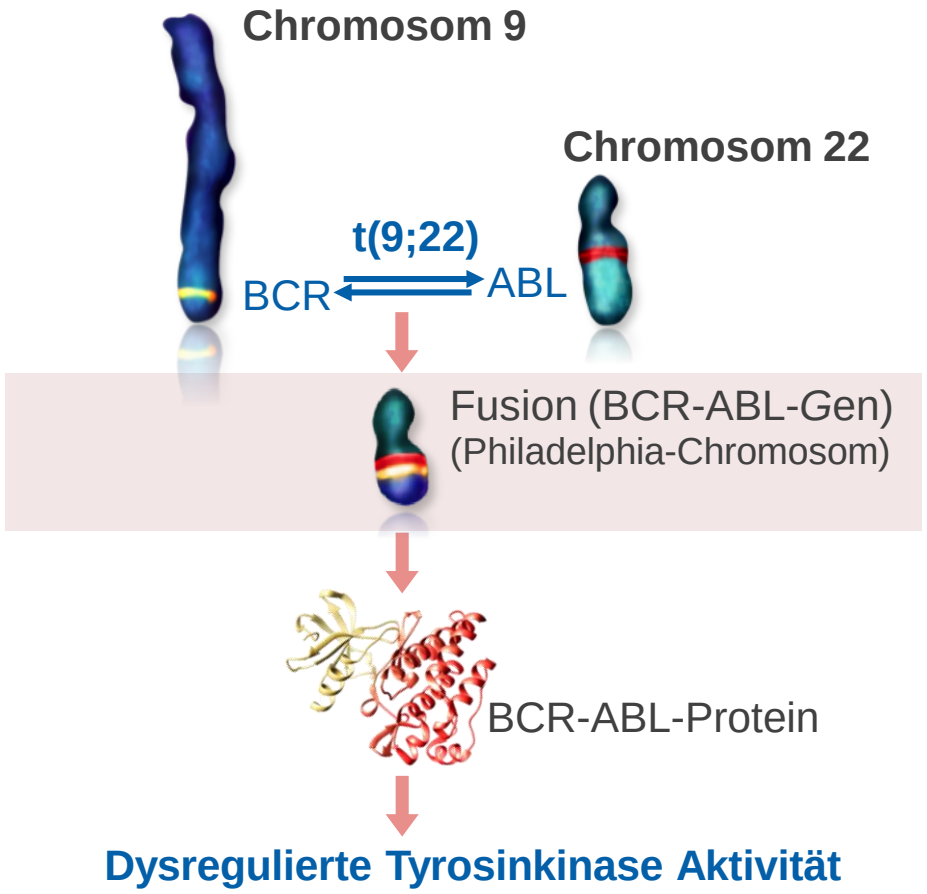
Erstlinientherapie der CML: Etabliertes Vorgehen und Studien

Philipp le Coutre, Charité

Disclosures:

- Novartis, BMS, Pfizer, Incyte, Blueprint, GSK, JAZZ

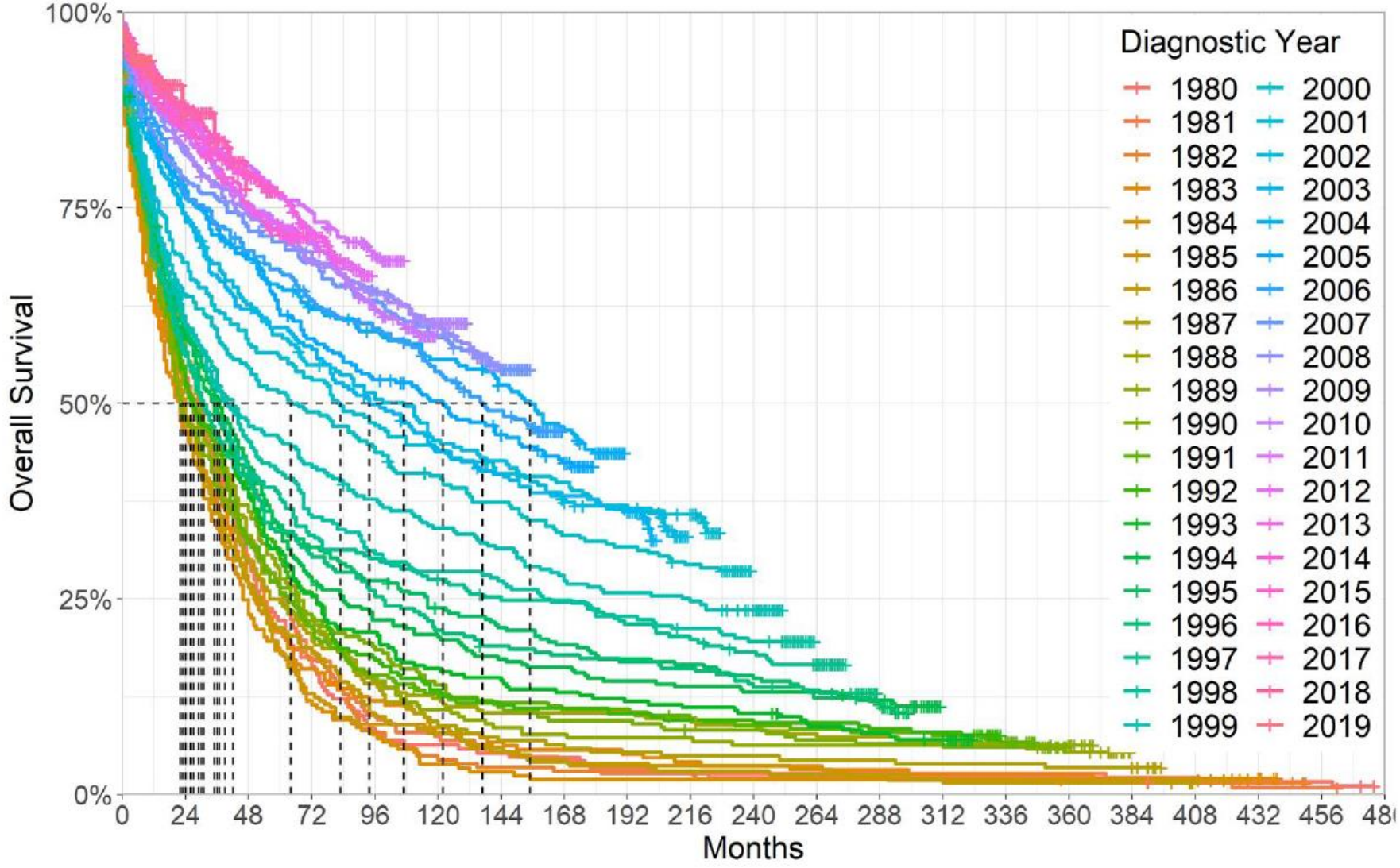
Die Philadelphia-Translokation



- Erkrankung der pluripotenten hämatopoetischen Progenitor- und Stammzelle[1-2]
- Nachweis Fusionsgen BCR::ABL1 (PCR) sowie Ph-Chromosom (Zytogenetik/FISH)[1-2]
- Inzidenz von 1-2 pro 100.000 Einwohner pro Jahr[3]
- 13% aller neudiagnostizieren Leukämien[3]
- Steigende Prävalenz durch sinkende Mortalitätsrate[4]

1 Faderl S, et al. N Engl J Med 1999.
2 Baccarani M, et al. Ann Oncol 2009
3. Rohrbacher M, et al. Best Pract Res Clin Haematol 2009
4. Huang X,et al. Cancer 2012

Prognose 1980 - 2019

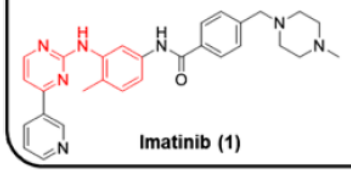


K Sasaki et al.: Cancer 2023

Untersuchungen bei Erstdiagnose

- Anamnese: Abgeschlagenheit, Schwäche, Appetitlosigkeit, Gewichtsverlust, Knochenschmerzen, Oberbauchbeschwerden
- Körperliche Untersuchung: Milz- und Lebergröße
- Blutbild: Leukozyten mit Differenzialblutbild, Plt, Hb und Hkt
- Peripheres Blut: Multiplex PCR auf BCR::ABL1 Transkripte
- KM Aspirate: Zytologie
Zytogenetik
- KM Biopsie: Fibrosegrad, Blasten

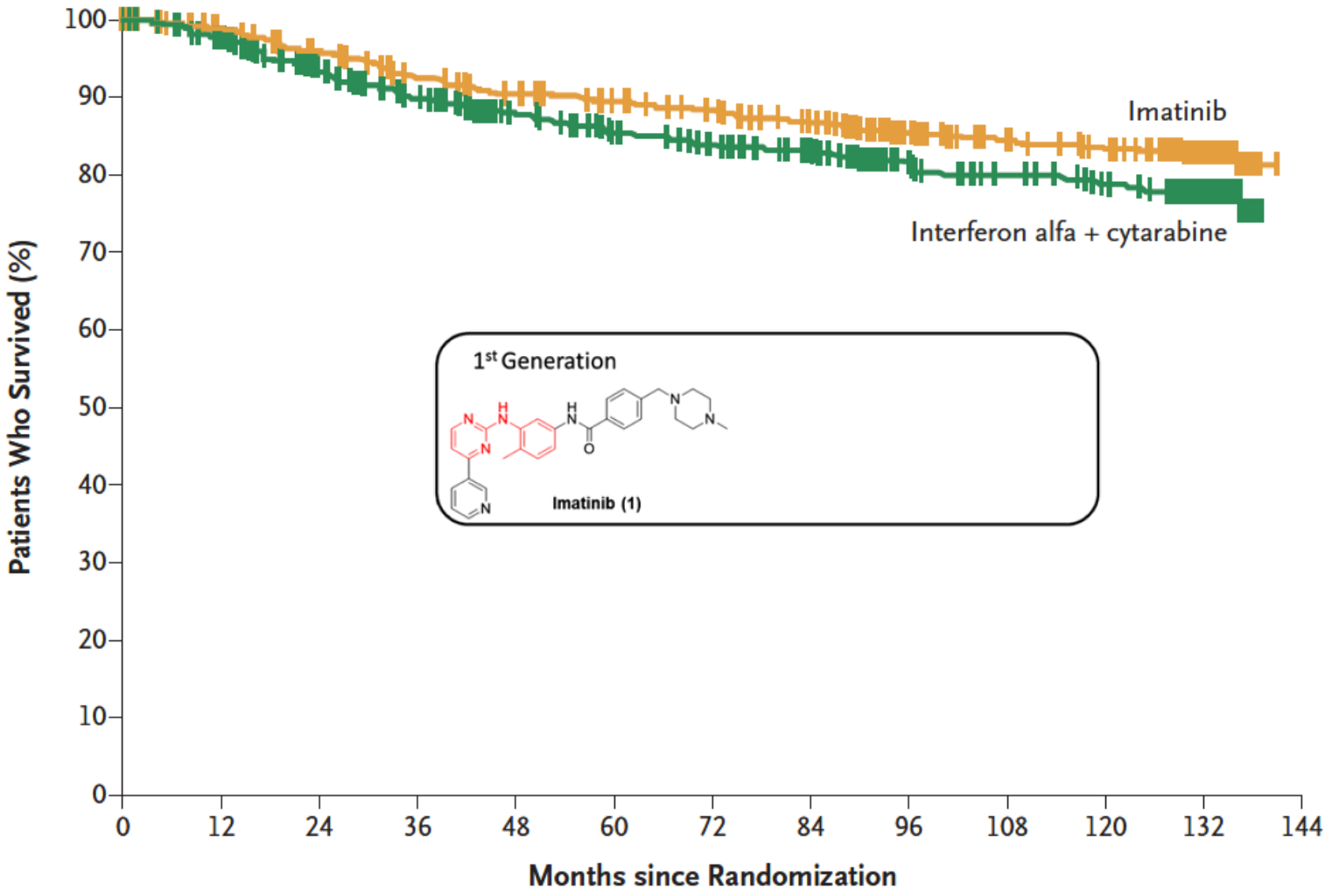
1st Generation



Imatinib (1)

