Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-226 Bosutinib

Stand: November 2017

Gemeinsamer Bundesausschuss

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 (CP)]**	
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 zutreffend*
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:** Nicht zutreffend **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 Beratungsanforderung/Fachinformation)
Zu prüfendes Arzneimittel:	
Bosutinib	<u>Geplantes Anwendungsgebiet:</u> Behandlung von Erwachsenen mit neu diagnostizierter Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie (Ph+-CML) in der chronischen Phase (CP)
Chemotherapien:	
Hydroxy-carbamid 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 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 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 einen 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 Potenzial für diese Indikation angesehen werden kann. …
Interferon alfa-2b L03AB05 (IntronA®)	<u>Chronische myeloische Leukämie:</u> *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 ≥ 34 %, 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

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Philadelphia-Chromosom-positiver chronischer myeloischer Leukämie* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.10.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 244 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 7 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

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

Abkürzungen:

AE	Adverse event
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
AP	Accelerated phase
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BC	Blast crisis
CCO	Cancer Care Ontario
CCyR	Complete cytogenetic response
CML	Chronische myeloische Leukämie
CMR	Complete molecular response
CP	Chronic phase
DAHTA	Datenbank der Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
ESMO	European Society for Medical Oncology
FEM	Fixed effects model
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KD	Kinase Domain
MMR	Major molecular response
$MR^{4.5}$	Deeper molecular responses
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PFS	Progression free survival
RCT	Randomized controlled trial
REM	Random effects model
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Tyrosine Kinase Inhibitor
TRIP	Turn Research into Practice Database
WHO	World Health Organization
zVT	Zweckmäßige Vergleichstherapie

IQWiG Berichte/G-BA Beschlüsse

Es konnten keine relevanten IQWiG Berichte/G-BA Beschlüsse identifiziert werden.

Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

Haguet H et al., 2017 [4].

Risk of arterial and venous occlusive events in chronic myeloid leukemia patients treated with new generation BCR-ABL tyrosine kinase inhibitors: a systematic review and meta-analysis

1. Fragestellung

To assess the absolute risk of arterial and venous occlusive events in CML patients treated with new generation BCR-ABL TKIs and to estimate the odds ratios (ORs) compared with imatinib.

2. Methodik

Population: patients with chronic myeloid leukemia
Intervention: TKIs (dasatinib, nilotinib and ponatinib)
Komparator: Imatinib
Endpunkt: risk of arterial and venous occlusive events

Suchzeitraum (Aktualität der Recherche): Bis 8. November 2016 in PubMed, Scopus, and the Cochrane library und Abstracts (American Society of Hematology, AmericanSociety of Clinical Oncology,and European Society of Medical Oncology)
Anzahl eingeschlossene Studien/Patienten (Gesamt): 12 RCTs, n=2217 Patienten
Qualitätsbewertung der Studien: Jadad Score; Statistical heterogeneity: Cochran's Q statistic and I^2 value. Publication bias was evaluated by funnel plots.

3. Ergebnisdarstellung

Qualität der Studien: The general characteristics of the selected studies are reported in Table 1. Funnel plots demonstrated no evidence of publication bias, and the I^2 statistic indicated no (arterial risk) or very low (venous risk) heterogeneity among studies.

Table 1. Characteristics of the selected clinical trials and quality assessment.

Study ID	Study design	*Experimental arm* Dosage Admin frequency	*Control arm* Dosage Admin frequency	No. of patients	Population	Age (mean ± SD)	% Male	Length of follow-up	Jadad score
NCT01650805 [9] *EPIC*	Randomized open-label	*Ponatinib* 45 mg once daily	Imatinib 400 mg once daily	307	Newly diagnosed patients with CP CML	51.5 ± 15.41	61.6	Median: 5.1 months	2
NCT00574873 *BELA*	Randomized open-label	*Bosutinib* 500 mg once daily	Imatinib 400 mg once daily	502	Newly diagnosed patients with CP CML	46.5 ± 14.61	56.6	Unknown	2
NCT00471497 [10] *ENESTnd*	Randomized open-label	*Nilotinib* 300/400 mg twice daily	Imatinib 400 mg once daily	846	Newly diagnosed patients with CP CML	Nilotinib: 47 Imatinib: 46	58.0	Unknown	3
NCT00760877 *ENESTcmr*	Randomized open-label	*Nilotinib* 400 mg twice daily	Imatinib 400/600 mg once daily	207	Patients with CP CML treated by imatinib with evidence of persistent leukemia	49.1 ± 13.16	65.7	24 months	2
NCT01275196 [8] *ENESTchina*	Randomized open-label	*Nilotinib* 300 mg twice daily	Imatinib 400 mg once daily	267	Patients with CP CML diagnosed within 6 months	40.6 ± 12.82	64	24 months	2
NCT00802841 *LASOR*	Randomized open-label	*Nilotinib* 400 mg twice daily	Imatinib 600 mg once daily	191	Patients with CP CML with suboptimal response to imatinib standard dose	44.4 ± 14.75	58.6	24 months	2
NCT00852566 [11] *NordCML006*	Randomized open-label	*Dasatinib* 100 mg once daily	Imatinib 400 mg once daily	46	Newly diagnosed patients with CP CML	56	48	36 months	3
NCT00070499	Randomized open-label	*Dasatinib* 100 mg once daily	Imatinib 400 once daily/800 mg	391	Newly diagnosed patients with CP CML	50	61.4	24 months	2
NCT00481247 *DASISION*	Randomized open-label	*Dasatinib* 100 mg once daily	Imatinib 400 mg once daily	519	Newly diagnosed patients with CP CML	46.7 ± 14.2	59.2	At least 5 years	3
NCT00103844 *START-R*	Randomized open-label	*Dasatinib* 70 mg twice daily	Imatinib 400 mg twice daily	150	Patients with CP CML resistant to imatinib	51 ± 13.6	50	24 months	2
NCT00320190	Randomized open-label	*Dasatinib* 100 mg once daily	Imatinib 400 mg twice daily	32	Patients with CP CML previously treated with imatinib	48.6 ± 14.85	71.9	24 months	2
NCT01460693 [12] *SPIRIT2*	Randomized open-label	*Dasatinib* 100 mg once daily	Imatinib 400 mg once daily	812	Newly diagnosed patients with CP CML	Unknown	Unknown	Median: 34 months	2

CP: Chronic phase; CML: chronic myeloid leukemia.

Arterial occlusive events

Overall, new generation TKIs were associated with an increased risk of arterial occlusive events compared with imatinib (REM ORPeto: 3.32; 95%CI: 2.29–4.81; siehe Tabelle 2. OR computed using the FEM is presented in Table 2 for consistency. In the included studies, 4.78%

(106/2217) of patients receiving new-generation TKIs developed arterial occlusive events compared with 0.96% (18/1884) receiving imatinib (Table 3). Stratification by treatment indicated significantly increased risks for dasatinib (REM ORPeto: 3.32; 95%CI: 1.37– 8.01), nilotinib (REM ORPeto: 3.69; 95%CI: 2.29–5.95), and ponatinib (REM ORPeto: 3.26; 95%CI: 1.12–9.50).

Table 2. Venous, arterial, and vascular occlusive events in patients with CML receiving new generation TKIs.

	Odds ratio (95%CI)		Heterogeneity	
	Fixed-effect model (Peto method)	Random-effects model (Peto method)	I^2 statistics	Q test P value
	Vascular occlusive events			
Overall	**3.16 (2.24–4.45)**	**3.16 (2.24–4.45)**	**0.00**	**0.84**
Bosutinib	1.77 (0.54–5.83)	1.77 (0.54–5.83)	0.00	1.00
Dasatinib	2.91 (1.43–5.94)	2.91 (1.43–5.94)	0.00	0.50
Nilotinib	3.48 (2.21–5.49)	3.48 (2.28–5.49)	0.00	0.81
Ponatinib	3.47 (1.23–9.78)	3.47 (1.23–9.78)	0.00	1.00
	Arterial occlusive events			
Overall	**3.32 (2.29–4.81)**	**3.32 (2.29–4.81)**	**0.00**	**0.80**
Bosutinib	1.77 (0.54–5.83)	1.77 (0.54–5.83)	0.00	1.00
Dasatinib	3.32 (1.37–8.01)	3.32 (1.37–8.01)	0.00	0.45
Nilotinib	3.69 (2.29–5.95)	3.69 (2.29–5.95)	0.00	0.76
Ponatinib	3.26 (1.12–9.50)	3.26 (1.12–9.50)	0.00	1.00
	Venous occlusive events			
Overall	**2.17 (0.90–5.25)**	**2.17 (0.76–6.20)**	**0.00**	**0.50**
Bosutinib	NA	NA	NA	NA
Dasatinib	2.24 (0.68–7.42)	2.24 (0.68–7.42)	0.00	0.50
Nilotinib	1.80 (0.45–7.15)	1.07 (0.08–14.93)	46.85	0.17
Ponatinib	7.29 (0.15–367.61)	7.29 (0.15–367.61)	0.00	1.00

Venus thrombosis

The statistical analysis of venous occlusive events established that new-generation TKIs are not significantly associated with a greater risk of venous occlusive events than imatinib but demonstrates a trend toward an increased risk with new-generation TKIs. Statistical analysis using the REM is presented in Table 2 and demonstrated similar conclusions due to very low heterogeneity. The rate of venous occlusive events was low in almost all the studies. Indeed, venous occlusive events occur in only 0.72% (16/2217) of patients treated with new-generation TKIs and in 0.27% (5/1884) of imatinib-treated patients.

