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-304 Venetoclax

Stand: Februar 2018

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

Venetoclax [zur Behandlung der chronischen lymphatischen Leukämie]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	allogene Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: – Idelalisib: Beschlüsse vom 15. September 2016 und 16. März 2017 – Ibrutinib: Beschlüsse vom 16. April 2015, 21. Juli 2016, 15. Dezember 2016 und 16. März 2017 – Venetoclax: Beschluss vom 15. Juni 2017 – Obinutuzumab: Beschluss vom 5. Februar 2015
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®	<u>Zugelassenes Anwendungsgebiet:</u> Venclyxto wird als Monotherapie angewendet bei Erwachsenen zur Behandlung einer chronischen lymphatischen Leukämie (CLL), die eine 17p-Deletion oder TP53-Mutation aufweisen und die für eine Behandlung mit einem Inhibitor des B-Zell-Rezeptor-Signalwegs nicht geeignet sind oder ein Therapieversagen zeigten. 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.
Zytostatische Wirkstoffe	
Bendamustin L01AA09 Levact®	Primärtherapie bei chronischer lymphatischer Leukämie (Binet-Stadium B oder C) bei Patienten, bei denen eine Fludarabin-Kombinations-Chemotherapie ungeeignet ist. Monotherapie bei indolenten Non-Hodgkin-Lymphomen bei Patienten mit Progression während oder innerhalb von 6 Monaten nach Behandlung mit Rituximab oder mit einer Rituximab-haltigen Therapie.
Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (CLL), […]
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)
Fludarabin L01BB05 Bendarabin®	Therapie der chronischen-lymphatischen Leukämie (CLL) vom B-Zell-Typ bei Patienten mit ausreichender Knochenmarksreserve.
B-Zell-Rezeptor-Inhibitoren	
Ibrutinib L01XE27 Imbruvica®	IMBRUVICA als Einzelsubstanz ist indiziert zur Behandlung erwachsener Patienten mit nicht vorbehandelter chronischer lymphatischer Leukämie (CLL) (siehe Abschnitt 5.1). 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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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). – als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, für die keine anderen Therapiengeeignet sind (siehe Abschnitt 4.4).
BCL-2-Inhibitoren	
Venetoclax L01XX52 Venclyxto®	Venclyxto wird als Monotherapie angewendet bei Erwachsenen zur Behandlung einer chronischen lymphatischen Leukämie (CLL), die eine 17p-Deletion oder TP53-Mutation aufweisen und die für eine Behandlung mit einem Inhibitor des B-Zell-Rezeptor-Signalwegs nicht geeignet sind oder ein herapieversagen zeigten. 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.
Anti-CD-20-Antikörper	
Obinutuzumab L01XC15 Gazyvaro®	Chronische lymphatische Leukämie (CLL) Gazyvaro in Kombination mit Chlorambucil wird bei erwachsenen Patienten mit nicht vorbehandelter chronischer lymphatischer Leukämie (CLL) angewendet, die aufgrund von Begleiterkrankungen für eine Therapie mit einer vollständigen Dosis von Fludarabin nicht geeignet sind (siehe Abschnitt 5.1).
Ofatumumab L01XC10 Arzerra®	<u>Nicht vorbehandelte chronische lymphatische Leukämie (CLL)</u> Arzerra in Kombination mit Chlorambucil oder Bendamustin ist angezeigt für die Behandlung von erwachsenen Patienten mit CLL, die noch keine vorangegangene Therapie hatten und die nicht für eine Fludarabin-basierte Therapie geeignet sind. Für weitere Informationen siehe Abschnitt 5.1. <u>Rezidivierte CLL</u> Arzerra in Kombination mit Fludarabin und Cyclophosphamid ist angezeigt für die Behandlung von erwachsenen Patienten mit rezidivierter CLL. Für weitere Informationen siehe Abschnitt 5.1. <u>Refraktäre CLL</u> Arzerra ist angezeigt für die Behandlung von erwachsenen Patienten mit CLL, die refraktär auf Fludarabin und Alemtuzumab sind. Für weitere Informationen siehe Abschnitt 5.1.
Rituximab L01XC02 MabThera®	MabThera ist in Kombination mit einer Chemotherapie für die Behandlung von nicht vorbehandelten 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.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Glucocorticoide	
Prednisolon H02AB06 Dermosolon®	Hämatologie/Onkologie: […] chronisch lymphatische Leukämie (DS e) […]
Prednison H02AB07 Cutason®	Hämatologie/Onkologie: […] chronische lymphatische Leukämie […]
Weitere Arzneimittel mit Zulassung für Non-Hodgkin-Lymphome	
Cytarabin L01BC01 ARA-cell®	ARA-cell® 100 mg/ml wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: – refraktären Non-Hodgkin-Lymphomen
Doxorubicin L01DB01 Adrimedac®	Non-Hodgkin-Lymphome
Trofosfamid L01AA07 Ixoten®	Dieses Arzneimittel ist ein Zytostatikum. Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet.
Vinblastin L01CA01 Vinblastinsulfat Teva®	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: – maligne Non-Hodgkin-Lymphome
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

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2017-B-304 (Venetoclax)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	06.02.2018

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 evidenzbasierten systematischen Leitlinien zur Indikation chronische lymphatischer Leukämie (CLL) durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 16.01.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, CCO, Clinical Evidence, DAHTA, ESMO, G-BA, GIN, IQWiG, NCCN, NCI, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 417 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 31 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Zur Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL).

Anwendungsgebiete:

Venclyxto wird als Monotherapie angewendet bei Erwachsenen zur Behandlung einer chronischen lymphatischen Leukämie (CLL), die eine 17p-Deletion oder TP53-Mutation aufweisen und die für eine Behandlung mit einem Inhibitor des B-Zell-Rezeptor-Signalwegs nicht geeignet sind oder ein Therapieversagen zeigten.

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.

Abkürzungen:

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 Siehe siehe **IQWiG, 2017 [17].**	**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. 1b) Patienten mit rezidivierender oder refraktärer CLL, für die eine Chemotherapie nicht angezeigt ist: **Zweckmäßige Vergleichstherapie:** Ibrutinib oder Idelalisib in Kombination mit Rituximab oder Best-Supportive-Care **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2017 [4]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-	**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,

Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ibrutinib (neues Anwendungsgebiet: chronische lymphatische Leukämie; in Kombination mit Bendamustin und Rituximab) vom 16. März 2017 siehe **IQWiG, 2017 [14].**	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 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 [5]. 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 siehe	**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**

IQWiG, 2016 [12].	**gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2015 [6]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ibrutinib, vom 16. April 2015 (Beschluss wurde aufgehoben) vom 16. April 2015 **IQWiG, 2016 [13].**	Beschluss wurde aufgehoben.
Gemeinsamer Bundesausschuss (G-BA), 2016 [3] 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 15. Dezember	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 26.Mai 2016):** IMBRUVICA als Einzelsubstanz ist indiziert zur Behandlung erwachsener Patienten mit nicht vorbehandelter chronischer lymphatischer Leukämie (CLL) (siehe Abschnitt 5.1). Hinweis: Über den Zusatznutzen von Ibrutinib für nicht-vorbehandelte Patienten mit chronischer lymphatischer Leukämie, die eine 17p-Deletion oder TP53-Mutation aufweisen, hat der G-BA bereits mit Beschluss vom 21. Juli 2016 entschieden. <u>1a) Patienten mit nicht vorbehandelter CLL, für die eine Therapie mit FCR infrage kommt</u> **Zweckmäßige Vergleichstherapie:** Fludarabin in Kombination mit Cyclophosphamid und Rituximab

2016 **(neues Anwendungsgebiet)**	(FCR) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Fludarabin in Kombination mit Cyclophosphamid und Rituximab:** Ein Zusatznutzen ist nicht belegt. 1b) Patienten mit nicht vorbehandelter CLL, für die eine Therapie mit FCR nicht infrage kommt **Zweckmäßige Vergleichstherapie:** Eine Chemo-Immuntherapie nach Maßgabe des Arztes unter Berücksichtigung des Zulassungsstatus **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. 2) Patienten mit nicht vorbehandelter CLL, für die eine Chemoimmuntherapie nicht infrage kommt und die keine 17p-Deletion oder TP53-Mutation aufweisen **Zweckmäßige Vergleichstherapie:** Best-Supportive-Care **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:** Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2017 [10]. 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 – Venetoclax vom 15. Juni 2017	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 5. Dezember 2016):** Venclyxto wird als Monotherapie angewendet bei Erwachsenen zur Behandlung einer chronischen lymphatischen Leukämie (CLL), die eine 17p-Deletion oder TP53-Mutation aufweisen und die für eine Behandlung mit einem Inhibitor des B-Zell-Rezeptor-Signalwegs nicht geeignet sind oder ein Therapieversagen zeigten. 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. **Ausmaß des Zusatznutzens:** a) Erwachsene Patienten mit CLL, die eine 17p-Deletion oder TP53-Mutation aufweisen und die für eine Behandlung mit einem Inhibitor des B-Zell-Rezeptor-Signalwegs nicht geeignet sind

siehe **IQWiG, 2017 [19].** Venetoclax (chronische lymphatische Leukämie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag G16-14	oder ein Therapieversagen zeigten Nicht-quantifizierbarer Zusatznutzen. b) Erwachsene Patienten mit CLL ohne Vorliegen einer 17p-Deletion oder TP53-Mutation, bei denen sowohl unter einer Chemo-Immuntherapie als auch unter einem Inhibitor des B-Zell-Rezeptor-Signalwegs ein Therapieversagen auftrat Nicht-quantifizierbarer Zusatznutzen.
Gemeinsamer Bundesausschuss (G-BA), 2016 [8]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Idelalisib Vom 15. September 2016 siehe **IQWiG, 2016[15] [16].**	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 23. 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-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)] **Anwendungsgebiet 1:** 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. <u>Teilpopulation 1b</u> Patienten mit rezidivierender oder refraktärer CLL, für die eine Chemotherapie nicht angezeigt ist: **Zweckmäßige Vergleichstherapie:** Ibrutinib oder Best-Supportive-Care **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:** Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen **Anwendungsgebiet 2:** Zur Fortsetzung der Therapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemoimmuntherapie ungeeignet waren und bei denen bereits eine Erstlinientherapie mit Idelalisib initiiert wurde. **Zweckmäßige Vergleichstherapie:** Ibrutinib oder Best-Supportive-Care (entsprechend der bereits initiierten Therapie) **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:** Ein Zusatznutzen ist nicht belegt.
Gemeinsamer Bundesausschuss (G-BA), 2015 [9]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Obinutuzumab, vom 05. Februar 2015	**Zugelassenes Anwendungsgebiet:** Obinutuzumab (GazyvaroTM) in Kombination mit Chlorambucil wird bei erwachsenen Patienten mit nicht vorbehandelter chronischer lymphatischer Leukämie (CLL) angewendet, die aufgrund von Begleiterkrankungen für eine Therapie mit einer vollständigen Dosis von Fludarabin nicht geeignet sind. **Ausmaß des Zusatznutzens:** nicht quantifizierbar

