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: 2020-B-360 Bosutinib

Stand: Januar 2021

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

Bosutinib
[neu diagnostizierte Philadelphia-Chromosom-positive chronische myeloische Leukämie (Ph+ CML) in der chronischen Phase]

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.	nicht angezeigt
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:** • Bosutinib: Beschluss vom 22.11.2018; befristet bis 1.6.2021 **Weitere Beschlüsse:** Nicht zutreffend
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:	
Bosutinib L01XE14 Bosulif®	zugelassenes Anwendungsgebiet: Bosulif ist angezeigt zur Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase.
Chemotherapien:	
Hydroxycarbamid L01XX05 (Litalir®, generisch)	Behandlung von Patienten mit chronischer myeloischer Leukämie (CML) in der chronischen oder akzelerierten Phase der Krankheit.
Proteinkinase-Inhibitoren:	
Dasatinib L01XE06 (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 Imatinibmesilat.
Imatinib L01XE01 (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 Knochenmarkstransplantation 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 L01XE08 (Tasigna®)	Tasigna ist angezeigt für die Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom positiver chronischer myeloischer Leukämie (CML) in der chronischen Phase.
Immunmodulatoren:	
Interferon alfa-2a L03AB04 (Roferon®-A)	Roferon-A wird für die Behandlung der folgenden Erkrankungen angewendet: • Philadelphia-Chromosom-positive, chronisch-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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

2GTKI	second generation tyrosine kinase inhibitors
AP	accelerated phase
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCyR	complete cytogenetic response
CML	chronische myeloischer Leukämie
CP	chronischen Phase
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MMR	major molecular response
NG	new-generation
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	Odds Ratio
Ph+	Philadelphia-Chromosom-positiv
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 mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase (CP).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 04.12.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 232 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen 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 7 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2018 [1].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 22. November 2018 - Bosutinib (neues Anwendungsgebiet: Chronische myeloische Leukämie, Ph+, Erstlinie)

Neues Anwendungsgebiet

Bosulif ist angezeigt zur Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase (CP).

Zweckmäßige Vergleichstherapie

Imatinib oder Nilotinib oder Dasatinib

Fazit / Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

keine

3.3 Systematische Reviews

Tang L et al., 2019 [6].

Comparative efficacy and tolerability of front-line treatments for newly diagnosed chronic-phase chronic myeloid leukemia: an update network meta-analysis

Fragestellung

To assess the efficacy and tolerability of all reported front-line treatments for patients with newly diagnosed CML, a multiple-treatments meta-analysis was performed, which accounted for both direct and indirect comparisons among those treatments.

Methodik

Population:

- newly diagnosed, previously untreated (except for treatment with hydroxyurea or anagrelide) CP-CML patients;

Intervention/Komparator

front-line treatments:

- TKI: imatinib, nilotinib, bosutinib, dasatinib, radotinib, ponatinib,

- interferon,
- cytarabine,
- chemotherapy

Endpunkte:

- major molecular response (MMR) and complete cytogenetic response (CCyR) within 12 months
- percentage of progression to accelerated phase (AP),
- serious adverse effects (AEs in 3 or 4 grade), overall discontinuation and discontinuation for drug-related AEs.

Recherche/Suchzeitraum:

- Systematische Recherche in MEDLINE, EMBASE, Cochrane library databases und ClinicalTrials.gov ; keine Angaben zum Suchzeitraum

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien: 21 RCTs

Charakteristika der Studien:

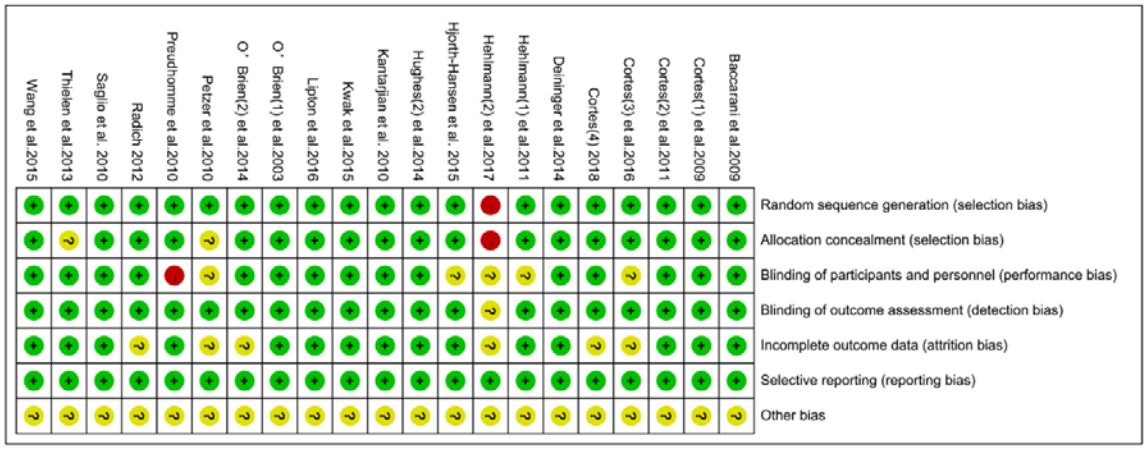
Table 1 Summary characteristics for the 21 eligible RCTs (10,187 patients)

Study Year	Journal Ref	Trial Number	Study Design	Treatment	Patients (N)	Male (%)	Age (yr)	Risk Group (%)					
								Sokal risk			Hasford risk		
								low	mid	high	low	mid	high
O'Brien (1) 2003	N Engl J Med [21–23]	NCT 00006343	Phase III, randomized, open-label, multicenter (IRIS)	Imatinib 400 mg qd	553	56.0	50(18–70)	53	29	18	46	44	10
				IFN-α + Ara-C	553	61.0	51(18–70)	47	30	22	45	45	10
Cortes (1) 2009	J Clin Oncol [24]	NCT 00124748	Phase III, randomized, multicenter	Imatinib 800 mg qd	319	57.4	48(18–75)	42.3	34.8	23.0	/	/	/
				Imatinib 400 mg qd	157	53.5	45(18–75)	39.5	33.8	27.0	/	/	/
Baccarani 2009	Blood [25]	NCT 00514488	Randomized, multicenter	Imatinib 800 mg qd	108	55.0	51(18–84)	/	/	/	/	/	/
				Imatinib 400 mg qd	108	57.0	51(18–81)	/	/	/	/	/	/
Preudhomme 2010	N Engl J Med [26]	NCT 00219739	Phase III, randomized (SPIRIT)	Imatinib 400 mg qd	159	69.0	50	38	38	24	/	/	/
				Imatinib 600 mg qd	160	56.0	51	37	38	28	/	/	/
				Imatinib 400 mg qd + Ara-C	158	58.0	55	37	41	23	/	/	/
				Imatinib 400 mg qd + IFN-α	160	65.0	51	36	40	24	/	/	/
Saglio 2010	N Engl J Med [27–30]	NCT 00471497	Phase III, randomized, open-label, multinational, multicenter (ENESTnd)	Nilotinib 300 mg bid	282	56.0	47(18–85)	37	36	28	/	/	/
				Nilotinib 400 mg bid	281	62.0	47(18–81)	37	36	28	/	/	/
				Imatinib 400 mg qd	283	56.0	46(18–80)	37	36	28	/	/	/
Kantarjian 2010	N Engl J Med [31–35]	NCT 00481247	Phase III, randomized, multicenter (DASISION)	Dasatinib 100 mg qd	259	56.0	46(18–84)	/	/	/	33	48	19
				Imatinib 400 mg qd	260	63.0	49(18–78)	/	/	/	33	47	19
Petzer 2010	Haematologica [36]	NCT 00327262	Randomized, multinational, multicenter (ISTAHIT)	Imatinib 800 mg qd	113	46.5	46(18–76)	/	/	/	/	/	/
				Imatinib 400 mg qd	113	42.5	46(20–68)	/	/	/	/	/	/
Cortes (2) 2011	Blood [37–39]	NCT 00574873	Randomized, multinational, multicenter (BELA)	Bosutinib 500 mg qd	250	60.0	48(19–91)	35	47	18	/	/	/
				Imatinib 400 mg qd	252	54.0	47(18–89)	35	47	18	/	/	/
Hehlmann (1) 2011	J Clin Oncol [40]	/	Randomized, multinational, multicenter	Imatinib 800 mg qd	338	59.0	52(18–86)	/	/	/	/	/	/
				Imatinib 400 mg qd	325	60.0	64(16–88)	/	/	/	/	/	/
				Imatinib 400 mg qd + IFN-α	351	61.0	54(16–83)	/	/	/	/	/	/
Radich 2012	Blood [41]	NCT 00070499	Phase III, randomized, multinational, multicenter	Dasatinib 100 mg qd	123	60.0	47(18–90)	/	/	/	36	33	32
				Imatinib 400 mg qd	123	59.0	50(19–89)	/	/	/	36	37	28
Thielen 2013	Ann Hematol [42]	NTR674	Phase III, randomized, multicenter	Imatinib 400 mg qd	55	NA	46(17–65)	29	44	22	/	/	/
				Imatinib 400 mg qd + Ara-C	54	NA	45(23–65)	37	39	20	/	/	/
Hughes 2014	Blood [43]	NCT 00760877	Phase III, randomized, open-label, multicenter (ENESTcmr)	Nilotinib 400 mg bid	104	68.3	46(23–82)	/	/	/	/	/	/
				Imatinib 400 mg qd	103	63.1	52(19–76)	/	/	/	/	/	/
O'Brien (2) 2014	Blood [44, 45]	/	Phase III, randomized, multinational, multicenter (SPIRIT2)	Dasatinib 100 mg qd	407	61.0	53(18–89)	/	/	/	/	/	/
				Imatinib 400 mg qd	407	60.0	53(18–87)	/	/	/	/	/	/
Deininger 2014	Br J Hematol [46]	NCT	Phase II, randomized	Imatinib 800 mg qd	73	64.0	52(19–82)	/	/	/	21	30	49

		00070499		Imatinib 400 mg qd	72	63.0	50(23–80)	/	/	/	21	30	49
Hjorth-Hansen 2015	Eu J Hematol [47]	NCT 00852566	Phase II, randomized multicenter (NordCML006)	Dasatinib 100 mg qd	22	32.0	53(29–71)	32	45	23	/	/	/
				Imatinib 400 mg qd	24	63.0	58(38–78)	49	34	17	/	/	/
Wang 2015	Blood [48]	NCT 01275196	Phase III, randomized, multicenter	Nilotinib 300 mg bid	134	68.0	41(18–76)	51	33	16	/	/	/
				Imatinib 400 mg qd	133	61.0	39(19–74)	52	32	16	/	/	/
Kwak 2015	Blood [49]	NCT 01511289	Phase III, randomized, open-label, multicenter (RERISE)	Radotinib 300 mg bid	79	66.0	45(20–75)	27	48	25	/	/	/
				Radotinib 400 mg bid	81	58.0	43(18–84)	27	48	25	/	/	/
				Imatinib 400 mg qd	81	64.0	45(18–83)	27	48	37	/	/	/
Lipton 2016	Lancet Oncol [50]	NCT 01650805	Phase III, randomized, open-label, multicenter	Ponatinib 45 mg qd	155	63.0	55(18–89)	41	41	17	/	/	/
				Imatinib 400 mg qd	152	61.0	52(18–86)	41	44	15	/	/	/
Cortes (3) 2016	Lancet Haematol [51]	NCT 00802841	Phase III, randomized, multicenter (LASOR)	Nilotinib 400 mg bid	96	56.0	46(32–46)	/	/	/	/	/	/
				Imatinib 600 mg qd	95	61.0	44(33–56)	/	/	/	/	/	/
Hehlmann (2) 2017	Leukemia [52, 53]	NCT 00055874	Randomized, open-label, multinational, multicenter	Imatinib 400 mg qd	400	61.0	53(16–88)	36	40	25	/	/	/
				Imatinib 400 mg qd + IFN-α	430	59.0	53(16–83)	39	39	22	/	/	/
				Imatinib 400 mg qd + Ara-C	158	63.0	52(18–79)	39	34	27	/	/	/
				Imatinib 400 mg qd after IFN-α	128	63.0	53(18–87)	40	45	15	/	/	/
				Imatinib 800 mg qd	420	59.0	51(18–85)	37	37	27	/	/	/
Cortes (4) 2018	J Clin Oncol [54]	NCT 02130557	Phase III, randomized, open-label, multicenter	Bosutinib 400 mg qd	268	57.7	52(18–84)	38	41	201	/	/	/
				Imatinib 400 mg qd	268	56.0	53(19–84)	40	39	21	/	/	/