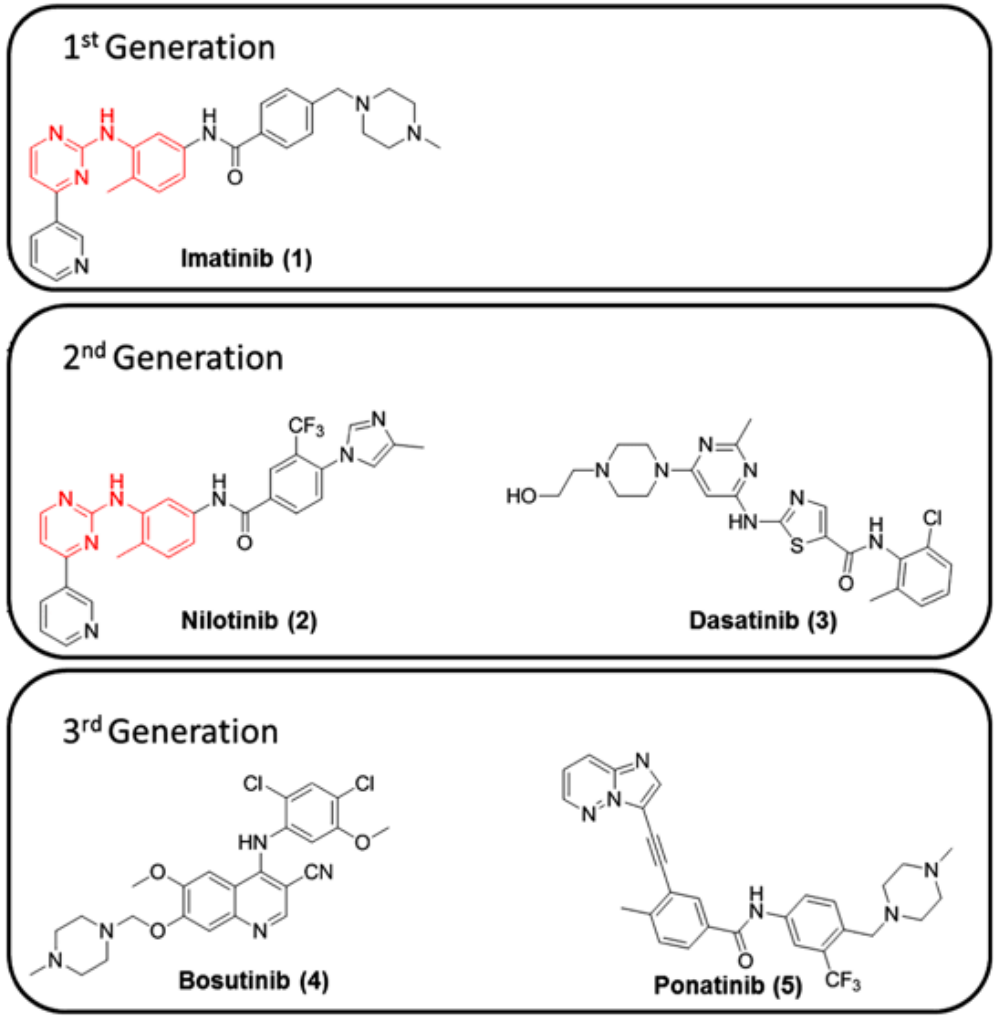
IRIS Studie 10 Jahre Follow Up

	No. of Patients	No. of Deaths	No. of Patients with Censored Data	10-Yr Survival % (95% CI)
Imatinib	553	89	464	83.3 (80.1–86.6)
Interferon alfa + cytarabine	553	105	448	78.8 (75.0–82.5)

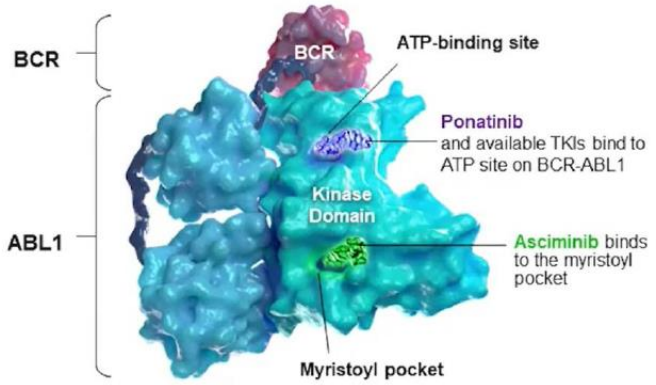


A Hochhaus et al.: NEJM 2017

Zugelassene Tyrosinkinaseinhibitoren



- Imatinib 400 mg
- Nilotinib 2 x 300 mg
- Dasatinib 100 mg
- Bosutinib 400/500 mg
- Ponatinib 45 mg

