Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-10-01-D-262 Ibrutinib (nAWG)

Stand: Juli 2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Ibrutinib **[als Monotherapie und in Kombination mit Bendamustin/Rituximab zur Therapie der vorbehandelten CLL]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- allogene Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss vom 5. Februar 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Obinutuzumab Beschluss vom 19. März 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Idelalisib Beschluss vom 16. April 2015 über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ibrutinib
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ibrutinib	Zugelassenes Anwendungsgebiet: „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."
Zytostatische Wirkstoffe	
Bendamustin L01AA09 Levact®	Primärtherapie bei chronisch-lymphatischer Leukämie (Binet-Stadium B oder C) bei Patienten, bei denen eine Fludarabin-Kombinations-Chemotherapie ungeeignet ist. Monotherapie bei indolenten Non-Hodgkin-Lymphomen bei Patienten mit Progression während oder innerhalb von 6 Monaten nach Behandlung mit Rituximab oder mit einer Rituximab-haltigen Therapie. (FI Levact®, November 2014)
Chlorambucil L01AA02 Leukeran®	Chronisch lymphatische Leukämie (FI Leukeran®, Juli 2014)
Cyclophosphamid L01AA01 generisch	Cyclophosphamid kann, abhängig von der Indikation, alleine oder in Kombination mit anderen Chemotherapeutika angewendet werden. Cyclophosphamid ist angezeigt zur Behandlung von: - Chronischer lymphatischer Leukämie (CLL) - […] (AMIS-Eintrag Cyclophosphamid HEXAL 1000 mg)
Fludarabin L01BB05 generisch	Therapie der chronischen-lymphatischen Leukämie (CLL) vom B-Zell-Typ bei Patienten mit ausreichender Knochenmarksreserve. Die First-Line-Therapie mit Bendarabin 50 mg sollte nur bei Patienten mit fortgeschrittener Erkrankung begonnen werden, einhergehend mit krankheitsbedingten Symptomen oder dem Nachweis der fortgeschrittenen Erkrankung. (FI Bendarabin®, September 2014)
B-Zell-Rezeptor-Inhibitoren	
Ibrutinib L01XE27 Imbruvica®	IMBRUVICA ist indiziert zur Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinien-Therapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemo-Immuntherapie nicht geeignet sind. […] (FI Imbruvica®, Juli 2015)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Idelalisib L01XX47 Zydelig®	Zydelig wird in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) angewendet: • die mindestens eine vorangehende Therapie erhalten haben, oder • ~~als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, die für eine Chemoimmuntherapie ungeeignet sind.~~ (FI Zydelig®, Juli 2015)
Glucocorticoide	
Prednisolon H02AB06 generisch	Hämatologie/Onkologie: Chronisch lymphatische Leukämie (FI Dermosolon®, August 2011)
Prednison H02AB07 generisch	Hämatologie/Onkologie: Chronisch lymphatische Leukämie (FI Cutason®, Februar 2015)
Anti-CD20-Antikörper	
Rituximab L01XC02 MabThera®	MabThera ist in Kombination mit einer Chemotherapie für die Behandlung von nichtvorbehandelten Patienten und von Patienten mit rezidivierender/refraktärer chronischer lymphatischer Leukämie angezeigt. Für Patienten, die bereits mit monoklonalen Antikörpern einschließlich MabThera behandelt wurden oder für Patienten, die refraktär auf eine vorherige Behandlung mit MabThera in Kombination mit Chemotherapie sind, liegen nur begrenzte Daten zur Wirksamkeit und Sicherheit vor. (FI MabThera®, Mai 2014)
Ofatumumab L01XC10 Arzerra®	Nicht vorbehandelte chronische lymphatische Leukämie (CLL): Arzerra in Kombination mit Chlorambucil oder Bendamustin ist angezeigt für die Behandlung von Patienten mit CLL, die noch keine vorangegangene Therapie hatten und die nicht für eine Fludarabin-basierte Therapie geeignet sind. (FI Arzerra®, Juli 2014)
Obinutuzumab L01XC15 Gazyvaro®	Gazyvaro® in Kombination mit Chlorambucil wird bei erwachsenen Patienten mit nicht vorbehandelter chronischer lymphatischer Leukämie (CLL) angewendet, die aufgrund von Begleiterkrankungen für eine Therapie mit einer vollständigen Dosis von Fludarabin nicht geeignet sind (siehe Abschnitt 5.1). (FI Gazyvaro®, Mai 2015)
Weitere Arzneimittel mit Zulassung für Non-Hodgkin-Lymphome	
Zytostatische Wirkstoffe	
Doxorubicin L01DB01 generisch	Non-Hodgkin-Lymphom (FI Adrimedac®, September 2013)
Trofosfamid L01AA07 Ixoten®	Ixoten wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet. (FI Ixoten®, Januar 2015)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Vinblastin L01CA01 Vinblastinsulfat Teva®	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: - maligne Non-Hodgkin-Lymphome (FI Vinblastinsulfat Teva®, Februar 2014)
Vincristin L01CA02 generisch	Vincristinsulfat-Teva® wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen (FI Vincristinsulfat-Teva®, September 2011)

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT) nach § 35a SGB V:

Inhalt

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „chronische lymphatische Leukämie“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 01.06.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, 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 535 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 16 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation

Kombinationstherapie von Ibrutinib mit Bendamustin/Rituximab bei erwachsenen CLL-Patienten, die mindestens eine vorangehende Therapie erhalten haben und für die eine Chemotherapie angezeigt ist.

Berücksichtigte Wirkstoffe/Therapien

Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Abkürzungen

AC	Advisory Council
AE	Adverse Events
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AWG	Anwendungsgebiet
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ASCO	American Society of Clinical Oncology
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BUB	Bewertung ärztlicher Untersuchungs- und Behandlungsmethoden
BCSH	British Committee for Standards in Haemotology
BR	Bendamustine / Rituximab
CCO	Cancer Care Ontario
CDEC	Canadian Drug Expert Committee
CI	Confidence Intervall
CLB oder Clb	Chlorambucil
CLL	Chronic Lymphocytic Leukemia
CRR	Complete Response Rate
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
EFS	Event-free Survival
EMBASE	Excerpta Medica Database
EP	Expert Panel
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EURETINA	European Society of Retina Specialists
FAS	Full Analysis Set
FC oder FluC	Fludarabine + Cyclophosphamide
FluCM	Fludarabine + Cyclophosphamide + Mitochantrone
FluCM-R	Fludarabine + Cyclophosphamide + Mitochantrone + Rituximab
FCR oder FluC-R	Fludarabine + Cyclophosphamide + Rituximab
FDA	Food and Drug Administration
FL	Follicular Lymphoma
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GITMO	Gruppo Italiano Trapianto di Midollo Osseo
GoR	Grade of Recommendation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment
ICTRP	International Clinical Trials Registry Platform
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISRCTN	International Standard Randomised Controlled Trial Number
LILACS	Latin American and Caribbean Health Sciences
LOCF	Last Observation Carried Forward
LoE	Level of Evidence
LS	Lesion Size
MCL	Mantel Cell Lymphoma
MD	Mean Difference
mRCT	metaRegister of Controlled Trials
MRD	Minimal Residual Disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
PEBC	Program in Evidence-Based Care
PFS	Progression-free Survival
PPS	Per Protocol Analysis Set
QoL	Quality of Life
RCT	Randomized Controlled Trial
RD	Response Duration
RR	Relatives Risiko
SAE	Serious Adverse Events
SCT	Stem Cell Transplantation
SD	Standard Deviation
SGB	Sozialgesetzbuch
SIE	Italian Societey of Hematology
SIES	Società Italiana di Ematologia Sperimentale
SIGN	Scottish Intercollegiate Guidelines Network
TEAE	Treatment-emergent Adverse Events
TRIP	Turn Research into Practice Database
TRM	Treatment-related Mortality
TTF	Time to Treatment Failure
WDAE	Withdrawal Due to Adverse Event
WHO	World Health Organization
WMD	Weighted Mean Difference

Gemeinsamer Bundesausschuss (G-BA), 2015 [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 Stand: 16. April 2015 vgl. auch - **G-BA 2015 [7].** - **IQWiG 2016 [8].**	**Zugelassenes Anwendungsgebiet:** Anwendungsgebiet 1: Ibrutinib (IMBRUVICA®) ist indiziert zur Behandlung erwachsener Patienten mit rezidiviertem oder refraktärem Mantelzell-Lymphom (MCL). Anwendungsgebiet 2: IMBRUVICA® ist indiziert zur Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben, oder zur Erstlinien-Therapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemo-Immuntherapie nicht geeignet sind. **Ausmaß des Zusatznutzens** Anwendungsgebiet 1: Behandlung erwachsener Patienten mit rezidiviertem oder refraktärem Mantelzell-Lymphom (MCL) - Nicht quantifizierbar. Anwendungsgebiet 2: a) Behandlung erwachsener Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben - Nicht quantifizierbar. b) Erstlinien-Therapie bei Patienten mit einer 17p-Deletion oder einer TP53-Mutation, die für eine Chemo-Immuntherapie nicht geeignet sind - Nicht quantifizierbar.
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 – Idelalisib Stand: 19. März 2015 vgl. auch **IQWiG 2014[9].**	**Zugelassenes Anwendungsgebiet:** Idelalisib (Zydelig®) wird in Kombination mit Rituximab zur Behandlung von erwachsenen Patienten mit chronischer lymphatischer Leukämie (CLL) angewendet: - die mindestens eine vorangehende Therapie erhalten haben, oder - als Erstlinientherapie bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, die für eine Chemoimmuntherapie ungeeignet sind. Idelalisib (Zydelig®) wird als Monotherapie zur Behandlung von erwachsenen Patienten mit follikulärem Lymphom (FL), das refraktär gegenüber zwei vorausgegangenen Therapielinien ist, angewendet. **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** Anwendungsgebiet 1: Zur Behandlung von Patienten mit chronischer lymphatischer Leukämie (CLL), die mindestens eine vorangehende Therapie erhalten haben. *Teilpopulation 1a:* Patienten mit rezidivierender CLL, für die eine Chemotherapie angezeigt ist. Zweckmäßige Vergleichstherapie:

	- Eine Chemotherapie in Kombination mit Rituximab nach Maßgabe des Arztes, unter Beachtung des Zulassungsstatus Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Chemotherapie in Kombination mit Rituximab: Da erforderliche Nachweise nicht vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V). *Teilpopulation 1b:* Patienten mit rezidivierender CLL, für die eine Chemotherapie nicht angezeigt ist. Zweckmäßige Vergleichstherapie: - Best-Supportive-Care Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen *Teilpopulation 1c:* Patienten mit refraktärer CLL, für die eine Chemotherapie oder Therapie mit Ofatumumab angezeigt ist. Zweckmäßige Vergleichstherapie: - Eine patientenindividuelle, optimierte Therapie nach Maßgabe des Arztes, unter Beachtung des Zulassungsstatus Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer patientenindividuellen, optimierten Therapie: Da erforderliche Nachweise nicht vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V). *Teilpopulation 1d:* Patienten mit refraktärer CLL, für die eine Chemotherapie oder Therapie mit Ofatumumab nicht angezeigt ist. Zweckmäßige Vergleichstherapie: - Best-Supportive-Care Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: Da erforderliche Nachweise nicht vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V). Anwendungsgebiet 2: Zur Erstlinientherapie der chronischen lymphatischen Leukämie (CLL) bei Vorliegen einer 17p-Deletion oder einer TP53-Mutation bei Patienten, die für eine Chemoimmuntherapie ungeeignet sind. Zweckmäßige Vergleichstherapie: - Best-Supportive-Care Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care: Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen Anwendungsgebiet 3: Zur Behandlung von Patienten mit follikulärem Lymphom (FL),

	das refraktär gegenüber zwei vorausgegangenen Therapielinien ist. Zweckmäßige Vergleichstherapie: - Best-Supportive-Care <u>Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Best-Supportive-Care:</u> Da erforderliche Nachweise nicht vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V).

