UNIVERSITÄTS KLINIKUM jena

Chronische myeloische Leukämie - Aktuelle Therapiestrategien

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DEUTSCHE CML.ALLIANZ

DEUTSCHE CML.STUDIENGRUPPE

Disclosure of conflicts of interest

1. **Employment or Leadership Position**
   Jena University Hospital

2. **Advisory Role or Expert Testimony**
   Novartis, TERNS, Ascentage

3. **Stock Ownership**
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4. **Patent, Copyright, Licensing**
   BCR::*ABL1* mutations

5. **Honoraria**
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6. **Financing of Scientific Research**
   Novartis, BMS, Pfizer, Incyte, Enliven

7. **Other Financial Relationships**
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8. **Immaterial Conflicts of Interest**

Myeloid proliferations and neoplasms

World Health Organization 5th edition

Myeloproliferative neoplasms

- Chronic myeloid leukaemia (IMMER BCR::ABL1 positiv)
- Chronic neutrophilic leukaemia
- Chronic eosinophilic leukaemia
- Polycythaemia vera
- Essential thrombocythaemia
- Primary myelofibrosis
- Juvenile myelomonocytic leukaemia
- Myeloproliferative neoplasm, NOS

~~Ph+ / BCR::ABL1+~~ CML

Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement

- Myeloid/lymphoid neoplasm with PDGFRA rearrangement
- Myeloid/lymphoid neoplasm with PDGFRB rearrangement
- Myeloid/lymphoid neoplasm with FGFR1 rearrangement
- Myeloid/lymphoid neoplasm with JAK2 rearrangement
- Myeloid/lymphoid neoplasm with FLT3 rearrangement
- Myeloid/lymphoid neoplasm with ETV6::ABL1 fusion
- Myeloid/lymphoid neoplasms with other tyrosine kinase gene fusions

Mastocytosis

- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell sarcoma

Khoury et al., Leukemia. 2022;36:1703-19

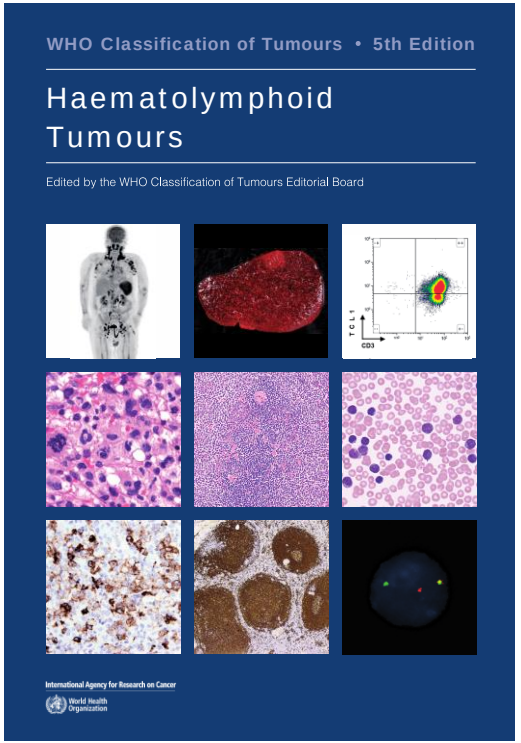
WHO Classification 2022
CML

2 phase disease

Diagnosis: CP (with clinical and biological risk factors)
BP (≥20% blasts)

On therapy: CP (Remission status according to ELN)
BP (≥20% blasts)

AP definition in TKI era less important.



Khoury et al., Leukemia. 2022;36:1703-19

CML AP outdated

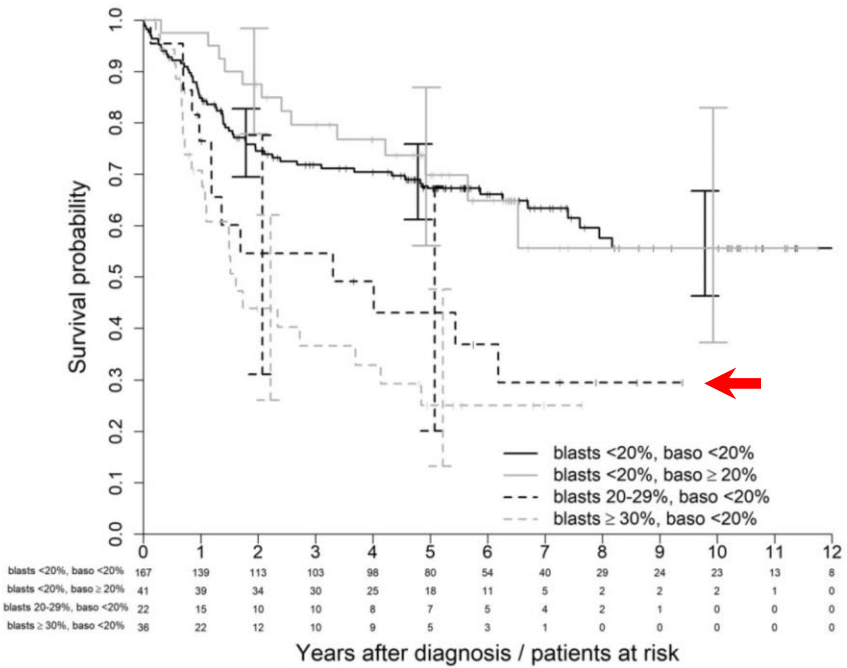
TABLE 1. Definitions of Accelerated- and Blastic-Phase Chronic Myeloid Lymphoma

	Modified MDACC Criteria*	WHO Criteria	IBMTR
Accelerated Phase	Blood or marrow blasts 15-29%	Blood or marrow blasts 10-19%	Hb $<$ 8 g/dL
	Blood or marrow blasts and promyelocytes $\geq$ 30%	Blood basophils $>$ 20%	WBC $>$ 100 $\times$ 10^9/L
	Blood basophils $>$ 20%	Plts $<$ 100 $\times$ 10^9/L or $>$1,000 $\times$ 10^9/L	Plts $<$ 100 $\times$ 10^9/L or $>$ 1,000 $\times$ 10^9/L
	Plts $<$ 100 $\times$ 10^9/L	Increasing spleen size and WBC	Splenomegaly unresponsive to busulfan and hydroxyurea
	CCA/Ph$^+$	CCA/Ph$^+$	Extramedullary disease
			CCA/Ph$^+$
			Blood or marrow blasts $>$ 10%
			Blood or marrow blasts plus promyelocytes $>$ 20%
			Blood basophils and eosinophils $>$ 20%
Blastic Phase	Blood or marrow blasts $\geq$ 30%	Blood or marrow blasts $>$ 20%	Blood or marrow blasts $\geq$ 30%
	Extramedullary blasts (apart from spleen)	Extramedullary blast proliferation	Extramedullary blasts (apart from spleen)
		Large foci or clusters of blasts on bone marrow biopsy	

Abbreviations: MDACC, The University of Texas MD Anderson Cancer Center; WHO, World Health Organization; IBMTR, International Bone Marrow Transplant Registry; CCA/Ph$^+$, clonal cytogenetic abnormalities in Ph$^+$ cells; Plts, platelets; WBC, white blood cells; Hb, hemoglobin.
*Commonly used in clinical trials.

Deininger ASCO Ed Book 2015

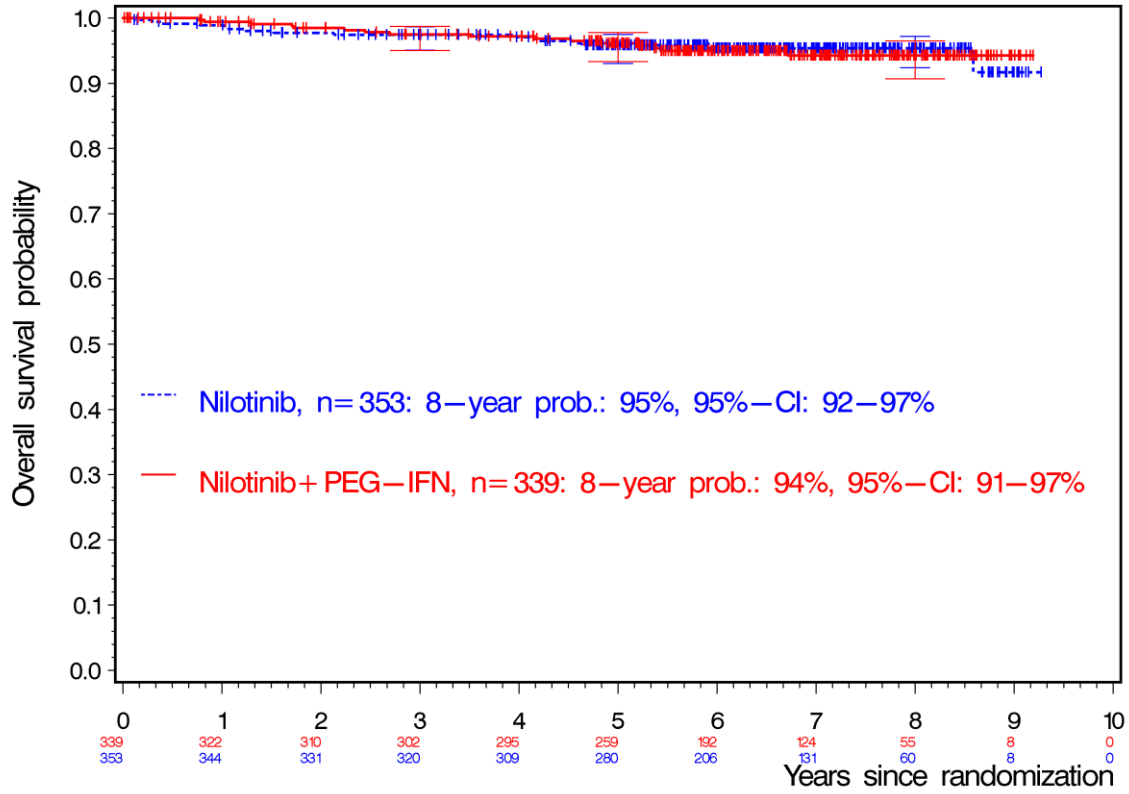
Evidenz für >20% Blasten als Definition der Blastenphase der CML



n=283 Patienten mit fortgeschrittener Erkrankung aus dem EUTOS-Register.

Lauseker et al. Am J Hematol. 2019;94:1236-43.

8 year overall survival 95% (TIGER)



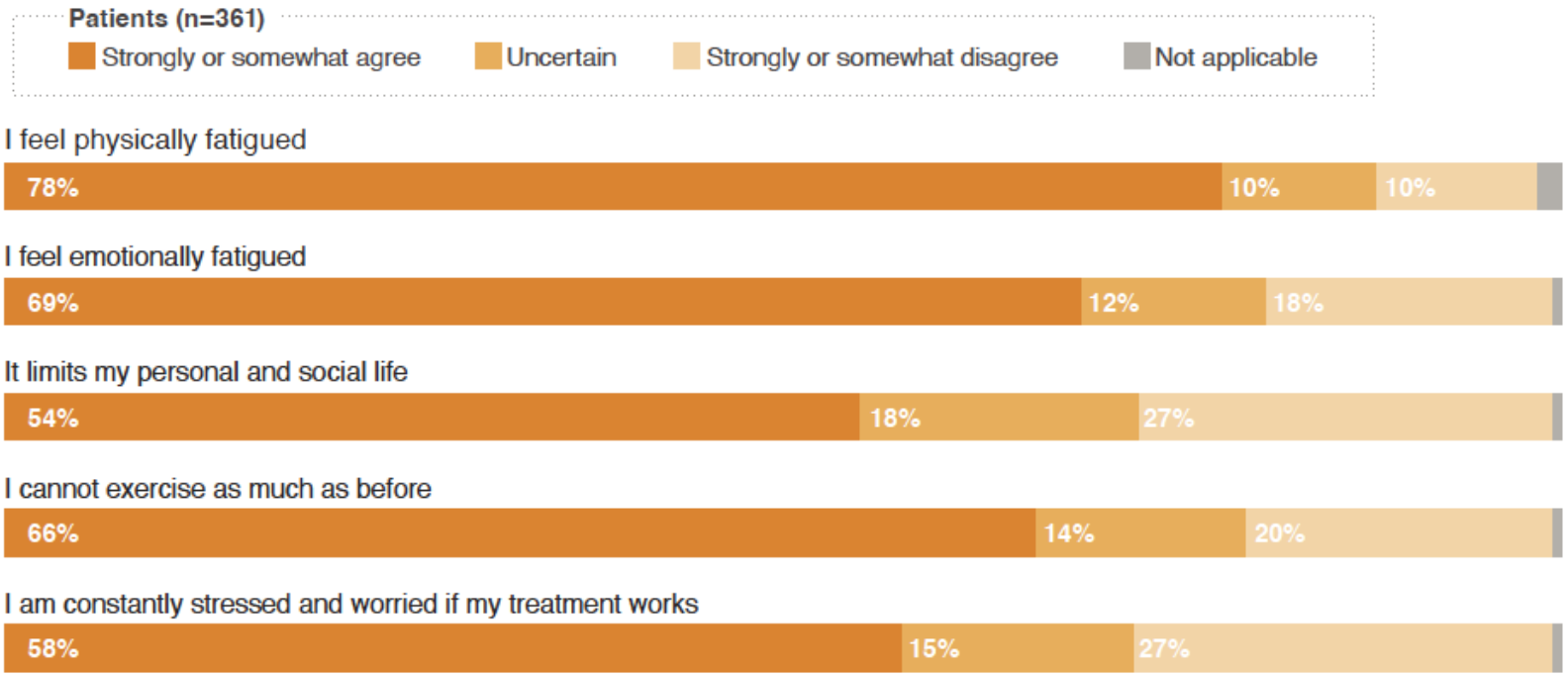
Chronic Myeloid Leukemia Survey on Unmet Needs (CML SUN):

P668

Balancing Tolerability and Efficacy Goals of Patients and Physicians Through Shared Treatment Decision-Making

Fabian Lang,[1] Zack Pemberton-Whiteley,[2] Joannie Clements,[3] Cristina Ruiz,[3] Delphine Rea,[4] Lisa Machado,[5] Naoto Takahashi,[6] Sung-Ho Moon,[7] Andrew Grigg,[8] Cornelia Borowczak,[9] Peter Schuld,[10] Pauline Frank,[10] Cristina Constantinescu,[11] Carla Boquimpani,[12,13] Jorge E. Cortes[14]
[1]Department of Hematology and Oncology, Goethe University Hospital, Frankfurt am Main, Germany; [2]Leukaemia Care, Worcester, UK; [3]CML Buster Foundation, Costa Mesa, CA, USA; [4]Hôpital Saint-Louis, Paris, France; [5]Canadian CML Network, Toronto, ON, Canada; [6]Akita University Graduate School of Medicine, Akita, Japan; [7]Korea Leukemia Patients Organization, Seoul, South Korea; [8]Austin Hospital, Melbourne, VIC, Australia; [9]LeukaNET, Hohenbrunn, Germany; [10]Novartis Pharma AG, Basel, Switzerland; [11]Ipsos, Basel, Switzerland; [12]Hemorio, Rio de Janeiro, Brazil; [13]Oncoclínicas, Rio de Janeiro, Brazil; [14]Georgia Cancer Center, Augusta University, Augusta, GA, USA

Patient Perceptions of How CML Treatment Affects Their Life

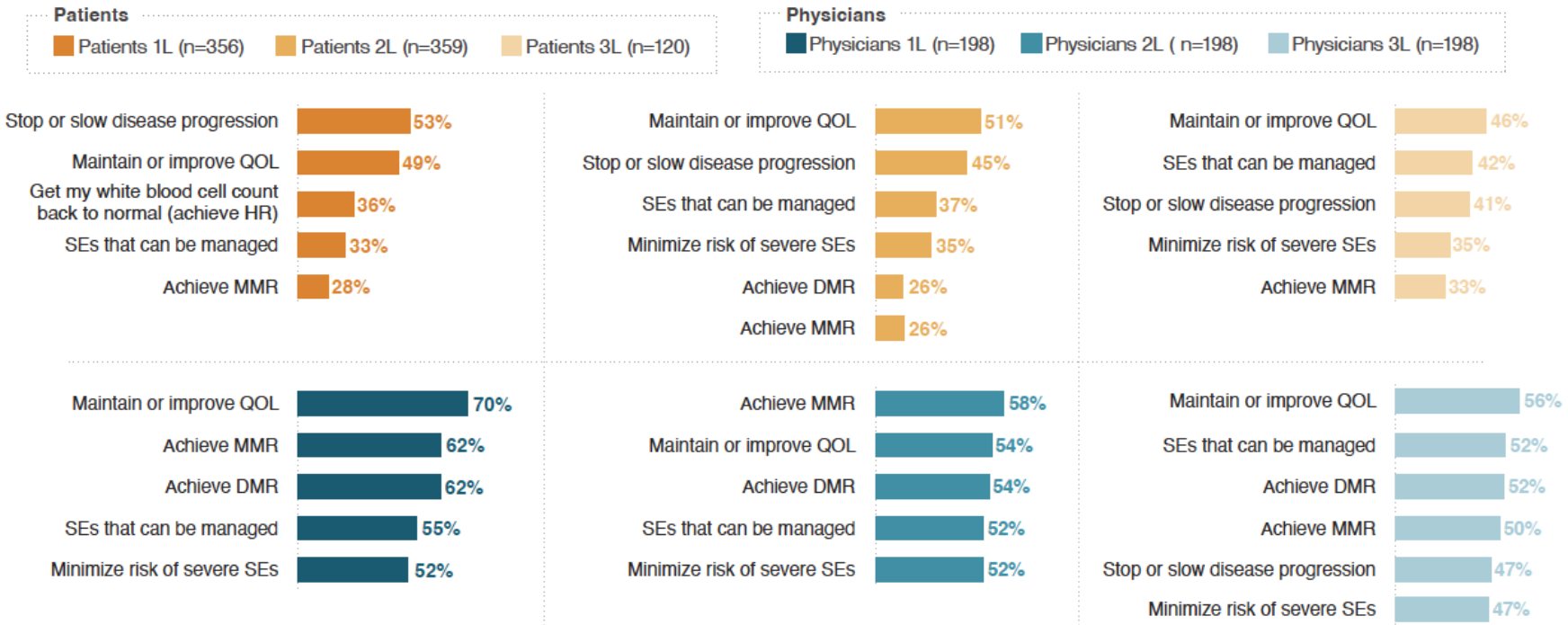


Lang et al., EHA 2023

TREATMENT GOALS

Top 5 Treatment Goals by Line of Therapy[a]

