Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-301 Asciminib

Stand: Februar 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Asciminib [chronisch myeloische Leukämie] Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	allogene Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Asciminib: Beschluss vom 16. März 2023 • Bosutinib: Beschlüsse vom 19. November 2021 und 21. Februar 2019 • Ponatinib: Beschluss vom 20. November 2020 • Bosutinib: Beschluss vom 21. Februar 2019
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:	
Asciminib L01EA06 Scemblix®	<u>Zugelassenes Anwendungsgebiet:</u> Scemblix wird angewendet zur Behandlung von erwachsenen Patienten mit Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie in der chronischen Phase (Ph+ CML-CP), die zuvor mit zwei oder mehr Tyrosinkinase-Inhibitoren behandelt wurden.
zytotoxische Chemotherapien:	
Busulfan L01AB01 Myleran	Chronische myeloische Leukämie (CML): Palliative Behandlung in der chronischen Phase der Erkrankung nach Versagen einer Primärtherapie (üblicherweise mit Hydroxyurea). Konditionierung von einer hämatopoetischen Stammzelltransplantation Myleran ist zur Konditionierung vor einer hämatopoetischen Stammzelltransplantation bei Patienten angezeigt, wenn die Kombination aus hochdosiertem Busulfan und Cyclophosphamid als die am besten geeignete Behandlungsmöglichkeit erachtet wird.
Cyclophosphamid L01AA01 Endoxan	Konditionierung vor allogener Knochenmarkstransplantation bei: Chronischer myeloischer Leukämie in Kombination mit Ganzkörperbestrahlung oder Busulfan (FI Endoxan)
Hydroxycarbamid L01XX05 (Litalir®, generisch)	Behandlung von Patienten mit chronischer myeloischer Leukämie (CML) in der chronischen oder akzelerierten Phase der Krankheit.
Mitoxantron L01DB07 Mitoxantron Teva	Mitoxantron ist in Kombinationsregimen indiziert zur Remissionsinduktion in der Blastenkrise der chronischen myeloischen Leukämie. (FI Mitoxantron Teva)
Vindesin L01CA03	Kombinationschemotherapie: Blastenschub bei chronischer myeloischer Leukämie

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Eldisine®	(FI Eldisine)
Proteinkinase-Inhibitoren:	
Bosutinib L01EA04 Bosulif®	Bosulif ist angezeigt zur Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase Bosulif ist angezeigt zur Behandlung von Erwachsenen mit Ph+ CML in der CP, akzelerierten Phase (AP) und Blastenkrise (BK), die mit mindestens einem Tyrosinkinaseinhibitor [TKI] vorbehandelt wurden und bei denen Imatinib, Nilotinib und Dasatinib nicht als geeignete Behandlungsoption angesehen werden
Ponatinib L01EA05 Iclusig®	Iclusig wird angewendet bei erwachsenen Patienten mit chronischer myeloischer Leukämie (CML) in der chronischen Phase, akzelerierten Phase oder Blastenkrise, die behandlungsresistent gegenüber Dasatinib bzw. Nilotinib sind, die Dasatinib oder Nilotinib nicht vertragen und bei denen eine anschließende Behandlung mit Imatinib klinisch nicht geeignet ist, oder bei denen eine T315I-Mutation vorliegt
Dasatinib L01EA02 Sprycel®	SPRYCEL ist angezeigt für die Behandlung erwachsener Patienten mit • neu diagnostizierter Philadelphia-Chromosom-positiver (Ph+) chronischer myeloischer Leukämie (CML) in der chronischen Phase. • CML in der chronischen oder akzelerierten Phase oder in der Blastenkrise mit Resistenz oder Intoleranz gegenüber einer vorherigen Behandlung einschließlich Imatinib
Imatinib L01EA01 Glivec®, generisch	Glivec ist angezeigt zur Behandlung von: • Erwachsenen und Kindern mit neu diagnostizierter Philadelphia-Chromosom (bcr-abl)-positiver (Ph+) chronischer myeloischer Leukämie (CML), für die eine Knochenmarktransplantation als Erstbehandlungsmöglichkeit nicht in Betracht gezogen wird. • Erwachsenen und Kindern mit Ph+ CML in der chronischen Phase nach Versagen einer Interferon-Alpha-Therapie, in der akzelerierten Phase oder in der Blastenkrise
Nilotinib L01EA03 Tasigna®	• Tasigna ist angezeigt für die Behandlung von: • erwachsenen Patienten, Kindern und Jugendlichen mit neu diagnostizierter Philadelphia-Chromosom positiver chronischer myeloischer Leukämie (CML) in der chronischen Phase • erwachsenen Patienten mit Philadelphia-Chromosom positiver CML in der chronischen und akzelerierten Phase mit Resistenz oder Unverträglichkeit gegenüber einer Vorbehandlung einschließlich Imatinib. Wirksamkeitsdaten zu Patienten mit CML in der Blastenkrise liegen nicht vor

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-301 (Asciminib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. Januar 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

2GTKI	second generation tyrosine kinase inhibitors
AE	Adverse effect
ALT	Alanine aminotransferase
AP	Accelerated phase
AST	Aspartate aminotransferase
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BC	Blast crisis
BSH	British Society for Haematology
CCyR	Complete cytogenetic response
CML	Chronische myeloische Leukämie
CP	Chronische Phase
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IFN	Interferon
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LL	Leitlinie
LoE	Level of Evidence
MMR	Major molecular response
NG	New-generation
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
PFS	Progression-free survival
RCT	Randomized controlled trial
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Tyrosine kinase inhibitors
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zur Behandlung von erwachsenen Patienten mit Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie in der chronischen Phase (Ph+ CML-CP), die zuvor mit zwei oder mehr Tyrosinkinase-Inhibitoren behandelt wurden.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *chronischer myeloischer Leukämie* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 12.12.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 298 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 8 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Atallah, E et al., 2023 [1].

Treatment-free remission after discontinuation of tyrosine kinase inhibitors in patients with chronic myeloid leukemia in the chronic phase: a systematic review and meta-analysis

Fragestellung

The objective of this study was to summarize the available evidence to compare the efficacy and safety of interventions in the treatment of CP-CML patients who had received ⩾2 prior TKIs.

Methodik

Population:

- treatment of CP-CML patients who had received ⩾2 prior TKIs.

Intervention:

- omacetaxine, olverembatinib, allogeneic stem cell transplantation (allo-SCT), hydroxycarbamide, radotinib, and asciminib, as well as TKIs

Komparator:

- Only two randomized trials, ASCEMBL and OPTIC, compared asciminib to bosutinib
- most studies evaluated a single intervention

Endpunkte:

- Complete cytogenetic response, Major molecular response, Overall survival, Progression-free survival

Recherche/Suchzeitraum:

- Comprehensive searches from the date of inception until May 2021
- Studies were identified through the database searches via Ovid platform (Embase, MEDLINE Epub Ahead of Print, In-Process and Other Non-Indexed Citations, and Cochrane Central Register of Controlled Trials), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), bibliographic search of relevant reviews, and proceedings from the previous 3 years of the key conferences in the field of oncology.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 38 relevant studies

- 2 were randomized trials (ASCEMBL and OPTIC), 13 were single-arm clinical trials, and the remaining 23 were observational studies (4 prospective studies, 18 retrospective studies, and 1 prospective and retrospective cohort study).

Charakteristika der Population/Studien:

- CP-CML patients who had received ⩾2 prior TKIs

Qualität der Studien:

- Based on the Cochrane Collaboration's Risk of Bias Tool for randomized trials, the ASCEMBL study was conducted well and had an overall low risk of bias, while the OPTIC trial had an overall unclear risk of bias as loss to follow-up was not reported and all patients were not evaluable for efficacy (Supplementary Table S6).

Studienergebnisse:

Evidence on efficacy

Complete cytogenetic response:

- The CCyR rate was reported in 31 studies.
- The CCyR rate ranged from 16.1% with omacetaxine to 64.8% with ponatinib at 6 months, and the corresponding values at 12 months were 16.2% to as high as 83.9% with bosutinib.
- Among the included interventions, the CCyR rates ranged from 38.7% at 6 months to 66% at 10.2 months for asciminib,20,32 16.2% at 12 months to 83.9% at 12 months for bosutinib,30,31 6% at 15 months to 69.6% at 40.8 months for ponatinib, 4% at 19.1 months to 16.1% at 6 months for omacetaxine,28,35 36.8% at 12.8 months to 65.9 at 7.9 months for olverembatinib, 24% at 12 months to 31% at 16 months for nilotinib,19,38 and 11% at 16 months to 46.2% at 12 months for dasatinib.19,39 The median time to CCyR was reported as 4.8 months in a study of ponatinib-treated patients.

Major molecular response:

- MMR was reported in 35 studies
- The MMR rate ranged from 10.5% with omacetaxine to as high as 66.7% with ponatinib at 6 months of follow-up and was 14–35% with ponatinib at 12 months of follow-up.

  Among the included interventions, the MMR rates ranged from 23.3% at 6 months to 41% at 10.2 months for asciminib,20,32 13.2% at 6 months to 76.4% at 24 months for bosutinib, 14% at 6 months to 66.7% at 6 months for ponatinib,27,29 10.5–19.2% at 6 months for omacetaxine 14.7% at 12.8 months to 48.8% at 7.9 months for olverembatinib, 13% at 16 months to 33.3% at 12 months for nilotinib and 20.8% at 12 months to 33.3% at 16 months for dasatinib.