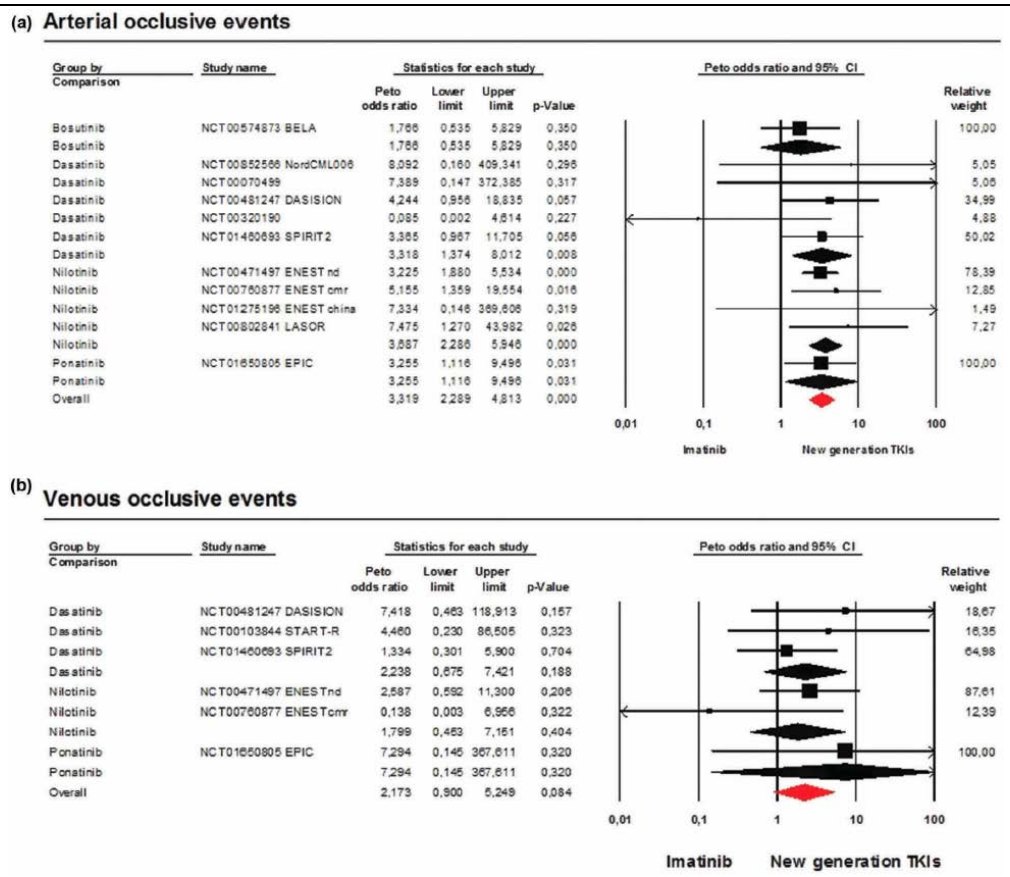


Figure 2. Forest plots of arterial and venous occlusive events in patients with chronicmyeloid leukemia treatedwith new generation TKI versus imatinib. (a) Forest plot of the risk of arterial occlusive events in patients with CML treated with new generation TKI versus imatinib. Study weights were assigned using the random-effectsmodel (b) Forest plot of the risk of venous occlusive events in patients with CML treated with new generation TKI versus imatinib. Venous occlusive events were analysed using a fixed-effect model.

Table 3. Rates of venous and arterial occlusive events across included studies stratified by treatment.

	Venous occlusive events		Arterial occlusive events	
Studies	New-generation TKIs	Imatinib	New-generation TKIs	Imatinib
NCT01650805 *EPIC* [9]	1/154 (0.65)	0/152 (0.00)	11/154 (7.14)	3/152 (1.97)
Ponatinib	**1/154 (0.65)**	**0/152 (0.00)**	**11/154 (7.14)**	**3/152 (1.97)**
NCT00574873 *BELA*	0/248 (0.00)	0/251 (0.00)	7/248 (2.82)	4/251 (1.59)
Bosutinib	**0/248 (0.00)**	**0/251 (0.00)**	**7/248 (2.82)**	**4/251 (1.59)**
NCT00471497 [10] *ENESTnd*	7/556 (1.26)	1/280 (0.36)	58/556 (10.43)	6/280 (2.14)
NCT00760877 *ENESTcmr*	0/101 (0.00)	1/103 (0.97)	8/101 (7.92)	1/103 (0.97)
NCT01275196 *ENESTchina* [8]	0/133 (0.00)	0/132 (0.00)	1/133 (0.75)	0/132 (0.00)
NCT00802841 *LASOR*	0/96 (0.00)	0/93 (0.00)	5/96 (5.21)	0/93 (0.00)
Nilotinib	**7/886 (0.79)**	**2/608 (0.33)**	**72/886 (8.13)**	**7/608 (1.15)**
NCT00852566 *NordCML006* [11]	0/22 (0.00)	0/24 (0.00)	1/22 (4.55)	0/24 (0.00)
NCT00070499	0/123 (0.00)	0/123 (0.00)	1/123 (0.81)	0/123 (0.00)
NCT00481247 *DASISION*	2/258 (0.78)	0/258 (0.00)	6/258 (2.33)	1/258 (0.39)
NCT00103844 *START-R*	2/101 (1.98)	0/49 (0.00)	0/101 (0.00)	0/49 (0.00)
NCT00320190	0/19 (0.00)	0/13 (0.00)	0/19 (0.00)	1/13 (7.70)
NCT01460693 *SPIRIT2* [12]	4/406 (0.99)	3/406 (0.74)	8/406 (1.97)	2/406 (0.50)
Dasatinib	**8/929 (0.86)**	**3/873 (0.34)**	**16/929 (1.72)**	**4/873 (0.46)**
Overall	**16/2217 (0.72)**	**5/1884 (0.27)**	**106/2217 (4.78)**	**18/1884 (0.96)**

Number of events/total number (%).

In addition, as the time to event was not reported in the different clinical trials included, we were unable to determine the time-to-onset of cardiovascular events between the different TKIs.

4. Anmerkungen/Fazit der Autoren

This meta-analysis indicates that vascular occlusive events associated with

	new-generation BCR-ABL TKIs in patients with CML are mainly driven by arterial occlusive events. 5. Kommentar der FBMed: In die Metaanalyse ist auch eine Studie eingeflossen, die Bosutinib mit Imatinib verglichen hat **sowie 4 Studien, in denen Patienten bereits im Voraus mit Imatinib behandelt wurden.** Die Auswirkungen auf das Gesamtergebnis sind nicht bekannt, da keine separaten Analysen diesbezüglich durchgeführt wurden. Weiterhin ist nicht klar ob Philadelphia negative Patienten eingeschlossen wurden, allerdings sind alle Arzneimittel ausschließlich für zur Behandlung von Ph+ Patienten zugelassen.
Douxfils J et al., 2016 [1]. Association Between BCR-ABL Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia and Cardio-vascular Events, Major Molecular Response, and Overall Survival: A Systematic Review and Meta-	1. Fragestellung To assess the risk of vascular occlusive events in patients with CML treated by new generations of TKIs and provide an overall assessment of the clinical benefit.
	2. Methodik **Population:** patients with chronic myeloid leukemia **Intervention:** TKIs (dasatinib, nilotinib and ponatinib) **Komparator:** Imatinib **Endpunkte:** Vascular occulsive events, OS, MMR **Suchzeitraum:** 21. Oktober 2014 (PubMed, Scopus, and the Cochrane library) und Abstracts Dezember 2011-Oktober 2014 (American Society of Hematology, AmericanSociety of Clinical Oncology,and European Society of Medical Oncology) **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 10 RCTs, n=3043 Patienten **Qualitätsbewertung der Studien:** Jadad Score; Statistical heterogeneity: Cochran's Q statistic and I^2 value. Publication bias was evaluated by funnel plots.
	3. Ergebnisdarstellung Qualität der Studien: Among all analyses performed, there was no evidence of publication bias nor heterogeneity among the studies. Für genaue Beschreibung der Studien, siehe oben Haguet (2017).

analysis

Table. Vascular Occlusive Events, Overall Survival, and Major Molecular Response to Evaluated BCR-ABL TKIs

