Spezifität und Verträglichkeit in der CML-Behandlung

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Charité

Medizinische Klinik m.S. Hämatologie, Onkologie und Tumorimmunologie

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Disclosures

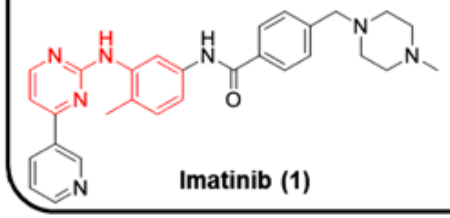
- Speakers´honoraria from Novartis, Incyte, AOP, Blueprint, JAZZ

Einleitung

- 1st Generation vs. 2nd & 3rd Generation TKI
- Resistance to TKI
- Toxicities to TKI
- Specificity
- STAMP inibitors

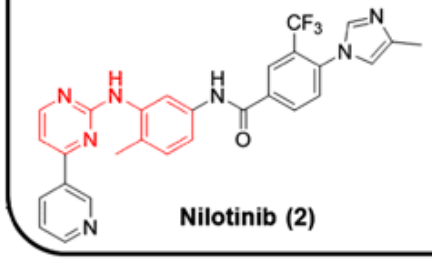
Erste, Zweite und Dritte Generation TKI

1st Generation

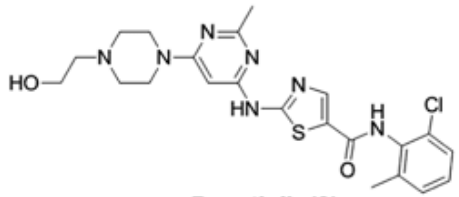


Imatinib (1)

2nd Generation

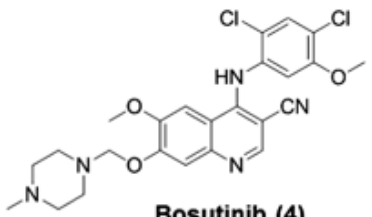


Nilotinib (2)

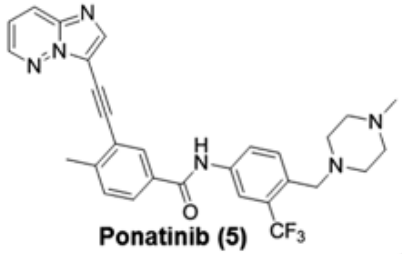


Dasatinib (3)

3rd Generation

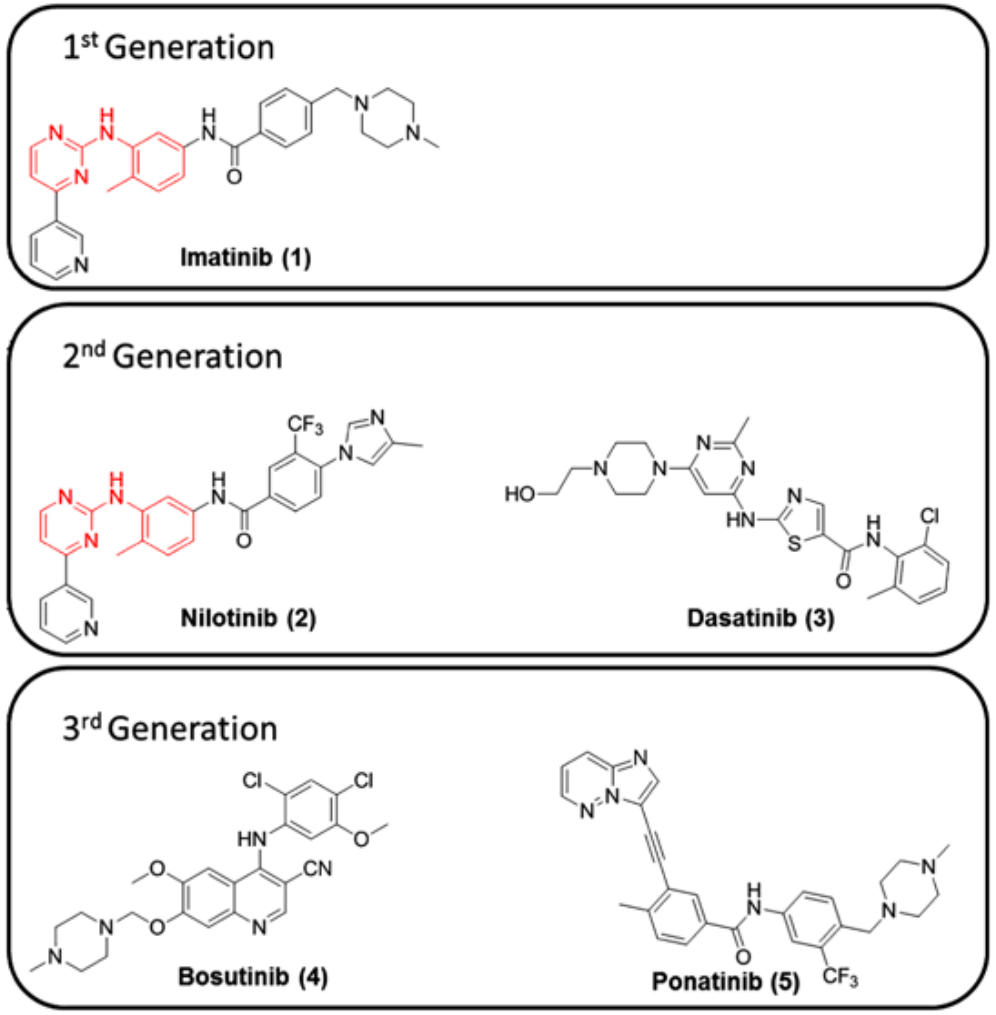


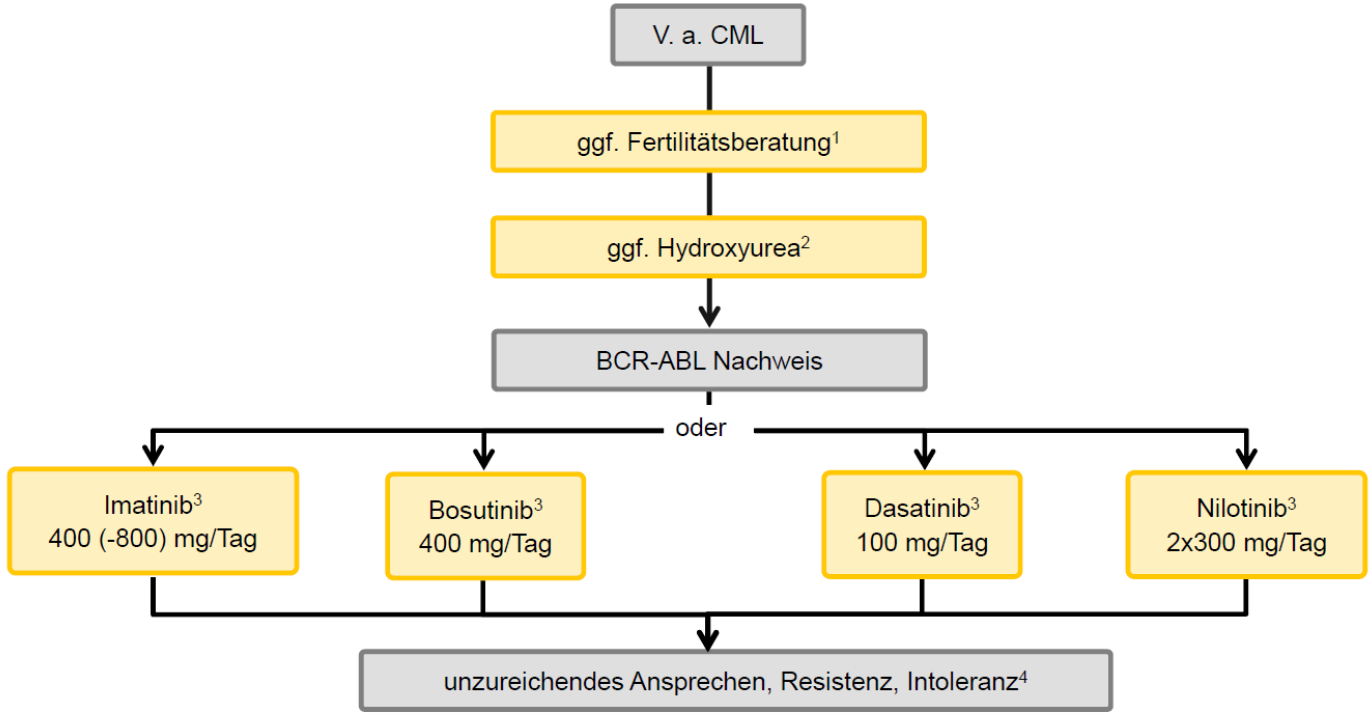
Bosutinib (4)



Ponatinib (5)

Erste, Zweite und Dritte Generation TKI





Onkopedia Leitlinie CML, Stand 2018, Herausgeber: Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO); https://www.onkopedia.com/de/onkopedia/guidelines/chronische-myeloische-leukaemie-cml/@@guideline/html/index.html (letzter Zugriff am 10.10.2024).