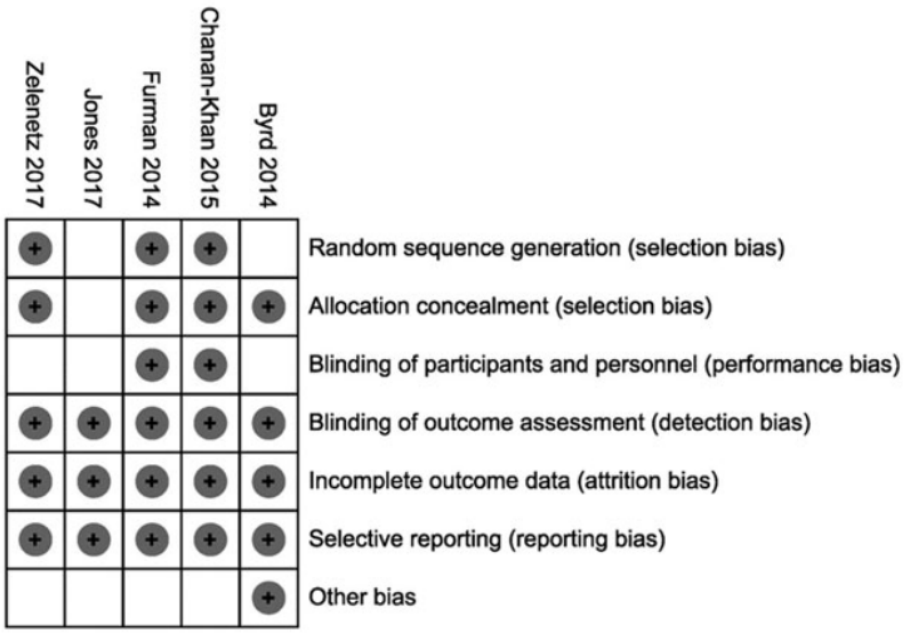
siehe **IQWiG, 2017 [18].**	

Cochrane Reviews

Es konnten keine relevanten CR zum vorliegenden AWG identifiziert werden.

Systematische Reviews

Pula A et al., 2017 [29]. Efficacy and safety of B-cell receptor signaling pathway inhibitors in relapsed/refractory chronic lymphocytic leukemia: a systematic review and meta-analysis of randomized clinical trials	1. Fragestellung The aim of the present study was to perform a meta-analysis comparing these BCR signaling pathway inhibitors with other therapeutic regimens to evaluate the role of ibrutinib and idelalisib in the treatment of patients with relapsed or refractory CLL.
	2. Methodik **Population:** patients with relapsed/refractory chronic lymphocytic leukemia **Intervention**: ibrutinib and idealisib **Komparator:** ofatumumab; Placebo + bendamustine + rituximab; Placebo + rituximab **Endpunkt:** progression-free survival (PFS), overall response rate (ORR) , overall survival (OS), adverse events (AE) **Suchzeitraum** (Aktualität der Recherche): until 04/2017 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 5 (n= 1866) **Qualitätsbewertung der Studien:** Study quality was determined using Cochrane's Risk of Bias Tool
	3. Ergebnisdarstellung **Qualität der Studien:**



- 5 RCTs: ibrutinib enrolled 969 patients, while the trials investigating idelalisib included 897 patients

PFS:

- Significantly better PFS than the control group (pooled HR 0.24; 95% CI: 0.19–0.30)
- moderate statistical heterogeneity was present (I^2=49.1%), no small-study effect was found (p=.33)

OS:

- The experimental group showed significantly better OS (combined HR 0.58; 95% CI: 0.46–0.73) with no difference between ibrutinib and idelalisib (Q=1.13, p=.72)
- No heterogeneity was present (I^2=0%)

ORR:

- The BCR pathway inhibitors significantly increased the chance of any response in CLL with a pooled RR of 3.54 (95% CI: 1.69–7.41)

AE:

- BCR pathway inhibitors increased the risk of any-grade AE in comparison with other drugs used in therapy of CLL (RR=1.02; 95% CI: 1.00–1.03, p=.04)
- The risk of grade 3/4 AE was increased by 25% (RR=1.25; 95% CI: 1.08–1.44, p<.01)
- Similar results were observed in the risk of serious AEs (RR=1.32; 95% CI: 1.17–1.50, p<.01)

	4. Anmerkungen/Fazit der Autoren In conclusion, ibrutinib and idelalisib, two novel BCR signaling pathway inhibitors, demonstrate better effectiveness against relapsed or refractory CLL than other examined therapeutic regimens. They result in better PFS, OS and response rates, and are characterized by a good safety profile. Although they are bound to a higher risk of serious AE, they do not significantly increase the risk of AEs causing discontinuation or death. Our results show comprehensively that both drugs should be considered as effective components of treatment regimens in patients with refractory/ relapsed CLL/SLL.
Vidal L et al., 2016 [31]. Chlorambucil for the treatment of patients with chronic lymphocytic leukemia (CLL) – a systematic review and meta-analysis of randomized trials	1. Fragestellung To assess the efficacy and safety of chlorambucil as frontline treatment, we conducted a systematic review and meta-analysis of randomized controlled trials.
	2. Methodik **Population:** patients with chronic lymphocytic leukemia (CLL) **Intervention:** Chlorambucil **Komparator:** alkylating agent-containing chemotherapy, purine analog containing chemotherapy, or their combination **Endpunkt:** primary: OS; secondary: PFS (as defined in each trial), quality of life, response rates and toxicity **Recherche:** 03/2015 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 18 RCTs (n=4869) **Qualitätsbewertung der Studien:** Risk of bias of included trials by domains of the Cochrane's tool. We used the GRADE system for assessment of quality of the evidence
	3. Ergebnisdarstellung **Qualität der Studien:**

OS:

- No effect on OS was demonstrated by chlorambucil treatment:
- chemotherapy without chlorambucil compared with chlorambucil (HR of death 0.99, 95% CI 0.91–1.08, p=0.85; I^2 heterogeneity 55%, 4117 patients
- The quality of that outcome was graded as moderate due to the clinical heterogeneity in the comparator intervention

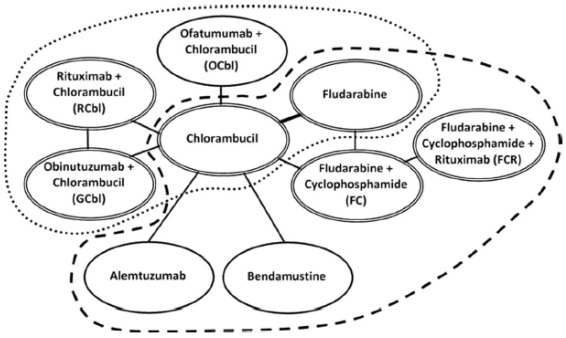
PFS:

- Eight trials reported on PFS
- statistically significant PFS benefit was shown for treatment with purine analogs treatment, compared with chlorambucil (HR of progression or death 0.78, 95% CI 0.69–0.87, I^2 of heterogeneity 78%, p=0.0004), with bendamustine (HR 0.28, 95% CI 0.19–0.42), with alemtuzumab: (HR 0.58, 95% CI 0.43–0.78) and with ibrutinib (HR 0.16, 95% CI 0.09–0.28)
- We graded the quality of PFS estimates as low due to lack of blinding that may affect assessment of subjective outcomes (detection bias), and serious inconsistency in trials' results

RR:

- Seventeen trials were eligible for the analysis of complete response (CR).