	Peto Method[12] Odds Ratio (95% CI)		Heterogeneity[a]	
TKI	Fixed Effects Model[a]	Random Effects Model	I^2 Statistic	*P* Value[b]
Vascular Occlusive Events				
Overall	3.45 (2.30-5.18)	3.45 (2.30-5.18)	0.000	.85
Bosutinib	2.77 (0.39-19.77)	2.77 (0.39-19.77)	NA	NA
Dasatinib	3.86 (1.33-11.18)	3.86 (1.33-11.18)	0.000	.42
Nilotinib	3.42 (2.07-5.63)	3.42 (2.07-5.63)	0.000	.72
Ponatinib	3.47 (1.23-9.78)	3.47 (1.23-9.78)	NA	NA
Overall Survival				
Overall	1.20 (0.63-2.29)	1.14 (0.46-2.81)	34.328	.17
Bosutinib	2.38 (0.82-6.89)	2.38 (0.82-6.89)	NA	NA
Dasatinib	0.42 (0.14-1.31)	0.46 (0.11-2.01)	13.506	.32
Nilotinib	1.51 (0.38-5.99)	1.01 (0.09-10.96)	39.176	.20
Ponatinib	2.00 (0.21-19.33)	2.00 (0.21-19.33)	NA	NA
Major Molecular Response				
Overall	2.22 (1.87-2.63)	2.22 (1.87-2.63)	0.000	.63
Bosutinib	1.86 (1.29-2.70)	1.86 (1.29-2.70)	NA	NA
Dasatinib	2.17 (1.66-2.83)	2.17 (1.66-2.83)	0.000	.61
Nilotinib	2.45 (1.85-3.24)	2.45 (1.84-3.26)	0.578	.37
Ponatinib	4.95 (0.97-25.19)	4.95 (0.97-25.19)	NA	NA

Vascular Occlusive Events

The Figure A provides the forest plot for vascular occlusive events stratified by treatment group. Vascular occlusive events occurred in 5,88% of patients (93 of 1582) treated with new generation TKIs vs 1.04% of patients (13 of 1253) treated with imatinib. The use of a newgeneration TKI was associated with a statistically significant increased risk of vascular occlusive events.

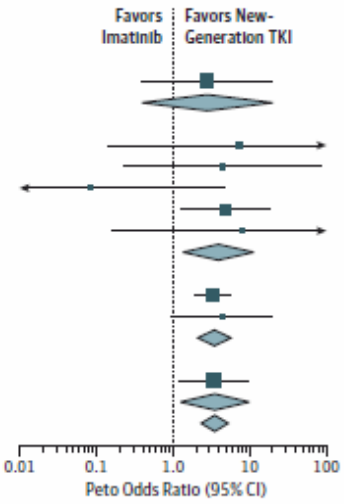
OS

The Figure B presents the forest plot for survival stratified by treatments. Death during the first year occurred in 22 (1.49%) of 1473 patients treated with a novel TKI compared with 24 (2.01%) of 1194 patients treated with imatinib. The analysis revealed a similar mortality rate at 1 year between new-generation TKIs and imatinib. Stratification by treatment did not change the results

Figure. Forest Plots of the Outcomes of Interest in Patients With Ph+ Leukemia Treated With New-Generation TKIs vs Imatinib

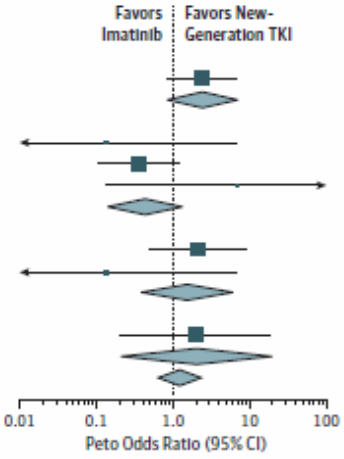
A Vascular occlusive events

Source	Peto Odds Ratio (95% CI)	P Value	Weight, %
Bosutinib			
NCT00574873-BELA	2.77 (0.39-19.77)	.31	100
Subtotal	2.77 (0.39-19.77)	.31	
Dasatinib			
NCT00070499	7.39 (0.15-372.38)	.32	7.37
NCT00103844-START-R	4.46 (0.23-86.51)	.32	12.88
NCT00320190	0.09 (0.00-4.61)	.23	7.11
NCT00481247-DASISION	4.86 (1.30-18.12)	.02	65.29
NCT00852566-NordCML006	8.09 (0.16-409.34)	.30	7.35
Subtotal	3.86 (1.33-11.18)	.01	
Nilotinib			
NCT00471497-ENESTnd	3.31 (1.95-5.61)	<.001	89.00
NCT00760877-ENESTcmr	4.45 (0.99-20.02)	.052	11.00
Subtotal	3.42 (2.07-5.63)	<.001	
Ponatinib			
NCT01650805-EPIC	3.47 (1.23-9.78)	.02	100
Subtotal	3.47 (1.23-9.78)	.02	
Overall	3.45 (2.30-5.18)	<.001	



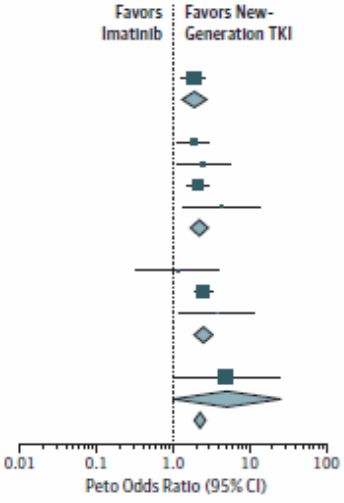
B Overall survival

Source	Peto Odds Ratio (95% CI)	P Value	Weight, %
Bosutinib			
NCT00574873-BELA	2.38 (0.82-6.89)	.11	100
Subtotal	2.38 (0.82-6.89)	.11	
Dasatinib			
NCT00070499	0.14 (0.00-6.82)	.32	8.24
NCT00481247-DASISION	0.36 (0.11-1.24)	.11	83.53
NCT00852566-NordCML006	6.80 (0.13-343.88)	.34	8.23
Subtotal	0.42 (0.14-1.31)	.14	
Nilotinib			
NCT00471497-ENESTnd	2.12 (0.48-9.25)	.32	87.60
NCT00760877-ENESTcmr	0.14 (0.00-6.89)	.32	12.40
Subtotal	1.51 (0.38-5.99)	.56	
Ponatinib			
NCT01650805-EPIC	2.00 (0.21-19.33)	.55	100
Subtotal	2.00 (0.21-19.33)	.55	
Overall	1.20 (0.63-2.29)	.58	



C Major molecular response

Source	Peto Odds Ratio (95% CI)	P Value	Weight, %
Bosutinib			
NCT00574873-BELA	1.86 (1.29-2.70)	.001	100
Subtotal	1.86 (1.29-2.70)	.001	
Dasatinib			
NCT00070499	1.84 (1.10-3.06)	.02	27.52
NCT00103844-START-R	2.50 (1.12-5.58)	.03	11.05
NCT00481247-DASISION	2.15 (1.51-3.07)	<.001	56.34
NCT00852566-NordCML006	4.33 (1.32-14.13)	.02	5.10
Subtotal	2.17 (1.66-2.83)	<.001	
Nilotinib			
NCT01400074-RE-NICE	1.14 (0.33-3.94)	.84	5.10
NCT00471497-ENESTnd	2.49 (1.85-3.34)	<.001	88.98
NCT00760877-ENESTcmr	3.77 (1.19-11.91)	.02	5.92
Subtotal	2.45 (1.85-3.24)	<.001	
Ponatinib			
NCT01650805-EPIC	4.95 (0.97-25.19)	.054	100
Subtotal	4.95 (0.97-25.19)	.054	
Overall	2.22 (1.87-2.63)	<.001	



In this illustration of statistical results, squares represent odds ratios (the size of the squares reflecting the weight assigned to the study) and the whiskers, 95%CIs, both calculated using the Petomethod.12 Diamonds reflect the summary effect for each treatment when the different studies were polled together. No forest plot contains all 10 trials because for each analysis (overall survival, major molecular response, and vascular occlusive events), at least 1 study did not report the event of interest. PH+ indicates Philadelphia chromosome–positive; TKI, tyrosine kinase inhibitor.