("/" means "not available")

Qualität der Studien:



Studienergebnisse:

Direkte Vergleiche (siehe Tab)

- newer TKIs (dasatinib, radotinib, bosutinib, nilotinib and ponatinib) showed higher efficacy than imatinib
- the traditional treatment (IFN-α and Ara-C) suggested significantly lower efficacy when compared to TKIs.
- Low-dose nilotinib (300 mg BID) and radotinib (300 mg BID) had higher efficacy than high-dose nilotinib (400 mg BID) and radotinib (400 mg BID), respectively.
- For overall discontinuation, traditional drugs showed higher dropout rate than TKIs.
- As for the discontinuation specially caused by drug-related AE, most treatments showed lower acceptability when compared to standard-dose imatinib (400 mg QD), such as traditional drugs, newer TKIs and higher-dose imatinib (600 or 800 mg QD).
- low-dose nilotinib (300mgQD) generated higher tolerability than standard-dose imatinib.
- Standard dose imatinib showed least probability of SAEs compared to other treatments.
- statistical heterogeneity

- statistical heterogeneity was moderate, although 95%CIs were wide for several comparisons, which portrayed the small number of studies available for the pairwise comparison.
- Substantial heterogeneity was observed when comparing imatinib 400mgQD with nilotinib 400 mg BID (I^2 =75.7%) for MMR or imatinib 40 mg QD + Ara-C (I^2= 87.3%) for CCyR.
- there was no evidence showing heterogeneity in other pooled results of the direct comparisons for the six outcomes.

Tab. Efficacy and tolerability of all treatments according to pairwise estimates

Treatment	Studies (N)	Patients (N)	Efficacy OR (95% CI)			Tolerability OR (95% CI)		
			MMR within 12 months	CCyR within 12 months	Progression to AP	Overall discontinuation	Discontinuation for drug-related AEs	Serious AEs
vs Imatinib 400mg QD								
IFN-α + Ara-C	1	1106	0.00(0.00, 0.03)	0.03(0.02, 0.05)	2.00(1.32, 3.02)	3.30(2.42, 4.51)	3.13(1.56, 6.26)	-
Imatinib 600mg QD	1	319	1.57(1.01, 2.45)	1.35(0.86, 2.12)	-	1.08(0.68, 1.70)	1.77(0.79, 4.00)	-
Imatinib 800mg QD	6	2546	1.82(1.39, 2.38)	1.60(1.21, 2.12)	0.97(0.54, 1.73)	1.00(0.41, 2.46)	2.83(1.49, 5.36)	1.24(0.18, 8.38)
Imatinib 400mg QD + Ara-C	3	984	0.93(0.58, 1.50)	1.14(0.49, 2.69)	1.13(0.58, 1.73)	5.95(0.33, 106.31)	3.95(0.50,31.26)	0.39(0.19, 0.78)
Imatinib 400mg QD + IFN-α	3	1805	1.44(1.06, 1.97)	1.07(0.89, 1.30)	1.36(0.59, 3.12)	2.61(0.22, 31.61)	22.94(11.23, 46.87)	0.40(0.25, 0.65)
Imatinib 400mg QD after IFN-α	1	528	0.20(0.11, 0.36)	0.17(0.11, 0.26)	0.81(0.40, 1.65)	-	-	0.12(0.01, 0.92)
Nilotinib 300mg BID	2	832	1.24(1.084, 1.429)	1.16(1.07, 1.26)	0.48(0.23, 0.99)	0.92(0.59, 1.45)	0.96(0.57, 1.63)	1.45(0.88, 2.40)
Nilotinib 400mg BID	2	769	1.68(0.56, 5.07)	1.90(1.31, 2.76)	1.30(0.53, 3.22)	1.64(0.53, 5.15)	2.01(0.61, 6.65)	1.27(0.98, 1.63)
Dasatinib 100mg QD	4	1625	1.44(1.29, 1.60)	1.34(1.25, 1.44)	0.78(0.49, 1.24)	0.74(0.58, 0.96)	1.48(1.11, 1.98)	1.54(1.02, 2.31)
Bosutinib 400mg QD	1	502	1.51(1.07, 2.14)	1.75(1.20, 2.57)	0.25(0.03, 2.23)	0.77(0.52, 1.14)	1.55(0.89, 2.71)	1.74(1.24, 2.45)
Bosutinib 500mg QD	1	536	1.90(1.30, 2.76)	1.11(0.76, 1.61)	2.71(0.95, 7.72)	1.60(1.06, 2.42)	4.11(2.34, 7.19)	1.92(1.35, 2.75)
Radotinib 300mg BID	1	160	2.56(1.34, 4.91)	3.15(1.24, 8.00)	-	0.64(0.27, 1.52)	0.14(0.01, 2.81)	-
Radotinib 400mg BID	1	162	2.00(1.05, 3.81)	1.35(0.63, 2.89)	-	1.75(0.83, 3.66)	2.08(0.50, 8.62)	-
Ponatinib 45mg QD	1	307	6.48(3.89, 10.82)	-	-	2.35(1.11, 4.98)	7.50(1.67, 33.60)	-
vs Imatinib 600mg QD								
Nilotinib 400mg BID	1	191	3.06(1.59, 5.88)	2.86(1.59, 5.16)	1.79(0.51, 6.33)	0.48(0.25,0.91)	0.09(0.14, 1.66)	1.37(0.75, 2.49)
Imatinib 400mg QD + Ara-C	1	318	0.90(0.58, 1.40)	1.27(0.79, 2.04)	-	23.50(11.76,46.96)	0.74(0.09, 0.29)	-
Imatinib 400mg QD + IFN-α	1	320	1.39(0.89, 2.15)	1.06(0.67, 1.68)	-	8.66(5.13, 14.64)	1.54(0.04, 0.14)	-
vs Imatinib 800mg QD								
Imatinib 400mg QD + Ara-C	1	578	0.34(0.23, 0.50)	0.34(0.23, 0.49)	1.21(0.54, 2.71)	-	-	2.30(0.97, 5.43)
Imatinib 400 mg QD + IFN-α	2	1188	0.52(0.38,0.70)	0.59(0.48, 0.74)	0.72(0.36, 1.43)	0.76(0.45, 1.31)	-	2.37(1.19, 4.72)
Imatinib 400 mg QD after IFN-α	1	548	0.09(0.05, 0.16)	0.10(0.06, 0.16)	1.16(0.48, 2.80)	-	-	0.27(0.03, 2.08)
vs Imatinib 400mg QD + Ara-C								
Imatinib 400mg QD + IFN-α	1	588	1.78(1.21, 2.64)	1.82(1.25, 2.64)	0.60(0.26, 1.40)	0.37(0.18, 0.77)	1.54(0.31, 0.75)	1.03(0.49, 2.17)
Imatinib 400mg QD after IFN-α	1	286	0.27(0.14, 0.52)	0.30(0.18, 0.49)	0.96(0.35, 2.65)	-	-	0.12(0.01, 0.92)
vs Imatinib 400mg QD + IFN-α								
Imatinib 400mg QD after IFN-α	1	558	0.15(0.08, 0.27)	1.00(0.57, 1.75)	1.60(0.64, 4.02)	-	-	0.11(0.02, 0.84)
vs Nilotinib 300mg BID								
Nilotinib 400mg BID	1	563	0.85(0.61, 1.18)	0.88(0.58, 1.31)	0.59(0.21, 1.66)	1.22(0.83, 1.81)	1.40(0.82, 2.40)	-
vs Radotinib 300mg BID								
Radotinib 400mg BID	1	160	0.78(0.42, 1.45)	0.43(0.16, 1.11)	-	2.74(1.20, 6.22)	0.25(0.22, 0.73)	-

("-" means "cannot be estimated for lack of primary data")

NMA

Netzwerkgeometrie

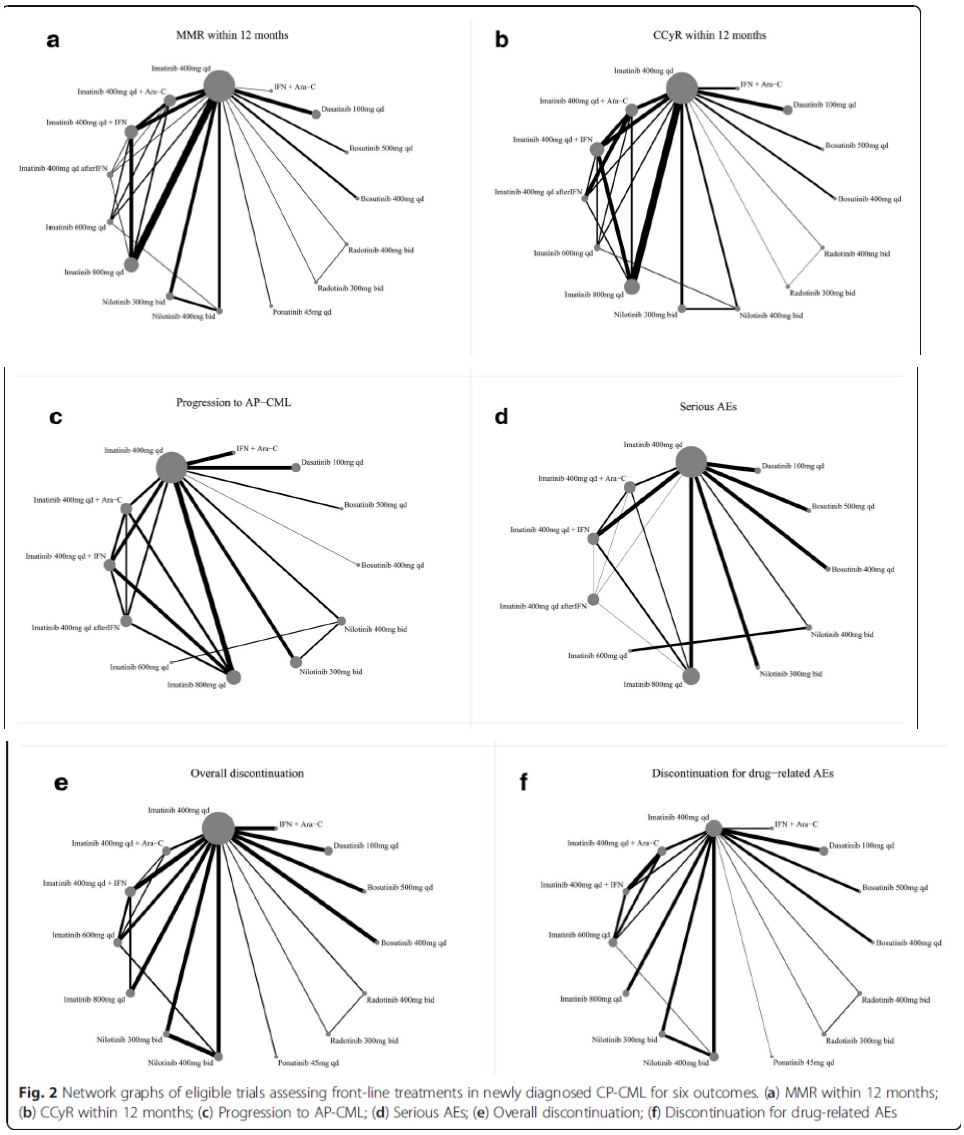


Fig. 2 Network graphs of eligible trials assessing front-line treatments in newly diagnosed CP-CML for six outcomes. (**a**) MMR within 12 months; (**b**) CCyR within 12 months; (**c**) Progression to AP-CML; (**d**) Serious AEs; (**e**) Overall discontinuation; (**f**) Discontinuation for drug-related AEs