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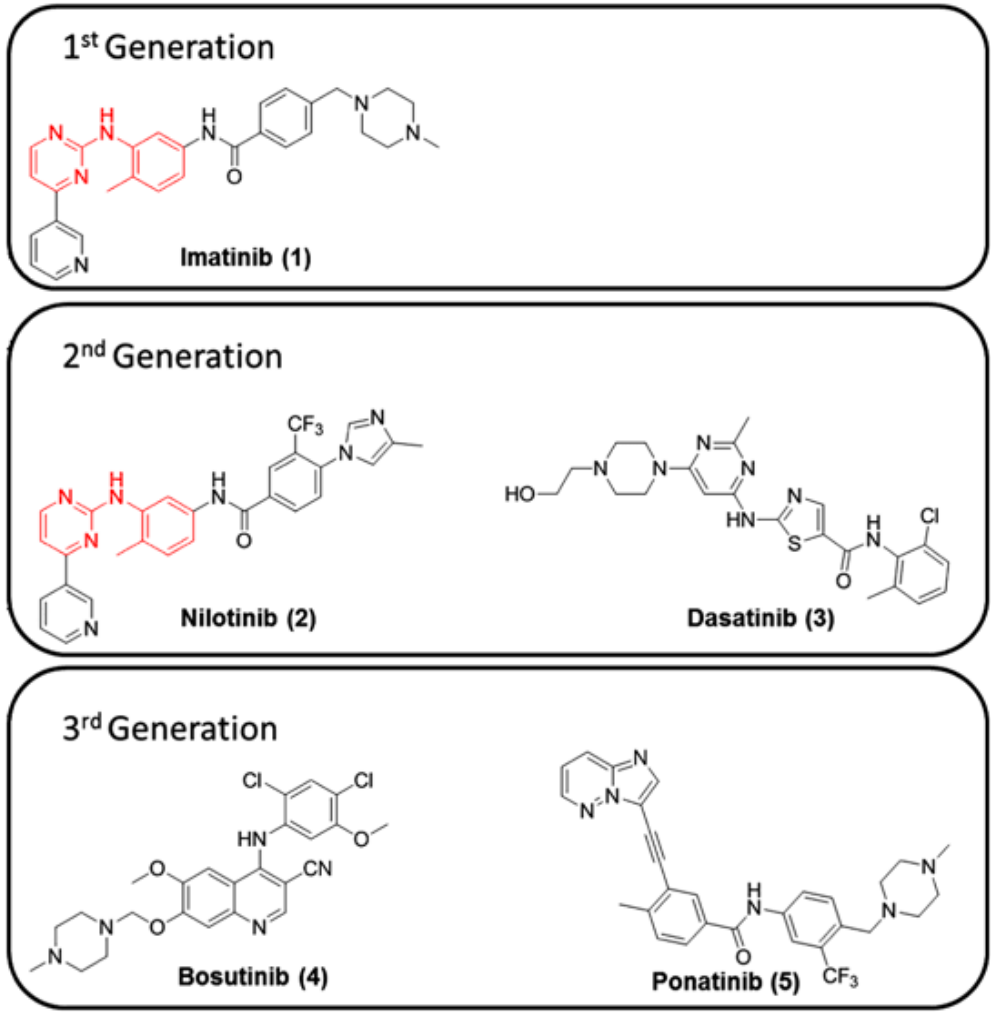
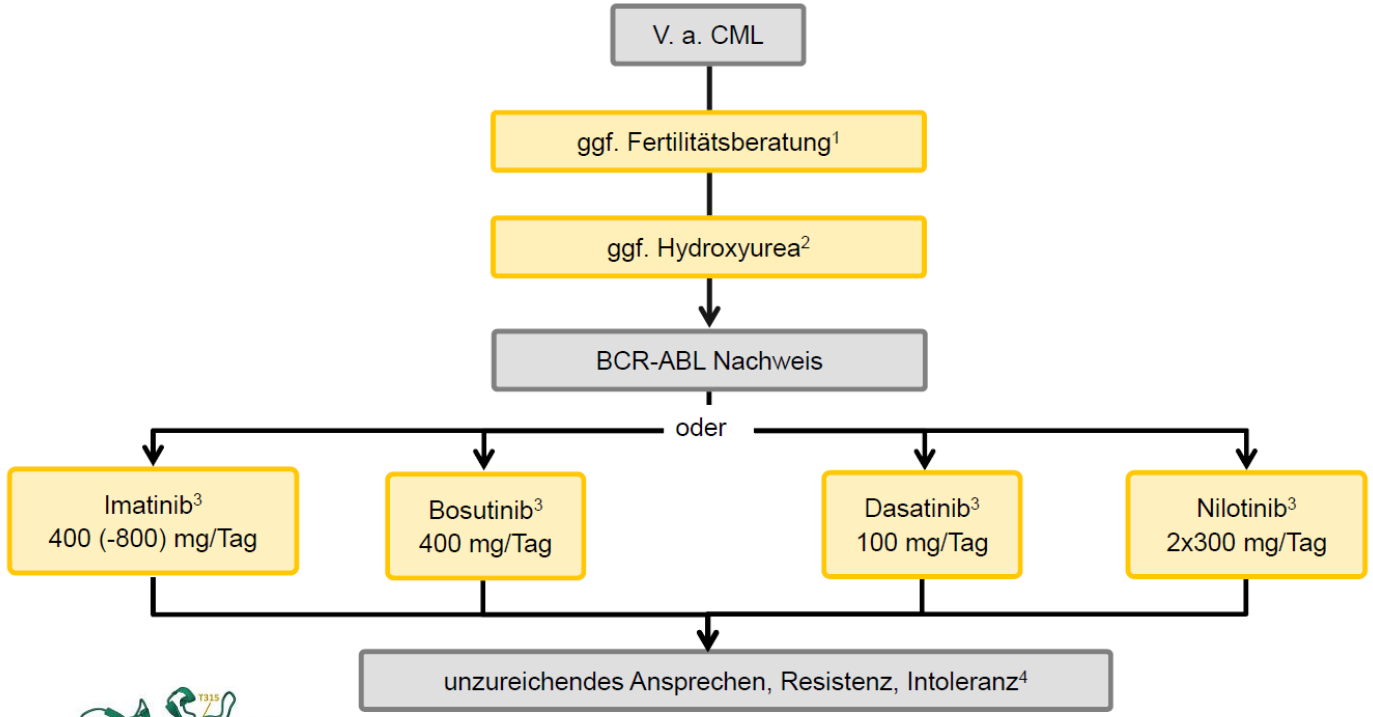
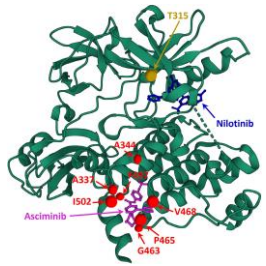
Erste, Zweite und Dritte Generation TKI



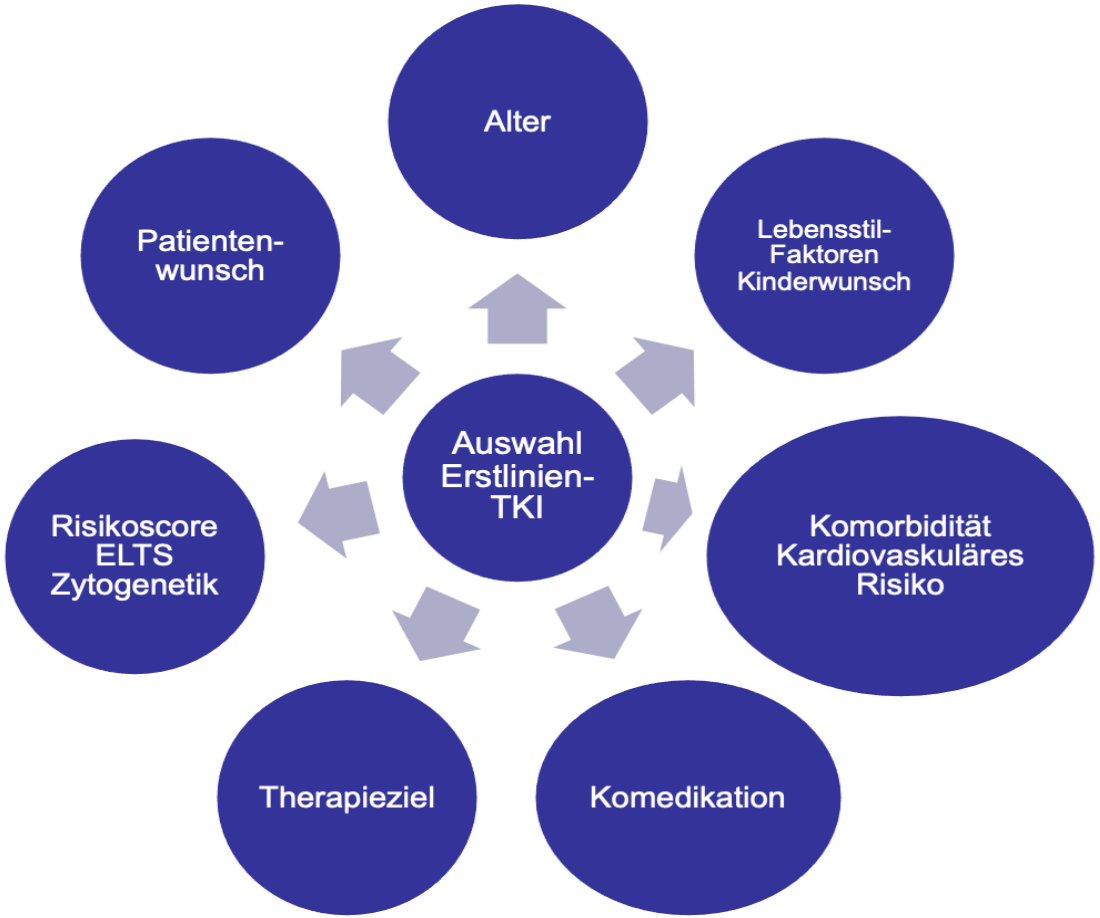




Asciminib

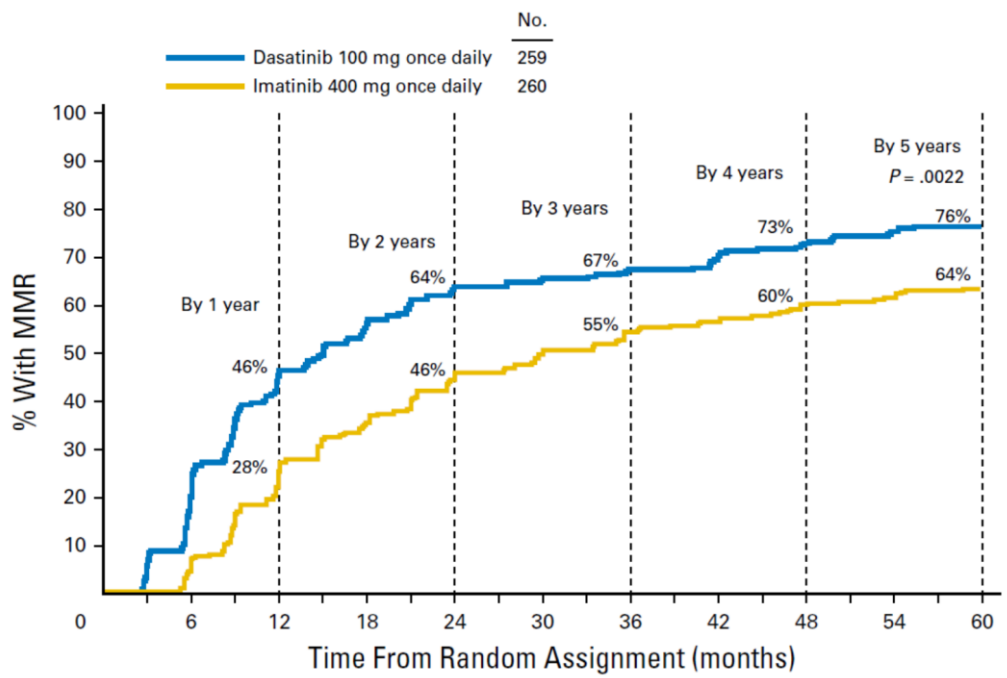
Onkopedia Leitlinie CML, Stand 2018, Herausgeber: Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO); https://www.onkopedia.com/de/onkopedia/guidelines/chronische-myeloische-leukaemie-cml/@@guideline/html/index.html (letzter Zugriff am 10.10.2024).

Relevante Faktoren der TKI Auswahl



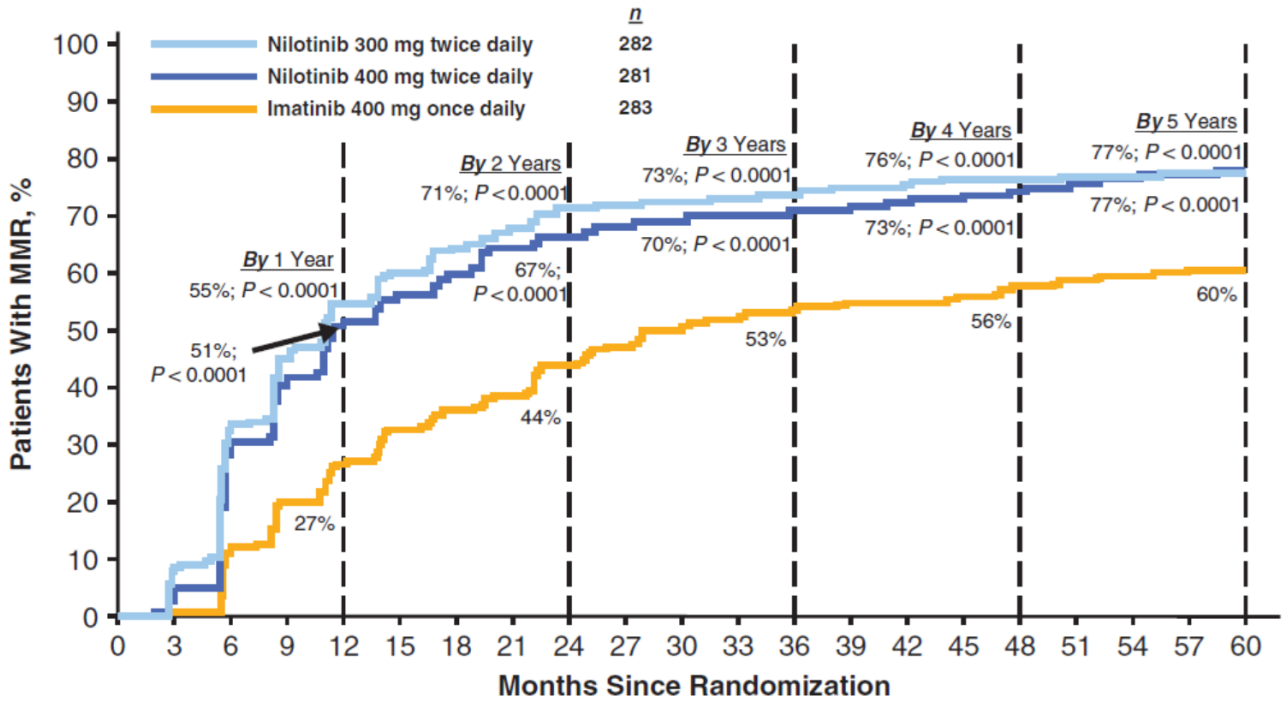
Überlegenheit der 2. Gen Tyrosinkinaseinhibitoren