Bauer K et al., 2012 [2]. Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia.	**1. Fragestellung** The objective of this review is to assess and summarise the evidence for the treatment of patients with CLL with monoclonal anti-CD20 antibodies.
	2. Methodik Population: CLL, pre-treated and chemotherapy-naive patients Intervention: Anti-CD20 antibody (rituximab, ofatumumab) given alone or in combination with chemotherapy as primary treatment or maintenance treatment Komparator: 'Watchful waiting' and conventional therapies such as fludarabine or Clb monotherapy, fludarabine in combination with other chemotherapeutic agents, or other antibody therapy. Kombinationen: 1. Anti-leukaemic therapy plus anti-CD20 antibody versus anti-leukaemic therapy alone; anti-leukaemic therapy identical in both groups. 2. Anti-leukaemic therapy with anti-CD20 antibody versus anti-leukaemic therapy without anti-CD20 antibody (antileukaemic therapy not identical in both groups). 3. Different dosages or times of anti-CD20 antibody (with or without identical chemotherapy in both arms). We did not identify any trial regarding the comparison of anti-CD20 antibody versus anti-leukaemic therapy. Endpunkte: Primär: OS Sekundär: PFS, time to next treatment, treatment-related mortality (TRM), complete response rate (CRR), overall response rate (ORR), minimal residual disease (MRD), adverse events (AE), number of patients discontinuing the study because of drug-related AEs Suchzeitraum: 1990 – 2012 in Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE as well as conference proceedings (American Society of Hematology, American Society of Clinical Oncology, European Hematology Association and European Society of Medical Oncology) for randomised controlled trials (RCTs) Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 RCT (n = 1.763 Patienten). Three trials with 1.421 participants provided information regarding outcome OS (2 trials with relapsed or refractory patients) Qualitätsbewertung der Studien: - To assess quality and risk of bias, we used a questionnaire (validity assessment form) containing the items as suggested in the Cochrane Handbook for Systematic Reviews of Interventions. - Heterogeneity: Because of the small number of studies in each analysis (two), the quantification of heterogeneity was not reliable, since the Cis were very wide. In meta-analyses with more trials, we would have assessed heterogeneity of treatment effects between trials… We explored potential causes of heterogeneity by sensitivity and subgroup

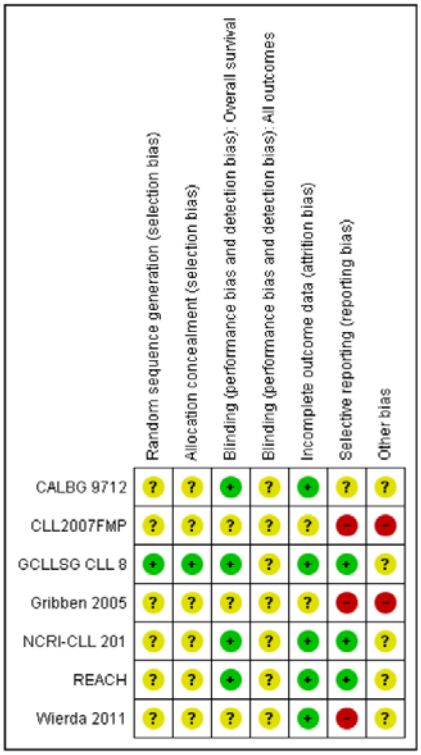
analyses.

- Sensitivity analysis: We did not perform any sensitivity analysis, because all these trials showed no differences regarding publication form (full-text publications/abstracts), type of results (preliminary results/mature results) or quality issues.

3. Ergebnisdarstellung

- Overall the quality of included trials was moderate to high. Two included trials were published as abstracts only (CLL2007FMP; Gribben 2005), therefore we were unable to assess the potential risk of bias for these trials in detail.

  Risk of bias



- Three trials included relapsed or refractory patients (Gribben 2005; NCRI-CLL 201; REACH)
- Four trials evaluated the anti-CD20 antibody in patients receiving first-line therapy.
- Risk of Bias: Gribben 2005 – unclear; NCRI-CLL 201 und REACH – low
- 3 eingeschlossene Studien (für rezidivierende CLL), davon 1 Studie nur als Abstract (n = 12): gesamt eingeschlossene Patienten n = 604 (aus 2 Studien mit Vollpublikation):
- NCRI-CLL 201 [previously treated with ≥ 1 chemotherapeutic regimen, WHO performance status 0 to 2; FluCM-R vs. FluCM; (n = 52)];
- REACH [minimum 1 lone treatment of the CLL; FluC-R vs. FluCM; n = 552])

- <u>Ergebnisse</u>

  Meta-analysis NCRI-CLL 201 and REACH

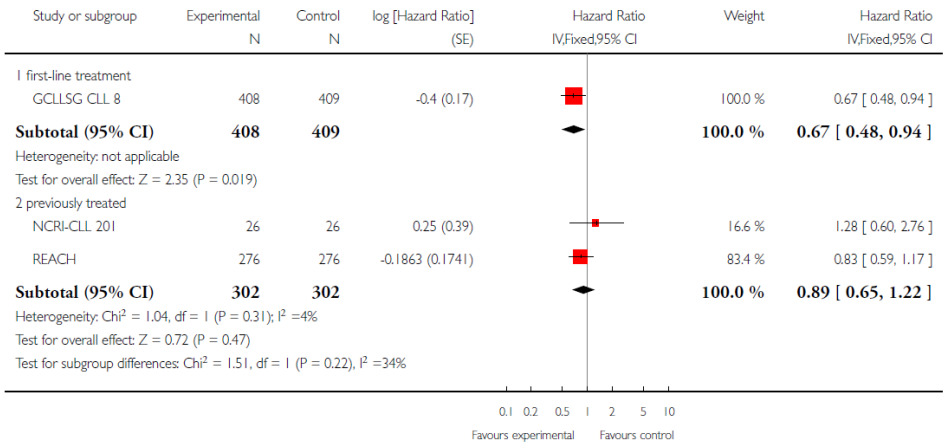
  <u>Overall survival</u>

Analysis 1.2. Comparison 1 Anti-leukaemic therapy plus anti-CD20 versus anti-leukaemic therapy alone (anti-leukaemic therapy identical in both groups), Outcome 2 OS - subgrouped by different anti-CD20 antibody treatment regimens.

Review: Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia

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

Outcome: 2 OS - subgrouped by different anti-CD20 antibody treatment regimens



Progression-free survival – subgrouped by different anti-CD20 antibody treatment regimens: Meta-analysis previously treated patients: HR: 0.75 [0.61; 0.94], p = 0.012.

Treatment-related mortality – subgrouped by different anti-CD20 antibody treatment regimens. Meta-analysis previously treated patients: Risk Ratio 1.46 [0.77, 2.75], p = 0.25.

SAE – subgrouped by different anti-CD20 antibody treatment regimens. Meta-analysis previously treated patients: Risk Ratio 1.05 [0.89, 1.23], p = 0.57

AE Grade 3/4 – subgrouped by different anti-CD20 antibody treatment regimens. Meta-analysis previously treated patients: Risk Ratio 1.08 [0.99, 1.18], p = 0.068

Gribben 2005

Treatment-related mortality – subgrouped by different anti-CD20 antibody treatment regimens. Meta-analysis relapse therapy: Risk Ratio 1.00 [0.13, 8.00], p = 1.0

Referenzen:

NCRI-CLL 201: Hillmen P et al. A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated chronic lymphocytic leukaemia. British Journal of Haematology 2011;152:570–8

REACH: Robak T et al: Rituximab plus fludarabine prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756 –1765

4. Fazit der Autoren

This meta-analysis showed that patients receiving chemotherapy plus rituximab benefit in terms of OS as well as PFS compared to those with chemotherapy alone. Therefore, it supports the recommendation of rituximab in combination with FluC as an option for the first-line treatment as well as for

	the people with relapsed or refractory CLL. The available evidence regarding the other assessed comparisons was not sufficient to deduct final conclusions.

Police RL et al., 2015 [14].

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

1. Fragestellung

This systematic literature review with meta-analysis was conducted on the clinical efficacy and safety of interventions used in the treatment of chronic lymphocytic leukemia (CLL).

We were particularly interested in whether there were treatments (chemotherapy or chemoimmunotherapy) that had better efficacy and safety than others and should be recommended as a standard against which to test drugs in development.

2. Methodik

Population: Patients with relapsed/refractory chronic lymphocytic leukemia.

Table 1 Definitions of Relapsed or Refractory Disease in Select Studies in CLL

Reference, Trial Identifier	Definition of Relapsed or Refractory Disease
Elter et al, 2011[14] NCT00086580	Based on the NCIWG 1996 criteria, with evidence of progressive disease that required treatment after 1 previous treatment for CLL
Faderl et al, 2006[15]	Based on the NCIWG 1996 criteria; patients who had received at least 1 course of treatment with a purine analogue and who either experienced recurrence during or within 6 months, or were intolerant
Hillmen et al, 2011[16]	Not clearly defined; methods state patients were previously treated with at least 1 therapy and now required therapy
O'Brien et al, 2009[17] NCT00024440	Definition adapted from the literature: patient was refractory if they failed to achieve at least a partial response or if disease recurred within 6 months of treatment
Robak et al, 2010[18] NCT00090051	Not defined
Wendtner et al, 2011[19] CC-5013-CLL-009	Not defined

Abbreviations: CLL = chronic lymphocytic leukemia; NCIWG = National Cancer Institute Working Group.

Intervention und Komparator: siehe Ergebnisdarstellung

Endpunkte: Objective response rate (ORR), progession-free survival (PFS), overall survival (OS), and adverse events (AE rates)

Suchzeitraum: 01/1997 – 08/20012, PubMed, Embase, and the Cochrane Library, additional sources: from the 2011 and 2012 meetings of the American Society of Clinical Oncology (ASCO), the European Hematology Association, and the 2010 and 2011 meetings of the American Society of Hematology (ASH) and the European Society for Medical Oncology (ESMO), the Clinicaltrials.gov database, and the bibliographies of included trials and recent reviews.

Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 RCT (range: n = 22 – 552 Patienten).
Three of the studies (in 4 reports) in patients with CLL had overlapping treatments, such that meta-analysis could be considered. 4 phase III trials (active therapies against each other), 2 phase II trials (different doses of same therapy).

Hinweis: Because autologous stem cell transplant was not a treatment of interest at level 2, RCTs that presented outcomes of transplant programs that did not separately present the short-term outcomes related to conventional-dose chemotherapy preceding high-dose transplant-preparative chemotherapy were excluded.

Qualitätsbewertung der Studien:
Assessment of the methodological quality of the included RCTs was based on guidance in the National Institute for Health and Care Excellence Single Technology Appraisal specification for manufacturer/sponsor submission of evidence 2009 and adapted from the Centre for Reviews and Dissemination guidance for undertaking reviews in health care.

3. Ergebnisdarstellung

Auszug aus Ergebnistabellen (vgl. Police et al Tabelle 3)

Summary of efficacy outcomes in studies of relapsed or refractory chronic lymphocytic leukemia

Reference, Trial Identifier	Median Duration of Response, Months	Median PFS, Estimated PFS Rate, Months	Median OS Estimated OS Rate
Elter et al, 2011[14] NCT00086580	NR for either treatment group	Fludarabine with alemtuzumab: 23.7 Fludarabine: 16.5 $P = .0003$	Fludarabine with alemtuzumab, NR Fludarabine, 52.9 months $P = .021$
Faderl et al, 2006[15,b]	NR for either treatment group	NR for either treatment group	NR for either treatment group
Hillmen et al, 2011[16]	NR for either treatment group	NR for either treatment group	NR for either treatment group
O'Brien et al, 2009[17] NCT00024440 **Five-year follow-up study to O'Brien et al, 2007**[13]	Outcome not measured in months in follow-up study	NR for either treatment group	FC, 31 Oblimersen with FC, 27.3 months (ITT population) NS
Robak et al, 2010[18] NCT00090051	FC, 27.7 FC-R, 39.6 $P = .025$	FC, 20.6 FC-R, 30.6 $P < .001$	FC, 52 months FC-R, NR $P =$ NS
Wendtner et al, 2011[19] CC-5013-CLL-009	NR for either treatment group	NR for either treatment group	NR for either treatment group

Abbreviations: FC = fludarabine and cyclophosphamide; FCM = fludarabine, cyclophosphamide, and mitoxantrone; FCM-R = fludarabine, cyclophosphamide, mitoxantrone, and rituximab; FC-R = fludarabine and cyclophosphamide, with rituximab; ITT = intention-to-treat; NS = not significant; OS = overall survival; PFS = progression-free survival.
[a]ORR as defined by Cheson et al, 1996.[20]
[b]Study terminated early because of lack of objective response to treatment.