	- CR rate was statistically significantly higher with chemotherapy not containing chlorambucil compared with chlorambucil, RR 1.79, 95% CI 1.58–2.02, I^2 of heterogeneity=90%, p<0.00001. - We graded the quality of response estimates as low due to lack of blinding that may affect assessment of subjective outcomes (detection bias) and serious inconsistency in trials' results. Quality of life: - Health-related quality of life (HRQoL) was considered in three trials - Eichhorst et al., significant improvements in favor of fludarabine compared with chlorambucil were shown in global, role and social HRQoL, while no change was shown in physical, emotional and cognitive HRQoL - In the study by Catovsky et al., HRQoL was assessed at eight time-points: baseline, 3 months, 6 months, 12 months and annually thereafter up to 5 years - In this study, the mean baseline quality of life scores did not appear to differ in the three treatment groups (chlorambucil, fludarabine, fludarabinecyclophosphamide) by more than four points in any of the 15 domains - Mulligan et al., HRQoL was assessed at 1 and 6 months, respectively, and only minor changes in quality of life according to treatment group were noted Safety: - Safety data has scarcely been reported and the rate of treatment discontinuation was higher with CHOP, purine analog and alemtuzumab and lower with ibrutinib compared with chlorambucil. - No statistically significant difference was shown when fludarabine was compared with chlorambucil
	4. Anmerkungen/Fazit der Autoren To conclude based on our results and the study by Goede et al., for the unfit patients with CLL/SLL, the two evidence-based treatment alternatives are chlorambucil in combination with obinutuzumab or ibrutinib as these regimens showed improved OS of patients with CLL/SLL. Unfit patients are underrepresented in clinical trials. As unfit patients is a group of patients that needs special considerations, and treatment other than the conventional FCR given for fit patients, more studies focusing on this group are required.
Ladyzynski P. et al., 2015 [21]. A network meta-analysis of progression free survival and overall survival in	1. Fragestellung „The objective of the current study was to conduct a network meta-analysis to compare survival data of therapies for previously untreated CLL"
	2. Methodik **Population:** nicht vorbehandelte Pat. mit symptomatischer CLL **Vergleiche:**

first-line treatment of chronic lymphocytic leukemia	 Fig. 2. Analysis networks for the network meta-analysis of: the progression free survival (names of drugs in single-line and double-lines ellipses), the overall survival (names of drugs in double-lines ellipses). A subgroup of trials in younger/fit patients is surrounded by the dashed line and a subgroup of trials in older/unfit patients is surrounded by the dotted line. **Endpunkte:** OS, PFS **Suchzeitraum** (Aktualität der Recherche): 01/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 (n=4.173) für Endpunkt PFS, 6 für Endpunkt OS (n=3.110) **Qualitätsbewertung der Studien:** Jadad Score, Bewertung der klinischen Heterogenität (anhand Patientencharakteristika, Dosierungsschemata)
	3. Ergebnisdarstellung - **OS** (median, 95% CrI) jüngere, gesündere Patienten: Fludarabin: 70 (61;87) FCR: 66 (51;-) Chlorambucil: 66 (61;74) FC: 59 (49;81) ältere, kränkere Patienten: GClb: 90 (48;-) Chlorambucil: 59 (47;-) RClb: 58 (37;-) Fludarabin: 44 (27;-) - **PFS (median, 95% CrI)** jüngere, gesündere Patienten: FCR: 75 (22;123) Bendamustin: 51 (11;79) FC: 43 (28;61) Alemtuzumab: 31 (21;48) Fludarabin: 26 (20;33) Chlorambucil: 19 (18;21) ältere, kränkere Patienten: GClb: 60 (8;333)

	RClb: 30 (7;307) OClb: 24 (5;294) Fludarabin: 17 (4;239) Chlorambucil: 16 (15;18)
	4. Anmerkungen/Fazit der Autoren “Our results suggest that FCR has higher potential of preventing CLL progression in younger/fit patients in terms of a median of the projected mean PFS not only over four therapy options, which were a subject of the previous meta-analysis, but also over bendamustine. However, the best efficacy of FCR in terms of the projected mean PFS does not entail prolonging of median OS in comparison with chlorambucil and it is out performed by a few months by fludarabine monotherapy in this group of patients. In older/unfit patients obinutuzumab with chlorambucil demonstrates longer median of the projected PFS than chlorambucil, fludarabine and chlorambucil with ofatumumab or with rituximab. The highest potential of GClb of preventing CLL progression is in this group of patients accompanied by the highest potential of prolonging patient’s overall survival.“
Messori A et al., 2015 [22]. First-line treatments for chronic lymphocytic leukaemia: interpreting efficacy data by network meta-analysis	1. Fragestellung The main purpose of our study was to comparatively evaluate the effectiveness of current treatments and to rank themaccording to their effectiveness.
	2. Methodik **Population:** previously untreated patients with CLL **Intervention/ Komparator:** k.A. (evaluation of treatments currently approved by EMA and/or FDA) **Endpunkt:** PFS **Suchzeitraum (Aktualität der Recherche):** bis Dez. 2014 (PubMed, Cochrane Library, ClinicalTrials.gov, EMA, FDA) **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 RCTs (n=3620) **Qualitätsbewertung der Studien:** risk of bias (Cochrane Collaboration’s tool) **Heterogenität:** k.A. **Bayesian network meta-analysis**
	3. Ergebnisdarstellung <u>Qualitätsbewertung</u> all studies were evaluated to have a low risk of bias

eingeschlossenen Studien

First author	Patient groups
Catovsky *et al.*[3]	CHL
	FLU
	CYC+FLU
Eichorst et al.[16]	CHL
	FLU
Eichorst et al.[17]	FLU
	CYC+FLU
Hillmen *et al.*[6]	CHL
	ALE
Hallek *et al.*[2]	CYC+FLU
	CYC+FLU+RIT
Knauf *et al.*[4]	CHL
	BEN
Flinn *et al.*[8]	FLU
	CYC+FLU
Lepretre *et al.*[5]	CYC+FLU+RIT
	CYC+FLU+ALE
Robak *et al.*[7]	CYC+FLU
	CYC+CLA

Abk.: CHL, chlorambucil; FLU, fludarabine; BEN, bendamustine; ALE, alentuzumab; CLA, cladribine.

Relevant sind 6 RCTs

Ergebnisse (siehe **Anhang 1**)

Eingeschlossenen Treatment-arms: four single-agent regimens (chlorambucil (CHL) in four treatment arms, fludarabine (FLU) in four treatment arms, bendamustine (BEN) in one treatment arm and alemtuzumab (ALE) in one treatment arm) and four combination regimens based on cyclophosphamide (CYC), i.e. CYC + FLU in five treatment arms, CYC + cladribine (CLA) in one treatment arm, CYC + FLU + rituximab (RIT) in two treatment arms and CYC + FLU + ALE in one treatment arm.

- combination treatments fared much better than monotherapies
- CYC + FLU + RIT ranked first in the great majority of the simulations. This regimen was significantly more effective than CYC + FLU (OR=0.443 with 95 % CrIs of 0.335 to 0.590, which is in line with the study by Hallek et al. [2]) and was also superior to CYC + CLA (OR=0.478 with 95 % CrI of 0.289 to 0.776 which is a comparison that was not tested by any real trial)
- The other three-agent regimen (CYC + FLU + ALE) fared numerically worse than CYC + FLU + RIT, but the difference was not statistically significant; this likely reflects the safety problems with CYC + FLU + ALE that have previously been highlighted by

	Lepretre et al. [5]
	4. Anmerkungen/Fazit der Autoren The main message arising from our study is that, among combination regimens, the CYC + FLU + RIT regimen not only ranked first in effectiveness but its superiority was statistically significant and clinically relevant in comparison with the other treatments we tested (with the exception of alemtuzumab monotherapy). On the other hand, all single-agent treatments (with the exception of alemtuzumab) occupied the worse ranks; in particular, bendamustine monotherapy fared worse in our indirect comparisons than in the results suggested by its pivotal trial.
Terasawa T et al., 2013 [30]. Comparative efficacy of first-line therapies for advanced-stage chronic lymphocytic leukemia: A multiple-treatment meta-analysis	1. Fragestellung we performed a systematic review and multiple treatment meta-analysis (MTM) of all clinically relevant CLL treatments.
	2. Methodik **Population:** all first-line therapy (CLL) **Intervention/ Komperator:** least two chemo- or chemoimmunotherapy regimens belonging to the 11 categories in adults **Table 1** Grouping of treatment regimens in main analyses and sensitivity analyses[a]. | # | Main analysis | Example | Sensitivity analysis[b] | |---|---|---|---| | 1 | Single-agent chlorambucil[c] | Chlorambucil | Conventional chemotherapies | | 2 | Conventional combination regimens | Cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) | | | 3 | Single-agent fludarabine | Fludarabine | Purine analogue monotherapies | | 4 | Single-agent cladribine. | Cladribine | | | 5 | Fludarabine-based combination regimens | Fludarabine, cyclophosphamide (FC) | Purine analogue-based combination | | 6 | Cladribine-based combination regimens | Cladribine, cyclophosphamide | regimens | | 7 | Fludarabine–rituximab-based chemoimmunotherapies | Fludarabine, cyclophosphamide, rituximab (FCR) | Purine analogue-based | | 8 | Pentostatin–rituximab-based chemoimmunotherapies | Pentostatin, cyclophosphamide, rituximab | chemoimmunotherapies | | 9 | Single-agent alemtuzumab | Alemtuzumab | Single-agent alemtuzumab | | 10 | Single-agent bendamustine | Bendamustine | Single-agent bendamustine | | 11 | High-dose chemotherapy with autologous stem cell transplantation[d] | NA | NA | [a] These treatment categories may or may not include steroids in addition to the chemotherapies (e.g., chlorambucil and prednisone, a steroid, was still categorized as single-agent chlorambucil). [b] Some of the treatment categories in the main analysis are aggregated: conventional chemotherapies (combining single-agent chlorambucil and conventional combination regimens); purine analogue monotherapies (single-agent fludarabine and single-agent cladribine); purine analogue-based combinations (fludarabine-based combination regimens and cladribine-based combination regimens); purine analogue-based chemoimmunotherapies (fludarabine–rituximab-based chemoimmunotherapies and pentostatin–rituximab-based chemoimmunotherapies). [c] Any chlorambucil monotherapies regardless of dose intensity. [d] No eligible studies used this treatment, and it is not analyzed further. **Endpunkt:** PFS, OS (primäre Endpunkte); treatment-related mortality (TRM) (sekundärer Endpunkt) **Suchzeitraum (Aktualität der Recherche):** Juni 2011 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 25 RCTs reported in 27 publications (19 full publications and 8 conference abstracts; 7926 patients total) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool **Heterogenität:** heterogeneity with Cochran's Q and quantified its extent with I^2
	3. Ergebnisdarstellung Hinweis: Da in der Meta-Analyse auch Wirkstoffe bzw. Wirkstoffkombinationen berücksichtigt wurden, die in Deutschland nicht

zugelassen sind, werden nachfolgend ausschließlich die direkten Vergleiche berichtet.