DASISION



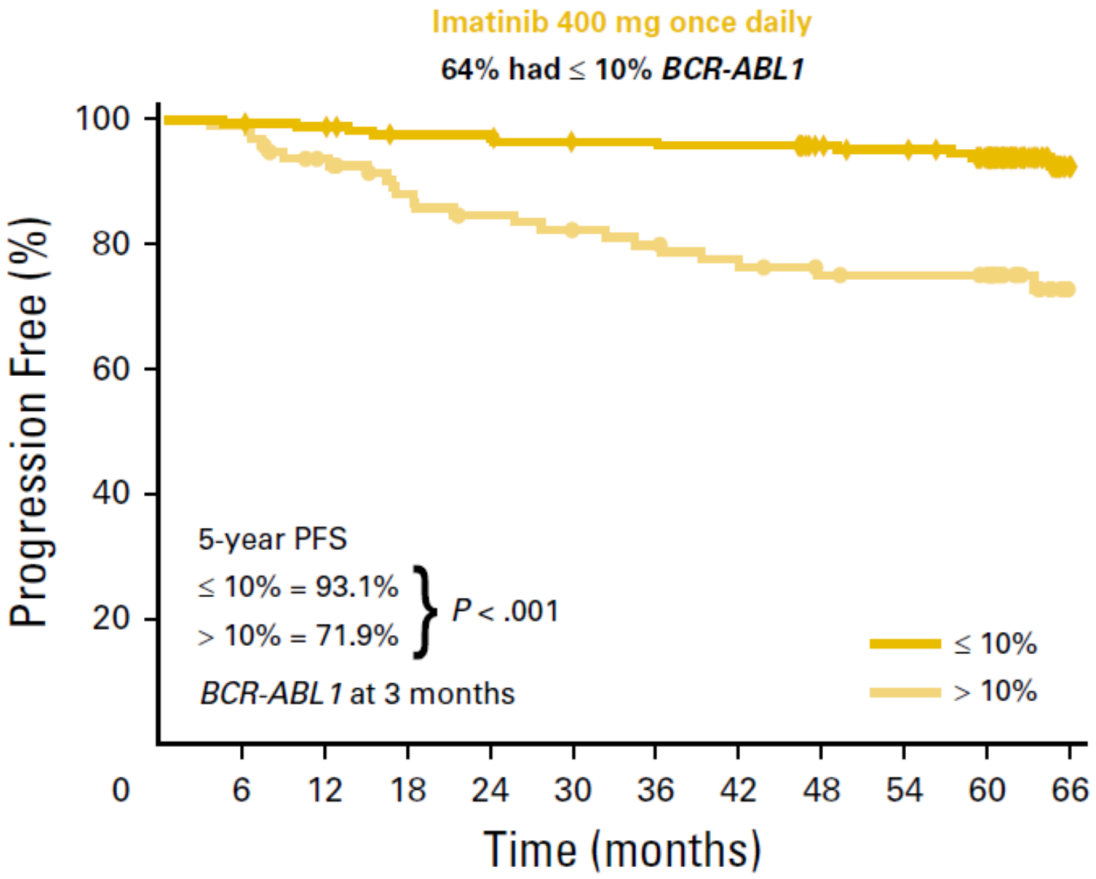
J Cortes et al.: JCO 2016

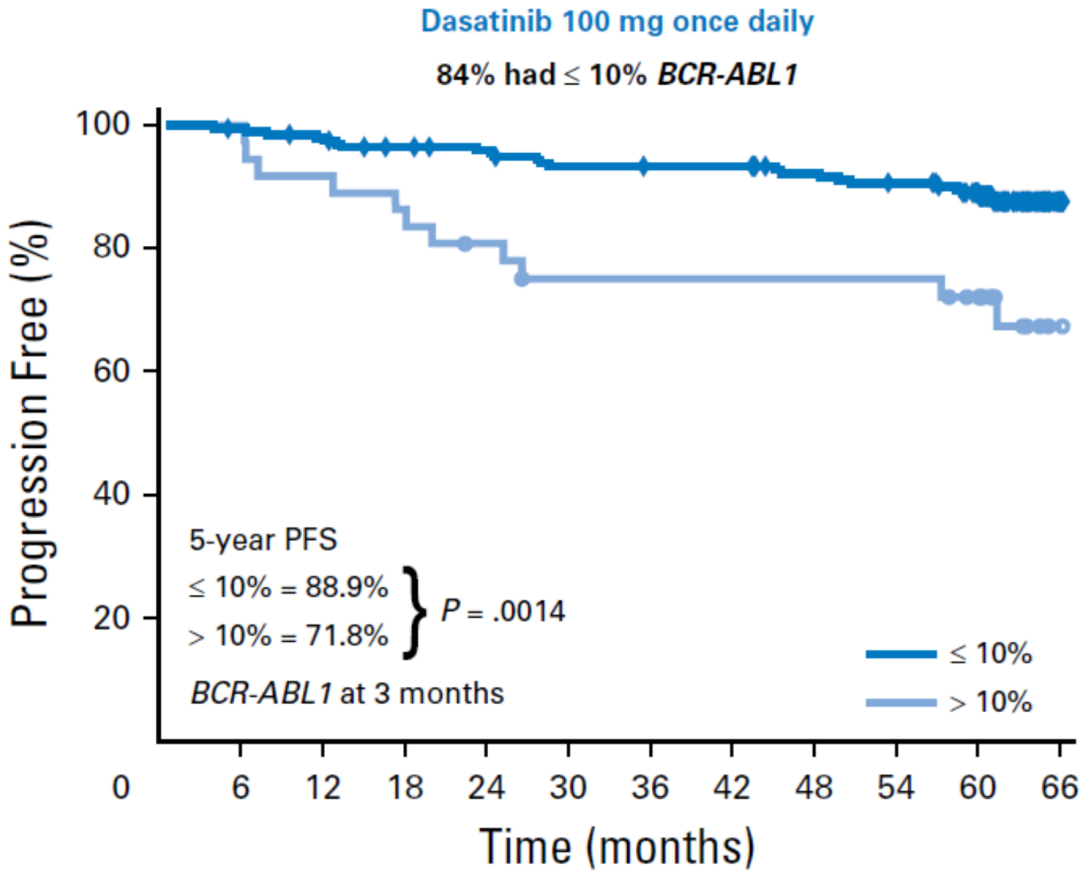
ENESTnd



A Hochhaus et al.: Leukemia 2016

Signifikanz der MRD-Kinetik zum Monat 3 (und 6)

