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: 2025-B-290-z Asciminib

Stand: Dezember 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 20. November 2025 (3. Linie) • Bosutinib: Beschluss vom 19. November 2021 (neu diagnostizierte CML) • Ponatinib: Beschluss vom 20. November 2020 (2. Linie) • Bosutinib: Beschluss vom 21. Februar 2019 (2. Linie)
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®	Anwendungsgebiet nach Positive Opinion: Scemblix ist indiziert für die Behandlung von erwachsenen Patienten mit Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie in der chronischen Phase (Ph+ CML-CP).
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:	
Asciminib L01EA06 Scemblix®	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
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	• 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
Immunmodulatoren:	
Interferon alfa-2a L03AB04 Roferon®-A[1]	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: • Philadelphia-Chromosom-positive, chronische-myeloische Leukämie (CML) in der chronischen Phase. Für CML-Patienten, die eine HLA-identischen Verwandten haben und für die eine allogene Knochenmarktransplantation in der näheren Zukunft geplant ist oder möglich erscheint, stellt die Therapie mit Roferon-A keine Alternative dar. Es ist noch unbekannt, ob eine Behandlung mit Roferon-A als Therapie mit kurativem Potential für diese Indikation angesehen werden kann.
Interferon alfa-2b L03AB05 IntronA®	Chronische myeloische Leukämie: Monotherapie: Behandlung erwachsener Patienten mit Philadelphia-Chromosom- oder bcr/abl-translokations-positiver, chronischer myeloischer Leukämie. Klinische Erfahrungen zeigen, dass bei der Mehrheit der behandelten Patienten ein hämatologisches und zytogenetisches Ansprechen in verschieden starkem Ausmaß erreicht werden kann. Ein zytogenetisches Ansprechen von starkem Ausmaß ist definiert durch < 34 % Ph+ Leukämie-Zellen im Knochenmark, während ein schwaches Ansprechen definiert ist durch ≥ 3,4 %, jedoch < 90 % Ph+ Zellen im Knochenmark. Kombinationstherapie Die Anwendung der Kombinationstherapie von Interferon alfa-2b mit Cytarabin (Ara-C) während der ersten 12 Behandlungsmonate zeigte eine signifikante Erhöhung der starken zytogenetischen Ansprechrate (Major Response) sowie eine signifikante Erhöhung der Gesamtüberlebensrate nach 3 Jahren im Vergleich zur Interferon-alfa-2b-Monotherapie.

Quellen: AMIce-Datenbank, Fachinformationen

[1] derzeit außer Vertrieb

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-290z (Beratung nach § 35a SGB V) Asciminib

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	26. November 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

Behandlung von erwachsenen Patienten mit Philadelphia-Chromosom-positiver chronisch myeloischer Leukämie in der chronischen Phase (Ph+ CML-CP).

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation chronisch myeloische 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), 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 der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 31.10.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 317 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. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. 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 3 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

3.2 Systematische Reviews

Zhang JJ et al., 2024 [3].

Comparative efficacy and safety of first-line tyrosine kinase inhibitors in chronic myeloid leukemia: a systematic review and network meta-analysis

Fragestellung

to compare the safety and efficacy of different TKIs as first-line treatments for CML

Methodik

Population:

- adult CML patients with ≥18 years of age (CML diagnosis was confirmed by typical clinical presentations and the presence of the Ph+ and/or BCR-ABL fusion gene in cytogenetic or molecular biology tests)

Intervention / Komparator:

- imatinib, nilotinib, dasatinib, radotinib, bosutinib, and flumatinib

Endpunkte:

- major molecular response (MMR) at 3, 6, 12 months,
- complete cytogenetic response (CCyR) rate at 6, 12 months,
- progression-free survival (PFS),
- overall survival (OS),
- adverse events

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), Wanfang, Chinese Science and Technology Periodical Databases (VIP), SinoMed, and ClinicalTrials.gov from inception to 21 July 2023.

Qualitätsbewertung der Studien:

- Cochrane RoB

Ergebnisse

Anzahl eingeschlossener Studien:

- 25 RCTs encompassing 6,823 patients

Charakteristika der Population/Studien:

Author, year	Country	Intervention		Sample size		Gender (male/female)		Age (years)		Outcomes
		Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Han, 2022 (15)	China	NIL 300 mg BID	IM 400 mg QD	34	34	20/14	19/15	20–55[a]	18–66[a]	①②③④⑤
Brümmendorf, 2022 (16); Cortes, 2018 (17)	Global, multicenter	BOS 400 mg QD	IM 400 mg QD	268	268	156/112	155/113	52 [18–84][b]	53 [19–84][b]	①②③⑤⑦ (5 years) ⑧⑨⑩⑪⑫⑬
NCT00481247 (18); Jabbour, 2014 (19); Kantarjian, 2012 (20); Kantarjian, 2010 (21)	Global, multicenter	DAS 100 mg QD	IM 400 mg QD	259	260	141/115	163/97	46 [18–84][b]	49 [18–78][b]	③⑤⑥ (2, 3, 5 years) ⑦ (2, 3, 5 years) ⑨⑩⑪
Li, 2021 (22)	China	NIL 300–400 mg BID	IM 400 mg QD	39	39	22/17	23/16	48.25±6.71[c]	47.03±6.42[c]	⑤⑥ (3 years) ⑦ (3 years)
Yu, 2021 (23)	China	DAS 70 mg QD	DAS 100 mg QD	29	22	13/16	15/7	47.13±15.15[c]	43.59±14.36[c]	②③④⑤⑫
Wang, 2020 (24)	China	NIL 400 mg BID	DAS 100 mg QD	12	13	7/5	7/6	35–65[a]	35–65[a]	③⑤⑧
Cortes, 2020 (25)	Global, multicenter	IM ≥400 mg OD or BID	DAS 100mg QD	86	174	70/16	133/41	40 [18–73][b]	35 [18–82][b]	③⑥ (2 years) ⑦ (2 years) ⑧⑨⑩⑪
Zhang, 2021 (11)	China	FLU 600 mg QD	IM 400 mg QD	196	197	126/70	119/78	45 [20–70][b]	45 [18–73][b]	②③④⑤⑨⑩⑪⑫⑬
Geng, 2018 (26)	China	DAS 100 mg QD	IM 400 mg QD	44	43	28/16	26/17	42.8±6.5[c]	43.1±6.8[c]	⑤⑧⑫
Wang, 2017 (27)	China	DAS 100 mg QD	IM 400 mg QD	10	10	7/3	6/4	40.25±10.13[c]	41.15±10.21[c]	⑤⑧⑫
Kwak, 2017 (28)	Global, multicenter	IM 400 mg QD; RAD 400 mg BID	RAD 300 mg BID	81; 81	79	50/31; 47/34	52/27	45 [18–83][b]; 43 [18–84][b]	45 [20–75][b]	①②③④⑤⑨⑩⑪⑫⑬
Hehlmann, 2017 (29)	Germany, Switzerland	IM 800 mg QD	IM 400 mg QD	420	400	248/172	244/156	51 [18–85][b]	53 [16–88][b]	③
Lu, 2016 (30)	China	DAS 100 mg QD	IM 400 mg QD	20	20	11/9	10/10	20–61[a]	20–60[a]	⑤⑧⑫
Liu, 2016 (31)	China	FLU 400 mg QD; FLU 600 mg QD	IM 400 mg QD	8; 9	7	15/9		38[d]		③
Wang, 2016 (32)	China	NIL 300 mg BID; DAS 100 mg QD	IM 400 mg QD	32; 32	32	17/15; 18/14	16/16	41.53±3.81[c]; 40.14±4.23[c]	39.81±3.25[c]	①②③④⑤⑧
Hjorth-Hansen, 2015 (33)	Finland, Norway, Sweden	DAS 100 mg QD	IM 400 mg QD	22	24	7/15	15/9	53 [29–71][b]	58 [38–78][b]	④⑤⑨⑩⑪
Zheng, 2013 (34)	China	DAS 100mg QD	IM 400 mg QD	13	12	NR	NR	NR	NR	⑤
Radich, 2012 (35)	United States, Canada	IM 400 mg QD	DAS 100 mg QD	123	123	72/51	74/49	50 [19–89][b]	47 [18–90][b]	⑤⑪
Cortes, 2012 (36)	Global, multicenter	BOS 500 mg QD	IM 400 mg QD	250	252	149/101	135/117	48 [19–91][b]	47 [18–89][b]	⑨⑩⑪⑫⑬
Hehlmann, 2011 (37)	Global, multicenter	IM 800 mg QD	IM 400 mg QD	338	325	199/139	195/130	52 [18–86][b]	54 [16–88][b]	②③④⑤⑨⑩⑪

Author, year	Country	Intervention		Sample size		Gender (male/female)		Age (years)		Outcomes
		Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	
Saglio, 2010 (38)	Global, multicenter	IM 400 mg QD; NIL 400 mg BID	NIL 300 mg BID	283; 281	282	158/125; 175/106	158/124	46 [18–80][b]; 47 [18–81][b]	47 [18–85][b]	①②③④⑤⑧⑫⑬
Preudhomme, 2010 (39)	France	IM 400 mg QD	IM 600 mg QD	159	160	109/50	89/71	50[d]	51[d]	③④⑤
Petzer, 2010 (40)	Austria	IM 800 mg QD	IM 400 mg QD	113	113	53/58	48/63	46.5±12.3[c]	45.5±13.4[c]	④
Cortes, 2010 (41)	Global, multicenter	IM 800 mg QD	IM 400 mg QD	319	157	183/136	84/73	48 [18–75][b]	45 [18–75][b]	①②③④⑤
Baccarani, 2009 (42)	Italy	IM 800 mg QD	IM 400 mg QD	108	108	60/48	62/46	51 [18–84][b]	56 [18–81][b]	①②③④⑤

[a], minimum-maximum; [b], median [Q1–Q3]; [c], mean ± SD; [d], mean. ① MMR rate at 3 months; ② MMR rate at 6 months; ③ MMR rate at 12 months; ④ CCyR rate at 6 months; ⑤ CCyR rate at 12 months; ⑥ PFS rate; ⑦ OS rate; ⑧ overall incidence of adverse events; ⑨ incidence of grade 3 or above anemia; ⑩ incidence of grade 3 or above thrombocytopenia; ⑪ incidence of grade 3 or above neutropenia; ⑫ incidence of ALT elevation of all grade; ⑬ incidence of AST elevation of all grade. IM, imatinib; QD, quaque die; BID, bid twice a day; DAS, dasatinib; NIL, nilotinib; BOS, bosutinib; FLU, flumatinib; RAD, radotinib; MMR, major molecular response; CCyR, complete cytogenic response; PFS, progression-free survival; OS, overall survival; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Qualität der Studien:

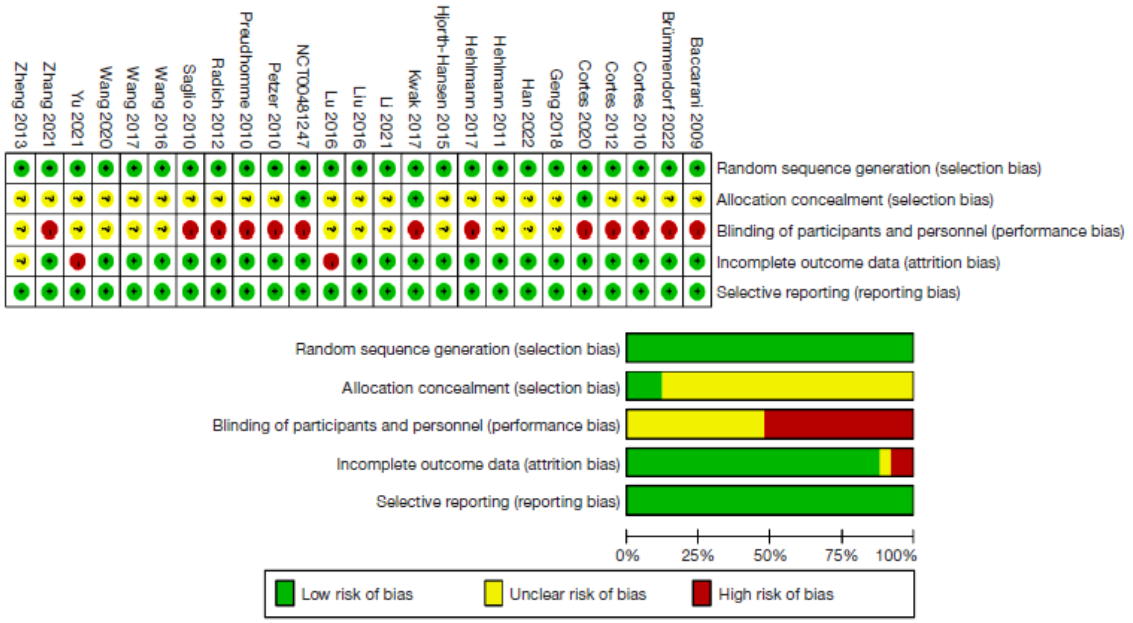
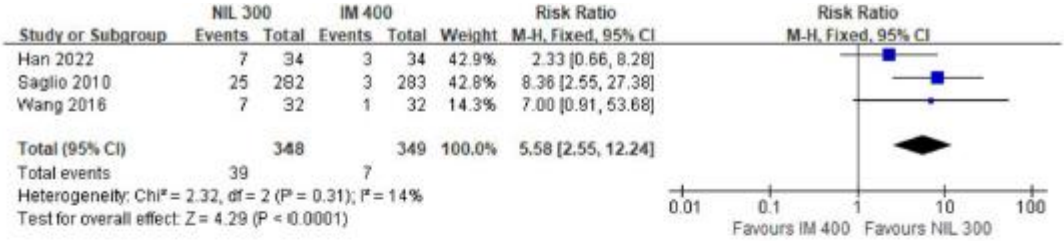


Figure 2 Bias assessment of the RCTs included for analysis. RCT, randomized controlled trial.

