patients should be observed carefully and fludarabine should be avoided in those where a history of fludarabine-associated AIHA is suspected.
[f]See Discussion for further information on oral fludarabine.
[h]Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[j]See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[k]Lenalidomide can be given as continuous or intermittent dosing for patients with CLL. Growth factors and/or dose adjustment may be needed to address cytopenias, without necessitating holding treatment. See Badoux XC, Keating MJ, O'Brien SM, et al. Blood 2011;118:Abstract 980. Badoux XC, Keating MJ, Wen S, et al. Blood 2011;118:3489-3498. Chanan-Khan A, Miller KC, Musial L, et al. J Clin Oncol 2006;24:5343-5349.
[l]While alemtuzumab is no longer commercially available for CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.
[m]This is not effective in patients with lymph nodes >5 cm.

Abbildung 5: CSLL-D 3 of 5

Alberta Provincial Hematology Tumour Team, 2017 [1]. Chronic lymphocytic leukemia	Fragestellung What are the recommended treatment strategies for adult patients in Alberta with newly diagnosed, relapsed, or refractory CLL?
	Methodik Grundlage der Leitlinie: repräsentatives Gremium, ausformulierte Fragestellungen, systematische Suche, Auswahl und Bewertung der Literatur, primär Leitlinienadaptation, Entwurf durchläuft (formale) Konsensusprozesse und sowohl interne als auch externe Konsultationen Suchzeitraum: bis Anfang 2015 LoE/GoR: *"Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations[5] 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 including:* *• Description of all known benefits and possible harms* *• Evidence summary, quality/quantity/consistency of discussion* *• Discussion of the role of clinical experience, theory, values and opinions in developing the recommendation"* *5. 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* Sonstige methodische Hinweise *"This guideline was originally developed in May, 2010 and subsequently revised in 2013, 2014, 2015, and 2017."*
	Freitext/Empfehlungen/Hinweise **RECOMMENDATIONS** <u>Second-Line Treatment Options:</u> 7. In fit patients, FCR is an effective regimen for rituximab naïve patients. Re-treatment with FCR is also an effective treatment option for patients experiencing a long remission (PFS more than three years) after initial FCR treatment. Because of the concern of second malignancy and/or prolonged cytopenias in patients retreated with fludarabine, BR is a reasonable re-treatment choice for patients who experience a long remission to first line chemo-imunotherapy. 8. High risk patients (those with PFS less than 3 years after chemoimmunotherapy) should be treated with one of the novel agents

	– ibrutinib or idelalisib + rituximab or considered for a clinical trial. 10. Venetoclax, a BCL2-inhibitor has efficacy in patients with del(17p) and is the treatment of choice in patients who fail BCR-inhibitors (ibrutinib or idelalisib + rituximab). 11. Patients who are intolerant to a BCR-inhibitor may respond to the alternate BCR-inhibitor or can be expected to respond to venetoclax. 12. Allogeneic stem cell transplantation (HSCT) should be considered for fit patients who are younger than 65 years of age and, have del(17p) and require treatment, have progressed on a targeted therapy or who have Richter's transformation with remission to the aggressive lymphoma. Allogeneic stem cell transplantation may be delayed in patients achieving responses to ibrutinib or idelalisib + rituximab; however HLA typing should be performed to identify a possible transplant donor. High risk features that should prompt earlier consideration of HSCT include patients who have had ≥ 3 prior lines of therapy and those with complex karyotypes by conventional cytogenetics. **DISCUSSION** Recommendations for second-line treatment of CLL should consider individual factors such as comorbidities and the length of the disease-free interval. In fit patients, FCR is an effective regimen in patients naïve to rituximab or FC; reuse of FCR or use of BR is also reasonable in patients experiencing a long remission (more than three years) after initial treatment.[57] 57. 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):1. Patients experiencing treatment failure within six months of treatment are identified as having refractory disease and are considered to be ultra high risk, similar to patients with del(17p) or TP53 mutations. These patients, and those who achieve short remissions after FCR (PFS < 3 years), patients with del(17p) and those who are unfit for cytotoxic chemotherapy, should be treated with one of the novel agents - ibrutinib or idelalisib + rituximab. [30-33] 30. 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. 31. 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. 32. Keating MJ, et al. Fludarabine: a new agent with major activity against chronic lymphocytic leukemia. Blood 1989 Jul;74(1):19-25. 33. Johnson S, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. The French Cooperative Group on CLL. Lancet 1996 May 25;347(9013):1432-1438. When initial remission after chemoimmunotherapy with FCR is greater