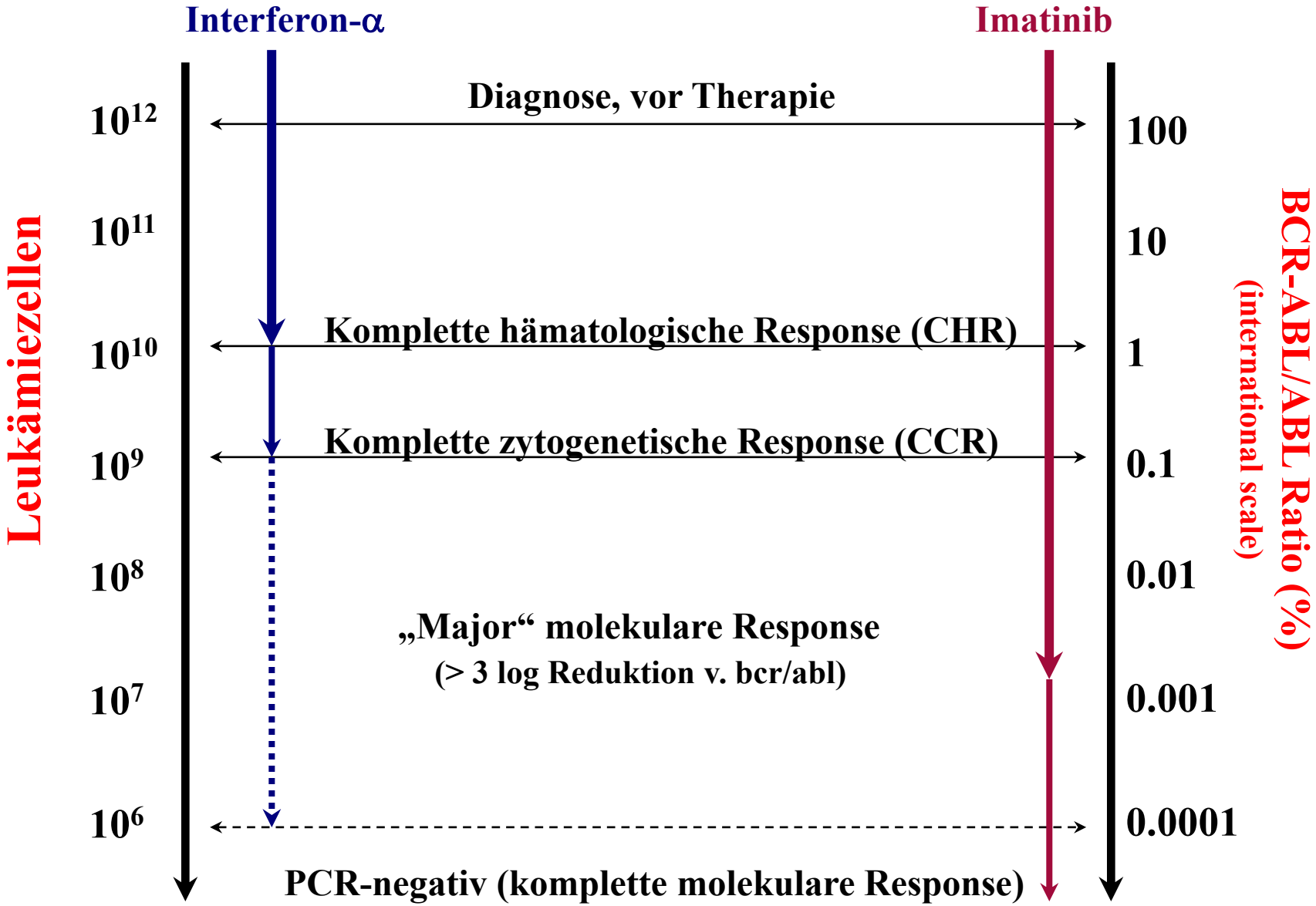


- Asciminib 2 x 40 mg

STAMP: (Specifically Targeting the ABL Myristoyl Pocket)

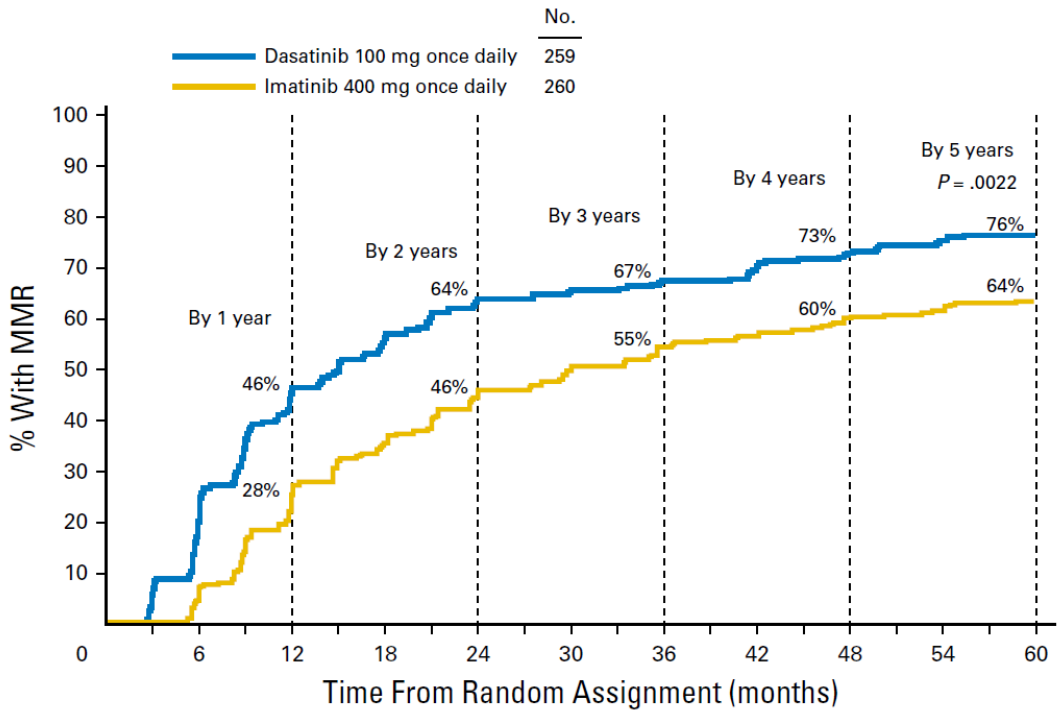
FC Vasconcelos et al.: Med Chem Res 2017