Transitivity and consistency assessment

- As there were no observed significant clinical differences in distribution of effect modifiers between trials comparing different sets of interventions, we considered that the transitivity assumption was almost met .
- All closed loops (networks of 3 comparisons that arise when collating studies involving different selections of competing treatments) were consistent, since the 95% CIs of inconsistency factors (IF, the difference between the direct and indirect estimate for one of the comparisons in a particular loop) included zero.
- Furthermore, inconsistency test by the node-splitting method indicated that there was no significant inconsistency between direct and indirect evidence for nearly all P values were higher than 0.05.
- Analysis of inconsistency indicated that there was inconsistency in the loop for “CCyR” (“imatinib 400 mg QD + Ara-C” - “imatinib 800 mg QD”), another loop for “discontinuation for drug-related AEs” (“imatinib 400 mg QD + Ara-C” - “imatinib 600 mg QD”) and none for other four outcomes.
- Furtherly, we identified slight gender and sex difference across comparisons in these 2 loops, which may account for the inconsistency.

Network estimation and cumulative ranking

Table 2 Efficacy and tolerability of all treatments for CP-CML according to Bayesian network meta-analysis

Imatinib 400mg qd	1.05 (0.65, 1.67)	1.96 (1.49, 2.48)	0.00 (0.00, 0.02)	0.83 (0.56, 1.19)	1.25 (0.91, 1.72)	3.24 (2.10, 4.95)	2.95 (1.95, 4.47)	2.06 (1.51, 2.97)	2.59 (1.16, 5.75)	2.01 (0.92, 4.49)	1.51 (0.85, 2.73)	1.88 (1.03, 3.47)	6.67 (3.30, 13.29)	0.18 (0.09, 0.37)
1.04 (0.37, 3.25)	Imatinib 600mg qd	1.87 (1.10, 3.12)	0.00 (0.00, 0.02)	0.79 (0.47, 1.32)	1.19 (0.72, 2.00)	3.08 (1.67, 5.74)	2.81 (1.66, 4.92)	1.98 (1.14, 3.63)	2.44 (0.99, 6.35)	1.91 (0.78, 4.91)	1.44 (0.70, 3.14)	1.80 (0.85, 3.92)	6.23 (2.76, 14.84)	0.18 (0.07, 0.40)
2.32 (1.00, 5.25)	2.23 (0.57, 8.59)	Imatinib 800mg qd	0.00 (0.00, 0.01)	0.42 (0.28, 0.63)	0.64 (0.47, 0.92)	1.66 (1.01, 2.77)	1.50 (0.94, 2.50)	1.05 (0.72, 1.69)	1.32 (0.58, 3.11)	1.02 (0.46, 2.43)	0.77 (0.42, 1.51)	0.96 (0.51, 1.90)	3.38 (1.63, 7.13)	0.09 (0.04, 0.19)
3.25 (0.85, 12.64)	3.13 (0.56, 16.64)	1.41 (0.29, 7.02)	IFN + Ara-C	249.74 (40.67, 3429.57)	380.31 (62.20, 5265.31)	981.73 (156.86, 13641.65)	896.95 (143.78, 12260.57)	632.83 (103.57, 8822.02)	793.41 (106.17, 12296.72)	613.89 (84.50, 9426.49)	466.09 (70.27, 6540.84)	578.18 (87.08, 8398.08)	2007.28 (294.80, 30945.78)	55.26 (7.89, 795.17)
4.94 (1.68, 12.42)	4.82 (1.27, 13.22)	2.14 (0.55, 7.18)	1.53 (0.26, 7.09)	Imatinib 400mg qd + Ara-C	1.51 (1.03, 2.30)	3.90 (2.25, 6.94)	3.56 (2.09, 6.24)	2.51 (1.54, 4.32)	3.10 (1.31, 7.75)	2.43 (1.02, 5.94)	1.83 (0.93, 3.72)	2.28 (1.16, 4.72)	7.98 (3.67, 17.70)	0.22 (0.10, 0.47)
14.05 (4.15, 45.81)	13.59 (3.64, 45.20)	6.09 (1.37, 25.05)	4.34 (0.70, 25.58)	2.80 (0.96, 10.34)	Imatinib 400mg qd + IFN	2.58 (1.51, 4.35)	2.34 (1.41, 3.87)	1.65 (1.06, 2.65)	2.03 (0.87, 4.91)	1.60 (0.69, 3.77)	1.21 (0.62, 2.36)	1.50 (0.77, 2.99)	5.23 (2.46, 11.34)	0.14 (0.07, 0.29)
1.28 (0.49, 3.88)	1.23 (0.31, 5.34)	0.55 (0.16, 2.27)	0.39 (0.08, 2.36)	0.26 (0.07, 1.27)	0.09 (0.02, 0.50)	Nilotinib 300mg bid	0.91 (0.57, 1.50)	0.64 (0.38, 1.14)	0.79 (0.33, 1.99)	0.62 (0.26, 1.55)	0.47 (0.23, 0.98)	0.58 (0.28, 1.25)	2.03 (0.91, 4.69)	0.06 (0.02, 0.13)
2.01 (0.94, 5.50)	1.94 (0.65, 6.77)	0.86 (0.29, 3.17)	0.62 (0.14, 3.32)	0.40 (0.14, 1.75)	0.14 (0.04, 0.66)	1.56 (0.54, 4.89)	Nilotinib 400mg bid	0.70 (0.42, 1.21)	0.89 (0.36, 2.15)	0.68 (0.28, 1.68)	0.51 (0.25, 1.06)	0.64 (0.31, 1.33)	2.26 (1.01, 4.98)	0.06 (0.03, 0.14)
1.42 (0.71, 2.81)	1.36 (0.35, 4.64)	0.61 (0.21, 1.77)	0.43 (0.09, 1.95)	0.29 (0.09, 1.07)	0.10 (0.02, 0.41)	1.11 (0.29, 3.55)	0.71 (0.20, 1.90)	Dasatinib 100mg qd	1.25 (0.52, 2.96)	0.97 (0.40, 2.25)	0.74 (0.36, 1.42)	0.91 (0.45, 1.78)	3.22 (1.45, 6.82)	0.09 (0.04, 0.19)
1.54 (0.30, 9.48)	1.49 (0.20, 11.59)	0.66 (0.11, 4.68)	0.47 (0.06, 4.88)	0.31 (0.05, 2.61)	0.11 (0.01, 0.97)	1.21 (0.16, 9.21)	0.78 (0.11, 5.33)	1.09 (0.19, 7.68)	Radotinib 300mg bid	0.78 (0.35, 1.68)	0.58 (0.22, 1.59)	0.72 (0.27, 1.98)	2.58 (0.87, 7.30)	0.07 (0.02, 0.21)
4.14 (0.92, 21.57)	3.98 (0.59, 28.95)	1.79 (0.32, 11.04)	1.27 (0.16, 10.94)	0.85 (0.15, 6.28)	0.30 (0.04, 2.28)	3.24 (0.49, 21.49)	2.07 (0.33, 12.57)	2.97 (0.56, 17.20)	2.65 (0.61, 12.05)	Radotinib 400mg bid	0.75 (0.28, 2.03)	0.94 (0.35, 2.55)	3.27 (1.13, 9.55)	0.09 (0.03, 0.27)
1.53 (0.43, 5.60)	1.47 (0.28, 7.50)	0.66 (0.15, 2.97)	0.47 (0.07, 3.10)	0.31 (0.07, 1.71)	0.11 (0.02, 0.65)	1.19 (0.22, 5.52)	0.77 (0.14, 3.23)	1.08 (0.25, 4.60)	0.99 (0.12, 8.04)	0.37 (0.05, 2.62)	Bosutinib 400mg qd	1.24 (0.54, 2.89)	4.40 (1.75, 10.79)	0.12 (0.05, 0.30)
4.18 (1.23, 16.04)	4.10 (0.71, 21.04)	1.82 (0.39, 9.21)	1.32 (0.20, 8.18)	0.85 (0.18, 4.79)	0.30 (0.05, 1.75)	3.34 (0.60, 15.91)	2.12 (0.41, 8.98)	2.97 (0.71, 13.61)	2.70 (0.33, 21.78)	1.01 (0.14, 7.37)	2.76 (0.45, 17.06)	Bosutinib 500mg qd	3.54 (1.40, 8.63)	0.10 (0.04, 0.25)
8.86 (1.48, 87.98)	8.46 (0.98, 104.39)	3.82 (0.54, 45.38)	2.77 (0.28, 38.49)	1.81 (0.24, 23.29)	0.63 (0.07, 8.06)	6.80 (0.82, 87.32)	4.32 (0.54, 48.99)	6.29 (0.93, 73.09)	5.75 (0.47, 95.73)	2.14 (0.19, 32.08)	5.64 (0.64, 78.19)	2.05 (0.24, 30.14)	Ponatinib 45mg qd	0.03 (0.01, 0.08)
-	-	-	-	-	-	-	-	-	-	-	-	-	-	Imatinib 400mg qd after IFN-α

Treatment	Discontinuation for Drug-related AEs (OR with 95% CI)	MMR within 12 months (OR with 95% CI)

Table 3 Surface under the cumulative ranking curve (SUCRA) data for six outcomes

Treatment	Surface Under the Cumulative Ranking Curve (SUCRA)					
	MMR within 12 months	CCyR within 12 months	Progression to AP-CML	Overall Discontinuation	Discontinuation for Drug-related AEs	Serious AEs
Bosutinib 400 mg qd	0.428	0.684	0.259	0.318	0.346	0.572
Bosutinib 500 mg qd	0.570	0.416	0.872	0.520	0.719	0.581
Dasatinib 100 mg qd	0.624	0.736	0.302	0.337	0.312	0.632
IFN + Ara-C	0.000	0.000	0.719	0.726	0.476	–
Imatinib 400 mg qd	0.209	0.335	0.406	0.383	0.158	0.481
Imatinib 400 mg qd + Ara-C	0.172	0.340	0.482	0.903	0.769	0.483
Imatinib 400 mg qd + IFN	0.321	0.411	0.350	0.653	0.958	0.488
Imatinib 400 mg qd after IFN	0.071	0.076	–	–	–	0.159
Imatinib 600 mg qd	0.449	0.311	0.254	0.352	0.187	0.477
Imatinib 800 mg qd	0.682	0.730	0.388	0.525	0.576	0.528
Nilotinib 300 mg bid	0.791	0.759	0.301	0.372	0.234	0.543
Nilotinib 400 mg bid	0.839	0.781	0.293	0.416	0.440	0.556
Ponatinib 45 mg qd	0.997	–	0.419	0.649	0.837	–
Radotinib 300 mg bid	0.750	0.895	–	0.283	0.343	–
Radotinib 400 mg bid	0.596	0.538	–	0.561	0.688	–

("-" means "can't be evaluated")

Anmerkung/Fazit der Autoren

Nilotinib (300/400 mg BID), dasatinib (100 mg QD) and radotinib (300 mg BID) prove to be the most recommended front-line treatments of the greatest efficacy and tolerability for CP-CML patients. High-dose therapies are recommended only for patients in accelerated phase/blast phase or with suboptimal CML-CP response, and management of adverse events should be carried out to avoid compromising the clinical efficacy.