	than 3 years, re-treatment with chemoimmunotherapy is appropriate. The median PFS after BR, CLB-R and CLB-O are shorter than after FCR. If patients achieve a PFS of more than 2-3 years with these regimens and remain fit for cytotoxic chemotherapy, they should also be considered for retreatment with chemoimmunotherapy. As the optimal relapsed/refractory regimen has not yet been clearly defined for most CLL patients, all patients should be considered for a clinical trial when available. **Ibrutinib** 58. Byrd JC, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014 Jul 17;371(3):213-223. **Idelalisib + rituximab** 54. Stilgenbauer S, Dohner H. Campath-1H-induced complete remission of chronic lymphocytic leukemia despite p53 gene mutation and resistance to chemotherapy. N Engl J Med 2002 Aug 8;347(6):452-453. 58. siehe oben 59. Furman RR, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 2014 Mar 13;370(11):997-1007. 60. O'Brien S, Lamanna N, Kipps TJ. Update on a ≥65 Years with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma Phase 2 Study of Idelalisib in Combination with Rituximab in Treatment-Naive Patients. ASH Annual Meeting Abstracts 2014:Abstract 1994. **Fludarabine and alemtuzumab combination therapy (FluCam)** 61. 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. **High dose corticosteroids** 62. Pileckyte R, et al. Dose-dense high-dose methylprednisolone and rituximab in the treatment of relapsed or refractory high-risk chronic lymphocytic leukemia. Leuk Lymphoma 2011 Jun;52(6):1055-1065. 63. Xu W, et al. High-dose methylprednisolone can induce remissions in patients with fludarabine-refractory chronic lymphocytic leukaemia. Eur J Cancer 2010 Aug;46(12):2145-2149. 64. Castro JE, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia 2009 Oct;23(10):1779-1789. 65. Castro JE, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of fludarabine refractory high-risk chronic lymphocytic leukemia. Leukemia 2008 Nov;22(11):2048-2053. 66. Dungarwalla M, et al. High dose methylprednisolone and rituximab is an effective therapy in advanced refractory chronic lymphocytic leukemia resistant to fludarabine therapy. Haematologica 2008 Mar;93(3):475-476. **Choosing between novel agents ibrutinib and idelalisib +/- rituximab** 67. Sharman JP, Courtre SE, Furman RR. Second Interim Analysis of a Phase 3 Study of Idelalisib (ZyDELIG(R)) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. ASH Annual Meeting Abstracts 2014:includes updated data not yet published. <u>Ibrutinib:</u> 68. Byrd JC, Hillmen P, James DF. Response: Additional data needed for a better understanding of the potential relationship between atrial fibrillation and ibrutinib. Blood 2015 Mar 5;125(10):621466. 69. Leong DP, Caron F, Hillis C, Duan A, Healey JS, Fraser G, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood 2016 Jul 07,;128(1):138-140. <u>Idelalisib +/-Rituximab:</u>

	58/59: siehe oben Venetoclax: 70. Stilgenbauer S, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016 Jun;17(6):768-778. Allogeneic stem cell transplantation ohne Quellenangaben
Prica A et al., 2017 [17]. Rituximab in Lymphoma and Chronic Lymphocytic Leukaemia: A Practice Guideline **siehe auch Prica A et al., 2015 [18].**	Fragestellung To provide an updated guideline on the use of rituximab in lymphoma and chronic lymphocytic leukemia (CLL). TARGET POPULATIONS Chronic Lymphocytic Leukemia: Adult patients with CLL at any stage.
	Methodik Grundlage der Leitlinie: repräsentatives Gremium, Interessenkonflikterklärungen liegen vor, systematische Suche, Auswahl und Bewertung der Literatur, ggf. metaanlytische Berechnungen, keine formalen Konsensusverfahren beschrieben, Zielgruppenkonsultationsverfahren, und Expertenreview durchgeführt Suchzeitraum: „update“ der Version 2 bis Oktober 2013 LoE/GoR: über Formulierungen abgebildet
	Ergebnisdarstellung **Recommendation 3** Chronic lymphocytic leukemia/small lymphocytic lymphoma: 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** 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 (siehe auch Tabelle im Anhang). The included studies did not detect any statistically significant between-group difference in grade 3 or 4 adverse events. 44. 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. Br J Haematol. 2011;152(5):570-8. 45. 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(10):1756-65.

	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.
Kharfan-Dabaja MA et al., 2016 [9]. Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation	Fragestellung American Society for Blood and Marrow Transplantation convened a group of experts to develop clinical practice recommendations related to the role of allo-HCT for CLL.
	Methodik Grundlage der Leitlinie: repräsentatives Gremium inklusive methodischer Expertise, Bearbeitung der Fragestellung anhand der GRADE Methodik, Konsulation der Anwender*innen durch eine standardisierte Befragung Suchzeitraum: PubMed from inception until May 28, 2015 LoE/GoR: über Formulierungen abgebildet *Sonstige methodische Anmerkungen: Als Basis der Empfehlungen wurde eine Querschnittserhebung von Anwender*innen zu folgenden Fragen durchgeführt:* *"Questions included panelists' demographics (age, gender, years of experience, practice focus), volume of CLL patients seen in a routine week, information relevant to their respective transplant program (number of allo-HCT performed per year, preferred preparative regimen(s), cell source and donor source, criteria for selection of patients and donors), and questions pertaining to risk definition, timeliness, and appropriateness of allo-HCT for CLL."*
	Ergebnisdarstellung We did not find any RCT that compared allo-HCT with conventional chemotherapy, chemoimmunotherapy, or nonchemotherapy-containing combinations. … In the end, the overall quality of evidence informing these recommendations was considered to be low/very low as per the GRADE method. … Three nonrandomized studies comparing allo-HCT