Overall survival:

- OS was reported in 18 studies, and an overview of studies reporting 1- to 5-year rates of OS are summarized in Table 2. The 1-year OS rate ranged from 91% with bosutinib to 100% with ponatinib.
- The 5-year OS rate ranged from 65% with mixed TKIs (dasatinib, nilotinib, bosutinib, and ponatinib) to 96% with bosutinib. In the majority of studies, OS was not reached. Among the included interventions, bosutinib reported highest OS at 2 years, ponatinib at 1 year, and dasatinib or nilotinib at 3 years. In the CML-203 study, the median OS in patients treated with omacetaxine was 30.1 months. In the studies where patients treated with asciminib, OS was not reported. Overall, OS rates decreased from 1 to 5 years.

Progression-free survival:

- PFS was reported in eight studies, and the reported 1- to 5-year PFS rates across studies are summarized in Table 2. PFS rates at 1 year ranged from 77% with bosutinib to 87% with ponatinib.
- Only two studies reported the 5-year PFS rate (54% with dasatinib or nilotinib and 53% with ponatinib).
- Among the included interventions, bosutinib reported highest PFS at 2 years, ponatinib at 3 years, and dasatinib or nilotinib at 5 years. In majority of the studies, PFS was not reached, and the median PFS was reported in three studies, ranging from 7 months for omacetaxine to 45 months for ponatinib.

Anmerkung/Fazit der Autoren

The findings from current SLR demonstrated the lack of data for patients with CML treated with ⩾2 TKIs. TKIs such as asciminib, ponatinib, and bosutinib are valid options for those patients. Further research is needed to identify the best treatment option for patients with CML receiving later lines of therapy.

Kommentare zum Review

Es wurden vorwiegend einarmige Studien eingeschlossen. Nur zwei randomisierte Studien, ASCEMBL und OPTIC, verglichen Asciminib mit Bosutinib, eingeschlossen. Zulassung der Wirkstoffe beachten.

Yassine F et al., 2022 [8].

Efficacy of Allogeneic Hematopoietic Cell Transplantation in Patients with Chronic Phase CML Resistant or Intolerant to Tyrosine Kinase Inhibitors.

Fragestellung

a systematic review/meta-analysis (SR/MA) of the available literature to assess the totality of evidence regarding the efficacy of allo-HCT in patients with TKI-resistant CP-CML.

Methodik

Population:

- patients who received an allo-HCT for treating CP-CML that was either TKI resistant or intolerant.

Intervention:

- allo-HCT

Komparator:

- other available therapies

Endpunkte:

- OS, progression-free survival [PFS], disease-free survival [DFS], complete remission [CR], and molecular response [MR]) and harms (NRM, relapse, and acute [aGVHD] and chronic [cGVHD] graft-versus-host disease

Recherche/Suchzeitraum:

- PubMed/MEDLINE and Embase on January 24, 2020

Qualitätsbewertung der Studien:

- The methodologic quality of eligible studies was assessed using the Newcastle Ottawa Scale modified for single-arm cohort studies

Ergebnisse

Anzahl eingeschlossener Studien & Charakteristika der Population/Studien:

- Only nine studies (n = 439 patients) met our inclusion criteria [4,12-19]. Stratification by age group yielded three studies (n = 200 patients) in the adult, one study (n = 28 patients) in the pediatric, and five studies (n = 211 patients) in the mixed population.

Qualität der Studien:

Table 2. Risk of bias in included studies.

Study	Representativeness of the patient cohort	Ascertainment of exposure	Demonstration that the outcome of interest was not present at the start of study	Assessment of outcome	Length of follow-up	Adequacy of follow-up
Adults						
Jabbour et al. [12]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nair et al. [13]	Unclear/high risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kondo et al. [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pediatric						
Suttorp et al. [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mixed/unclear						
Bornhäuser et al. [16]	Low risk	Low risk	Low risk	Low risk	Unclear/high risk	Low risk
Perz et al. [17]	Unclear/high risk	Low risk	Low risk	Low risk	Unclear/high risk	Low risk
Saussele et al. [4]	Low risk	Unclear/high risk	Low risk	Low risk	Low risk	Low risk
Lee et al. [18]	Unclear/high risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kruger et al. [19]	Unclear/high risk	Low risk	Low risk	Low risk	Low risk	Low risk

Studienergebnisse:

- For adult allo-HCT recipients, the pooled OS, DFS, CR and, MR were 84% [95% confidence interval (CI) 59-99%], 66% (95% CI 59-73%), 56% (95% CI 30-80%), and 88% (95% CI 62-98%), respectively.
- Pooled NRM and relapse were 20% (95% CI 15-26%) and 19% (95% CI 10-28%), respectively.

Fazit der Autoren

In conclusion, our results suggest that allo-HCT is an effective treatment strategy for CML patients who are resistant or intolerant to TKIs.

Singh, A. K. et al., 2022 [4].

Impact of imatinib treatment on renal function in chronic myeloid leukaemia patients.

Fragestellung

to summarize the impact of imatinib use on renal function in CML patients.

Methodik

Population:

- CML patients

Intervention:

- imatinib

Komparator:

- non-imatinib/other TKIs

Endpunkte:

- renal dysfunction risk (characterized by a decline in eGFR)

Recherche/Suchzeitraum:

- MEDLINE and Embase from inception to 20 August 2021

Qualitätsbewertung der Studien:

- Newcastle-Ottawa scale (NOS) / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 studies

Charakteristika der Population/Studien:

- All included studies were retrospective cohort in nature except the study, which was prospective in nature. Studies were conducted between 2011 and 2020. Three studies were conducted in Japan, two in the US, one in each Brazil, China, and Italy. The current study was based on 1680 patients exposed to imatinib, and the mean follow-up period of the patients was 6.64 years. The median duration of imatinib treatment varies from 42 to 108 months. Imatinib was given in the dose of 400 mg/day in majority of the included studies. At the baseline, patients in all the included studies were in stage-II CKD (eGFR between 60 and 89 ml/min/1.73 m2) except in the study by Cortes et al. (stage-III CKD).

Qualität der Studien:

- The majority of the included studies were found to be of moderate risk of bias.
- GRADE criteria revealed low certainty of evidence

Studienergebnisse:

- Majority of the studies (n = 6) reported significantly ($p < .05$) decrease in estimated glomerular filtration rate (eGFR) after imatinib treatment.
- The risk of developing renal dysfunction (chronic kidney disease or acute kidney injury) was found to be significantly higher in imatinib users as compared to other tyrosine kinase inhibitor (TKI) users with a pooled relative risk of 2.70 (95% CI: 1.49–4.91).
- Sensitivity analysis also revealed a consistently high risk of renal dysfunction with imatinib use.

Fazit der Autoren

This meta-analysis found a significantly increased risk of renal dysfunction (CKD or AKI) in imatinib users compared to other TKI users. Observed risk was of low certainty as per the GRADE methodology. We recommend judicial use of imatinib in CML patients with co-morbidities or at risk of renal function decline. We also recommend close monitoring of renal function in CML patients with pre-existing renal impairment and to avoid use of other nephrotoxic drugs.

Mulas O et al., 2021 [2].

Arterial Hypertension and Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia: A Systematic Review and Meta-Analysis

Fragestellung

to evaluate with a systematic review and meta-analysis the real incidence of hypertension in CML patients treated with second- or third-generation TKI.

Methodik

Population:

- CML patients treated with new-generation TKI (NGTKI)

Intervention:

- secondor third-generation TKI

Komparator:

- imatinib

Endpunkte:

- Cardiovascular, Chronic Myeloid Leukemia, Tyrosine kinases inhibitor, and Hypertension

Recherche/Suchzeitraum:

- The PubMed database, Web of Science, Scopus, and ClinicalTrials.gov were systematically searched for studies published between January 1, 2000, and January 30, 2021

Qualitätsbewertung der Studien:

- Quality rating of randomized clinical trials and observational studies was performed using the NIH Study Quality Assessment Tools

Ergebnisse

Anzahl eingeschlossener Studien:

- 29 articles were included in the qualitative analysis, with a total sample of 5,533 patients examined. Overall, 29 studies were considered for the quantitative analysis, 28 in the pooled analysis, and 10 in the meta-analysis

Charakteristika der Population/Studien:

- A pooled analysis of hypertension incidence was 10% for all new-generation TKI, with an even higher prevalence with ponatinib (17%).

Qualität der Studien:

Study	Treatment	Quality assessment
Bfore[21]	Bosutinib	Fair
García-Gutiérrez 2018[26]	Bosutinib	Poor
Hino 2020[22]	Bosutinib	Fair
Gambacorti-Passerini 2018[24]	Bosutinib	Good
Bela[23]	Bosutinib	Fair
Caocci 2019[25]	Bosutinib	Fair
Maiti 2020[27]	Dasatinib	Good
Dasision[28]	Dasatinib	Fair
S0325[30]	Dasatinib	Poor
Suh 2017[32]	Dasatinib	Poor
START Rollover[29]	Dasatinib	Fair
Star-R[31]	Dasatinib	Fair
ENESTnd[33]	Nilotinib	Good
Lasor[34]	Nilotinib	Fair
Saydam 2018[35]	Nilotinib	Fair
ENESTcmr[36]	Nilotinib	Fair
NCT00129740[38]	Nilotinib	Fair
ENEST1st[37]	Nilotinib	Good
Caocci 2019[39]	Ponatinib	Fair
Devos 2019[40]	Ponatinib	Poor
Fava 2019[41]	Ponatinib	Poor
Epic[47]	Ponatinib	Fair
Binotto 2018[44]	Ponatinib	Fair
Heiblig 2018[42]	Ponatinib	Fair
Pace[6]	Ponatinib	Fair
Breccia 2018[43]	Ponatinib	Fair
NCT01570868[46]	Ponatinib	Fair
Iurlo 2020[45]	Ponatinib	Fair
NCT01746836[47]	Ponatinib	Good

Studienergebnisse:

- The comparison with the first generation imatinib confirmed that nilotinib was associated with a significantly increased risk of hypertension (RR 2; 95% CI; 1.39-2.88, I2=0%, z=3.73, p=0.0002).
- The greatest risk was found with ponatinib (RR 9.21; 95% CI; 2.86-29.66, z=3.72, p=0.0002).