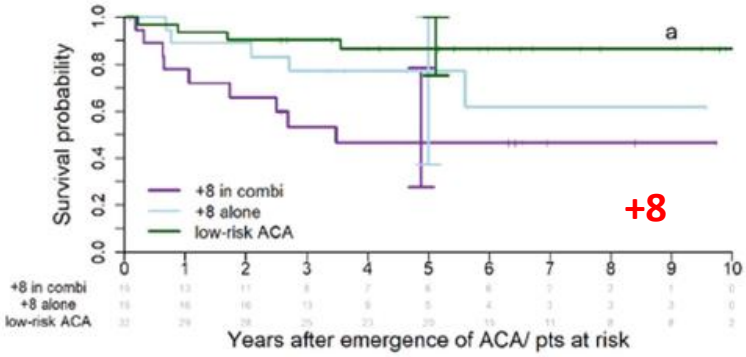
- Patients focused on stopping/slowing disease progression, maintaining/improving QOL, and minimizing/managing SEs as treatment goals, while physicians placed higher emphasis on molecular response goals. Treatment selection and goals should not sacrifice patient QOL, while ensuring efficacy of treatment
- The decreasing proportion of physicians who reported some treatment goals as their patients progress to later lines of therapy highlights the challenge of managing patients with advanced disease

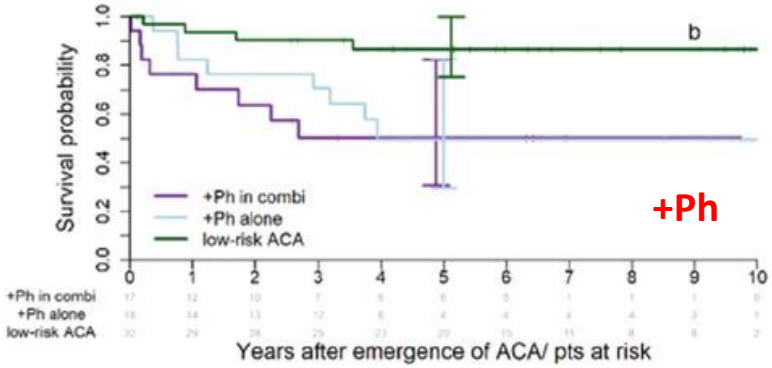


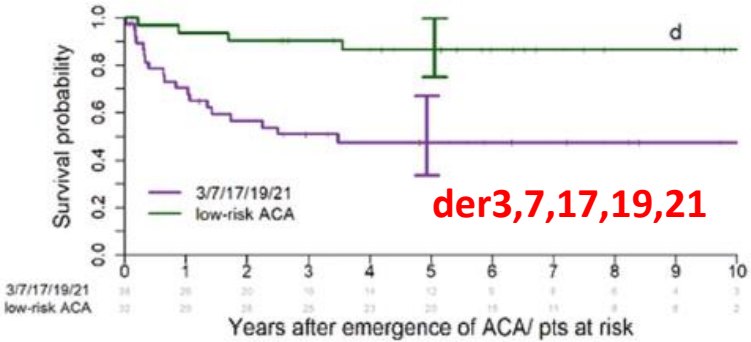
[a] Patients ranked their top 3 most important treatment goals by line of therapy; physicians selected any goals that they have by line of therapy.

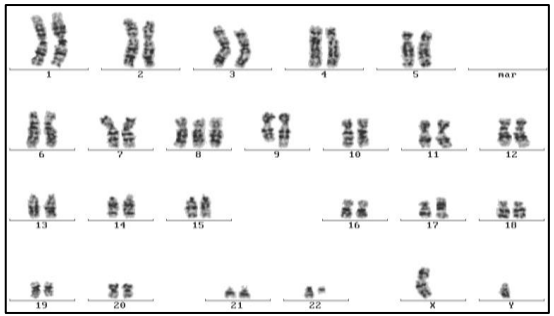
Lang et al., EHA 2023

Hochrisiko-Veränderungen der Zytogenetik



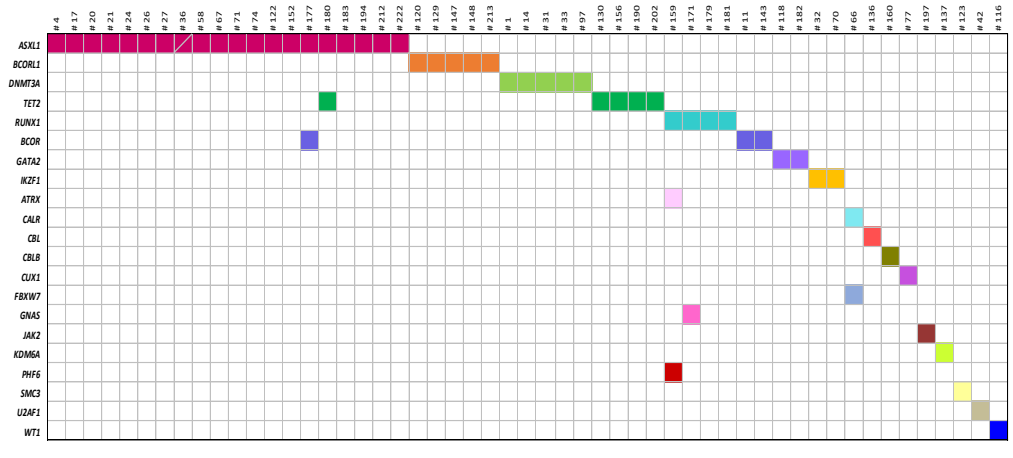






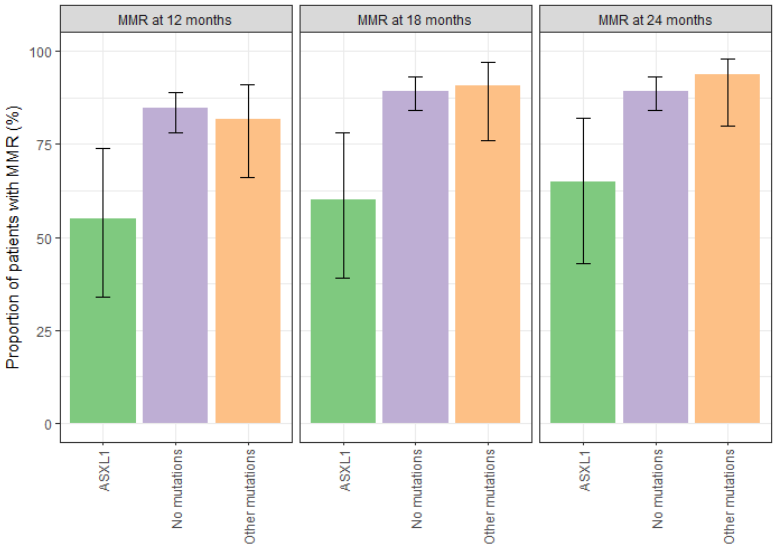
Hehlmann et al., Leukemia. 2020;34:2074-86

Inzidenz von ASXL1-Mutationen in 222 neudiagnostizierten CML-Patienten und Einfluss auf das Erreichen einer MMR



53/222 CML Patienten wiesen 60 Mutationen zur Diagnose auf
20/222 trugen ASXL1 Mutationen

Einfluss der ASXL1-Mutationen auf die Chance zur MMR



Schönfeld et al., Leukemia. 2022

Tab. 1 Parameter der chronischen Phase der chronischen myeloischen Leukämie (CML), die mit einem erhöhten Risiko für das Fortschreiten der Krankheit assoziiert sind		
Zum Zeitpunkt der Diagnose		
Hoher ELTS-Wert [18]		
10–19 % Blasten im peripheren Blut und/oder Knochenmark		
≥ 20 % Basophile im peripheren Blut		
Zusätzliche Chromosomenanomalien in Philadelphia(Ph)-Chromosom-positiven (Ph+) Zellen, einschließlich 3q26.2-Rearrangements, Monosomie 7, Isochromosom 17q und komplexer Karyotyp		
Cluster kleiner Megakaryozyten (einschließlich echter Mikromegakaryozyten, wie sie bei myelodysplastischen Neoplasien vorkommen), verbunden mit signifikanter Retikulin- und/oder Kollagenfibrose in der Knochenmarkhistologie		
ELTS-Score [18]	0,0025 × (Alter/10)^3 +0,0615 × Milzgröße in cm unter Rippenbogen +0,1052 × % Blasten im peripheren Blut +0,4104 × (Thrombozyten × 10^9/l/1000) – 0,5	Low Risk: < 1,5680 Intermediate Risk: 1,5680–2,2185 High Risk: > 2,2185
Auftreten im Verlauf		
Resistenz gegen TKI gemäß der ELN-Definition 2020 [5] einschließlich Verlust eines früheren Ansprechens, Auftreten von zytogenetischen Zusatzaberrationen von hohem Risiko und von *BCR*::*ABL1*-Kinase-Domäne-Mutationen		
ELN European LeukemiaNet, *ELTS* EUTOS-Long-Term-Survival-Score, *TKI* Tyrosinkinaseinhibitoren		

Definition der Blastenphase

1. ≥ 20 % Blasten im Blut oder Knochenmark oder
2. Vorhandensein einer extramedullären Proliferation von Blasten oder
3. Vorhandensein von echten Lymphoblasten im peripheren Blut oder Knochenmark

Khoury et al. Leukemia. 2022;36:1703-19.

Therapiebeginn während der laufenden Diagnostik

Leukozytose >100.000/µl:

- Hydroxyurea (40 mg/kg KG) > später ausschleichen
- Natrumbicarbonat i.v. oder p.o.
- Urin-pH 6,4-6,8
- Flüssigkeit (3 l / Tag)

Bei fehlender Dringlichkeit *BCR*::*ABL1*-Nachweis abwarten

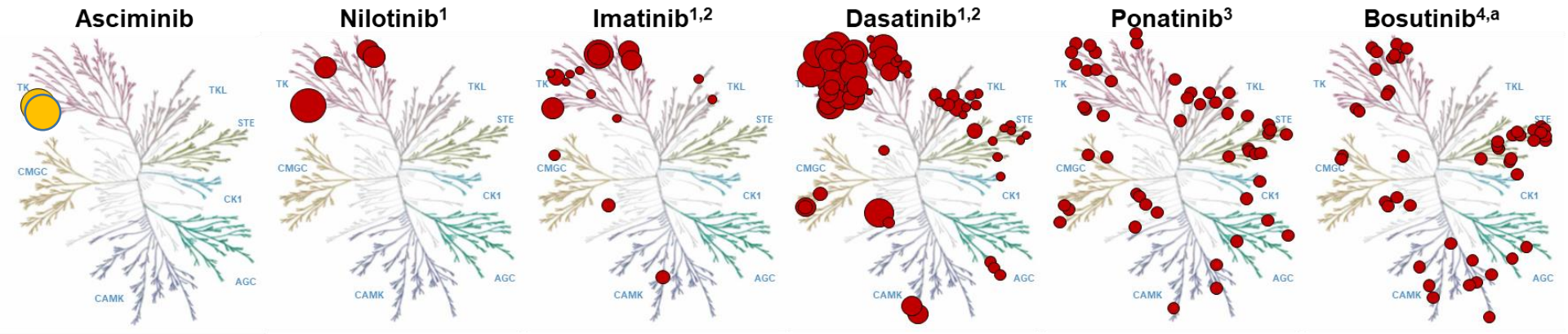
BCR::*ABL1*-Nachweis:

- unmittelbar Beginn Tyrosinkinaseinhibitor p.o.

ELN - Empfehlungen zur CML

	2006	2009	2013	2020
Erstlinie	Imatinib	Imatinib	Imatinib, Nilotinib, Dasatinib	Imatinib, Nilotinib, Dasatinib, Bosutinib
Zweitlinie	Keine (Hochdosis-Imatinib)	Nilotinib, dasatinib, high-dose imatinib	• Ima → Nilo, Dasa, Bosu • Dasa → Nilo, Bosu, Pona • Nilo → Dasa, Bosu, Pona • T315I: Pona	• Ima → Nilo, Dasa, Bosu, Pona • Dasa → Nilo, Bosu, Pona • Nilo → Dasa, Bosu, Pona • Bosu → Dasa, Nilo, Pona • T315I: Pona
Andere Optionen	IFN/allogene SZT	keine	Keine	***(Asciminib)***
Salvage	Allogene SZT	Allogene SZT, Nilotinib,Dasatinib	Allogene SZT	Allogene SZT
Meilensteine	CCyR	CCyR → MR	MMR	MMR → TMR
Probleme	• Kurzer Verlauf, • Mutationen	Mutationsrisiko gesunken	TFR für wen?	Langzeit-Nebenwirkungen

Selektivität der Kinase-Inhibitoren



Selectivity of kinase inhibitors:

Kinases bound by ATP-competitive TKIs are indicated by **red** circles.
Kinases bound by STAMP inhibitor are indicated by a **yellow** circles.

[a] Bosutinib inhibits additional kinases that are not depicted in the dendrogram.
ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor;
STAMP, Specifically Targeting the ABL Myristoyl Pocket.

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.

Wahl des TKI

- Ziel der Therapie?
- Klinische und biologische Risikofaktoren?
- Komorbiditäten? Nebenwirkungsrisiko?
- Verfügbarkeit? Finanzierung?

→ **Gemeinsame Entscheidungsfindung**

Alle TKI haben spezifische Nebenwirkungen und individuelle Kontraindikationen:

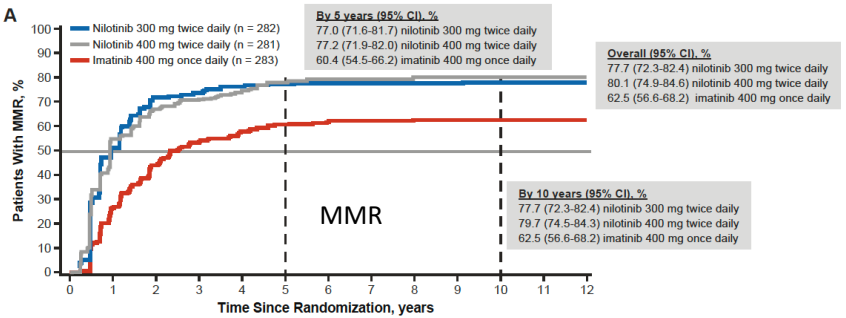
- Arterielle Verschlußkrankheit, metabolische Erkrankungen: Nilotinib, Ponatinib Risiko
- Lungenerkrankungen: Dasatinib Risiko
- Niereninsuffizienz: Imatinib Risiko

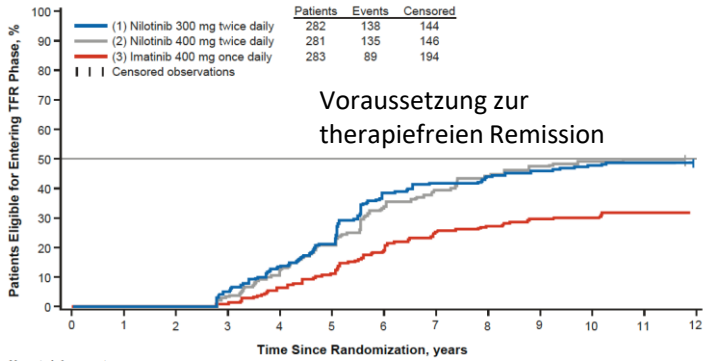
Hochhaus A, et al. Leukemia. 2020;34:966-84.

ENESTnd: Nilotinib vs. Imatinib Erstlinientherapie: 10 Jahres-Ergebnisse.

Neudiagnostizierte Ph+ CML in CP

- Nilotinib 2*300 mg/Tag
- Nilotinib 2*400 mg/Tag
- Imatinib 400 mg/Tag





Kantarjian et al. Leukemia. 2021;35:440-53.