Qualitätsbewertung

Appendix Table 3. Quality assessment of trials included in the network meta-analysis*

Trial ID	Appropriate random allocation	Appropriate allocation concealment	Complete follow-up (>80%)	Double blinding	Intention to treat analysis	Re-treatment strategy defined?	Similarity of groups
PETHEMA 1982	nd	nd	nd	n	y†	n	nd
FCG-CLL 80B	nd	y	nd	n	y†	y	y
PETHEMA 1988	nd	nd	n	n	n	n	nd
LGCS 1982	nd	nd	nd	n	n	y	y
UK MRC CLL 1	nd	nd	nd	n	nd	n	nd
ECOG EST 2480	nd	nd	nd	n	n	n	y
Danish CLL-2	nd	nd	nd	n	y†	y	nd
FCG-CLL 85B	nd	y	nd	n	y†	n	y
IGCI CLL-02	nd	nd	nd	n	y†	y§	n
CALGB 9011	nd	y	nd	n	n	y§	y
UK NCRI LRF CLL4	y	y	nd	n	n‡	n	y
GCLLSG CLL5	nd	y	nd	n	n‡	y§	y
PALG CLL 1	nd	y	nd	n	n	y	y
Knauf 2009	nd	nd	nd	n	y	n	y
CAM 307	nd	nd	nd	n	y	n	y
FCG-CLL 90	nd	y	nd	n	n	y	y
GCLLSG CLL4	nd	y	nd	n	n‡	y§	y
US intergroup E2997	nd	nd	nd	n	y†	n	y
GCLLSG CLL8	y	y	nd	n	y	n	y
PALG CLL 3	nd	y	nd	n	n	n	y
PALG CLL 2	nd	y	nd	n	n	n	y

* Only full-text publications were assessed.
† Some randomized patients might have been excluded from analysis although they were not explicitly reported.
‡ Intention-to-treat analysis was described in the method but some randomized patients were excluded from analysis.
§ At least some salvage treatment strategies were described although not fully reported.
nd = no data.

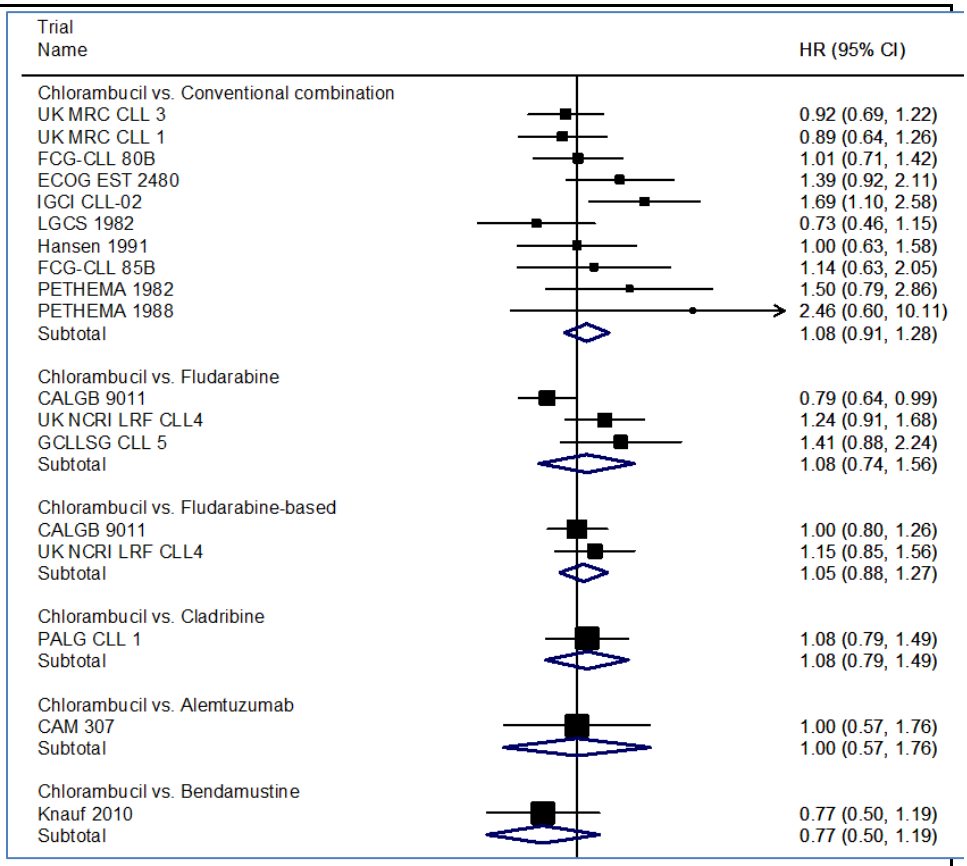
eingeschlossenen Studien

No eligible trial included high-dose chemotherapy with autologous stem cell transplantation, leaving 10 out of the 11 prespecified treatment categories in our analyses. Four trials compared three treatment categories.[38–40,46,54] Only one trial[53] also included previously treated patients (20% of total enrollees), which was excluded post-hoc in sensitivity analysis.

Ergebnisse zum OS

Direkte Evidenz

Statistically significant difference was found in only 1 (from a single trial) out of 13 treatment contrasts with data on OS: fludarabine-rituximab-based immunochemotherapy was superior to fludarabine-based combination (summary HR = 0.67, 95% CI: 0.48, 0.92).



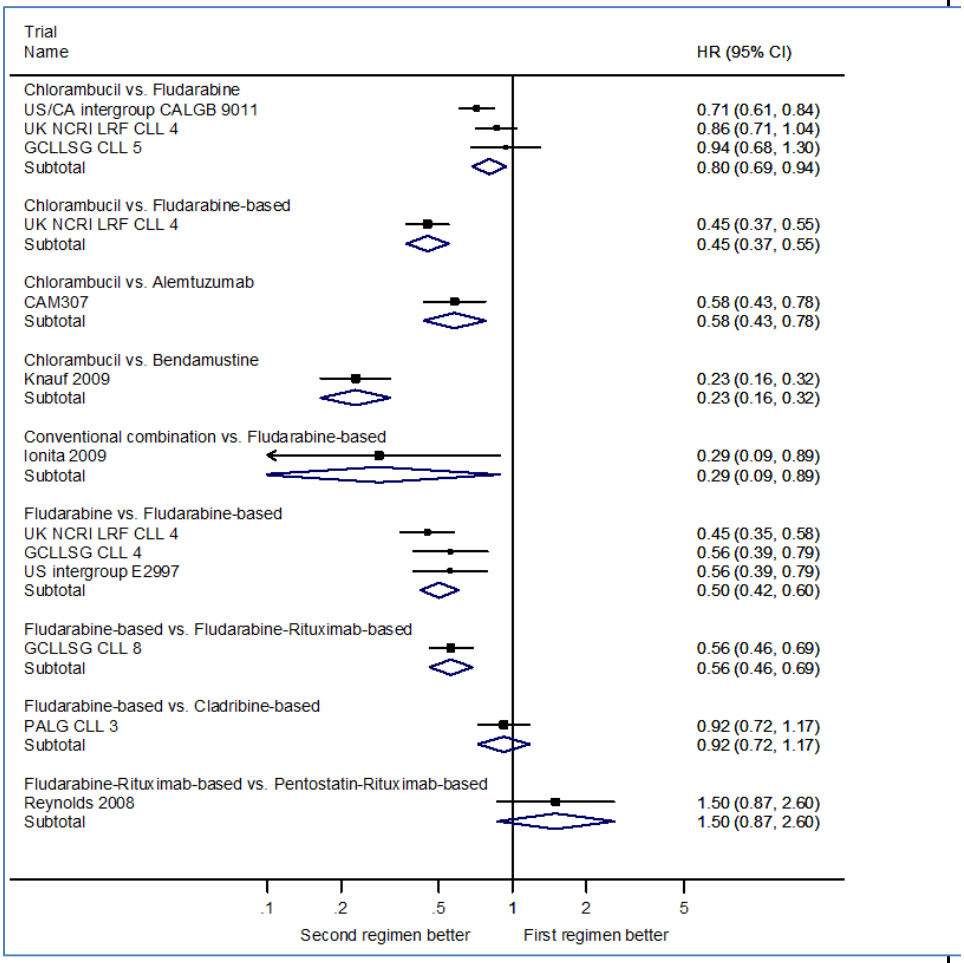
Evidence for statistical heterogeneity was found in 1 of 6 contrasts with 2 or more comparisons (chlorambucil versus fludarabine, 3

comparisons, I^2 = 75%)