Anmerkung/Fazit der Autoren

In conclusion, NGTKIs are associated with higher incidence of hypertension. Timely recognition and treatment would allow a reduced risk of developing cardiovascular events.

Wang Z et al., 2021 [7].

Comparison of Hepatotoxicity Associated with New BCR-ABL Tyrosine Kinase Inhibitors vs Imatinib Among Patients with Chronic Myeloid Leukemia: A Systematic Review and Meta-analysis.

Fragestellung

The aim of this study was to compare the risk of all grades and high grades (grades 3 and 4) hepatotoxicity associated with 4 new-generation BCR-ABL TKIs (bosutinib, dasatinib, nilotinib, and ponatinib) vs the first generation BCR-ABL TKI imatinib in patients with CML.

Methodik

Population:

- patients with the chronic phase of CML (CP CML)

Intervention:

- new generation of BCR-ABL TKI (bosutinib, dasatinib, nilotinib, or ponatinib)

Komparator:

- imatinib

Endpunkte:

- primary outcome: hepatotoxicity, including all grades and grades 3 and 4 of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation
- Adverse events, OS and the MMR reported at 12 months

Recherche/Suchzeitraum:

- from January 2000 to April 2020: PubMed, Embase, and Cochrane library databases

Qualitätsbewertung der Studien:

- Jadad

Ergebnisse

Anzahl eingeschlossener Studien:

- a total of 9 studies with 3475 patients were included for statistical analysis

Charakteristika der Population:

- The studies included in the meta-analysis were published between 2010 and 2018. TKIs included in the analysis were bosutinib (n = 2), dasatinib (n = 3), nilotinib (n = 3), and ponatinib (n = 1). As per inclusion criteria, all included studies were randomized, imatinib-controlled trials. Only one study was conducted in a single country (China), and 6 of 9 studies (67%) were conducted in the US or Canada in partnership with other countries. All 3475 patients included in this meta-analysis were diagnosed with the chronic phase of CML (CP CML); 2059 (59.2%) were male patients; and the median (range) patient age was 49 (18 to 91) years.

eTable 2: Characteristics of included studies and quality assessment.

Authors (year)	Trial register	Trial desig	Country	Treatment arm	Number of	Population	Median age	Male,n (%)	Jadad
Gambacorti-Passerini et al,[23]	NCT00574873	Phase III; RCT	30 countries	bosutinib	250	chronic phase CML	48(19-	149(59.	2
				imatinib 400	252		47(18-89)	135(53.6)	
Cortes et al,[24] 2018	NCT02130557	Phase III;	27 countri	bosutinib	268	chronic phase	53(18-	156(58.	2
				imatinib	268		53(19-	155(57.	
Hjorth-Hansen et al,[25] 2014	NCT00852566	Phase II; RCT	Finland, Norway	dasatinib	22	chronic phase CML	53(29-	7(31.8)	2
				imatinib 400	24		58(38-78)	15(62.5)	
Kantarjian et al,[26]	NCT00481247	Phase III;	28 countri	dasatinib	259	chronic phase	46(18-	144(56)	3
				imatinib	260		49(18-	163(63)	
Radich et al,[27] 2012	NCT00070499	Phase II;	Canada, United	dasatinib	123	chronic phase	47(18-	75(61)	3
				imatinib	123		50(19-	72(58.5)	
Hughes et al,[28] 2014	NCT00760877	Phase III;	6 countri	nilotinib	104	chronic phase	46 (23-	71(68.3)	2
				imatinib	103		52 (19-	65(63.1)	
Saglio et al,[29] 2010	NCT00471497	Phase III;	36 countri	nilotinib	563	chronic phase	47(18-	333(59.	3
				imatinib	283		46(18-	158(56)	
Wang et al,[30] 2015	NCT01275196	Phase III;	China	nilotinib	134	chronic phase	41(18-	91(67.9)	3
				imatinib	133		39(19-	81(60.9)	
Lipton et al,[31] 2016	NCT01650805	Phase III;	25 countri	ponatinib	154	chronic phase	55 (18-	97(63)	3
				imatinib	152		52 (18-	92(61)	

Qualität der Studien:

- Since most of the trials were not blinded, all included studies had low to moderate quality with a Jadad score of 2 or 3 (the Jadad score scale ranges from 0 to 5, with higher scores indicating higher study quality).
- Siehe oben, eTable2

Studienergebnisse:

ALT Elevation

- All grades of ALT elevation occurred in 654 of 1840 patients (35.5%) treated with new-generation TKIs vs 151 of 1564 patients (9.7%) treated with imatinib. The use of new-generation TKIs was associated with a statistically significant overall increase in the risk of developing all grades of ALT elevation compared with imatinib (RR, 2.89; 95%CI, 1.78-4.69; P < .001). When stratified by type of drug, bosutinib (RR, 4.27; 95%CI, 2.85-6.39; P < .001), nilotinib (RR, 2.54; 95%CI, 1.26-5.11; P = .009), and ponatinib (RR, 9.87; 95%CI, 2.35-41.50; P = .002) were associated with an increased risk of all grades of ALT elevation, but dasatinib was not associated with an increased risk of all grades of ALT elevation (RR, 0.43; 95%CI, 0.11-1.67; P = .22).
- Grades 3 and 4 ALT elevation was observed in 150 of 1718 patients (8.73%) treated with new-generation TKIs compared with 24 of 1440 patients (1.67%) treated with imatinib. Patients who received new-generation TKIs were more likely to develop grades 3 and 4 elevation of ALT levels (RR, 4.36; 95%CI, 2.00-9.50; P < .001) compared with controls.

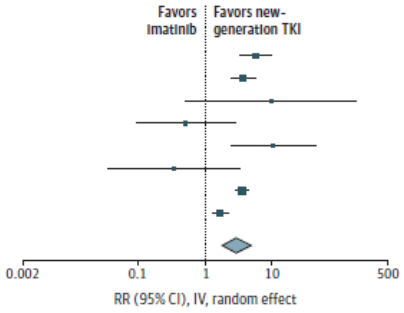
Subgroup analysis indicated that bosutinib (RR, 7.91; 95%CI, 3.77-16.60; P < .001) and nilotinib (RR, 2.94; 95%CI, 1.42-6.06; P < .001) were associated with an increased risk of grades 3 and 4 ALT elevation, whereas dasatinib (RR, 0.50; 95%CI, 0.09-2.71; P = .42) and ponatinib (RR, 14.81; 95%CI, 0.85-256.99; P = .06) were not.

Figure 1. Pooled Analysis of All-Grade and Grades 3-4 Alanine Aminotransferase Elevation

A All grades

Study	New-generation TKI Events	New-generation TKI Total	Imatinib Events	Imatinib Total	RR (95% CI), IV, random effect	Weight, %
Cortes et al,[24] 2018	82	268	15	265	5.41 (3.20-9.12)	18.0
Gambacorti-Passerini et al,[23] 2014	81	248	23	251	3.56 (2.32-5.47)	19.3
Hughes et al,[28] 2014	4	101	0	103	9.18 (0.50-168.27)	2.5
Kantarjian et al,[26] 2011	2	258	4	258	0.50 (0.09-2.71)	6.0
Lipton et al,[31] 2016	20	154	2	152	9.87 (2.35-41.50)	7.6
Radich et al,[27] 2012	1	122	3	123	0.34 (0.04-3.19)	3.9
Saglio et al,[29] 2010	387	556	57	280	3.42 (2.69-4.34)	21.6
Wang et al,[30] 2015	77	133	47	132	1.63 (1.24-2.13)	21.2
Total (95% CI)		**1840**		**1564**	**2.89 (1.78-4.69)**	**100**
Total events	**654**		**151**			

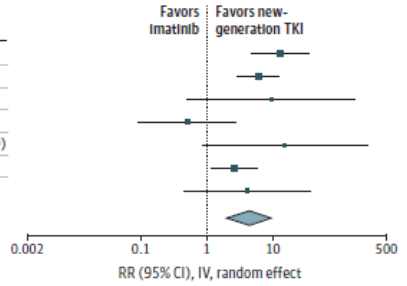
Heterogeneity: $\tau^2=0.27$; $\chi^2=36.39$; $df=7$ ($P<.001$); $I^2=81\%$
Test for overall effect: $Z=4.29$ ($P<.001$)