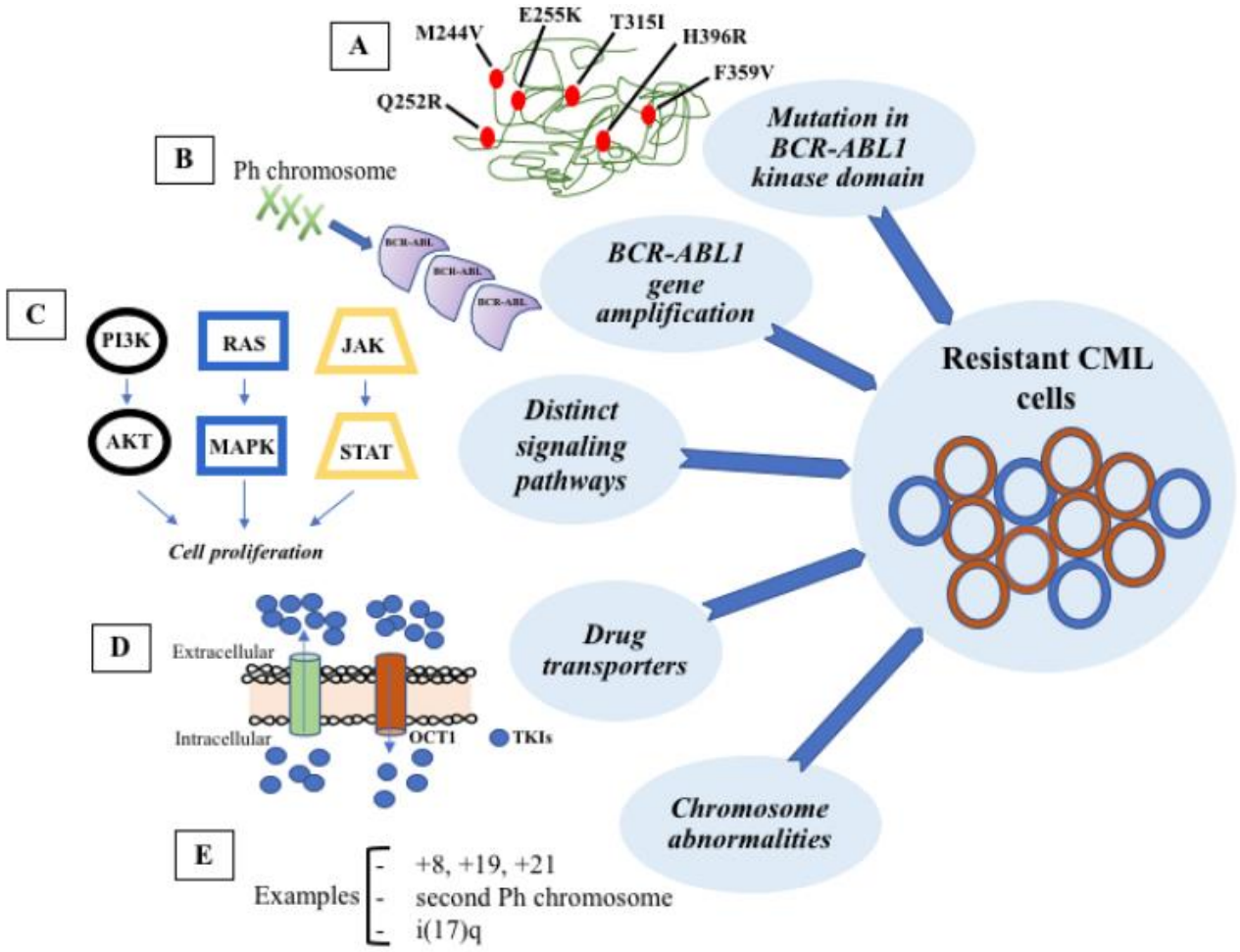


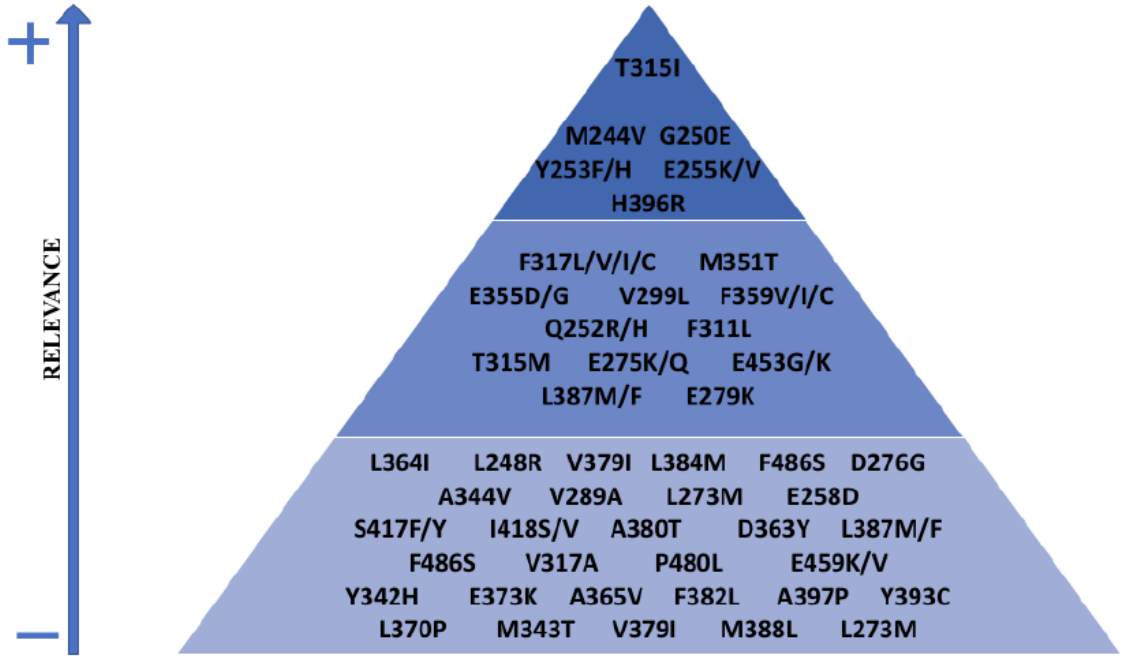


DASISION

J Cortes et al.: JCO 2016

Resistenzmechanismen





G P Amarante-Mendes et al.: Pharmaceutics 2022

Punktmutationen und IC50

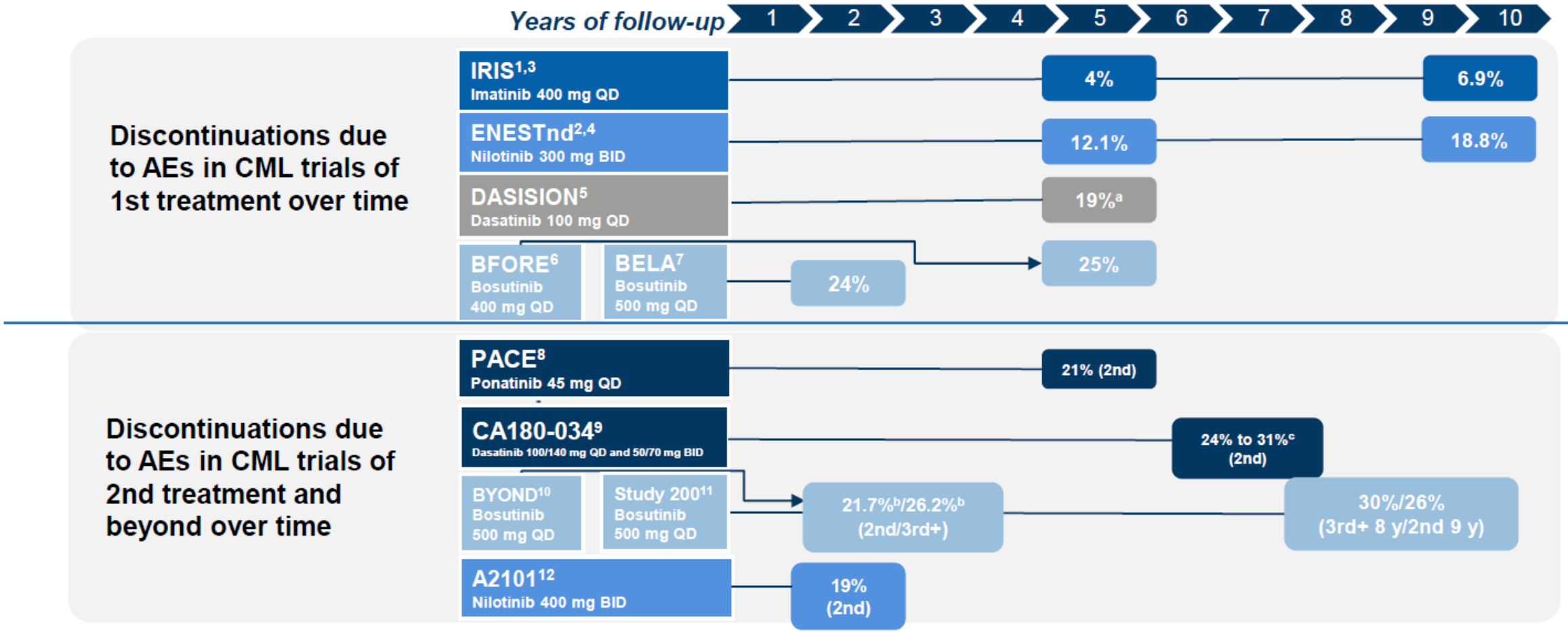
Location of Mutation	Mutation	IC_{50}-fold increase (WT = 1)				
		Imatinib	Bosutinib	Dasatinib	Nilotinib	Ponatinib
	Parental	10.8	38.3	568.3	38.4	570.0
	WT	1	1	1	1	1
P-loop	M244V	0.9	0.9	2.0	1.2	3.2
	L248R	14.6	22.9	12.5	30.2	6.2
	L248V	3.5	3.5	5.1	2.8	3.4
	G250E	6.9	4.3	4.4	4.6	6.0
	Q252H	1.4	0.8	3.1	2.6	6.1
	Y253F	3.6	1.0	1.6	3.2	3.7
	Y253H	8.7	0.6	2.6	36.8	2.6
	E255K	6.0	9.5	5.6	6.7	8.4
	E255V	17.0	5.5	3.4	10.3	12.9
C-helix	D276G	2.2	0.6	1.4	2.0	2.1
	E279K	3.6	1.0	1.6	2.0	3.0
	E292L	0.7	1.1	1.3	1.8	2.0
ATP binding region	V299L	1.5	26.1	8.7	1.3	0.6
	T315A	1.7	6.0	58.9	2.7	0.4
	T315I	17.5	45.4	75.0	39.4	3.0
	T315V	12.2	29.3	738.8	57.0	2.1
	F317L	2.6	2.4	4.5	2.2	0.7
	F317R	2.3	33.5	114.8	2.3	4.9
	F317V	0.4	11.5	21.3	0.5	2.3
SH2-contact	M343T	1.2	1.1	0.9	0.8	0.9
	M351T	1.8	0.7	0.9	0.4	1.2
Substrate binding region	F359I	6.0	2.9	3.0	16.3	2.9
	F359V	2.9	0.9	1.5	5.2	4.4
A-loop	L384M	1.3	0.5	2.2	2.3	2.2
	H396P	2.4	0.4	1.1	2.4	1.4
	H396R	3.9	0.8	1.6	3.1	5.9
C-terminal lobe	F486S	8.1	2.3	3.0	1.9	2.1
	L248R 1 F359I	11.7	39.3	13.7	96.2	17.7

Sensitive	≤2
Moderately resistant	2.1–10
Highly resistant	>10

S Redaelli et al.: A J Hematol 2012

Früher Einsatz von 2nd Gen TKI in der CML Behandlung !

Rate und Zeitpunkt von Therapieabbruch: Erst- und Zweitlinientherapie



1. Hochhaus A, et al. *N Engl J Med*. 2017;376: 917-927. 2. Kantarjian HM, et al. *Leukemia*. 2021;35:440-453. 3. Druker BJ, et al. *N Engl J Med*. 2006;355:2408-2417. 4. Hochhaus A, et al. *Leukemia*. 2016;30:1044-1054. 5. Cortes JE, et al. *J Clin Oncol*. 2016;34:2333-2340. 6. Brümmendorf TH, et al. *Blood*. 2020;136(suppl 1). Abstract 46. 7. Brümmendorf TH, et al. *Br J Haematol*. 2015;168:69-81. 8. Cortes JE, et al. *Blood*. 2018;132:393-404. 9. Shah NP, et al. *Am J Hematol*. 2016;91:861-874. 10. Hochhaus A, et al. *Leukemia*. 2020;34:2125-2137. 11. Cortes JE, et al. Presented at: EHA25 Virtual; June 11-21, 2020. Abstract EP766. 12. Kantarjian HM, et al. *Blood*. 2011;117(4):1141-1145.

TKI: Charakteristische Toxizitäten I

	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib	Asciminib
Hematological						
Neutropenia	++	++	+	+	++	+
Thrombocytopenia	+	++	+	++	++	++
Anemia	+	+	+	+	++	+
Nonhematological						
Edema	+++	–	–	+	–	+
Nausea	++	+	+	+++	+	+
Vomiting	++	+	+	++	+	+
Muscle spasms	+++	–	–	–	–	–
Rash	+	–	+++	+	+++	–
Pleural effusion	–	+++	–	+	–	–
Headache	–	–	+	+	+++	+
Diarrhea	+	+	–	+++	+	–
Fatigue	+	+	+	+	++	+
Liver dysfunction	+	++	+++	+++	+	–
Arterial occlusive events	-	+	++	-	+++	?

K Yoshifuji and K Sasaki: Front in Oncol 2022

TKI: Charakteristische Toxizitäten II

Adverse event profile influencing 2 Gen TKI selection for management of CML	
Dasatinib	Hematologig toxicity, Pleural/pericardial effusion PAH
Nilotinib	AOE Hyperlipidemia Hyperglycemia/DM Pancreatitis
Bosutinib	GI toxicity Hepatotoxicity Nephrotoxicity
Ponatinib	AOE Hypertension Pancreatitis

Mofified from: JM Stempel et al.: Leuk & Lymph, 2024

TKI: Charakteristische Toxizitäten II

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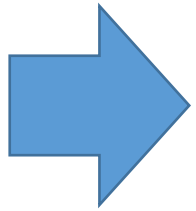
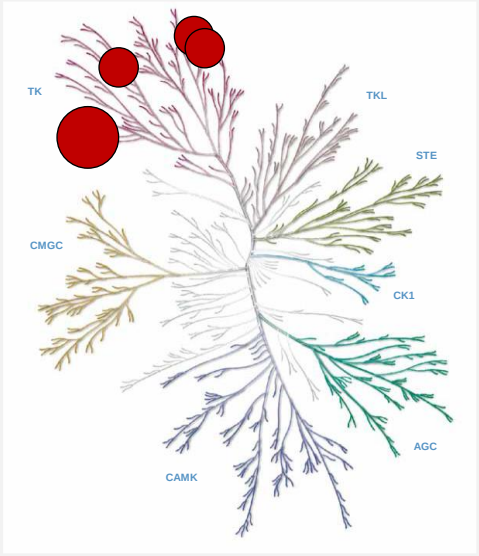


Therapie - umstellung

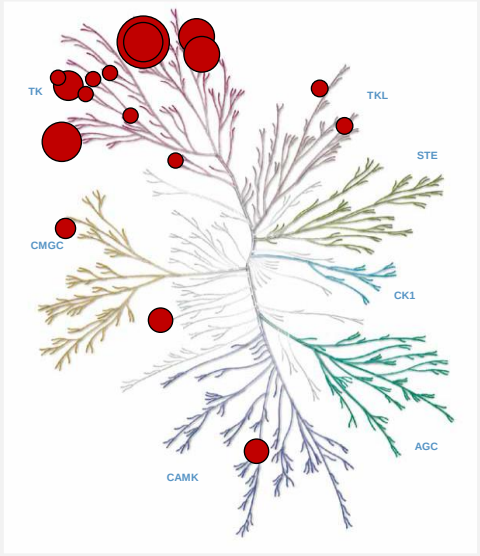
Mofified from: JM Stempel et al.: Leuk & Lymph, 2024