Kommentare zum Review

- Untersuchte Interventionen umfassen auch Ponatinib und Radotinib, welche keine Zulassung im AWG haben

- Keine Angaben, welche konkreten Effektmodifikatoren zur Prüfung der Transitivitäts-annahme untersucht wurden; Informationen zur Verteilung potentieller Effektmodifikatoren auf Vergleichsebene (z.B. in Summary tables organised by class pair-wise comparisons) liegen nicht vor.

Pan P et al., 2020 [4].

Systematic Review and Meta-Analysis of -New-Generation Tyrosine Kinase Inhibitors versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia

Fragestellung

to compare the efficacy of new-generation tyrosine kinase inhibitors (NG-TKIs; including dasatinib, nilotinib, bosutinib, radotinib, and ponatinib) versus imatinib for patients with newly diagnosed chronic myeloid leukemia (CML)

Methodik

Population:

- adults older than 18 years with newly diagnosed CML-CP who had never been treated with any TKI

Intervention:

- any NG-TKI

Komparator:

- imatinib

Endpunkte:

- MMR and CCyR rates at 12 months
- MMR at 24 months and 3–5 years; CCyR at 24 months;
- MR4.5 (BCR-ABLIS ≤0.0032%) at 12 and 24 months and 3–5 years;
- early molecular response (EMR; defined as BCR-ABLIS ≤10%) at 3 months);
- the rate of patients progressing to AP/BC at 12, 24, and 36 months and 5 years;
- OS (death due to any cause while on treatment or during follow-up after the discontinuation of treatment) at 12, 24, and 36 months and 5 years;
- PFS (progression to AP/BC or death due to any cause while on treatment), and
- CML-related death at 12 and 24 months and 5 years

Recherche/Suchzeitraum:

- We searched the PubMed, Cochrane library, and EMBASE databases to identify published SR or meta-analyses comparing the efficacy of NG-TKIs with imatinib as the first-line treatment for newly diagnosed, previously untreated CML-CP patients from the inception dates to April 30, 2019.
- We identified relevant original RCTs included in the systematic reviews or meta-analyses.
- An additional search was performed to identify recently published RCTs (within the last 5y)

Gemeinsamer Bundesausschuss

Qualitätsbewertung der Studien:

- Criteria based on Cochrane handbook, version 5.1.0.The following domains were evaluated: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data reporting, and selective outcome reporting. Each item was graded as low risk, high risk, or unclear risk. The included trials were graded as low quality, high quality, or moderate quality based on the criteria of Zhao et al.

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 RCTs (4 of dasatinib, 2 of bosutinib, 2 of nilotinib, 1 of ponatinib, and 1 of radotinib).

Charakteristika der Studien:

Study	Type of TKI and dosage compared to imatinib 400 mg/day	Patients, *n*		Median age, years		Gender male, *n* (%)		Risk group, *n* (%)		ECOG, *n* (%)	
		exp	ctrl	exp	ctrl	exp	ctrl	exp	ctrl	exp	ctrl
DASISION [10, 18–20] NCT00481247	Dasatinib (100 mg/day)	259	260	46 (18–84)	49 (18–78)	144 (56)	163 (63)	low: 86 (33) int: 124 (48) high: 49 (19)	low: 87 (33) int: 123 (47) high: 50 (19)	0: 213 (82) 1: 46 (18) 2: 0 (0)	0: 205 (79) 1: 53 (20) 2: 2 (1)
BELA [12, 25, 27] NCT00574873	bosutinib (500 mg/day)	250	252	48 (19–91)	47 (18–89)	149 (60)	135 (54)	low: 88 (35) int: 117 (47) high: 45 (18)	low: 89 (35) int: 118 (47) high: 45 (18)	0: 185 (74) 1: 65 (26)	0: 181 (72) 1: 71 (28)
BFORE [26] NCT02130557	bosutinib (400 mg/day)	246	241	52 (18–84)	53 (19–84)	142 (58)	135 (56)	low: 94 (38.2) int: 101 (41.1) high: 51 (20.7)	low: 95 (39.4) int: 95 (39.4) high: 51 (21.2)	0: 174 (70.7) 1: 72 (29.3)	0: 170 (70.5 1: 70 (29.0)
ENESTchina [32] NCT01275196	Nilotinib (300 mg bid)	134	133	41 (18–76)	39 (19–74)	91 (68)	81 (61)	low: 69 (52) int: 44 (33) high: 21 (16)	low: 69 (52) int: 43 (3) high: 21 (16)	0–2: 134 (100)	0–2: 133 (1(
ENESTnd [11, 28–31, 33] NCT00471497	Nilotinib (300 mg bid [G1] 400 mg bid [G2])	563 (G1, 282; G2, 281)	283	47 (18–85)	47 (18–81)	333 (59)	158 (56)	low: 206 (37) int: 201 (36) high: 156 (28)	low: 104 (37) int: 101 (36) high: 78 (28)	0–2: 563 (100)	0–2: 283 (1(
EPIC [13] NCT01650805	Ponatinib (45 mg/day)	154	152	55 (18–89)	52 (18–86)	97 (63)	92 (61)	low: 64 (41) int: 64 (41) high: 27 (17)	low: 62 (41) int: 67 (44) high: 23 (15)	0: 116 (75) 1: 37 (24) 2: 1 (1)	0: 119 (78) 1: 32 (21) 2: 1 (1)
NordCML006 [24] NCT00852566	Dasatinib (100 mg/day)	22	24	53 (29–71)	58 (38–78)	7 (32)	15 (63)	low: 7 (32) int: 10 (45) high: 5 (23)	low: 12 (50) int: 8 (33) high: 4 (17)	0–1: 22 (100)	0–1: 24 (10(
RERISE [14, 34] NCT01511289	Radotinib (300 mg bid [G1] 400 mg bid [G2])	160 (G1, 79; G2, 81)	81	44 (18–84)	45 (18–83)	99 (62)	50 (64)	low: 43 (27) int: 76 (48) high: 41 (26)	low: 22 (27) int: 39 (48) high: 20 (25)	1: 108 (67.5) 1: 51 (31.9) 2: (0.6)	0: 51 (63) 1: 29 (36) 2: 1 (1)
S0325 [23] NCT00070499	Dasatinib (100 mg/day)	123	123	47 (18–90)	50 (18–89)	74 (60)	72 (59)	low: 44 (36) int: 40 (33) high: 39 (32)	low: 44 (36) int: 45 (37) high: 34 (28)	0: 71 (58) 1: 47 (39) 2: 4 (3)	0: 76 (63) 1: 44 (36) 2: 1 (1)
Spirit 2 [21, 22] NCT01460693	Dasatinib (100 mg/day)	406	406			Not reported					

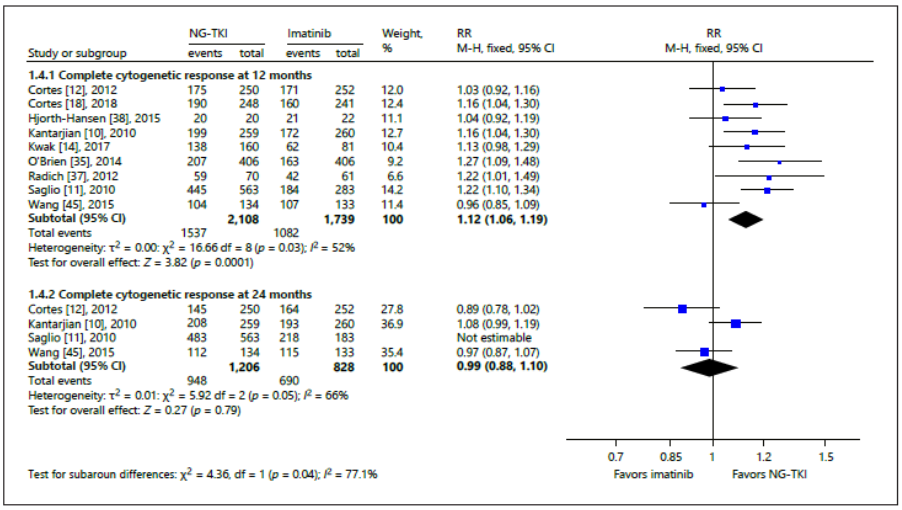
exp, experiment; ctrl, control; int, intermediate.

Qualität der Studien:

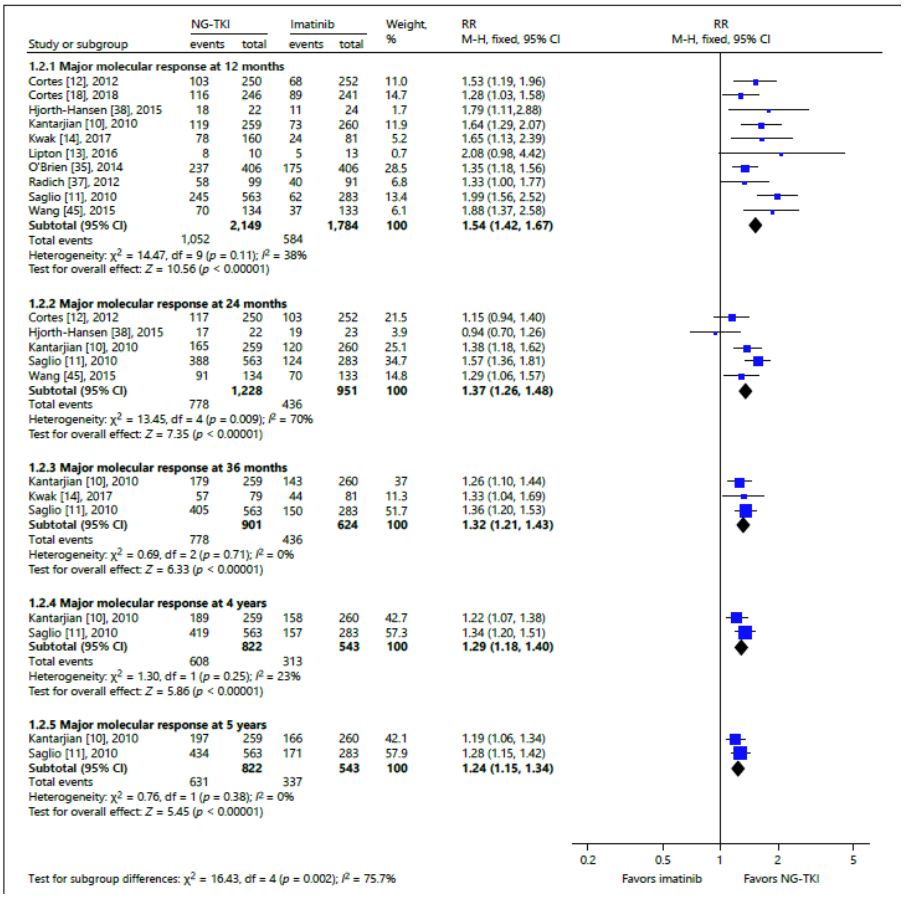
- All studies were randomized trials; 6 trials did not report methods of sequence generation and allocation concealment, therefore we judged them as unclear risk of selection bias [12, 18, 35, 37, 38, 45]. One trial described the methods used for allocation concealment without reporting the sequence generation process [10]. Three trials reported methods both of sequence generation and allocation concealment [11, 13, 14]. Thus, 3 trials were assessed as high quality, and the others were moderate quality
  - o