B Grades 3-4

Study	New-generation TKI Events	New-generation TKI Total	Imatinib Events	Imatinib Total	RR (95% CI), IV, random effect	Weight, %
Cortes et al,[24] 2018	51	268	4	265	12.61 (4.62-34.39)	20.1
Gambacorti-Passerini et al,[23] 2014	46	248	8	251	5.82 (2.80-12.08)	23.8
Hughes et al,[28] 2014	4	101	0	103	9.18 (0.50-168.27)	5.8
Kantarjian et al,[26] 2011	2	258	4	258	0.50 (0.09-2.71)	12.5
Lipton et al,[31] 2016	7	154	0	152	14.81 (0.85-256.99)	6.0
Saglio et al,[29] 2010	36	556	7	280	2.59 (1.17-5.75)	22.9
Wang et al,[30] 2015	4	133	1	132	3.97 (0.45-35.05)	9.0
Total (95% CI)		**1718**		**1441**	**4.36 (2.00-9.50)**	**100**
Total events	**150**		**24**			

Heterogeneity: $\tau^2=0.52$; $\chi^2=13.79$; $df=6$ ($P=.03$); $I^2=56\%$
Test for overall effect: $Z=3.71$ ($P<.001$)

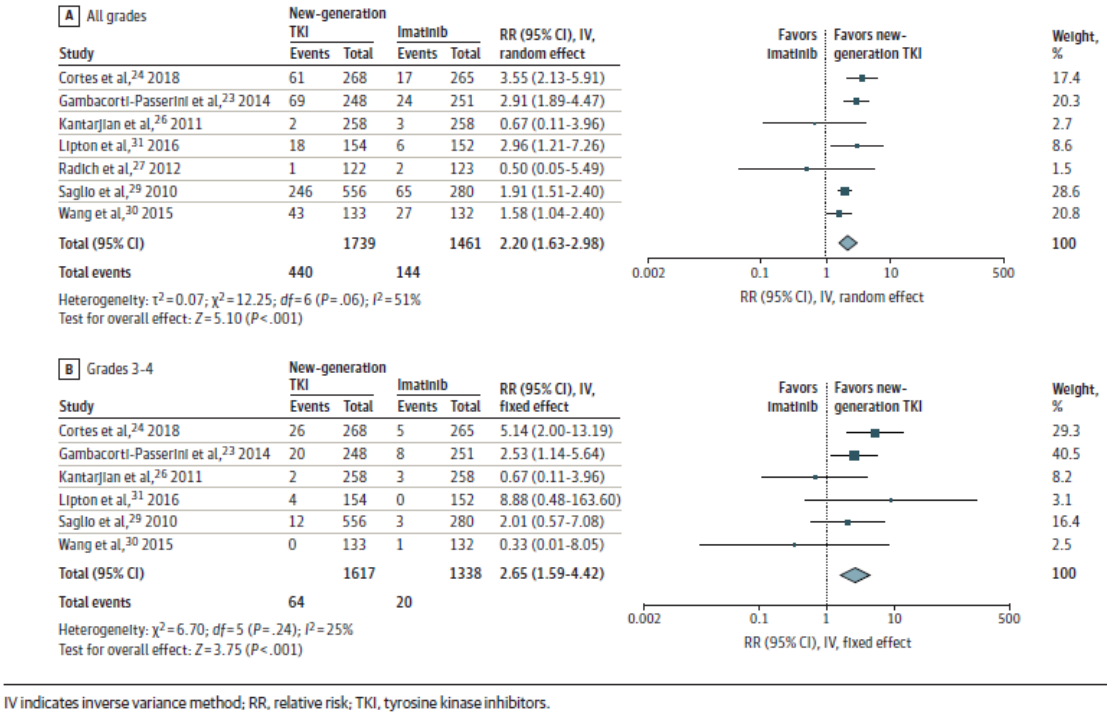


IV indicates inverse variance method; RR, relative risk; TKI, tyrosine kinase inhibitors.

AST Elevation

- All grades of AST elevation occurred in 440 of 1739 patients (25.3%) treated with new-generation TKIs vs 144 of 1461 patients (9.9%) treated with imatinib. New-generation TKIs were also associated with a significantly increased risk of all grades of AST elevation compared with imatinib (RR, 2.20; 95%CI, 1.63-2.98; P < .001). Subgroup analysis indicated that the difference was statistically significant for bosutinib (RR, 3.16; 95%CI, 2.27-4.39; P < .001), nilotinib (RR, 1.82; 95% CI, 1.49-2.23; P < .001), and ponatinib (RR, 2.96; 95%CI, 1.21-7.26; P = .02), whereas no difference was found for dasatinib (RR, 0.60; 95%CI, 0.14-2.51; P = .49).
- Grades 3 and 4 AST elevation was observed in 64 of 1617 patients (3.9%) treated with new-generation TKIs vs 20 of 1338 patients (1.5%) treated with imatinib. Compared with imatinib, new-generation TKIs were associated with a significantly increased risk of high-grade AST elevation (RR, 2.65; 95%CI, 1.59-4.42; P < .001). Significantly increased risks were observed for bosutinib (RR, 3.41; 95%CI, 1.85-6.27; P < .001) but not the other TKIs (dasatinib: RR, 0.67; 95%CI, 0.11-3.96; P = .66; nilotinib: RR, 1.58; 95%CI, 0.49-5.09; P = .44; and ponatinib: RR, 8.88; 95%CI, 0.48-163.6; P = .14).

Figure 2. Pooled Analysis of All-Grade and Grades 3-4 Aspartate Aminotransferase Elevation



IV indicates inverse variance method; RR, relative risk; TKI, tyrosine kinase inhibitors.

Overall Survival

- As shown in Figure 3A, death during the first year occurred in 23 of 1875 patients (1.23%) treated with new-generation TKIs compared with 31 of 1592 patients (1.95%) treated with imatinib. There was no statistical difference in mortality rate at 1 year between new-generation TKIs and imatinib (RR, 1.00; 95%CI, 1.00-1.01; P = .33). Stratification by treatment did not change the results (bosutinib: RR, 1.01; 95%CI, 0.99-1.02; P = .25; dasatinib, RR, 1.00; 95%CI, 0.97-1.02; P = .81; nilotinib: RR, 1.00; 95%CI, 0.99-1.01; P = .83; and ponatinib: RR, 1.01; 95%CI, 0.98-1.03; P = .55).

MMR

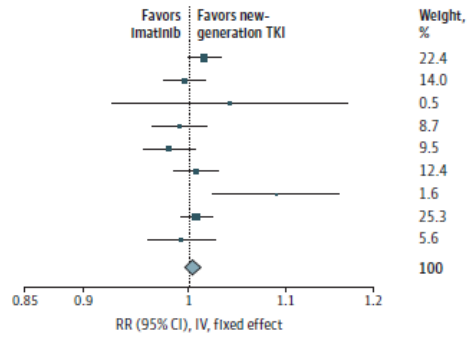
- As shown in Figure 3B, 754 of 1629 patients (46.3%) treated with new-generation TKIs achieved an MMR at 1 year compared with 401 of 1356 patients (29.6%) treated with imatinib. Pooled data showed that new-generation TKIs were associated with a higher rate of MMR at 1 year compared with imatinib (RR, 1.59; 95%CI, 1.44-1.75; P < .001). Similar results were observed for each TKI, although the increase of MMR rate for ponatinib did not achieve statistical significance (bosutinib: RR, 1.37; 95%CI, 1.16-1.61; P < .001; dasatinib: RR, 1.60; 95%CI, 1.34-1.90; P < .001; nilotinib: RR, 1.84; 95%CI, 1.56-2.19; P < .001; and ponatinib: RR, 2.08; 95%CI, 0.98-4.42; P = .06).

Figure 3. Pooled Analysis of Overall Survival and Major Molecular Response

A Overall survival

Study	New-generation TKI Events	New-generation TKI Total	Imatinib Events	Imatinib Total	RR (95% CI), IV, fixed effect	Weight, %
Cortes et al,[24] 2018	268	268	261	265	1.02 (1.00-1.03)	22.4
Gambacorti-Passerini et al,[23] 2014	244	248	248	251	1.00 (0.98-1.02)	14.0
Hjorth-Hansen et al,[25] 2014	22	22	23	24	1.04 (0.93-1.17)	0.5
Hughes et al,[28] 2014	103	104	103	103	0.99 (0.96-1.02)	8.7
Kantarjian et al,[26] 2011	250	258	255	258	0.98 (0.96-1.01)	9.5
Lipton et al,[31] 2016	154	155	150	152	1.01 (0.98-1.03)	12.4
Radich et al,[27] 2012	121	123	111	123	1.09 (1.02-1.16)	1.6
Saglio et al,[29] 2010	559	563	279	283	1.01 (0.99-1.02)	25.3
Wang et al,[30] 2015	131	134	131	133	0.99 (0.96-1.03)	5.6
Total (95% CI)		**1875**		**1592**	**1.00 (1.00-1.01)**	**100**
Total events	**1852**		**1561**			

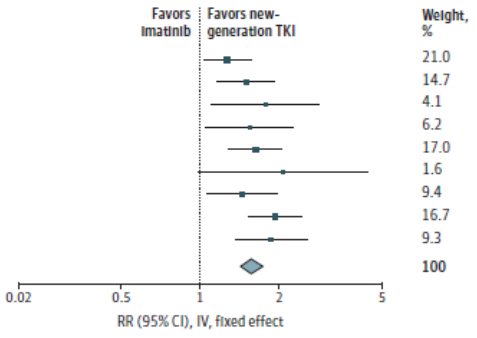
Heterogeneity: $\chi^2 = 14.40$; $df = 8$ ($P = .07$); $I^2 = 44\%$
Test for overall effect: $Z = 0.97$ ($P = .33$)