	versus nontransplant strategies provide evidence favoring the option of allo-HCT for relapsed or refractory CLL [31-33]. 31. Kharfan-Dabaja MA, et al. 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. Bone Marrow Transplant. 2012;47:1164-1170. 32. Herth I, et al. The impact of allogeneic stem cell transplantation on the natural course of poor-risk chronic lymphocytic leukemia as defined by the EBMT consensus criteria: a retrospective donor versus no donor comparison. Ann Oncol. 2014;25:200-206. 33. Poon ML, et al. Allogeneic stem cell transplant in patients with chronic lymphocytic leukemia with 17p deletion: consult-transplant versus consult-no-transplant analysis. Leuk Lymph. 2015; 56:711-715. *Summary of Indications for Allo-HCT in High-Risk CLL at Time of Transplant Evaluation* **High-risk CLL at time of transplant evaluation** The panel <u>does not recommend</u> offering an allogeneic HCT in the front-line consolidation setting (Strong) The panel <u>does not recommend</u> offering an allogeneic HCT for patients who relapse after front-line therapy and demonstrate sensitive disease after second line therapy (not BCR inhibitors) (Weak) The panel <u>recommends</u> allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line (not BCR inhibitors), but show an objective response to BCR inhibitors or to a clinical trial (Strong) The panel <u>recommends</u> allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line therapy including BCR inhibitors (not BCL-2 inhibitors), but show an objective response to BCL-2 inhibitors, namely venetoclax, or to a clinical trial (Strong) The panel <u>recommends</u> allogeneic HCT when there is lack of response or there is progression after BCL-2 inhibitors, namely venetoclax (Strong) **Richter transformation** The panel <u>recommends</u> allogeneic HCT for patients with Richter transformation after achieving an objective response to anthracycline-based chemotherapy (Strong) **Purine analogue relapsed and/or refractory disease** The panel <u>considers</u> purine analogue relapsed and/or refractory disease high-risk disease but <u>not</u> an indication for immediate allogeneic HCT (Strong) *High-risk is defined as the presence of Del17p and/or TP53 mutations and/or complex karyotype.* *Recommendations for Allo-HCT–Specific Management (Based on Voting Limited to Predominantly Transplant Physicians and Physicians with Mixed Transplant/Nontransplant Practice)*

Donor eligibility and selection (also refer to Figure 1)

The panel recommends that siblings who are identified as suitable donors should be tested to rule out CLL or monoclonal B cell lymphocytosis* (Strong)

The panel does not recommend initiation of an unrelated donor search as first priority before testing siblings for suitability (Strong)

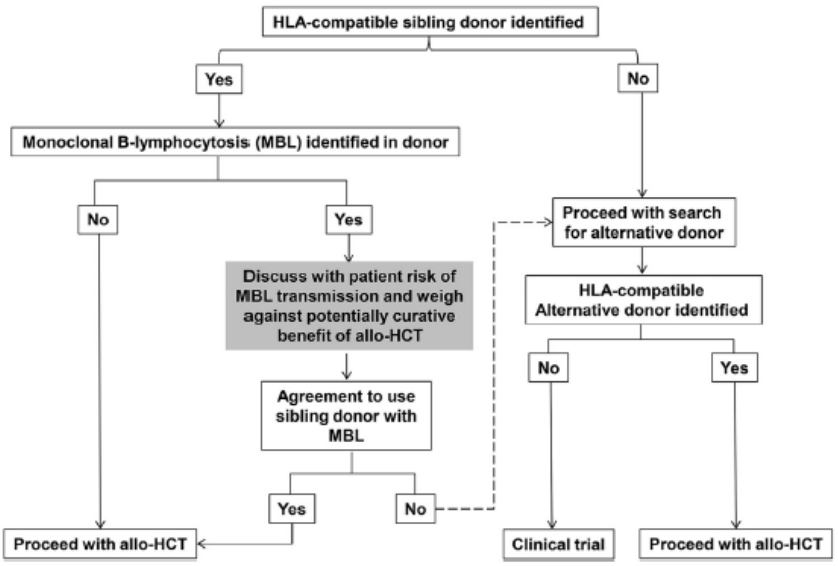


Figure 1. Donor selection in the presence of MBL in HLA-compatible sibling donors.