Ergebnisse zum PFS

Direkte Evidenz

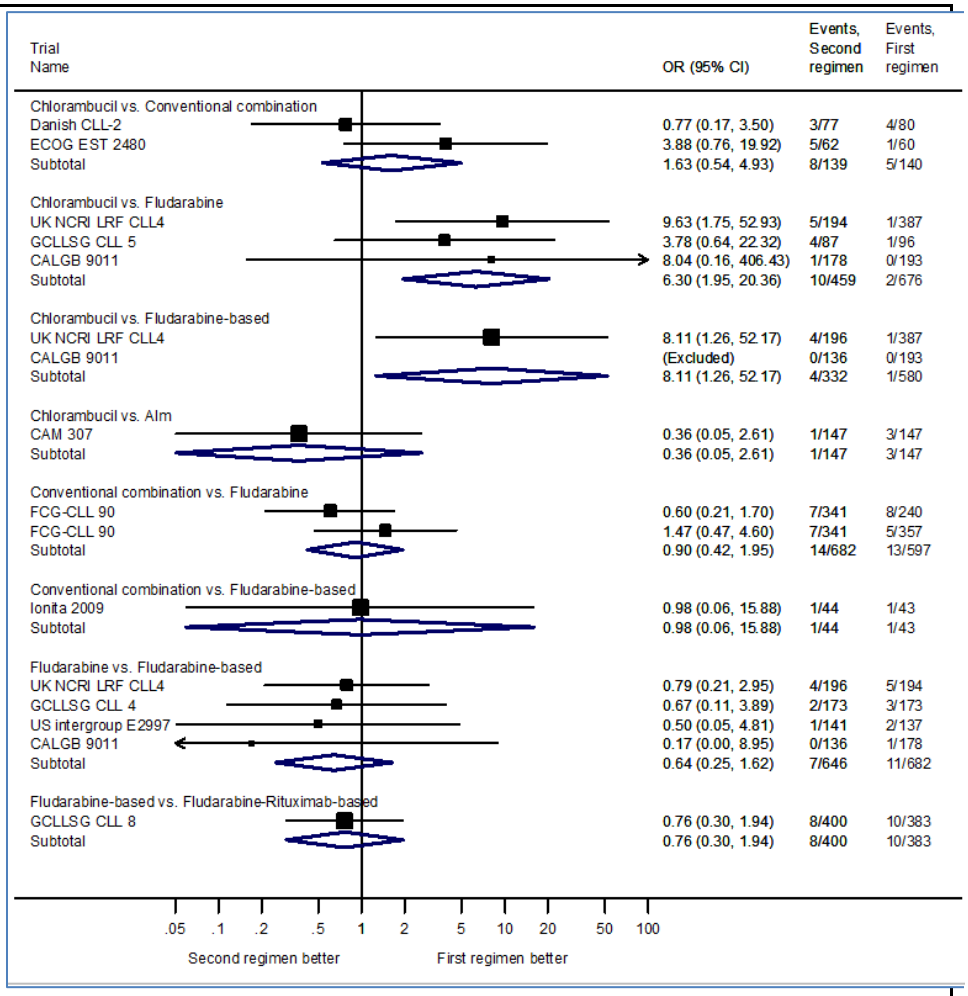
For PFS, 7 out of 9 treatment contrasts showed statistically significant differences, but most were based on data from a single trial.



Ergebnisse zum TRM

Direkte Evidenz

Meta-analyses for TRM found significant difference in 2 out of 8 contrasts: chlorambucil had lower TRM than fludarabine-based combination or fludarabine alone; however, these two comparisons were based on only two studies each There was evidence of statistical heterogeneity only in the contrast between chlorambucil versus conventional combination regimens.



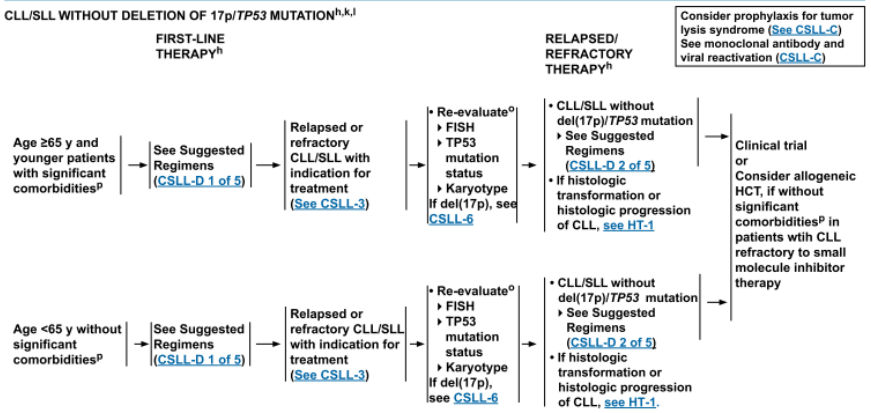
4. Anmerkungen/Fazit der Autoren

There was no evidence for inconsistency between direct and indirect data. Based on combined direct and indirect data, no single treatment showed significantly better overall survival than any other, and credible intervals were wide. Among six newer treatments with longer progression-free survival compared with chlorambucil, fludarabine-rituximab-based chemoimmunotherapy (HR = 0.24, 95% CrI: 0.13–0.51) and bendamustine (HR = 0.23, 95% CrI: 0.13–0.42) had the largest PFS benefit.

Limited data on treatment-related mortality precluded multiple-treatment meta-analysis. In conclusion, published randomized evidence on overall survival is insufficient to recommend any particular first-line treatments. Any progression-free survival differences may be applicable to relatively young uncomplicated patients.

Leitlinien

National Comprehensive Cancer Network (NCCN), 2017 [23]. Chronic lymphocytic leukemia/ small lymphocytic lymphoma: Version 2.2018	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



[h] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[l] Given incurability with conventional therapy, consider including clinical trial as first-line therapy.
[o] Re-evaluation of FISH [t(11;14); t(11q;v); +12; del(11q); del(13q); del(17p)] and TP53 mutation status is necessary prior to initiation of treatment.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
NCCN Evidence Blocks™

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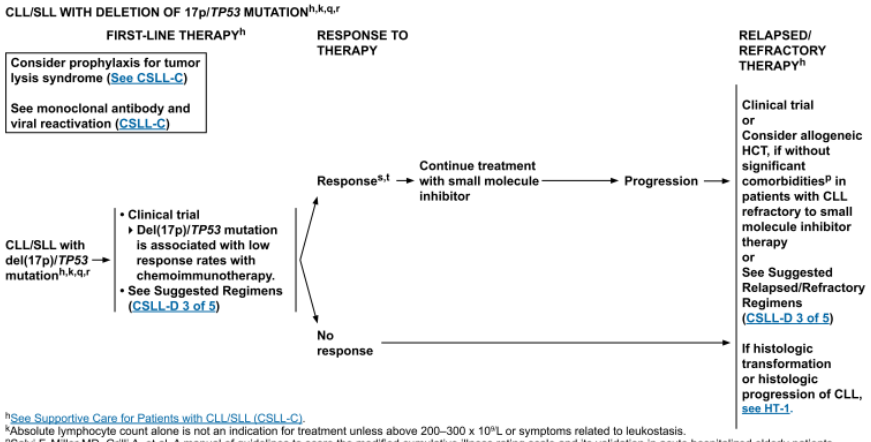

[h] See Supportive Care for Patients with CLL/SLL (CSLL-C).
[k] Absolute lymphocyte count alone is not an indication for treatment unless above 200–300 x 10^9/L or symptoms related to leukostasis.
[p] Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc 2008;56:1926-1931.
[q] CPG-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 Definition after Treatment for CLL/SLL (CSLL-E).
[t] For patients with complex karyotype (≥3 abnormalities) in achieving remission with or after BTK-inhibitor therapy, consider discussion of allogeneic HCT although data available do not support this as highly effective (Jaglowski et al. Br J Haematol 2012;159:82-87).

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Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma
NCCN Evidence Blocks™

5 E = Efficacy of Regimen/Agent
4 S = Safety of Regimen/Agent
3 Q = Quality of Evidence
2 C = Consistency of Evidence
1 A = Affordability of Regimen/Agent
E S Q C A

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EVIDENCE BLOCKS FOR FIRST-LINE THERAPY FOR CLL/SLL WITHOUT del(17p)/TP53 MUTATION

Frail Patient with Significant Comorbidity

Preferred Regimens
Obinutuzumab + chlorambucil
Ibrutinib
Ofatumumab + chlorambucil
Rituximab + chlorambucil
Other Recommended Regimens
Obinutuzumab
High-dose methylprednisolone (HDMP) + rituximab
Rituximab
Chlorambucil

Post First-line Maintenance Therapy

Lenalidomide maintenance

Patients ≥65 y and Younger Patients with Significant Comorbidities

Preferred Regimens
Obinutuzumab + chlorambucil
Ibrutinib
Ofatumumab + chlorambucil
Rituximab + chlorambucil
Bendamustine
Bendamustine + rituximab
Bendamustine + obinutuzumab
Bendamustine + ofatumumab
Other Recommended Regimens
Obinutuzumab
High-dose methylprednisolone (HDMP) + rituximab
Rituximab
Chlorambucil

Patients <65 y without Significant Comorbidities

Preferred Regimens
Fludarabine, cyclophosphamide and rituximab (FCR)
Ibrutinib
Bendamustine
Bendamustine + rituximab
Bendamustine + obinutuzumab
Bendamustine + ofatumumab
Other Recommended Regimens
Fludarabine and rituximab (FR)
High-dose methylprednisolone (HDMP) + rituximab
Pentostatin, cyclophosphamide and rituximab (PCR)

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SUGGESTED TREATMENT REGIMENS[a,b]

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

Relapsed/Refractory Therapy

See Evidence Blocks on CSLL-D (EB-2)

- **Frail patient with significant comorbidity or age ≥65 y and younger patients with significant comorbidities**
  - **Preferred regimens**
    - ◊ **Ibrutinib[c] (category 1)**
    - ◊ **Idelalisib + rituximab[c,j] (category 1)**
    - ◊ **Venetoclax[c,k,l] ± rituximab**
  - **Other recommended regimens**
    - ◊ **Idelalisib[c]**
    - ◊ **Reduced-dose FCR[f,g,h]**
    - ◊ **Reduced-dose PCR**
    - ◊ **HDMP + rituximab**
    - ◊ **Rituximab + chlorambucil**
    - ◊ **Ofatumumab**
    - ◊ **Obinutuzumab**
    - ◊ **Lenalidomide[m] ± rituximab**
    - ◊ **Alemtuzumab[n] ± rituximab**
    - ◊ **Dose-dense rituximab (category 2B)**
    - ◊ **Bendamustine (70 mg/m² in cycle 1 with escalation to 90 mg/m² if tolerated), rituximab ± ibrutinib[c] or idelalisib[c] (category 2B for BR and BR + ibrutinib; category 3 for BR + idelalisib)**