CML: Therapieziele in der Imatinib-Ära

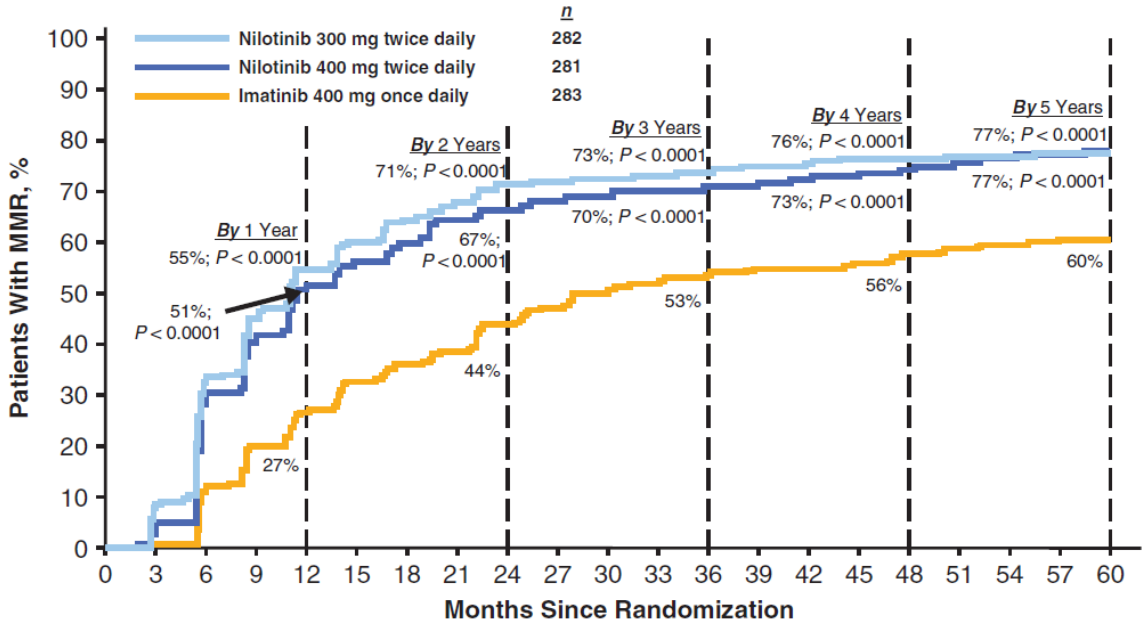


2 Generations TKI

DASISION



ENESTnd



J Cortes et al.: JCO 2016

A Hochhaus et al.: Leukemia 2016

Prognosescores

Empfehlung

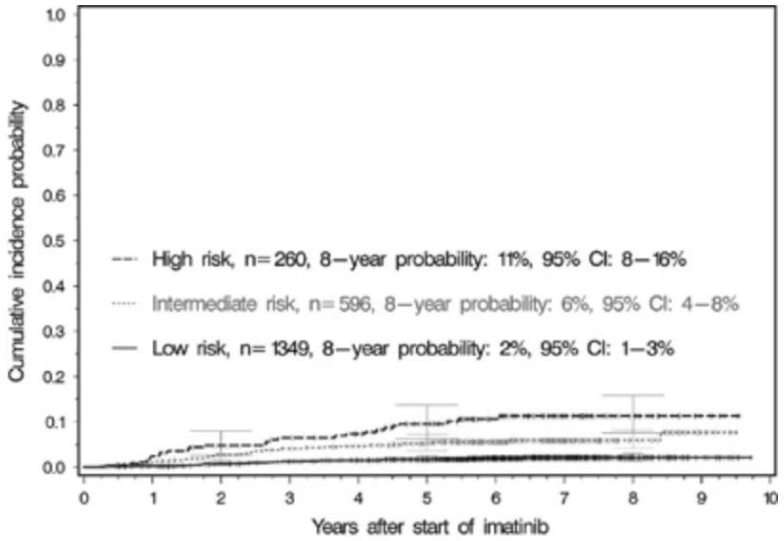
	Sokal (prä-TKI)	EURO (prä-TKI)	EUTOS*	ELTS
Alter (Jahre)	√	√	-	√
Milz (cm)	√	√	√	√
Thrombo (/nl)	√	√	-	√
Blasten pB (%)	√	√	-	√
Basophile (%)	-	√	√	-
Eosiniphile (%)	-	√	-	-

* Nur Niedrig- und Hochrisiko

https://www.kompetenznetz-leukaemie.de/content/aerzte/cml/scores/eutos_score/

Erkrankungsprognose unter Imatinib:
EUTOS Long-term Survival Score (ELTS)

Milzgröße unter Rippenbogen – Blasten (PB) – Thrombozyten (PB) - Alter



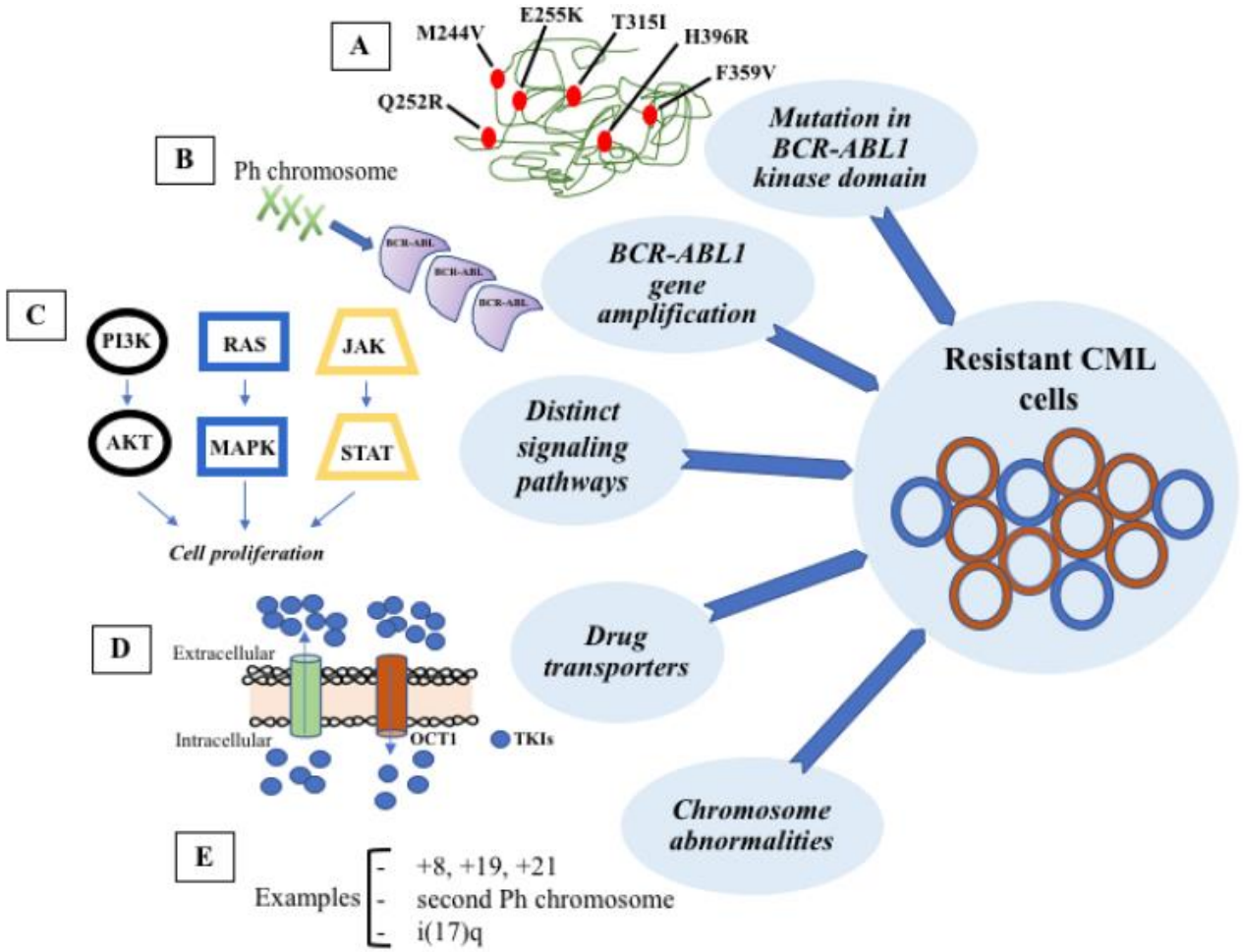
Number of patients still at risk (n) at different years of observation