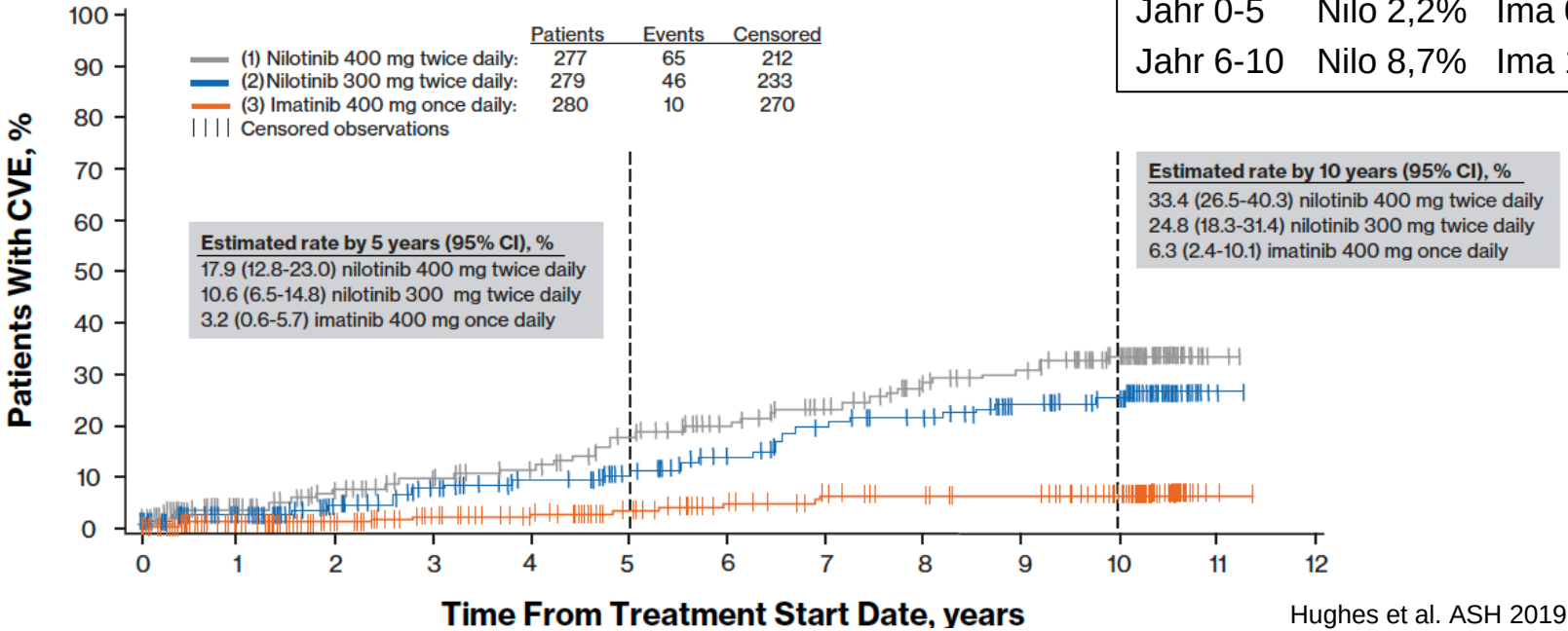
ENESTnd: Nilotinib vs Imatinib in der Erstlinientherapie: Kardiovaskuläre Ereignisse.

Inzidenz kardivaskulärer Ereignisse

Framingham Nierdigrisiko:

Jahr 0-5 Nilo 2,2% Ima 0,5%

Jahr 6-10 Nilo 8,7% Ima 1,1%



Hughes et al. ASH 2019

Kantarjian et al. Leukemia. 2021;35:440-453.

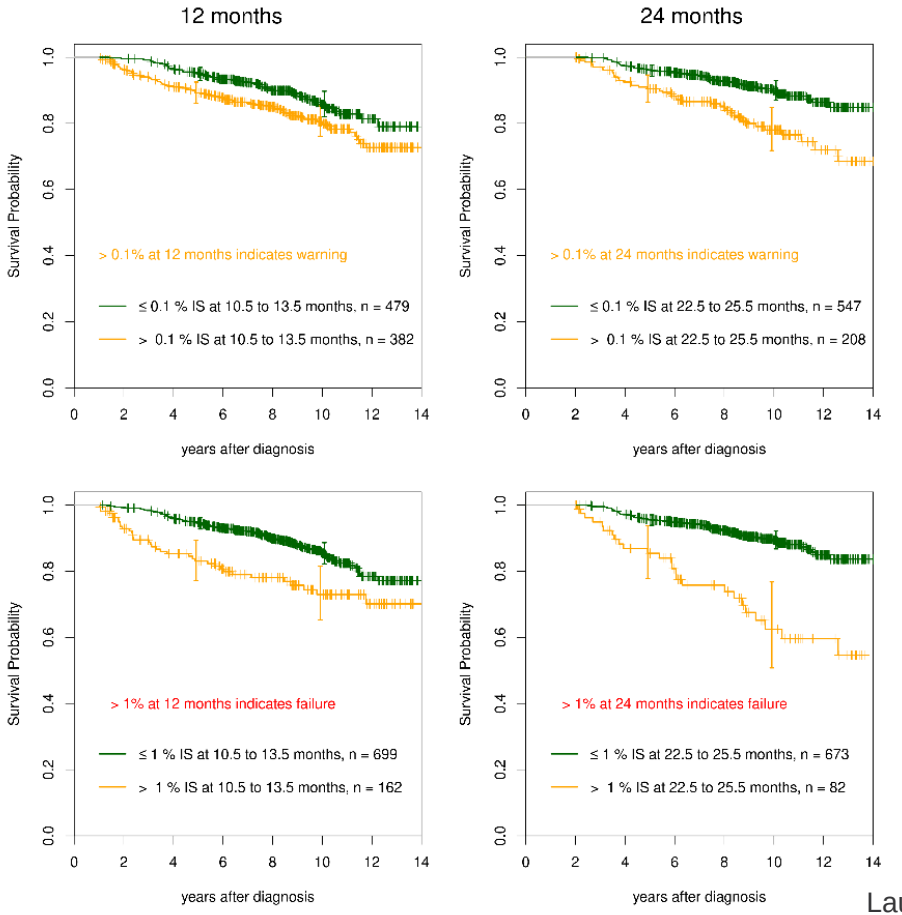
Meilensteine des Therapieansprechens 2020 (Erst- und Zweitlinie)

	Optimal	Warnung	Versagen
Bei Diagnose		Hochrisiko-ACA Hochrisiko ELTS-Score	
3 Monate	BCR::ABL1 ≤10%	BCR::ABL1 >10%	BCR::ABL1 >10%, falls bestätigt innerhalb 1-3 Monaten
6 Monate	BCR::ABL1 ≤1%	BCR::ABL1 >1-10%	BCR::ABL1 >10%
12 Monate	BCR::ABL1 ≤0,1%	BCR::ABL1 >0,1-1%	BCR::ABL1 >1%
Danach und zu jeder Zeit	BCR::ABL1 ≤0,1%	BCR::ABL1 >0,1-1%, Verlust MMR	BCR::ABL1 >1%, Resistenzmutationen, Hochrisiko-ACA

Für Patienten, die eine TFR erreichen wollen, ist das optimale Ansprechen MR^4 (BCR::ABL1 ≤0,01% IS)

Leukemia. 2020;34:966-84

Outcome after failing ELN milestones (German CML Study IV)

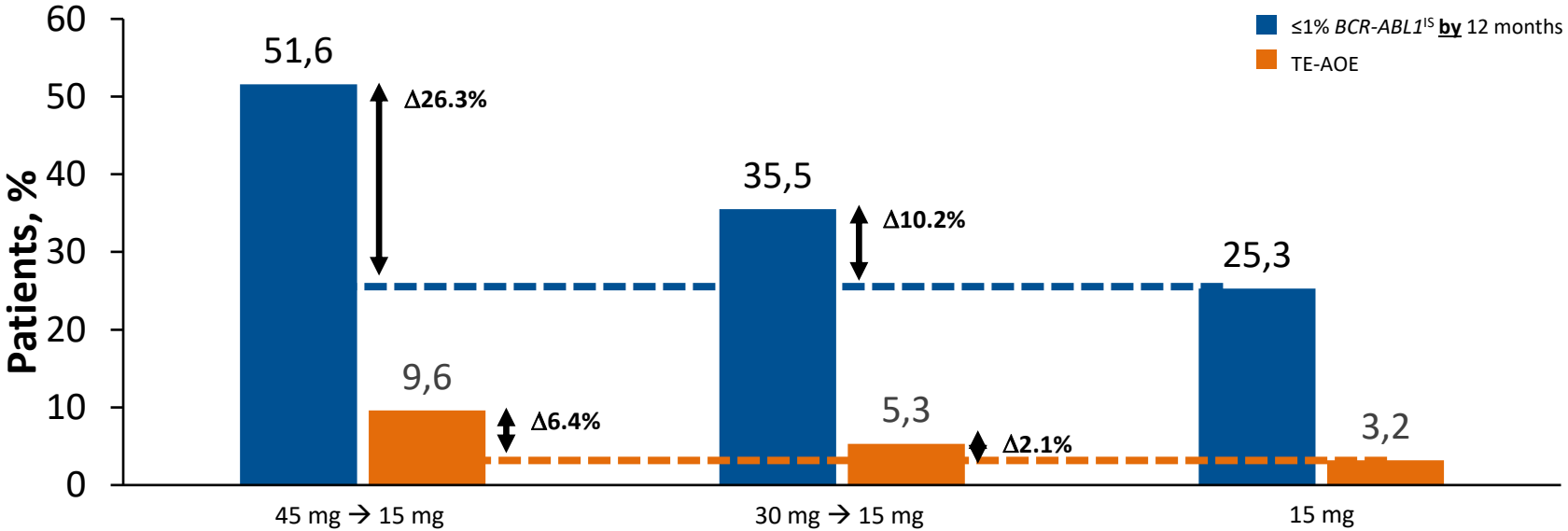


Lauseker et al., Leukemia. 2023;37:2231-6.

Welche Dosis sollte verabreicht werden?

Medi-kament	Nach Resistenz			Erstlinie		
	Ursprünglich zugelassen	Zur Zeit	Annahme	Ursprünglich zugelassen	Zur Zeit	Annahme
Imatinib	400 mg	400 mg	600-800 mg	400 mg	400 mg	600-800 mg
Dasatinib	70 mg 2*	100 mg	70-100 mg ? 5 Tage/Wo. ?	100 mg	100 mg	70 mg ? 5 Tage/Wo. ?
Nilotinib	400 mg 2*	400 mg 2*	300 mg 2* ?	300-400 mg 2*	300 mg 2*	300 mg 2*
Bosutinib	500 mg	500 mg	300 - 400 mg	500 mg	400 mg	300 - 400 mg
Ponatinib	45 mg	45 -> 15 mg	45 -> 15 mg	45 mg	--	--

OPTIC: Arterielle Verschlüsse vs. molekulares Ansprechen nach Startdosis



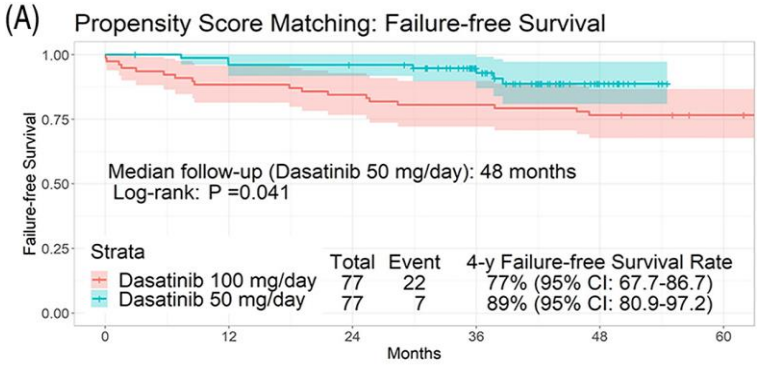
- The percentage of patients with ≤1% *BCR-ABL1*^{IS} decreased with decreasing doses
- The incidence of TE-AOEs decreased with decreasing doses

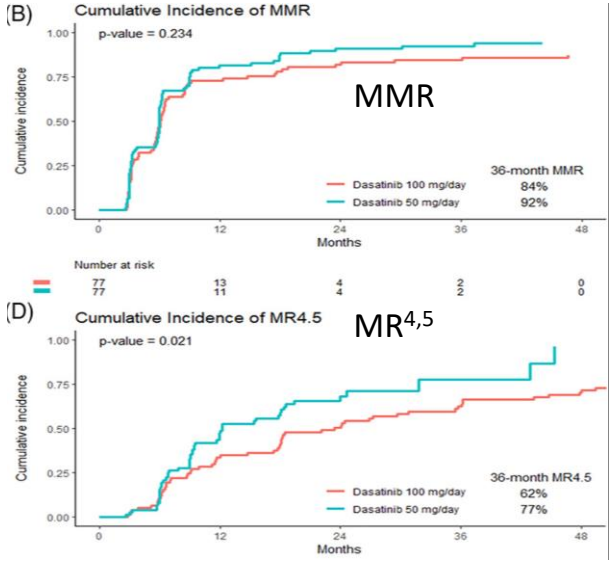
TE-AOE, treatment-emergent arterial occlusive event

Cortes JE et al. EHA 2021

Effektivität von Low-dose Dasatinib 50 mg/Tag

Jabbour et al. Am J Hematol 2022;97:1413-8.

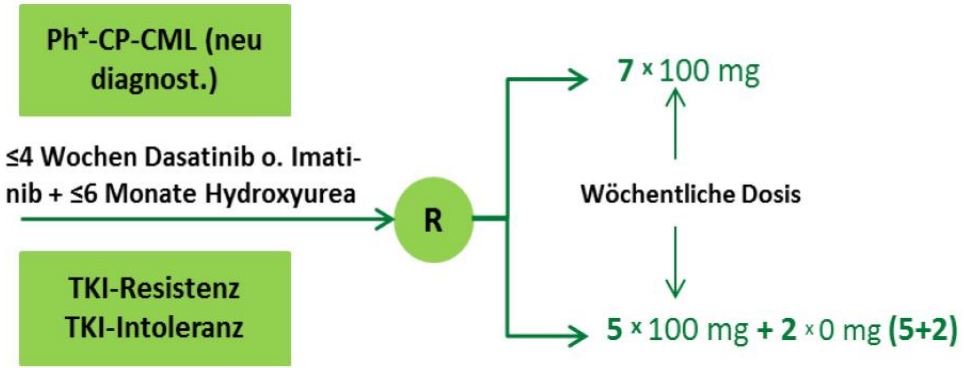


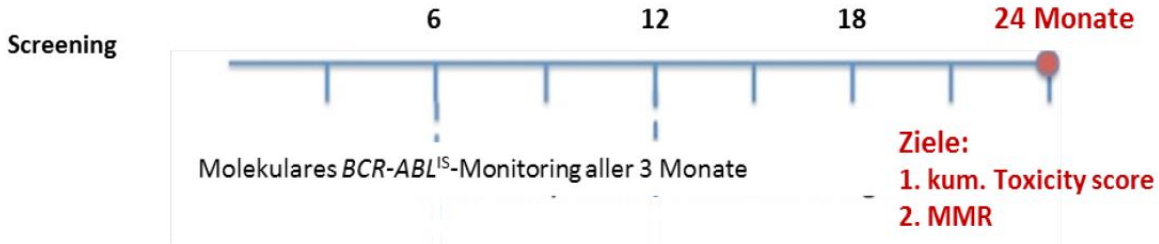


Low Dose Dasatinib:
Vorteil bezüglich „Failure free survival“ ?

Historische Kontrolle!
Keine randomisierte Studie.
Kein Nichtunterlegenheits-Design.
Validierung erforderlich !

- **Multicenter, prospective, randomized, unblinded phase III**
- **Non-inferiority (MMR @ 24 ms)**





Cumulative Toxicity (24 ms)

1: Pleural Effusion
2: Fluid Retention
3: Hematologic Toxicity
4: Other (GI, Skin, Musculo-skeletal)

ELN 2020 recommendations on treatment beyond 2nd line

Treatment beyond second-line

The definition of an acceptable response to third, fourth, or fifth-line treatment cannot be formalized, but a BCR-ABL1 transcript level >1% or a cytogenetic response less than complete (Ph+ >0%) are insufficient for optimal survival. There are no comparative studies and the choice of TKI should be guided by the sensitivity profile of specific BCR-ABL1 KD-mutations if possible, and, in particular T315I where only ponatinib is efficacious. Suboptimal response to two or more TKIs should lead to prompt consideration of an allogeneic stem cell transplantation (allo-SCT).