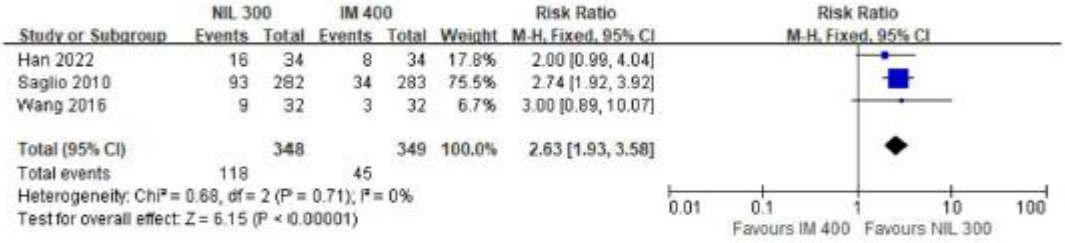
Among these studies, 3 reported concealments of the randomization sequence. A total of 13 studies were conducted in an open-label manner, meaning that blinding was not implemented for the participants; 3 studies demonstrated a risk of incomplete outcome data, and the remaining studies did not report relevant information.

Results of the direct comparison meta-analysis:

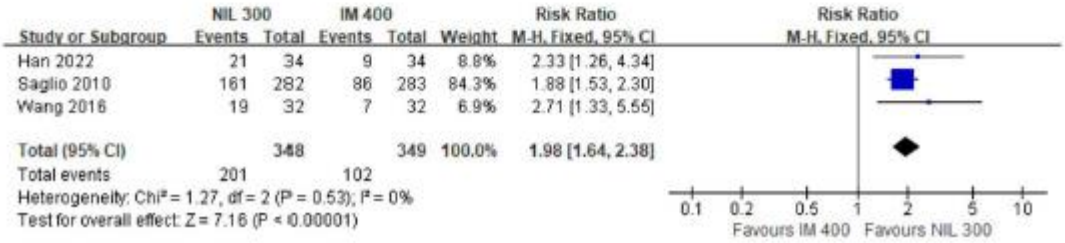
- Compared to **imatinib 400 mg, nilotinib 300 mg** showed superior efficacy in terms of MMR at 3 months (RR =5.58, 95% CI: 2.55–12.24), MMR at 6 months (RR =2.63, 95% CI: 1.93–3.58), MMR at 12 months (RR =1.98, 95% CI: 1.64–2.38), CCyR at 6 months (RR =1.38, 95% CI: 1.14–1.68), and CCyR at 12 months (RR =1.23, 95% CI: 1.13–1.35), with all differences being statistically significant.



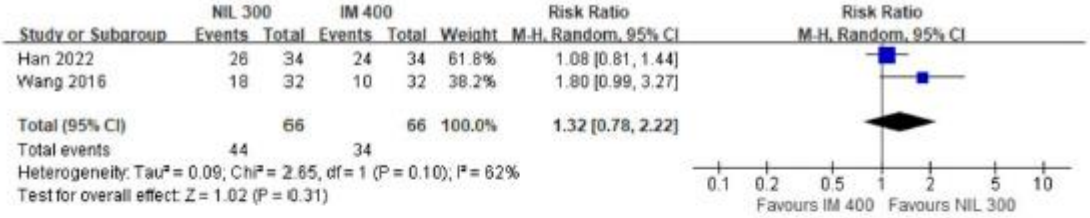
MMR6



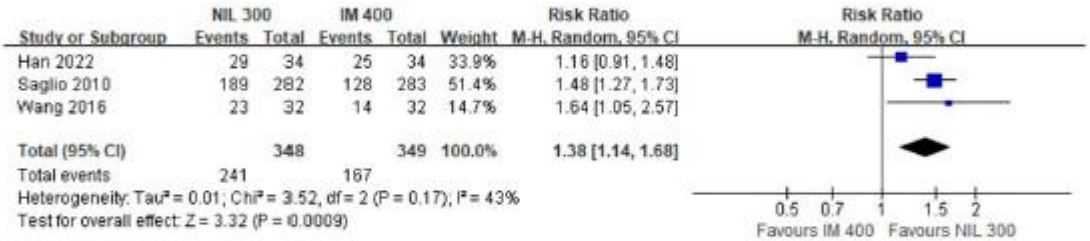
MMR12



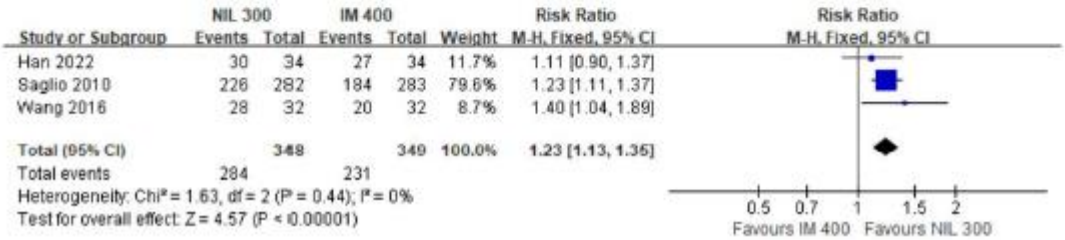
CCyR 3



CCyR 6



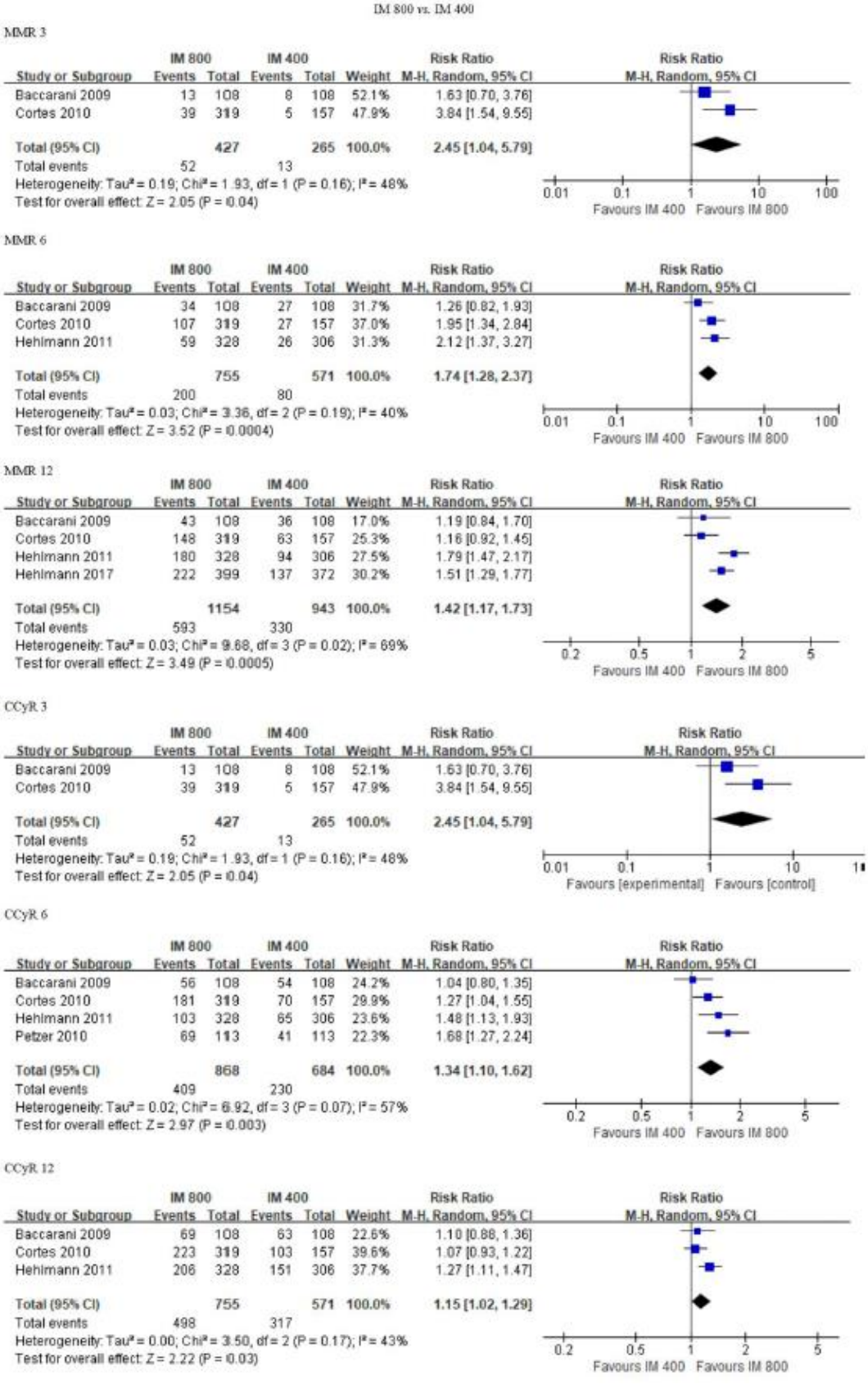
CCyR 12



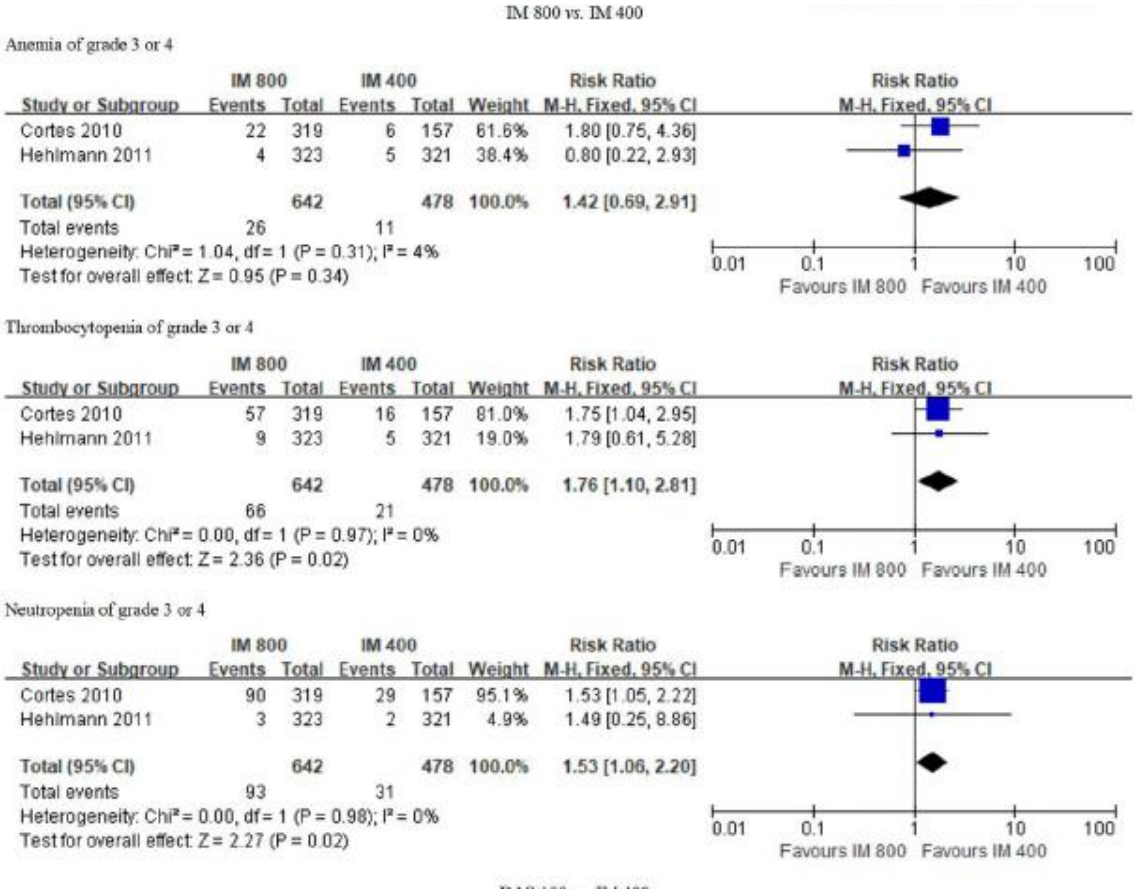
IM 800 vs. IM 400

- In comparison with **imatinib 400 mg, imatinib 800 mg** was more effective in achieving MMR at 3 months (RR =2.45, 95% CI: 1.04–5.79), MMR at 6 months (RR =1.74, 95% CI:

1.28–2.37), MMR at 12 months (RR =1.42, 95% CI: 1.17–1.73), CCyR at 6 months (RR =1.34, 95% CI: 1.10–1.62), and CCyR at 12 months (RR =1.15, 95% CI: 1.02–1.29), with all these differences being statistically significant.



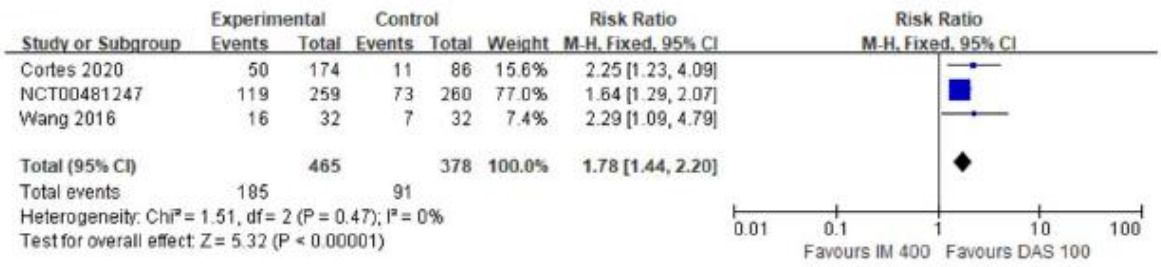
- compared to imatinib 400 mg, imatinib 800 mg had a higher risk of grade 3–4 thrombocytopenia (RR =1.76, 95% CI: 1.10–2.81) and neutropenia (RR =1.53, 95% CI: 1.06–2.20).



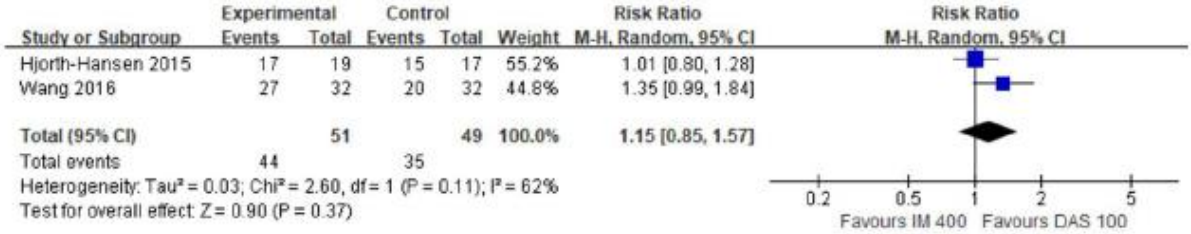
- **Dasatinib 100 mg** outperformed **imatinib 400 mg** in MMR at 12 months (RR =1.78, 95% CI: 1.44–2.20) and CCyR at 12 months (RR =1.28, 95% CI: 1.11–1.47), with these differences also being statistically significant.

DAS 100 vs. IM 400

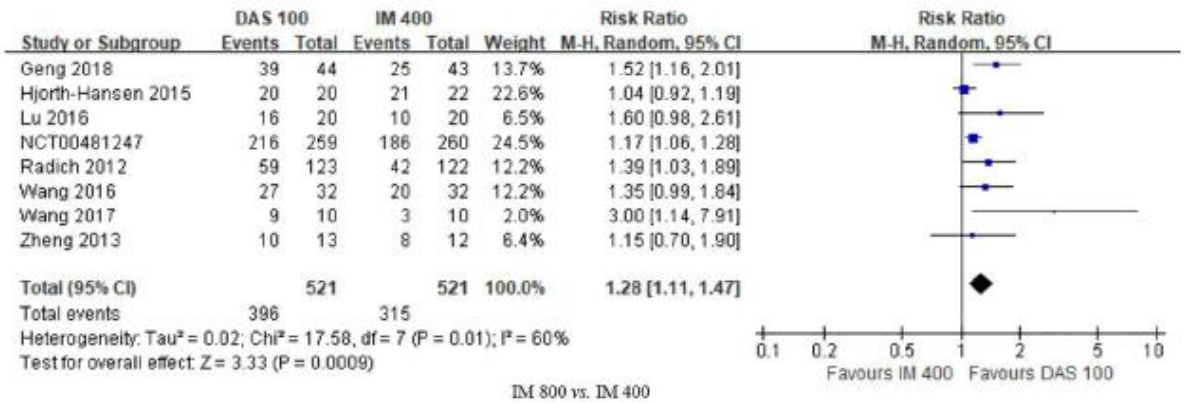
MMR 12



CCyR 6



CCyR 12



IM 800 vs. IM 400

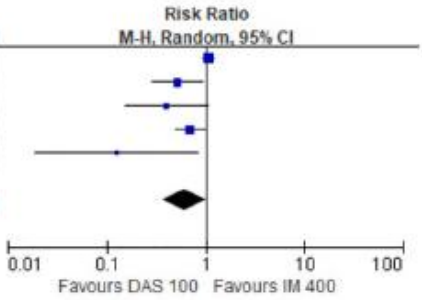
- Dasatinib 100 mg also showed a significantly higher rate of grade 3–4 thrombocytopenia compared to imatinib 400 mg (RR =1.65, 95% CI: 1.14–2.39). Compared to dasatinib 100 mg, imatinib 400 mg exhibited a greater risk of all-grade ALT elevation (RR =6.33, 95% CI: 1.17–34.20) and all-grade AST elevation (RR =5.49, 95% CI: 3.82–7.89).

DAS 100 *vs.* IM 400

Adverse events

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Cortes 2020	141	171	67	86	30.3%	1.06 [0.93, 1.21]
Geng 2018	11	44	21	43	21.9%	0.51 [0.28, 0.93]
Lu 2016	4	20	10	20	14.6%	0.40 [0.15, 1.07]
Wang 2016	18	32	26	32	27.1%	0.69 [0.49, 0.98]
Wang 2017	1	10	8	10	6.0%	0.13 [0.02, 0.82]
Total (95% CI)		**277**		**191**	**100.0%**	**0.61 [0.37, 1.03]**
Total events	175		132			

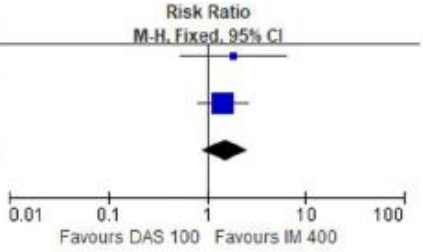
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 22.53$, df = 4 (P = 0.0002); $I^2 = 82\%$
Test for overall effect: Z = 1.85 (P = 0.06)



Anemia of grade 3 or 4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cortes 2020	11	171	3	86	18.2%	1.84 [0.53, 6.44]
Hjorth-Hansen 2015	0	22	0	24		Not estimable
NCT00481247	26	258	18	258	81.8%	1.44 [0.81, 2.57]
Total (95% CI)		**451**		**368**	**100.0%**	**1.52 [0.90, 2.56]**
Total events	37		21			

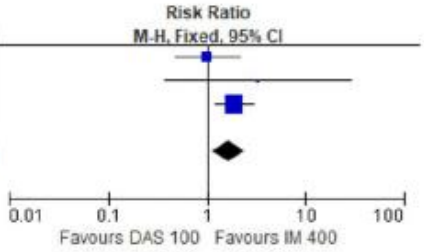
Heterogeneity: $Chi^2 = 0.12$, df = 1 (P = 0.73); $I^2 = 0\%$
Test for overall effect: Z = 1.56 (P = 0.12)



Thrombocytopenia of grade 3 or 4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cortes 2020	18	171	9	86	30.8%	1.01 [0.47, 2.14]
Hjorth-Hansen 2015	3	22	1	24	2.5%	3.27 [0.37, 29.18]
NCT00481247	49	258	26	258	66.8%	1.88 [1.21, 2.94]
Total (95% CI)		**451**		**368**	**100.0%**	**1.65 [1.14, 2.39]**
Total events	70		36			

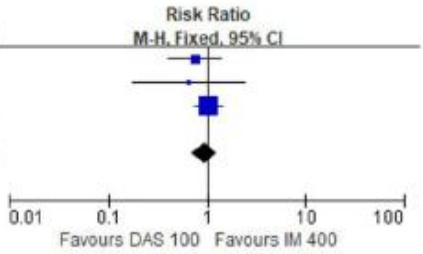
Heterogeneity: $Chi^2 = 2.36$, df = 2 (P = 0.31); $I^2 = 15\%$
Test for overall effect: Z = 2.63 (P = 0.009)



Neutropenia of grade 3 or 4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cortes 2020	21	171	14	86	24.7%	0.75 [0.40, 1.41]
Hjorth-Hansen 2015	3	22	5	24	6.3%	0.65 [0.18, 2.42]
NCT00481247	54	258	52	258	69.0%	1.04 [0.74, 1.46]
Total (95% CI)		**451**		**368**	**100.0%**	**0.94 [0.71, 1.26]**
Total events	78		71			

Heterogeneity: $Chi^2 = 1.10$, df = 2 (P = 0.58); $I^2 = 0\%$
Test for overall effect: Z = 0.39 (P = 0.70)

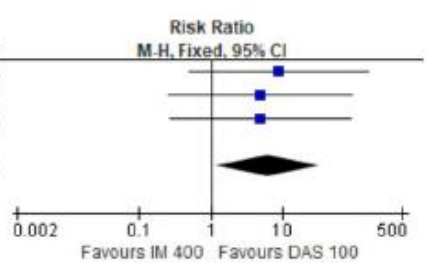


IM 400 *vs.* DAS 100

ALT elevation of all grade

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Geng 2018	4	43	0	43	33.3%	9.00 [0.50, 162.22]
Lu 2016	2	20	0	20	33.3%	5.00 [0.26, 98.00]
Wang 2017	2	10	0	10	33.3%	5.00 [0.27, 92.62]
Total (95% CI)		**73**		**73**	**100.0%**	**6.33 [1.17, 34.20]**
Total events	8		0			

Heterogeneity: $Chi^2 = 0.11$, df = 2 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 2.15 (P = 0.03)



- **imatinib**'s risk of all-grade AST elevation was also higher than that associated with **bosutinib 400 mg** (RR =3.67, 95% CI: 2.58–5.23).

Anmerkung/Fazit der Autoren

This study indicates that second-generation TKIs have certain advantages over first-generation imatinib in treating patients with CML. However, imatinib demonstrates relatively better safety, and different TKIs have different types and rates of adverse reactions and different advantages. Thus, the clinical choice of TKIs should consider efficacy, safety and cost and be based on the patient's specific clinical conditions. Nonetheless, more high-quality research is needed to validate these findings due to the limited number and quality of original studies.