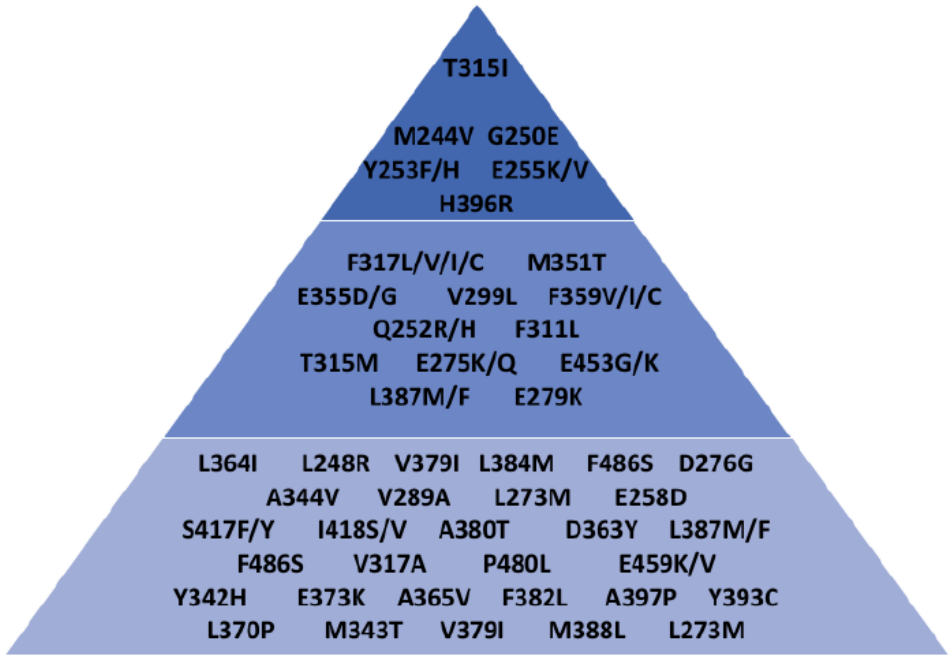
Year	*0*	*2*	*5*	*8*
High risk, n	260	226	179	28
Intermediate risk, n	596	557	451	60
Low risk, n	1349	1283	1113	132

Cumulative incidence probabilities of dying because of CML in 2205 patients from the in-study registry stratified for the risk groups according to the ELTS score. At 2, 5 and 8 years, horizontal crossbars indicate the upper and lower limit of the 95% CI for the estimated probability.

Pfirrmann M. Leukemia 2015.

Resistenzmechanismen





G P Amarante-Mendes et al.: Pharmaceutics 2022

Mutationsprofil versus IC50

Mutated region	BaF3 (*BCR::ABL*) Mutant Cells	Anti-proliferation Assay (IC50, nM)					
		Imatinib	Nilotinib	Dasatinib	Asciminib	Ponatinib	HQP1351
Wild-type	-	565 ± 656	31 ± 4	10 ± 3	31 ± 4	11	6 ± 3
SH2-contract region	M351T	1298 ± 542	37 ± 4	8 ± 4	47 ± 34	13 ± 1	9 ± 1
Substrate-binding region	F359V	>10000	1710 ± 635	598 ± 624	6066 ± 355	466 ± 73	50 ± 16
P-loop	E255K	8222 ± 484	648 ± 395	14 ± 1	10	49 ± 4	22 ± 13
	Y253H	8936±1774	497 ± 122	11 ± 2	28 ± 13	37 ± 4	7 ± 1
	E255V	7565±3268	587 ± 151	29 ± 15	24 ± 4	56 ± 1	27 ± 11
	M244V	2963 ± 83	236 ± 152	40 ± 1	5223 ± 4899	75 ± 42	41 ± 8
Gate keeper	T3151	>10000	3425 ± 650	2525 ± 322	148 ± 14	33 ± 11	24 ± 10
Hinge region	F317L	526 ± 56	89 ± 8	11 ± 1	6 ± 3	7 ± 1	8 ± 3
	F311I	3547 ± 223	226 ± 122	13 ± 0	107 ± 1	30 ± 8	23 ± 13
SH3-contact region	V299L	1987 ± 1237	103 ± 6	118 ± 2	562 ± 552	10 ± 4	8 ± 4
T3 151 + Other Compound Mutation	T315I/E255V	>10000	646 7± 4431	3571 ± 1385	93 ± 86	244 ± 125	26 ± 11
	T315I/F359V	>10000	4586 ± 1397	3392 ± 211	6631 ± 1201	101 ± 22	20 ± 10
	T315I/G250E	>10000	8511 ± 5599	5001 ± 2939	7451 ± 3057	130 ± 16	33 ± 2
	T315I/E255K	>10000	>10000	470 6± 803	8944 ± 748	339 ± 12	40 ± 5
	T315I/E453K	8466 ± 1628	>10000	4724 ± 155	2931 ± 74	130 ± 5	61 ± 27
	T315I/M351T	7603 ± 1498	>10000	7683 ± 3645	>10000	127 ± 5	67 ± 44
	T315I/F311I	7144 ± 2459	>10000	4789 ± 1739	7061 ± 1423	438 ± 88	78 ± 46
	T315I/H396R	8953 ± 5314	>10000	9286 ± 3386	>10000	211 ± 134	79 ± 54
	T315I/Y253H	>10000	>10000	7080 ± 3233	6981 ± 2481	889 ± 100	114 ± 1
	T315I/F317L	>10000	>10000	>10000	860 ± 96	688 ± 412	117 ± 23
	T315M	>10000	>10000	>10000	996 ± 405	1987 ± 1414	217 ± 131
Other Compound Mutation	G250E/V299L	6486 ± 2622	641 ± 368	570 ± 599	2601 ± 2903	12 ± 3	14 ± 2
	F317L/F359V	7195 ± 1729	926 ± 24	50 ± 12	5214 ± 810	24 ± 12	25 ± 13
	Y253H/E255V	>10000	7026 ± 2183	231 ± 92	5014 ± 2920	772 ± 220	122
	T253H/F359V	>10000	>10000	110 ± 1	>10000	432 ± 23	311 ± 35