T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib[a], or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib[a], or ponatinib

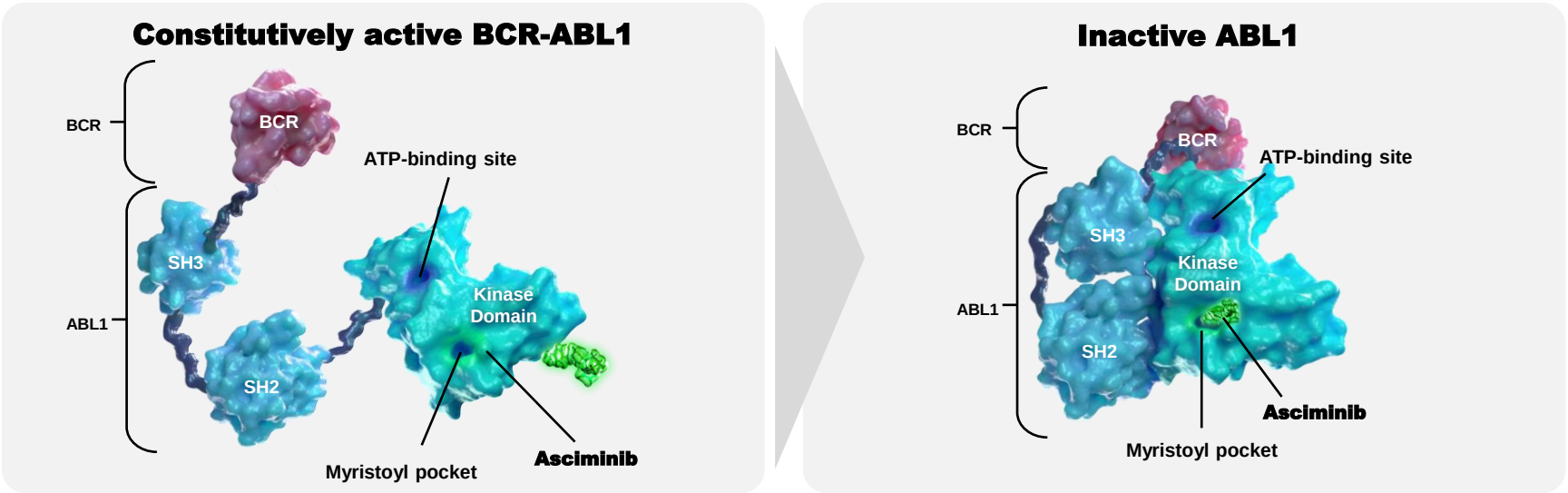
Leukemia 2020; 34:966-84

Expert opinion—management of chronic myeloid leukemia after resistance to second-generation tyrosine kinase inhibitors

Andreas Hochhaus[1] · Massimo Breccia[2] · Giuseppe Saglio[3] · Valentín García-Gutiérrez[4] · Delphine Réa[5] · Jeroen Janssen[6] · Jane Apperley[7]

Leukemia. 2020;34:1495-1502

Asciminib ist ein STAMP Inhibitor (Specifically Targeting the BCR-ABL1 Myristoyl Pocket)



Unlike ATP-competitive TKIs that target the ATP-binding site, asciminib has a unique mechanism of action.[1,2] It is a first-in-class STAMP inhibitor[3]:

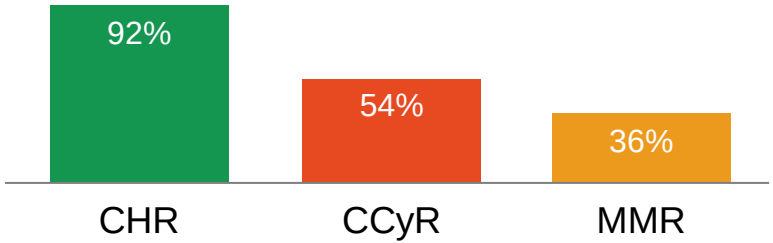
- Asciminib mimics myristate by binding the myristoyl pocket of ABL1 (normally bound by the myristoylated N-terminal of ABL1)[4,5]
- Upon binding, asciminib restores inhibition of the ABL1 kinase activity[4-7]

Hughes TP, et al. N Engl J Med. 2019;381:2315-26

Asciminib: Response rates in phase 1

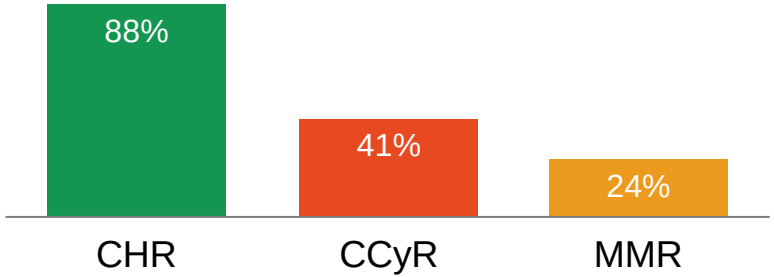
Asciminib was active in **heavily pretreated patients** with CML, including patients **pre-treated with ponatinib** and patients with a **T315I mutation**

12 months
CP patients without T315I



- 87% of patients maintained CCyR by 12 months
- 95% of patients maintained MR3 by 12 months
- MMR in patients with <2 previous TKIs: 47%
- MMR in patients with >2 previous TKIs: 34%
- MMR in patients pretreated with ponatinib: 40%

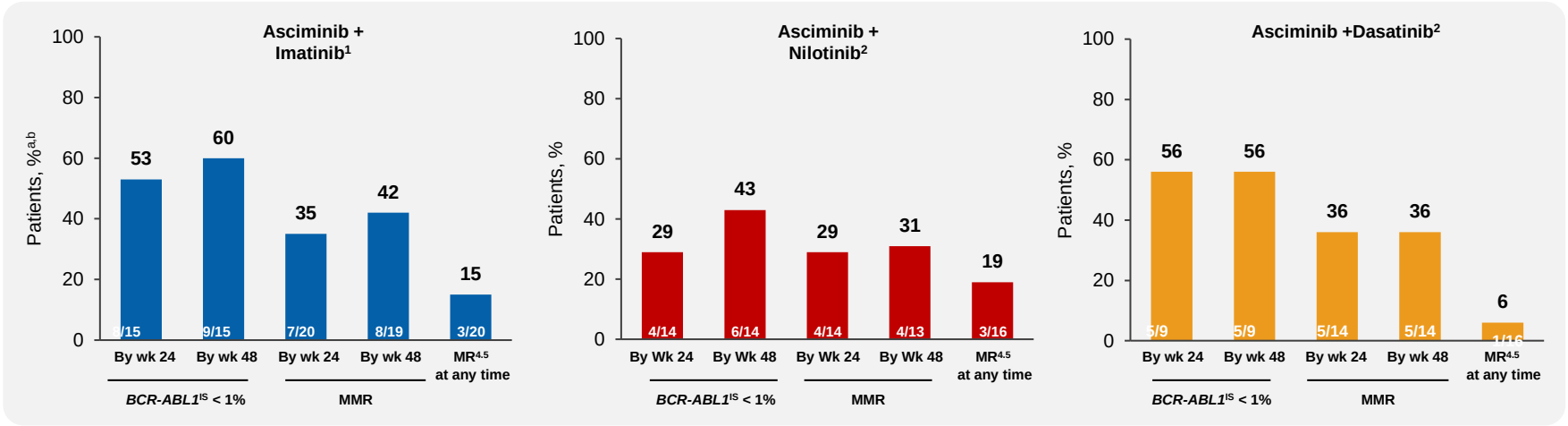
12 months
CP patients with T315I



- 67% of patients maintained CCyR by 12 months
- 1/18 patient maintained MR3 by 12 months
- MMR in patients with <2 previous TKIs: 38%
- MMR in patients with >2 previous TKIs: 11%
- MMR in patients pretreated with ponatinib: 17%

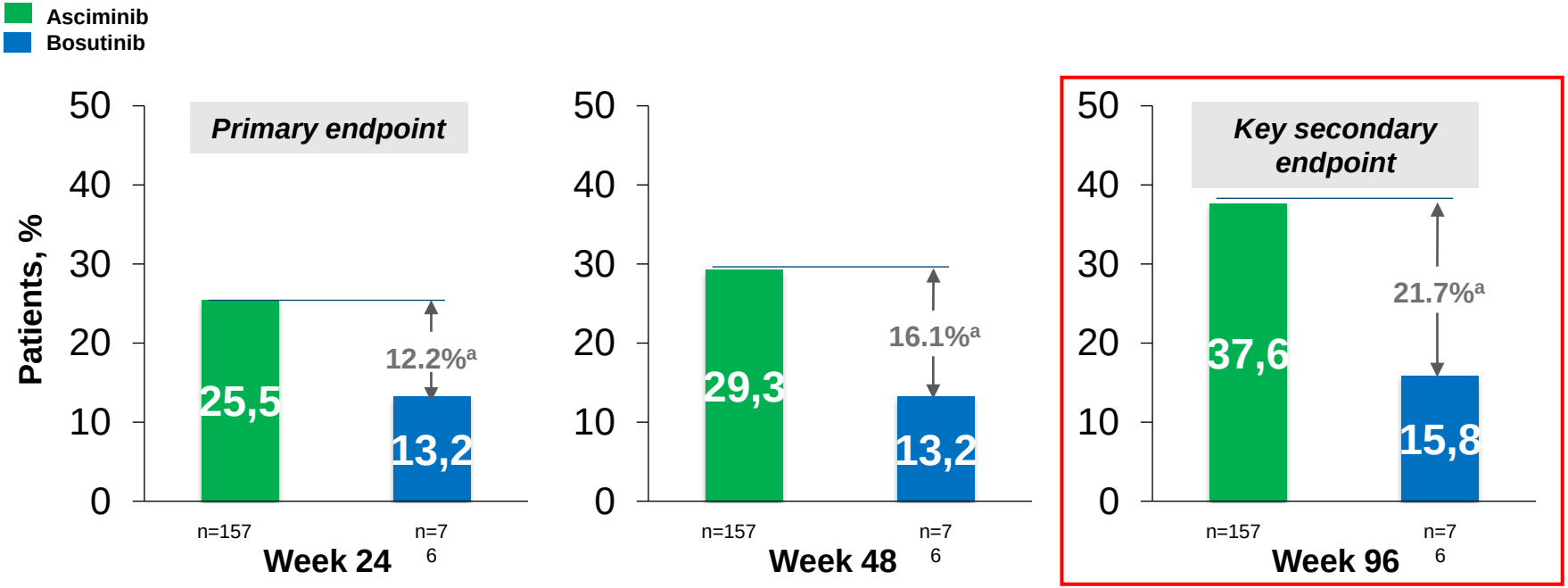
Hughes et al. N Engl J Med. 2019;381:2315-26.

Asciminib in combination with imatinib, nilotinib, or dasatinib shows clinical activity in pretreated patients with CML-CP or -AP



Cortes et al. Presented at the 24th EHA Annual Congress. Abstract 1685.
Mauro et al. Presented at the 24th EHA Annual Congress. Abstract 1684.

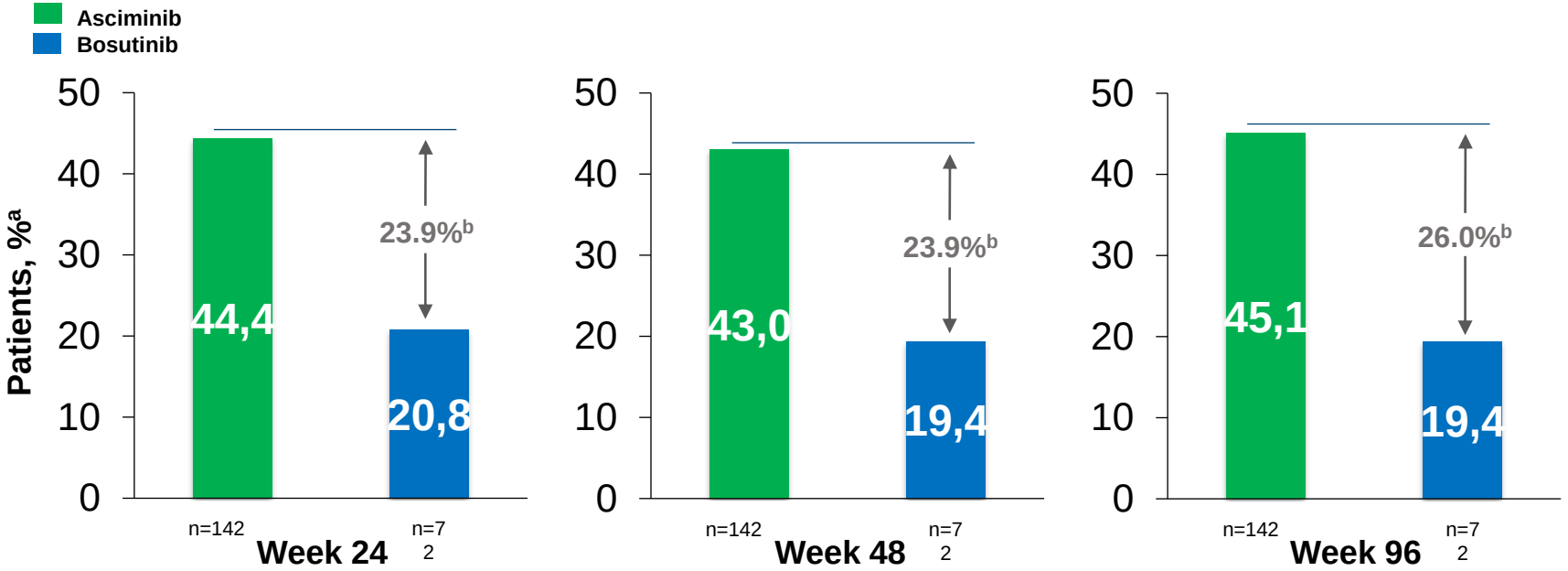
ASCEMBL: MMR Rates at Weeks 24, 48, and 96



- The MMR rate with asciminib increased consistently over time suggesting the long-term benefit of continuing treatment with asciminib

[a] The treatment difference after adjusting for baseline MCyR status was 12.24% (95% CI, 2.19%-22.30%; 2-sided *P*=0.029) at week 24, 16.09% (95% CI, 5.69%-26.49%; 2-sided *P*=0.007) at week 48, and 21.74% (95% CI: 10.53%-32.95%; 2-sided *P*=0.001) at week 96.

Rates of *BCR::ABL1*^{IS} ≤1% at Weeks 24, 48, and 96 and Maintenance

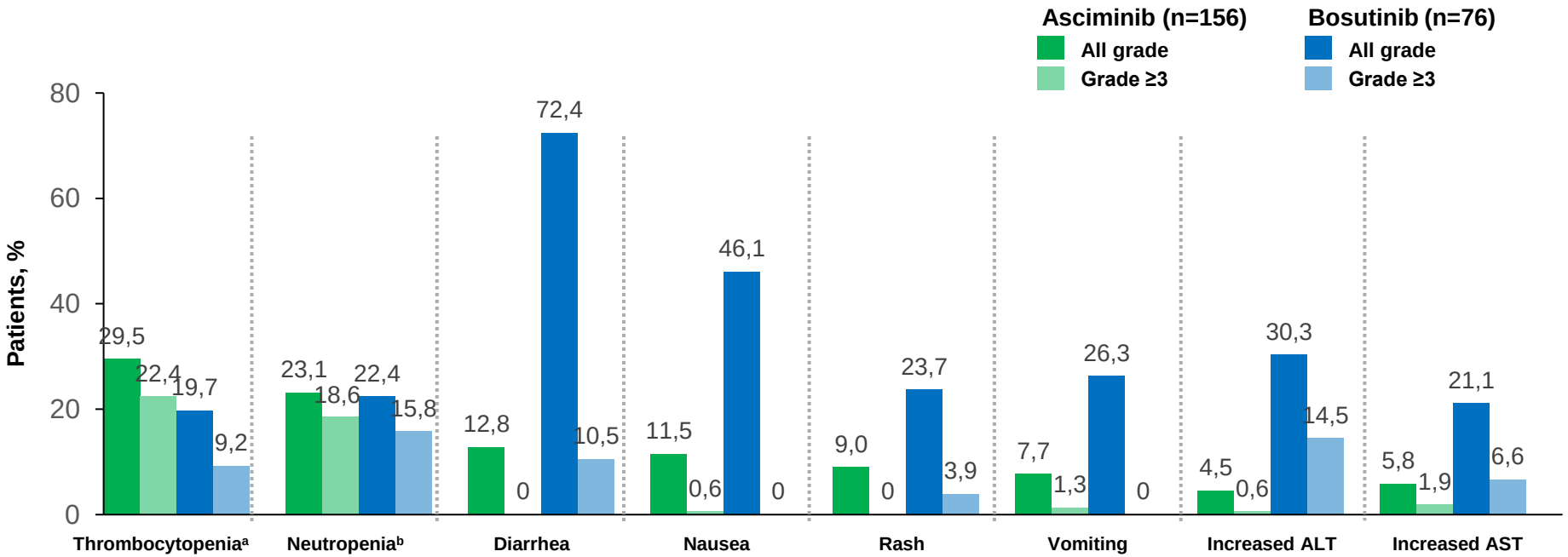


Maintenance of *BCR::ABL1*^{IS} ≤1%[c]

- The probability (95% CI) of maintaining *BCR::ABL1*^{IS} ≤1% for at least 72 weeks was **94.6%** (86.2%-97.9%) with **asciminib** and **95.0%** (69.5%-99.3%) with **bosutinib**

[a] Based on 142 of 157 patients (90.4%) receiving asciminib and 72 of 76 (94.7%) receiving bosutinib with *BCR::ABL1*^{IS} >1% at baseline.
[b] The treatment difference after adjusting for baseline MCyR status was 23.92% (95% CI: 11.36%, 36.49%; 2-sided *P*=0.000) at week 24, 23.85% (95% CI: 11.36%, 36.33%; 2-sided *P*=0.000) at week 24, and 26.02% (95% CI, 13.48%-38.56%; 2-sided *P*=0.000) at week 96.
[c] Based on 78 of 157 patients (49.7%) receiving asciminib and 24 of 76 (31.6%) receiving bosutinib, who achieved *BCR::ABL1*^{IS} ≤1%.

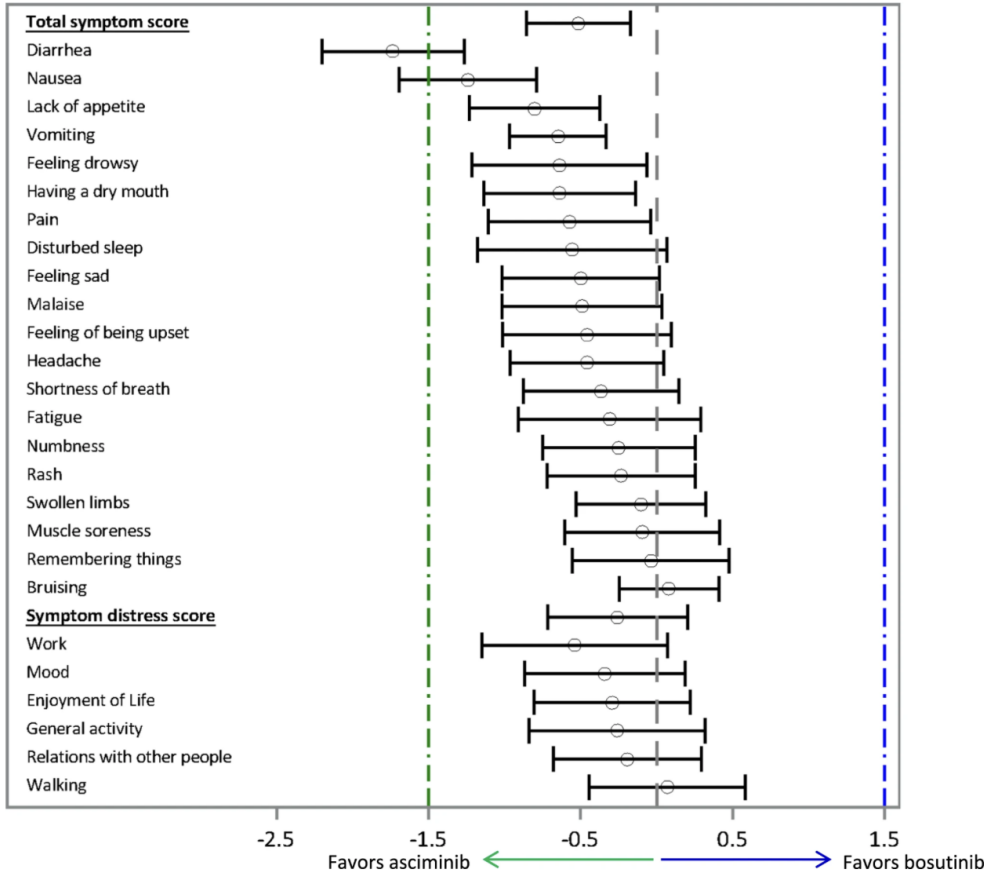
Most Frequent All-Grade AEs (in ≥20% of Patients in Any Arm)



- Regardless of the longer duration of exposure, safety and tolerability of asciminib remained consistent with that at the time of the primary analysis, and continued to be better than with bosutinib with longer follow-up

[a] Includes thrombocytopenia and platelet count decreased.
[b] Includes neutropenia and neutrophil count decreased.