	MMR-Rate The Figure, C presents the forest plot for MMR rate at 1 year: 607 (44.18%) of 1374 patients treated with a new-generation TKI achieved an MMR compared with 288 (27,35%) of 1053 patients treated with imatinib. This led to a significant result favoring new-generation TKIs rather than imatinib. Stratification by treatment indicated similar results for each TKI except for ponatinib.
	4. Anmerkungen/Fazit der Autoren This meta-analysis demonstrates a significant increase in the rate of vascular occlusive events associated with the use of dasatinib, nilotinib, and ponatinib compared with imatinib. However, even if no statistical significance was found for bosutinib, a trend was also found. Treatment with dasatinib, nilotinib, and ponatinib should be associated with frequent cardiovascular monitoring and an intensive support of comorbidities. Ponatinib should be reserved for patients with advanced disease, with the T315I mutation, or for whom other treatments cannot be used. 5. Kommentar der FBMed: In die Metaanalyse ist auch eine Studie eingeflossen, die Bosutinib mit Imatinib verglichen hat, sowie **4 Studien, in denen Patienten bereits mit Imatinib behandelt wurden**. Die Auswirkungen auf das Gesamtergebnis sind nicht bekannt, da keine separaten Analysen diesbezüglich durchgeführt wurden. Weiterhin ist nicht klar ob Philadelphia negative Patienten eingeschlossen wurden, allerdings sind alle Arzneimittel ausschließlich für zur Behandlung von Ph+ Patienten zugelassen.
Gurion R et al., 2016 [3]. First line treatment with newer tyrosine kinase inhibitors in chronic myeloid leukemia associated with deep and	1. Fragestellung To update a meta-analysis comparing the role of the newer TKIs to imatinib for first line treatment in CP-CML patients.
	2. Methodik **Population:** Philadelphia positive CP-CML patients **Intervention:** TKIs (nilotinib, dasatinib, bosutinib and ponatinib) **Komparator:** Imatinib **Endpunkte**: Primary Outcomes: MMR at 12 months and complete molecular response (CMR) at 12 months; Secondary Outcomes: CCyR at 12 months; MMR at 3, 18, 24 and 48 months; early monecular response; patients progressing to AP/BC at 12, 18, 24 and 60 months; Mortality at 12, 24 months and 3-5 years; CML-related mortality; AE requiring discontinuation **Suchzeitraum (Aktualität der Recherche):** PubMed (January 1966–August 2015), Cochrane CENTRAL (Issue 2, 2014); conference

durable molecular response - systematic review and meta-analysis	proceedings for trials in hematology (2004-2014/2015) **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 8 RCTs,n=3553 Patienten. Patients were randomized between imatinib and a second or third generation TKI, including nilotinib-2 trials, dasatinib-4 trials, bosutinib-1 trial and ponatinib-1 trial. **Qualitätsbewertung der Studien:** critical assessment separately for each domain according to the criteria specified in the Cochrane Handbook version 5.1.0; heterogenity with I^2
Yun S et al., 2016 [7].	3. Ergebnisdarstellung Qualität der Studien: Regarding the risk of bias, six trials did not report methods of sequence generation and allocation concealment, and therefore were judged as unclear risk of selection bias.

Comparative Effectiveness of Newer Tyrosine Kinase Inhibitors Versus Imatinib in the First-Line Treatment of Chronic-Phase Chronic Myeloid Leukemia Across Risk Groups: A Systematic Review and Meta-Analysis of Eight Randomized Trials	

Table 1. Characteristics of included studies.

Study	Type of TKI and dosage compared to imatinib 400 mg	No. of patients randomized (newer TKI vs. imatinib)	Median age in years (range) (newer TKI vs. imatinib)	Sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias) and blinding of outcome assessors (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Saglio et al. [5,16,19,21]	Nilotinib 300/400 mg	563 vs. 283	47 (18–85) vs. 46 (18–80)	Low risk (using computer random number)	Low risk (central randomization)	Unclear risk	Low risk	Low risk
Kantarjian et al. [4,15,22]	Dasatinib 100 mg	260 vs. 259	46 (18–84) vs. 49 (18–78)	Unclear risk	Low risk (central randomization)	Unclear risk	Low risk	Low risk
Radich et al. [14]	Dasatinib 100 mg	126 vs. 127	48 (19–91) vs. 51 (20–89)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
Gambacorti-Passerini et al. [6,17,18]	Bosutinib 500 mg	250 vs. 252	48 (19–91) vs. 47 (18–89)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
Lipton et al. [7]	Ponatinib 45 mg	154 vs. 152	55 (18–89) vs. 52 (18–86)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
O'Brien et al. [23]	Dasatinib 100 mg	407 vs. 407	No data	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Hjorth-Hansen et al. [20]	Dasatinib 100 mg	22 vs. 24	53 (29–71) vs. 58 (38–78)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
Wang et al. [13]	Nilotinib 300 mg	134 vs. 133	41 (18–76) vs. 39(19–74)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk

No.: number; TKI: tyrosine kinase inhibitor.

Table 2. Rates of MMR and CMR at different time points.

Study	MMR								CMR (MR 4.5)			
	12 months		18 months		24 months		4 years		12 months		24 months	
	N TKI	IM	N TKI	IM	N TKI	IM	N TKI	IM	N TKI	IM	N TKI	IM
Saglio et al. [5,16,19,21]	245/563 44%	62/283 22%	360/563 64%	113/283 40%	388/563 69%	125/283 44%	419/563 75%	159/283 56%	98/563 17%	17/283 6%	203/563 36%	51/283 18%
Kantarjian et al. [4,15,22]	119/259 46%	73/260 28%	148/259 57%	107/260 41%	166/259 64%	120/260 46%	189/259 73%	156/260 60%	- -	- -	44/259 17%	21/260 8%
Radich et al. [14]	58/123 59%	39/123 43%	- -	- -	- -	- -	- -	- -	21/99 21%	14/91 15%	- -	- -
Gambacorti-Passerini et al. [6,17,18]	103/250 41%	68/252 27%	115/250 46%	96/252 38%	123/250 49%	106/252 42%	- -	- -	30/250 12%	8/252 3%	- -	- -
Lipton et al. [7]	19/22 86%	9/27 33%	- -	- -	- -	- -	- -	- -	7/22 32%	0/27 0%	- -	- -
O'Brien et al. [23]	237/406 58%	175/406 43%	- -	- -			- -	- -	54/406 13%	24/406 6%	- -	- -
Hjorth-Hansen et al. [20]	18/22 80%	11/23 47%	17/22 77%	15/23 65%	17/22 78%	19/23 82%	- -	- -	7/20 35%	2/23 8%	12/21 57%	5/22 23%
Wang et al. [13]	70/134 52.2%	37/133 27.8%	87/134 65%	60/133 45%	91/134 68%	70/133 53%	- -	- -	- -	- -	- -	- -

CMR:complete molecular response; IM, imatinib; m: months; MMR: major molecular response; N TKI:newer tyrosine kinase inhibitors; y:years.
Nominator is the number of patients achieving MMR or CMR and denominator is the total number of patients randomized to each arm.
'-' = no data reported.

MMR

All trials, 3286 patients, were included for this analysis. At 12 months, there was a significant advantage in favor of the newer TKIs compared with imatinib (RR 1.60, 95% CI 1.47–1.75).

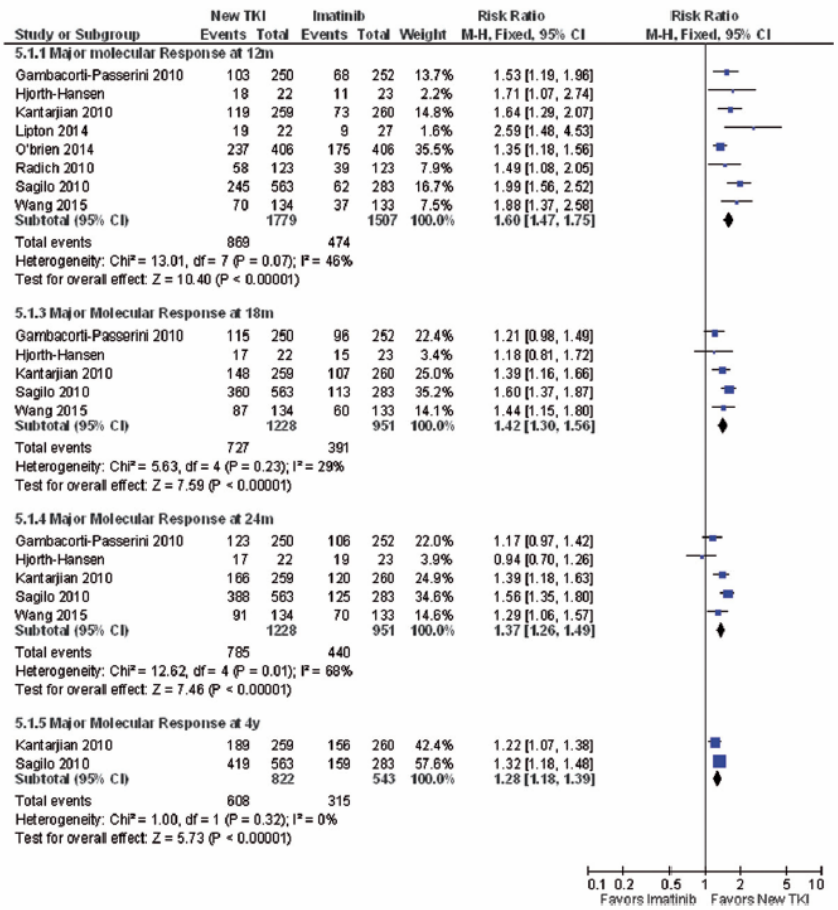


Figure 2. Imatinib versus newer TKIs: rate of patients who achieved major molecular response at 12, 18, 24 and 48 months. The black squares represent point estimate, their sizes represent the weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. CI: confidence interval; m: months; RR, relative risk; TKIs: tyrosine kinase inhibitors; y: years.