B Major molecular response

Study	New-generation TKI Events	New-generation TKI Total	Imatinib Events	Imatinib Total	RR (95% CI), IV, fixed effect	Weight, %
Cortes et al,[24] 2018	116	246	89	241	1.28 (1.03-1.58)	21.0
Gambacorti-Passerini et al,[23] 2014	101	248	68	251	1.50 (1.17-1.93)	14.7
Hjorth-Hansen et al,[25] 2014	18	22	11	24	1.79 (1.11-2.88)	4.1
Hughes et al,[28] 2014	20	24	15	28	1.56 (1.05-2.29)	6.2
Kantarjian et al,[26] 2011	119	259	73	260	1.64 (1.29-2.07)	17.0
Lipton et al,[31] 2016	8	10	5	13	2.08 (0.98-4.42)	1.6
Radich et al,[27] 2012	58	123	40	123	1.45 (1.06-1.99)	9.4
Saglio et al,[29] 2010	244	563	63	283	1.95 (1.54-2.47)	16.7
Wang et al,[30] 2015	70	134	37	133	1.88 (1.37-2.58)	9.3
Total (95% CI)		**1629**		**1356**	**1.59 (1.44-1.75)**	**100**
Total events	**754**		**401**			

Heterogeneity: $\chi^2 = 9.28$; $df = 8$ ($P = .32$); $I^2 = 14\%$
Test for overall effect: $Z = 9.36$ ($P < .001$)



IV indicates inverse variance method; RR, relative risk; TKI, tyrosine kinase inhibitors.

Anmerkung/Fazit der Autoren

This meta-analysis found a significant increase in the risk of hepatotoxicity associated with the use of bosutinib, nilotinib, and ponatinib compared with imatinib. Treatment with these TKIs should be considered with frequent hepatic function monitoring. As the risk of hepatotoxicity of nilotinib seems to be associated with the dose administered, further studies are needed to clearly define the dose regimen of each BCR-ABL TKI, which will provide the best clinically relevant benefit risk profile.

Kommentare zum Review

- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.
- Untersuchte Interventionen umfassen auch Ponatinib, welches keine Zulassung im AWG hat

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Vener C et al., 2020 [6].

First-line imatinib vs second- and third-generation TKIs for chronic-phase CML: a systematic review and meta-analysis

Fragestellung

to provide comprehensive, updated, and precise information regarding the comparative efficacy and safety of TKIs (imatinib vs dasatinib, nilotinib, bosutinib, ponatinib), with particular emphasis on drug-related AEs.

Methodik

Population:

- adults with newly diagnosed Ph1 CP CML

Intervention:

- imatinib

Komparator:

- second-generation (dasatinib, nilotinib, bosutinib) and third generation (ponatinib) TKIs

Endpunkte:

- OS, progression-free survival (PFS), response, and safety (hematological and nonhematological AEs)

Recherche/Suchzeitraum:

- PUBMED, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.Gov databases
- RCTs or quasi-RCTs conducted between 1990 and 28 May 2019

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven RCTs published between 1990 and 2019 (involving 3262 participants)

Qualität der Studien:

- All of the articles were at low risk except for the risk-of-performance bias (although it must be remembered that blinding trial participants and study personnel may not be ethical in an oncological setting) and the risk of “other bias” (6 of the 7 trials [85.7%] were sponsored by a pharmaceutical company).
- GRADE showed that the certainty of the evidence ranged from high to moderate.

Studienergebnisse:

- Two RCTs (imatinib vs nilotinib and imatinib vs dasatinib) found no difference in 5-year OS or PFS.
- Second- and third-generation TKIs improved 3-month major molecular responses (relative risk [RR], 4.28; 95% confidence interval [CI], 2.20-8.32) and other efficacy outcomes, decreased accelerated/blastic-phase transformations (RR, 0.44; 95% CI, 0.26-0.74), but were associated with more cases of thrombocytopenia (RR, 1.57; 95% CI, 1.20-2.05), cardiovascular events (RR, 2.54; 95% CI, 1.494.33), and pancreatic (RR, 2.29; 95% CI, 1.32-3.96) and hepatic effects (RR, 3.51; 95% CI 1.557.92).

Anmerkung/Fazit der Autoren

In conclusion, on the basis of secondary efficacy outcomes, the findings of our meta-analysis, supported by GRADE-assessed quality evidence,28 suggest that patients with newly diagnosed CP CML without comorbidities should receive second- or third-generation TKIs; however, on the basis of toxicity outcomes, patients with comorbidities should preferably be treated with imatinib. The use of imatinib is further supported by the current availability of a cheaper generic imatinib. Our data could be used to implement a health

technology assessment, and the updated RCT FU data may be useful for making a meta-analysis of primary efficacy outcomes such as OS and PFS after 60 months or more.

We cannot recommend a specific newer TKI because there are no head-to-head RCTs: a network meta-analysis is required. The definition of the optimal TKI for patients with newly CP CML should consider AEs and comorbidities as well as molecular/cytogenetic responses and transformation rates.

3.3 Leitlinien

Smith G et al., 2020 [5].

British Society for Haematology (BSH)

A British Society for Haematology Guideline on the diagnosis and management of chronic myeloid leukaemia.

Zielsetzung/Fragestellung

To provide healthcare professionals with clear guidance on the investigation and management of CML in adults and children.

Methodik

This guideline was compiled according to the British Society for Haematology (BSH) process described at http://www.b-sh.org.uk/guidelines.

Grundlage der Leitlinie

- Repräsentativität des LL-Gremiums unklar; Patientenvertretung im Reviewprozess involviert (This guideline has also been reviewed by patient representatives from CML Support (http://www.cmlsupport.org). These organisations do not necessarily endorse the contents.)
- Interessenkonflikte und finanzielle Unabhängigkeit: The BSH paid expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and task force Chairs which may be reviewed upon request.
- Systematische Suche der Literatur ausführlich dargelegt
- Keine Informationen zur systematischen Auswahl und Bewertung der Literatur
- Keine Angaben zum Konsensusprozess
- Externes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig.
- Verbindung zwischen Empfehlung und zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- In MEDLINE and EMBASE up to January 2018.

LoE/GoR

- The Grading of Recommendations Assessment (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations.

Sonstige methodische Hinweise

- *Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.*

Recommendation for primary therapy for patients in chronic phase

- Imatinib is the recommended first-line treatment for the majority of adults and children with CML presenting in CP. Grade IA

- All patients should have baseline assessment with an electrocardiogram (ECG), lipid profile, fasting glucose or HbA1c, cardiovascular disease risk assessment, and hepatitis B and C screening. Grade 2B
- Consider a 2GTKI for:
  - patients with a high or intermediate ELTS or Sokal score. Grade 2B
  - patients who wish to explore treatment discontinuation at an early stage, e.g. female patients who wish to become pregnant. Grade 2B
- Co-morbidities should be assessed to help in the choice of 2GTKI. Grade 2B

Background:

- Four TKIs— imatinib, and the second generation (2G) TKIs bosutinib, dasatinib and nilotinib — are now licensed for use in newly diagnosed patients, of which all but bosutinib are NICE-approved. The 2GTKIs have been trialled directly against imatinib in large phase III randomised studies with remarkably similar results to each other (Appendix 1).
- The majority of patients diagnosed in 2019 have a realistic prospect of a life expectancy similar to that of the normal population.[11] For many patients there is no reason to choose a 2GTKI over imatinib which has a well-established safety profile with no life-threatening long-term side effects identified to date.[63] More patients are likely to die of causes other than their leukaemia, and co-morbidities are more predictive of death.[136] Furthermore the German CML IV study showed that 88% of imatinib-treated patients (some receiving higher doses of 800 mg) achieved a major molecular response (MMR) by 10 years suggesting efficacy similar to that seen with 2GTKIs.[58] In children, first-line imatinib therapy achieves 60–70% complete cytogenetic response (CCyR) rates and 45% MMR rates at 12 months.[150]
- However, there are some groups in CP that might benefit from 2GTKIs upfront:
  - 1. Patients with high or intermediate ELTS or Sokal scores in whom a reduction in disease progression has been demonstrated with a first-line 2GTKI.[30,79,96,158]
  - 2. Women who wish to have children, where the more rapid molecular response achieved with a 2GTKI is desirable (see the section ‘CML and parenting’).
  - 3. ‘Younger’ patients, nominally the under 30s, and children, who are excellent candidates for stem cell transplantation if the need arises, and in whom concerns have been raised regarding more aggressive disease at presentation.[17] In a Phase II study as first-line therapy in children, dasatinib achieved a 92% CCyR and 52% MMR at 12 months in CP CML leading to a licence for its use.[51]
- The early use of a more potent TKI should be balanced against the risk of inducing and/or exacerbating concomitant illnesses (Table II). This is particularly pertinent in older patients as the number of co-morbidities increases with advancing age.[136] Although there is no evidence that older patients respond less well to TKI[10,15,28] older subjects may handle drugs differently and/or be receiving other medications affecting the CYP450 pathway (which decrease TKI metabolism and enhance their complications) and hence often require more frequent dose reductions or treatment interruptions than younger patients.[97]
- All patients should have assessment of cardiac risk using a cardiovascular disease (CVD) risk assessment algorithm (QRisk3) -or equivalent, electrocardiogram (ECG), baseline estimates of lipid profiles, and fasting glucose and/or HbA1c levels.[154] Given recent data suggesting the use of TKIs may be associated with reactivation of hepatitis viruses, all patients should have pre-treatment hepatitis B and C serology assessments.[74]

Table II. Guidelines for first-line TKI choice by pre-existing medical condition (adapted from Michael Deininger, personal communication).