Kommentare zum Review

- Keine Darstellung der Ergebnisse der NMA, da keine hinreichende Untersuchung der Ähnlichkeitsannahme der eingeschlossenen Studien erfolgte
- Die Publikation berichtet scheinbar nur signifikante Ergebnisse.

3.3 Leitlinien

Smith G et al., 2020 [2].

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

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

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;
- Aktualisierungsprozess beschrieben, aber nicht öffentlich einsehbar dokumentiert

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.

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

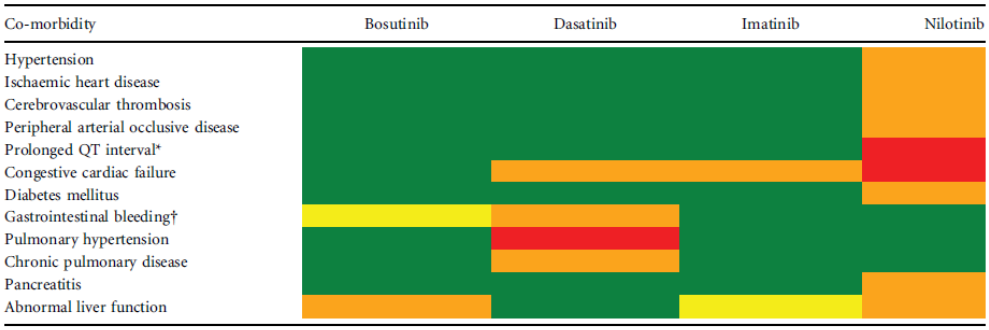
Background:

- 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).



■, 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

Table IV. Clinical significance of *BCR-ABL1* resistance-associated mutations.

Mutation	Intervention
T315I	Allogeneic stem cell transplant (alloSCT), ponatinib, investigational drugs including asciminib[71]
T315A, F317L/V/I/C	Consider nilotinib, bosutinib or ponatinib rather than dasatinib
Y253H, F359V/C/I, E255K/V	Consider dasatinib, bosutinib or ponatinib rather than nilotinib
V299L	Consider nilotinib or ponatinib rather than dasatinib or bosutinib
Any other mutation	Clinical significance unclear: consider high-dose TKI, alternative TKI, alloSCT, investigational drugs

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), 2025 [1].

Chronic myeloid leukemia; version 1.2026

Methodik

Grundlage der Leitlinie

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

- Repräsentatives Gremium unklar
- Interessenkonflikte dargelegt, finanzielle Unabhängigkeit unklar;
- Systematische Suche in Pubmed, systematische Auswahl und Bewertung der Evidenz bleibt jedoch unklar; auch Referenzen die nicht mittels systematischer Suche identifiziert wurden, konnten berücksichtigt werden.
- 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 (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended	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.

Empfehlungen

Management of Chronic Phase CML

Primary Treatment

Long-term efficacy data from randomized phase III studies for first-line TKI therapy in patients with newly diagnosed CP-CML are summarized in Table 1.[101-105] In summary, 1) all TKIs are highly effective as primary treatment for patients with newly diagnosed CP-CML, with long-term OS expected to be similar to that of aged-matched controls; 2) 2G TKIs (bosutinib, dasatinib, and nilotinib) and asciminib (allosteric TKI; STAMP inhibitor) generally result in faster cytogenetic and molecular responses with less progression to advanced phase CML compared to imatinib; and 3) in randomized clinical trials, as of yet, there are no significant differences in OS between imatinib and a 2G TKI or asciminib.

Clinical Considerations for the Selection of First-Line Therapy

The selection of first-line TKI therapy (asciminib, bosutinib, dasatinib, imatinib, or nilotinib) in a given patient should be based on the risk score, toxicity profile and dosing schedule of TKI, patient's age, ability to tolerate therapy, and the presence of comorbid conditions, patient preference, treatment goals, and medication costs (CML-2).

BCR::ABL1 Transcript Type

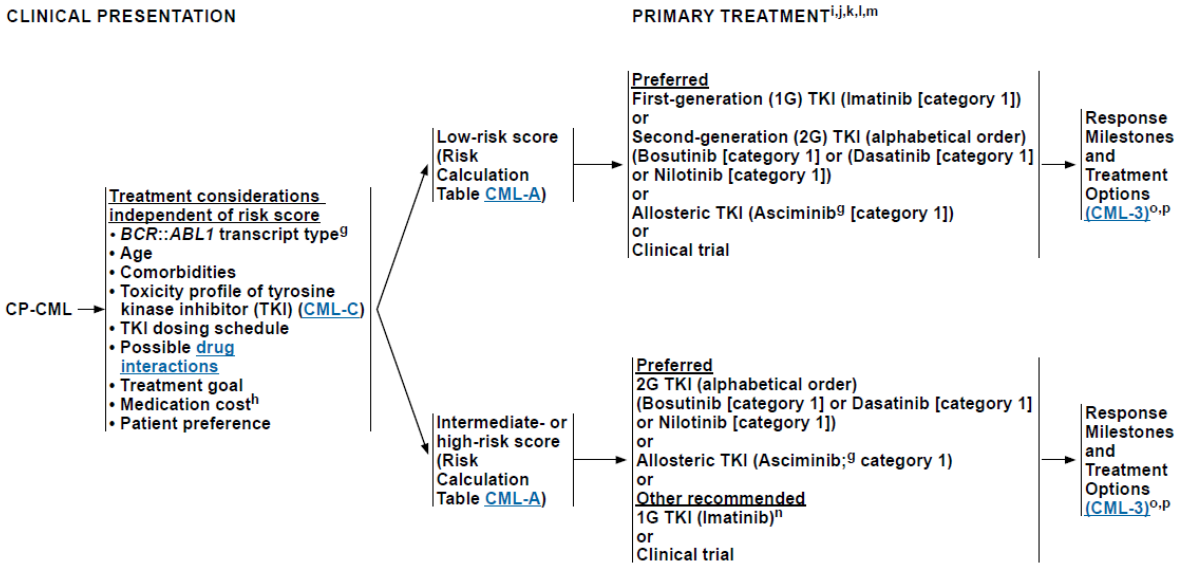
BCR::ABL1 variants lacking ABL1 exon 2 (referred to as *BCR::ABL1*/ b2a3 or *BCR::ABL1*/b3a3 isoforms) are present in a minority of patients with CML and these isoforms confer a high degree of resistance to asciminib (allosteric TKI; specially targeting the ABL1 myristoyl pocket [STAMP]) that cannot be overcome with higher doses of asciminib.[21,106,107] Therefore, asciminib is contraindicated for CML with *BCR::ABL1*/ b2a3 or *BCR::ABL1*/b3a3 isoforms.

Risk Score

Asciminib, bosutinib, dasatinib, imatinib, or nilotinib are all appropriate options for first-line TKI therapy for patients with CP-CML across all risk scores.[101-105]

Disease progression is more frequent in patients with intermediate- or high-risk score, and prevention of disease progression to AP-CML or BP-CML is the primary goal of TKI therapy in patients with CP-CML. 2G TKIs and asciminib are associated with a lower risk of disease progression than imatinib and are preferred for patients with an intermediate- or high-risk Sokal or Euro score. 2G TKIs result in quicker molecular responses and higher rates of MMR (≤0.1% *BCR::ABL1* IS) and deep molecular response (DMR) (MR4.0 [≤0.01% *BCR::ABL1* IS] or MR4.5 [≤0.0032% *BCR::ABL1* IS]) in patients with CP-CML across all risk scores (Table 2), which may facilitate subsequent discontinuation of TKI therapy in selected patients.[102-104] In the ASC4FIRST study, asciminib also resulted in higher rates of MMR compared to investigator-selected TKI (imatinib or 2G TKIs) in patients across all risk scores. There was a significant difference versus imatinib ($P < .001$), but there was no statistically significant difference in MMR rates versus 2G TKI. Therefore, 2G TKIs and asciminib are preferred for patients with an intermediate-risk or high-risk score.[105]

2G TKIs and asciminib should also be considered for specific subgroups (based on the assessment of treatment goals and benefit/risks), for example in younger patients who are interested in ultimately discontinuing treatment, particularly in young patients assigned female at birth with a goal of achieving a deep and rapid molecular response which may allow for eventual discontinuation of TKI therapy for family planning purposes. Imatinib may be preferred for older patients with comorbidities, especially cardiovascular comorbidities.



Footnotes on CML-2A

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

CML-2

FOOTNOTES FOR CHRONIC PHASE CML

[g] Asciminib is contraindicated in patients with CML lacking ABL1 exon 2 (eg, b2(e13)a3, b3(e14)a3 isoforms) as it has no clinical activity in these cases (Leske IB, Hantschel O. Leukemia 2024;38:2041-2045; Leyte-Vidal A, et al. Leukemia 2024;38:2046-2050).

[h] The cost of generic TKIs can be substantially less than that of brand name TKIs. The cost of treatment to both the patient and to society can be considered.

[i] If treatment is needed during pregnancy, it is preferable to initiate treatment with interferon. In the United States, peginterferon alfa-2a and ropeginterferon alfa-2b are available for clinical use. There are very limited data for the use of ropeginterferon alfa-2b in CML during pregnancy. TKI therapy, particularly during the first trimester, should be avoided because of teratogenic risk. See Management of CML During Pregnancy (CML-E).

[j] 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.

[k] 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.

[l] TKIs 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.

[m] FDA-approved generic drugs are appropriate substitutes for brand name drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.

[n] Imatinib may be preferred for patients who are older with comorbidities such as cardiovascular disease.

[o] Criteria for Response and Relapse (CML-F).

[p] Monitoring Response to TKI Therapy and Mutational Analysis (CML-G).

Table 1: First-Line TKI Therapy for CP-CML: Long-Term Follow-up Data from Phase III Studies

Trial	Study Arms	No. of Patients	Median Follow-up	CCyR[a]	MMR[b]	Disease Progression n (%)	PFS[c]	OS
IRIS[101,d]	**Imatinib (400 mg once daily)**	553	11 years	83%	—	38 (7)	92%	83%
	Interferon alpha plus low-dose cytarabine	553		—	—	71 (13)	—	79%[e]
DASISION[102]	**Dasatinib (100 mg once daily)**	259	5 years	—	76% (*P* = .002)	12 (5)	85%	91%
	Imatinib (400 mg once daily)	260		—	64%	19 (7)	86%	90%
ENESTnd[103]	**Nilotinib (300 mg twice daily)**	282	10 years	—	78% (*P* < .0001)	11 (4)	86%	88%
	Imatinib (400 mg once daily)	283		—	63%	24 (8.5)	87%	88%
BFORE[104]	**Bosutinib (400 mg once daily)**	268	60 months	83%	74%	6 (2)	—	95%
	Imatinib (400 mg once daily)	268		77%	65%	7 (3)	—	95%
ASC4FIRST[105]	**Asciminib**	101	16 months (16.3)	84%	69%	—	—	—
	Imatinib	102		62%	40%	—	—	—
	Asciminib	100	16 months (15.7)	90%	66%	—	—	—
	Investigator-selected 2G TKI	102		83%	58%	—	—	—

CCyR, complete cytogenetic response (≤1% *BCR::ABL1* IS); MMR, major molecular response (≤0.1% *BCR::ABL1* IS); OS, overall survival; PFS, progression-free survival

a. Confirmed CCyR rate at 12 months was the primary endpoint of DASISION study.
b. MMR (≤0.1% *BCR::ABL1* IS) rate at 12 months (48 weeks) was the primary endpoint of ENESTnd, BFORE, and ASC4FIRST studies.
c. Primary endpoint of IRIS trial in the imatinib group.
d. Due to the high rate of crossover to imatinib (66%) and the short duration of therapy (<1 year) before crossover among patients who had been randomly assigned to interferon alfa plus cytarabine, the long-term follow-up data focused on patients who had been randomly assigned to receive imatinib.
e. Data include survival among the 363 patients who crossed over to imatinib.