CCyR

CCyR at 12 months was significantly improved with the newer TKIs compared to imatinib (RR 1.12, 95% CI 1.03–1.23, I^2=68%, seven trials). At 18 and 24 months the advantage in favor of the newer TKIs arm disappeared.

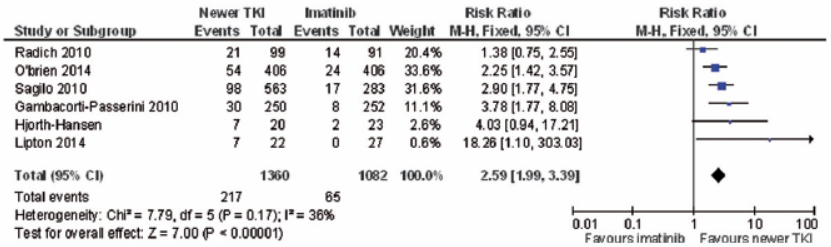


Figure 3. Imatinib versus newer TKIs: rate of patients who achieved complete molecular response at 12 months. The black squares represent point estimate, their sizes represent the weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. CI: confidence interval; m: months; RR: relative risk; TKIs: tyrosine kinase inhibitors.

CMR

CMR was examined at 12 months (six trials were included in the analysis) and at 24 months (three trials were included in the analysis). At both time points, the newer TKIs had significant advantage over imatinib (RR 2.59, 95% CI 1.99–3.39 and RR 2.06, 95% CI 1.64–2.59, respectively)

Early molecular response

There was a statistically significant advantage in favor of the newer TKIs compared to imatinib in terms of early molecular response at three months (RR 1.33, 95% CI 1.26–1.39, I2=0%, six trials).

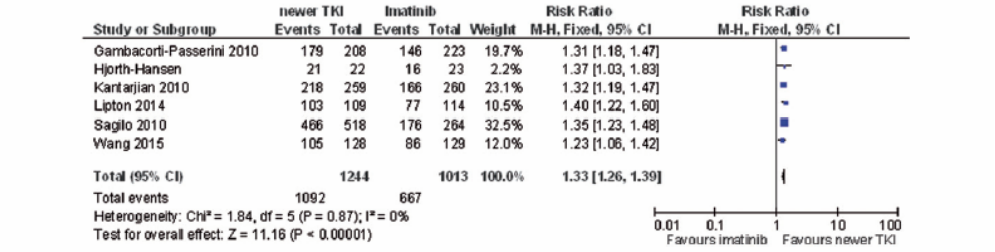


Figure 4. Imatinib versus newer TKIs: rate of patients who achieved early molecular response at 3 months. The black squares represent point estimate, their sizes represent the weight in the pooled analysis, and the horizontal bars represent the 95% CI. The black diamond at the bottom represents the pooled point estimate. CI: confidence interval; RR: relative risk; TKIs: tyrosine kinase inhibitors; m: months.

Progressing to AP/BC

The newer TKIs had a favorable effect on progression to AP/ BC at 12 months (RR 0.40, 95% CI 0.24–0.67, I2=0%, six trials), 24 months (RR 0.43, 95% CI 0.26–0.70, I2=4%, five trials) and 5 years (RR 0.47, 95% CI 0.29–0.76, I2=0%, two trials).

Mortality

No difference in all-cause mortality between the groups at all time points

Toxicity

Mortality attributed to CML was significantly increased in the imatinib arm compared to the newer TKIs at 12 months (RR 0.45, 95% CI 0.22–0.94, four trials), 24 months (RR 0.56, 95% CI 0.33–0.94, four trials), and at the end of follow-up (RR 0.40, 95% CI 0.23–0.67, three trials).

Toxicity – In these safety analyses, RR <1 favored newer TKIs. The rate of adverse events requiring treatment discontinuation, was higher with the newer TKIs compared to imatinib (RR 1.61, 95% CI 1.14–2.28, I2=59%, REM, eight trials). There was no difference in grade 3–4 anemia or neutropenia, yet there was more grade 3–4 thrombocytopenia in the newer TKIs arm (RR 1.49, 95% CI 1.06–2.10, I2=68%, REM, eight trials). Any arterial cardiovascular events, including peripheral occlusive arterial disease, ischemic heart disease and cerebrovascular accident, occurred more frequently with the newer TKIs (RR 2.99, 95% CI 1.94–4.62, I2=0%, seven trials) as compared to imatinib. Moreover, there was a statistically significantly increased incidence of pleural effusion of any grade (RR 11.14, 95% CI 3.46–35.91, I2=70%, REM, six trials). The incidence of pleural effusion requiring discontinuation also increased with the newer TKIs (RR 14.23, 95% CI 3.95–51.18, I2=0%, four trials). TKIs in these trials included dasatinib and bosutinib only. Grade 3–4 edema and grade 3–4 diarrhea occurred at the same rate in both arms (four trials, respectively).

4. Anmerkungen/Fazit der Autoren

In conclusion, the present meta-analysis supports our previous results showing that the newer TKIs are associated with more efficacy, but there is

	no proof for better OS. Furthermore, it also reinforces our findings regarding 'softer' clinical outcomes, such as CML-related mortality and progression to AP/BC. 5. Kommentar der FBMed • In der Studie Gambacorti-Passerini et al. wurde Bosutinib eingesetzt. Da keine Sensitivitätsanalysen ohne Bosutinib durchgeführt wurden, kann nicht abschließend abgeschätzt werden, welchen Einfluss dies auf das Gesamtergebnis hat. In Bezug auf den primären Endpunkt waren zu Monat 12 wiesen jedoch alle eingeschlossenen Studien eine statistische Signifikanz auf. • Der in **Yun S et al. [7]** untersuchten, vergleichbare Fragestellung lagen fast dieselben Studien zugrunde, mit Ausnahme einer zusätzlichen Studie mit nicht zugelassenem Komparator und einer nicht eingeschlossenen Studie zu Dasatinib. Der Grund für die Divergenz ist nicht ersichtlich. Die Autoren zeigten dabei vergleichbare Ergebnisse: In our meta-analysis of randomized controlled trials of patients with CP-CML, the NG-TKIs nilotinib, dasatinib, bosutinib, ponatinib, and radotinib were associated with greater MMR rates and lower rates of progression to AP/BC but not with significant differences in CCyR, PFS, OS, or KD mutation rates relative to imatinib at 12 months of TKI treatment. However, the NG-TKIs approved for first-line treatment (nilotinib, dasatinib, and, in Korea, also radotinib) were associated with greater CCyR and MMR rates and lower rates of progression to AP/BC but not with significant differences in PFS, OS, or KD mutation.
Firwana B et al., 2016 [2]. Tyrosine kinase inhibitors as a first-line treatment in patients with newly diagnosed chronic myeloid leukemia in chronic phase: A mixed-	1. Fragestellung In our study, we sought to summarize the evidence of TKI efficacy, comparing second-generation TKI directly and in-directly in patients with newly diagnosed chronic-phase CML.
	2. Methodik **Population**: newly diagnosed chronic CML adults **Intervention:** dasatinib, nilotinib, bosutinib or ponatinib **Komparator:** Imatinib **Endpunkt:** MMR; deeper molecular responses, OS, PFS **Suchzeitraum** (Aktualität der Recherche): bis Januar 2015 in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials CENTRAL, Web of Science and Scopus **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 6 RCTs, n=2456 Patienten. Baseline characteristics of the studies: In the Appendix of this document **Qualitätsbewertung der Studien:** Cochrane Collaboration's risk-of-bias tool; heterogeneity with I^2 statistic

treatment comparison	Mixed-treatment comparison: Bayesian approach

3. Ergebnisdarstellung

Qualität der Studien: In general, the overall quality of the six trials was appropriate with likely low risk of bias:

Study ID	*Adequate sequence generation*	*Allocation concealment*	*Blinding*	*Baseline characteristics imbalance*	*Lost to follow up (%)*	*Source of study funding*	*Incomplete data*
DIAISON	Low risk; patients were randomly assigned, in a 1:1 ratio; method not reported	High risk; this study is an open-label trial	High risk; this study is an open-label trial	Low-risk; baseline characteristics are well-matched.	Low-risk; <1% at 3-year follow-up; results were reported on intention-to-treat basis.	Supported by Bristol-Myers Squibb.	-
ENESTnd	Low risk; patients were randomly assigned, in a 1:1:1 ratio; method not reported	High risk; this study is an open-label trial	High risk; this study is an open-label trial	Low-risk; baseline characteristics are well-matched	Low-risk; 0%; results were reported on intention-to-treat basis.	Supported by Novartis Pharmaceuticals.	CCyR was not reported at the long-term follow-up.
BELA	Low risk; patients were randomly assigned 1:1ratio; method not reported.	High risk; this study is an open-label trial	High risk; this study is an open-label trial	Low-risk; baseline characteristics are well-matched	Low-risk; <1% at 1-year follow-up.	Editorial/medical writing support was provided by Kimberly Brooks, PhD, of SciFluent and was funded by Pfizer. Remuneration: Laimonas Griskevicius, Novartis	Reported data are at 12-month follow-up.
SO325	Low risk; patients were randomly assigned, in a 1:1 ratio; method not reported	Unclear	Unclear	Low-risk; baseline characteristics are well-matched except for median white-cell count was higher in dasatinib group compared to imatinib group	Low-risk; 0% at 1-year follow-up.	This work was supported in part by Public Health Service Cooperative Agreement grants from the National Institutes of Health, and Canadian Cancer Society Research Institute.	Reported data are at 12-month follow-up.
EPIC	Low risk; patients were randomized; method not reported	Unclear	Unclear	Low-risk; reportedly, baseline characteristics were balanced	Low-risk; 0% at 5-month follow-up.	Study was sponsored by Ariad Pharmaceuticals.	Outcomes at 12-mont follow-up and further were lacking due to early termination of study.
Zhuo 2013	Low risk; reportedly randomized; method not reported	Unclear	Unclear	Low-risk; baseline characteristics are well-matched	Low-risk; 0% at 24-month follow-up.	Not reported.	-

Direct comparision of second-generation TKIs with imatinib

At 12 months follow-up and compared to imatinib, dasatinib and nilotinib had a statistically significant improvement in MMR [RR 1.57 (CI 1.30, 1.89) and 2.20 (CI 1.63, 2.96), respectively], which was sustained throughout treatment period at 2, 3, 4 and 5 years.