Summary of safety outcomes in studies of relapsed or refractory

	chronic lymphocytic leukemia (Police et al. Tabelle 4, siehe Anhang, Abbildung 1)
	4. Fazit der Autoren In the 6 studies, the most commonly investigated therapies were fludarabine and rituximab, both of which are currently recommended by ESMO for treatment of R/R CLL. Other drugs and combination regimens have not been as successful, in some instances perhaps because trials evaluating these treatments have been terminated early because of lack of patient enrollment. However, ongoing phase III clinical trials in patients with indolent NHL indicate an increased interest in studying the R/R CLL population and a need for developing novel effective and well-tolerated therapies to treat these patients. Additional well designed RCTs are needed to rigorously understand the efficacy and safety of more recently developed therapies in the R/R CLL population and the remaining medical unmet needs for this patient population. **5. Hinweise durch FB Med** - The decision to exclude high-dose therapies with hematopoietic stem cell support in R/R CLL, which encompassed studies of high-dose chemotherapy with allogeneic and autologous stem cell support, might be considered a limitation - Some RCTs included a mixed population of patients who were naive to therapy and patients who had relapsed or were refractory to previous treatment, which made it impossible to present results in the R/R setting separately. - Variability in the definition of “relapsed and/or refractory” further complicate evaluation of these 6 studies. (siehe oben) - Work supported by funding from Sanofi Aventis - Authors are employes of Sanofi
Lepretre S et al., 2012 [10]. The value of rituximab for the treatment of fludarabine-refractory chronic lymphocytic leukemia: a systematic review and qualitative analysis of the literature.	**1. Fragestellung** The aim of the present review is to evaluate the efficacy and safety of rituximab, administered alone or in combination, in patients refractory to fludarabine, as there are no randomized controlled trials (RCTs) in this setting.
	2. Methodik <u>Population</u>: Patients with fludarabine-refractory chronic lymphocytic leukemia. (Definition of fludarabine-refractory: Failure to achieve partial response (PR) or complete response (CR) to a fludarabine-containing regimen, or relapse within 6 months of the last treatment.) <u>Intervention:</u> Rituximab monotherapy or in combination with different agents <u>Komparator:</u> siehe Ergebnisdarstellung <u>Suchzeitraum:</u> Systematic searches that had previously been

	undertaken for a previous review were updated to September 2011. Medline, Embase and The Cochrane Library were searched to identify studies of any treatment for patients with refractory CLL. In addition, conference proceedings from the American Society of Hematology, the American Society of Clinical Oncology, the Proceedings of the International Conference on Malignant Lymphoma Meeting, the International Workshop on Chronic Lymphocytic Leukemia and the European Hematology Association were searched. Anzahl eingeschlossene Studien/Patienten (Gesamt): 13, (siehe Ergebnisdarstellung) <u>Qualitätsbewertung der Studien:</u> RCT quality was assessed by two independent reviewers according to recommended methods (Higgins 2006). In the absence of recommended methods for appraising non-RCTs, these were reviewed for reporting quality and completeness. Referenz: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & Sons, Ltd.
	3. Ergebnisdarstellung - Thirteen studies (reported in 17 publications) either included only, or mostly, fludarabine-refractory patients or considered a mixed population but reported stratified data for fludarabine-refractory patients for at least one efficacy outcome. - Response/Remission: <u>Rituximab in combination with methylprednisolone</u>: Two studies evaluated rituximab in combination with methylprednisolone. Castro et al. included 14 patients with fludarabine-refractory CLL. Dungarwalla et al. also included 14 heavily pretreated patients with CLL, and 13 (93%) had previously received fludarabine. The median number of previous treatments was 2 (range: 1 – 4 for patients with fludarabine-refractory CLL and 2 – 5 for heavily pretreated patients) in both cases. The efficacy outcomes reported by Castro et al. were CR, PR, nPR, PD, OR and PFS. The number of patients showing CR, PR and nPR was five (36%), six (43%) and two (14%), respectively; PD was reported in one (7%) patient and OR was reported in 13 patients (93%). Median time to progression was 15 months (range: 3.2 – 23.0 months). Dungarwalla et al. reported CR, PR, nPR, PD and OR, as well as OS and PFS. The number of patients with CR, PR and nPR was two (14%), 10 (71%) and one (7%), respectively. An OR was reported in 13 (93%) patients. Median OS was 20 months and median PFS was

	reported as 7 months. FCR and CFAR combination studies: Wierda et al. and Badoux et al. evaluated FCR in 177 and 280 patients with relapsed/refractory CLL, respectively. The median number of previous treatments was 2 (range: 1 – 10). These two publications report results from the same trial: Wierda et al. presented interim results and Badoux et al. reported the final results after the inclusion of over 100 additional patients. The trial is part of the group of trials performed at the M. D. Anderson Cancer Center, Houston, Texas. Wierda et al. presented data on 145 (82%) patients previously exposed to fludarabine. Of these, 37 (21%) were fludarabine-refractory. Results for 33 fludarabine-refractory patients were reported. Four fludarabine-refractory patients were part of the FC patient group, for which outcomes were not reported in a stratified manner. The efficacy outcomes CR, PR, nPR and OR were used. CR, PR and nPR were observed in 2/33 (6%), 3/33 (9%) and 14/33 (42%) patients, respectively, while the number of patients achieving OR was 19/33 (58%). Badoux et al. included 53 (19%) fludarabine-refractory patients. The reported efficacy outcomes were CR, OR and OS. CR was reported in 4/53 (8%) patients and OR in 30/53 (57%) patients. Median OS was 37 months. Keating et al. also evaluated FCR (n= 33), but results are presented with results for CFAR-treated patients (n= 9). The efficacy outcomes reported were CR, PR and OR. The number of patients achieving CR was 12 (29%), PR was 14 (33%), nPR was nine (21%) and OR was 35 (83%). Median time to progression was 45 months, median time to treatment failure was 20 months and median OS was 44 months. All patients in this study were fludarabine-refractory. Rituximab in patients previously treated with FCR: Wierda et al. (rituximab in combination with fludarabine and cyclophosphamide) included 43 patients previously treated with FCR. CR and PR were achieved by 19% and 37% of patients, respectively. Overall Survival: Increasing patient survival is without doubt one of the main goals of treatment. OS was considered in six publications. The 6-month survival rate reported by Tsimberidou et al. was 89%. Median OS was 37 months for FCR, 20 months for rituximab with methylprednisolone. Safety: Two trials considered rituximab in combination with methylprednisolone. Death rates were 29% and 57%, respectively. Interestingly, while infections were the most

	important adverse event in one trial, affecting 50% of patients, they affected only 7% of patients in the other trial, which reported fluid retention in most patients and 29% of grade 3 or 4 neutropenia or thrombocytopenia. - One trial (interim results in Wierda et al., final results in Badoux et al.) used rituximab in combination with fludarabine and cyclophosphamide. Myelosuppression led to discontinuation in 26% and 23% of patients, respectively. Infection was responsible for 6% and 12% of discontinuations, respectively. Grade 3 or 4 neutropenia was also an important adverse event, affecting 62% and 56% of treatment courses, respectively. Wierda et al. reported major infections in 16% of patients, while 16% were affected by pneumonia or sepsis according to Badoux et al.
	4. Fazit der Autoren This systematic review has identified the available published information in this setting. The resulting information, although of moderate quality and without direct comparative evidence, suggests that regimens containing rituximab are a viable treatment option in the refractory CLL setting. **5. Hinweise durch FB Med** - Most studies were uncontrolled studies. No comparison to other treatment regimens for refractory CLL can be made. - Numbers of fludarabine-refractory patients available for inclusion in the trials were low, impacting on the significance of the results. - Studienqualität bei der Bewertung und Synthese nicht berücksichtigt - The study sponsor, F. Hoffman-La Roche Ltd (Roche), provided assistance with literature searching and identification of studies in fludarabine-refractory patients. The manuscript was written by Dr. Lepretre, with some third-party editorial assistance provided by an independent medical writing agency funded by Roche.

National Comprehensive Cancer Network (NCCN), 2016 [12]. Non-Hodgkin's Lymphomas. Stand: 03.2016	**Fragestellung** Evidenz- und Konsensus-LL des National Comprehensive Cancer Netzwork zu Non-Hodgkin`s Lymphomas
	Methodik <u>Grundlage der Leitlinie</u> - Update 2016 - Suchzeitraum: 10/2013 – 12/2014, Recherche in PubMed, last updated 03/2015 - NCCN Guidelines are based on critical analysis of the evidence by multidisciplinary expert clinicians and reaching consensus on which interventions constitute appropriate care. - NCCN categories for recommendations are based on both the level of clinical evidence available and the degree of consensus within the NCCN Guidelines Panel. Evidence of both efficacy and safety of interventions is considered by the Panel. LoE/GoR - Extent of data (e.g., number of trials, size of trials, clinical observations only), - Consistency of data (e.g., similar or conflicting results across available studies or observations), and - Quality of data based on trial design and how the results/observations were derived (e.g., RCTs, non-RCTs, meta-analyses or systematic reviews, clinical case reports, case series). **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.**
	Empfehlungen Siehe Anhang Abbildung 2 bis Abbildung 8. Alle Empfehlungen sind NCCN Category 2A, sofern nichts anderes spezifiziert ist.

Relapsed or Refractory Disease

The current standards of care for relapsed or refractory CLL are ibrutinib monotherapy and idelalisib plus rituximab.

Ibrutinib showed remarkable monotherapy activity with favorable toxicity profile in patients with relapsed/refractory B-cell malignancies.[123] The safety and efficacy of ibrutinib in relapsed or refractory CLL/SLL was first evaluated in a phase Ib/II study (n = 85; 51 patients received 420 mg and 34 patients received 840 mg).[77] The majority of patients were considered to have high-risk features (advanced-stage disease, del (17p) and del (11q) were present in 65%, 33% and 36% of patients respectively). The ORR was the same (71%) in the two dose groups. Among the subgroup of 28 patients with del(17p), the ORR was 68% (CR in 3.5%). PR with lymphocytosis was observed in 20% and 15% of patients in the two dose groups, (420 mg and 840 mg) respectively. The

Ibrutinib was approved by the FDA for the treatment of patients with CLL who received at least one previous therapy and for first-line therapy in patients with del(17p) CLL.

Idelalisib, the isoform-selective oral inhibitor of PI3K-delta, demonstrated promising clinical activity in phase I-II studies in patients with relapsed/refractory CLL, both as monotherapy and in combination with rituximab.[78,122] In the multicenter phase III randomized study, 220 patients with relapsed CLL were randomized to receive rituximab with either idelalisib (150 mg) or placebo.[78] Majority of the patients (78%)

Second-line Therapy

Based on the recent FDA approvals, ibrutinib (category 1)[124] and idelalisib ± rituximab [78,182] are included as preferred options for patients with relapsed or refractory disease, regardless of their age and comorbidities.

For patients 70 years or older and younger patients with comorbidities, the NCCN Guidelines included reduced-dose FCR or PCR, bendamustine with or without rituximab, HDMP or chlorambucil with rituximab, monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or dose-dense rituximab as alternative options.

For patients younger than 70 years without significant comorbidities, the NCCN Guidelines included chemoimmunotherapy (FCR, PCR, bendamustine with or without rituximab, fludarabine with alemtuzumab, CHOP with rituximab, OFAR), monotherapy with ofatumumab or obinutuzumab, lenalidomide or alemtuzumab with or without rituximab, or HDMP with rituximab as alternative options. Allogeneic HSCT can be considered for select patients (without significant comorbidities) after re-induction of remission.

See *"Suggested Treatment Regimens: CLL without del(17p) or del(11q)"* in the guidelines for a list of other suggested regimens

CLL with del(17p)

Outcomes remain poor with currently available chemoimmunotherapy regimens. Based on the recent FDA approval, ibrutinib is included as an option for first-line therapy and for relapsed or refractory CLL.[117-119,124]

alemtuzumab with or without rituximab. The efficacy of ibrutinib in relapsed or refractory CLL with del(17p) patients exceeds the results of alternative regimens in the upfront setting and should be considered as the best choice in the absence of a contraindication to give this treatment.

Patients with no response to first-line therapy, patients who respond to first-line therapy but are not eligible for allogenic HSCT and for those with no response to allogenic HSCT should be enrolled in clinical trials or be treated with second-line therapy for relapsed or refractory disease. Ibrutinib and idelalisib ± rituximab are the preferred options for relapsed or refractory disease.