Studienergebnisse:

Complete cytogenetic response in patients with CML treated with NG-TKIs versus imatinib

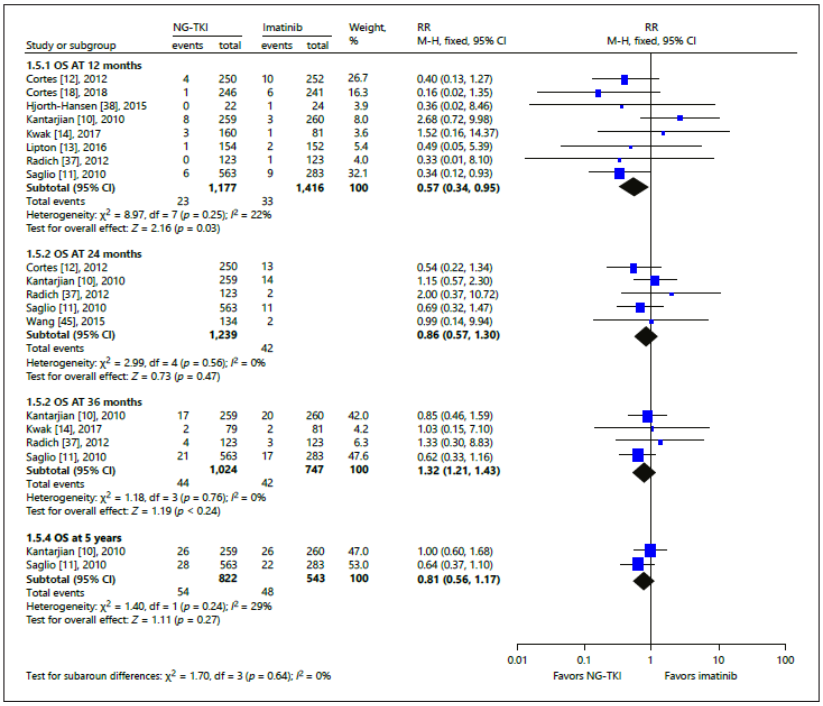


MMR in patients with CML treated with NG-TKIs versus imatinib



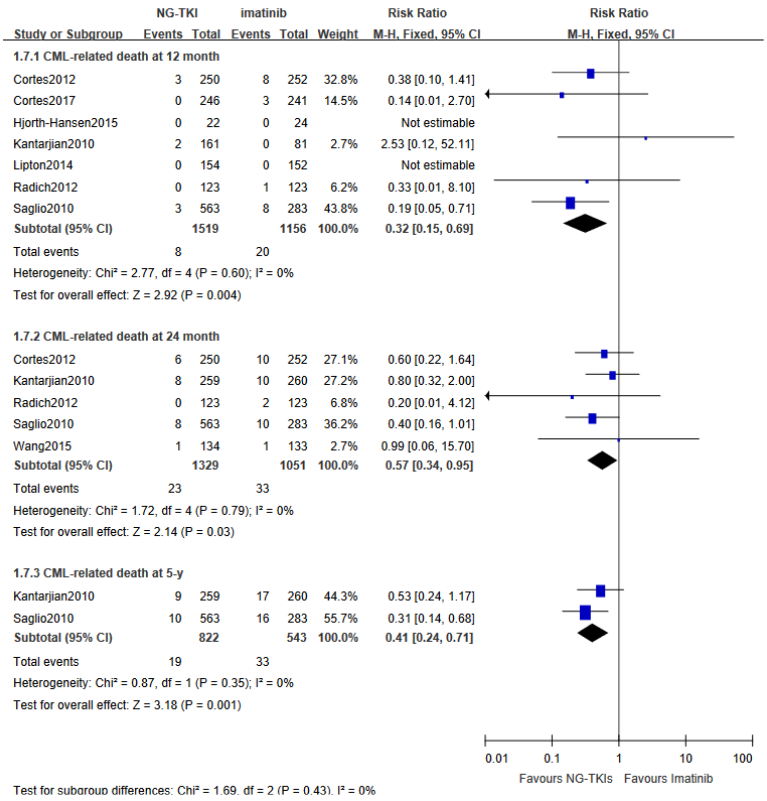
Overall Survival

A statistically significant difference was found in the OS analysis in favor of NG-TKIs over imatinib at 12 months , but there was no difference between the two groups at 2, 3, and 5 years:



CML-Related Death

Mortality attributed to CML was significantly decreased in patients treated with NG-TKIs than in those treated with imatinib at 12 months, 24 months, and 5 years:



Progression to AP/BC

The pooled analyses demonstrated significantly lower progression to AP/BC rates in patients treated with NGTKIs compared with those treated with imatinib at 12 months (RR 0.44, 95% CI

0.27–0.71), 24 months (RR 0.44, 95% CI 0.27–0.71), 36 months (RR 0.51, 95% CI 0.32–0.82), and 5 years (RR 0.47, 95% CI 0.29–0.76;).

Progression-Free Survival

- There were no statistically significant differences in PFS at 12 months and 3 and 5 years (RR 0.63, 95% CI 0.35–1.14; RR 0.71, 95% CI 0.48–1.04, and RR 0.90, 95% CI 0.65–1.24, respectively).
- Patients treated with NG-TKIs had significantly lower PFS rates compared with the imatinib-treated patients at 24 months (RR 0.60, 95% CI 0.36–0.98).
- The heterogeneity in the analysis of the results of the 12th month was mostly attributed to the study by Saglio et al. [11], which increased the heterogeneity from 0 to 53%, but the results were unchanged either by excluding the trial or by using REM (RR 0.65, 95% CI 0.23–1.85;).

Safety

- The rate of adverse events requiring treatment discontinuation was higher with the NG-TKIs compared with imatinib (RR 1.71, 95% CI 1.38–2.12).
- Grade 3–4 anemia occurred at the same rate in both arms (RR 1.06, 95% CI 0.79–1.41),
- there was more grade 3–4 thrombocytopenia (RR 1.52, 95% CI 1.10–2.10,) but less grade 3–4 neutropenia (RR 0.70, 95% CI 0.54–0.91) in the NG-TKI arm.
- There was less grade 3–4 edema (RR 0.33, 95% CI 0.11–0.98).
- grade 3–4 diarrhea (RR 4.44, 95% CI 2.46–7.99) and nausea or vomiting (RR 4.53, 95% CI 1.86–11.52) occurred more frequently with the NGTKIs when compared with imatinib.
- there was a statistically significantly increased incidence of grade 3–4 ALT elevation (RR 7.06, 95% CI 3.37–14.78) and grade 3–4 AST elevation (RR 3.79, 95% CI 2.28–6.30).

Anmerkung/Fazit der Autoren

Our meta-analysis of RCTs of patients with CML-CP found that NG-TKIs were associated with superior OS at 12 months. Although there was no long-term survival advantage, patients treated with NG-TKIs had a greater molecular response at all time points. Furthermore, NGTKIs were better at “softer” clinical outcomes, such as progression to AP/BC and CML-related mortality. Further large-scale clinical trials with longer follow-up periods are required to assess long-term survival outcomes.

Kommentare zum Review

- Untersuchte Interventionen umfassen auch Ponatinib und Radotinib, welche keine Zulassung im AWG haben.
- Siehe auch weiterer SR mit der gleichen Fragestellung: Vener C et al. 2020 [7] (Fazit: Two RCTs (imatinib vs nilotinib and imatinib vs dasatinib) found no difference in 5-year OS or PFS. On the basis of secondary efficacy outcomes, the findings of our meta-analysis suggest that patients with newly diagnosed CP CML without comorbidities should receive second- or third-generation TKIs; however, on the basis of toxicity outcomes, patients with comorbidities should preferably be treated with imatinib.)

Haguet NN et al., Jahr [3].

Long-Term Survival, Vascular Occlusive Events and Efficacy Biomarkers of First-Line Treatment of CML: A Meta-Analysis

Fragestellung

To evaluate the long-term efficacy and the occurrence of vascular occlusion with second-generation BCR-ABL TKIs compared with imatinib in patients with CML

Methodik

Population:

- patients with CML

Intervention:

- second-generation TKI approved for first-line CML treatment

Komparator:

- imatinib

Endpunkte:

- Overall survival,
- major molecular response and complete cytogenetic response,
- arterial occlusive events and venous thromboembolism

Recherche/Suchzeitraum:

- Three scientific databases (PubMed (from 1966), Scopus (from 1995) and CENTRAL (Cochrane Central Register of Controlled Trials; from 1996)), a clinical trial registry (clinicaltrials.gov) and abstracts from the last 3 years of 3 meetings (i.e., ASCO, ESMO and ASH congresses) were searched up to 14 January 2019.

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s risk of bias 2 (RoB 2) tool for RCT

Ergebnisse

Anzahl eingeschlossener Studien:14 RCT

Charakteristika der Studien:

Table S1. Main characteristics of the 14 included clinical trials.