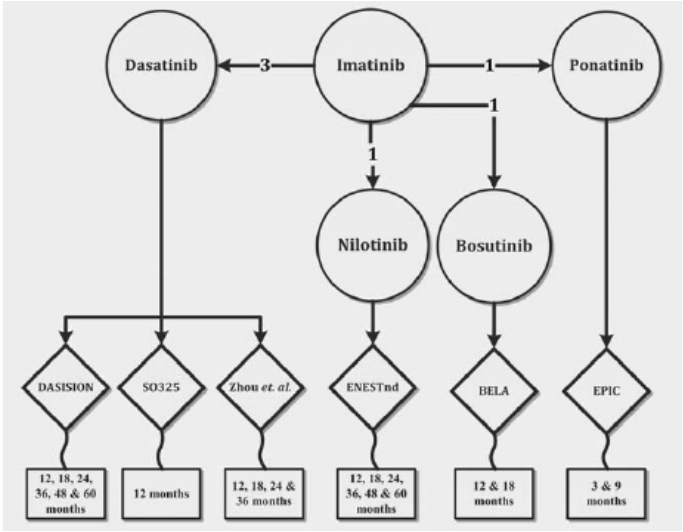
Mixed-treatment comparison analysis

Nilotinib, among other TKIs, had the highest probability of sustaining major and deeper molecular response, MMR and $MR^{4.5}$ at 5 years. Nilotinib has also ranked first among other TKIs in achieving the highest OS and PFS; this improvement in OS and PFS, although appears to be statistically significant, is modest and likely has a questionable clinical significance. Compared to dasatinib, both nilotinib 300 mg twice daily and nilotinib 400 mg twice daily had higher $MR^{4.5}$ at 5 years but no difference in MMR (Table 2). In sensitivity analysis, the fixed-effect results were very similar to the random effect results suggesting robustness of analysis to the choice of model

Table 2. Results of mixed-treatment comparison for imatinib, dasatinib and nilotinib using fixed-effect Bayesian method

Comparison	Mean effect (difference in means; 95% CrI) compared to reference standard (imatinib)					
	MMR at 60 months	MMR 4.5 at 60 months	PFS at 60 months	OS at 60 months	Probability treatment is best according to MMR analysis	Rank
Imatinib	Reference	Reference	Reference	Reference	0	4
Dasatinib	0.59 (0.21 to 0.98)	0.39 (0.02 to 0.75)	−0.1 (−0.59 to 0.39)	0.13 (−0.46 to 0.73)	13%	3
Nilotinib 300	0.80 (0.44 to 1.17)	0.95 (0.61 to 1.3)	0.8 (0.07 to 1.57)	0.33 (−0.32 to 1.0)	44%	1
Nilotinib 400	0.80 (0.43 to 1.17)	0.91 (0.57 to 1.25)	1.46 (0.57 to 2.47)	0.80 (0.07 to 1.57)	43%	2
Nilotinib 300 *vs.* Dasatinib	0.21 (−0.32 to 0.74)	0.57 (0.07 to 1.06)	0.20 (−0.69 to 1.09)	0.90 (0.01 to 1.81)	–	–
Nilotinib 400 *vs.* Dasatinib	0.21 (−0.32 to 0.74)	0.52 (0.02 to 1.02)	1.56 (0.54 to 2.68)	0.67 (−0.28 to 1.64)	–	–

Abbreviations: CrI: credible intervals; MMR: major molecular response, BCR-ABLIS ≤0.1%; $MMR^{4.5}$: deeper molecular responses, BCR-ABLIS ≤0.0032%; PFS: progression-free survival; OS: overall survival; AE: adverse events.



Tyrosine kinase inhibitors for CML network: each edge (circle) represents a treatment; connecting lines indicate pairs of treatments which have been directly compared in randomized trials. The numbers on the lines indicate the numbers of trials making that comparison.

4. Anmerkungen/Fazit der Autoren

In conclusion, both nilotinib and dasatinib are associated with significantly better MMR and survival profile compared to imatinib. At 12-month as well as at 60-month treatment period, nilotinib ranked first to achieve MMR and MR$^{4.5}$. This analysis shows that new-generation TKIs are not only showing faster response but also maintaining a more potent one through longer follow-up period. It is important to note out that MTC is not a substitute for well-conducted RCTs investigating direct comparisons.

5. Kommentar der FBMed

Es ist nicht klar, ob Philadelphia negative Patienten eingeschlossen wurden. Allerdings sind die untersuchten Arzneimittel nur bei Ph+ CML Patienten zugelassen

Leitlinien

<table>
<tr><td rowspan="3">National Comprehen-sive Cancer Network (NCCN), 2017 [5].

Chronic Myeloid Leukemia; Version 2.2018</td><td>Fragestellung/Zielsetzung:
To discuss the clinical management of CML in all three phases (chronic, accelerated, or blast phase)</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie: Update der LL von 01.2018, Systematik der Literatursuche und -bewertung nicht vollständig transparent dargestellt, Diskussion der Literatur und Empfehlungen im Expertenpanel, Interessenkonflikte unklar

Literatursuche: in PubMed zwischen 04/2016 und 03/2017

GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

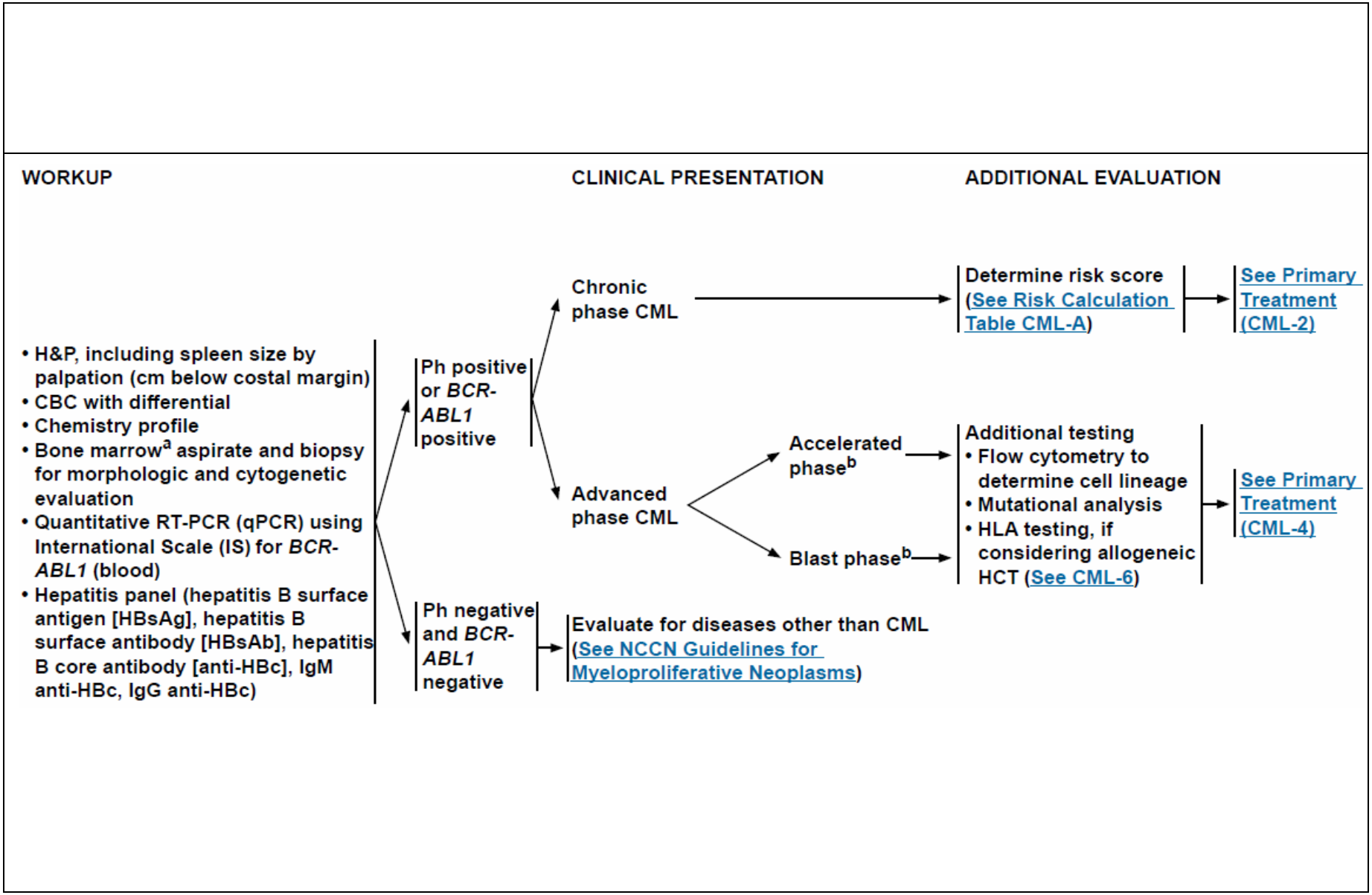
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