Table 2: First-Line TKI Therapy for CP-CML: Outcomes According to Risk Score

Trial	Study Arms	Low-Risk			Intermediate-Risk			High-Risk		
		MMR	MR4.5	PFS/OS[a]	MMR	MR4.5	PFS/OS[a]	MMR	MR4.5	PFS/OS[a]
DASISION[102] (Euro risk score)	**Dasatinib (100 mg once daily)**	90%	55%	—	71%	43%	—	67%	31%	—
	Imatinib (400 mg once daily)	69%	44%	—	65%	28%	—	54%	30%	—
ENESTnd[103] (Sokal risk score)	**Nilotinib (300 mg twice daily)**	—	51%	94%/95%	—	55%	87%/88%	—	40%	74%/77%
	Imatinib (400 mg once daily)	—	39%	98%/99%	—	30%	84%/84%	—	23%	78%/79%
BFORE[104] (Sokal risk score)	**Bosutinib (400 mg once daily)**	76%	54%	—	74%	43%	—	70%	46%	—
	Imatinib (400 mg once daily)	73%	43%	—	64%	37%	—	51%	25%	—

MMR, major molecular response (≤0.1% *BCR::ABL1* IS); MR, molecular response; MR4.5: 4.5-log reduction in *BCR::ABL1* transcripts from baseline; OS, overall survival; PFS, progression-free survival
a. 10-year outcomes according to Sokal risk score.

Table 3. Adverse Events of First-Line TKI Therapy in CP-CML

Toxicity	DASISION[102]		ENESTnd[103]		BFORE[104]		ASC4FIRST[105]		
	Dasatinib 100 mg QD	Imatinib 400 mg QD	Nilotinib 300 mg BID	Imatinib 400 mg QD	Bosutinib 400 mg QD	Imatinib 400 mg QD	Asciminib 80 mg QD or 40 mg BID	Imatinib 400 mg QD	2G TKI
Biochemical abnormalities (Grade 3 or 4; *any grade)									
Increased glucose	NR	NR	9%	<1%	4%*	6%*	NR	NR	NR
Increased ALT	NR	NR	4%	3%	34%*	6%*	2%	2%	8%
Increased AST	NR	NR	NR	NR	26%*	7%*	<1%	1%	3%
Nonhematologic toxicities (any grade)[a]									
Rash	13%	18%	39%	21%	23%	15%	13%	10%	22%
Headache	13%	11%	34%	25%	19%	13%	14%	8%	22%
Fatigue	9%	11%	25%	20%	19%	18%	14%	8%	22%
Diarrhea	21%	22%	21%	48%	75%	40%	16%	26%	26%
Constipation	NR	NR	23%	9%	NR	NR	10%	4%	13%
Nausea	10%	24%	22%	42%	37%	42%	9%	21%	18%
Vomiting	5%	11%	17%	28%	21%	20%	6%	12%	6%
Muscle spasms	23%	41%	14%	35%	4%	31%	2%	19%	5%
Peripheral or Periorbital edema	13%	37%	12%	23%	2%	17%	1%	10%	1%
Pleural effusion	28%	<1%	NR	NR	5%	2%	NR	NR	NR
Hypertension	NR	NR	16%	6%	10%	11%	NR	NR	NR
Pulmonary hypertension	5%	<1%	NR	NR	NR	NR	NR	NR	NR

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; NR, not reported; QD, once daily; TKI, tyrosine kinase inhibitor.
a. Non-hematologic toxicities from the DASISION study (except pleural effusion) are from the 3-year follow-up. No new adverse events were observed with 5-year follow-up.

Table 4: High-Dose Imatinib as First-Line Therapy for CP-CML: Long-Term Follow-up Data from Phase III Studies

Trial	Study Arms	No. of Patients	Median Follow-up	MMR	MR4.5	PFS	OS
TOPS study[120,a]	Imatinib (800 mg once daily)	319	42 months	79%	—	96% at 48 months	93% at 48 months
	Imatinib (400 mg once daily)	157		76%	—	94% at 48 months	94% at 48 months
SWOG study[121,c]	Imatinib (800 mg once daily)	73	12 months	53%	19%	92% (4-year PFS)	95% (4-year OS)
	Imatinib (400 mg once daily)	72		36%	9%	80% (4-year PFS)	90% (4-year OS)
CML IV study[122,b]	Imatinib (800 mg once daily)	420	10 years	89%	71%	77%	79%
	Imatinib (400 mg once daily)	400		92%	67%	80%	80%

MMR, major molecular response (≤0.1% *BCR::ABL1* IS); MR, molecular response; MR4.5: ≥4.5-log reduction in *BCR::ABL1* transcripts from baseline; OS, overall survival; PFS, progression-free survival

a. Primary endpoint: MMR rate at 12 months (≤0.1% *BCR::ABL1*), which corresponds to a 3-log reduction in *BCR::ABL1* transcripts compared with the standardized baseline established in IRIS study.
b. Primary endpoint: The impact of MMR on survival at 12 months. This study had 5 treatment arms (imatinib 400 mg once daily alone; imatinib 800 mg twice daily; imatinib 400 mg once daily with interferon or cytarabine; and imatinib after prior interferon treatment). Only the data for imatinib 400 mg once daily alone vs. imatinib 800 mg twice daily are included in this table.
c. Primary endpoint: MR4.0 (≥4-log reduction in *BCR::ABL1* transcripts from baseline) at 12 months. Results from the first part of SWOG S0325 study; follow-up after 12 months was not required for this study.

Table 5. Early Molecular Response (≤10% *BCR::ABL1* IS at 3 months) After First-Line TKI Therapy and Survival Outcomes

Trial	Study Arms	5-Year PFS		5-Year OS	
		BCR::ABL1 ≤10%	*BCR::ABL1* >10%	*BCR::ABL1* ≤10%	*BCR::ABL1* >10%
DASISION[102]	Dasatinib (100 mg once daily)	89%	72%	94%	81%
	Imatinib (400 mg once daily)	93%	72%	95%	81%
CML IV Study[151]	Imatinib (400 mg once daily)	92%	87%	94%	87%
ENESTnd[152]	Nilotinib (300 mg twice daily)	95%	78%	98%	82%
	Nilotinib (400 mg twice daily)	96%	89%	96%	93%
	Imatinib (400 mg once daily)	98%	79%	99%	79%

OS, overall survival; PFS, progression-free survival

Table 6. Second-Line and Subsequent TKI Therapy for CP-CML: Long-Term Follow-up Data from Phase II/III Studies

TKI/Trial	Study Arms (No. of patients)	Median Follow-up	MCyR	CCyR	MMR	PFS	OS
Dasatinib[179,a] (100 mg once daily)	Imatinib-R (n = 124)	7 years	—	—	43%	39%	63%
	Imatinib-I (n = 43)		—	—	55%	51%	70%
Nilotinib[180,b] (400 mg twice daily)	Imatinib-R (n = 226) Imatinib-I (n = 95)	4 years	59%	45%	—	57%	78%
Bosutinib (BYOND) (500 mg once daily)[182]	Imatinib-R (n = 53)	≥3 years	86%	84%	73%	—	—
	Dasatinib and/or nilotinib-R (n = 29)		69%	62%	41%	—	—
	TKI intolerant (n = 74)		88%	87%	82%	—	—
Ponatinib (PACE)[184,c] (45 mg once daily)	Dasatinib or nilotinib-R or I (n = 203)	57 months	56%	49%	35%	52% at 5 years	76% at 5 years
	T315I mutation (n = 64)		72%	70%	58%	50% at 5 years	66% at 5 years
Ponatinib (OPTIC)[185]	45 mg (n = 93)	32 months	51%	44%	34%	73% at 3 years	89% at 3 years
	30 mg (n = 93)		33%	29%	25%	66% at 3 years	89% at 3 years
	15 mg (n = 91)		44%	23%	23%	70% at 3 years	92% at 3 years
Asciminib (ASCEMBL) (40 mg twice daily)[186,d]	Asciminib (40 mg twice daily; n = 157)	4 years	—	54%[e] at 156 weeks	45% at 156 weeks	85% at 3 years	92% at 3 years
	Bosutinib (500 mg once daily; n = 76)		—	Not evaluable at 156 weeks	24% at 156 weeks	84% at 3 years	97% at 3 years

CCyR, complete cytogenetic response; I, Intolerant; MCyR, major cytogenetic response; MMR, major molecular response (≤0.1% *BCR::ABL1* IS); OS, overall survival; PFS, progression-free survival; R, resistant; TKI, tyrosine kinase inhibitor

a. Primary endpoint: MCyR rate at 6 months when administered 100 mg once daily versus 70 mg twice daily.
b. Primary endpoint: MCyR rate in patients with imatinib intolerance or imatinib-resistant disease.
c. Primary endpoint: MCyR at any time within the first 12 months.
d. Primary endpoint: MMR rate at 24 weeks; Secondary endpoint: MMR rate at 96 weeks.
e. CCyR rate in patients who were not in CCyR at baseline.

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Table 8. Adverse Events of Second-Line and Subsequent TKI Therapy in CP-CML

Toxicity (any grade)	Dasatinib[179] (100 mg once daily)	Nilotinib[180] (400 mg twice daily)	Bosutinib[181] (500 mg once daily)	Ponatinib[184] (45 mg once daily)	Asciminib[186] (40 mg twice daily)
Rash	33%	31%	15%	47%	10%
Headache	—	18%	28%	43%	19%
Fatigue	37%	21%	24%	30%	15%
Myalgias/Arthralgias	38%	11%	14%	24%/33%	6%/15%
Pleural effusion	28%	—	17%	—	1%
Hypertension	—	—	—	37%	15%
Hemorrhage	26%	—	—	—	—
Diarrhea	42%	12%	88%	20%	13%
Constipation	—	13%	17%	41%	—
Nausea	27%	25%	40%	29%	12%
Vomiting		13%	33%	19%	8%
Increased blood creatinine	—	—	15%	—	—
Increased lipase	—	—	—	27%	—
Increased ALT/AST	—	—	20% (AST) 26% (ALT)	—	6% (AST) 5% (ALT)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TKI, tyrosine kinase inhibitor.

MS-38

EARLY TREATMENT RESPONSE MILESTONES
CRITERIA FOR RESPONSE AND RELAPSE

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

COLOR	CONCERN	CLINICAL CONSIDERATIONS[u]	RECOMMENDATIONS[l,m,u]
RED	TKI-resistant disease[t]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[v] • 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[t]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[v]	Switch to alternate TKI (CML-5) or Continue same TKI[r]
ORANGE	Possible TKI resistance[t]	• Evaluate patient adherence and drug interactions • Consider *BCR::ABL1* kinase domain mutational analysis[v] • Consider bone marrow cytogenetic analysis to assess for complete cytogenetic response (CCyR) at 12 mo	Consider switch to alternate TKI[s] (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[t,w]
GREEN	TKI-sensitive disease	• Evaluate patient adherence and drug interactions • Monitor response (CML-G)	Continue same TKI[x]

Footnotes on CML-3A

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

FOOTNOTES FOR EARLY TREATMENT RESPONSE MILESTONES

[l] TKIs 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.

[m] FDA-approved generic drugs are appropriate substitutes for brand name drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.

[q] *BCR::ABL1* IS ≤0.1% at 12 months is associated with a very low probability of subsequent loss of response and a high likelihood of achieving a subsequent deep molecular response (DMR MR4.0; *BCR::ABL1* IS ≤0.01%), which is a prerequisite for a trial of treatment-free remission (TFR).

[r] Achievement of response milestones must be interpreted within the clinical context. Patients with *BCR::ABL1* only slightly >10% at 3 months and/or with a steep decline from baseline may achieve <10% at 6 months and have generally favorable outcomes. Therefore, it is important to interpret the value at 3 months in this context before making drastic changes to the treatment strategy. Same dose of TKI can be continued for another 3 months but imatinib is associated with slower molecular responses.

[s] Achievement of response milestones must be interpreted within the clinical context. Patients achieving MCyR (*BCR::ABL1* IS ≤10%) at 12 months have good long-term survival. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of TKI for another 3 months. Consider switching to alternate 2G TKI or 3G TKI or allosteric TKI in the absence of continuing decline in *BCR::ABL1* transcript levels.

[t] Consider referral to a specialized CML center and/or enrollment in a clinical trial.

[u] Switching to an alternate TKI for intolerance is appropriate for patients with disease responding to TKI therapy. See Special Considerations for the use of TKI Therapy (CML-C).

[v] Consider myeloid mutation panel to identify *BCR::ABL1*–independent resistance mutations in patients with no *BCR::ABL1* kinase domain mutations.

[w] Switching from imatinib to a 2G TKI or allosteric TKI may improve response. The side effect profile of alternative TKIs may differ.

[x] Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-H).