CLL with del(11q)

Patients with no response to first-line therapy and patients with PR to first-line therapy but are not eligible for allogenic HSCT should be enrolled in clinical trials or can be treated with second-line therapy for relapsed or refractory disease. Ibrutinib and idelalisib ± rituximab are the preferred options for relapsed or refractory disease. See *"Suggested Treatment Regimens: CLL with del(11q)"* in the guidelines for a list of other suggested regimens based on the patient's age and the presence or absence of significant comorbidities.

Prica A et al., 2015 [15]. **Cancer Care Ontario, Toronto (CAN)** Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline, vers. 3	**Fragestellung** Target Population: Chronic Lymphocytic Leukemia - Adult patients with CLL at any stage. Research Questions: Chronic Lymphocytic Leukemia 1. What beneficial outcomes are associated with the use of rituximab for the treatment of patients with CLL? Outcomes of interest are OS, disease control (as assessed by measures such as PFS, EFS, TTF, or RD), and response rate. 2. What is the toxicity associated with the use of rituximab? 3. Which patients are more or less likely to benefit from treatment with rituximab?
	Methodik <u>Grundlage der Leitlinie (Evidenz- und konsensbasierte LL)</u> - systematische Recherche und Auswahl der Literatur (update von 1999 und 2006), bei homogener Datenlage Metaanalysen durchgeführt, informaler Konsensusprozess („considered judgement of benefits and harms“) führt zu Empfehlungsvorschlägen, external Review by Ontario Clinicians and other experts, • updated through an annual assessment and subsequent review process. - If one or more existing systematic reviews were identified that addressed the research questions and were of reasonable quality, then those systematic reviews would form the core of the evidence review. - Suchzeitraum (letztes Update): Oktober 2013, in den Datenbanken MEDLINE, EMBASE, the Cochrane Library, Clinicaltrials.gov, ASH und ASCO nach Abstracts - Qualitätsbewertung eingeschlossener Studien, LoE/GoR: deskiptiv - detaillierte Angaben zur Qualität und Eigenschaften sowie zu Ergebnissen der eingeschlossen Studien sind in Evidenztabellen aufbereitet <u>Sonstige methodische Hinweise</u> - Conflict of interest: 5/6 member of the working group declared no conflict of interest, 1/6 received grants/research support from pharmaceutical company. - Funding: The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.
	Empfehlungen/Hinweise <u>Recommendation 3</u> *Chronic lymphocytic leukemia/small lymphocytic lymphoma* *Patients with Relapsed/Refractory Disease*

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

Summary of Key Evidence for Recommendation 3

- two systematic reviews included patients with fludarabine-resistant CLL
- review by Lepretre et. al included randomized and nonrandomized trials
- AMSTAR tool applied: review by Bauer et. al was of best quality
- Working Group decided not to use any of the existing systematic reviews of summary data because of differences in questions, population, or provincial context

Anmerkung FB Med: Lepretre et. al im Kapitel Systematic Reviews und Bauer et. al im Kapitel Cochrane Reviews extrahiert.

Referenzen:

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

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

Patients with Relapsed/Refractory Disease

Two studies, represented by six publications, were included. This body of evidence indicates a benefit for PFS, FFS, and response with the use of rituximab in addition to fludarabine-based chemotherapy when compared with chemotherapy alone. The included studies did not detect any statistically significant between-group difference in grade 3 or 4 adverse events.

- sample size: 52 patients in phase II study [44], 552 in the other [45]
- rituximab in combination with fludarabine-based chemotherapy vs. chemotherapy alone
- overall response [44], PFS [45] as primary outcomes, other outcomes reported: OS, QOL

Quality of Included Studies

- two studies reported as full-text publications
- NCRI CLL201 trial [44]: phase II study with a smaller sample
- BO17072 study [45]: open-label trial, at moderate risk of bias (no report on random sequence generation and allocation concealement; no blinded patients, clinicians or outcome assessors; intention-to-treat analysis conducted without report on all outcomes stated in methods section)
- The overall quality of the studies of first-line treatment was high, although all of the studies were open label. Among the studies of second-line treatment, one was a phase II smaller study [44] and the other [45] was considered to be of moderate quality because it

	was at risk for selection bias. Referenzen: 44. Hillmen P, Cohen DR, Cocks K, Pettitt A, Sayala HA, Rawstron AC, et al. A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated chronic lymphocytic leukaemia. Br J Haematol. 2011;152(5):570-8. 45. Robak T, Dmoszynska A, Solal-Celigny P, Warzocha K, Loscertales J, Catalano J, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1756-65. <u>Justification for Recommendation 3</u> Rituximab is effective in extending life and prolonging PFS and EFS in previously untreated patients, when administered in combination with fludarabine-based chemotherapy, and in extending PFS when added to chlorambucil. Rituximab is also effective in extending PFS in the relapsed setting when added to fludarabine-based chemotherapy, and this consistent benefit formed the basis for the recommendation in this setting. <u>Qualifying Statements for Recommendation 3</u> 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. Finally, the group recognized these trials studied the addition of rituximab to a fludarabine-based chemotherapy backbone, which may not be applicable to older, frail CLL patients. The Hematology DSG does recognize the consistent and moderate benefit in PFS and OS in the phase III setting and the acceptable toxicity profile of rituximab; the DSG felt that the addition of rituximab to fludarabine-based chemotherapy should be recommended in the treatment of CLL and SLL. More recently, the comparison of chlorambucil alone to rituximab and chlorambucil in the older, frail patient population also demonstrated a significant improvement in PFS. Thus, the DSG felt the addition of rituximab to single-agent chlorambucil can be considered.
Oscier D et al., 2012 [13]. **British Committee for Standards in Haematology (BCSH)** Guidelines on the diagnosis, investigation and management of chronic lymphocytic	**Fragestellung** The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with chronic lymphocytic leukaemia. (LL-Version von 2012, Oscier et al., 2012) Considering the significant developments in the treatment of CLL in the last 18 months, the BCSH Guidelines group have asked the CLL Guidelines Panel to provide an interim update for the BCSH guidelines website. This interim statement has not been peer-reviewed, but it is anticipated that a definitive rewriting of the CLL Guidelines will be completed before the end of 2015.
	Methodik (Angaben zur Methodik aus der LL-Version von 2012, Quelle Oscier et al., 2012)

leukaemia Und: **Follows GA et al., 2015 [4].** Interim statement from the BCSH CLL Guidelines Panel	<u>Grundlage der Leitlinie</u> – This guideline replaces the previous BCSH guideline on chronic lymphocytic leukaemia published in 2004 and should be read in conjunction with the IWCLL guidance published in 2008. – The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH (British Committee for Standards in Haematology) and the British Society for Haematology Committee and comments incorporated where appropriate. – Suchzeitraum: bis August 2011 (Update der Version von 2004), Datenbanken: Medline/Pubmed <u>LoE/GoR:</u> Auswertung gemäß GRADE Guidelines prior to 2010 used the classification of evidence and grading of recommendations as devised by the US Agency for Health Care Policy and Research (AHCPR). Guidelines published from 2010 onwards have used the 'GRADE' nomenclature. *Strengh of Recommendation:* Strong (grade 1), Weak (grade 2) *Quality of Evidence:* (A)High: further research is very unlikely to change our confidence in the estimate of effect, (B)Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, (C)Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, (D) Very Low: any estimate of effect is very uncertain. <u>Sonstige methodische Hinweise</u> Conflicts of interest statements provided. UK CLL Forum is a registered charity that receives funding from a number of pharmaceutical companies including Roche, GSK, Janssen, Gilead, Napp.
	Empfehlungen **Relapse Therapy** (aus Follows 2015) With very heavily pre-treated frail patients, idelalisib + rituximab has been shown to be superior to monotherapy rituximab in terms of response rate, depth of remission, duration of remission and overall survival [Furman et al., 2014]. Similar striking benefit has also been shown for ibrutinib compared with ofatumumab in the relapse / refractory setting [Byrd et al., 2014]. Therefore, relapsed / refractory patients who meet appropriate criteria should be considered for

	treatment with either idelalisib+ rituximab or ibrutinib. The NHS England CDF panel has included these drugs in the CDF as long as specific inclusion criteria are met. Deciding whether ibrutinib or idelalisib + rituximab is most appropriate for an individual patient will depend on a range of factors. The trial inclusion criteria for treatment were not overlapping, so certain patients will only meet treatment criteria for one drug. The side effect profile and the convenience of delivery is different between the regimens and this may influence clinician / patient choice. Therefore, with particular reference to patients relapsing after a prolonged first remission it is less likely that they will meet criteria for treatment with either idelalisib+ rituximab or ibrutinib. For these patients, treatment with chemotherapy or immunochemotherapy, as per the existing BCSH guidelines remains recommended. Unfortunately the quality of data from relapsed trials with immunochemotherapy is poor, and choice of chemotherapy regimen will depend on previous therapy and co-morbidities. For patients treated with more intensive intent this is likely to be FCR or BR, while more palliative patients may be re-treated with CBL. As the data stands, no firm recommendations can be made as to how patients relapsing after treatment with ibrutinb or idelalisib+rituximab should be managed. The NHS England CDF has specifically excluded funding of patients crossing from one therapy to another, although clarification is awaited to confirm that this exclusion does not apply if the first therapy was delivered within a clinical trial. Data on the use of either idelalisib + rituximab or ibrutinib as a bridge to allogeneic transplant is very limited and individual cases would need to be discussed with specialist transplant centres to assess suitability. <u>Recommendation</u> • Patients relapsing at least 2 years after FC, FCR or similar regimens who have not acquired a TP53 abnormality, remain fit enough for fludarabine-based treatment and in whom there is a clinical indication for treatment, should receive FCR. Further studies are required to evaluate the role of bendamustine in combination with an anti CD20 antibody in fit patients with relapsed disease (GRADE B2) (Quelle: Oscier 2012) • Patients relapsing after chlorambucil can be retreated with chlorambucil. Entry into trials which include bendamustine or chlorambucil and an anti-CD20 antibody is strongly recommended. In the absence of a suitable trial, BR should be considered for patients refractory to chlorambucil. The minority of patients relapsing after chlorambucil who are fit enough to receive fludarabine-based therapy should be considered for FCR. Other options for patients who are refractory to chlorambucil and unable to tolerate myelosuppressive therapy include high dose steroids, alone or in combination with rituximab, and alemtuzumab. (GRADE B2) (Quelle: Oscier 2012) • Idelalisib + rituximab or ibrutinib is the treatment of choice for

	patients with relapsed CLL who meet specific criteria – see appendix 1 (GRADE A1) (Quelle: Follows 2015) • Patients with relapsed CLL who do not meet the treatment criteria for either idelalisib + rituximab or ibrutinib should be treated with chemotherapy+/- rituximab, most likely BR or FCR although the quality of data to support this choice is limited. CBL is an option where a more palliative approach is required (GRADE B2) (Quelle: Follows 2015) <u>Appendix 1</u> <u>Idelalisib + rituximab inclusion criteria from Furman et al NEJM 2014</u> 1. CLL that had progressed within 24 months after their last treatment 2. Previous treatment must have included either a CD20 antibody–based regimen or at least two previous cytotoxic regimens. 3. Not able to receive cytotoxic agents for one or more of the following reasons: a. severe neutropenia or thrombocytopenia caused by cumulative myelotoxicity from previous therapies, b. an estimated creatinine clearance of less than 60 ml per minute, c. a score on the Cumulative Illness Rating Scale (CIRS) of more than 6 for coexisting illnesses not related to CLL. d. 17p deletion or mutation (added by CDF) <u>Ibrutinib inclusion criteria from Byrd et al NEJM 2014</u> 1. Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog–based therapy, defined by at least one of the following criteria: a. Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analog–based therapy and anti-CD20–containing chemoimmunotherapy regimen after at least two cycles. b. Age ≥70 years, or age ≥65 and the presence of comorbidities (Cumulative Illness Rating Scale [CIRS] ≥6 or creatinine clearance <70 ml/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analog–based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent–based (or purine analog–based) anti-CD20 antibody–containing chemoimmunotherapy regimen. CIRS score can be determined using a web-based tool. c. History of purine analog–associated autoimmune anemia or autoimmune thrombocytopenia. d. Fluorescent hybridization showing del17p in ≥20% of cells (either at diagnosis or at any time before study entry) either alone or in combination with other cytogenetic abnormalities, provided the patient