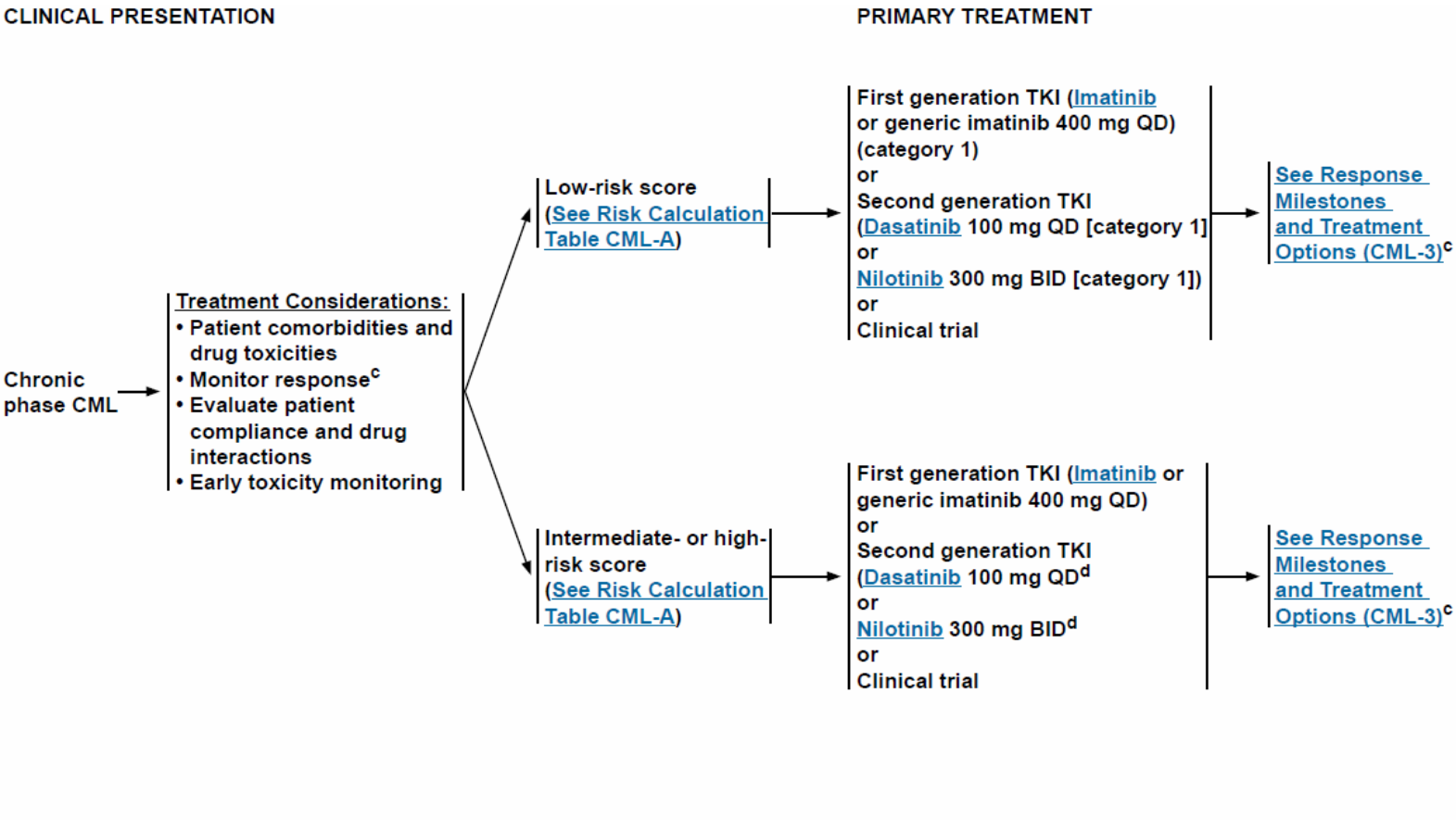
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.</td></tr>
<tr><td>Empfehlungen:

CML-1</td></tr>
</table>


WORKUP
CLINICAL PRESENTATION
ADDITIONAL EVALUATION
• H&P, including spleen size by palpation (cm below costal margin)
• CBC with differential
• Chemistry profile
• Bone marrow[a] aspirate and biopsy for morphologic and cytogenetic evaluation
• Quantitative RT-PCR (qPCR) using International Scale (IS) for BCR-ABL1 (blood)
• Hepatitis panel (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], hepatitis B core antibody [anti-HBc], IgM anti-HBc, IgG anti-HBc)
Ph positive or BCR-ABL1 positive
Ph negative and BCR-ABL1 negative
Chronic phase CML
Advanced phase CML
Accelerated phase[b]
Blast phase[b]
Determine risk score (See Risk Calculation Table CML-A)
Additional testing
• Flow cytometry to determine cell lineage
• Mutational analysis
• HLA testing, if considering allogeneic HCT (See CML-6)
See Primary Treatment (CML-2)
See Primary Treatment (CML-4)
Evaluate for diseases other than CML (See NCCN Guidelines for Myeloproliferative Neoplasms)



[c]See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[d]Long-term follow-up data suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from dasatinib or nilotinib. See Discussion for additional information.

TREATMENT OPTIONS BASED ON BCR-ABL1 MUTATION PROFILE

Mutation	Treatment Recommendation[j]
Y253H, E255K/V, or F359V/C/I	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib,[k] Omacetaxine,[l] allogeneic HCT (CML-6), or clinical trial

[j]Patients with disease that is resistant to primary treatment with imatinib should be treated with nilotinib, dasatinib, or bosutinib in the second-line setting. Patients with disease that is resistant to primary treatment with nilotinib or dasatinib could be treated with an alternate TKI (other than imatinib) in the second-line setting.
[k]Ponatinib is a treatment option for patients with a T315I mutation or for patients for whom no other TKI is indicated
[l]Omacetaxine is a treatment option for patients with disease that is resistant and/or intolerant to 2 or more TKIs.

RISK CALCULATION TABLE

Study	Calculation	Risk Definition by Calculation	
Sokal et al, 1984[1]	Exp 0.0116 x (age in years - 43.4) + (spleen - 7.51) + 0.188 x [(platelet count ÷ 700)^2 - 0.563] + 0.0887 x (blast cells - 2.10)	Low Intermediate High	<0.8 0.8 - 1.2 >1.2
Hasford et al, 1998[2]	0.666 when age ≥ 50 years + (0.042 x spleen) + 1.0956 when platelet count > 1500 x 10^9/L + (0.0584 x blast cells) + 0.20399 when basophils > 3% + (0.0413 x eosinophils) x 100	Low Intermediate High	≤780 781 - 1480 >1480

Calculation of relative risk found at http://www.icsg.unibo.it/rrcalc.asp. Age is in years. Spleen is in centimeter below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are in percents of peripheral blood differential. All factors must be collected prior to any treatment.

 Baccarani M, Cortes J, Pane F, Niederwieser D, et al. European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol 2009;27(35):6041-6051.

[1]Sokal J, Cox E, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-799. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6584184.

[2]Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-858. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9625174.

Treatment Considerations (CML-2)

The selection of first-line TKI therapy in a given patient should be based on the risk score, toxicity profile of TKI, patient's age, ability to tolerate therapy, and the presence of comorbid conditions. Allogeneic HCT is no longer recommended as a first-line treatment option for patients with CP-CML.