Co-morbidity	Bosutinib	Dasatinib	Imatinib	Nilotinib
Hypertension				
Ischaemic heart disease				
Cerebrovascular thrombosis				
Peripheral arterial occlusive disease				
Prolonged QT interval*				
Congestive cardiac failure				
Diabetes mellitus				
Gastrointestinal bleeding†				
Pulmonary hypertension				
Chronic pulmonary disease				
Pancreatitis				
Abnormal liver function				

■, no contra-indication; ■, low risk of exacerbation of pre-existing condition; ■, intermediate risk of exacerbation of pre-existing condition; ■, avoid if possible.

*Some evidence that all 2GTKI prolong QT.

†Imatinib has been associated with the development of gastric antral vascular ectasia (GAVE).

Appendix 1

First-line TKI therapy.

- Studies of imatinib versus 2GTKIs show that, with a maximum of five years follow-up, there are no differences in OS,[30,32,66,79,85,88,90,96,133] although differences are beginning to emerge with respect to a lower incidence of CML-related deaths in the 2GTKI arms, particularly with nilotinib.[66]
- This is supported by a reduction in the number of patients experiencing disease progression on 2GTKI. It is also clear that the 2GTKIs not only induce deeper molecular responses in a higher proportion of patients, but also achieve these responses more rapidly (Table AI).

Table AI. Outcome of first-line therapy with TKIs, derived from Phase II randomised commercial studies* and TIDEL-II reflecting early switch of imatinib to nilotinib.

	Imatinib vs. bosutinib[1]	Imatinib vs. dasatinib	Imatinib vs. nilotinib[2]	TIDEL-II Single arm
5-yr overall survival (%)	NA	90 vs. 91	91·7 vs. 93·7	96
PFS (%)	NA	86 vs. 85	91 vs. 92·2	95
5-yr freedom from CML- related death(%)	NA	NG	93·8 vs. 97·7	NG
No. of progressions				
12 months	6 vs. 4	9 vs. 5	11 vs. 2	NG
36 months	NA	13 vs. 8	12 vs. 2	7
60 months	NA	19 vs. 12	21 vs. 10	NA
No. of patients dying of CML by five years		17 vs. 9	16 vs. 6	5
CCyR (%)				
12 months	66·4 vs. 77·2	72 vs. 83	65 vs. 80	87
24 months	NA	82 vs. 86	77 vs. 87	83
36 months	NA	83 vs. 87	NG	NG
MR3 (MMR) (%)				
12 months	36·9 vs. 47·2	28 vs. 46	27 vs. 55	62
24 months	NA	46 vs. 64	44 vs. 67	70
60 months	NA	64 vs. 76	60·4 vs. 77	NG
MR4 (%)				
24 months	NA	22 vs. 44	18 vs. 33	33
60 months	NA	NG	41·7 vs. 65·6	NG
MR4·5 (%)				
24 months	NA	8 vs. 19	9 vs. 25	32
60 months	NA	33 vs. 42	31·4 vs. 53·5	NG
MR3 (MMR) at three years (%) Hasford[d]/Sokal[n]				
Low	46·3 vs. 58·1**	65 vs. 83	62·5 vs. 76·7	79[3]
Intermediate	39·1 vs. 44·9**	57 vs. 65	54·5 vs. 75·2	
High	16·7 vs. 34**	42 vs. 61	38·5 vs. 66·7	72

1 = 12 months follow-up data only available at the FDA approved starting dose of 400 mg daily.
2 = Nilotinib results given for 300 mg bd as this is the dose licensed for use in newly diagnosed patients
3 = results at 24 months.
[d] = dasatinib, [n] = nilotinib, NA = not applicable, NG = not given, ** = results at 12 months.
*The following studies are included: 30,32,66,79,85,88,90,96,133. Direct comparison of the individual trials is not possible because of differences between studies including eligibility/ineligibility criteria, definitions of response evaluations and methodology of analysis.

Management of patients who are resistant to or intolerant of first-line therapy

Recommendations

- Change to an alternative TKI should be considered if treatment failure on first-line therapy is documented. Grade 1A
- The choice of second-line therapy in resistant patients is initially guided by BCR-ABL1 KD mutational analysis. Grade 1B
- Dose escalation to 600 mg of imatinib per day is reasonable for patients with a suboptimal response meeting the ELN 'warning' criteria and with good tolerance of the standard dose. Grade 2B
- In the absence of specific mutations the patients preexisting co-morbidities and the known side effect profiles of the 2GTKIs should inform the treatment choice. Grade 2B

Management of patients with advanced-phase disease — accelerated phase and blast crisis

Recommendations

- Patients in de novo AP CML should ideally be treated with a 2GTKI or with consideration of alloSCT if suboptimal response. Grade 1B
- All responding, transplant-eligible patients in BC CML should proceed to alloSCT. Grade 1B

Allogeneic stem cell transplantation in CML

Recommendations

- AlloSCT should be considered for CP CML patients who are resistant to at least one 2GTKI, though a trial of a 3GTKI is reasonable prior to committing to transplantation. Some patients with intolerance to multiple TKIs may justifiably proceed to fourth-line therapy. Grade 2B
- Use of TKIs post-transplant may be needed in selected patients previously in AP or BC CML, especially following a RIC transplant. Grade 2B
- AlloSCT is recommended for the majority of eligible patients progressing to AP CML, but not those presenting in AP and achieving an optimal cytogenetic and MR to TKI therapy. Grade 2A
- Achievement of CP2 using chemotherapy/alternative TKIs prior to allograft is recommended. Grade 2A
- Three-monthly molecular monitoring post-transplant and intervention with DLI and/or TKI (if there is a drug available to which the patient is not resistant) is advised to treat MRD and/or molecular relapse. Grade 2A

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National Comprehensive Cancer Network (NCCN), 2024 [3].

Chronic myeloid leukemia; version 3.2025 - November 27, 2024

Zielsetzung/Fragestellung

Management of CML.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar
- Interessenkonflikte und finanzielle Unabhängigkeit unklar;
- Systematische Suche, Auswahl und Bewertung der Evidenz unklar;
- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar;

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- unklar

LoE/GoR

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 indicated.

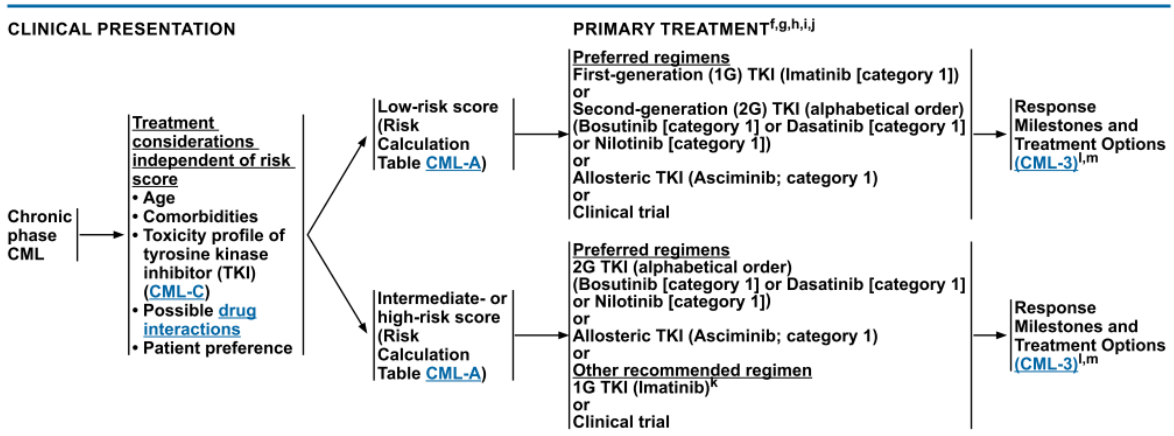
NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Sonstige methodische Hinweise

- *Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.*

Empfehlungen



[f] If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon alfa-2a; in the United States, peginterferon alfa-2a is the only interferon available for clinical use. TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. See Management of CML During Pregnancy (CML-E).
[g] Based on follow-up data from the BFORE, DASISION, ENESTnd, and ASC4FIRST trials, 2G TKIs (bosutinib, dasatinib, or nilotinib) and allosteric TKIs (asciminib) are preferred for patients with an intermediate- or high-risk score. 2G and allosteric TKIs should also be considered for specific subgroups (based on the assessment of treatment goals and benefit/risks), for example, younger patients who are interested in ultimately discontinuing treatment and especially young patients assigned female at birth whose goal is to achieve a deep and rapid molecular response and eventual discontinuation of TKI therapy for family planning purposes.
[h] Limited available evidence from small cohort studies suggests that initiation of first-line TKIs (bosutinib, dasatinib, or nilotinib) at lower doses (to minimize treatment-related adverse events) and dose reduction (with close monitoring) in patients who achieve optimal responses are appropriate strategies to reduce the risk of long-term toxicities. However, the minimum effective dose or optimal de-escalation of TKI (bosutinib, dasatinib, or nilotinib) has not yet been established in prospective randomized clinical trials. See the Discussion section for *Dose Modifications of TKI Therapy*.
[i] TKIs (e.g. nilotinib) are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[j] Innovator and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. FDA-approved generic versions are appropriate substitutes for innovator drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116).
[k] Imatinib may be preferred for patients who are older with comorbidities such as cardiovascular disease.
[l] Criteria for Response and Relapse (CML-F).
[m] Monitoring Response to TKI Therapy and Mutational Analysis (CML-G).