Dose-intensity of the preparative regimen

The panel recommends RIC for allo-HCT whenever indicated (Strong)

Preferred cell source

The panel recommends filgrastim mobilized PBSCs as a preferred cell source for allo-HCT for CLL (Weak)

MRD assessment†

The panel recommends performing MRD assessment in patients planned for an allo-HCT (Strong)

The panel does not recommend considering the presence of MRD positivity (ie, persistent disease) a contraindication for proceeding with an allo-HCT (Strong)

The panel recommends to use MRD for monitoring disease after allo-HCT (Strong)

The panel recommends using MRD for disease monitoring after allo-HCT starting no earlier than 30 days and no later than 90 days (Weak)

** According to published literature, the morbidity and mortality risks related to donor MBL appear to be exceedingly rare when compared with the usually known risks of allo-HCT, namely graft-versus-host disease and its associated complications as well as disease relapse or progression. This should be kept in mind when explaining the risks associated with MBL transmission to the patient.*

† The prognostic value of MRD is mostly relevant to patients without radiologic and/or BM

	morphologic evidence of disease.
Oscier D et al., 2012 [14]. British Committee for Standards in Haematology (BCSH) Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia Und: **Follows GA et al., 2015 [3].** 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. (aus LL-Version von 2012, Oscier 2012) 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. (aus Follows 2015
	Methodik (Angaben zur Methodik aus der LL-Version von 2012, Quelle Oscier 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. – 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), Datenbanken: Medline/Pubmed LoE/GoR: Auswertung gemäß GRADE Guidelines prior to 2010 used the classification of evidence and grading of recommendations as devised by the US Agency for Health Care Policy and Research (AHCPR). Guidelines published from 2010 onwards have used the 'GRADE' nomenclature. *Strengh of Recommendation:* Strong (grade 1), Weak (grade 2) *Quality of Evidence:* (A) High: further research is very unlikely to change our confidence in the estimate of effect, (B) Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, (C) Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the

	estimate, (D) Very Low: any estimate of effect is very uncertain. <u>*Sonstige methodische Hinweise*</u> *Conflicts of interest statements provided. UK CLL Forum is a registered charity that receives funding from a number of pharmaceutical companies including Roche, GSK, Janssen, Gilead, Napp.*
	Ergebnisdarstellung **Relapse Therapy** (aus Follows 2015) Of note, patients who were less heavily pre-treated, or who had experienced a prolonged first remission with immunochemotherapy were excluded from both the ibrutinib and idelalisib randomised relapse trials. Furthermore, neither ibrutinib nor idelalisib + rituximab have been evaluated prospectively against immunochemotherapy in the relapse setting. We, therefore, do not know whether patients relapsing after a prolonged first remission will benefit more from earlier treatment with a BCR pathway inhibitor, rather than re-treatment with immunochemotherapy. Although, retrospective subgroup analysis of the RESONATE trial has suggested that patients treated after fewer lines of therapy appear to have a prolonged PFS compared with the patients treated later in their disease [Brown et al., 2014], interpreting this retrospective data needs caution, as there will be inherent bias in favour of better outcomes for the less heavily pre- treated patients. 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 Therefore, with particular reference to patients relapsing after a prolonged first remission it is less likely that they will meet criteria for treatment with either idelalisib+ rituximab or ibrutinib. For these patients, treatment with chemotherapy or immunochemotherapy, as per the existing BCSH guidelines remains recommended. Unfortunately the quality of data from relapsed trials with immunochemotherapy is poor, and choice of chemotherapy regimen will depend on previous therapy and co-morbidities. For patients treated with more intensive intent this is likely to be FCR or BR, while more palliative patients may be re-treated with CBL. As the data stands, no firm recommendations can be made as to how patients relapsing after treatment with ibrutinb or idelalisib+rituximab should be managed. The NHS England CDF has specifically excluded funding of patients crossing from one therapy to another, although clarification is awaited to confirm that this exclusion does not apply if the first therapy was delivered within a clinical trial. Data on the use of either idelalisib + rituximab or ibrutinib as a bridge to allogeneic transplant is very limited and individual cases would need to be

	discussed with specialist transplant centres to assess suitability. **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 BR or FCR although the quality of data to support this choice is limited. CBL is an option where a more palliative approach is required (GRADE B2) **Appendix 1** <u>Idelalisib + rituximab inclusion criteria from Furman et al NEJM 2014</u> 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) <u>Ibrutinib inclusion criteria from Byrd et al NEJM 2014</u> 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. Referenzen: 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. 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
Mauro FR et al., 2012 [10]. Italian Society of Hematology (SIE), affiliate societies SIES (Società Italiana di Ematologia Sperimentale), GITMO (Gruppo Italiano Trapianto di Midollo Osseo) Updated clinical recommendations for the management of chronic lymphocytic leukemia	Fragestellung Issue 6: therapy of refractory or relapsed patients (evidence-based recommendations)
	Methodik Grundlage der Leitlinie: 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. • During a first meeting the panel decided which of the original clinical issues needed an update and the issues for which there was the need for a critical evidence appraisal. On this basis, we identified and produced recommendations about 6 clinical issues. • 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 – 3/2011 (updated review of literature) LoE/ GoR: In areas covered by the evidence, the production of recommendations was performed according GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.
	Ergebnisdarstellung