Relapsed/Refractory Therapy

See Evidence Blocks on CSLL-D (EB-3)

- **Age <65 y without significant comorbidities**
  - **Preferred regimens**
    - ◊ **Ibrutinib[c] (category 1)**
    - ◊ **Idelalisib + rituximab[c,j] (category 1)**
    - ◊ **Venetoclax[c,k,l] ± rituximab**
  - **Other recommended regimens**
    - ◊ **Idelalisib[c]**
    - ◊ **FCR[f,g,h]**
    - ◊ **FC + ofatumumab**
    - ◊ **PCR**
    - ◊ **Bendamustine + rituximab**
    - ◊ **HDMP + rituximab**
    - ◊ **Ofatumumab**
    - ◊ **Obinutuzumab**
    - ◊ **Lenalidomide[m] ± rituximab**
    - ◊ **Alemtuzumab[n] ± rituximab**
    - ◊ **Bendamustine, rituximab + ibrutinib[c] (category 2B)**
    - ◊ **Bendamustine, rituximab + idelalisib[c] (category 2B)**

Consider prophylaxis for tumor lysis syndrome (See CSLL-C)
See monoclonal antibody and viral reactivation (See CSLL-C)

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

See Evidence Blocks on CSLL-D (EB-3)

- **Other recommended regimens**
  - **Lenalidomide maintenance[e]**
  - **Ofatumumab maintenance (category 2B)**

See Suggested Regimens for CLL/SLL with del(17p) (3 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 (CSLL-F).
[e] Minimal residual disease (MRD) evaluation with a sensitivity of 10^{-4} according to the standardized ERIC method.
[f] 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.
[g] See Discussion for further information on oral fludarabine.
[h] Rituximab and hyaluronidase human injection for subcutaneous use may be used for CLL in combination with fludarabine and cyclophosphamide (FC) regimen after patients have received at least one full dose of a rituximab product by intravenous route.
[j] 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.)
[k] Particularly for patients deemed intolerant or refractory to ibrutinib or idelalisib.
[l] See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[m] 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.
[n] 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.

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CSLL-D

EVIDENCE BLOCKS FOR RELAPSED/REFRACTORY THERAPY FOR CLL/SLL WITHOUT del(17p)/TP53 MUTATION

Frail Patient with Significant Comorbidity and Patients ≥65 y or Younger Patients with Significant Comorbidities

Preferred Regimens	
Ibrutinib	
Idelalisib + rituximab	
Venetoclax	
Venetoclax + rituximab	

Other Recommended Regimens	
Idelalisib	
Reduced-dose FCR	
Reduced-dose PCR	
High-dose methylprednisolone (HDMP) + rituximab	
Rituximab + chlorambucil	
Ofatumumab	
Obinutuzumab	
Lenalidomide	
Lenalidomide + rituximab	
Alemtuzumab	
Alemtuzumab + rituximab	
Dose-dense rituximab	
Bendamustine + rituximab	
Bendamustine, rituximab and ibrutinib	
Bendamustine, rituximab and idelalisib	

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E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent
E S Q C A
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EVIDENCE BLOCKS FOR RELAPSED/REFRACTORY THERAPY FOR CLL/SLL WITHOUT del(17p)/TP53 MUTATION

Patients <65 y without Significant Comorbidities

Preferred Regimens	
Ibrutinib	
Idelalisib + rituximab	
Venetoclax	
Venetoclax + rituximab	

Other Recommended Regimens	
Idelalisib	
Fludarabine, cyclophosphamide, and rituximab (FCR)	
Fludarabine, cyclophosphamide, and ofatumumab	
Pentostatin, cyclophosphamide, and rituximab (PCR)	
Bendamustine + rituximab	
High-dose methylprednisolone (HDMP) + rituximab	
Ofatumumab	
Obinutuzumab	
Lenalidomide	
Lenalidomide + rituximab	
Alemtuzumab	
Alemtuzumab + rituximab	
Bendamustine, rituximab and ibrutinib	
Bendamustine, rituximab and idelalisib	

Post Second-Line Maintenance Therapy

Lenalidomide maintenance	
Ofatumumab maintenance	

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CSLL-D

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SUGGESTED TREATMENT REGIMENS[a,b]
CLL/SLL with del(17p)/*TP53* mutation

First-line Therapy
- Preferred regimen
  - Ibrutinib[c]
- Other recommended regimens
  - HDMP + rituximab
  - Obinutuzumab
  - Alemtuzumab[n] ± rituximab

Post First-line Maintenance Therapy
- Other recommended regimen
  - Consider lenalidomide maintenance for high-risk patients (blood MRD ≥10^{-2} or ≥10^{-4} and <10^{-2} with unmutated IGHV or del(17p)/TP53 mutation)[e] after first-line therapy (category 3)

Relapsed/Refractory Therapy
- Preferred regimens
  - Ibrutinib[c]
  - Venetoclax[c,l] ± rituximab
  - Idelalisib + rituximab[c,j]
- Other recommended regimens
  - Idelalisib[c]
  - HDMP + rituximab
  - Lenalidomide[m] ± rituximab
  - Alemtuzumab[n] ± rituximab
  - Ofatumumab[o]

Post Second-line Maintenance Therapy
(for complete or partial response after relapsed or refractory therapy)
- Other recommended regimens
  - Lenalidomide maintenance[e]
  - 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)

See Evidence Blocks on CSLL-D (EB-4)

[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 (CSLL-F).
[e]Minimal residual disease (MRD) evaluation with a sensitivity of 10^{-4} according to the standardized ERIC method.
[l]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.)
[l]See Venetoclax: Recommended TLS Prophylaxis and Monitoring Based on Tumor Burden (CSLL-G).
[m]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.
[n]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.
[o]This is not effective in patients with lymph nodes >5 cm.

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E S Q C A

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EVIDENCE BLOCKS FOR THE TREATMENT OF CLL/SLL WITH del(17p)/TP53 MUTATION

First-line Therapy

Preferred Regimen	
Ibrutinib	
Other Recommended Regimens	
HDMP + rituximab	
Obinutuzumab	
Alemtuzumab	
Alemtuzumab + rituximab	

Post First-line Maintenance Therapy

Lenalidomide maintenance	

Relapsed/Refractory Therapy

Preferred Regimen	
Ibrutinib	
Venetoclax	
Venetoclax + rituximab	
Idelalisib + rituximab	
Other Recommended Regimens	
Idelalisib	
HDMP + rituximab	
Lenalidomide	
Lenalidomide + rituximab	
Alemtuzumab	
Alemtuzumab + rituximab	
Ofatumumab	

Post Second-line Maintenance Therapy

Lenalidomide maintenance	
Ofatumumab maintenance	

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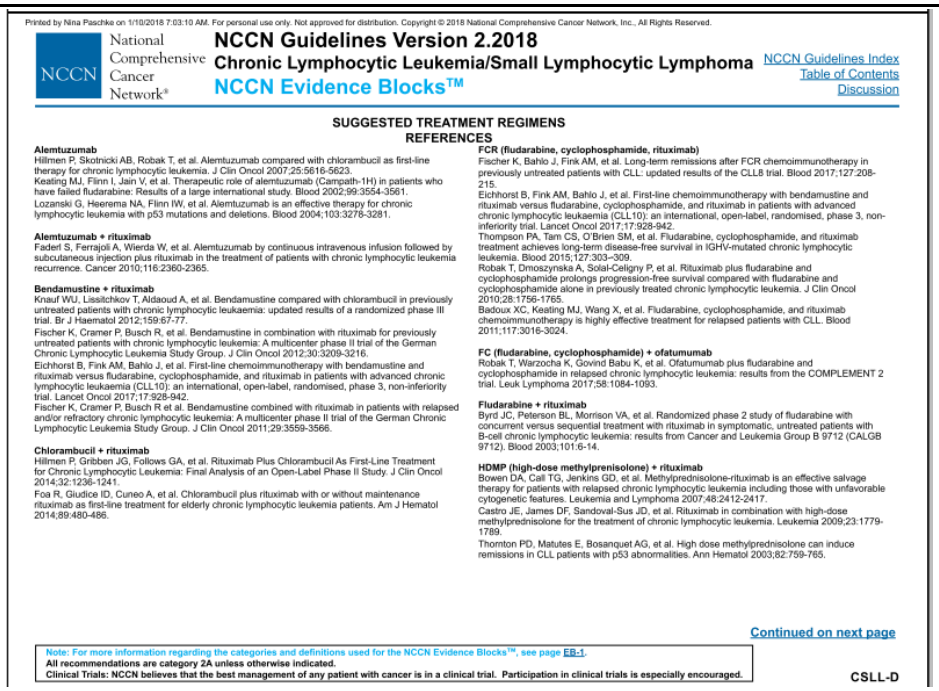