Note: All recommendations are category 2A unless otherwise indicated.

CML-2

EARLY TREATMENT RESPONSE MILESTONES
CRITERIA FOR RESPONSE AND RELAPSE

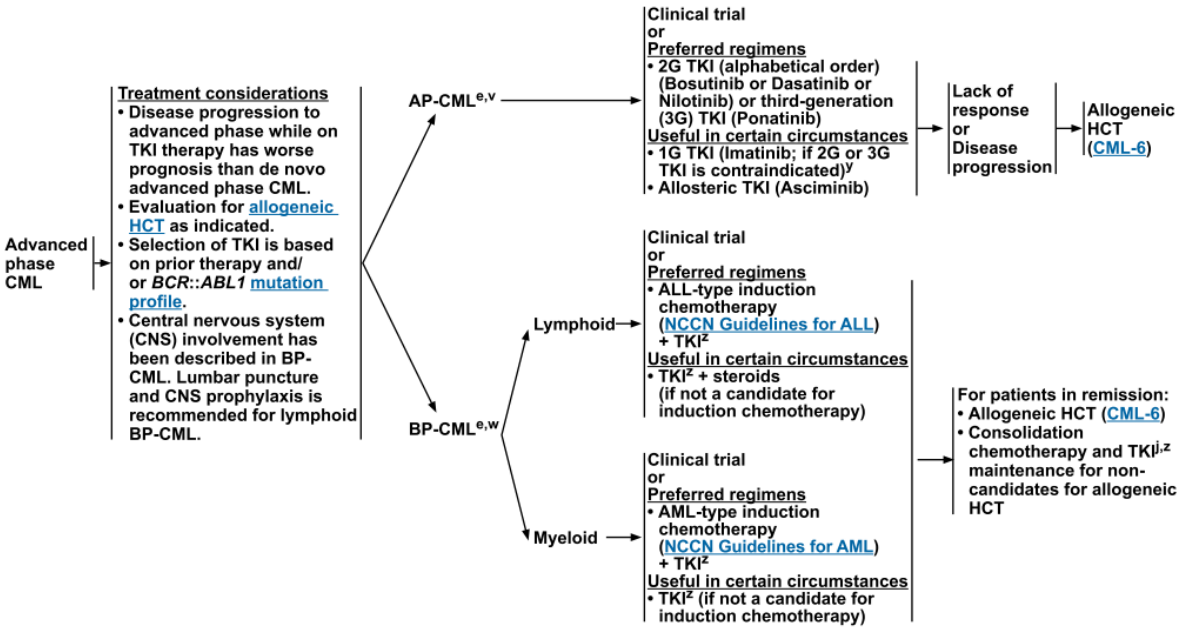
BCR::ABL1 (IS)	3 months	6 months	12 months[n]
>10%[o]	YELLOW	RED	
>1%–10%[p]	GREEN		ORANGE
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS[r]	RECOMMENDATIONS[r,i]
RED	TKI-resistant disease[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s] • Consider bone marrow cytogenetic analysis to assess additional chromosomal abnormalities (ACAs)	Switch to alternate TKI (CML-5) (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s]	Switch to alternate TKI (CML-5) or Continue same TKI[o]
ORANGE **NEW**	Possible TKI resistance[q]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[s] • Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo	Consider switch to alternate TKI[p] (CML-5) or Continue the same TKI if CCyR is achieved
LIGHT GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[q,t]
GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • Monitor response (CML-G)	Continue same TKI[u]

Footnotes on CML-3A

Note: All recommendations are category 2A unless otherwise indicated.

CLINICAL PRESENTATION — **TREATMENT[f,j,x]**



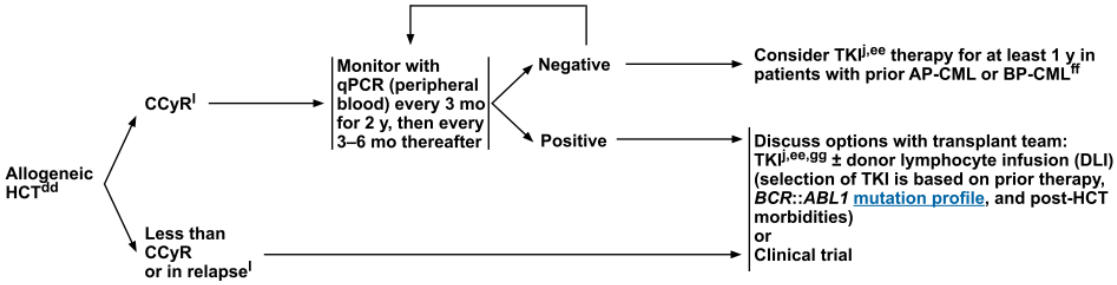
Footnotes on CML-4A

Note: All recommendations are category 2A unless otherwise indicated.

FOOTNOTES FOR ADVANCED PHASE CML

[e] Definitions of Advanced Phase CML (CML-B).
[f] If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon alfa-2a; in the United States, this is the only interferon available for clinical use. TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. See Management of CML During Pregnancy (CML-E).
[j] Innovator and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. FDA-approved generic versions are appropriate substitutes for innovator drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116).
[v] The presence of major route ACAs in Ph-positive cells (trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) may have a negative prognostic impact on survival. Patients who present with accelerated phase at diagnosis should be treated with a TKI at the FDA-approved dose for accelerated phase, followed by evaluation for allogeneic HCT, based on response to therapy. Consider evaluation for allogeneic HCT if response milestones are not achieved at 3, 6, and 12 months as outlined on CML-3.
[w] TKI (alone or in combination with minimal chemotherapy or steroids) is less effective in BP-CML compared to Ph-positive ALL. Interphase FISH for the detection of *BCR::ABL1* transcript on blood granulocytes is recommended to differentiate between de novo BP-CML and de novo Ph-positive ALL.
[x] TKI dose for advanced phase CML may differ from CP-CML. TKIs (e.g. nilotinib) are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[y] Imatinib is not recommended for patients with disease progression on prior TKI therapy.
[z] 2G or 3G TKI is preferred. Consider imatinib for patients with contraindications to 2G or 3G TKI.

ADDITIONAL THERAPY[i]



[i] TKIs (e.g. nilotinib) are available in different formulations, dosage forms, and strengths that are subject to different administration instructions. These products are not interchangeable. Refer to package insert for full prescribing information for specific TKIs: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[j] Innovator and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. FDA-approved generic versions are appropriate substitutes for innovator drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116).
[l] Criteria for Response and Relapse (CML-F).
[dd] Indications for allogeneic HCT: CP-CML with resistance and/or intolerance to all available TKIs; advanced phase CML at presentation or disease progression to BP-CML. Outcomes of allogeneic HCT are dependent on age, comorbidities, donor type, and transplant center.
[ee] Ponatinib is a treatment option for patients with a T315I mutation in any phase (preferred for AP-CML or BP-CML). It is also a treatment option for CP-CML with resistance or intolerance to at least two prior TKIs or for patients with AP-CML or BP-CML for whom no other TKI is indicated. There are compound mutations (defined as harboring ≥2 mutations in the same *BCR::ABL* allele) that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.
[ff] Carpenter PA, et al. Blood 2007;109:2791-2793; Olavarria E, et al. Blood 2007;110:4614-4617; DeFilipp Z, et al. Clin Lymphoma Myeloma Leuk 2016;16:466-471.
[gg] Asciminib is a treatment option for patients with CP-CML having the T315I mutation and/or previously treated CP-CML.

Note: All recommendations are category 2A unless otherwise indicated.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library – Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2024) am 11.12.2024

#	Suchschritt
1	[mh “Leukemia, Myelogenous, Chronic, BCR-ABL Positive”]
2	Chronic:ti,ab,kw OR (“Philadelphia+” OR “Ph1 Positive” OR “Ph Positive” OR “ph+” OR “Philadelphia Positive” OR “Philadelphia+” OR “BCR-ABL Positive” OR “BCR-ABL+” OR “chromosome positive” OR “chromosome +”):ti,ab,kw
3	(myeloid OR myelogenous OR myelocytic or myelos?s OR granulocytic):ti,ab,kw
4	(leu?em* OR leu?*m* OR “cancer of blood” OR “malignant neoplastic disease”):ti,ab,kw
5	#2 AND #3 AND #4
6	(CML OR CGL):ti,ab,kw
7	#1 OR #5 OR #6
8	#7 with Cochrane Library publication date from Dec 2019 to present, in Cochrane Reviews