Therapy of refractory or relapsed patients (evidence-based recommendations)

In 2006, the SIE-SIES-GITMO group recommended that patients refractory to first-line chlorambucil or relapsed within 6 months from a first-line therapy should receive fludarabine or fludarabine containing regimens. In order to address the optimal second-line treatment approach, four factors were considered of relevance by the EP: the timing of relapse, the response to the prior treatment, the presence of deletion 17p- and/or p53 mutations, age and fitness status of patients.

3.6.1. Chemoimmunotherapy

[35] 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;28:1756–65.

[36] Badoux XC, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood 2011;117:3016–24.

[37] Engert E, et al. Overall survival advantage and acceptable safety profile with fludarabine in combination with alemtuzumab (FluCam) in previously treated patients with advanced stage chronic lymphocytic leukemia. Blood 2010;116, abstract 919.

3.6.2. Oblimersen *(ohne Zulassung in Deutschland)*

[38] O'Brien S, et al. Randomized phase III trial of Fludarabine plus cyclophosphamide with or without oblimersen sodium (BCL2-antisense) in patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2007;25:1114–20.

[39] O'Brien S, et al. Five-year survival in patients with relapsed or refractory chronic lymphocytic leukemia in a randomized, phase III trial of Fludarabine plus cyclophoshamide with or without oblimersen. J Clin Oncol 2009;27:5208–12.

[40] Dreger P, et al. Allogeneic stem cell transplantation provides durable disease control in poor-risk chronic lymphocytic leukemia.:long-term clinical and MRD results of the GCLLSG CLL3X trial. Blood 2010;116:2438–47.

[41] Sorror ML, et al. Five year follow-up of patients with advanced chronic lymphocytic leukaemia treated with allogeneic hematopoietic cell transplantation after nonmyeloablative conditioning. J Clin Oncol 2008;30:4912–20.

[42] Schetelig J, et al. Allogeneic hematopoietic stem-cell transplantation for chronic lymphocytic leukemia with 17 p deletion. A retrospective european group for blood and marrow transplantation analysis. J Clin Oncol 2008;26:5094–100.

[43] Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology 2010;48:1–488.

[44] Stilgenbauer S, et al. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia:clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2009;27:3994–4001.

[45] Wierda WG, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749–55.

3.6.3. 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.

	- 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 well matched unrelated donor, should be offered after an appropriate cytoreductive treatment. **Clinical questions and strength and direction of the recommendations formulated by the panel using GRADE system on the issue of second-line therapy.** 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

Grössmann N, 2016 [8]. Venetoclax (Venclexta?) for the treatment of relapsed or refractory chronic lymphocytic leukaemia (CLL) with chromosome 17p deletion	**6 Current treatment** • observation in asymptomatic CLL patients • 1st-line therapy options: chlorambucil-based chemotherapy, FCR, bendamustine + rituximab • no agreed standard therapy for relapsed or refractory CLL patients • early relapse and del(17p) CLL: clinical trials, ibrutinib, idelalisib + rituximab • late relapse CLL: retreatment with the prior therapy, ibrutinib, alternatively idelalisib + rituximab
National Institute for Health and Clinical Excellence (NICE), 2015 [13]. Idelalisib for treating chronic lymphocytic leukaemia TA359	**1 Guidance** 1.1 Idelalisib, in combination with rituximab, is recommended: • for untreated chronic lymphocytic leukaemia in adults with a 17p deletion or TP53 mutation or • for chronic lymphocytic leukaemia in adults when the disease has been treated but has relapsed within 24 months. Idelalisib is recommended only if the company provides the drug with the discount agreed in the simple discount agreement. 1.2 People whose treatment with idelalisib 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. **Current practice (Clinical need of patients, including the availability of alternative treatments)** The Committee heard from the clinical experts that treatment options for disease which has been previously treated depends on the person's suitability for certain treatments, the treatments they have already had and the time since the last disease relapse. The clinical experts advised that re-treatment with fludarabine-based regimens (such as fludarabine, cyclophosphamide and rituximab) or alkylating agents (such as bendamustine plus rituximab or chlorambucil plus rituximab) is suitable for people whose disease has relapsed more than 24 months after their last treatment. The clinical experts noted that for people whose disease had relapsed less than 24 months after their last treatment, options are limited. Re-treatment is less effective and can cause the disease to develop deletions and mutations which in turn lead to chemotherapy-resistant chronic lymphocytic leukaemia. The Committee also discussed the clinical management of untreated chronic lymphocytic leukaemia in people with a 17p deletion or TP53 mutation. It heard from the clinical experts that people with this type of disease have very limited treatment options, which can include high-dose pulsed steroids with alemtuzumab. The Committee concluded