TREATMENT RECOMMENDATIONS BASED ON *BCR::ABL1* MUTATION/VARIANT PROFILE

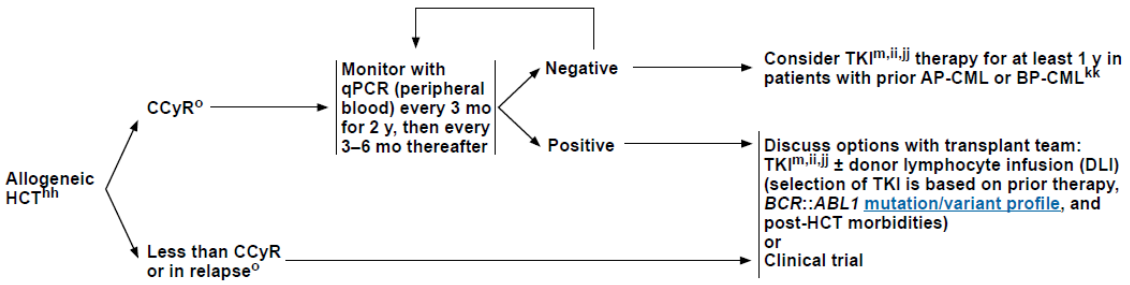
- **Patients with disease resistant to primary treatment with imatinib should be treated with an alternate TKI, taking into account *BCR::ABL1* kinase domain mutation status.**
- **Patients with disease resistant to primary treatment with asciminib, bosutinib, dasatinib, or nilotinib can be treated with an alternate TKI (other than imatinib), taking into account *BCR::ABL1* kinase domain mutation status. Subsequent therapy with an alternate TKI would be effective only in patients with identifiable *BCR::ABL1* mutations that confer resistance to TKI therapy. Ponatinib is preferred for patients with no identifiable *BCR::ABL1* mutations.**
  - **Asciminib is a treatment option for patients with CP-CML and AP-CML having the T315I mutation and/or previously treated CP-CML and AP-CML.**
  - **Ponatinib[dd] 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.**
- **Select *BCR::ABL1* kinase domain mutations may be more sensitive to certain TKIs based on the IC_{50} values. See Discussion. *BCR::ABL1* kinase domain mutations that should NOT be treated with asciminib, bosutinib, dasatinib, or nilotinib are listed in the table below.**

THERAPY	CONTRAINDICATED MUTATIONS/VARIANTS[ee]
Asciminib	A337T, P465S, M244V, or F359V/I/C; b2(e13)a3, b3(e14)a3
Bosutinib	T315I, V299L, G250E, or F317L[ff]
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib or allogeneic HCT	None[gg]

[dd] Initiation of ponatinib at lower doses and dose reduction (with close monitoring) in patients who achieve optimal responses are appropriate strategies to reduce the risk of cardiovascular toxicities. See the Discussion section for Dose Modifications of TKI Therapy.
[ee] Mutations contraindicated for imatinib are too numerous to include. *BCR::ABL35*$_{INS}$ has been reported in patients with disease not responding to imatinib; however, there are not enough data to confirm that 2G TKIs could overcome this resistance (Berman E, et al. Leuk Res 2016;49:108-112). See Discussion.
[ff] Bosutinib has minimal activity against F317L mutation. Nilotinib may be preferred over bosutinib in patients with F317L mutation.
[gg] There are compound mutations (defined as harboring ≥2 mutations in the same *BCR::ABL1* allele) that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.

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

ADDITIONAL THERAPY[l]



[l] TKIs 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.
[m] FDA-approved generic drugs are appropriate substitutes for brand name drugs (Kantarjian H, et al. Lancet Haematol 2022;9:e854-e861; Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116). Brand name and generic drugs approved by the regulatory authorities based on pharmacokinetic equivalence can be used interchangeably. Clinicians should be aware of the potential pharmacokinetic variability and monitor patients closely during transitions, particularly for drugs with narrow therapeutic windows such as nilotinib and bosutinib.
[o] Criteria for Response and Relapse (CML-F).
[hh] Indications for allogeneic HCT: CP-CML with resistance and/or intolerance to all available TKIs; disease progression to AP-CML during TKI therapy; BP-CML in patients who achieve morphologic remission. Outcomes of allogeneic HCT are dependent on age, comorbidities, donor type, pretransplant disease status, and transplant center.
[ii] 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.
[jj] Asciminib is a treatment option for patients with CP-CML and AP-CML having the T315I mutation and/or previously treated CP-CML and AP-CML.
[kk] 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.e1.

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

SPECIAL CONSIDERATIONS FOR THE USE OF TKI THERAPY

- Switching to an alternate TKI should be considered for the following non-hematologic adverse events[a,b,c]:
  - Arterial and vascular adverse events (more common with nilotinib and ponatinib)
  - Severe hypertension not responsive to antihypertensive medications (ponatinib and asciminib)
  - Pulmonary hypertension (dasatinib)
  - Recurrent pleural or pericardial effusions despite dose reduction (dasatinib; less common with bosutinib)
  - Recurrent pancreatitis despite dose reduction (most common with nilotinib, ponatinib, and asciminib)
  - Hyperglycemia (most common with nilotinib)
  - Persistent moderate to severe nephrotoxicity (all TKIs)
  - Liver function test (LFT) abnormalities (more common with bosutinib and imatinib)
  - Gastrointestinal bleeding (dasatinib)
  - Immune-mediated adverse events (all TKIs; eg, colitis, pneumonitis, hepatitis, myocarditis, pericarditis, or nephritis)
  - Neurotoxicity (rarely seen with imatinib and dasatinib; eg, dementia-like condition, parkinsonism, and intracranial hypertension)
- Patients should be counseled on the potential risk factors for cardiovascular disease (CVD), increased risk of CVD associated with long-term TKI therapy (based on comorbidity or risk factors), and on the ABCDEs of prevention of CVD.[d] See the Principles of Cardiovascular Disease Risk Assessment in the NCCN Guidelines for Survivorship.
- Recommendations for monitoring and management of non-hematologic adverse events are outlined in Table 1.[a]
- Hematologic toxicities (anemia, neutropenia, and thrombocytopenia) may persist after switching to alternate TKI. Growth factor support can be considered for persistent cytopenias.[e]

[a] Lipton JH, et al. Blood Rev 2022;56:100968.
[b] Haddad FG, Kantarjian H. J Natl Compr Canc Netw 2024;22:e237116.
[c] Oehler VG, et al. J Natl Compr Canc Netw 2024;22:e247044.
[d] Barber MC, et al. Hematology Am Soc Hematol Educ Program 2017;2017:110-114.
[e] Consider bone marrow evaluation to rule out disease progression to AP-CML or BP-CML or the emergence of other myeloid neoplasms after TKI therapy. Refer to package insert for monitoring hematologic toxicities: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

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

DISCONTINUATION OF TKI THERAPY

General Considerations

- Discontinuation of TKI therapy appears to be safe in select patients with CML.
- Consult with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have used strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in patients who give consent after a thorough discussion of the potential risks and benefits.
- Consultation with an NCCN Panel Member or center of expertise is recommended in the following circumstances:
  - Any significant adverse event believed to be related to treatment discontinuation.
  - There is progression to AP-CML or BP-CML at any time.
  - MMR is not regained after 3 months following treatment reinitiation.
- Outside of a clinical trial, discontinuation of TKI therapy should be considered only if ***all*** of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- CP-CML. No prior history of AP-CML or BP-CML.
- On approved TKI therapy for at least 3 years.[a,b]
- Prior evidence of quantifiable *BCR::ABL1* transcript.
- Stable molecular response (MR4; *BCR::ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[b]
- Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR::ABL1* ≤0.0032% IS) and that provides results within 2 weeks.
- Molecular monitoring every 1–2 months for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR::ABL1* ≤0.1% IS).
- Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. If MMR is not achieved after 3 months of TKI resumption, *BCR::ABL1* kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.

[a] The feasibility of TFR following discontinuation of TKIs other than dasatinib, imatinib, or nilotinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained DMR (MR4.0; ≤0.01% *BCR::ABL1* IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.
[b] Disease characteristics at diagnosis, blast cell and platelet count in peripheral blood, a higher Sokal risk score, female gender, lower natural killer (NK) cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy and DMR prior to TKI discontinuation have been identified as independent factors predictive of recurrence after TKI discontinuation. In the EURO-SKI study, only the duration of TKI therapy prior to discontinuation was significantly associated with the maintenance of MMR at 36 months after TKI discontinuation (Mahon FX, et al. J Clin Oncol 2024;42:1875-1880). Lack of MR4.0 at 36 months after discontinuation of TKI was highly predictive of subsequent loss of MMR (Richter J, et al. Leukemia 2021;35:2416-2418).

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

with adherence (which can be common given drug toxicity at the initiation of therapy), rate of decline in *BCR::ABL1*, and how far from the cutoff the *BCR::ABL1* value falls.

Patients with *BCR::ABL1* that is slightly >10% at 3 months (with a steep decline from baseline level) may achieve <10% *BCR::ABL1* IS at 6 months and have favorable outcomes.[155-158] Therefore, many patients with >10% *BCR::ABL1* at 3 months can continue the same dose of TKI (asciminib, bosutinib, dasatinib, imatinib, or nilotinib) for another 3 months (but imatinib is associated with slower molecular responses) or switch to alternate TKI. *BCR::ABL1* mutational analysis should be considered.

Achievement of ≤10% *BCR::ABL1* IS (which correlates with MCyR) within 2 years is associated with favorable long-term OS, even if deeper molecular response is not achieved.[171] These data suggest that patients with >1% to 10% *BCR::ABL1* at 12 months have favorable outcomes. Patients with a >50% reduction in *BCR::ABL1* levels compared to baseline or if *BCR::ABL1* is minimally above the 10% cutoff at 12 months can continue the same dose of TKI for another 3 months. Bone marrow cytogenetics should be considered to assess for CCyR at 12 months in cases where the *BCR::ABL1* transcript level is between 1% and 10%. The same dose of TKI can be continued if CCyR is achieved. Switching to alternate 2G TKI or asciminib or 3G TKI should be considered if CCyR is not achieved or in the absence of continuing decline in *BCR::ABL1* transcript levels. *BCR::ABL1* mutational analysis should be considered.

In patients with >0.1% to 1% *BCR::ABL1* IS at 12 months, shared decision-making is recommended depending on the goal of therapy in individual patients (longer-term survival vs. TFR). As discussed before, although not associated with increased OS, MMR at 12 months is associated with a lower rate of disease progression and a higher likelihood of achieving DMR, which is a prerequisite for TFR.[46,167] Switching from imatinib to a 2G TKI or asciminib may increase the probability of achieving MMR (≤0.1% *BCR::ABL1* IS) at 12 months. However, the side effect profile of alternative TKIs may differ. Referral to specialized CML centers and/or enrollment in a clinical trial should be considered.

Patients with >10% *BCR::ABL1* IS at 6 and 12 months are considered to have TKI-resistant disease. Evaluation for allogeneic HCT (discussion with a transplant specialist, which might include HLA testing) is recommended. Bone marrow cytogenetic analysis to assess ACAs should be considered. Alternative treatment options should be considered as described below.

Second-Line Therapy

Dose escalation of imatinib up to 800 mg daily has been shown to overcome some cases of primary resistance and is particularly effective for cytogenetic relapse in patients who had achieved cytogenetic response with imatinib 400 mg daily, although the duration of responses has typically been short.[172-175] However, it is unlikely to benefit patients who do not achieve hematologic response or those who never had a cytogenetic response with imatinib 400 mg daily.

In patients with >10% *BCR::ABL1* IS at 3 months after imatinib 400 mg, switching to nilotinib or dasatinib has been shown to result in higher rates of MMR at 12 months than dose escalation of imatinib.[176-178] Although dose escalation of imatinib has been shown to be beneficial for patients in CCyR without MMR, no randomized studies have shown that a change of therapy would improve PFS or EFS in this group of patients.[168,169]

Dasatinib and nilotinib retain activity against many of the imatinib-resistant BCR::ABL1 kinase domain mutants except T315I and are effective treatment options for CP-CML that is resistant to imatinib and also for patients who are intolerant to imatinib.[179,180] Bosutinib also has demonstrated activity in CP-CML that is resistant to multiple TKIs (imatinib, dasatinib, and nilotinib).[181-183] Ponatinib and asciminib are active against most of the resistant BCR::ABL1 kinase domain mutants, including T315I.[184-187]

Long-term efficacy data from clinical trials on second-line and subsequent TKI therapy for CP-CML are summarized in Table 6.