Selektivität zugelassener TKI

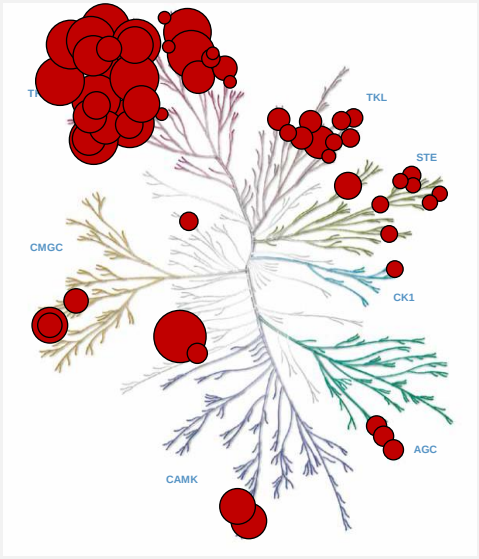
Nilotinib[1]



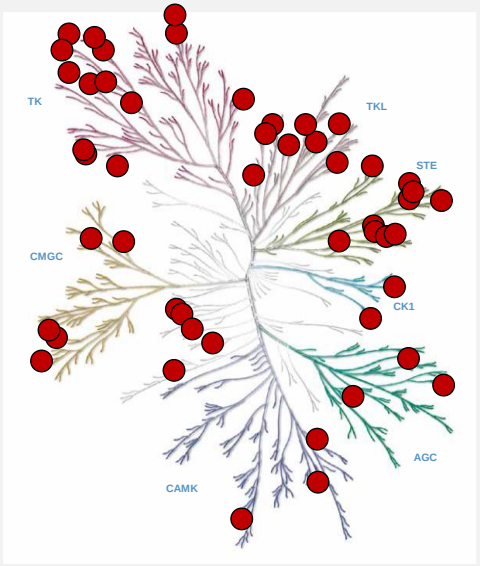
Imatinib[1,2]



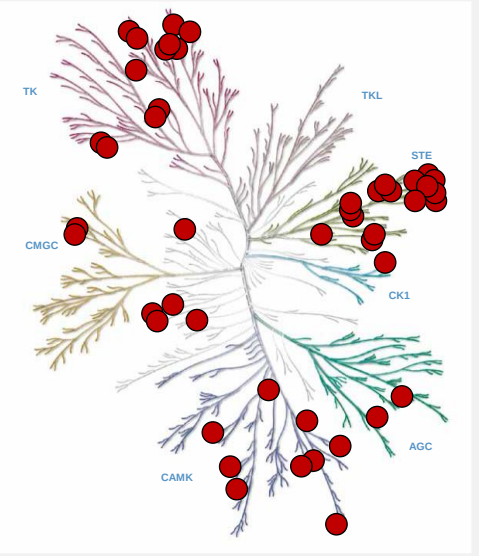
Dasatinib[1,2]



Ponatinib[3]



Bosutinib[4,a]



● *Indicates kinases bound by ATP-competitive TKIs.*[1-7]

AGC, protein kinase families A, G, and C; ATP, adenosine triphosphate; CAMK, calmodulin-dependent protein kinase; CK1, casein kinase 1; CMGC, cyclin-dependent kinase, mitogen-activated protein kinase, glycogen synthase kinase, and CDC-like kinase; CML, chronic myeloid leukemia; STE, sulfotransferase; TK, tyrosine kinase; TKI, tyrosine kinase inhibitor; TKL, tyrosine kinase like.

1. Steegmann JL, et al. *Leuk Lymphoma*. 2012;53:2351-2361. 2. Karaman MW, et al. *Nat Biotechnol*. 2008;26:127-132. 3. Lang JD, et al. *Clin Cancer Res*. 2018;24:1932-1943. 4. Remsing Rix LL, et al. *Leukemia*. 2009;23:447-485. 5. Fabian MA, et al. *Nat Biotechnol*. 2005;23:329-336. 6. Deininger MW, Manley P. *Leuk Res*. 2012;36:253-261. 7. Giri AK, et al. *Cell Biol Toxicol*. 2019;35:485-487.

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Tyrosine kinase inhibitor targets

TKI	Year of approval	Tyrosine kinase targets
Imatinib	2001	ABL1/2, PDGF-α/β, FLT3, c-KIT
Dasatinib	2006	ABL1, PDGF-α/β, c-KIT, DDR1/2, FGR2, SRC family
Nilotinib	2007	ABL1, PDGF-α/β, c-KIT, DDR
Bosutinib	2014	ABL1, PDGF-α/β, FGFR1-3, FLT1, 3, 4, CAMK2G, EPH, KDR, STE20, TEC, SRC
Ponatinib	2012	ABL1, PDGF-α/β, c-KIT, FGFR1-4, FLT1, 3, 4, KDR, STE20, TEC, SRC, TIE2, VEGF1-3

A Iurlo et al.: Curr Treat Opt Oncol, 2023

Tyrosine kinase inhibitor targets

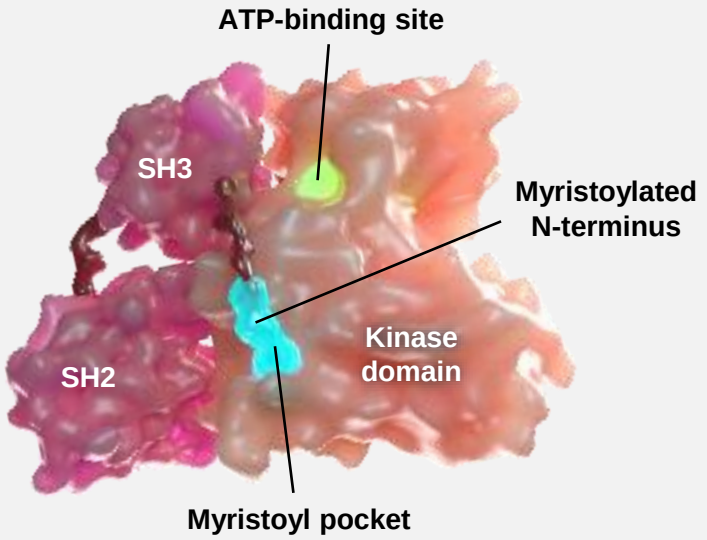
Target	Physiological function	Significance in AOE
ABL1/2	Cell differentiation, division, adhesion	Unclear
PDGF-α/β	Cellular growth, differentiation	Unclear
C-KIT	Semcell factor, pigmentation	Unclear
FGFR1-3	Cell activation (eosinophils)	Unclear
FLT1, 3, 4	Proliferation and differentiation, stimulates dendritic cells	Unclear
KDR	(VEGFR-2) Microvessel density	Unclear
STE20	Multiple functions	Unclear
TEC	T helper cell processes	Unclear
SRC	Adhesion, transcription	Unclear
TIE2	Angiopoesis	Unclear
VEGF1-3	Angiogenesis	Unclear

Takizawa Y et al.: 2004; Lei H et al.: 2009; Y Yarden et al.: 1987; N Itoh et al.: 1990; C Hannum et al.: 1994

Asciminib ist der erste zugelassene BCR::ABL1 Inhibitor der STAMP Klasse (Specifically Targeting the ABL Myristoyl Pocket)

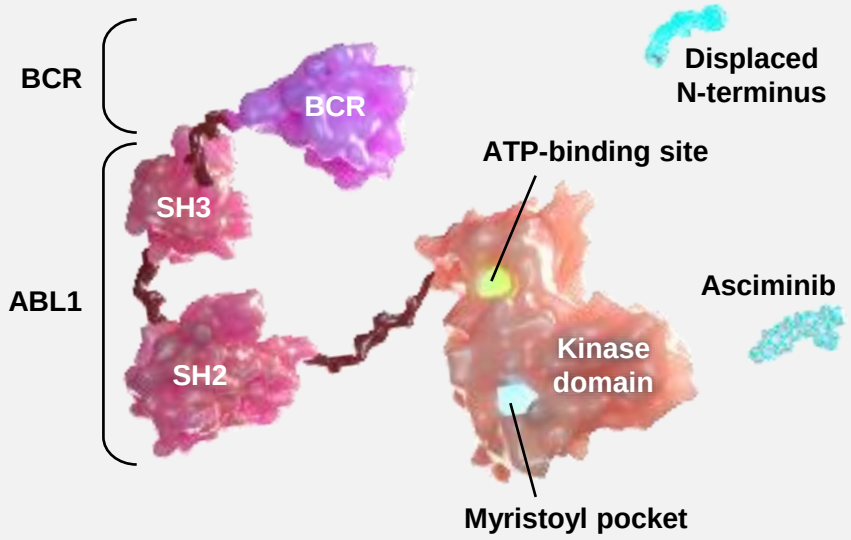
Normal conditions

Inactive ABL1
with N-terminus binding



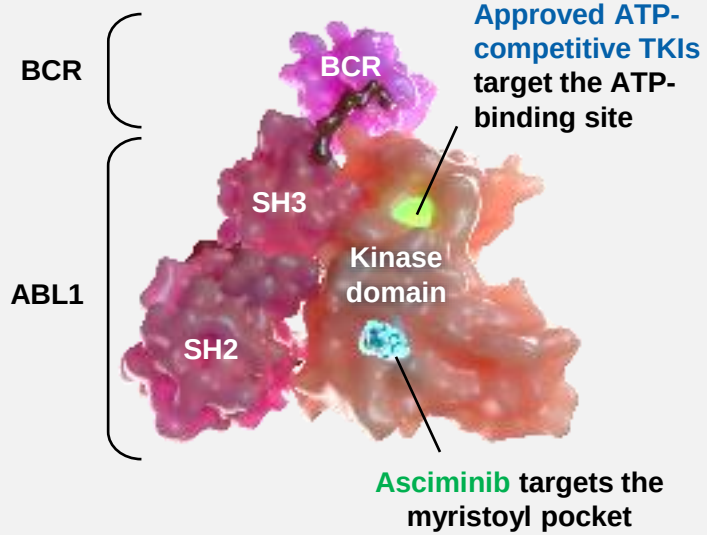
In CML

Constitutively active BCR::ABL1
with loss of N-terminus



In CML with asciminib

Inactive BCR::ABL1
with asciminib binding

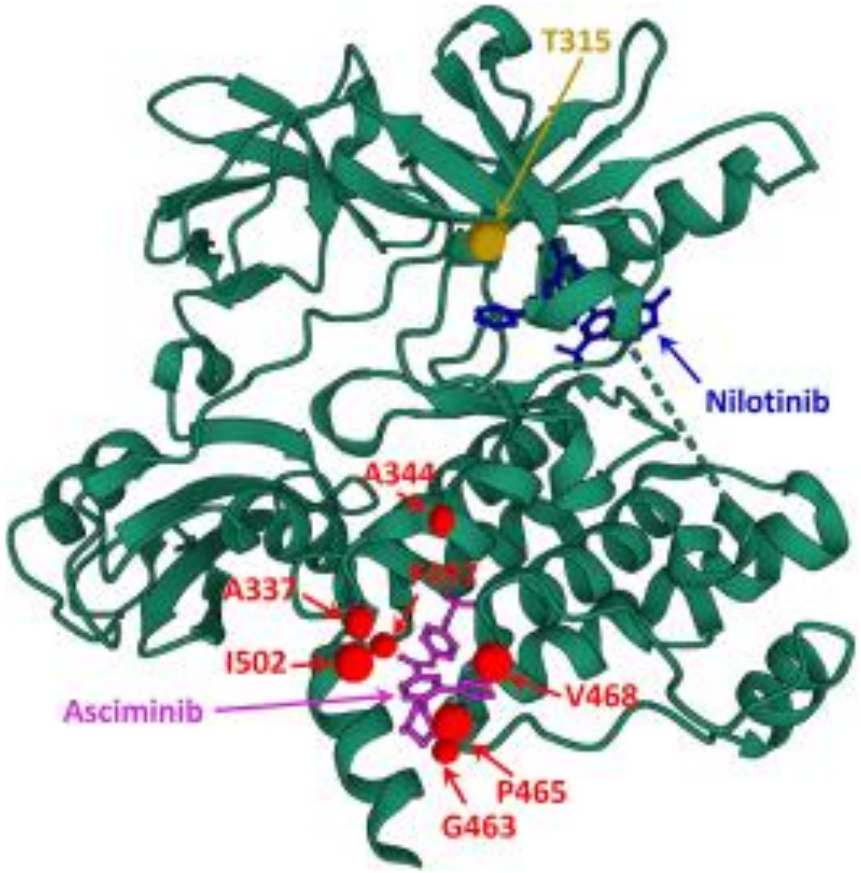


Mauro MJ, et al. Presented at the 63rdAmerican Society of Hematology Annual Meeting. Abstract 310. Reprinted with permission by the author.