Leitlinien und systematic Reviews in PubMed am 11.12.2024

verwendeter Suchfilter für Leitlinien ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchschritt
	Leitlinien
1	“leukemia, myelogenous, chronic, bcr abl positive”[mh]
2	chronic[tiab] OR Ph1 Positive[tiab] OR Ph Positive[tiab] OR Ph1+[tiab] OR Ph+[tiab] OR Philadelphia Positive[tiab] OR Philadelphia+[tiab] OR BCR-ABL Positive[tiab] OR “BCR-ABL +”[tiab] OR “chromosome positive”[tiab] OR “chromosome +”[tiab]
3	(myeloid [tiab] OR myelogenous[tiab] OR myelocytic[tiab] OR myelosis[tiab] OR myeloses[tiab] OR granulocytic[tiab])
4	(leukem*[tiab] OR leucem*[tiab] OR leukaem*[tiab] OR leucaem*[tiab])
5	#2 AND #3 AND #4
6	CML[tiab] OR CGL[tiab] OR “chronic myelosis”[tiab]
7	Leukemia, Myeloid[mh:noexp]
8	Myeloproliferative Disorders[mh:noexp]
9	(myeloid [ti] OR myelogenous[ti] OR myelocytic[ti] OR myelosis[ti] OR myeloses[ti] OR granulocytic[ti])
10	(leukem*[ti] OR leucem*[ti] OR leukaem*[ti] OR leucaem*[ti])
11	#9 AND #10
12	myeloproliferative[ti]
13	#1 OR #5 OR #6 OR #7 OR #8 OR #11 OR #12
14	(#13) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
15	(#14) AND (“2019/12/01”[PDAT] : “3000”[PDAT])
16	(#15) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	systematische Reviews
17	#1 OR #5 OR #6
18	(#17) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR “overview of reviews”[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence

#	Suchschritt
	review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR (((“evidence based” [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR “risk of bias”[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR 29ochrane[tiab] OR pubmed[tiab] OR “web of science” [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
19	(#18) AND (“2019/12/01”[PDAT] : “3000”[PDAT])
20	(#19) NOT “The Cochrane database of systematic reviews”[Journal]
21	(#20) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])
	systematische Reviews ohne Leitlinien
22	(#21) NOT (#16)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 12.12.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-301

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	3. Januar 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
Behandlung von Erwachsenen mit Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie in der chronischen Phase (Ph+ CML-CP), die zuvor mit zwei oder mehr Tyrosinkinase-Inhibitoren behandelt wurden
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Es wird vorausgesetzt, dass die o. g. Behandlungsindikation zusätzlich beinhaltet, dass die Patientinnen und Patienten auf die laufende Therapie nicht ausreichend ansprechen oder diese nicht ausreichend gut vertragen und deshalb eine weitere Therapieoption gesucht werden muss. Für die Auswahl der weiteren Therapiestrategie sollten die folgenden Fragen geklärt sein: • Welche Tyrosinkinase-Inhibitoren wurden mit welchem Therapieergebnis in den vorangegangenen Linien verwendet? • Ist der Patient aufgrund von Allgemeinzustand, Alter und Begleiterkrankungen für eine allogene Stammzelltransplantation geeignet? Wie hoch wäre das transplantationsbedingte Risiko von Tod oder schweren Komplikationen einzuschätzen? • Besteht die Indikation zum Wechsel der Therapie in einer Intoleranz oder in einer unzureichenden Wirksamkeit der letzten Therapie? Für die Definition einer unzureichenden Wirksamkeit erfolgt meist eine Orientierung an den Empfehlungen des European LeukemiaNet (1). • Falls eine unzureichende Wirksamkeit vorliegt: Konnte eine BCR::ABL-Mutation gefunden werden, die das fehlende Ansprechen erklärt? Für Patienten, bei denen keine BCR::ABL-Mutation gefunden wird, die ein unzureichendes Ansprechen erwarten lässt (insbesondere T315I), war in der randomisierten ASCEMBL-Studie Asciminib Bosutinib überlegen und ist nach derzeitigem Stand Therapie der Wahl (2). In der

genannten Studie wurde auch diese wirksame Therapie mit Asciminib jedoch nur bei gut der Hälfte der Patientinnen und Patienten langfristig erfolgreich fortgeführt. Insbesondere bei Patientinnen und Patienten, bei denen die Therapie versagte (im Unterschied zu einer Unverträglichkeit) – als Indikation für die Drittlinientherapie –, sollte deshalb eine allogene Stammzelltransplantation unter Beachtung der transplantationsbedingten Risiken zur Konsolidierung oder auch als Reserveoption bei ungenügendem Ansprechen erwogen werden. Für Patientinnen und Patienten, die Asciminib bereits in der 1. oder 2. Therapielinie erhalten haben (in dieser Indikation in Deutschland aber bisher nicht zugelassen), sollte unter Beachtung des Nebenwirkungsprofils und möglicherweise nachgewiesener Resistenzmutationen ein anderer zugelassener Tyrosinkinase-Inhibitor gewählt werden. Eine eindeutig zu bevorzugende Substanz ist in dieser Konstellation nicht definiert. In dieser Konstellation ist eine allogene Stammzelltrans-plantation zur Konsolidierung zu empfehlen, wenn machbar. Bei Patienten mit BCR::ABL-Mutation T315I wird bei Beachtung entsprechender Kontraindikationen (insbesondere kardiovaskuläre Erkrankungen oder erhöhtes kardiovaskuläres Risiko) Ponatinib empfohlen, das bei dieser Mutation wirksamer ist als andere Tyrosinkinase-Inhibitoren (3, 4). Auch hier ist konsolidierend eine allogene Stammzelltransplantation indiziert, wenn der Zustand des Patienten dies zulässt.
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o. g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Kriterien für die Auswahl der Therapieoptionen siehe oben.

Referenzliste:

1. Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 2020; 34(4):966–84. doi: 10.1038/s41375-020-0776-2.
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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2024-B-301

Verfasser	
Institution	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie DGHO
Sachverständige	
Datum	8. Januar 2025

Indikation
Behandlung von Erwachsenen mit Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie in der chronischen Phase (Ph+ CML-CP), die zuvor mit zwei oder mehr Tyrosinkinase-Inhibitoren behandelt wurden
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Standard in der Therapie von Patientinnen und Patienten (Pat.) mit Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie in der chronischen Phase (Ph+ CML-CP), nach Vorbehandlung mit zwei oder mehr Tyrosinkinase-Inhibitoren ist eine Therapie nach ärztlicher Maßgabe unter Berücksichtigung von Vortherapie, Mutationsstatus, Komorbidität und Kapazität der normalen Hämatopoese. Spezifisch für diese Situation stehen zur Verfügung:

- Asciminib
- Ponatinib
- Allogene Stammzelltransplantation

Stand des Wissens

Die Auswahl der Therapie in den späteren Therapielinien erfolgt nach klinischen Kriterien und vorliegenden BCR::ABL1-Mutationen. Grundsätzlich können TKI eingesetzt werden, die in der sog. Erst- und Zweitlinientherapie bereits zugelassen sind. Hierzu gehören (alphabetische Reihenfolge): Bosutinib, Dasatinib, Imatinib und Nilotinib.

Nach Vortherapie mit zwei oder mehr Tyrosinkinase-Inhibitoren wird eine individualisierte Therapie nach zytogenetischem und molekularem Ansprechen, nach klinischen Kriterien in Bezug auf das Nebenwirkungsspektrum und nach Mutationsstatus bei Resistenz auf die Primärtherapie empfohlen. Zugelassen und empfohlen für diese Situation sind:

- Asciminib

  Asciminib ist zugelassen zur Behandlung von Pat. mit Philadelphia-Chromosom-positiver CML in der chronischen Phase (Ph+CML-CP) nach Vorbehandlung mit zwei oder mehr Tyrosinkinase-Inhibitoren. Asciminib ist ein Tyrosinkinase-Inhibitor (TKI) mit einem neuen Wirkmechanismus. In der Zulassungsstudie ASCEMBL führte Asciminib gegenüber Bosutinib

zu einer höheren Rate guter molekularer Remissionen (MMR) und kompletter zytogenetischer Remissionen (CCyR) [1, 2].]. Für die Behandlung von Pat. mit T315I-Mutation sind höhere, in der EU bisher nicht zugelassene Dosierungen erforderlich.

- Ponatinib

  Ponatinib ist zugelassen für die Therapie von Pat., die nicht auf Dasatinib oder Nilotinib ansprechen bzw. nicht tolerieren, und für die für eine Therapie mit Imatinib nicht in Frage kommt. Bei Patienten mit T315I-Mutation ist in Standarddosierung lediglich für Ponatinib eine Wirksamkeit nachweisbar [3]. Ponatinib ist nur eingeschränkt indiziert für Patienten mit vaskulären Komorbiditäten.

- Allogene Stammzelltransplantation

  Die allogene Stammzelltransplantation ist eine kurative Option für Patienten nach Versagen der Standardtherapie oder bei Vorliegen schwerer biologischer Befunde, die den raschen Übergang in eine Blastenphase befürchten lassen (zytogenetische Hochrisiko-Aberrationen, rezidivierende schwere Zytopenien). Die Durchführung der Transplantation in chronischer Phase ist mit deutlich besseren Ergebnissen als in fortgeschrittenen Stadien der CML verbunden, deshalb sollte die Indikationsstellung möglichst früh erfolgen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, diese sind oben dargestellt.

Referenzliste:

1. Réa D, Mauro MJ, Boquimpani C et al.: A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 138:2031–2041, 2021. DOI: 10.1182/blood.2020009984
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3. Cortes JE, Kim DW, Pinilla-Ibarz J et al.: A phase 2 trial of ponatinib in Philadelphia-chromosome – positive leukemias. N Engl J Med 369:1783-1796, 2013. DOI: 10.1056/NEJMoa1306494