	has received at least one prior therapy. Referenzen: Brown JR, Hillmen P, O'Brien S et al., Updated Efficacy Including Genetic and Clinical Subgroup Analysis and Overall Safety in the Phase 3 RESONATETM Trial of Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Abstract 3331, ASH 2014 Byrd JC, Brown JR, O'Brien S et al., RESONATE Investigators.Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia.N Engl J Med. 2014 Jul 17;371(3):213-23. doi: 10.1056/NEJMoa1400376. Epub 2014 May 31. Dreger P, Schetelig J, Andersen N et al., European Research Initiative on CLL (ERIC) and the European Society for Blood and Marrow Transplantation (EBMT).Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents? Blood. 2014 Dec 18;124(26):3841-9. doi: 10.1182/blood-2014-07-586826. Epub 2014 Oct 9. Review. Furman RR, Sharman JP, Coutre SE et al., Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.N Engl J Med. 2014 Mar 13;370(11):997-1007. doi: 10.1056/NEJMoa1315226. Epub 2014 Jan 22 O'Brien S, Jones JA et al., Efficacy and Safety of Ibrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Leukemia with 17p Deletion: Results from the Phase II RESONATE™-17 Trial Abstract 327, ASH 2014 Sharman JP, Coutre SE, Furman RR et al., Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. Abstract 330, ASH 2014
Mauro FR et al., 2012 [11]. SIE, SIES, GITMO updated clinical recommendations for the management of chronic lymphocytic leukemia	Italian Society of Hematology (SIE), SIES Società Italiana di Ematologia Sperimentale (SIES) and GITMO (Gruppo Italiano Trapianto di Midollo Osseo) **Fragestellung** Using GRADE system we updated the guidelines for management of CLL issued in 2006 from SIE, SIES and GITMO group.
	Methodik A 3-member Advisory Council (AC) with expertise in clinical epidemiology, hematology, critical appraisal and research synthesis oversaw the process. An expert panel (EP) was selected according to the conceptual framework elements of the NIH Consensus Development Program. During a first meeting the panel decided which of the original clinical issues needed an update and the issues for which there was the need for a critical evidence appraisal. On this basis, we identified and produced recommendations about 6 clinical issues. <u>Grundlage der Leitlinie (Evidenz- und konsensbasierte Leitlinie)</u> – Using a modified Delphi process, the list of produced statements was circulated electronically to all participants through 2 iterations.

	Participants voted on which statements they felt warranted discussion, and provided comments on the wording of the statements which were progressively finalized. – Final adjudication of the recommendation (s) was made through the three face-to-face meetings held in Bologna, Italy. Recommendations were both classified into four mutually exclusive categories: do it, probably do it, probably don't do it, don't do it, according to GRADE suggestions, and were also provided in conversational form following the comments derived from the discussion of the EP. – updated review of literature, Suchzeitraum: 2006 – 3/2011, LoE/ GoR: In areas covered by the evidence, the production of recommendations was performed according GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system.
	Empfehlungen (Recommendation siehe Anhang, Abbildung 9) <u>Therapy of refractory or relapsed patients (evidence-based recommendations)</u> In 2006, the SIE-SIES-GITMO group recommended that patients refractory to first-line chlorambucil or relapsed within 6 months from a first-line therapy should receive fludarabine or fludarabinecontaining regimens. In order to address the optimal second-line treatment approach, four factors were considered of relevance by the EP: the timing of relapse, the response to the prior treatment, the presence of deletion 17p- and/or p53 mutations, age and fitness status of patients. - In patients requiring a second-line treatment, del [17p] and/or p53 mutations should be checked. - In patients with no del [17p] and/or p53 mutations and relapsed after 24 months, the same front-line therapy including rituximab can be considered. - In patients with del [17p] and/or p53 mutations, in patients refractory or relapsed within 24 months from a fludarabine-based treatment, alemtuzumab containing regimens, or experimental treatment approaches within controlled trials should be given. - in poor prognosis younger patients with adequate fitness status and no significant co-morbidities, a treatment approach including an allogeneic SCT, from either a sibling or wellmatched unrelated donor, should be offered after an appropriate cytoreductive treatment. <u>Referenzen</u> [35] Robak T, Dmoszynska A, Solal-Céligny P, Warzocha K, Loscertales J, Catalano J, et al. Rituximab plus Fludarabine prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28:1756–65. [36] Badoux XC, Keating MJ, O'Brien SM, Faderl S, Burger J, Koller C, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly

effective treatment for relapsed patients with CLL. Blood 2011;117:3016–24.

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Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Eichhorst B et al., 2015 [3]. **ESMO** Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	**Fragestellung** Chronic Lymphocytic Leukaemia: Clinical Practice Guideline for diagnosis, treatment and follow-up. **Methodik (nicht systematische, Experten-LL)** <u>Grundlage der Leitlinie</u> – Update-Version der ESMO-LL aus 2003 und 2011, letztes Update August 2015 – Keine Angaben zur Literaturrecherche LoE/GoR **Table 3.** Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a]) Levels of evidence I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity III Prospective cohort studies IV Retrospective cohort studies or case–control studies V Studies without control group, case reports, experts opinions Grades of recommendation A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional D Moderate evidence against efficacy or for adverse outcome, generally not recommended E Strong evidence against efficacy or for adverse outcome, never recommended [a]By permission of the Infectious Diseases Society of America [32]. <u>Sonstige methodische Hinweise</u> Conflict of interest: All authors got funding by pharmaceutical companies. **Empfehlungen** <u>Treatment of relapse and refractory disease.</u> As for the first-line therapy, treatment at relapse should only be started in symptomatic patients. Many patients with relapsed but

	asymptomatic CLL can be followed with no therapy for a long period of time. First-line treatment may be repeated if the relapse or progression occurs at least 24–36 months after chemoimmunotherapy and if TP53 deletion/mutation was excluded [III, B]. If relapse occurs within 24–36 months after chemoimmunotherapy, or if the disease does not respond to any first-line therapy, the therapeutic regimen should be changed. Treatment options include [III, B]: – BCL2 antagonists alone or in combination within a clinical study – Bruton's tyrosine kinase inhibitor ibrutinib – PI3K inhibitor idelalisib in combination with rituximab – Other chemoimmunotherapy combinations should only be administered if TP53 deletion/mutation was excluded (siehe Anhang, Abbildung 10). Referenzen: 23. Byrd JC, Brown JR, O'Brien S et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014; 371: 213–223. 24. Furman RR, Sharman JP, Coutre SE et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 2014; 370: 997–1007. Patients not responding nor progressing upon therapy with kinase inhibitors might be switched to a different kinase inhibitor or to BCL2 antagonists when available (according to clinical trials). Fit patients achieving second remission following the second application of an inhibitor should proceed to allogeneic HSCT [V, B]. Referenzen: 22. Dreger P, Schetelig J, Andersen N et al. Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents? Blood 2014; 124: 3841–3849. <u>Role of haematopoietic stem-cell transplantation.</u> Autologous stem-cell transplantation is not useful in CLL [I, A]. An alloSCT should be considered in patients achieving remission with kinase inhibitors or BCL2 antagonists after early relapse from chemoimmunotherapy and/or with del(17p) or TP53 mutation. In this situation, long-term treatment with inhibitors is an alternative option. The decision should be based on transplant- and disease-risk (e.g. availability of matched donor, patient age and comorbidities and response to treatment) and the patient's preferences, following a careful discussion of the risks and benefits of an allogeneic transplant. In patients failing to several lines of therapy, allogeneic bone marrow transplantation should be considered [III, B]. Referenzen: 22. Dreger P, Schetelig J, Andersen N et al. Managing high-risk CLL during transition

	to a new treatment era: stem cell transplantation or novel agents? Blood 2014; 124: 3841–3849. 25. Brion A, Mahé B, Kolb B et al. Autologous transplantation in CLL patients with B and C Binet stages: final results of the prospective randomized GOELAMS LLC 98 trial. Bone Marrow Transplant 2012; 47: 542–548.
Alberta Provincial Hematology Tumour Team, 2015 [1]. Alberta Health Services Chronic Lymphocytic Leukemia. Clinical Practice Guideline LYHE-007, Version 3. June 2015	**Fragestellung** - What are the recommended diagnostic and staging criteria for adult patients in Alberta with CLL? - What are the recommended treatment strategies for adult patients in Alberta with newly diagnosed, relapsed, or refractory CLL? - What are the recommended follow-up and supportive care practices for adult patients in Alberta with CLL? **Methodik** <u>Grundlage der Leitlinie (Evidenz- und konsensbasierte Leitlinie)</u> – Portions of this guideline document were adapted, with permission, from recommendations developed by a steering committee consisting of hematologists from across Canada. This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team – originally developed in May, 2010 and subsequently revised in March, 2013 and again in October, 2014 and June, 2015 – updated review of literature, Suchzeitraum: to May 2015, Datenbanken: Medline, EMBASE, Cochrane Database of Systematic Reviews, PubMed LoE/ GoR: Evidence Foundations and Strength of Recommendations. 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 <u>Sonstige methodische Hinweise</u> Details zur Methodik im Guideline Resource Unit Handbook: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-utilization-handbook.pdf Conflict of interest: Some members of the Alberta Provincial Hematology Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner. **Empfehlungen/Hinweise**

	Anmerkung FB Med: Qualität der Evidenz unklar Second-Line Treatment Options for Relapsed and Refractory Patients with CLL Recommendations for second-line treatment of CLL should consider individual factors such as comorbidities and the length of the disease-free interval. 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. 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. 9. Relapsed patients who are deemed unfit for fludarabine-based therapy should also be treated with ibrutinib or idelalisib + rituximab. 10. The combination of fludarabine and low-dose alemtuzumab (FluCam) is a safe and effective therapy for relapsed/refractory CLL. 11. Allogeneic stem cell transplantation (HSCT) should be considered for fit patients who are younger than 65 years of age and who have not responded to therapy, have progressive disease within 1 year of fludarabine treatment or within 3 years of fludarabine-based chemoimmunotherapy, or those whose CLL possesses del(17p) and require treatment. 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. Choosing between novel agents ibrutinib and idealisib +/- rituximab Both of the novel agents have demonstrated impressive efficacy in patients with relapsed/refractory CLL. Several factors can be considered when selecting between these agents including expected toxicities and availability/willingness to receive concurrent rituximab. Referenzen 13. 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 Jan;21(1):12-17 PubMed ID 17109028. 26. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, et al. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. N Engl J Med 2000 Dec 14;343(24):1750-1757 PubMed ID 11114313. 27. Keating MJ, O'Brien S, Albitar M, Lerner S, Plunkett W, Giles F, 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 PubMed

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Wendtner C-M et al., 2014 [16]. **Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)** Chronische Lymphatische Leukämie (CLL) Stand: November 2014	Leitlinie Chronisch Lymphatische Leukämie <u>Zweitlinientherapie</u> Die Auswahl der Rezidivtherapie hängt von individuellen Faktoren ab. Dies sind neben Alter und Komorbidität des Patienten vor allem klinische Parameter wie die Art der Primärtherapie und die damit erreichte Remissionsdauer. (siehe Anhang, Abbildung 11) Wenn immer möglich, soll die Therapie im Rahmen klinischer Studien erfolgen. Patienten, die auf die derzeitigen Standardtherapien (FCR, BenR, CbR, CbObi, CbOfa, BenOfa) refraktär sind oder nur eine kurze Remission (<2 Jahre) erzielen, oder rezidivierte Patienten mit Nachweis einer del(17p13) bzw. einer TP53-Mutation, haben eine schlechte Prognose. Sie werden auch als Hochrisiko-CLL (high-risk CLL, highest risk CLL, ultra high risk CLL) bezeichnet [17]. Ihre mittlere Gesamtüberlebenszeit beträgt 1 – 2 Jahre, gerechnet ab dem Zeitpunkt der Salvagetherapie. Bei Patienten mit aggressivem Verlauf der CLL im Sinne einer Richter-Transformation kann eine Chemoimmuntherapie auf der Basis von R-CHOP wie bei Non-Hodgkin-Lymphomen durchgeführt werden. Aktuell wurden zwei neue Substanzen allein oder in Kombination mit Antikörpern bei der refraktären / rezidivierten CLL zugelassen. Der BTK-Inhibitor Ibrutinib führte im Vergleich mit Ofatumumab zu einer signifikanten Verlängerung des progressionsfreien Überlebens und des Gesamtüberlebens. Auch für den PI3K-Inhibitor Idelalisib gibt es in Kombination mit Rituximab entsprechende Phase-III-Daten mit Nachweis eines Überlebensvorteils (PFS/OS) gegenüber einer Rituximab-Monotherapie. Der monoklonale anti-CD20 Antikörper Ofatumumab ist für Patienten