ABL1, Abelson tyrosine kinase 1; ATP, adenosine triphosphate; BCR, breakpoint cluster region; CML, chronic myeloid leukemia; MOA, mechanism of action; SH, Src homology; TKI, tyrosine kinase inhibitor.

1. Colicelli J. *Sci Signal*. 2010;3:re6. 2. Hughes TP, et al. *N Engl J Med.* 2019;381:2315-2326. 3. Hantschel O. *Genes Cancer*. 2012;3:436-446. 4. Manley PW, et al. *Leuk Res.* 2020;98:106458. 5. Mauro MJ, et al. Oral presentation at: 63rd ASH Annual Meeting & Exposition; December 11–14, 2021; San Diego, CA, and virtual. Presentation 310.

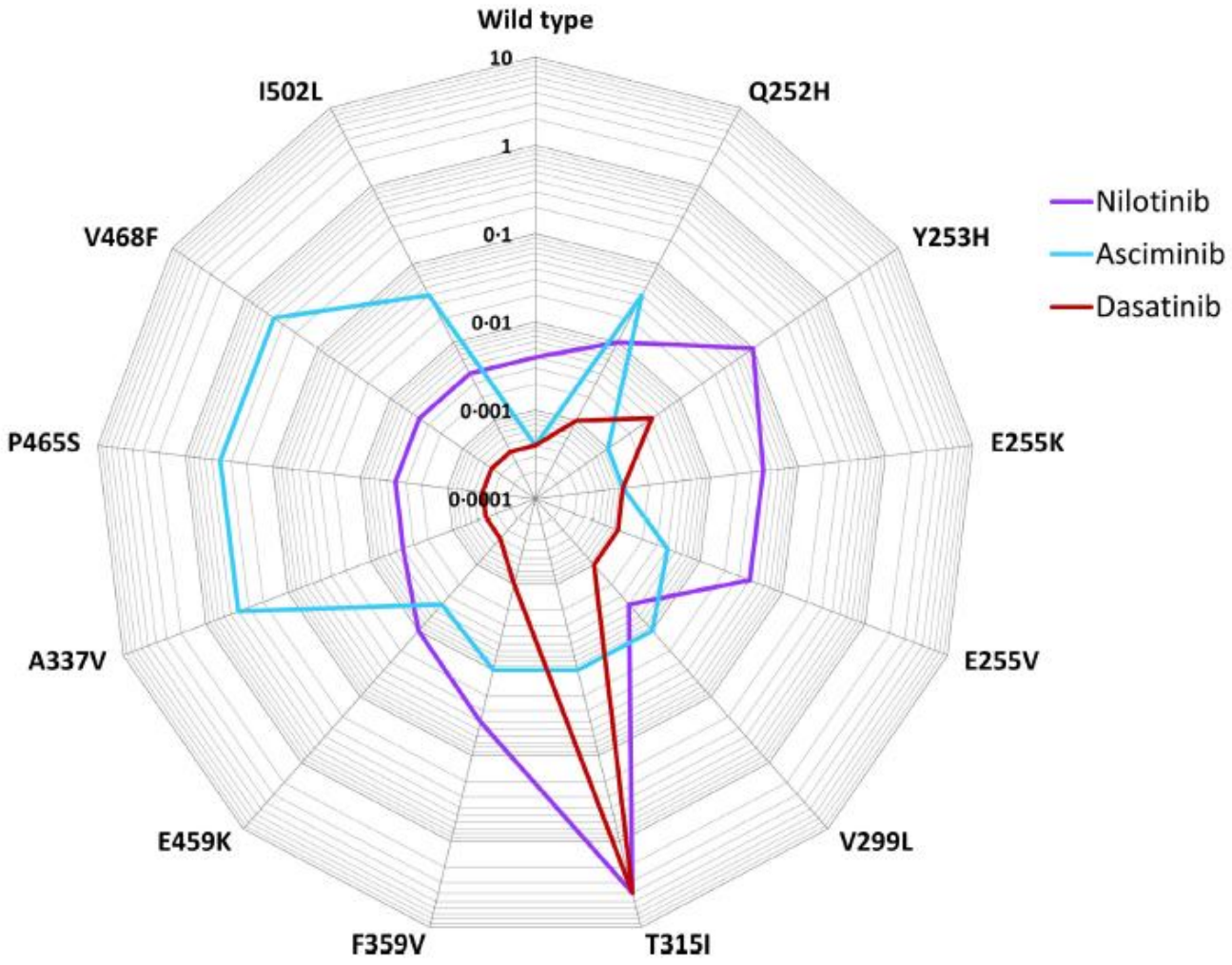
Asciminib



Mutations	
In vitro	Emergence on clinical trials
A337V	G109D
A344P	Y115N
P465S	A337T
F497L	G463D
-	P465S
-	V468F
-	I512L

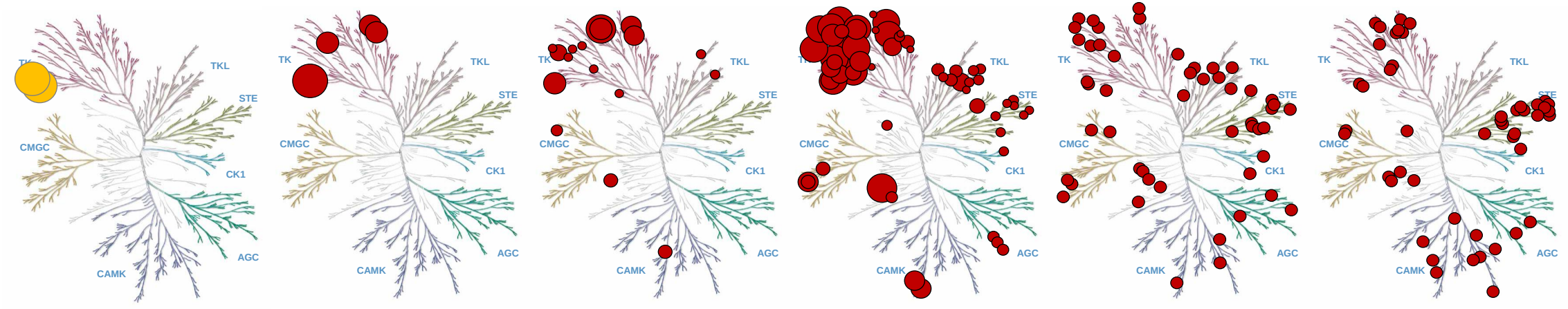
N Shanmuganathan & T Hughes: BJHaem, 2022

Asciminib: Selektivität im Vergleich zu relevanten Mutationen bei Versagen unter Dasatinib oder Nilotinib



N Shanmuganathan & T Hughes: BJHaem, 2022

Die Spezifität von Asciminib führt zu weniger Off-Target Effekten



Asciminib[1] Nilotinib[2] Imatinib[2,3] Dasatinib[2,3] Ponatinib[4] Bosutinib[5,a]

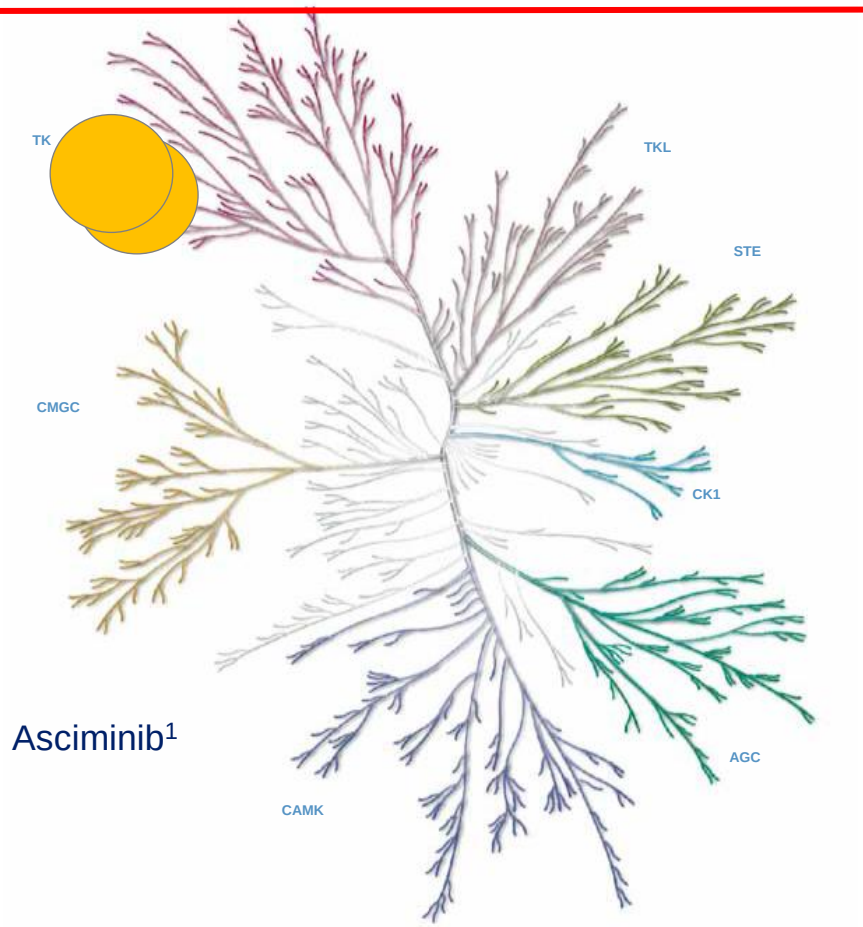
STAMP

durch ATP-kompetitive TKI gebundene Kinasen

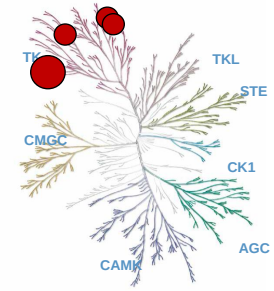
[a] Bosutinib hemmt weitere Kinasen, die im Dendrogramm nicht dargestellt sind.

1. Hantschel O. et al. Vortrag V820 bei der Jahrestagung der DGHO, 7.–10. Oktober 2022, Wien. **2.** Steegmann JL. et al. Leuk Lymphoma. 53(12):2351–2361 (2012). **3.** Karaman MW. et al. Nat Biotechnol. 26(1):127–132 (2008). **4.** Lang JD. et al. Clin Cancer Res. 24(8):1932–1943 (2018). **5.** Remsing Rix LL. et al. Leukemia. 23(3):447–485 (2009).

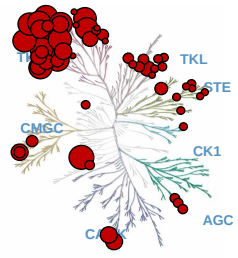
Die Spezifität von Asciminib führt zu weniger Off-Target Effekten



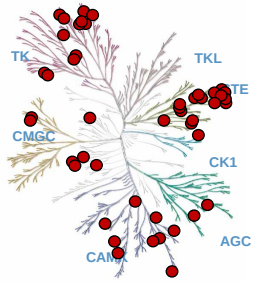
Asciminib[1]



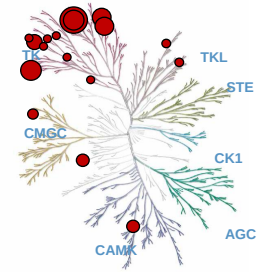
Nilotinib[2]



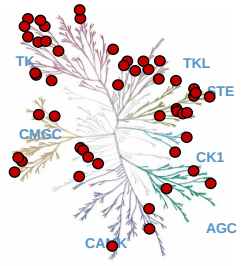
Dasatinib[2,3]



Bosutinib[5,a]



Imatinib[2,3]



Ponatinib[4]

STAMP

durch ATP-kompetitive TKI gebundene Kinasen

[a] Bosutinib hemmt weitere Kinasen, die im Dendrogramm nicht dargestellt sind.