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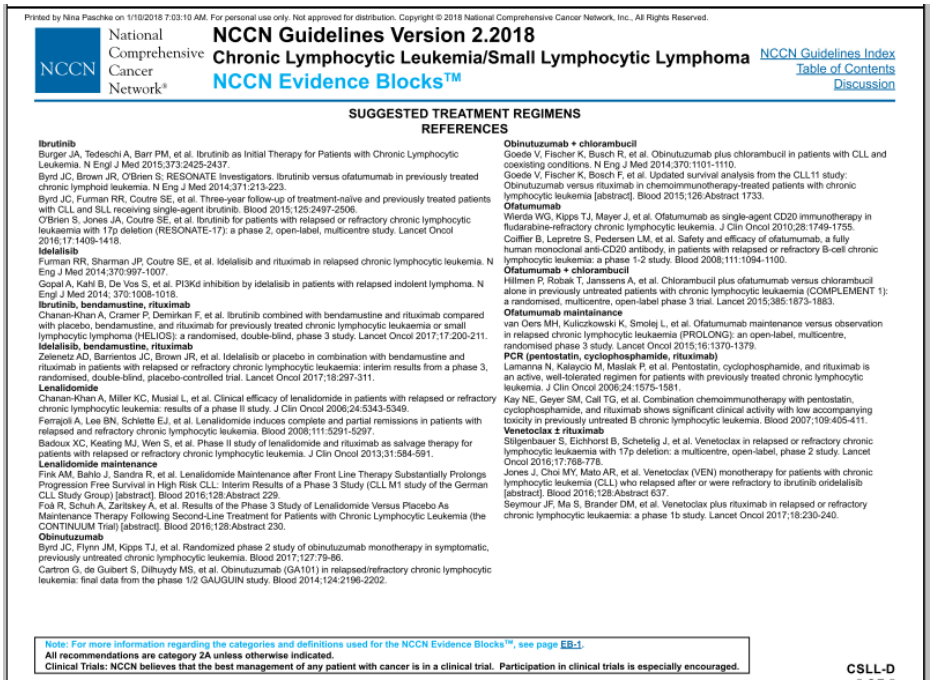

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CSLL-D

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.

Ibrutinib:

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.

Idelalisib +/-Rituximab:

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 [27]. Rituximab in Lymphoma and Chronic Lymphocytic Leukaemia: A Practice Guideline **siehe auch Prica A et al., 2015 [28].**	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 10/2013 LoE/GoR: über Formulierungen abgebildet
	Freitext/Empfehlungen/Hinweise **Recommendation 3** <u>Chronic lymphocytic leukemia/small lymphocytic lymphoma: Patients with Relapsed/Refractory Disease</u> 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** <u>Patients with Relapsed/Refractory Disease</u> 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

<table>
<tr><td></td><td>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.</td></tr>
<tr><td rowspan="2">Garcia-Marco JA et al., 2017 [2].

Update of the Grupo Espanol de Leucemia Linfocitica Cronica clinical guidelines of the management of chronic lymphocytic</td><td>Fragestellung

The broad therapeutic arsenal and the biological heterogeneity of patients with chronic lymphocytic leukemia (CLL) makes it difficult to standardize treatment for CLL patients with specific clinical settings in routine clinical practice. These considerations prompted us to elaborate the present consensus document, which constitutes an update of the previous version published in 2013, mainly focusing on novel treatment strategies that have been developed over last 5 years, namely B-cell receptor inhibitors (ibrutinib and idelalisib), anti-CD20 monoclonal antibodies (ofatumumab and obinutuzumab), and Bcl-2 inhibitors (venetoclax).</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie: To obtain a consensus document with the most up-to-date information, we reviewed the studies published in the MEDLINE and EMBASE databases and the abstracts reported at the annual meeting of the American Society of Hematology (2015). This document is an update of the guidelines published in 2013.

Suchzeitraum: from 2010 until 01/2016

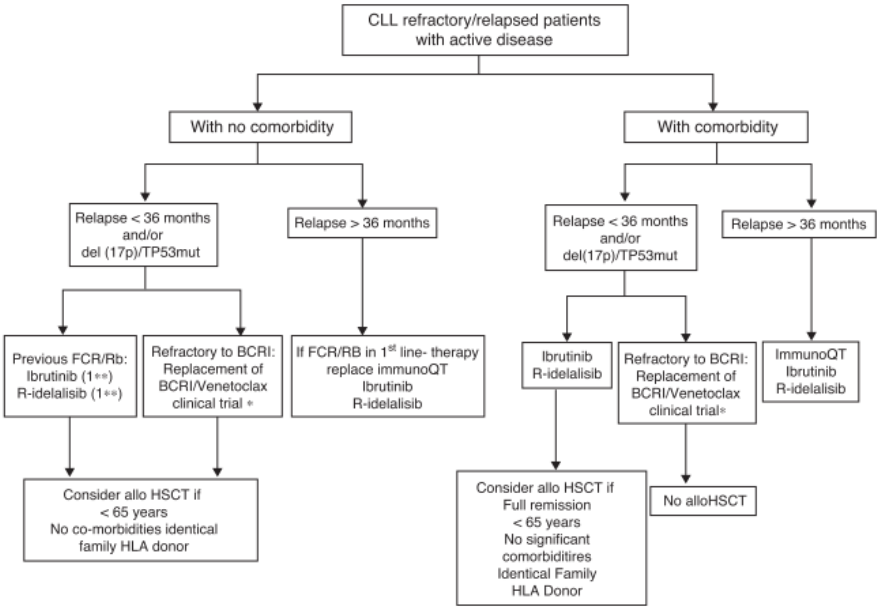
LoE/GoR:

Levels of evidence and degrees of recommendation

<table>
<tr><th colspan="2">Level of evidence</th></tr>
<tr><td>Level 1a</td><td>Meta-analysis of well-designed, randomized, controlled clinical trials</td></tr>
<tr><td>Level 2b</td><td>At least one randomized controlled trial</td></tr>
<tr><td>Level 2a</td><td>At least one well-designed randomized controlled trial</td></tr>
<tr><td>Level 2b</td><td>At least one non-fully experimental, well-designed study, such as cohort studies</td></tr>
<tr><td>Level 3</td><td>Well-designed non-experimental descriptive</td></tr>
</table>
</td></tr>
</table>

	studies such as comparative studies, correlation studies or case-control studies
Level 4	Documents or opinions of expert committees or clinical experiences from prestigious authorities or case series studies
Degrees of recommendation	
Category 1	Available evidence is high quality evidence and there is consensus among experts
Category 2A	Available evidence is moderate quality evidence and there is consensus among experts
Category 2B	Available evidence is moderate quality evidence and there is no unanimous consensus among experts
Category 3	Available evidence is of any degree and there is no consensus among experts

Freitext/Empfehlungen/Hinweise



Algorithm for the treatment of refractory and relapsed patients.
AlloHSCT: allogeneic haematopoietic stem cell transplantation; FCR: fludarabine, cyclophosphamide and rituximab; HLA: human leukocyte antigens; BCRI: B-cell receptor inhibitors; ImmunoQT: immunochemotherapy; CLL: chronic lymphocytic leukemia; R: rituximab; RB: rituximab-bendamustine. *Expert group recommendation. ** Level of evidence (the level is shown in brackets).

	Treatment of refractory and relapsed patients In accordance with iwCLL criteria, refractoriness is defined as the lack of response to treatment or disease progression within 6 months following the last therapy received. In the choice of treatment of these patients, associated comorbidity and presence of del(17p) or TP53mut (level of evidence 2) should be taken into account:[35] Patients without comorbidity: the recommendation is to obtain the best possible clinical response and to consider the allogeneic hematopoietic stem cell transplantation (allo-HSCT), depending on the risk factors of the patient.25 Treatment with ibrutinib or rituximab-idelalisib is recommended in refractory patients (purine analogs, bendamustine), regardless of the occurrence of del(17p)/TP53mut (level of evidence 1b).[27,28] Administering venetoclax or acalabrutinib should be evaluated in patients refractory to ibrutinib/rituximab-idelalisib (level of evidence 2a).[36,37] When BCR or Bcl-2 inhibitors are contraindicated, the most accepted treatment is alemtuzumab alone or in combination (with steroids, for example) (level of evidence 2b).[31,37] The therapeutic objective for patients with comorbidities is to control the symptomatology and maintain an optimal quality of life. The treatment of choice is ibrutinib or rituximab-idelalisib. Alemtuzumab, with or without corticosteroids, can be used in specific situations, although with caution given the risk of toxicity (infections). The most recommended treatment options for patients without comorbidities are RB and FCR. RB treatment is recommended in patients without del(17p) or TP53mut and relapse beyond 36 months of first-line treatment with FCR. In those patients who did not receive first-line FCR, this treatment could be administered as a rescue regimen in the first relapse (level of evidence 1b) (Fig. 2).[38] In the case of early relapse (<12 months after immunochemotherapy) rescue therapy with BCR inhibitors (ibrutinib, rituximab-idelalisib) and consolidation with allo-HSCT is recommended. We should note that retreatment with fludarabine-based regimens causes bone marrow toxicity problems. The most frequent recommendations for patients with comorbidities are rituximab-Clb and RB. Other options, such as ibrutinib or rituximab-idelalisib, should be considered in patients with del(17p)/TP53mut. Recently, the European Society for Medical Oncology has recommended to repeat first-line therapy in those patients who have relapsed or progressed at least 24–36 months after immunochemotherapy, regardless of their comorbidity and without the presence of del(17p)/MutTP53 (level of evidence 3).[39.40] However, our consensus group has agreed that under this situation the recommendation should include replacing by a second-line therapy, such as ibrutinib, rituximab-idelalisib and Bcl-2 antagonists

(level of evidence 3).[27,28] In addition, when patients fail to respond or the disease progresses with a BCR inhibitor, this inhibitor may be replaced by alternative BCR inhibitors (ibrutinib to rituximab-idelalisib or vice versa, acalabrutinib) or Bcl-2 antagonist (venetoclax), if appropriate, (level of evidence 2a, grade 2B recommendation; consensus recommendation based on clinical experience following use of AbbVie, Janssen, and Gilead research drug access programs).

27. 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;371:213–23.

28. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014;370:997–1007.