	that more treatment options are needed.
Rothschedl E et al., 2014 [19]. Idelalisib (Zydelig(R)) in addition to rituximab for the treatment of relapsed chronic lymphocytic leukaemia	**5 Current treatment** Various treatment options exist for CLL patients depending on patient characteristics such as age or comorbidities and tumour characteristics. Depending on the patient's response to first-line therapy, relapsed or refractory disease can be differentiated. Relapsed disease is defined as a progressive disease after a period of six months or more after either a complete or partial remission had been achieved [14]. If patients do not respond 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, they have refractory disease [15]. After first-line therapy, further treatment will depend on the regimen ad-ministered previously, duration of remission, age and comorbidities. The following therapy options exist [1]: <u>Second and subsequent line chemotherapy:</u> o 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 [16] or bendamustine and rituximab (well-established, but few RCTs). o 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> o Rituximab may be used in combination with chemotherapy agents. o Other anti-CD20 monoclonal antibodies, such as ofatumumab, may be considered; ofatumumab is currently being used predominantly in patients who are refractory to rituximab and alemtuzumab. o Ibrutinib for CLL patients with 17p deletion which is associated with poor responses to standard treatment of CLL (approved by the FDA for this indication in July 2014)[5]. o Allogeneic stem-cell transplantation should be considered for fit patients with high-risk CLL and should ideally be performed in the setting of a remission. o 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 authorisation holder in Europe in 2012 [17]. <u>Radiotherapy</u>: o rarely used, may be indicated for patients with en-larged lymph nodes/spleen or prior to bone marrow transplant [1]. [1] National Institute for Health Research – Horizon Scanning Centre. Idelalisib with rituximab for

	chronic lymphocytic leukaemia. Birmingham: NIHR Horizon Scanning Centre (NIHR HSC) 2013. [14] Hallek M, 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):5446-56. [15] Hallek M CB, 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 Jun 15;111(12):5446-56. [16] Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology / the Education Program of the American Society of Hematology American Society of Hematology Education Program. 2010;2010:481-8. [17] European Medicines Agency. Public statement - MabCampath (alemtuzumab) Withdrawal of the marketing authorisation in the European Union 2012. **6 Evidence** • one phase III trial [18] included in this report [18] Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. New England Journal of Medicine. 2014 Mar 13;370(11):997-1007. **8 Ongoing research (4 ongoing phase III trials 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** 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.
Nachtnebel A et al., 2014 [11]. Ibrutinib (Imbruvica®) for relapsierte oder refraktäre chronisch lymphatische Leukämie.	**5 Current treatment** • siehe Rothschedl E, et al. 2014 [18] **6 Evidence** • two references were included: one phase III trial [21] and one phase II study [22] [21] Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014 Jul 17;371(3):213-23. [22] Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013 Jul 4;369(1):32-42. **8 Ongoing research (4 ongoing phase III trials identified for**

	relapsed or refractory CLL patients) NCT01611090: to examine the safety and efficacy of ibrutinib ad-ministered in combination w ith bendamustine and rituximab in patients w ith relapsed or refractory CLL or SLL. Estimated prima-ry completion date: August 2015. NCT01973387: to evaluate the efficacy and safety of ibrutinib ver-sus rituximab in adult Asia-Pacific region patients w ith relapsed or refractory CLL or SLL. Estimated primary completion date: Au-gust 2015. NCT01724346: open-label extension study in patients 65 years or older w ith CLL or SLL w ho participated in study PCYC-1115-CA (PCI-32765 versus chlorambucil). Estimated primary completion date: June 2015. NCT01804686: to collect long-term safety and efficacy data for par-ticipants treated with PCI-32765 (ibrutinib) and to provide ongoing access to PCI-32765 for participants who are currently enrolled in PCI-32765 studies that have been completed according to the par-ent protocol, are actively receiving treatment w ith PCI-32765, and w ho continue to benefit from PCI-32765 treatment. Estimated pri-mary completion date: January 2016. **9 Commentary** New treatment options for CLL, primarily for difficult-to-treat patients with relapsed or refractory disease or with poor prognostic characteristics such as del(17p) or p53 mutations are needed. Foremost for these patients, ibrutinib offers an alternative.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 09.12.2016**