	zugelassen, die auf ein Fludarabin-haltiges Schema und Alemtuzumab refraktär waren (Deutschland, Österreich) und / oder für diese Therapien nicht geeignet sind (Schweiz). Ofatumumab war allerdings der Ibrutinib-Therapie unterlegen, so dass dieser Antikörper bei Rezidiv/Refraktarität erst bei Versagen einer Ibrutinibtherapie eingesetzt werden sollte, wobei in dieser Sequenz keine belastbaren Daten für Ofatumumab existieren. Referenzen 19. Byrd JC, Brown JR, O'Brien S, et al: Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 371:213-223, 2014. DOI: 10.1056/NEJMoa1400376 20. Furman RR, Sharman JP, Coutre SE, et al: Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med 370:997-1007, 2014. DOI: 10.1056/NEJMoa1315226 Allogene Stammzelltransplantation Für Patienten mit Therapie – refraktärer, früh rezidivierter CLL oder Nachweis von del(17p13) bzw. TP53-Mutation (Hochrisiko-CLL) stellt die allogene Stammzelltransplantation eine sinnvolle Option dar, sofern der Verlauf und der körperliche Zustand dies zulassen. Eine weitere Indikation im Rezidiv ist der Nachweis einer del(17p13) bzw. TP53-Mutation bei therapiebedürftiger Erkrankung. Auch Patienten mit CLL und Richter-Transformation sollten einer allogenen Transplantation zugeführt werden, sofern dies die Fitness des Patienten und die Spendersituation erlauben. Der Stellenwert der allogenen Transplantation als Konsolidierungsmaßnahme nach initialer Remission auf gezielte Medikamente wie Ibrutinib und Idelalisib/Rituximab steht derzeit unter Diskussion und wird außerhalb von Studien nicht generell empfohlen. Referenzen 22. Dreger P, Döhner H, Ritgen M et al: Allogeneic stem transplantation provides durable disease control in patients with chronic lymphocytic leukemia: long-term clinical and MRD results of the German CLL Study Group CLL3X trial. Blood 116:2438-2447, 2010. DOI: 10.1182/blood-2010-03-275420

Detaillierte Darstellung der Recherchestrategie

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#2	Search chronic[Title/Abstract]
#3	Search ((((lymphocytic[Title/Abstract]) OR lymphoid*[Title/Abstract]) OR lymphatic*[Title/Abstract]) OR lymphoblastic[Title/Abstract])
#4	Search ((leukemia*[Title/Abstract]) OR leukaemia*[Title/Abstract])
#5	Search (#2 AND #3 AND #4)
#6	Search (#1 AND #2)
#7	Search ((chronic[Title/Abstract]) AND (leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract]))
#8	Search ((chronic[Title/Abstract]) AND lymph*[Title/Abstract] AND (leukemia*[Title/Abstract] OR leukaemia*[Title/Abstract]))
#9	Search CLL[Title/Abstract]
#10	Search (#5 OR #6 OR #7 OR #8 OR #9)
#11	Search (#10 AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract]))
#12	Search (#10 AND (Guideline[ptyp] OR Practice Guideline[ptyp] or guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title/Abstract])) Filters: published in the last 5 years
#13	Search (#12 NOT ((comment[Publication Type]) OR letter[Publication Type]))

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

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

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

Abbildung 1: Zusammenfassung der Sicherheitsendpunkte (Quelle Police et al. 2015 [14])

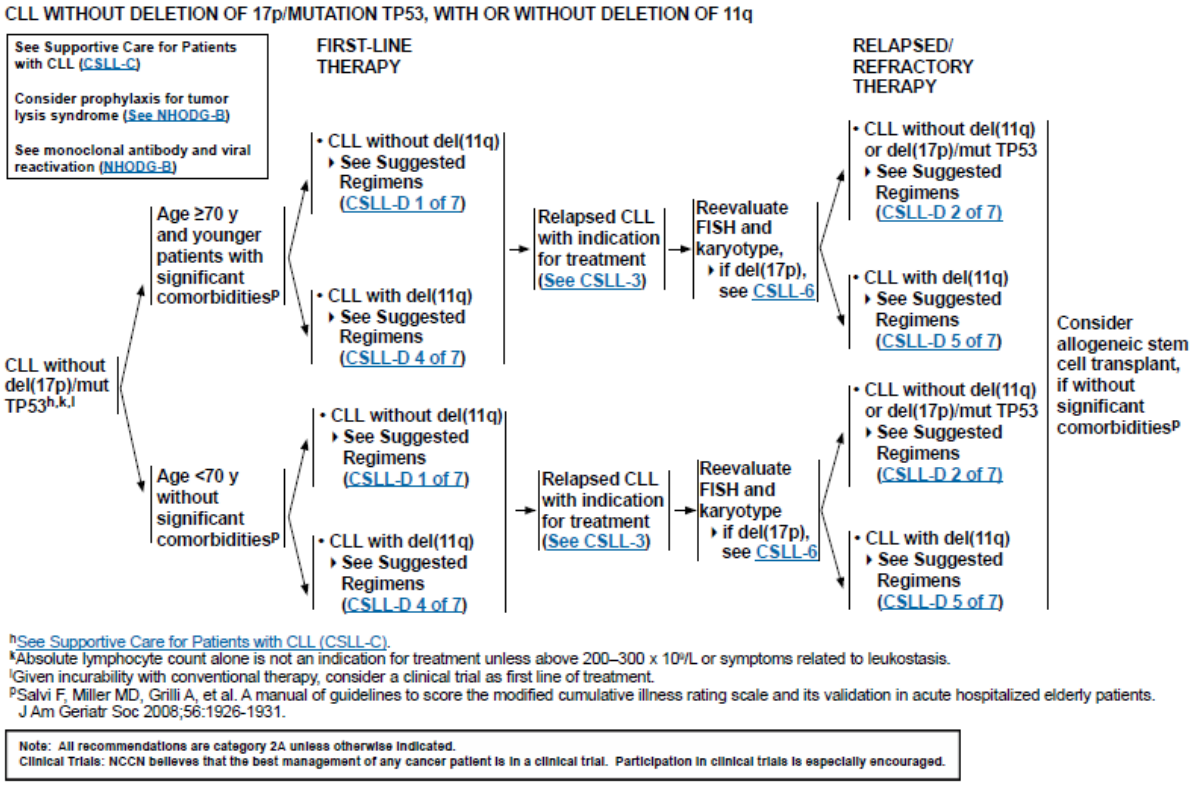


Abbildung 2: Zusammenfassung Empfehlung NCCN Guidelines Version 3.2016 CLL/SLL – Teil I (Quelle NCCN 2016 [12])

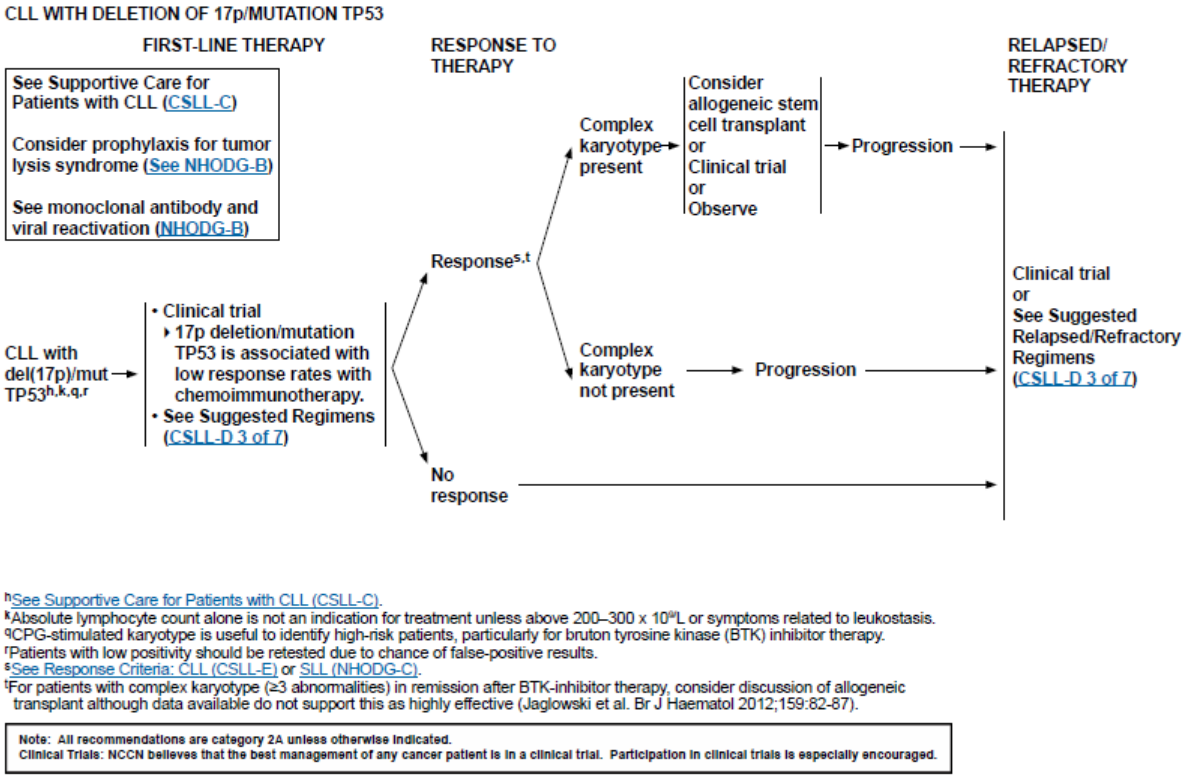


Abbildung 3: Zusammenfassung Empfehlung NCCN Guidelines Version 3.2016 CLL/SLL – Teil II (Quelle NCCN 2016 [12])

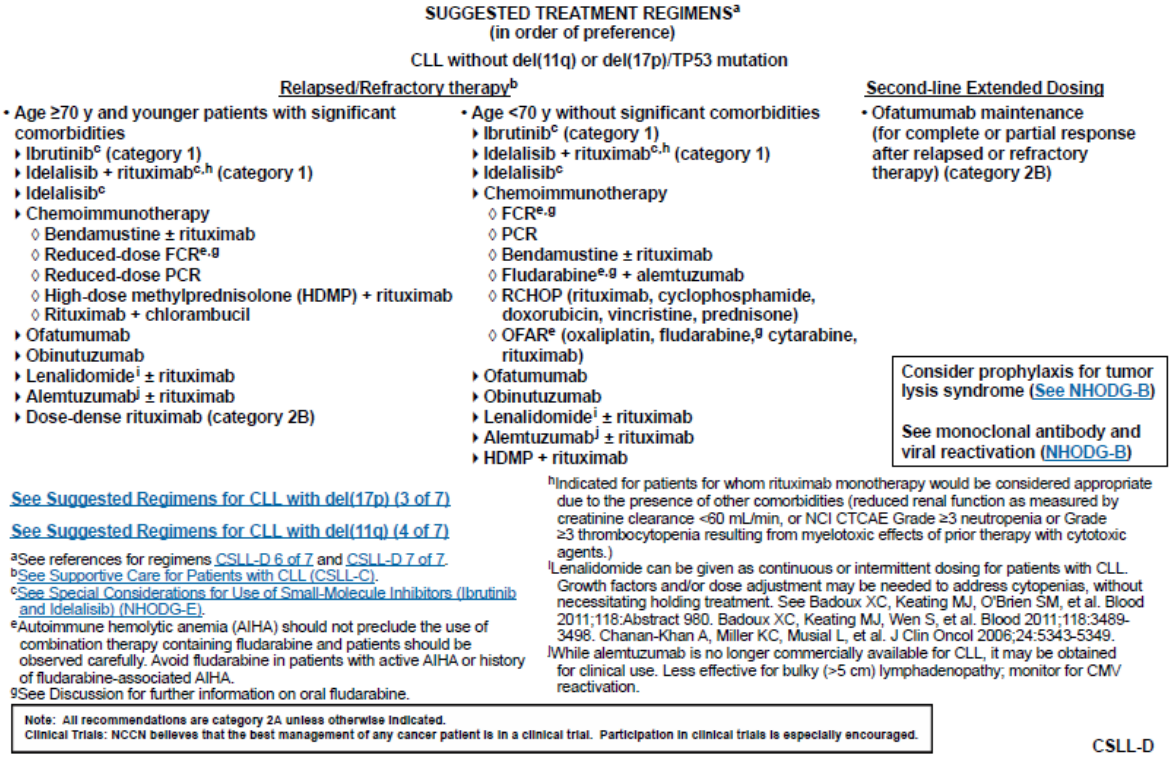


Abbildung 4: Zusammenfassung Empfehlung NCCN Guidelines Version 3.2016 CLL/SLL – Relapsed / Refractory Therapy, CLL without del(11q) or del(17p) / TP53 Mutation (Quelle NCCN 2016 [12])