	Sensitive. IC_{50}≤100nM
	Intermediate sensitive IC_{50}=100 -1000 nM
	Insensitive IC_{50}>1000 nM

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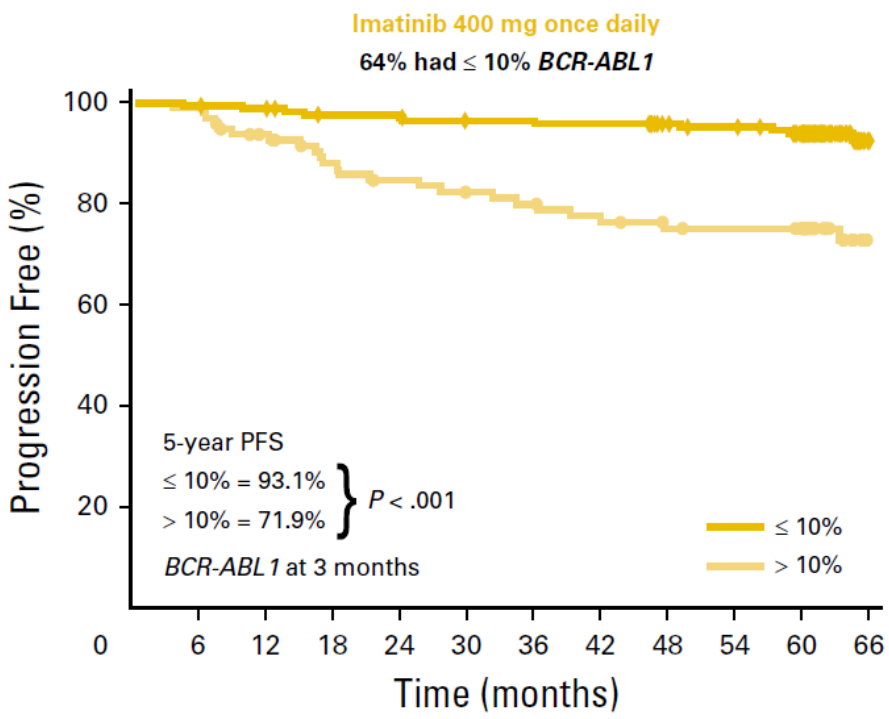
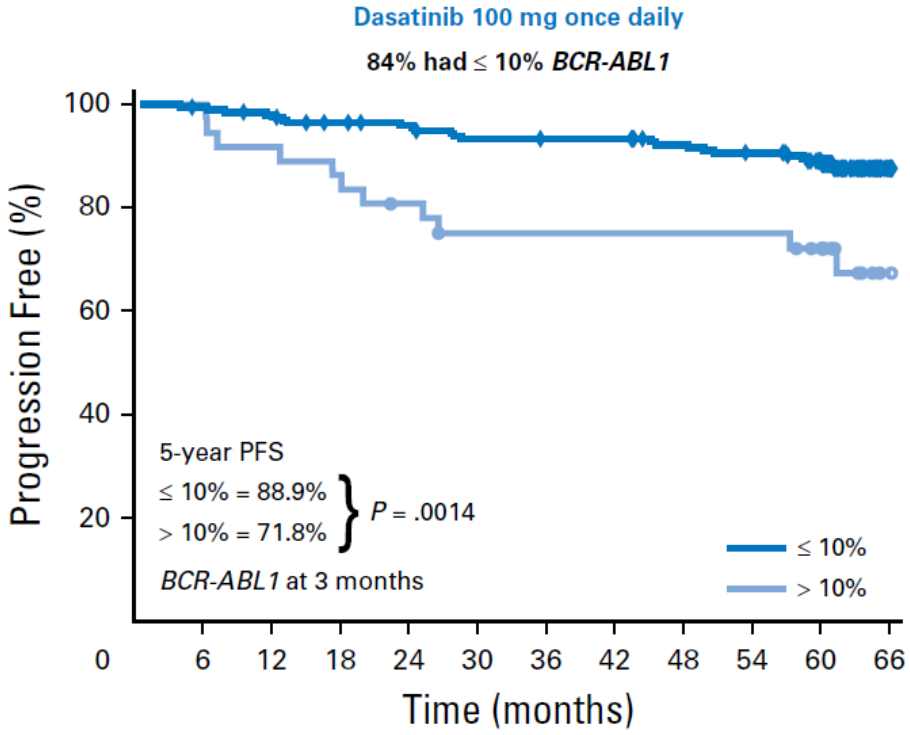
J Senapati et al.: Blood Cancer Journal 2023