#	Suchfrage
#1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees
#2	Chronic:ti,ab,kw or b-cell:ti,ab,kw (Word variations have been searched)
#3	lymphocytic:ti,ab,kw or lymphoid*:ti,ab,kw or lymphatic*:ti,ab,kw or lymphoblastic:ti,ab,kw or Lymphoplasmacytoid:ti,ab,kw (Word variations have been searched)
#4	leukemia*:ti,ab,kw or leukaemia*:ti,ab,kw (Word variations have been searched)
#5	CLL:ti,ab,kw (Word variations have been searched)
#6	#2 and #3 and #4
#7	#1 or #5 or #6
#8	#7 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 14.12.2016

#	Suchfrage
#1	Search Leukemia, Lymphocytic, Chronic, B-Cell[MeSH Terms]
#2	Search (Chronic[Title/Abstract]) OR b-cell[Title/Abstract]
#3	Search (((((lymphocytic[Title/Abstract]) OR lymphoid*[Title/Abstract]) OR lymphatic*[Title/Abstract]) OR lymphoblastic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract])
#4	Search ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
#5	Search (#2 AND #3 AND #4)
#6	Search CLL[Title/Abstract]
#7	Search (#1 OR #5 OR #6)
#8	Search #7 AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((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]))))
#9	#8 Publication date from 2011/12/01 to 2016/12/14

Leitlinien in Medline (PubMed) am 14.12.2016

#	Suchfrage
#1	Search Leukemia, Lymphocytic, Chronic, B-Cell[MeSH Terms]
#2	Search (Chronic[Title/Abstract]) OR b-cell[Title/Abstract]
#3	Search (((((lymphocytic[Title/Abstract]) OR lymphoid*[Title/Abstract]) OR lymphatic*[Title/Abstract]) OR lymphoblastic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract])
#4	Search ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
#5	Search (#2 AND #3 AND #4)
#6	Search CLL[Title/Abstract]
#7	Search (#1 OR #5 OR #6)
#8	Search ((Non-Hodgkin*[Title] OR b-cell[Title])) AND lymphoma*[Title]
#9	Search #7 OR #8
#10	Search #9 AND ((((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title])
#11	#10 Publication date from 2011/12/01 to 2016/12/14

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6. **Gemeinsamer Bundesausschuss (G-BA).** 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 (neues Anwendungsgebiet: chronische lymphatische

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Anhang:

Table 20. Summary of study characteristics of the included study of ibrutinib in patients with CLL or SLL with or without del 17p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog.[5,38]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
RESONATE NCT01578707 Phase 3 open label multicentre study N=391 Ibrutinib n=195 Ofatumumab n=196 67 centres in 9 countries: Europe, Australia, and North America Patients enrolled from June 2012 to April 2013	**Inclusion Criteria:** • ECOG performance status of 0-1. • Diagnosis of relapsed or refractory CLL or SLL. • Active disease meeting at least 1 of the IWCLL 2008 criteria for requiring treatment. • Must have received at least one prior therapy for CLL/SLL. • Considered not appropriate for treatment or retreatment with purine analog based therapy because they had a short progression-free interval after chemoimmunotherapy or because they had coexisting illnesses, an age of 70 years or more, or a chromosome 17p13.1 deletion. • Measurable nodal disease by CT. • Patients must be able to receive outpatient treatment and laboratory monitoring at the institution that administers study drug for the entire study. **Exclusion Criteria:** • Known CNS lymphoma or leukemia. • No documentation of cytogenetic and/or FISH in patient records prior to first dose of study drug. • Any history of Richter's transformation or prolymphocytic leukemia. • Uncontrolled Autoimmune Hemolytic Anemia or idiopathic thrombocytopenia purpura. • Prior exposure to ofatumumab or to ibrutinib.	Patients were randomly assigned to receive either: • Oral ibrutinib (at a dose of 420 mg once daily) until disease progression or the occurrence of unacceptable toxic effects • Intravenous ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks.	**Primary Outcome Measures:** • PFS **Secondary Outcome Measures:** • OS • Response Rate • Hematological Improvements • Improvement of disease-related symptoms (fatigue, night sweats, and splenomegaly)

Abbildung 6: aus Pan-Canadian Oncology Drug Review. 2016

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Funded by: Pharmacyclics and Janssen	• Prior autologous transplant within 6 months prior to first dose of study drug. • Prior allogeneic stem cell transplant within 6 months or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug. • History of prior malignancy, with the exception of certain skin cancers and malignancies treated with curative intent and with no evidence of active disease for more than 3 years. • Serologic status reflecting active hepatitis B or C infection. • Unable to swallow capsules or disease significantly affecting gastrointestinal function. • Uncontrolled active systemic fungal, bacterial, viral, or other infection. • History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug. • Requires anticoagulation with warfarin.		