1. Hantschel O. et al. Vortrag V820 bei der Jahrestagung der DGHO, 7.–10. Oktober 2022, Wien. **2.** Steegmann JL. et al. Leuk Lymphoma. 53(12):2351–2361 (2012). **3.** Karaman MW. et al. Nat Biotechnol. 26(1):127–132 (2008). **4.** Lang JD. et al. Clin Cancer Res. 24(8):1932–1943 (2018). **5.** Remsing Rix LL. et al. Leukemia. 23(3):447–485 (2009).

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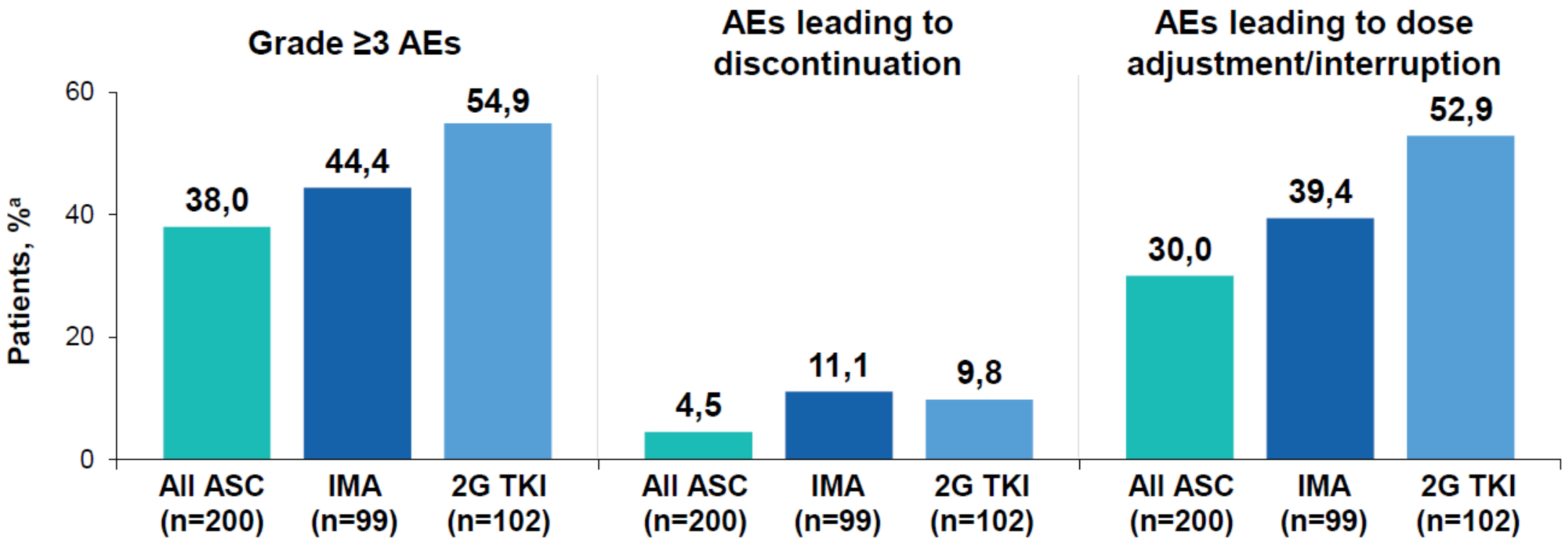
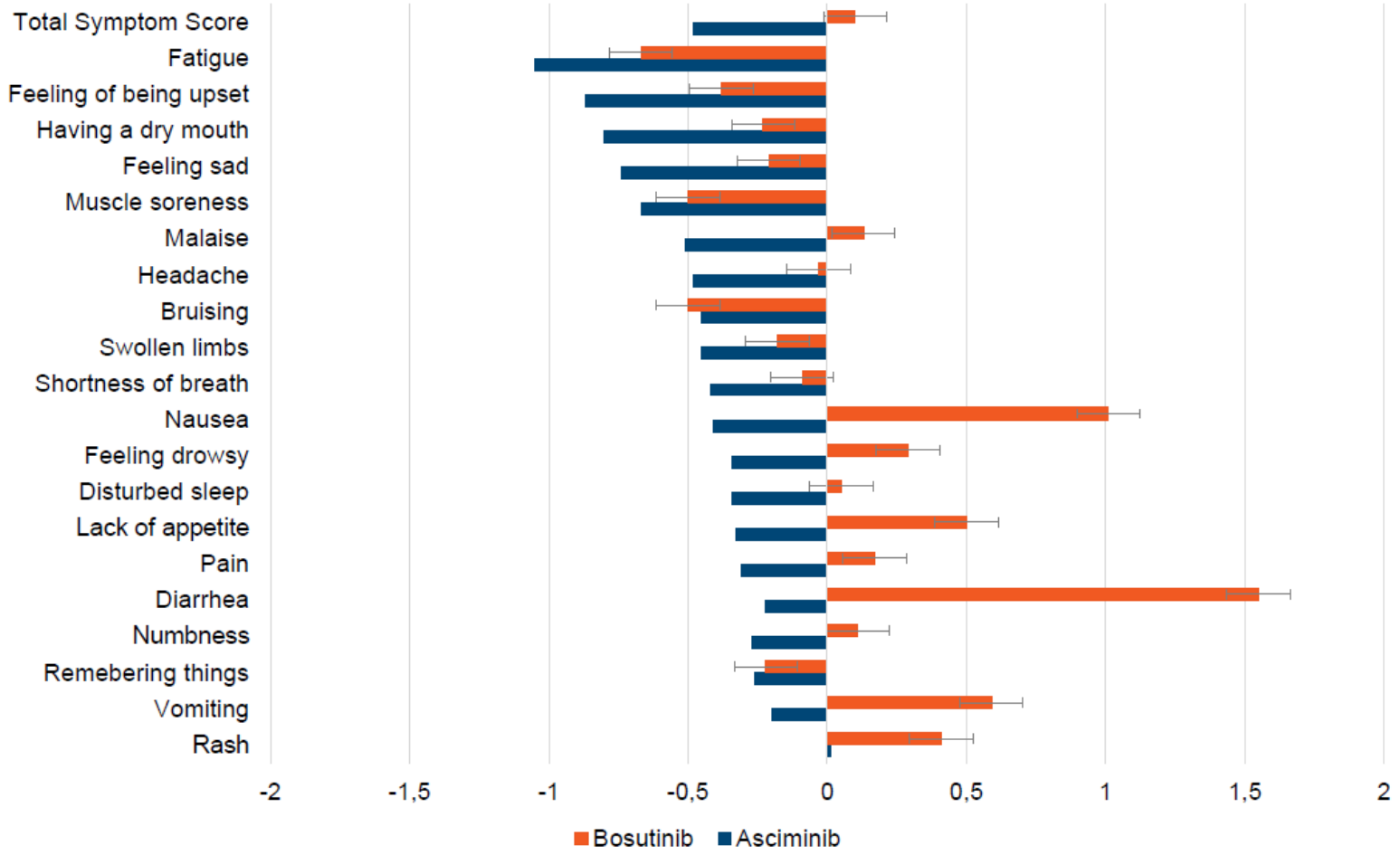
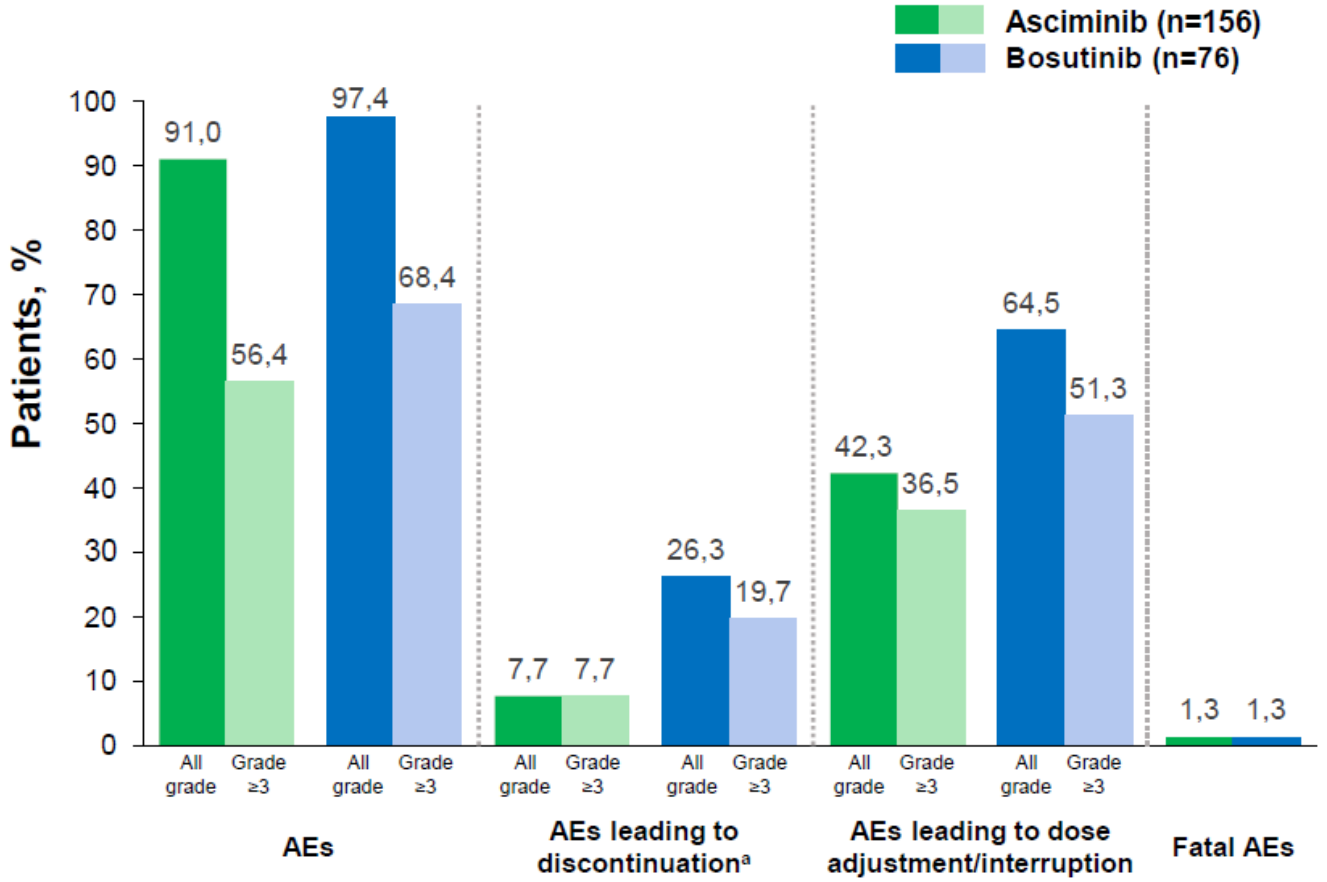
ASC4FIRST: Adverse Event Profile