Ponatinib was initially approved as a treatment option for patients with a T315I mutation and/or for patients for whom no other TKI is indicated based on the results of the PACE trial.[184] Ponatinib, at the recommended initial dose of 45 mg once daily, was associated with increased risk of arterial and vascular adverse events. The incidence of cardiovascular adverse events was highest among patients with preexisting cardiovascular risk factors.[184,188-190] In the PACE trial, serious arterial and vascular adverse events (cardiovascular, cerebrovascular, and peripheral vascular) and venous thromboembolic events occurred in 31% and 6% of patients, respectively.[184] Cardiovascular, cerebrovascular, and peripheral vascular adverse events were reported in 16%, 13%, and 14% of patients, respectively.

See *Special Considerations for the Use of TKI Therapy* in the algorithm for the supportive care interventions and treatment recommendations for the management of arterial and cardiovascular adverse events associated with ponatinib.

In the OPTIC trial that evaluated the safety and efficacy of response-adjusted dosing regimen, patients were randomized to ponatinib starting doses of 45 mg, 30 mg, and 15 mg, with dose reduction to 15 mg with achievement of ≤1% *BCR::ABL1* (IS) in the 45 mg and 30 mg cohorts.[185] Ponatinib was effective at all 3 dose levels (45 mg, 30 mg, and 15 mg) and the maximum benefit was observed with 45 mg. After a median follow-up of 32 months, *BCR::ABL1* (IS) ≤1% at 12 months was achieved in 44% of patients in the 45 mg cohort compared to 29% and 23% in the 30 mg and 15 mg cohorts, respectively. After response-based dose reduction to 15 mg, responses were maintained in 73% and 79% of patients in the 45 mg and 30 mg cohorts, respectively. The rate of any arterial and vascular adverse events reported in the OPTIC trial (10% in the 45 mg cohort; 5% and 3% in the 30 mg and 15 mg cohorts, respectively) was lower than that reported for ponatinib 45 mg in the PACE trial. Based on the results of the OPTIC trial, the FDA has approved a response-adjusted dosing regimen for ponatinib [starting dose of 45 mg once daily with a reduction to 15 mg upon achievement of *BCR::ABL1* (IS) ≤1%] for patients with CP-CML with resistance or intolerance to at least two prior kinase inhibitors.

Asciminib is approved for CP-CML with T315I mutation and/or previously treated CP-CML. In the phase III randomized study (ASCEMBL), asciminib 40 mg twice daily achieved higher molecular response rates (MMR, MR4.0, and MR4.5) than bosutinib 500 mg once daily in patients with CP-CML previously treated with ≥2 prior TKIs.[186] Gastrointestinal toxicities (diarrhea, nausea, and vomiting) and biochemical abnormalities (increased ALT and AST levels) were notably higher with bosutinib. Arterial and vascular adverse events were reported in 3% and 1% of patients treated with asciminib and bosutinib, respectively. The incidence of adverse events leading to treatment discontinuation were also lower with asciminib (8% vs. 28%).[186] Patients with detectable bosutinib-resistant *BCR::ABL1* mutations (T315I or V299L) were ineligible to participate in the ASCEMBL trial. The results of the phase I dose escalation study confirmed the efficacy of asciminib in patients with previously treated CP-CML with a T315I mutation.[187] The recommended initial dose of asciminib is 80 mg once daily or 40 mg twice daily in patients without a T315I mutation and 200 mg twice daily in patients with a T315I mutation.

Clinical Considerations for the Selection of Second-Line TKI Therapy

EMR (≤10% *BCR::ABL1* IS at 3 and 6 months) after second-line TKI therapy with dasatinib or nilotinib has also been reported to be a prognosticator of OS and PFS (Table 7).[179,180] Patients who do not achieve cytogenetic or molecular responses at 3, 6, or 12 months after second-line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible.

BCR::ABL1 kinase domain mutation analysis (see below), evaluation of drug interactions, and adherence to therapy are recommended prior to the initiation of second-line TKI therapy. As discussed earlier, myeloid mutational analysis using NGS to identify *BCR::ABL1*–independent mutations may also be useful for patients with CP-CML who do not achieve optimal response milestones due to the presence of cytopenias and for those with TKI-resistant disease.

Drug Interactions

All TKIs are metabolized in the liver by cytochrome P450 (CYP) enzymes and concomitant use of drugs/food/fruits/fruit juices/supplements metabolized by CYP enzymes alter the therapeutic effect of TKIs.[191-193]

Drugs that are CYP3A4 or CYP3A5 inducers may decrease the therapeutic plasma concentration of TKIs, whereas CYP3A4 inhibitors and drugs that are metabolized by the CYP3A4 or CYP3A5 enzyme might result in increased plasma levels of TKIs. In addition, imatinib is also a weak inhibitor of the CYP2D6 and CYP2C9 isoenzymes and nilotinib is a competitive inhibitor of CYP2C8, CYP2C9, CYP2D6, and UGT1A1, potentially increasing the plasma concentrations of drugs eliminated by these enzymes. Asciminib is also a CYP2C9 inhibitor and concomitant use of asciminib increases the plasma concentration of other drugs that are CYP2C9 substrates.

Fruits/fruit juices that inhibit the activity of CYP3A4 enzyme (eg, grapefruit, star fruit, black mulberry, black raspberry, wild grape, pomegranate) should be avoided since they increase the therapeutic plasma concentration of TKIs.[191] If coadministration of medications and supplements that are metabolized by CYP enzymes cannot be avoided, dose modification should be considered, and appropriate alternatives should be explored to minimize toxicity. Alternative acid-reducing strategies such as the use of H2RAs or spacing out PPI use from TKI administration may be preferable if coadministration of TKIs with PPIs cannot be avoided. A pH-independent formulation of dasatinib that can be administered concomitantly with PPIs or H2RAs has been approved by the FDA as an alternative treatment option for adult patients with CML.

See *Drug Interactions of TKIs* in the algorithm (CML-D) for specific interactions of TKIs with the most commonly used medications, supplements, and fruits/fruit juices.

Adherence to Therapy

Treatment interruptions and non-adherence to therapy may lead to undesirable clinical outcomes.[194-196] In the ADAGIO study, non-adherence to imatinib was associated with poorer response. Patients with suboptimal response missed significantly more imatinib doses (23%) than did those with optimal response (7%).[194] Adherence to imatinib therapy has been identified as the only independent predictor for achieving complete molecular response (CMR) on standard-dose imatinib.[195] The 6-year probability of achieving CMR was significantly higher for patients with a >90% adherence rate (44% compared to 0% for patients with ≤90% adherence rate; $P = .002$).[195] Poor adherence to imatinib therapy has also been identified as the most important factor contributing to cytogenetic relapse and inadequate response to imatinib.[196] Patients with adherence of ≤85% had a higher probability of losing CCyR at 2 years than those with adherence of >85% (27% and 2%, respectively). Poor adherence to

therapy has also been reported in patients receiving dasatinib and nilotinib following inadequate response to imatinib.[197,198]

Patient education on adherence to therapy and close monitoring of each patient's adherence is critical to achieving optimal responses. In a significant proportion of patients with TKI-induced toxicities, responses have been observed with doses well below their determined maximum tolerated doses.[199] Short interruptions or dose reductions, when medically necessary, may not have a negative impact on disease control or other outcomes. Adequate and appropriate management of side effects and scheduling appropriate follow-up visits to review side effects may be helpful to improve patient adherence to therapy.[200]

Switching to an alternate TKI because of intolerance is appropriate for patients with disease responding to TKI therapy and it might be beneficial for selected patients with acute grade ≥3 nonhematologic toxicities or in those with chronic, low-grade nonhematologic toxicities that are not manageable with adequate supportive care interventions.[201,202] Asciminib and ponatinib are appropriate treatment options for CP-CML with intolerance to prior 2G TKIs.

Adverse events of second-line and subsequent TKI therapy in patients with CP-CML are summarized in Table 8.

Resistance to TKI Therapy

Aberrant expressions of drug transporters[203-205] and plasma protein binding of TKI[206-208] could contribute to primary resistance by altering the intracellular and plasma concentration of TKI.

Pretreatment levels of organic cation transporter 1 (OCT1) have been reported as the most powerful predictor of response to imatinib.[209] On the other hand, cellular uptake of dasatinib or nilotinib seems to be independent of OCT1 expression, suggesting that patients with low OCT1 expression might have better outcomes with dasatinib or nilotinib than with imatinib.[210-213]

Monitoring imatinib plasma levels may be useful in determining patient adherence to therapy. However, there are no data to support that change of therapy based on plasma imatinib levels will affect treatment outcomes, and assays that measure plasma levels of imatinib are not widely available.

BCR::ABL1 Kinase Domain Mutation Analysis

Point mutations in the *BCR::ABL1* kinase domain are a frequent mechanism of secondary resistance to TKI therapy.[214-219] The efficacy of a TKI against *BCR::ABL1* kinase domain mutations varies based on the IC_{50} values (concentration of TKI required for 50% inhibition), with select mutations conferring a lesser degree of resistance to a given TKI and other mutations conferring a stronger degree of resistance to the same TKI.[220]

T315I confers complete resistance to imatinib, dasatinib, nilotinib, and bosutinib.[221,222] T315A, F317L/I/V/C, and V299L mutants are resistant to dasatinib and the E255K/V, F359V/C, and Y253H mutants are resistant to nilotinib.[223-226] The G250E and V299L mutants are resistant to bosutinib.[227] E255K/V, F359C/V, Y253H, and T315I mutants are most commonly associated with disease progression and relapse.[226,228] There are limited data available regarding the impact of new myristoyl-pocket mutations detected during asciminib treatment on the efficacy of asciminib, and patients with detectable bosutinib-resistant *BCR::ABL1* mutations (T315I or V299L) were ineligible to participate in the ASCEMBL trial.[186] A337T, P465S, F359V/I/C, and M244V are considered as contraindicated mutations to asciminib.[229,230]

Dasatinib and bosutinib have demonstrated activity in patients with *BCR::ABL1* mutants resistant to nilotinib (Y253H, E255K/V, and

F359C/I/V).[181,182,225] Bosutinib has minimal activity against the F317L mutation (which is resistant to dasatinib) and nilotinib may be preferred over bosutinib in patients with the F317L mutation.[224,226,231] Ponatinib is active against *BCR::ABL1* mutants resistant to dasatinib or nilotinib, including E255V, Y253H, F359V, and T315I.[184] Asciminib is active against select *BCR::ABL1* mutants resistant to bosutinib, dasatinib, or nilotinib (G250E, Y253H, E255V, and T315I).[186]

A 35-bp insertion in the *BCR::ABL1* gene (*BCR::ABL1*^{35INS}) has been associated with resistance to imatinib.[232,233] In one study, *BCR::ABL1*^{35INS} was detected in 23% of patients (64 out of the 284 patients; 45 patients with CP-CML).[233] Among the 34 patients with CP-CML treated with imatinib, primary refractory disease, disease progression while on imatinib, and disease progression after dose interruption were reported in 24% (n = 8), 32% (n = 11), and 12% (n = 4) of patients, respectively. *BCR::ABL1*^{35INS} was also associated with grade 3 or 4 hematologic toxicity. This study, however, was not powered to determine the efficacy of 2G TKI against *BCR-ABL1*^{35INS} since very few patients with this mutation received either dasatinib or nilotinib.

BCR::ABL1 compound mutations (variants containing ≥2 mutations within the same *BCR::ABL1* allele that presumably arise sequentially) confer different levels of resistance to TKI therapy, and compound mutants involving T315I confer the highest level of resistance to all TKIs, including ponatinib.[220,234,235] In another study that used NGS to detect low-level and *BCR::ABL1* compound mutations in 267 patients with heavily pretreated CP-CML from the PACE trial, no compound mutation was identified that consistently conferred resistance to ponatinib, suggesting that such compound mutations are uncommon following treatment with bosutinib, dasatinib, or nilotinib for CP-CML.[236]

BCR::ABL1 kinase domain mutational analysis is helpful in the selection of subsequent TKI therapy for patients with inadequate initial response to first-line or second-line TKI therapy.[237] The guidelines recommend *BCR::ABL1* kinase domain mutational analysis for patients who do not achieve response milestones, for those with any sign of loss of response (hematologic or cytogenetic relapse), and if there is a 1-log increase in *BCR::ABL1* level with loss of MMR. *BCR::ABL1* kinase domain mutational analysis provides additional guidance for selecting subsequent TKI therapy only in patients with identifiable mutations. Treatment recommendations based on BCR::ABL1 kinase domain mutation status are outlined on CML-5.