MDASI-CML Overall Quality of Life change from baseline (MMRM): Symptom items

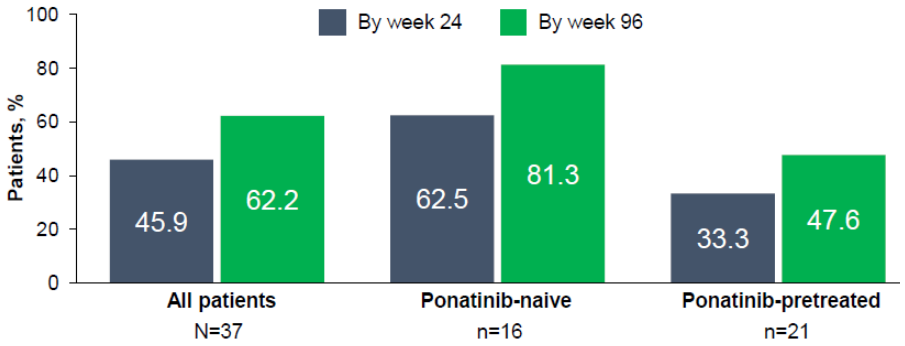


CI = confidence interval, LS Mean=least squares mean. LS mean (95% CI) for difference in change from baseline scores between treatment arms. Dashed lines = clinically meaningful differences (green in favor of asciminib; blue in favor of bosutinib).

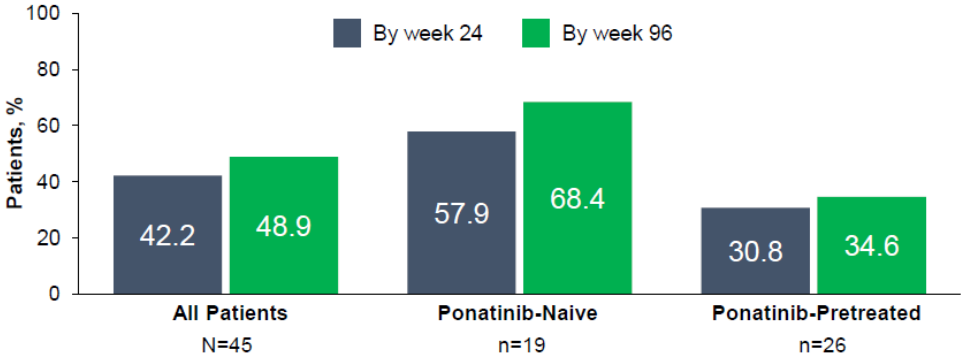
Réa et al. Leukemia. 2023;37:1060-7.

Asciminib at 200mg BID in T315I in Ponatinib-Naïve and Ponatinib-Pretreated Patients

Cumulative *BCR::ABL1*^{IS} ≤1%

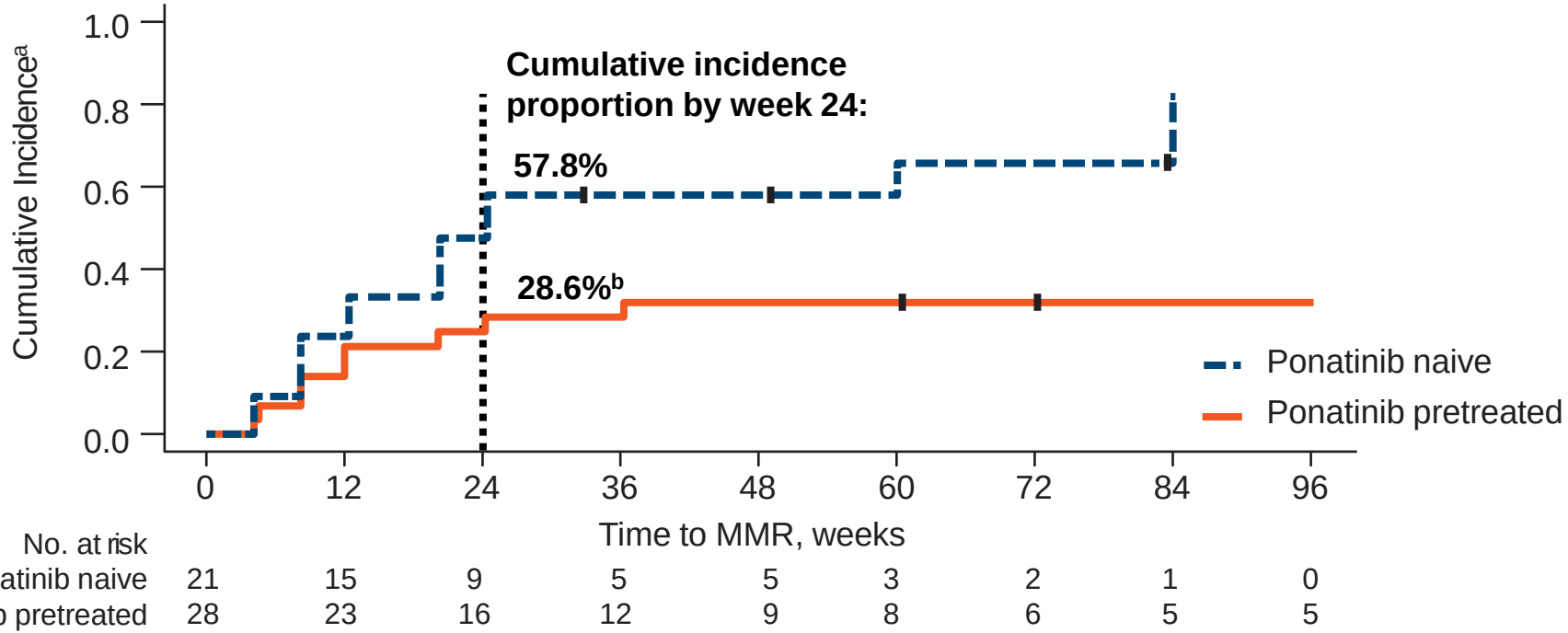


Cumulative MMR Rates



Hughes et al. EHA 2022. P704

Responses by prior ponatinib in patients with CML-CP/-AP and T315I mutations treated with asciminib 200 mg bid in the Phase I study

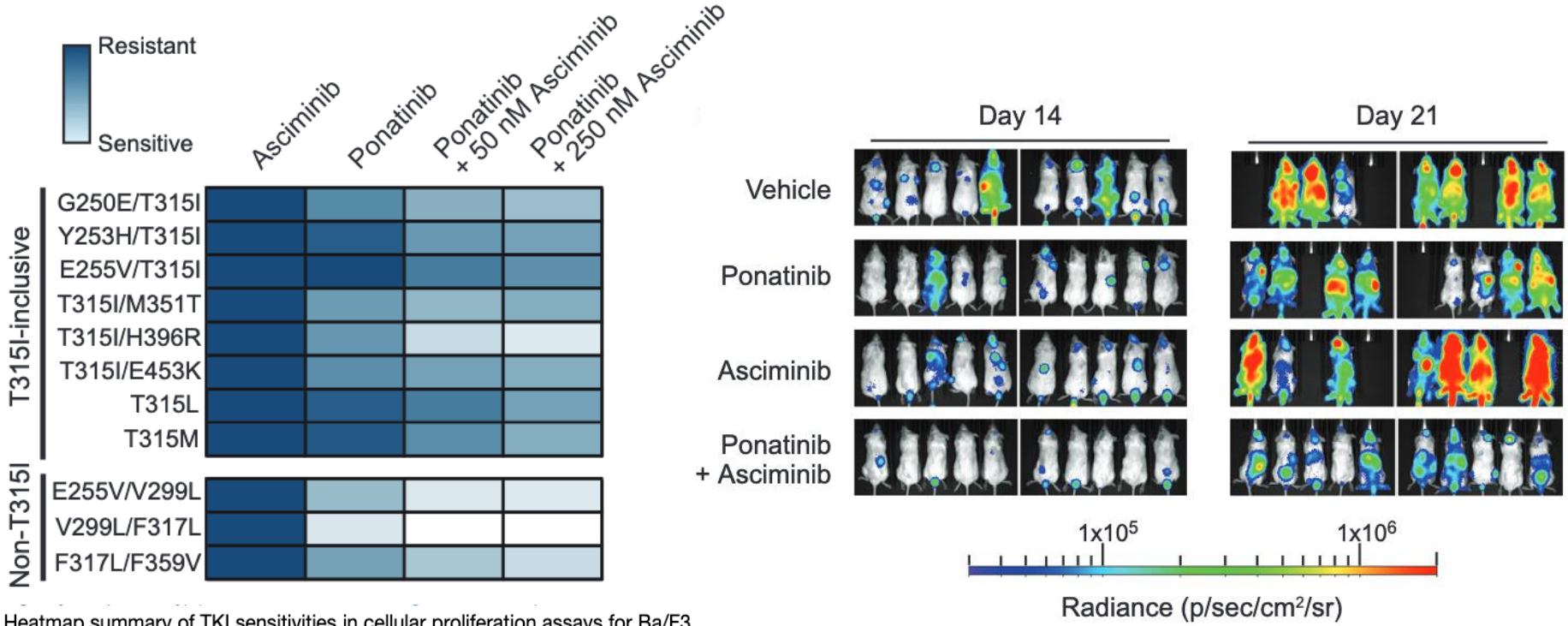


Reprinted from Cortes J, et al. Blood. 2020;136(Suppl1):47-50, Copyright 2020, with permission from Elsevier.

[a] Discontinuations and deaths treated as competing risks. [b] Includes 5 patients who showed signs of resistance to ponatinib prior to study entry.

Cortes et al. Presented at: 62nd ASH Virtual Annual Meeting 2020. Abstract 650.

Combining Asciminib with Ponatinib suppresses Emergence of and Restores Efficacy against highly Resistant BCR::ABL1 mutants



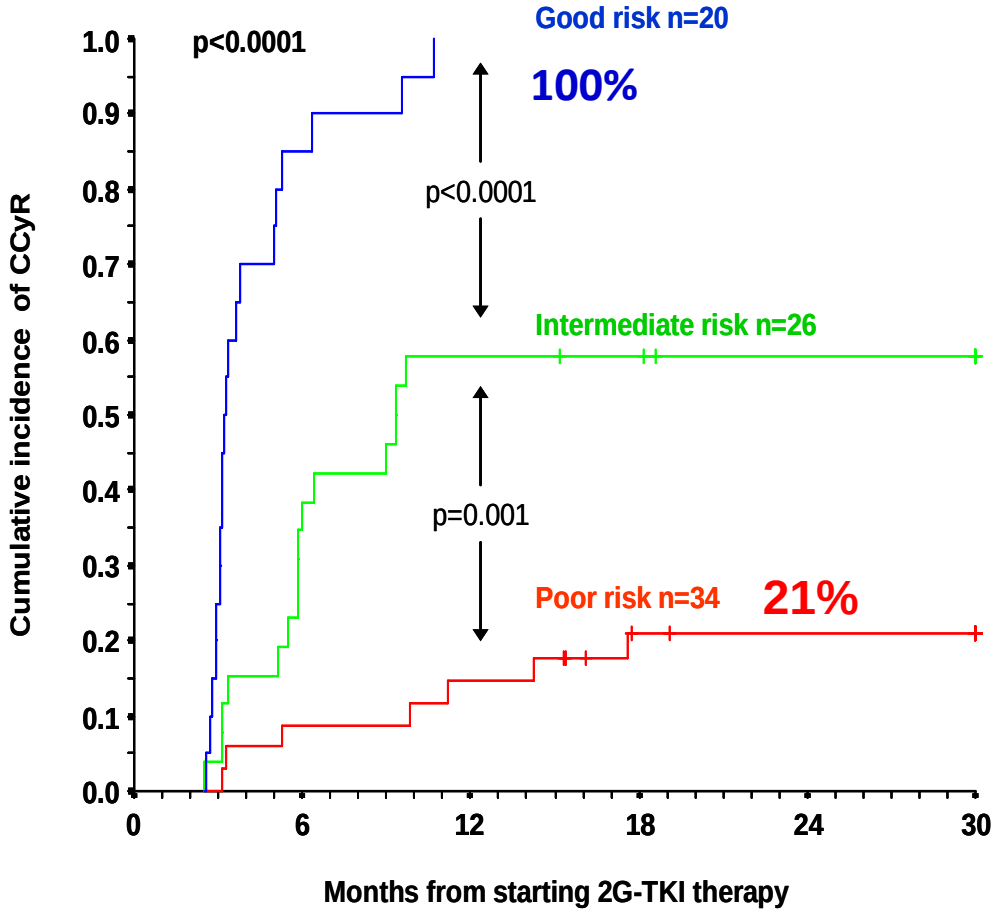
(B) Heatmap summary of TKI sensitivities in cellular proliferation assays for Ba/F3 white (sensitive) to dark blue (insensitive) denotes the sensitivity to asciminib alone, ponatinib alone, or ponatinib in combination with either 50 or 250 nM asciminib.

Eide et al. Cancer Cell, 2019;36:431-43.

Predicting responses to second line TKI

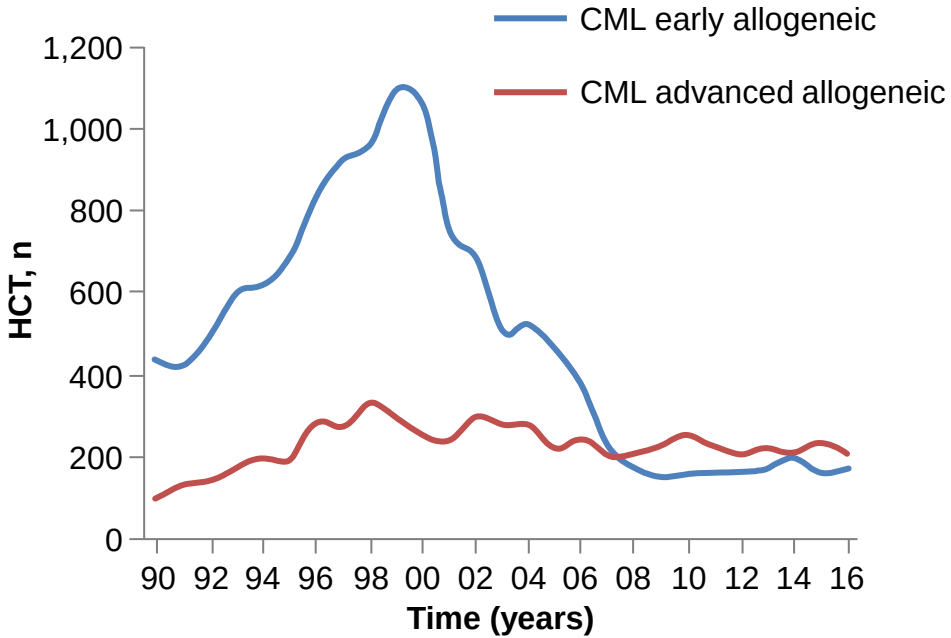
- Cytogenetic response to imatinib
- Risk score (here: Sokal)
- Recurrent neutropenia

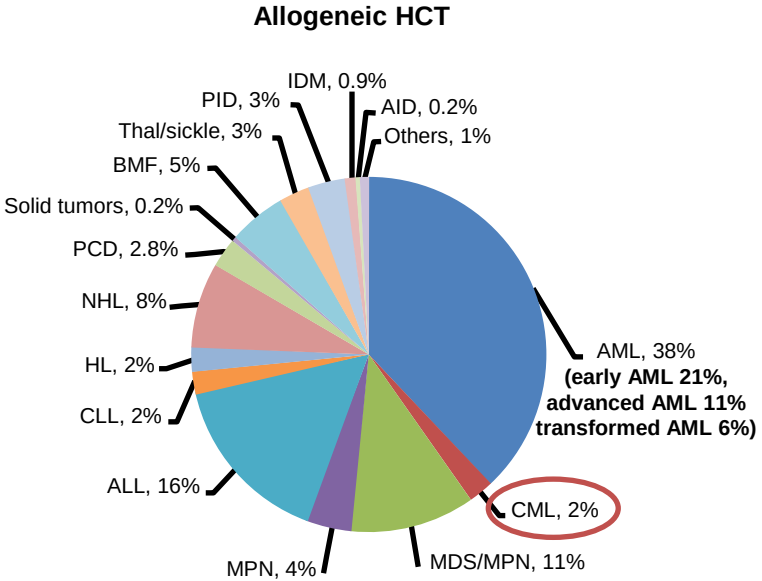
Score	Risk
<1.5	good
≥1.5 <2.5	intermediate
>2.5	poor



Milojkovic et al, Haematologica 2010

Allogeneic HCT in CML in Europe: EBMT report





EBMT, European Society for Blood and Marrow Transplantation;
HCT, hematopoietic cell transplantation.