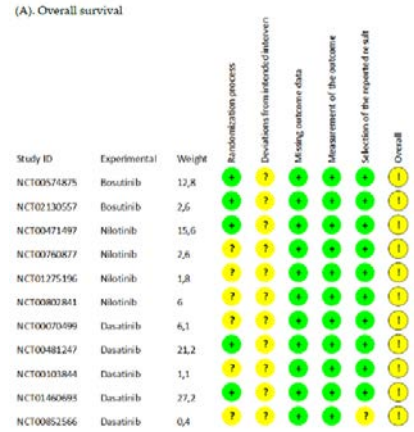
NCT Study Name	Study Design	NG-TKI Dosage Frequency	Imatinib Dosage Frequency	Nb of Patients (ITT)	Population	Age (Mean ± SD)	Sex (% Male)	Primary Endpoint	Secondary Endpoint(s)	Key Inclusion Criteria	Key Exclusion Criteria
NCT00574873 BELA	randomized open-label	Bosutinib 500 mg QD	Imatinib 400 mg QD	502	newly diagnosed CP-CML	46.5 ± 14.61	56.6%	CCyR at 12 months	MMR at 12 months	- Cytogenetic diagnosis of CP Ph+ CML diagnosed less than 6 months. - Diagnosis of CML chronic phase confirmed. - Adequate hepatic and renal function.	- Philadelphia negative CML. - Prior anti-leukemia treatment. - Prior stem cell transplant.
NCT02130557 BFORE	randomized open-label	Bosutinib 400 mg QD	Imatinib 400 mg QD	536	newly diagnosed CP-CML	53.0	58.0%	MMR at 12 months	MMR by 18 months CCyR by 12 months OS at 12 months	- Molecular diagnosis of CP CML of ≤ 6 months. - Adequate hepatic, renal and pancreatic function.	- Any prior medical treatment for CML, including TKIs, with the exception of hydroxyurea and/or anagrelide treatment - Any past or current Central Nervous System involvement. - Extramedullary disease only. - Major surgery or radiotherapy within 14 days of randomization. **- History of clinically significant or uncontrolled cardiac disease.** - History of another malignancy within 5 years (exception accepted)
NCT00471497 ENESTnd	randomized open-label	Nilotinib 300 mg BID Nilotinib 400 mg BID	Imatinib 400 mg QD	846	newly diagnosed CP-CML	46.7	58.0%	MMR at 12 months	Durable MMR at 24 months CCyR at 12 months	- CML in CP patients within the first 6 months of diagnosis. - Diagnosis of CML in CP with confirmation of Philadelphia chromosome of (9:22) translocations	- Previously documented T315I mutation - Treatment with a TKI prior to study entry - Any medical treatment for CML with the exception of hydroxyurea and/or anagrelide **- Impaired cardiac function.** **- Severe or uncontrolled medical conditions (i.e., uncontrolled diabetes, active or uncontrolled infection).** - Use of therapeutic coumarin derivatives (i.e., warfarin, acenocoumarol, phenprocoumon) **- Currently receiving treatment with any medications that have the potential to prolong the QT interval.**
NCT00760877 ENESTcmr	randomized open-label	Nilotinib 400 mg BID	Imatinib 400 mg QD Imatinib 600 mg QD	207	CP-CML previously treated with imatinib for at least 2 years	49.1 ± 13.16	65.7%	Rate of best CMR	OS	- Diagnosis of CML associated with BCR-ABL quantifiable by RQ-PCR - Documented CCyR by bone marrow or BCR-ABL < 1% IS in the past 12 months - Persistent disease demonstrated by 2 PCR positive tests 3 months apart both during the past 6 months. - Treatment with imatinib for at least 2 years with 400 mg or 600 mg and a stable dose - No other current or planned anti-leukemia therapies	- Evidence of rising PCR - Treatment with another investigational agent within last 6 months or TKIs other than imatinib - Prior allogeneic stem cell transplantation **- Impaired cardiac function including: inability to monitor the QT interval on electrocardiogram, long QT syndrome or a known family history of long QT syndrome, clinically significant resting brachycardia (< 50 beats per minute), QTc > 450 msec on baseline ECG, other clinically significant uncontrolled heart disease (e.g., unstable angina, congestive heart failure or uncontrolled hypertension), history of or presence of clinically significant ventricular or atrial tachyarrhythmias** - Administration of cytokine therapy (e.g., G-CSF, GM-CSF or SCF) within 4 weeks prior to study entry
NCT01275196 ENESTchina	randomized open-label	Nilotinib 300 mg BID	Imatinib 400 mg QD	267	newly diagnosed CP-CML Chinese patients	40.6 ± 12.82	64.4%	MMR at 12 months	MMR rate at 3, 6, 9, 12, 15, 18, 21, 24 and 36 months OS	- Patients of Chinese ethnicity - Patients with CML-CP (Ph+) within 6 months of diagnosis - No evidence of extramedullary leukemic involvement, with the exception of hepatosplenomegaly - Adequate organ function	- Previously documented T315I mutations. - Treatment with TKIs prior to study entry - Treatment with IFN for more than 3 months. **- Impaired cardiac function including any one of the following: complete left bundle branch block, long QT syndrome or a known family history of long QT syndrome, history of or presence of clinically significant ventricular or atrial tachyarrhythmias, clinically significant resting bradycardia (< 50 beats per minute), QTc > 450 msec, history of clinically documented myocardial infarction within past 12 months, history of unstable angina during the last 12 months, other clinically significant heart disease (e.g., congestive heart failure or uncontrolled hypertension).** **- Severe or uncontrolled medical conditions (i.e., uncontrolled diabetes, active or uncontrolled infection).** - History of significant congenital or acquired bleeding disorder unrelated to cancer. - Major surgery within 4 weeks. - Treatment with other investigational agents within 30 days. - Another primary malignancy except if the other primary malignancy is neither currently clinically significant or requiring active intervention. - Acute or chronic liver, pancreatic or severe renal disease considered unrelated to disease. **- Current intake of any medications that have the potential to prolong the QT interval**
NCT00802841 LASOR	randomized open-label	Nilotinib 400 mg BID	Imatinib 600 mg QD	191	CP-CML with suboptimal response to imatinib standard dose	44.4 ± 14.75	58.6%	CCyR at 6 months	MMR at 12 and 24 months CCyR at 12 and 24 months OS	- Ph+ CML in CP - No evidence of extramedullary leukemia involvement, with the exception of hepatosplenomegaly - Suboptimal response to 400 mg imatinib	- Prior AP or BC CML. - Prior therapy with imatinib in combination with any other CML drug other than Hydroxyurea and/or Anagrelide; - Imatinib therapy started more than 12 months after the date of the original diagnosis. - Unable to tolerate imatinib at 400 mg. - Previous treatment with any other TKI except Glivec and/or CML therapy other than IFN, hydroxyurea, and /or anagrelide; - Myelotoxicity ≥ Grade 2 present at the time of randomization, - Previously documented T315I mutations **- Impaired cardiac function including: long QT syndrome or family history of long QT syndrome, clinically significant resting brachycardia (< 50 bpm), QTcF >450 msec on screening ECG, myocardial infarction ≤ 12 months prior to the first dose of study drug, other clinically significant heart disease (e.g., CHF, uncontrolled hypertension, unstable angina, significant ventricular or atrial tachyarrhythmias)** **- Currently receiving treatment with any medications that have the potential to prolong the QT interval** - History of another primary malignancy that is currently clinically significant or currently requires active intervention; - Any other clinically significant medical or surgical condition which, according to investigators' discretion, should preclude participation; - Use of investigational agent within 28 days prior to enrollment;

NCT01400074 RE-NICE	randomized open-label	Nilotinib 400 mg BID	Imatinib 400 mg BID	43	CP-CML with suboptimal response to imatinib at a minimum dose of 400 mg daily	40.1	74.4%	Cumulative rate of MMR at 12 months	Safety analyses	- Diagnosis of Ph+ CML in CP - Patients with suboptimal molecular response	- Late CP who started imatinib more than 6 months after diagnosis - Prior AP or BP CML - Previously documented T315I mutations. - Intolerance to imatinib 400 mg daily. - Patients treated with imatinib more than 400 mg daily - Achieved prior MMR or CCyR on imatinib and lost response to entering the study. - Previous treatment with interferon or any other TKI except imatinib (allow hydroxyurea or anagrelide) **- Impaired cardiac function** **- Treatment with inhibitors of CYP3A4 or medications well documented to prolong the QT interval are contraindicated** - Any other malignancy that is clinically significant or requires active intervention. **- Severe or uncontrolled medical conditions** - History of significant congenital or acquired bleeding disorder unrelated to cancer. - Previous radiotherapy to ≥ 25% of the bone marrow. - Major surgery within 4 weeks or who have not recovered from prior surgery. - Treatment with other investigational agents within 30 days.
NCT00070499	randomized open-label	Dasatinib 100 mg QD	Imatinib 400 mg QD	248	newly diagnosed CP-CML	48.5	59.8%	MMR rate at 12 months	2-year OS Toxicity	- CML in CP - Registration on this study within 180 days after the date of first being diagnosed with CML. **- With an electrocardiogram within 42 days, and without any of the following cardiac symptoms: uncontrolled angina, congestive heart failure or myocardial infarction within 6 months, diagnosed or suspected congenital long QT syndrome, history of clinically significant ventricular arrhythmias, prolonged corrected QT interval**	- Prior treatment for CML with the exception of hydroxyurea and/or anagrelide - Any prior chemotherapy regimen for peripheral blood stem cell mobilization; - Major surgery within 28 days before registration, or without having fully recovered from any other prior major surgery - Other prior malignancy (exception are allowed) - History of significant bleeding disorder unrelated to cancer, including congenital bleeding disorders and acquired bleeding disorder within one year
NCT00481247 DASISION	randomized open-label	Dasatinib 100 mg QD	Imatinib 400 mg QD	519	newly diagnosed CP-CML	46.7 ± 14.2	59.2%	Best confirmed CCyR within 12 months	Participants remaining in cCCyR at 2, 3, 4 and 5 years MMR at any time OS	- CP Philadelphia Chromosome-positive CML	**- Pleural Effusion** **- Uncontrolled cardiovascular disease** - Significant bleeding disorder unrelated to CML - Prior treatment with interferon/imatinib/dasatinib/anti-CML systemic treatments except anagrelide/hydroxyurea
NCT00103844 START-R	randomized open-label	Dasatinib 70 mg BID	Imatinib 400 mg BID	150	CP-CML resistant to imatinib at 400–600 mg daily	51 ± 13.6	50.0%	MCyR at 12 weeks	MMR CCyR after crossover AEs, SAEs, deaths and hematologic toxicities	- Subjects with CP Ph+ CML. - Subjects have not been treated with imatinib at a dose >600 mg/day. - Subjects developed resistance to disease while receiving an imatinib dose 400–600 mg/day. - Able to tolerate imatinib at the highest dose the subject had received in the past. - Adequate renal and hepatic function.	- Prior treatment with imatinib at a dose >600 mg/day. - Subjects who have previously identified specific BCR-ABL mutations. - Previous diagnosis of AP or BC CML. - Intolerance to imatinib at any dose. - Subjects who are eligible and willing to undergo transplantation during the screening period. - Serious uncontrolled medical disorder or active infection. **- Uncontrolled or significant cardiovascular disease.** **- Uncontrolled hypertension.** - Evidence of organ dysfunction. - Use of imatinib within 7 days. - Use of interferon or cytarabine within 14 days. - Use of a targeted small molecule anticancer agent within 14 days. **- Subjects taking certain medications that are accepted to have a risk of causing Torsades de Pointes.** - Subjects taking medications that irreversibly inhibit platelet function or anticoagulants. - Prior therapy with BMS-354825.
NCT00320190	randomized open-label	Dasatinib 100 mg QD	Imatinib 400 mg BID	32	CP-CML with suboptimal response after imatinib 400 mg daily	48.6 ± 14.85	71.9%	MMR rate at 12 months	Death, AEs, treatment-related AEs, SAEs, treatment-related SAEs and AEs leading to discontinuation On-study AEs of special interest CCyR at 6	- CP Ph+ CML demonstrating only a suboptimal response	- Previous diagnosis of AP or BC CML **- Uncontrolled or significant cardiovascular disease** - History of significant bleeding disorder unrelated to CML - Concurrent malignancies - Intolerance of imatinib 400 mg - Prior treatment with imatinib at a dose higher than 400 mg - Prior stem cell transplantation and/or high-dose chemotherapy for CML
NCT01460693 SPIRIT2	randomized open-label	Dasatinib 100 mg QD	Imatinib 400 mg QD	812	newly diagnosed CP-CML	54.4	55.6%	5-year EFS	MMR	- Enrolled within 3 months of initial diagnosis of CML-CP - Cytogenetic confirmation of the Philadelphia chromosome or variants of (9;22) translocations - No evidence of extramedullary leukaemic involvement, with the exception of the hepatosplenomegaly.	- Patients with Ph-negative, BCR-ABL-positive disease. - Any prior treatment for CML with: any TKI; busulphan; interferon-alpha; homoharringtonine; cytosine arabinoside; any other investigational agents (hydroxycarbamide and anagrelide are the only drugs permitted). - Patients who received prior chemotherapy. - Patient who have had any form of prior haemopoietic stem cell transplant, either autograft or allograft. - Patients with International normalized ratio (INR) or partial thromboplastin time (PTT) > 1.5 x IULN, with the exception of patients on treatment with oral anticoagulants. **- Patients with uncontrolled medical disease such as diabetes mellitus, thyroid dysfunction, neuropsychiatric disorders, infection, angina, or Grade 3/4 cardiac problems as defined by the New York Heart Association Criteria.** - Patients who have undergone major surgery within 4 weeks, or who have not recovered from prior major surgery. - Patients with a history of another malignancy either currently or within the past five years (exception).
NCT01593254 DASCERN	randomized open-label	Dasatinib 100 mg QD	Imatinib 400 mg or more QD	260	CP-CML without optimal response to imatinib 400 mg	37.0	78.0%	MMR at 12 months of CML treatment	OS Safety profile Cyotgenetic response over time	- CP-CML Ph+ patients with complete hematologic response (CHR) but without one log BCR-ABL reduction (BCR-ABL level >10% IS) 3 months of imatinib 400 mg treatment. - Currently tolerating imatinib 400 mg QD. - Adequate renal function - Adequate hepatic function	- Previous diagnosis of AP or BC - Subjects with clonal evolution in Ph+ cells observed in ≥2 metaphases at baseline bone marrow cytogenetic test, unless the same abnormalities were present at diagnosis. - Subjects with less than CHR after 3 months of imatinib treatment or lost CHR after initial achievement - Documented T315I/A, F317L, or V299L mutations - A serious uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy

NCT00852566 NordCML006	randomized open-label	Dasatinib 100 mg QD	Imatinib 400 mg QD	46	newly diagnosed CP-CML	55.6	47.8%	Ph-positive cells in stem cell compartments at 6 months	Molecular and cytogenetic responses at 3, 6, 12 and 18 months	- CML in CP - No evidence of extramedullary leukemia apart from hepatosplenomegaly - Ph+ or variants must be demonstrated by BM cytogenetics, FISH or PCR. - Previously untreated CML in CP, with the exception of hydroxyurea or anagrelide - Enrolled in this study within 90 days after the date of first being diagnosed with CML - Adequate hepatic function - Adequate renal function	- A serious uncontrolled medical disorder or active infection that would impair the ability of the subject to receive protocol therapy. **- Known pleural effusion at baseline.** **- Uncontrolled or significant cardiovascular disease** - History of significant bleeding disorder unrelated to CML. - Prior chemotherapy for peripheral stem cell mobilization. - Prior or concurrent malignancy. - Any prior treatment with interferon, dasatinib or imatinib - Any other prior systemic treatments, with anti-CML activity [except for anagrelide, or hydroxyurea (HU)]. **- Current uptake of drugs that are generally accepted to have a risk of causing Torsades de Pointes.**

Qualität der Studien:

Risk of bias für OS



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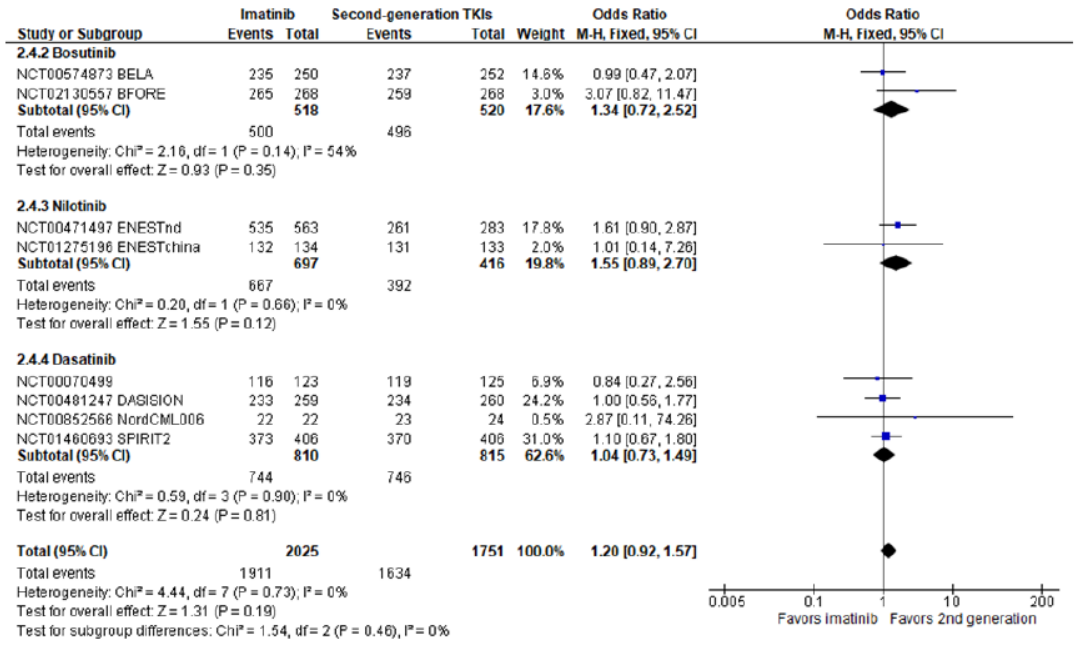
Studienergebnisse: (Fokus auf Patienten ohne Vorbehandlung)

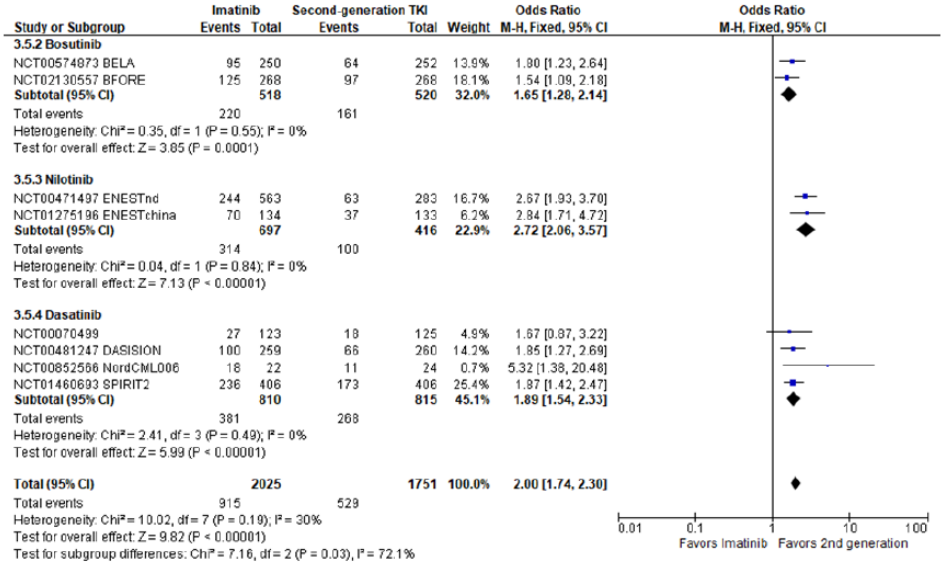
Overall survival

(D) Forest plot of OS in treatment-naïve patients

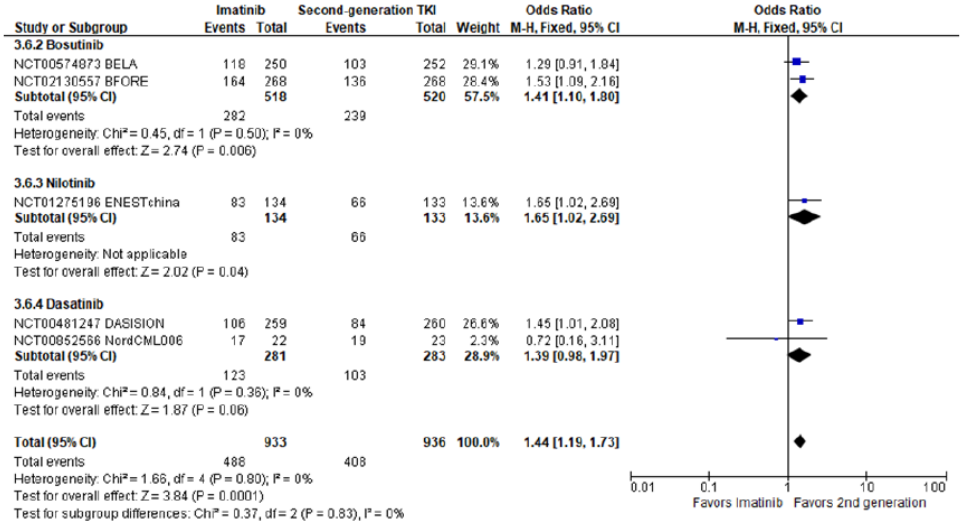


Major molecular response

(A) Forest plot of MMR at 12 months in treatment-naïve patients.

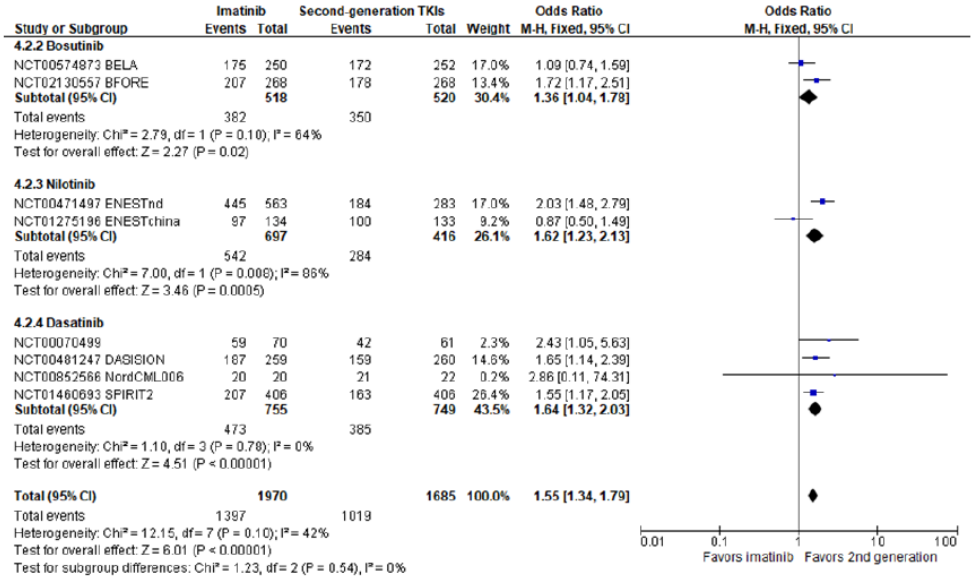


(B) Forest plot of MMR at 24 months in treatment-naïve patients.



Complete cytogenetic response

(C) Forest plot of CCyR at 12 months in treatment-naïve patients.