Treatment Recommendations Based on Risk Stratification

Dasatinib or nilotinib are associated with higher rates of molecular response and lower risk of disease progression than imatinib in intermediate- and high-risk patients.[53,55] In the DASISION study, the MMR rates were higher for dasatinib than for imatinib in patients with intermediate (71% and 65%, respectively) and high (67% and 54%, respectively) Hasford (Euro) risk scores, and achievement of MMR after first-line dasatinib is associated with reduced risk of progression to AP-CML or BP-CML.[53,57] In the ENESTnd study, fewer patients with intermediate and high Sokal risk score progressed to AP-CML or BP-CML in the nilotinib arm (2 patients with intermediate-risk score and 7 patients with high-risk score) than in the imatinib arm (10 patients with intermediate-risk score and 11 patients with high-risk score).[55] The estimated 5-year PFS rates were 93% and 86% for patients with intermediate- and high-risk scores, respectively, in the nilotinib arm. The corresponding PFS rates for imatinib were 88% and 83%, respectively. In the IRIS trial, the estimated 10-year OS rates were higher for patients with a low or intermediate Sokal score than for patients with a high Sokal score (90%, 80%, and 69%, respectively).[43]

Dasatinib (100 mg once daily), imatinib (400 mg daily), and nilotinib (300 mg twice daily) are included as options for primary treatment (category 1 for patients with low-risk score; category 2A for patients with intermediate- or high-risk score). Long-term follow-up data from DASISION and ENESTnd studies suggest that patients with an intermediate- or high-risk Sokal or Hasford score may preferentially benefit from dasatinib or nilotinib.[53,55] Since both dasatinib and nilotinib have very good efficacy in the upfront setting, differences in their potential toxicity profiles may inform the selection of either one of these TKIs over imatinib in patients with a low-risk score. Dasatinib may be preferred in patients with a history of arrhythmias, heart disease, pancreatitis, or hyperglycemia. Nilotinib may be preferred for patients with a history of lung disease or deemed to be at risk of developing pleural effusions.

43. Hochhaus A, Larson RA, Guilhot F, et al. Long-term outcomes of imatinib treatment for chronic myeloid leukemia. N Engl J Med 2017;376:917-927. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28273028.

53. Cortes JE, Saglio G, Kantarjian HM, et al. Final 5-year study results of DASISION: the dasatinib versus imatinib study in treatment-naive chronic myeloid leukemia patients trial. J Clin Oncol 2016;34:2333-2340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27217448.

55. Hochhaus A, Saglio G, Hughes TP, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial.

57. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010;362:2260-2270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20525995.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

National Institute for Health and Care Excellence (NICE), 2016 [6]. Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia	Fragestellung: The appraisal committee reviewed the data available on the clinical and cost effectiveness of dasatinib, having considered evidence on the nature of chronic myeloid leukaemia (CML) and the value placed on the benefits of dasatinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources. Methodik: The appraisal committee considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund partial reconsideration of the published NICE technology appraisal guidance on dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence and the history for full details of the evidence used for NICE's original technology appraisal guidance on dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. For the assessment of effectiveness, a literature search was conducted in a range of electronic databases including MEDLINE, EMBASE and the Cochrane Library (2002- May 2011) (Dasatinib, Nilotinib, and standard dose Imatinib for the first-line treatment of chronic myeloid leukaemia: systematic reviews and economic analyses; Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence) Empfehlungen: • Imatinib is recommended as an option for untreated, chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults. • Dasatinib and nilotinib are recommended, within their marketing authorisations, as options for untreated chronic-phase Philadelphiachromosome- positive chronic myeloid leukaemia in adults. The drugs are recommended only if the companies provide them with the discounts agreed in the relevant patient access schemes.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 12.10.2017

#	Suchfrage
1	MeSH descriptor: [Leukemia, Myelogenous, Chronic, BCR-ABL Positive] explode all trees
2	chronic:ti,ab,kw
3	(Ph1-Positive or Ph-Positive or “Ph1+” or “Ph+” or Philadelphia-Positive or “Philadelphia+”):ti,ab,kw
4	#2 or #3
5	(myeloid or myelogenous or myelocytic or myelosis or granulocytic):ti,ab,kw
6	(leukem* or leucem* or leukaem* or leucaem*):ti,ab,kw
7	#4 and #5 and #6
8	(CML or CGL):ti,ab,kw
9	#1 or #7 or #8
10	#9 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 13.10.2017

#	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 “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 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 ("2012/10/01"[PDAT] : "2017/10/31"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 13.10.2017

#	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 AND #3
5	((((“myeloid”[Tiab]) OR “myelogenous”[Tiab]) OR “myelocytic”[Tiab]) OR “myelosis”[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*[Title])*
11	(((#10) AND ("2012/10/01"[PDAT] : "2017/10/31"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

Literatur

1. **Douxfils J, Haguet H, Mullier F, Chatelain C, Graux C, Dogne JM.** Association Between BCR-ABL Tyrosine Kinase Inhibitors for Chronic Myeloid Leukemia and Cardiovascular Events, Major Molecular Response, and Overall Survival: A Systematic Review and Meta-analysis. JAMA Oncol 2016;2(5):625-632.

2. **Firwana B, Sonbol MB, Diab M, Raza S, Hasan R, Yousef I, et al.** Tyrosine kinase inhibitors as a first-line treatment in patients with newly diagnosed chronic myeloid leukemia in chronic phase: A mixed-treatment comparison. Int J Cancer 2016;138(6):1545-1553.

3. **Gurion R, Raanani P, Vidal L, Leader A, Gafter-Gvili A.** First line treatment with newer tyrosine kinase inhibitors in chronic myeloid leukemia associated with deep and durable molecular response - systematic review and meta-analysis. Acta Oncol 2016;55(9-10):1077-1083.

4. **Haguet H, Douxfils J, Mullier F, Chatelain C, Graux C, Dogne JM.** Risk of arterial and venous occlusive events in chronic myeloid leukemia patients treated with new generation BCR-ABL tyrosine kinase inhibitors: a systematic review and meta-analysis. Expert Opin Drug Saf 2017;16(1):5-12.

5. **National Comprehensive Cancer Network (NCCN).** Chronic Myeloid Leukemia; Version 2.2018 [online]. Fort Washington (USA): NCCN; 2017. [Zugriff: 07.11.2017]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.

6. **National Institute for Health and Care Excellence (NICE).** Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia [online]. 21.12.2016. London (GBR): NICE; 2016. [Zugriff: 16.10.2017]. (NICE technology appraisal guidance; Band 426). URL: https://www.nice.org.uk/guidance/ta426.

7. **Yun S, Vincelette ND, Segar JM, Dong Y, Shen Y, Kim DW, et al.** Comparative Effectiveness of Newer Tyrosine Kinase Inhibitors Versus Imatinib in the First-Line Treatment of Chronic-Phase Chronic Myeloid Leukemia Across Risk Groups: A Systematic Review and Meta-Analysis of Eight Randomized Trials. Clin Lymphoma Myeloma Leuk 2016;16(6):e85-94.

Anlage

Table 1 Baseline characteristics (Firwana B et al., 2016 [2])

Table 1. Baseline characteristics

			Second- and third-generation TKI									Imatinib						
Study ID	No. of patients	Comparisons	No. of patients	Age (median)	Gender, male (%)	Sokal; low, intermediate, high (%)	ECOG; 0, 1, 2 (%)	Hasford; low, intermediate, high (%)	White cell count, $10^{-3}/mm^3$ (median)	Platelet count, $10^{-3}/mm^3$ (median)	No. of patients	Age (median)	Gender, male (%)	Sokal; low, intermediate, high (%)	ECOG; 0, 1, 2 (%)	Hasford; low, intermediate, high (%)	White cell count, $10^{-3}/mm^3$ (median)	Platelet count, $10^{-3}/mm^3$ (median)
Dasatinib																		
DASISION	519	• Intervention: Dasatinib 100 mg once a day. • Control: Imatinib 400 mg once a day.	259	46	56	–	82, 18, 0	33, 48, 19	25	448	260	49	63	–	79, 20, 1	33, 47, 19	24	390
SO325	246	• Intervention: Dasatinib 100 mg once a day. • Control: Imatinib 400 mg once a day.	123	47	60	–	58, 38, 3	36, 33, 32	89	363	123	50	59	–	63, 36, 1	36, 37, 28	52	378
Zhou 2013	37	• Intervention: Dasatinib 100 mg once a day. • Control: Imatinib 400 mg once a day.	18	44	77	–	55, 45, 0	50, 0, 50	–	–	19	41	52	–	58, 42, 0	68, 0, 32	–	–
Nilotinib																		
ENESTnd	846	• Interventions: Nilotinib 300 mg twice a day. • Intervention: Nilotinib 400 mg twice a day. • Control: Imatinib 400 mg once a day.	Nilotinib 300: 282 Nilotinib 400: 281	47	56	37, 36, 28	88, 12, 0	–	23	424	283	46	56	37, 36, 28	85, 13, 2	–	26	375
Bosutinib																		
BELA	502	• Intervention: Bosutinib 500 mg once a day. • Control: Imatinib 400 mg once a day.	250	48	60	35, 47, 13	74, 26, 0	–	22	386	252	47	54	35, 47, 13	72, 28, 0	–	24	451
Ponatinib																		
EPIC	267	• Intervention: Ponatinib 45 mg once a day. • Control: Imatinib 400 mg once a day.	154	55	Reported to be balanced	27, 65, 64	–	–	–	–	152	52	Reported to be balanced	23, 67, 62	–	–	–	–