Passweg et al. Bone Marrow Transplantation. 2018;53:1139-48.

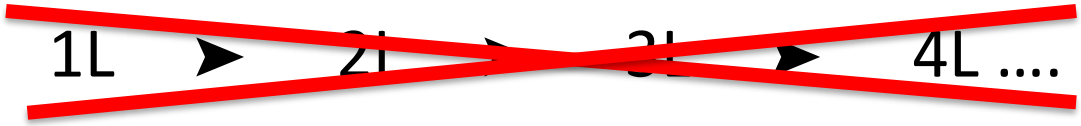
Rough guide to 3L+ therapies

	Rotation of 2G-TKI	Ponatinib	Asciminib	Allo-SCT
Intolerance to ≥ 2 previous TKI	+		+++	
Resistance with BCR::ABL1 mutations	+	++	++	
T315I mutation		++	(+, US only)	++
Resistance without BCR::ABL1 mutations	+	++	++	+
High risk ACAs		+		+++
Recurrent cytopenias	+		++	+++

Personal preferences

onkopedia

Neu: Linien-agnostische Therapieempfehlungen nach Klinik und Biologie

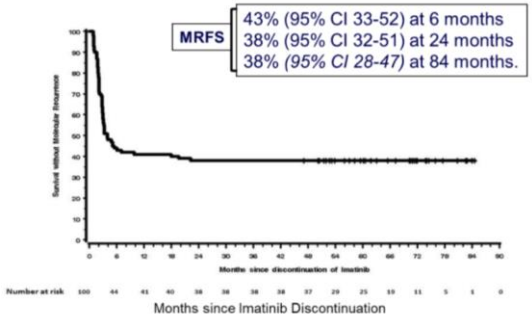


- Neudiagnose
- Intoleranz
- Resistenz
- Zytopenien
- Komorbiditäten
- Begleitmedikation

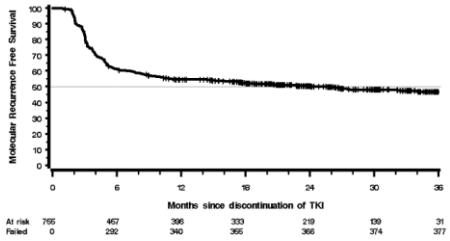
TFR nach Stop von Erst- und Zweitgenerations-TKI

Imatinib

STIM (N=100)[1]

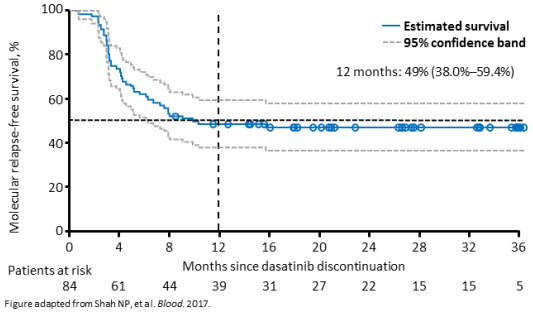


EURO-SKI (N=755)[2]

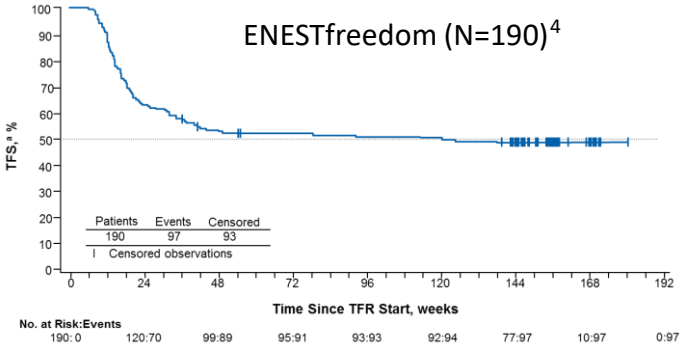


Zweitgenerations-TKI

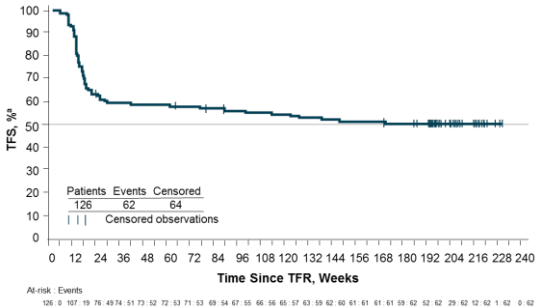
DASFree (N=84)[3]



ENESTfreedom (N=190)[4]

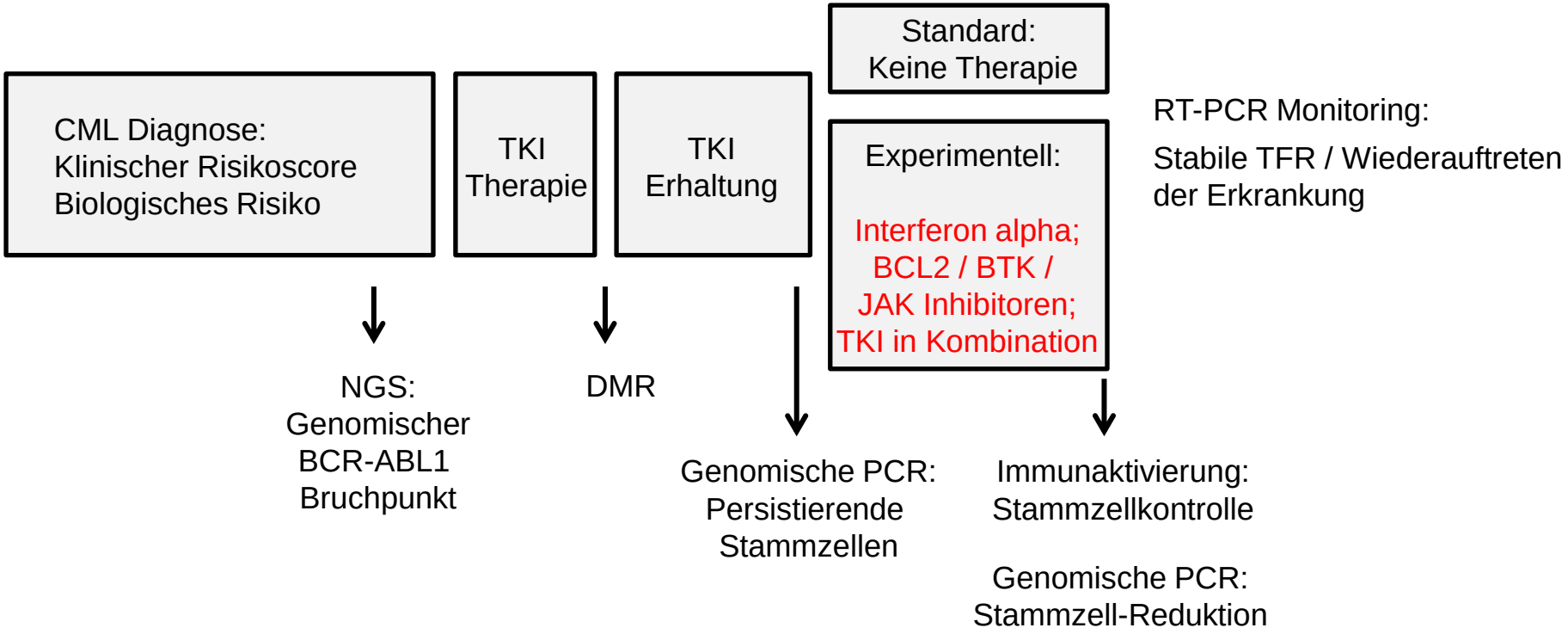


ENESTop (N=126)[5]



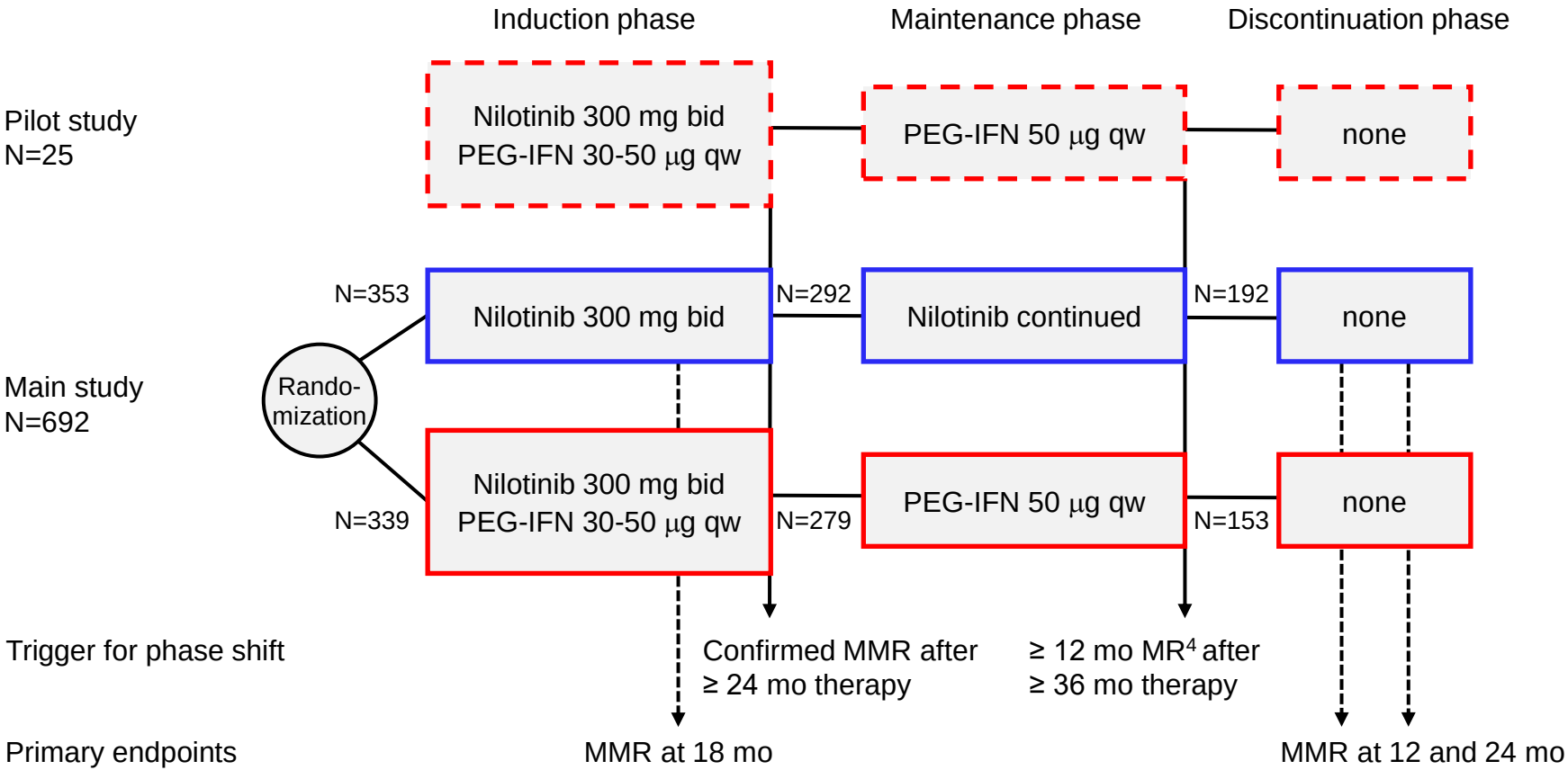
ENEST, Evaluating Nilotinib Efficacy and Safety in Clinical Trials. MRFS: molecular relapse-free survival; TKI: tyrosine kinase inhibitor; TFR: Treatment-free remission; TFS: Treatment-free survival1. Etienne G, et al. *J Clin Oncol* 2017;35:298ff.. 2. Saussele S, et al. *Lancet Oncol* 2018;19:747–757. 3. Shah NP, et al. *Blood* 2017;130(suppl 1) [abstract 314]. 4. Ross DM, et al. PF409 EHA 2019. 5. Mahon FX, et al. EHA 2019.

Parameter zur Verbesserung der Chancen auf therapiefreie Remission

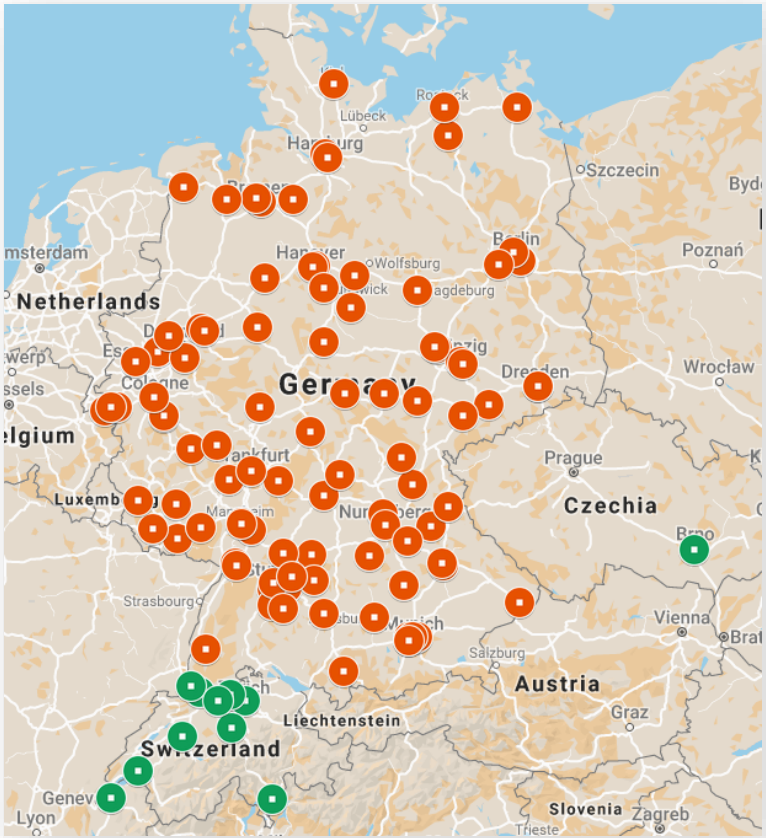


TIGER STUDY

N=717 (Median follow up 6.4 years)



Participating sites (n=110)



TIGER = TKI + Interferon initiated in Germany

EudraCT no.	2010-024262-22
Clinicaltrials.gov	NCT01657604
Recruitment	2012-2017

German CML Study Group

East German Study Group on Hematology and Oncology, OSHO

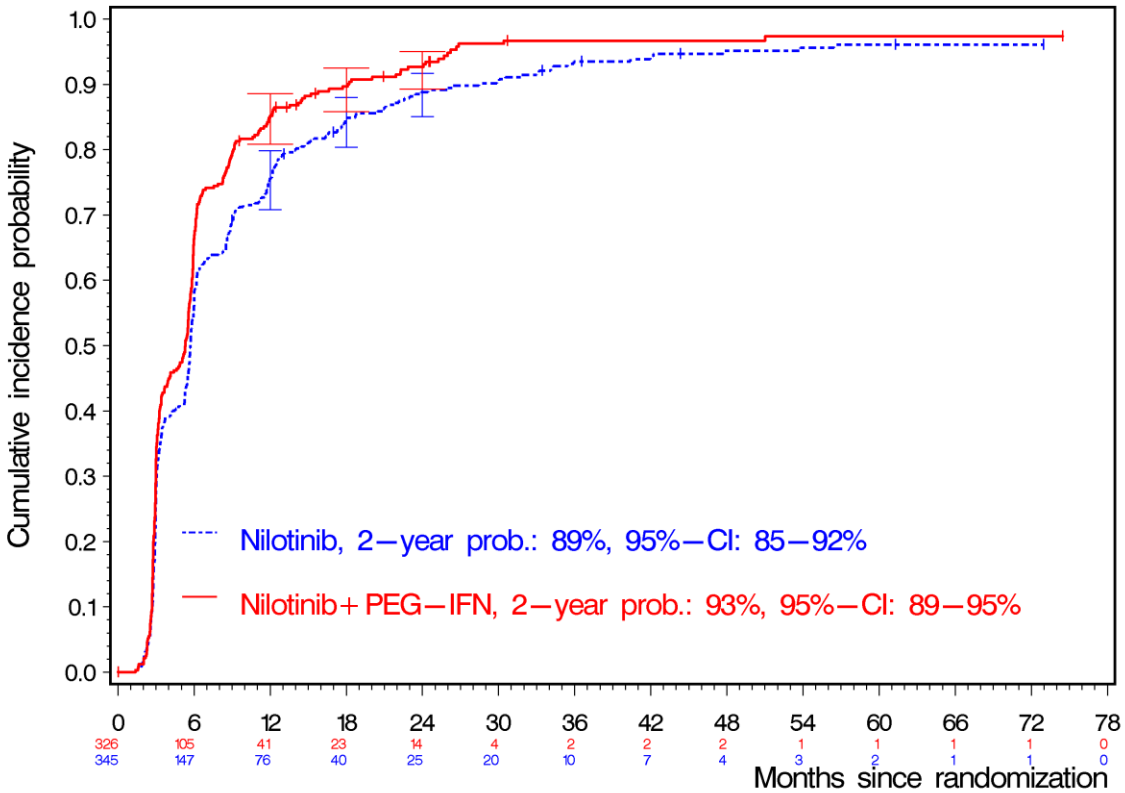
Swiss Group for Clinical Cancer Research, SAKK

Czech Leukemia Study Group, CELL

Participating sites:

99	Germany	35	Academic departments
10	Switzerland	44	Regional hospitals
1	Czech Republic	31	Resident physicians

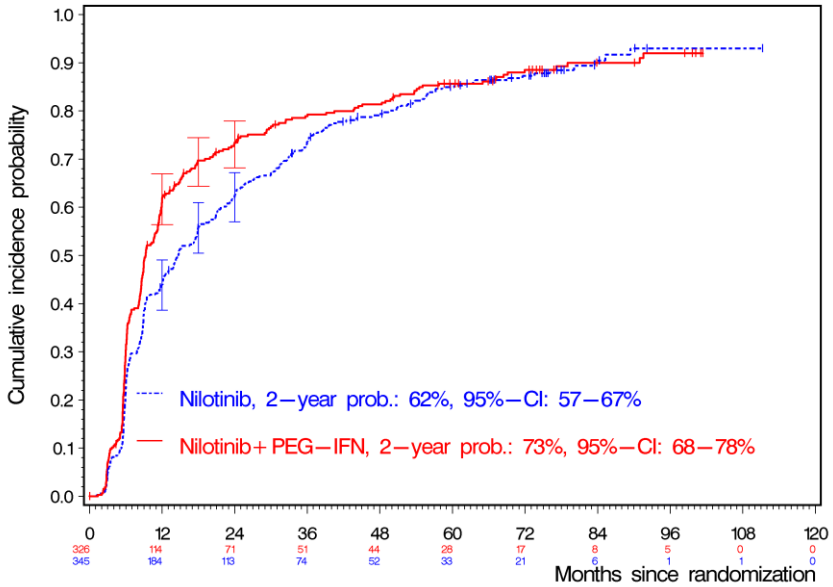
Cumulative incidence of MMR



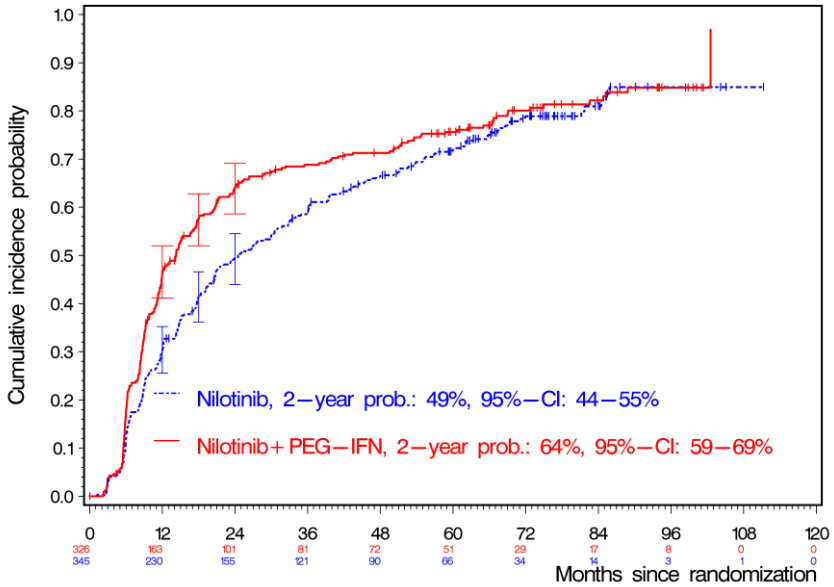
6 EUTOS IS standardized central labs; typical transcripts only

Cumulative incidence of DMR

MR^4



$MR^{4.5}$



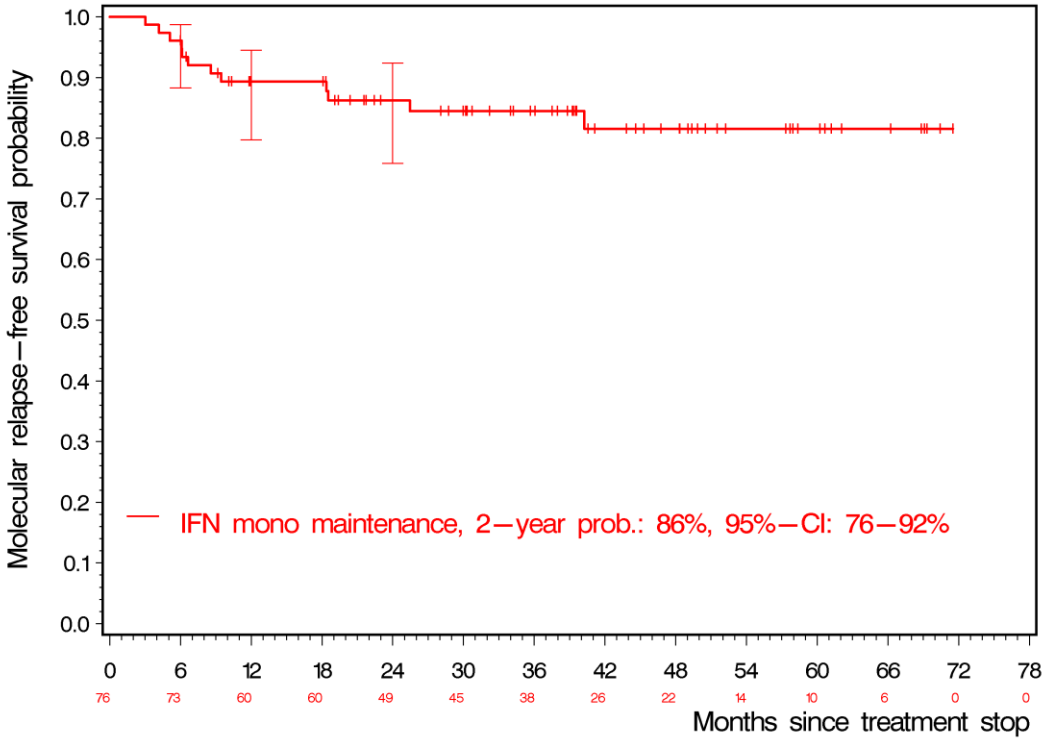
6 EUTOS IS standardized central labs; typical transcripts only

IFN monotherapy (maintenance): Molecular relapse free survival after discontinuation

79 patients started TFR phase, median observation time: 39 months

Of these 79 patients

a) 3 had no follow-up
b) 11 lost MMR (1 of 11 with blast crisis)
c) 1 died before loss of MMR
d) 1 restarted TKI before loss of MMR

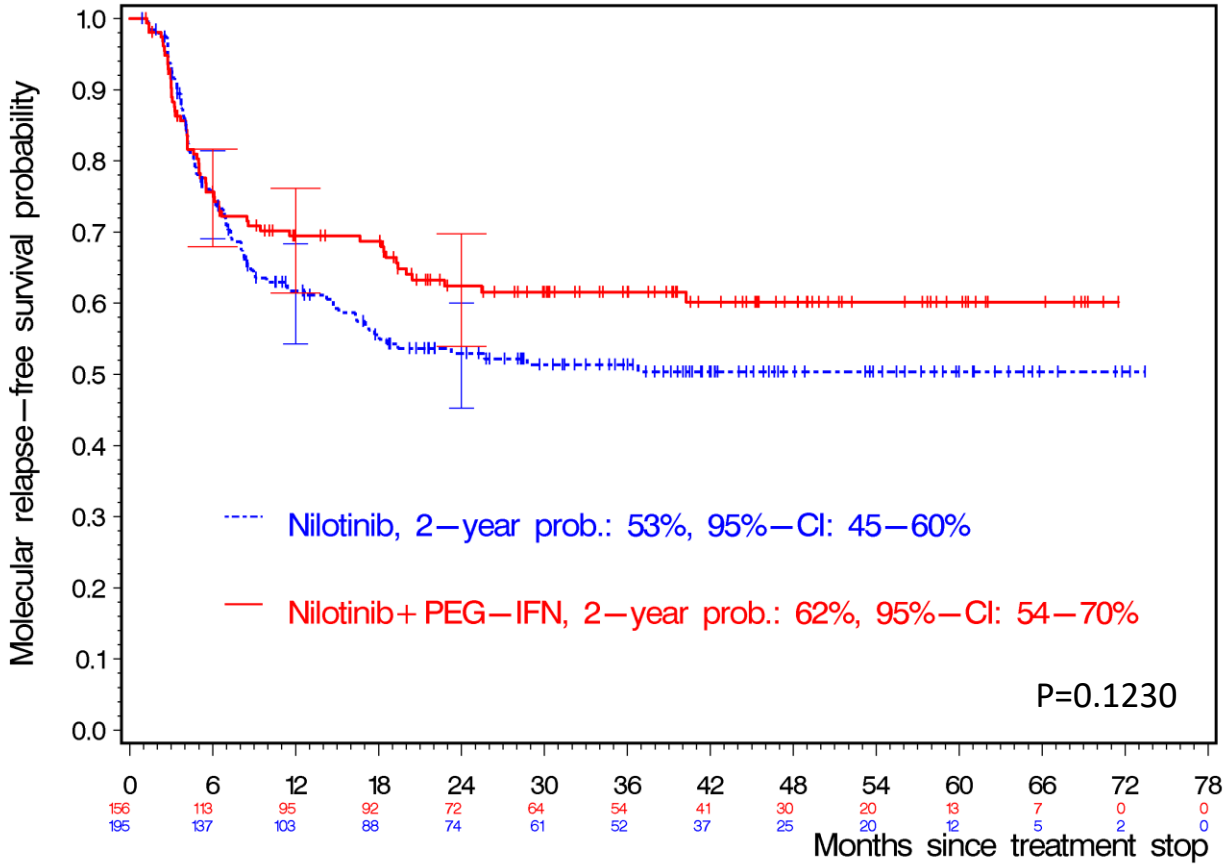


Molecular relapse free survival after discontinuation, ITT

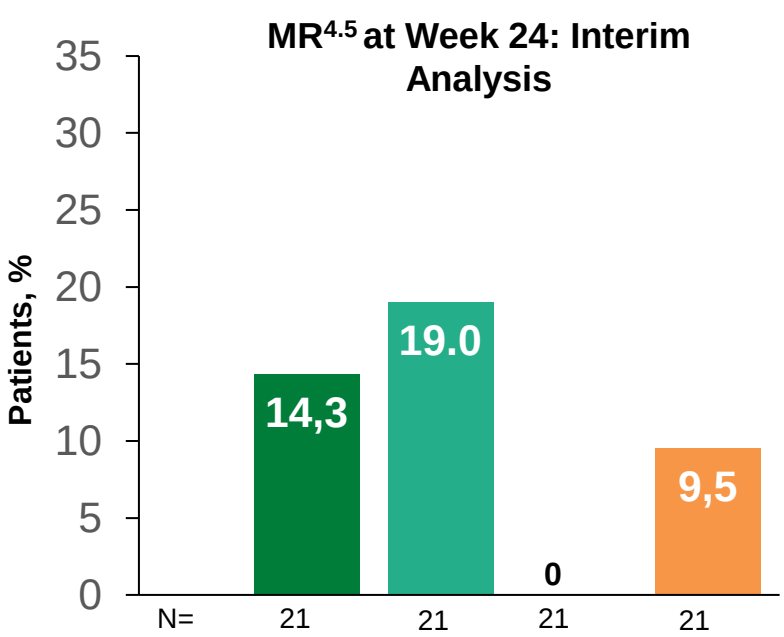
Probability of MMR **at** 12 months after discontinuation:

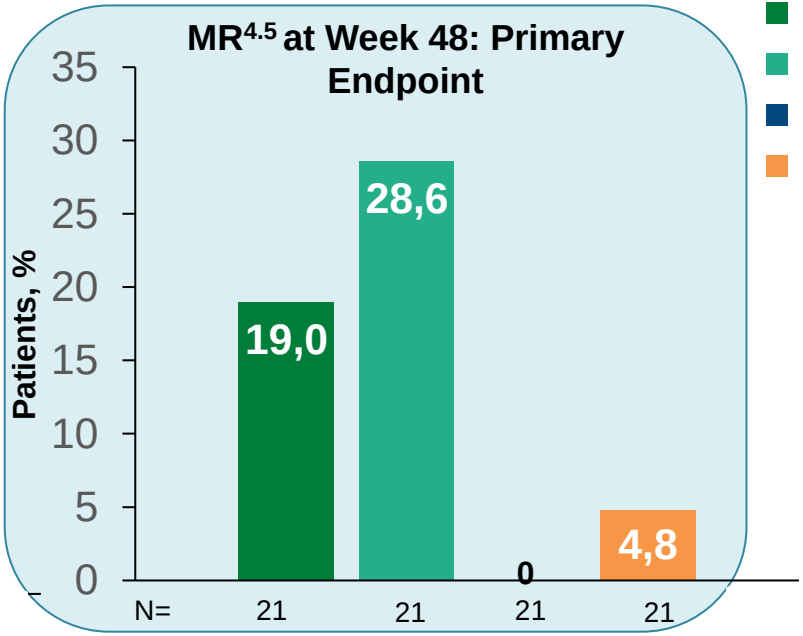
Nilotinib (n=195):
62% (95%-CI: 54-68%)

Nilotinib + IFN (n=156):
69% (95%-CI: 61-76%)



ASC4MORE: MR$^{4.5}$ at Weeks 24 and 48

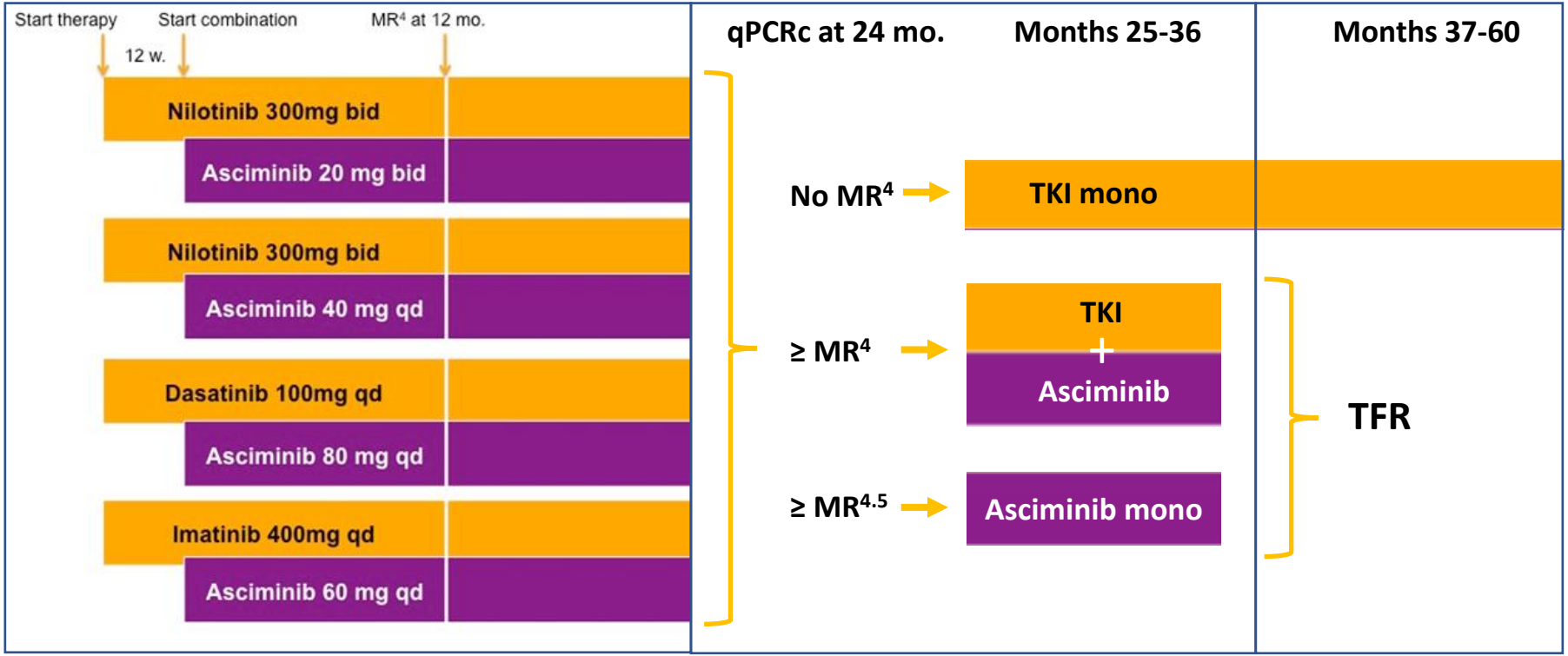




ASC 40 + IMA
ASC 60 + IMA
Continued IMA
Switch to NIL

- More patients were able to achieve MR$^{4.5}$ with **asciminib add-on** to imatinib vs continued **imatinib** or switch to **nilotinib**
- No patients in the continued **imatinib** arm were in MR$^{4.5}$ at week 48, although more patients in this arm were in MMR at baseline than in the **asciminib add-on** arms