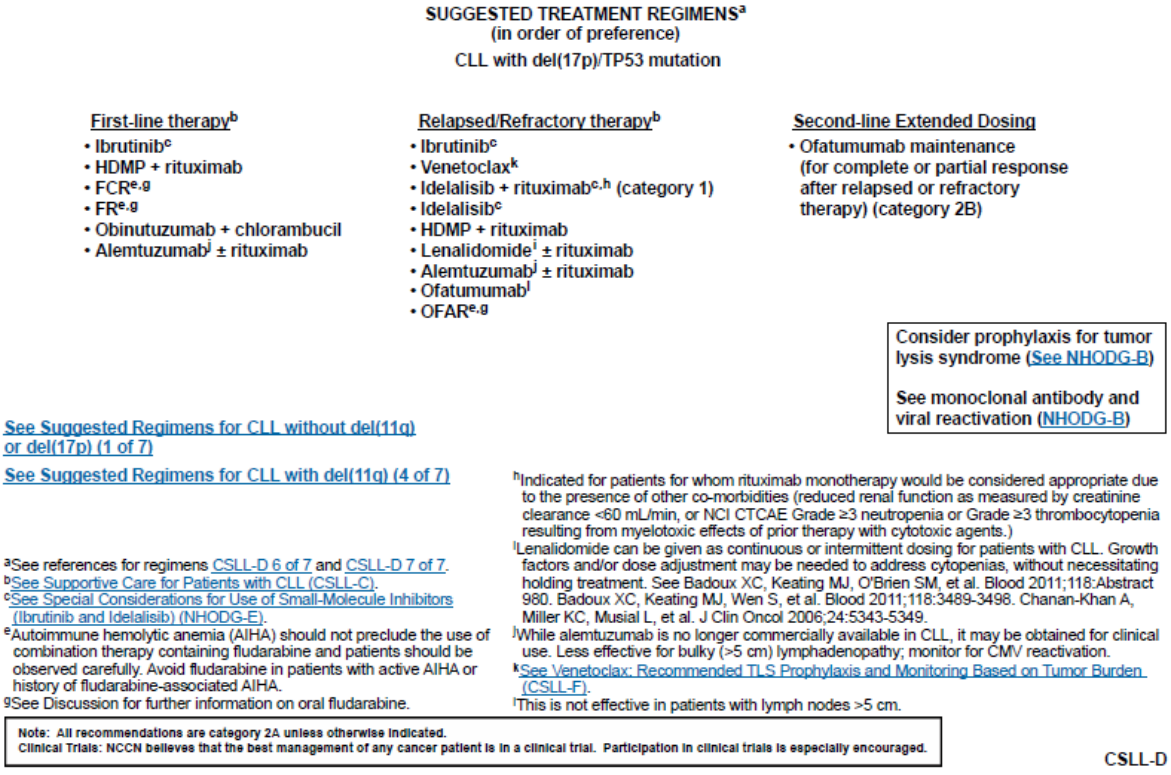
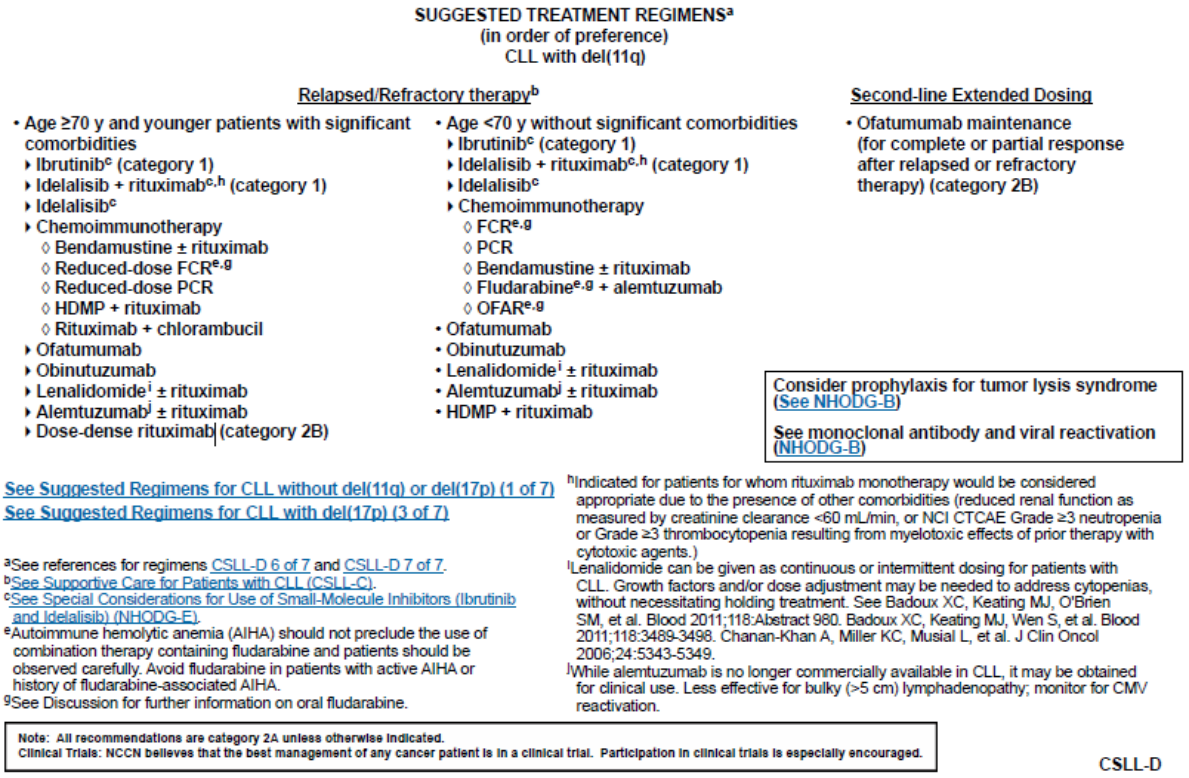


Abbildung 5: Zusammenfassung Empfehlung NCCN Guidelines Version 3.2016 CLL/SLL – Relapsed / Refractory Therapy, CLL with del(17p) / TP53 Mutation (Quelle NCCN 2016 [12])



SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)
CLL with del(11q)

Relapsed/Refractory therapy[b]

- Age ≥70 y and younger patients with significant comorbidities
  - Ibrutinib[c] (category 1)
  - Idelalisib + rituximab[c,h] (category 1)
  - Idelalisib[c]
  - Chemoimmunotherapy
    - Bendamustine ± rituximab
    - Reduced-dose FCR[e,g]
    - Reduced-dose PCR
    - HDMP + rituximab
    - Rituximab + chlorambucil
  - Ofatumumab
  - Obinutuzumab
  - Lenalidomide[i] ± rituximab
  - Alemtuzumab[j] ± rituximab
  - Dose-dense rituximab (category 2B)
- Age <70 y without significant comorbidities
  - Ibrutinib[c] (category 1)
  - Idelalisib + rituximab[c,h] (category 1)
  - Idelalisib[c]
  - Chemoimmunotherapy
    - FCR[e,g]
    - PCR
    - Bendamustine ± rituximab
    - Fludarabine[e,g] + alemtuzumab
    - OFAR[e,g]
  - Ofatumumab
  - Obinutuzumab
  - Lenalidomide[i] ± rituximab
  - Alemtuzumab[j] ± rituximab
  - HDMP + rituximab

Second-line Extended Dosing

- Ofatumumab maintenance (for complete or partial response after relapsed or refractory therapy) (category 2B)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

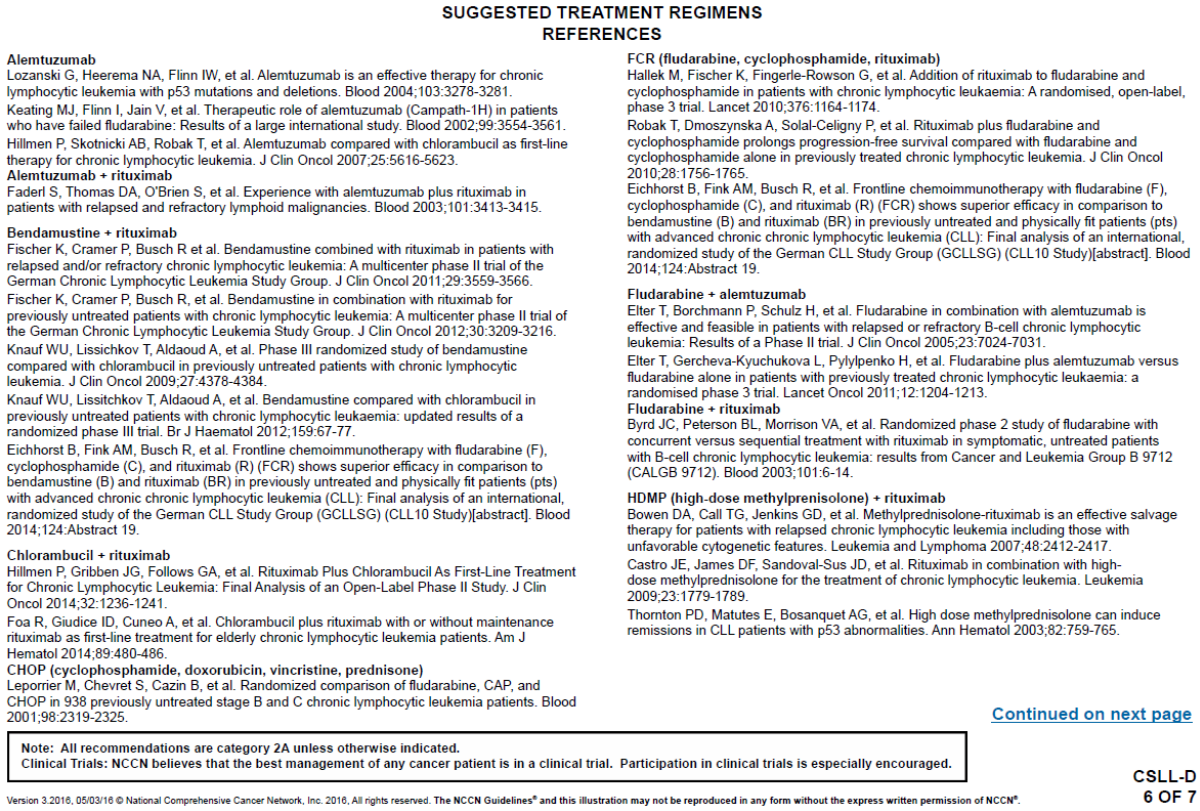
See Suggested Regimens for CLL without del(11q) or del(17p) (1 of 7)
See Suggested Regimens for CLL with del(17p) (3 of 7)

[a]See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b]See Supportive Care for Patients with CLL (CSLL-C).
[c]See Special Considerations for Use of Small-Molecule Inhibitors (Ibrutinib and Idelalisib) (NHODG-E).
[e]Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully. Avoid fludarabine in patients with active AIHA or history of fludarabine-associated AIHA.
[g]See Discussion for further information on oral fludarabine.
[h]Indicated for patients for whom rituximab monotherapy would be considered appropriate due to the presence of other comorbidities (reduced renal function as measured by creatinine clearance <60 mL/min, or NCI CTCAE Grade ≥3 neutropenia or Grade ≥3 thrombocytopenia resulting from myelotoxic effects of prior therapy with cytotoxic agents.)
[i]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.
[j]While alemtuzumab is no longer commercially available in CLL, it may be obtained for clinical use. Less effective for bulky (>5 cm) lymphadenopathy; monitor for CMV reactivation.

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

CSLL-D

Abbildung 6: Zusammenfassung Empfehlung NCCN Guidelines Version 3.2016 CLL/SLL – Relapsed / Refractory Therapy, CLL with del(11q) (Quelle NCCN 2016 [12])



SUGGESTED TREATMENT REGIMENS
REFERENCES

Alemtuzumab
Lozanski G, Heerema NA, Flinn IW, et al. Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions. Blood 2004;103:3278-3281.
Keating MJ, Flinn I, Jain V, et al. Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: Results of a large international study. Blood 2002;99:3554-3561.
Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007;25:5616-5623.