Switching to an alternate TKI (based on the BCR::ABL1 kinase domain mutation status) is recommended for patients with disease that is resistant to primary treatment with imatinib. Patients with disease that is resistant to primary treatment with asciminib, bosutinib, dasatinib, or nilotinib could be switched to an alternate TKI (based on the BCR::ABL1 kinase domain mutation status). However, there is no clear evidence to support that switching to an alternate TKI would improve long-term clinical outcome for this group of patients.[238] Ponatinib is a treatment option for patients with a T315I mutation in any phase (preferred for AP-CML or BP-CML) and asciminib is a treatment option for patients with CP-CML having a T315I mutation.

Subsequent therapy with an alternate TKI is expected to be effective only in patients with identifiable *BCR::ABL1* mutations that confer resistance to TKI therapy. In patients with no identifiable mutations, the selection of subsequent TKI therapy should be based on the patient's age, ability to tolerate therapy, presence of comorbid conditions, and toxicity profile of the TKI. Ponatinib is preferred for patients with no identifiable *BCR::ABL1* mutations. Evaluation of allogeneic HCT or enrollment in a clinical trial should be considered for this group of patients.

Rising BCR::ABL1 Transcripts

Rising *BCR::ABL1* transcripts are associated with an increased likelihood of detecting BCR::ABL1 kinase domain mutations and cytogenetic relapse.[239-243] In patients who had achieved very low levels of *BCR::ABL1* transcripts, emergence of BCR::ABL1 kinase domain mutations was more frequent in those who had a >2-fold increase in *BCR::ABL1* transcripts compared to those with stable or decreasing *BCR::ABL1* transcripts.[239] A serial rise has been reported to be more reliable than a single ≥2-fold increase in *BCR::ABL1* transcripts.[240,241] Among patients in CCyR with a ≥0.5-log increase in *BCR::ABL1* transcripts on at least two occasions, the highest risk of disease progression was associated with loss of MMR and >1-log increase in *BCR::ABL1* transcripts.[241]

Rising transcript levels should prompt an investigation of treatment adherence and reassessment of coadministered medications. The precise increase in *BCR::ABL1* transcripts that warrants a mutation analysis depends on the performance characteristics of the qPCR assay.[243] Some laboratories have advocated a 2- to 3-fold range,[164,242,243] while others have taken a more conservative approach (5- to 10-fold).[241] Obviously, some common sense must prevail, since the amount of change in absolute terms depends on the level of molecular response. For example, a finding of any *BCR::ABL1* after achieving a DMR (MR4.5; ≤0.0032% *BCR::ABL1* IS) is an infinite increase in *BCR::ABL1* transcripts. However, a change in *BCR::ABL1* transcripts from a barely detectable level to MR4.5 is clearly different from a 5-fold increase in *BCR::ABL1* transcripts after achieving MMR.

Currently there are no specific guidelines for changing therapy only based on rising *BCR::ABL1* levels as detected by qPCR, and it should be done only in the context of a clinical trial.

Discontinuation of TKI Therapy

The feasibility of discontinuation of TKI therapy (dasatinib, imatinib, or nilotinib) with close monitoring in carefully selected patients who have achieved and maintained DMR (≥MR4.0; ≤0.01% *BCR::ABL1* IS) for ≥2 years has been evaluated in several clinical studies.[244-258] Longer-term follow-up data from the TKI discontinuation trials are summarized in Table 9.

The results of the RE-STIM study demonstrated the safety of a second TKI discontinuation after a first unsuccessful attempt.[259] The rate of molecular relapse after the first TKI discontinuation attempt was the only factor significantly associated with outcome. The TFR rate 24 months after the second TKI discontinuation was higher for patients who remained in DMR within the first 3 months after the first TKI discontinuation (72% vs. 32% for other patients).

Approximately 40% to 60% of patients who discontinue TKI therapy after achieving DMR experience recurrence within 12 months of treatment cessation, in some cases as early as 1 month after discontinuation of TKI therapy. Disease characteristics at diagnosis, blast cell and platelet count in peripheral blood, a higher Sokal risk score, female gender, lower natural killer (NK) cell counts, suboptimal response or resistance to imatinib, duration of TKI therapy, and DMR prior to TKI discontinuation have been identified as independent factors predictive of risk of recurrence after TKI discontinuation.[244,249,253,258] The duration of TKI therapy prior to discontinuation was significantly associated with the maintenance of MMR between 6 and 36 months after TKI discontinuation in the EURO-SKI study.[258] The EURO-SKI study also reported that the presence of transcript type e13a2 together with e14a2 was associated with a higher probability of maintaining MMR over 36 months compared to the presence of e13a2 alone.[258]

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2025) am 30.10.2025

#	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*):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 Oct 2020 to present, in Cochrane Reviews

Leitlinien und systematische Reviews in PubMed am 30.10.2025

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

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	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]

#	Suchschritt
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*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
15	(#14) AND ("2020/10/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
17	#1 OR #5 OR #6
18	(#17) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] 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 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 cochrane[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"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
19	(#18) AND ("2020/10/01"[PDAT] : "3000"[PDAT])
20	(#19) NOT "The Cochrane database of systematic reviews"[Journal]
21	(#20) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
22	(#21) NOT (#16)
23	(#22) AND ("2023/10/01"[PDAT] : "3000"[PDAT])

#	Suchschritt
24	#22 NOT #23

Iterative Handsuche nach grauer Literatur, abgeschlossen am 31.10.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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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.: 2025-B-290-z

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)
Datum der Erstellung	21. November 2025

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation
1. Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase (CP) 2. Behandlung von Erwachsenen mit Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase (CP), welche zuvor mit einem TKI 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?
Zu 1.) Eine zytostatische Therapie mit Hydroxyurea wird heutzutage nur noch vor Bestätigung der endgültigen Diagnose und gegebenenfalls bei Hyperleukozytose einige Tage darüber hinaus eingesetzt. Seit der Einführung von Imatinib ist eine zielgerichtete Therapie mit einem BCR::ABL-Tyrosinkinase-Inhibitor (TKI) die Therapie der Wahl (1, 2). Mit einer solchen Therapie kann in der Mehrheit der Fälle eine Krankheitsprogression verhindert und häufig auch eine „majore“ molekulare Remission (MMR, das heißt eine Reduktion von BCR::ABL < 0,1 % im Vergleich zum Kontrollgen nach internationalem Standard) erreicht werden. Wird eine MMR erreicht, so ist die Prognose für ein rezidivfreies Überleben exzellent. Ein dauerhaftes Überleben in Remission ist seitdem ein realistisches Therapieziel für die Mehrheit der Patienten. In den ersten Jahren nach Einführung der TKI wurde davon ausgegangen, dass für die Aufrechterhaltung einer Remission eine lebenslange Therapie notwendig ist. In den darauffolgenden Jahren hat sich jedoch herausgestellt, dass bei einer länger dauernden tiefen molekularen Remission (BCR::ABL < 0,01 % oder niedriger) bei etwa der Hälfte der Patienten die Dauertherapie mit TKI unter engmaschigen Kontrollen abgesetzt werden kann, ohne dass es zu einem Rezidiv kommt. Es wird damit eine therapiefreie Remission (TFR) erreicht, was heute ein für einen relevanten Teil der Patienten ein realistisches Ziel ist (1, 2). Neben Imatinib sind heute in Deutschland die TKI der zweiten Generation Nilotinib, Dasatinib und Bosutinib für die Behandlung der CML in der ersten Therapielinie zugelassen. Diese sind alle etwas potenter und führen zu einer schnelleren und tieferen molekularen Remission als Imatinib (3, 4). Ein Vorteil für das Gesamtüberleben konnte für keine der drei Substanzen gezeigt werden, vermutlich

auch, weil diese Medikamente auch in der zweiten Therapielinie noch hoch effektiv wirksam sind. Die höheren Raten tiefer molekularer Remissionen unter TKI der 2. Generation lassen jedoch erhoffen, dass auch höhere Raten an TFR erzielt werden können, weshalb sich eine Therapie mit TKI der zweiten Generation in Deutschland weitgehend durchgesetzt hat. Das Nebenwirkungsprofil der TKI ist unterschiedlich (u. a. Muskelkrämpfe, Ödeme, Übelkeit bei Imatinib; Pleuraerguss, pulmonale Hypertonie bei Dasatinib; kardiovaskuläre Ereignisse bei Nilotinib; Lebertoxizität und Diarrhoe bei Bosutinib) und sollte insbesondere in Bezug auf Begleiterkrankungen bei der Auswahl der Therapiestrategie berücksichtigt werden (1, 2).

Eine Vergleichstherapie (Behandlungsstandard), die den heutigen Standard in Deutschland abbildet, wäre somit eine Therapie mit einem der zugelassenen TKI nach Wahl des Behandlers unter Berücksichtigung möglicher Nebenwirkungen in Zusammenschau mit Begleiterkrankungen der einzelnen Patienten. Alternativ könnte als Vergleichstherapie ein einzelner TKI der zweiten Generation festgelegt werden. Abhängig von Begleiterkrankungen wäre dies dann jedoch nicht die ideale Option für einen Teil der Patienten, sodass diese dann besser eine Therapie außerhalb einer Studie erhalten würden.

Zu 2.)
Ein Umsetzen des TKI auf eine andere Therapie kann zwei wesentliche Gründe haben:
a) zum einen ein unzureichendes Ansprechen gemessen an hämatologischen und molekularen Parametern, orientiert an den ELN Empfehlungen (1),
b) zum anderen eine subjektive oder objektive Intoleranz des Medikaments.
a) Bei einem unzureichenden Ansprechen (1) sollte nach BCR::ABL-Mutationen und zusätzlichen genetischen Veränderungen gesucht werden. Der Nachweis einer Mutation kann hilfreich sein, zu entscheiden, welcher alternative TKI erfolgversprechend eingesetzt werden kann. Dies gilt insbesondere für die T315I-Mutation, bei der die Substanz Ponatinib häufig erfolgreich eingesetzt werden kann. Bei zusätzlichen prognostisch ungünstigen genetischen Veränderungen (Hochrisiko ACA) sollte außerdem insbesondere bei jungen Patienten in gutem Allgemeinzustand eine allogene Stammzelltransplantation erwogen werden (1, 2).
b) Bei schwerwiegenden oder subjektiv intolerablen Nebenwirkungen sollte ein anderer TKI eingesetzt werden, bei dem diese Nebenwirkungen erfahrungsgemäß seltener auftreten und das Nebenwirkungsprofil engmaschig kontrolliert werden. Rezidivierende Zytopenien, die immer wieder Therapiepausen verursachen, sind häufig ein Gruppeneffekt aller zur Verfügung stehenden TKI. Da in diesen Fällen häufig auch keine befriedigende Remissionstiefe erreicht wird, sollte auch hier eine allogene Stammzelltransplantation diskutiert werden (1, 2).

Die Auswahl der adäquaten Therapie in der zweiten Therapielinie hängt somit von zahlreichen Faktoren ab: Erstlinientherapie, Grund des Therapiewechsels, Nebenwirkungsprofil infrage kommender Therapien, genetische Untersuchungen (BCR::ABL-Mutationen, ACA). Behandlungsstandard ist in den meisten Fällen die Auswahl eines TKI nach Maßgabe des Experten, in einzelnen Fällen die allogene Stammzelltransplantation. Die Festlegung auf einen spezifischen TKI in der zweiten Therapielinie würde bedeuten, dass nur eine Subgruppe der Patienten für diese Therapie optimal geeignet wäre.

Tritt mit zwei TKI hintereinander ein Grund für ein Umsetzen der Therapie auf, so ist eine Therapie mit dem Medikament Asciminib nach einer großen randomisierten Studie wirksamer und besser verträglich als Bosutinib (5). Asciminib ist nach Einsatz von mindestens zwei anderen TKI in Deutschland zugelassen und hat sich in dieser Behandlungssituation als Standard etabliert, mit Ausnahme fitter Patienten mit schlechter Prognose, für die eine allogene Stammelltransplantation diskutiert werden sollte.

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?
Diese sind im oberen Abschnitt mit aufgeführt.

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