Vascular Occlusion (previoulsy treated and untreated patients)

Arterial occlusive events:

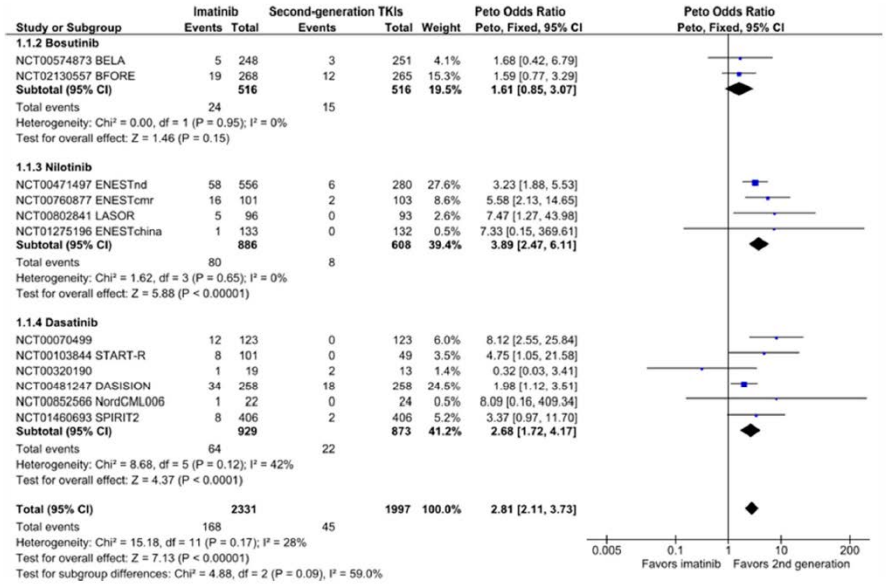
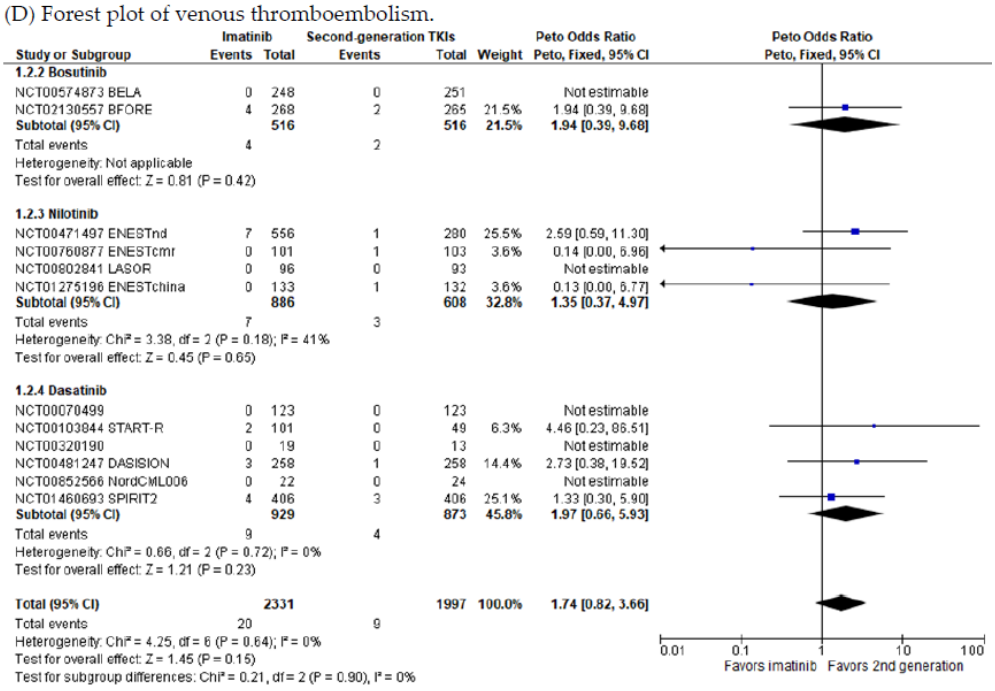


Figure 3. Forest plot of arterial occlusive events in patients with CML treated with second-generation TKIs versus imatinib.

Thromboembolism:

(D) Forest plot of venous thromboembolism.



Anmerkung/Fazit der Autoren

The long-term benefits of second-generation TKIs are restricted to surrogate outcomes and do not translate into prolonged survival compared to imatinib. Given the long-term use, frontline therapy should be chosen carefully, with special attention to the patients' quality of life and cardiovascular risks.

Kommentare zum Review

- 6 der 14 eingeschlossenen Studien untersuchen mit Imatinib vorbehandelte Patienten. Die dargestellten Ergebnisse zu OS und Ansprechen beziehen sich auf unvorbehandelte Patienten. Für Vascular Occlusion liegen keine entsprechenden Subgruppenanalysen vor.
- Weiterer SR zum Risiko für Gefäßverschluss: Haguet et al. 2017 [2]

3.4 Leitlinien

Smith G et al., 2020 [5].

British Society for Haematology (BSH)

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

Zielsetzung/Fragestellung

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

Methodik

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

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- In MEDLINE and EMBASE up to January 2018.

LoE/ GoR

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

Sonstige methodische Hinweise

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

Gemeinsamer Bundesausschuss

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 ECG, lipid profile, fasting glucose or HbA1c, CVD 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

Abbreviations: 2GTKI: second generation tyrosine kinase inhibitors; ELTS: EUTOS Long-Term Survival

Background:

Four TKIs— imatinib, and the second generation (2G) TKIs bosutinib, dasatinib and nilotinib — are now licensed for use in newly diagnosed patients, of which all but bosutinib are NICE-approved. The 2GTKIs have been trialled directly against imatinib in large phase III randomised studies with remarkably similar results to each other (Appendix 1).
The majority of patients diagnosed in 2019 have a realistic prospect of a life expectancy similar to that of the normal population.[11] For many patients there is no reason to choose a 2GTKI over imatinib which has a well-established safety profile with no life-threatening long-term side effects identified to date.[63] More patients are likely to die of causes other than their leukaemia, and co-morbidities are more predictive of death.[136] Furthermore the German CML IV study showed that 88% of imatinib-treated patients (some receiving higher doses of 800 mg) achieved a major molecular response (MMR) by 10 years suggesting efficacy similar to that seen with 2GTKIs.[58] In children, first-line imatinib therapy achieves 60–70% complete cytogenetic response (CCyR) rates and 45% MMR rates at 12 months.[150]

However, there are some groups in CP that might benefit from 2GTKIs upfront:
1. Patients with high or intermediate ELTS or Sokal scores in whom a reduction in disease progression has been demonstrated with a first-line 2GTKI.[30,79,96,158]
2. Women who wish to have children, where the more rapid molecular response achieved with a 2GTKI is desirable (see the section 'CML and parenting').
3. 'Younger' patients, nominally the under 30s, and children, who are excellent candidates for stem cell transplantation if the need arises, and in whom concerns have been raised regarding more aggressive disease at presentation.[17] In a Phase II study as first-line therapy in children, dasatinib achieved a 92% CCyR and 52% MMR at 12 months in CP CML leading to a licence for its use.[51]

The early use of a more potent TKI should be balanced against the risk of inducing and/or exacerbating concomitant illnesses (Table II). This is particularly pertinent in older patients as the number of co-morbidities increases with advancing age.[136] Although there is no evidence that older patients respond less well to TKI[10,15,28] older subjects may handle drugs differently and/or be receiving other medications affecting the CYP450 pathway (which decrease TKI metabolism and enhance their complications) and hence often require more frequent dose reductions or treatment interruptions than younger patients.[97]
All patients should have assessment of cardiac risk using a cardiovascular disease (CVD) risk assessment algorithm (QRisk3) - or equivalent, electrocardiogram (ECG), baseline estimates of lipid profiles, and fasting glucose and/or HbA1c levels.[154] Given recent data suggesting the use of TKIs may be associated with reactivation of hepatitis viruses, all patients should have pre-treatment hepatitis B and C serology assessments.[74]

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

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

■ no contra-indication; ■ low risk of exacerbation of pre-existing condition; ■ intermediate risk of exacerbation of pre-existing condition; ■ avoid if possible.
*Some evidence that all 2GTKI prolong QT.
†Imatinib has been associated with the development of gastric antral vascular ectasia (GAVE).

Appendix 1

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

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

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

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

Referenzen

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2020) am 03.12.2020

#	Suchfrage
1	[mh “Leukemia, Myelogenous, Chronic, BCR-ABL Positive”]
2	Chronic:ti,ab,kw OR ("Philadelphia+"):ti,ab,kw OR (“Ph1 Positive”):ti,ab,kw OR (“Ph Positive”):ti,ab,kw OR ("ph+"):ti,ab,kw OR ("Philadelphia Positive"):ti,ab,kw OR ("Philadelphia+"):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	{AND #2-#4}
6	(CML OR CGL):ti,ab,kw
7	{OR #1,#5-#6}
8	#7 with Cochrane Library publication date from Dec 2015 to present

Systematic Reviews in Medline (PubMed) am 04.12.2020

#	Suchfrage
1	“leukemia, myelogenous, chronic, bcr abl positive”[mh]
2	chronic[tiab]
3	(((((Ph1 Positive[Tiab]) OR Ph Positive[tiab]) OR Ph1+[tiab]) OR Ph+[tiab]) OR Philadelphia Positive[tiab]) OR Philadelphia+[tiab]
4	#2 OR #3
5	(((((myeloid [tiab]) OR myelogenous[tiab]) OR myelocytic[tiab]) OR myelosis[tiab]) OR myeloses[tiab]) OR granulocytic[tiab]
6	(((leukem*[tiab]) OR leucem*[tiab]) OR leukaem*[tiab]) OR leucaem*[tiab]
7	((#4) AND #5) AND #6
8	((cml[tiab]) OR cgl[tiab]) OR “chronic myelosis”[tiab]
9	((#1) OR #7) OR #8
10	(#9) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw]

	OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
11	((#10) AND ("2015/12/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 04.12.2020

#	**Suchfrage**
1	“leukemia, myelogenous, chronic, bcr abl positive”[mh]
2	chronic[tiab]
3	(((((Ph1 Positive[Tiab]) OR Ph Positive[tiab]) OR Ph1+[tiab]) OR Ph+[tiab]) OR Philadelphia Positive[tiab]) OR Philadelphia+[tiab]
4	#2 OR #3
5	(((((myeloid [tiab]) OR myelogenous[tiab]) OR myelocytic[tiab]) OR myelosis[tiab]) OR myeloses[tiab]) OR granulocytic[tiab]
6	(((leukem*[tiab]) OR leucem*[tiab]) OR leukaem*[tiab]) OR leucaem*[tiab]
7	((#4) AND #5) AND #6
8	((cml[tiab]) OR cgl[tiab]) OR “chronic myelosis”[tiab]
9	((#1) OR #7) OR #8
10	(#9) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
11	(((#10) AND ("2015/12/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
12	(#11) NOT (retracted publication [pt] OR retraction of publication [pt])

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

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Indikation gemäß Beratungsantrag

ist angezeigt zur Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase (CP).

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz in "*der Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase (CP)*"? Wie sieht die Versorgungspraxis in Deutschland aus?

Der Behandlungsstandard ist die Gabe eines von vier in dieser Indikation zugelassenen oralen BCR-ABL1-Tyrosinkinase-Inhibitoren. Erst in zweiter Linie kommen Kombinationen mit Interferon alfa oder eine allogene Blutstammzelltransplantation infrage (1).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von *Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+ CML) in der chronischen Phase (CP)* die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Kriterien für die Auswahl eines der vier BCR-ABL1-Tyrosinkinase-Inhibitoren sind das Therapieziel, Alter und Begleiterkrankungen des Patienten, das Nebenwirkungsprofil des Arzneimittels und die Patientenpräferenz. Insbesondere hinsichtlich des Alters ist das Therapieziel entscheidend. So wird man bei über 80-jährigen Patienten eher die Krankheitskontrolle bei bestmöglicher Verträglichkeit anstreben und dafür in der Regel Imatinib wählen. Bei jüngeren Patienten dagegen wird das Ziel ein möglichst rasches Erreichen einer tiefen molekularen Remission (MR) sein (MR 4,5 – besser noch MR 5), um nach ausreichend langer Behandlung eine Therapiepause und vielleicht sogar eine Therapiefreiheit zu erreichen. Hierfür wird man in der Regel die Tyrosinkinase-Inhibitoren der zweiten Generation (Nilotinib, Dasatinib, Bosutinib) wählen. Allerdings ist die Geschwindigkeit, in der eine MR 4,5 oder MR 5 erzielt wird, bislang noch nicht mit dem Erreichen der Therapiefreiheit assoziiert. Damit ist die Entscheidung für einen der drei Wirkstoffe im Wesentlichen abhängig vom Nebenwirkungsspektrum unter Berücksichtigung der individuellen Risikofaktoren und der Patientenpräferenz (1).

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