35. Gonzalez D, Martinez P, Wade R, Hockley S, Oscier D, Matutes E, et al. Mutational status of the TP53 gene as a predictor of response and survival in patients with chronic lymphocytic leukemia: results from the LRF CLL4 trial. J Clin Oncol.2011;29:2223–9.

36. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:311–22.

37. Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:323–32.

38. Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010;28:1756–65.

40. Cramer P, Isfort S, Bahlo J, Stilgenbauer S, Döhner H, Bergmann M, et al. Outcome of advanced chronic lymphocytic leukemia following different first-line and relapse therapies: a meta-analysis of five prospective trials by the German CLL Study Group (GCLLSG). Haematologica. 2015;100:1451–9.

Hematopoietic stem cell transplantation

The use of autologous transplantation (auto-HSCT) should be individualized. The ideal candidate is the patient with poor prognosis, without a donor of identical, family or nonrelated human leukocyte antigens (HLA), (level of evidence 3). By auto-HSCT, the PFS can be extended, although it has no effect on the OS.[41] The current indication for allo-HSCT includes patients at high-risk CLL (del[17p]/TP53mut) who have obtained clinical response after receiving first-line or relapsed BCR inhibitors (ibrutinib, idelalisib) (Fig. 2). Patients below 65 years old, with an identical HLA family donor and presence of del(17p)/TP53mut should be offered allo-HSCT in the first clinical response to new drugs and evaluating the

	pros and cons of the procedure (age, associated comorbidities, adverse allo-HSCT factors, such as availability of donor type). In turn, patients should consider allo-HSCT after rescue therapy with any other BCR inhibitor or venetoclax. Younger patients with refractoriness or early relapse to first-line immunochemotherapy (including purine analogs) should be treated with BCR inhibitors and should be offered allo-HSCT depending on the degree of clinical response, adverse factors of allo-HSCT and patient preferences (level of evidence 3).[42] On the contrary, patients with high-risk, advanced, co-morbidities, and non-HLA-identical family donors should be treated with new drugs (ibrutinib, idelalisib) until relapse. Then, allo-HSCT should be evaluated after response to rescue therapy with any alternative BCR inhibitor or venetoclax. 41. Dreger P, Döhner H, McClanahan F, Busch R, Ritgen M, Greinix H, et al. Early autologous stem cell transplantation for chronic lymphocytic leukemia: long-term follow-up of the German CLL Study Group CLL3 trial. Blood. 2012;119:4851–9. 42. Dreger P, Corradini P, Kimby E, Michallet M, Milligan D, Schetelig J, et al. Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus. Leukemia. 2007;21:12–7.
Kharfan-Dabaja MA et al., 2016 [20]. 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 05/2015 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.“*

	Freitext/Empfehlungen/Hinweise 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 considers purine analogue relapsed and/or refractory disease high-risk disease but not 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)

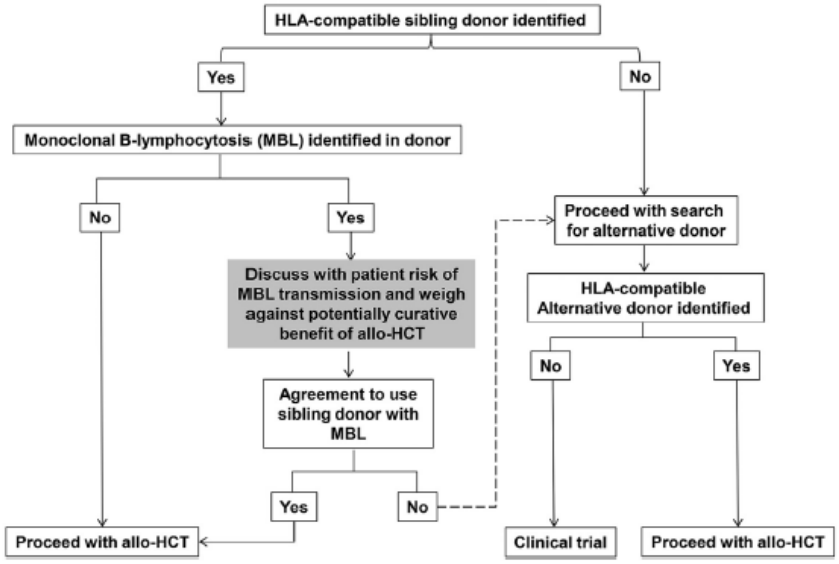


Figure 1. Donor selection in the presence of MBL in HLA-compatible sibling donors.

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.*

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Clinical Excellence (NICE), 2015 [25]. Idelalisib for treating chronic lymphocytic leukaemia TA359	Recommendations 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.
National Institute for Health and Clinical Excellence (NICE), 2017 [24]. Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic	Recommendations 1.1 Ibrutinib alone is recommended within its marketing authorisation as an option for treating chronic lymphocytic leukaemia in adults: • who have had at least 1 prior therapy or • who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable and • only when the company provides ibrutinib with the discount agreed in the patient access scheme. The committee concluded that idelalisib plus rituximab was the most relevant comparator and, for those who cannot take idelalisib plus rituximab, best supportive care was the best comparator in both

lymphocytic leukaemia with 17p deletion or TP53 mutation	populations. The committee was aware that it had not been presented with evidence comparing ibrutinib with best supportive care. The committee concluded that ibrutinib offered a more preferable toxicity profile, and was likely to offer progression-free and overall survival benefits compared with idelalisib plus rituximab, but was mindful that the extent of this benefit was uncertain. No evidence was presented for ibrutinib compared with best supportive care. However, the committee concluded that it was likely that ibrutinib would be more effective compared with best supportive care than when compared with idelalisib plus rituximab. The committee agreed that ibrutinib represented an important and effective treatment in CLL. It was satisfied that, in both populations of this appraisal, the incremental cost-effectiveness ratios (ICERs) for ibrutinib fell within the range normally considered as a cost-effective use of NHS resources for a treatment that fulfils the end-of-life criteria, when incorporating the confidential updated patient access scheme for ibrutinib and the existing patient access scheme for idelalisib. **Current practice (Clinical need of patients, including the availability of alternative treatments)** The committee heard from clinical and patient experts that current treatment options are associated with significant adverse effects that are often life threatening. The committee understood the importance of the availability of different treatment options for treating CLL. The committee concluded that idelalisib plus rituximab was the most relevant comparator in clinical practice for patients who had relapsed within 2 years and, for those who cannot take idelalisib plus rituximab, best supportive care was the alternative.
National Institute for Health and Clinical Excellence (NICE), 2017 [26]. Venetoclax for treating chronic lymphocytic leukaemia	Recommendations 1.1 Venetoclax is recommended for use within the Cancer Drugs Fund, within ist marketing authorisation, as an option for treating chronic lymphocytic leukaemia, that is, in adults: • with a 17p deletion or TP53 mutation and when a B-cell receptor pathway inhibitor is unsuitable, or whose disease has progressed after a B-cell receptor pathway inhibitor or • without a 17p deletion or TP53 mutation, and whose disease has progressed after both chemo-immunotherapy and a B-cell receptor pathway inhibitor and • only if the conditions in the managed access agreement are followed. **Current practice (Clinical need of patients, including the availability of alternative treatments)** The committee heard that current treatments are associated with adverse reactions, and that because many people diagnosed with CLL are older and may have comorbidities, many of these treatments are

	often not tolerated. The clinical expert stated that, once treatment options have been exhausted, prognosis is poor.
Grössmann N et al., 2016 [11]. 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

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 12.01.2018

#	Suchfrage
#1	MeSH descriptor: [Leukemia, Lymphocytic, Chronic, B-Cell] explode all trees
#2	Chronic:ti,ab,kw or b-cell:ti,ab,kw
#3	lymphocytic:ti,ab,kw or lymphoid*:ti,ab,kw or lymphatic*:ti,ab,kw or lymphoblastic:ti,ab,kw or Lymphoplasmacytoid:ti,ab,kw
#4	leukemia*:ti,ab,kw or leukaemia*:ti,ab,kw
#5	#2 and #3 and #4
#6	CLL:ti,ab,kw
#7	#1 or #5 or #6
#8	#7 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 12.01.2018

#	Suchfrage
1	Leukemia, Lymphocytic, Chronic, B-Cell[MeSH Terms]
2	(Chronic[Title/Abstract]) OR "b-cell"[Title/Abstract]
3	(((((lymphocytic[Title/Abstract]) OR lymphoid*[Title/Abstract]) OR lymphatic*[Title/Abstract]) OR lymphoblastic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract])
4	((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
5	(#2 AND #3 AND #4)
6	CLL[Title/Abstract]
7	(#1 OR #5 OR #6)
8	(#7) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
9	(#7) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
10	(#8 OR #9)
11	(#10) AND ("2013/01/01"[PDAT] : "2018/01/12"[PDAT])

12	(#11) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 12.01.2018

#	Suchfrage
1	Leukemia, Lymphocytic, Chronic, B-Cell[MeSH Terms]
2	Lymphoma, Non-Hodgkin[mh:noexp] OR Lymphoma, B-Cell[mh:noexp]
3	(Chronic[Title/Abstract]) OR “b-cell”[Title/Abstract]
4	(((((lymphocytic[Title/Abstract]) OR lymphoid*[Title/Abstract]) OR lymphatic*[Title/Abstract]) OR lymphoblastic[Title/Abstract]) OR lymphoplasmacytoid[Title/Abstract])
5	((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
6	(#3 AND #4 AND #5)
7	CLL[Title/Abstract]
8	((Non-Hodgkin*[Title] OR "b-cell"[Title])) AND lymphoma*[Title]
9	(#1 OR #2 OR #6 OR #7 OR #8)
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
11	(#10) AND ("2013/01/01"[PDAT] : "2018/01/12"[PDAT])

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