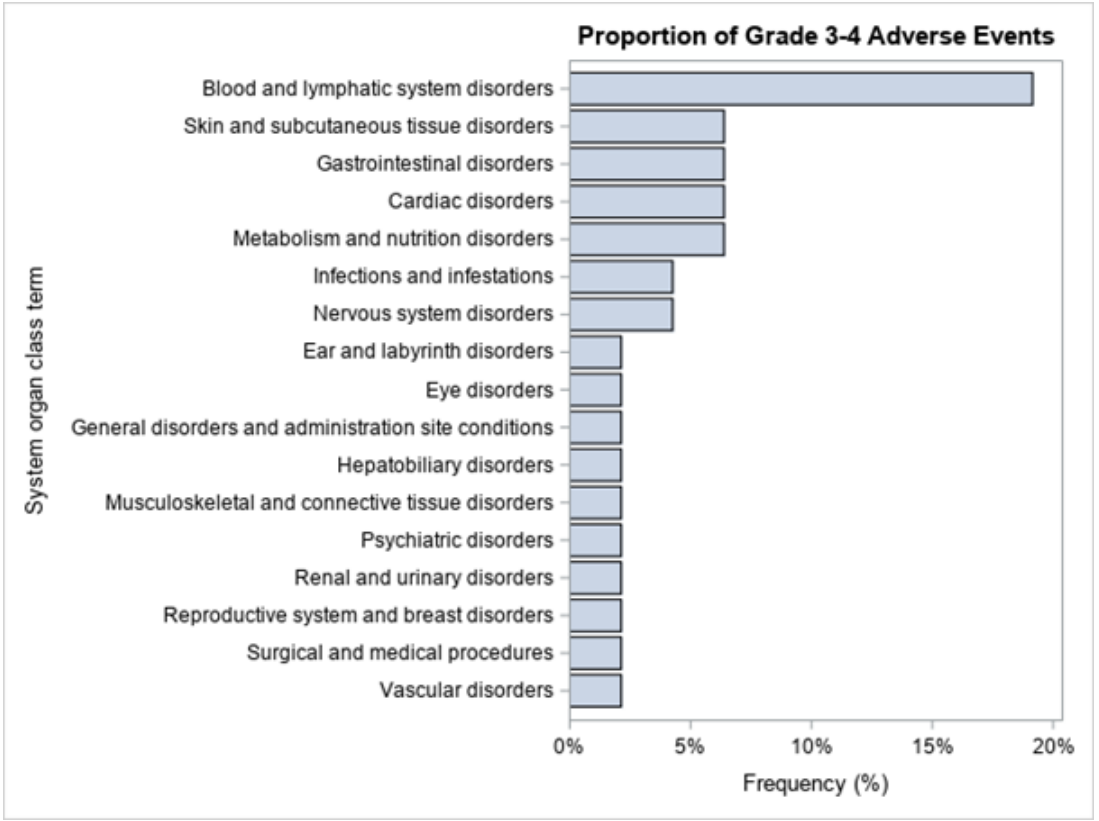
Fascination: Studiendesign



Adverse events (CTC grades 3 + 4)

FAsciNation

Cohort	AE grades 3 + 4 (%)
Nilotinib + Asciminib (20mg BID)	13 (10)
Nilotinib + Asciminib (40mg QD)	15 (12)
Dasatinib + Asciminib	10 (8)
Imatinib + Asciminib	9 (7)
Total	**47 (38)**



Reasons for discontinuation of the combination therapy within the first 12 months (n=21)

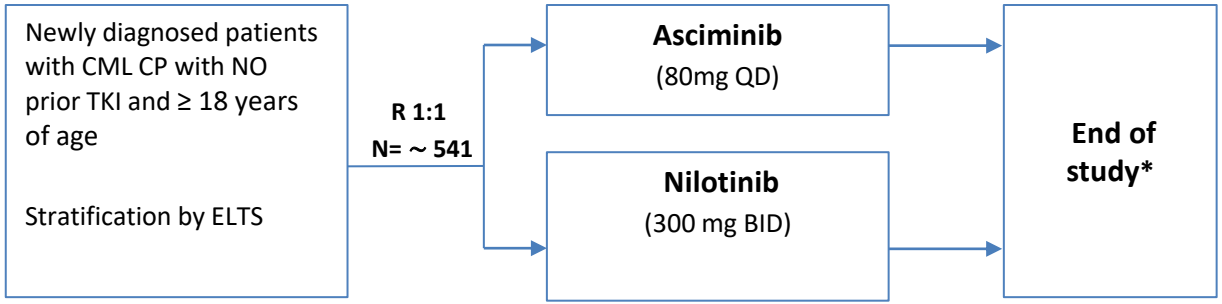
Reason	Number of pts
Skin toxicity	4
Gastroenterological toxicity	4
Treatment failure/progression	3
Cytopenia	2
Papillitis/ocular papillar edema	1
Polyneuropathy	1
Pain	1
Incompliance	1
Withdrawal of consent	4

Molecular response

	MMR (%)	MR^4 (%)	$MR^{4.5}$ (%)	MR^5 (%)	$MR^{5.5}$ (%)	N (total)
At month 3	26 (21)	5 (4)	2(2)	1 (1)	0	124
At month 6	69 (57)	28 (23)	13 (11)	6 (5)	2 (2)	121
At month 9	73 (63)	33 (29)	19 (17)	6(5)	3 (3)	115
At month 12	77 (68)	43 (38%)	25 (22)	9 (8)	3 (3)	114

ASC4START: Study Design / Patient Population

A phase IIIb, multi-center, open-label, randomized study of tolerability and efficacy of oral asciminib versus nilotinib in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase



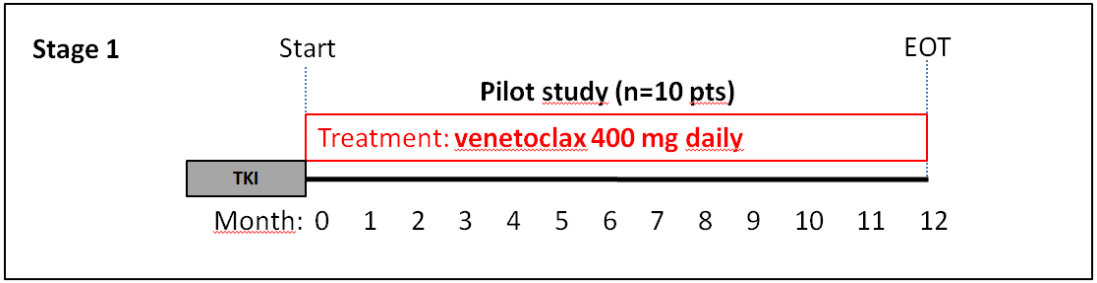
*Participants can be treated in the study until approximately 64 discontinuations of study treatment due to AE (TTDAE) are met. End of study is defined as when the necessary number of events has been reached and when end of treatment and the last assessments as per Table 1-1 are completed. Refer to Section 6.1.5 Treatment Duration for additional details.

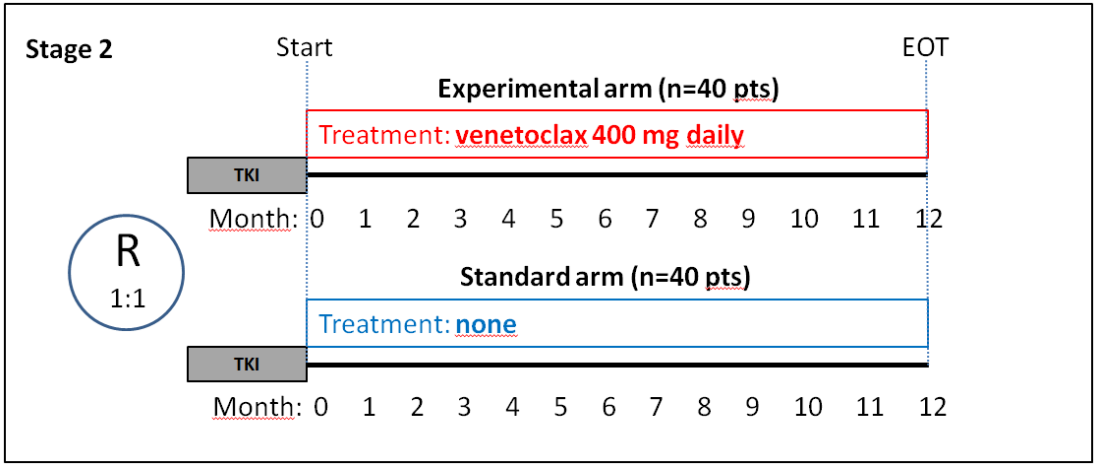
N= Approximate number of participants required to achieve 64 events (refer to Section 9.9)

Data on file. Study Protocol No. CABL001J12302 Clinical Trial Protocol.

Venetoclax after TKI to target persisting stem cells in CML

Variant: Pilot study





ELVN-001 is Selective for BCR::ABL1

- ELVN-001 has a very **selective** kinase profile
  - Clean vs. key off-targets in cells
  - 372 kinases screened at 1 µM compound (100 µM ATP)
  - Kinases with >50% inhibition selected for IC_{50} determination
  - >100x window vs. all but 2 kinases profiled
- ELVN-001 is also very **clean** (>10 µM) in an *in vitro* safety panel of >130 receptors

Cellular Phosphorylation IC_{50} (nM)

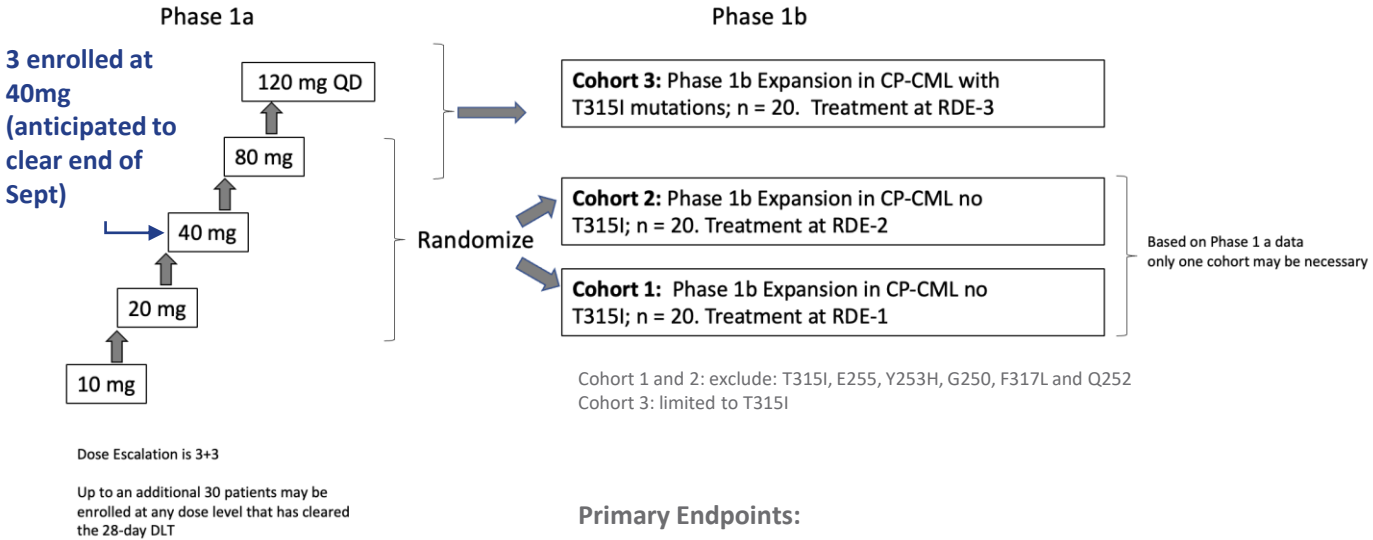
	cKIT	FLT3wt	PDGFRb	VEGFR2	cSRC
ELVN-001	>10,000	>10,000	>10,000	>10,000	>10,000
Ponatinib	30	3.8	89	4.8	630
Nilotinib	200	>10,000	720	2,900	>10,000
Dasatinib	0.6	>1,000	7.1	>1,000	10
Bosutinib	1,000	4,700	7,900	>10,000	16

Ba/F3 Mutant Cell line	Asciminib Fold IC_{50} over Native BCR-ABL1	ELVN-001 Fold IC_{50} over Native BCR-ABL1
Native BCR-ABL1	1	1
M244V	1*	1
G250E	0.2	>10
Y253F	3	8
Y253H	2	>10
E255K	2	>10
T315A	2	1
F317L	>10	>10
F317V	7	1
M351T	7	1
F359V	>10	1
H396P	>10	1

Reference: Abl kinases are required for vascular function, Tie2, and angiopoietin-1-mediated survival. Pendergast et al. *PNAS*. 2013;110(30):12432-7.

ELVN-001-101 Phase 1 Dose Escalation & Expansion in CML

- Chronic Phase CML
- Failed or intolerant to available therapies known to be active for treatment of their CML
  - Failed per 2020 ELN Recommendations
  - Intolerant per Investigator
  - No bone marrow biopsy/aspirate required



Cohort 1 and 2: exclude: T315I, E255, Y253H, G250, F317L and Q252
Cohort 3: limited to T315I

Primary Endpoints:

- Incidence of AEs, ECG and lab abnormalities

Secondary Endpoints:

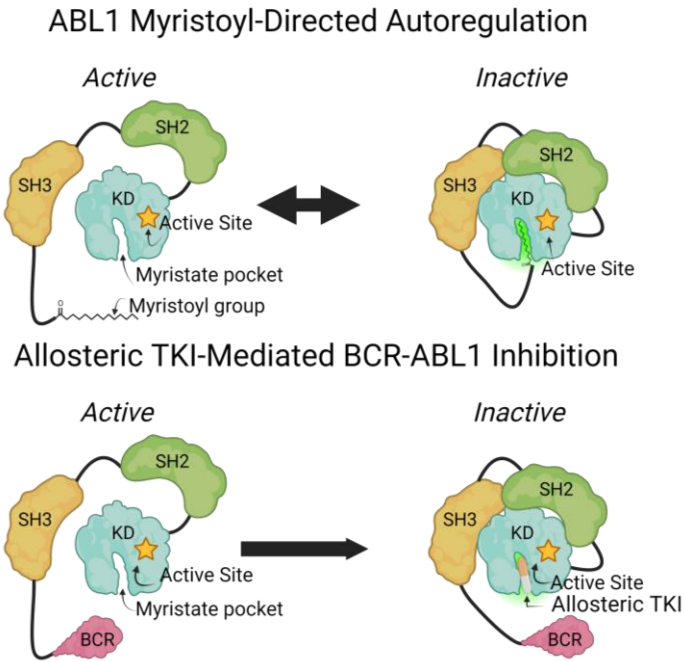
- Molecular response
- PK parameters

CP = chronic phase
AP = accelerated phase
ELN = European Leukemia Net
RDE = Recommended Dose for Expansion
AE = adverse event
ECG = electrocardiogram
PK = pharmacokinetic

TERN-701: Allosteric BCR::ABL1 inhibitor

TERN-701 is an allosteric inhibitor of BCR::ABL1

- Potent allosteric inhibitor of BCR::ABL1, optimized for selectivity and pharmacokinetic parameters, that binds the myristate pocket
- Maintains activity against ATP site mutations which confer resistance to active site-targeting TKIs

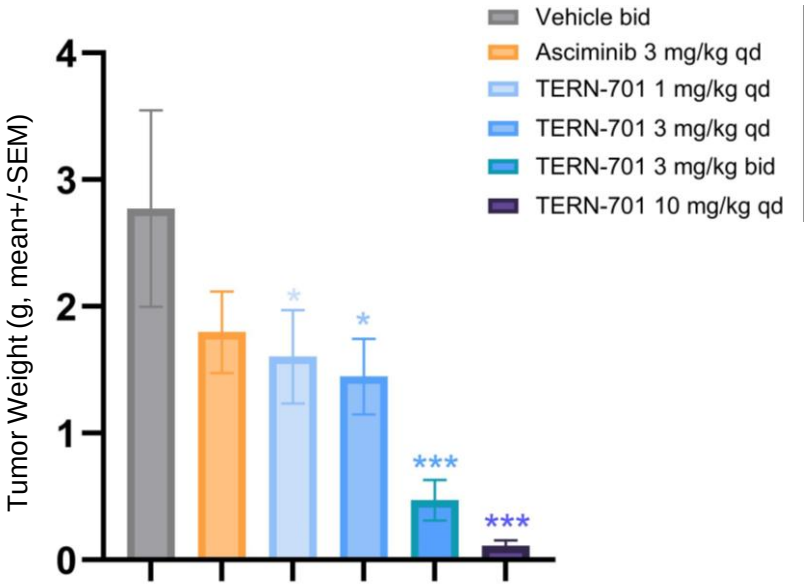


Source: Alves R, et al. Cancers (Basel). 2021.

In Preclinical Models of CML, TERN-701 Showed a Greater Anti-Tumor Effect vs. Asciminib at Equivalent Doses & Dosing Frequency

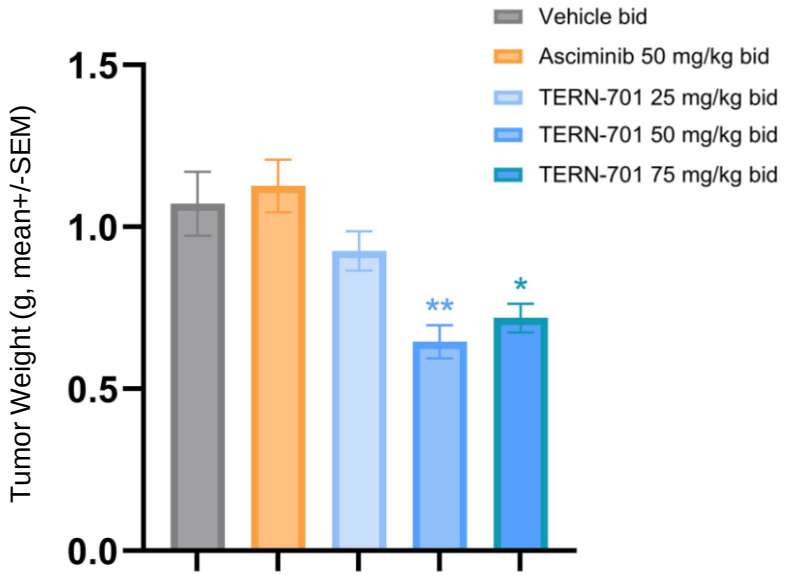
K562 Xenograft

(Day 14)



Ba/F3 BCR::ABL1-T315I Allograft

(Day 15)



Note: NOD-SCID (K562) and BALB/c nude mice (Ba/F3T315I) were implanted with CML cells, randomized, and administered the indicated TKIs once tumor volumes reached a mean size of 110 mm. Mean tumor weights for each of the treatment groups at the conclusion of the study. All error bars represent the SEM. *p<0.05, **p<0.01, ***p<0.001.

1. asciminib was utilized as the free base, TERN-701 was formulated as an optimized salt form

Source: Zhou et al. ASPET 2023. TERN-701 poster

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