Alemtuzumab + rituximab
Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. Blood 2003;101:3413-3415.

Bendamustine + rituximab
Fischer K, Cramer P, Busch R et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2011;29:3559-3566.
Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: A multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209-3216.
Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol 2009;27:4378-4384.
Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. Br J Haematol 2012;159:67-77.
Eichhorst B, Fink AM, Busch R, et al. Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic chronic lymphocytic leukemia (CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study)[abstract]. Blood 2014;124:Abstract 19.

Chlorambucil + rituximab
Hillmen P, Gribben JG, Follows GA, et al. Rituximab Plus Chlorambucil As First-Line Treatment for Chronic Lymphocytic Leukemia: Final Analysis of an Open-Label Phase II Study. J Clin Oncol 2014;32:1236-1241.
Foa R, Giudice ID, Cuneo A, et al. Chlorambucil plus rituximab with or without maintenance rituximab as first-line treatment for elderly chronic lymphocytic leukemia patients. Am J Hematol 2014;89:480-486.

CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
Leporrier M, Chevret S, Cazin B, et al. Randomized comparison of fludarabine, CAP, and CHOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. Blood 2001;98:2319-2325.

FCR (fludarabine, cyclophosphamide, rituximab)
Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. Lancet 2010;376:1164-1174.
Robak T, Dmoszynska A, Solal-Celigny P, 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;28:1756-1765.
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Fludarabine + alemtuzumab
Elter T, Borchmann P, Schulz H, et al. Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: Results of a Phase II trial. J Clin Oncol 2005;23:7024-7031.
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Byrd JC, Peterson BL, Morrison VA, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712 (CALGB 9712). Blood 2003;101:6-14.

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Bowen DA, Call TG, Jenkins GD, et al. Methylprednisolone-rituximab is an effective salvage therapy for patients with relapsed chronic lymphocytic leukemia including those with unfavorable cytogenetic features. Leukemia and Lymphoma 2007;48:2412-2417.
Castro JE, James DF, Sandoval-Sus JD, et al. Rituximab in combination with high-dose methylprednisolone for the treatment of chronic lymphocytic leukemia. Leukemia 2009;23:1779-1789.
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Continued on next page

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

CSLL-D
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Abbildung 7: Referenzen NCCN Guidelines Version 3.2016 CLL/SLL – Teil I [12]

SUGGESTED TREATMENT REGIMENS
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Ibrutinib
Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015;373:2425-2437.
Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Eng J Med 2013;369:32-42.
Byrd JC, Brown JR, O'Brien S; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Eng J Med 2014;371:213-223.
O'Brien SM, Furman RR, Coutre SE, et al. Independent evaluation of ibrutinib efficacy 3 years post-initiation of monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic leukemia including deletion 17p disease [abstract]. J Clin Oncol 2014;32(15_ suppl):Abstract 7014

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Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Eng J Med 2014;370:997-1007.
Gopal A, Kahl B, De Vos S, et al. PI3Kd inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014; 370:1008-1018.

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Chanan-Khan A, Miller KC, Musial L, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol 2006;24:5343-5349.
Ferrajoli A, Lee BN, Schlette EJ, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood 2008;111:5291-5297.
Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2013;31:584-591.

Obinutuzumab
Flynn JM, Byrd JC, Kipps TJ, et al. Obinutuzumab (GA101) 1,000 mg versus 2,000 mg in patients with chronic lymphocytic leukemia (CLL): Results of the phase II GAGE (GAO4768g) trial [abstract]. J Clin Oncol 2014;32(15_suppl):Abstract 7083.
Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. Blood 2014;124:2196-2202.

Obinutuzumab + chlorambucil
Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Eng J Med 2014;370:1101-1110.
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Ofatumumab
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Coiffier B, Lepretre S, Pedersen LM, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008;111:1094-1100.

Ofatumumab + chlorambucil
Hillmen P, Robak T, Janssens A, et al. Ofatumumab + chlorambucil versus chlorambucil alone in patients with untreated chronic lymphocytic leukemia (CLL): Results of the phase III study Complement 1 (OMB110911) [abstract]. Blood 2013;122:Abstract 528.

Ofatumumab maintainance
van Oers MH, Kuliczkowski K, Smolej L, et al. Ofatumumab maintenance versus observation in relapsed chronic lymphocytic leukaemia (PROLONG): an open-label, multicentre, randomised phase 3 study. Lancet Oncol 2015;16:1370-1379

OFAR (oxaliplatin, fludarabine, cytarabine, rituximab)
Tsimberidou AM, Wierda WG, Plunkett W, et al. Phase I-II study of oxaliplatin, fludarabine, cytarabine, and rituximab combination therapy in patients with Richter's Syndrome or fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2008;26:196-203.
Tsimberidou AM, Wierda WG, Wen S, et al. Phase I-II clinical trial of oxaliplatin, fludarabine, cytarabine, and rituximab therapy in aggressive relapsed/refractory chronic lymphocytic leukemia or Richter syndrome. Clin Lymphoma Myeloma Leuk 2013;13:568-574.

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Kay NE, Geyer SM, Call TG, et al. Combination chemoimmunotherapy with pentostatin, cyclophosphamide, and rituximab shows significant clinical activity with low accompanying toxicity in previously untreated B chronic lymphocytic leukemia. Blood 2007;109:405-411.

Venetoclax
Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax (ABT-199/GDC-0199) monotherapy induces deep remissions, including complete remission and undetectable MRD, in ultra-high risk relapsed/refractory chronic lymphocytic leukemia with 17p deletion: results of the pivotal international phase 2 study [abstract]. Blood 2015;126:Abstract LBA-6.
Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:311-322.

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

Abbildung 8: Referenzen NCCN Guidelines Version 3.2016 CLL/SLL – Teil II [12]

Table 3
Clinical questions and strength and direction of the recommendations formulated by the panel using GRADE system on the issue of second-line therapy.

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

Abbildung 9: Recommendation of second-line therapy (Quelle: Mauro et al. 2012 [11])

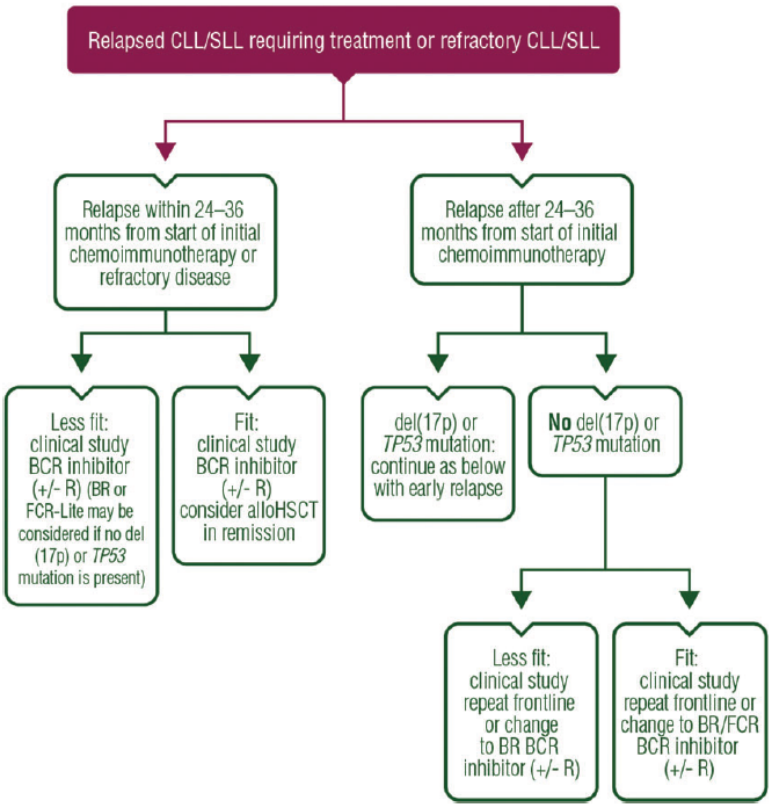
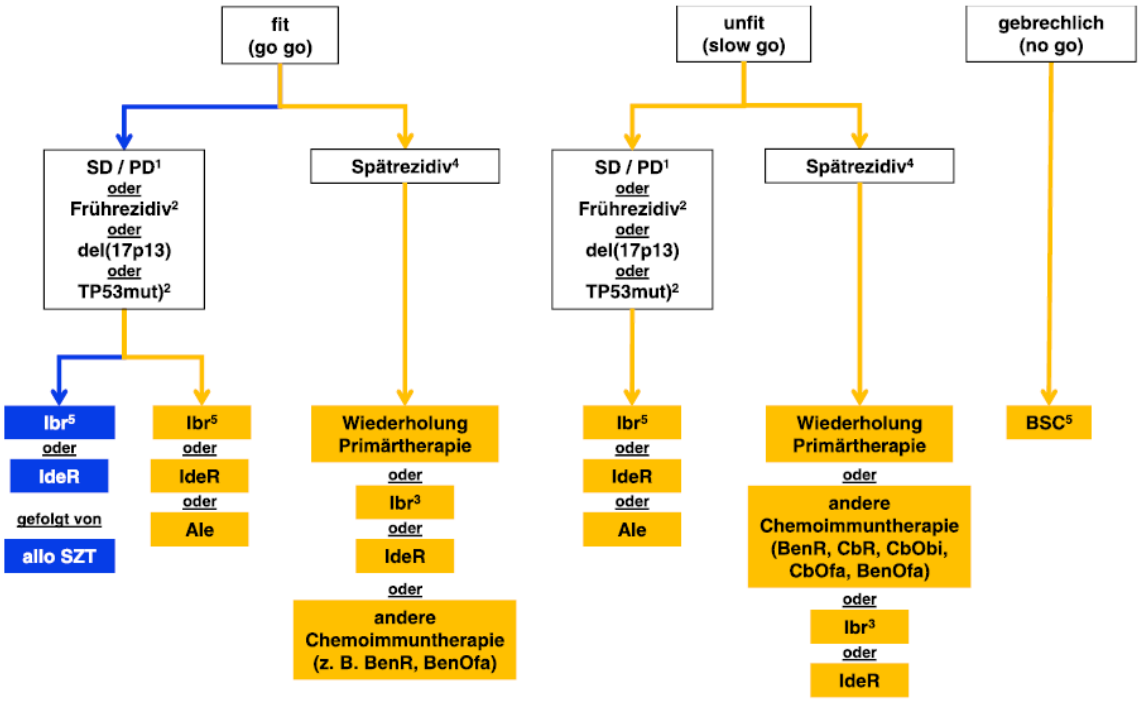


Figure 2. Relapse treatment. CLL, chronic lymphocytic leukaemia; SLL, small lymphocytic leukaemia; BCR, B-cell receptor; R, rituximab; BR, bendamustine plus rituximab; FCR, fludarabine, cyclophosphamide and rituximab; alloHSCT, allogeneic haematopoietic stem cell transplantation.

Abbildung 10: Therapieschema relapsed CLL-Patienten (Quelle: Eichhorst et al. 2015 [3])

Abbildung 5: Zweitlinientherapie der CLL



Legende:

palliativer Therapieansatz; kurativer Therapieansatz;

[1] PD – Progress, PR – partielle Remission, R – Rituximab, SD – stabile Erkrankung;
[2] Frührezidiv – innerhalb von 2-3 Jahren;
[3] zur Methodik siehe Kapitel 5.2. Diagnostik;
[4] Spätrezidiv – nach > 2-3 Jahren;
[5] Therapie: Ale – Alemtuzumab, Ben - Bendamustin, BSC – Best Supportive Care, Cb – Chlorambucil, Ibr – Ibrutinib, Ide – Idelalisib, Obi – Obinutuzumab, Ofa – Ofatumumab, P – Prednison, R – Rituximab

Abbildung 11: Zweitlinientherapie der CLL (Quelle: DGHO 2014 [16])

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7. 2. **Bauer K, Rancea M, Roloff V, Elter T, Hallek M, Engert A, et al.** Rituximab, ofatumumab and other monoclonal anti-CD20 antibodies for chronic lymphocytic leukaemia. Cochrane Database of Systematic Reviews [online]. 2012; (11):Cd008079. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008079.pub2/abstract.

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