CLL= chronic lymphocytic leukemia; CNS= central nervous system; CT= computerized axial tomography; FISH= fluorescent *in situ* hybridization IWCLL= International Workshop on Chronic Lymphocytic Leukemia; OS= overall survival; PFS= progression free survival; RCT= randomized controlled trial; SLL= small lymphocytic lymphoma

Abbildung 7: Fortsetzung aus Pan-Canadian Oncology Drug Review. 2016

Table 18. Summary of Trial characteristics of the included Study[2,64]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
NCT01539512 GS US 312-0116 Furman et al, 2014 Phase 3, randomized, double blind N=220 Study start date: April 2012 Primary Study completion date: October 2013 90 study locations in: France, Germany, Italy, the United Kingdom and the United States Funded by: Gilead Sciences	**Inclusion Criteria:** • Adult subjects with previously treated recurrent CLL who have measurable lymphadenopathy • Require therapy for CLL • Have experienced CLL progression < 24 months since the completion of the last prior therapy • Currently not sufficiently fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or comorbidities. **Exclusion criteria** • Known histological transformation from CLL to an aggressive lymphoma. • Presence of intermediate or high-grade myelodysplastic syndrome. • History of prior allogeneic bone marrow progenitor cell or solid organ transplantation. • Ongoing immunosuppressive therapy other than corticosteroids. • Prior therapy with any inhibitor of AKT, Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3 kinase (PI3K: including IDELALISIB), or spleen tyrosine kinase (SYK). • History of anaphylaxis with previous use of monoclonal antibodies. • Prior or ongoing clinically significant illness or medical condition in the investigator's opinion, could adversely affect the safety of the subject or the assessment of study results.	idelalisib 150 mg tablet administered orally twice daily plus rituximab administered intravenously 8 times through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter vs. Placebo plus rituximab administered intravenously 8 times through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter	**Primary Outcome:** • Progression-free survival **Secondary Outcomes:** • Overall response rate • Lymph node response rate • Overall survival • Complete response rate
CLL= Chronic lymphocytic leukemia			

Abbildung 8: aus Pan-Canadian Oncology Drug Review. 2015

Table 3
Randomized controlled trials evaluating chemotherapy plus rituximab versus non-rituximab regimens in patients with chronic lymphocytic leukemia

Author, study	N	Patients	Treatment	Follow-up	Response rate	Disease control	Overall survival, median (mo/yrs) or % surviving
CALGB 9712, Woyach [45]	104	Symptomatic, previously untreated, patients with B-cell CLL	Concurrent vs. sequential F with R	117 mo	CR: 47% vs. 28% ORR: 90% vs. 77%	$PFS_{2\text{-years}}$: 70% vs. 70%, NS	OS: NS
CLL2007FMP, Lepretre [46]	178	Previously untreated patients with B-CLL	FCR vs. FCCam	Median 38 mo	CR: 33.7% vs. 19.2%, p=0.04	$PFS_{3\ years}$: 82.6% vs. 72.5%, NS	90.1% vs. 86.4%, NS
CLL8, Hallek [47]	817	Previously untreated patients with CLL	FCR vs FC	8 yrs	CR: 44% vs. 22%, p<0.0001 ORR: 90% vs. 80%, p<0.0001	$PFS_{3\ years}$: 51.8 mo vs. 32.8 mo, p<0.0001	$OS_{3\text{-years}}$: 87% vs. 83%, p=0.012
CLL 11, Goede [75]	781	Previously untreated CLL patients with comorbidities	R + Chl vs. GA101 + Chl vs. Chl alone	*nr*	R-Chl vs. Chl CR: 8.3% vs. 0% ORR: 65.9% vs. 30%, p<0.001	PFS: 15.7 mo vs. 10.8 mo, HR 0.32, p<0.0001	OS: NS
REACH, Robak [48]	552	Previously treated CLL patients	FCR vs. FC	25 mo	24.3% vs. 13%, p<0.001	PFS_{10}: 30.6 mo vs. 20.6 mo, p<0.001 TTNT: Not reached vs. 34.3 mo, p=0.0024	Median not reached vs. 52 months, NS
NCRI CLL201, Hillmen [49]	52	Patients with relapsed CLL	FCM-R vs. FCM	38 mo	FCM-R: CR: 15% vs. 8% OR: 65% vs. 58%	PFS: NS	OS: NS

Abbreviations: Ch, chlorambucil; CLL, chronic lymphocytic leukaemia; CR, complete response; F, fludarabine; FC, fludarabine and cyclophosphamide; FCCam, fludarabine; cyclophosphamide, and alemtuzumab; FCM, (F)ludarabine, (C)yclophosphamide, and (M)itoxantrone; FCR, fludarabine, cyclophosphamide, and rituximab; GA101, Obinutuzumab; *nr*, not reported, NS, p-value not significant; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; RD, response duration; RM, rituximab maintenance; RR, response rate; TTNT, time to next treatment; yrs, years.

Abbildung 9: aus Prica A, et al. 2016