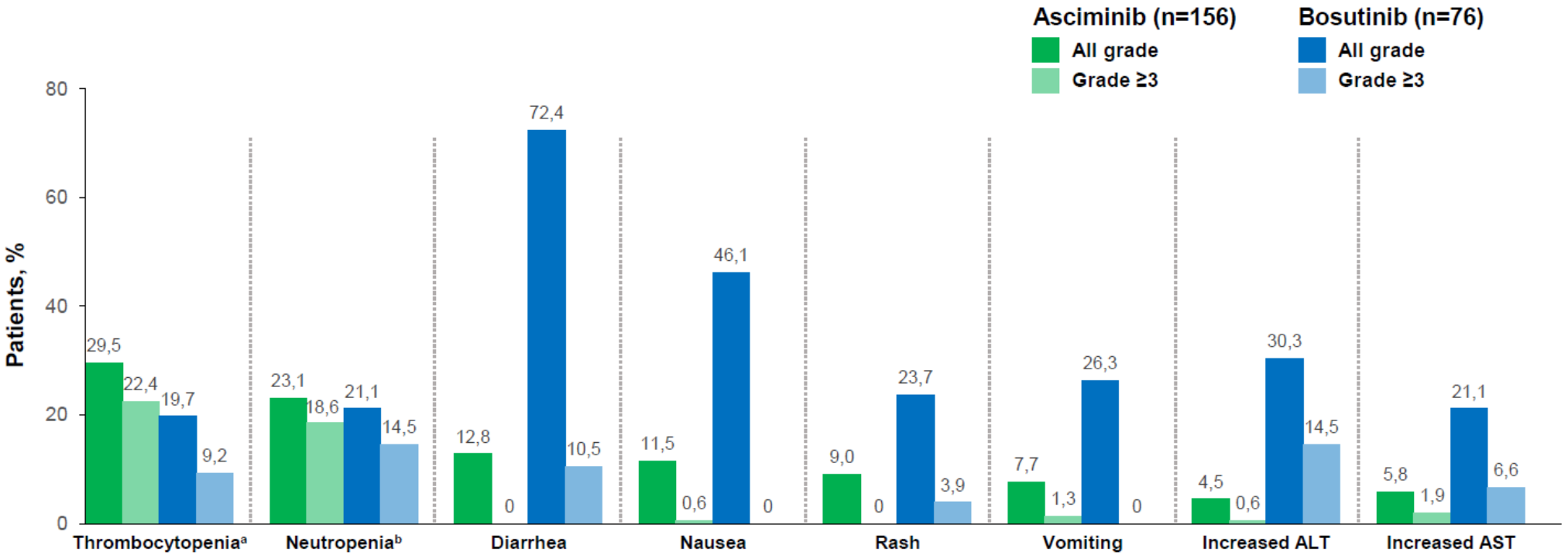
Ascembl: QoL Assessment Bosutinib versus Asciminib



Ascembl: Frequency of AEs



Ascembl: Toxicity profile Bosutinib versus Asciminib



Zusammenfassung

- Früher Einsatz hochspezifischer TKI
- TKI Wahl anhand individualisiertem Tolerabilitätsprofil
- Asciminib ist aktuell der am besten verträgliche TKI

Zusammenfassung

Ochi Y. Genetic landscape of chronic myeloid leukemia. Int J Hematol. 2023; 117(1): 30–36

Wirksamkeit und Evolution unter verschiedenen Kinase-Inhibitoren

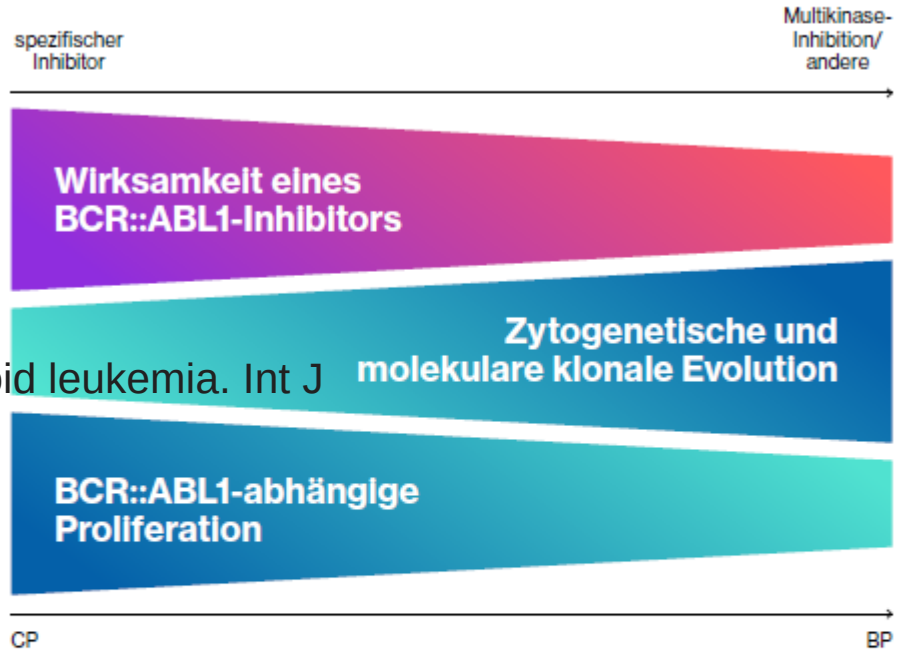
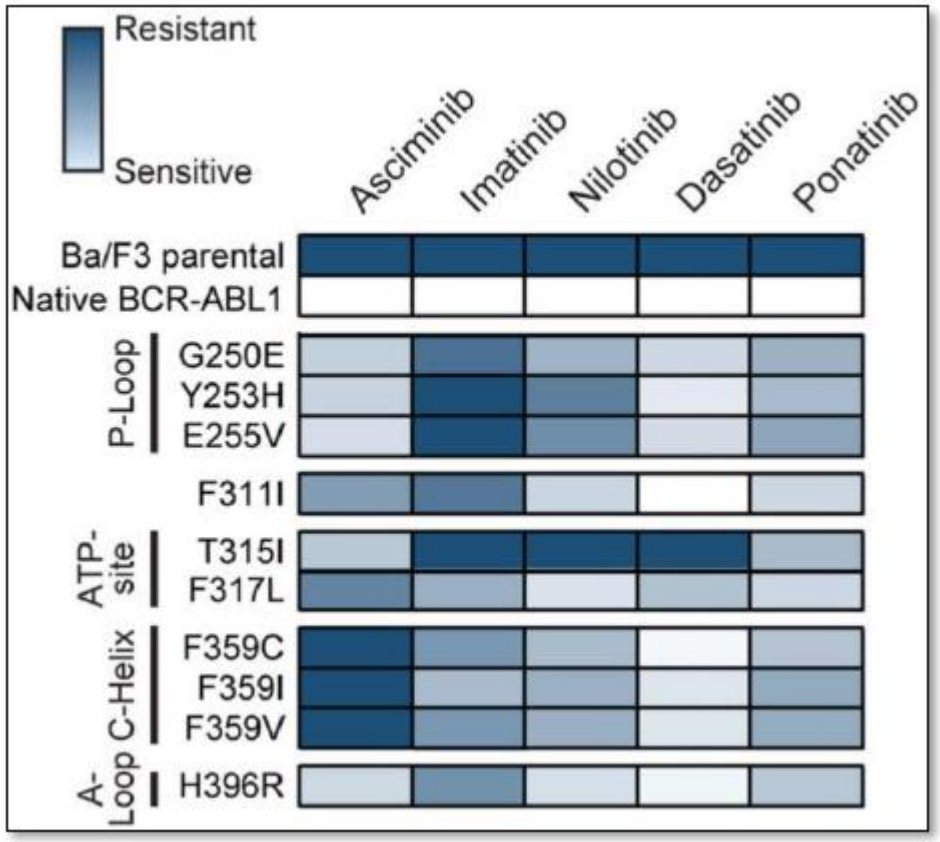


Abb. 4: Wirksamkeit und klonale Evolution (mod. nach 32).

Im natürlichen Verlauf der Erkrankung sowie therapieabhängig können Mutationen im *BCR::ABL1*-Gen auftreten, die zur Therapieresistenz beitragen können.[32] Darüber hinaus können weitere, auch somatische, Mutationen einen Einfluss auf den Erkrankungsverlauf haben und die leukämische Transformation fördern.[32] Der möglichst frühe Einsatz eines spezifischen BCR::ABL1-Inhibitors wird daher als vielversprechend angesehen.[32]

Zusammenfassung



Eide et al. Cancer Cell 2019

2nd generation tox

Table 3. Second-generation TKI toxicity.

TKI treatment	Adverse events	Incidence (%)	Number of patients (total number of enrolled patients)	Clinical trial
Nilotinib (300 mg/ twice daily)	Medically severe fluid retention Cardiovascular events Hypertension Significant bleeding Second malignancies Hepatotoxicity Pancreatitis Symptomatic QT prolongation (syncope or convulsion)	11.1 16.5 10.4 3.6 4.7 1.8 1.8 1.8	282 (846)	ENESTnd[5,10]
Nilotinib (400 mg/ twice daily)	Medically severe fluid retention Cardiovascular events Hypertension Significant bleeding Second malignancies Hepatotoxicity Pancreatitis Symptomatic QT prolongation (syncope or convulsion)	14.4 23.5 8.3 5.4 3.2 5.4 2.9 2.5	283 (846)	ENESTnd[5,10]
Dasatinib (100 mg/ daily)	Pleural effusions Neutropenia Thrombocytopenia Cardiovascular events Anemia Pulmonary hypertension	37 29 22 15 13 5	259 (519)	DASISION[6]
Bosutinib (400 mg/ daily)	Diarrhea Nausea Thrombocytopenia Increased ALT Increased AST Hematological Musculoskeletal Infections	70.1 35.1 35.1 30.6 22.8 45.5 29.5 44.4	268 (536)	BFORE[7]

ALT, alanyl aminotransferase; AST, aspartate aminotrasferase; TKI, tyrosine kinase inhibitor.

so et al.: Ther Adv Hematol, 2023

2nd Generation TKI Erstlinie

Second-generation TKI (dose)	Number of patients treated with second-generation TKI (total number of enrolled patients)	Result obtained with IM	Improvement obtained by second-generation TKI	Clinical trial
Nilotinib (300 mg/twice daily)	282 (846)	31% 5-year DMR	54% 5-year DMR	ENESTnd[5]
Nilotinib (400 mg/twice daily)	283 (846)	31% 5-year DMR	52% 5-year DMR	ENESTnd[5]
Dasatinib (100 mg/daily)	259 (519)	64% 3-month *BCR::ABL1* ⩽ 10% 64% 5-year MMR 33% 5-year MR4.5	84% 3-months *BCR::ABL1* ⩽ 10% 76% 5-year MMR 42% 5-year MR4.5	DASISION[6]
Bosutinib (400 mg/daily)	268 (536)	- 66.4% 12-month CCyR - 57.3% 3-month *BCR::ABL1* ⩽ 10% - 36.9% 12-month MMR	- 77.2% 12-month CCyR - 75.2% 3-month *BCR::ABL1* ⩽ 10% - 47.2% 12-month MMR	BFORE[7]

CCyR, complete cytogenetic response; DMR, deep molecular response; IM, imatinib; MMR, major molecular response; MR4.5, molecular response 4.5; TKI, tyrosine kinase inhibitors.

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ASC4FIRST: Subgroups

Subgroup	MMR ASC, %	MMR All IS-TKIs, %	Treatment difference (95% CI)
All patients	67.7	49.0	18.6 (9.2 to 28.1)
ELTS			
Low	72.1	57.6	14.5 (2.8 to 26.3)
Intermediate	64.3	36.8	27.4 (9.7 to 45.2)
High	52.2	31.8	20.4 (-7.9 to 48.6)
Sex			
Female	64.3	54.4	9.9 (-5.8 to 25.6)
Male	69.5	45.6	23.9 (12.1 to 35.6)
Age category			
18 to <65 years	64.5	48.4	16.1 (5.2 to 27.0)
65 to <75 years	75.0	55.9	19.1 (-2.8 to 41.0)
≥75 years	90.0	40.0	50.0 (19.0 to 81.0)