Signifikanz der BCR::ABL1 Last Monat 3

Significance of BCR::ABL 1 evaluation after 3 months





Month 3: BCR::ABL1 < 10 %
Month 6: BCR::ABL1 < 1 %

J Cortes et al.: JCO 2016

Meilensteine des Ansprechens auf die TKI Therapie

Meilenstein	Versagen	Warnung	Optimales Ansprechen
Diagnose		Hochrisiko-Score; Zytogenetische Zusatz-Aberrationen: +Ph, +8, +19, iso(17), -7, 3q-Aberrationen, komplex aberranter Karyotyp	
3 Monate	Keine CHR Ph >95%	Ph 36–95% BCR-ABL1 >10%	Ph ≤35% BCR-ABL1 ≤10%
6 Monate	Ph >35% BCR-ABL1 >10%	Ph 1–35% BCR1 >1–10%	Ph 0% BCR-ABL1 ≤1%
12 Monate	Ph ≥1% BCR-ABL1 >1%	BCR-ABL1 >0,1–1%	BCR-ABL1 ≤0,1%
>18 Monate			BCR-ABL1 ≤0,1%
Jederzeit	Verlust der MMR mit mindestens 5-fachem BCR-ABL 1-Anstieg		

- Ph, Philadelphia-Chromosom; CHR, komplette hämatologische Remission; MMR, major molecular response.

- Onkopedia Leitlinie CML, https://www.onkopedia.com

Monitoring

	ED	Bis Monat 3	Monat 3	Monat 6	Später
Hämatologisch	√	√ 14tägig bis CHR	√	√	√ Alle 3 Monate
Zytogenetisch	√		√	√	√ Alle 6 Monate bis zur CCyR √ Bei Zytopenie und V.a. Resistenz
Molekular	√		√	√	√ Alle 3 Monate bis MMR Alle 3 – 6 Moante bis DMR √ Nach Absetzen: • Alle 4 Wochen im ersten Halbjahr • Alle 6 Wochen im zweiten Halbjahr • Dannach alle drei Monate

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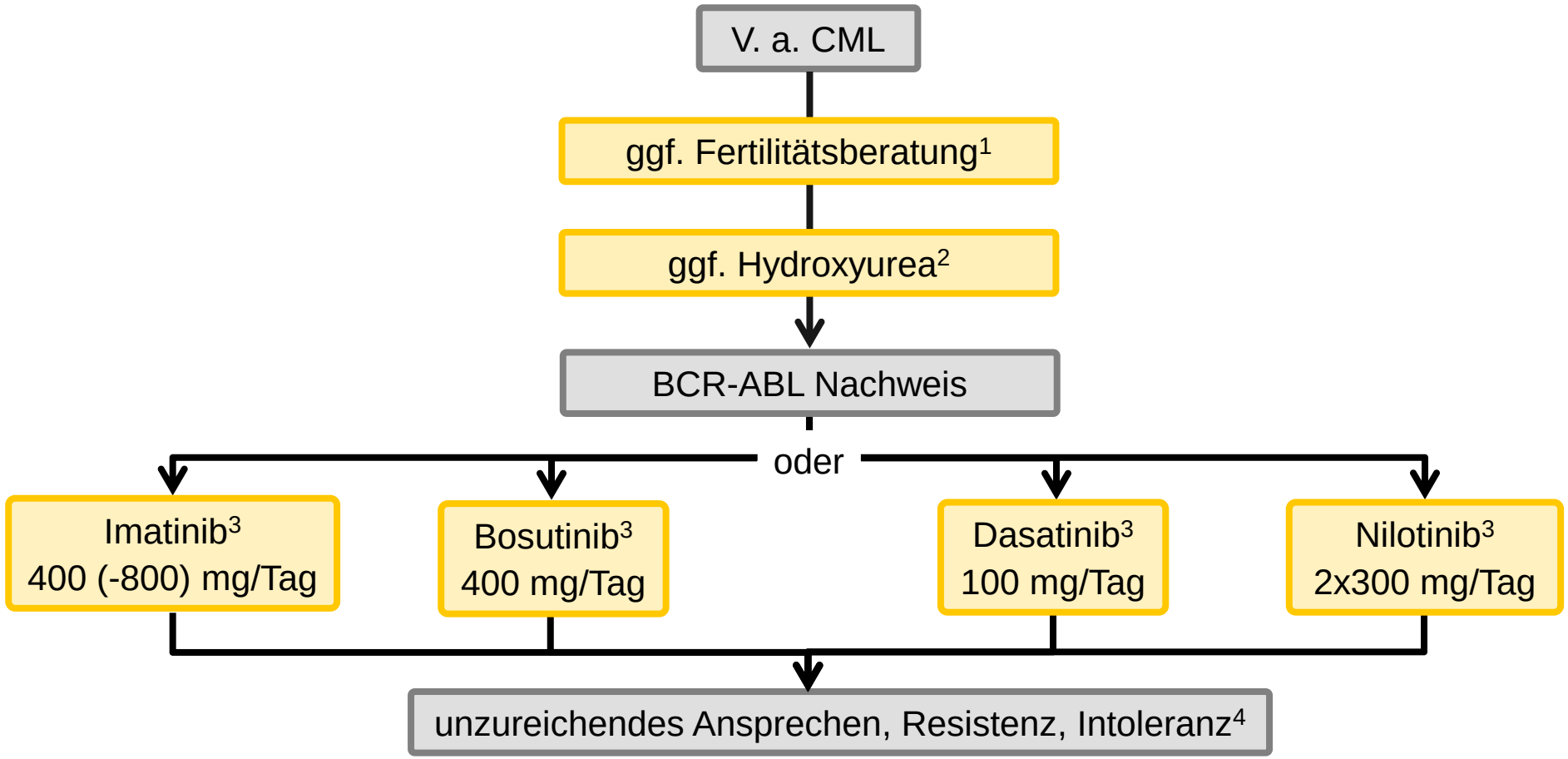
Modified from: https://www.onkopedia.com/de

Auswahl der Erstlinientherapie DGHO



- 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 23.02.2022).

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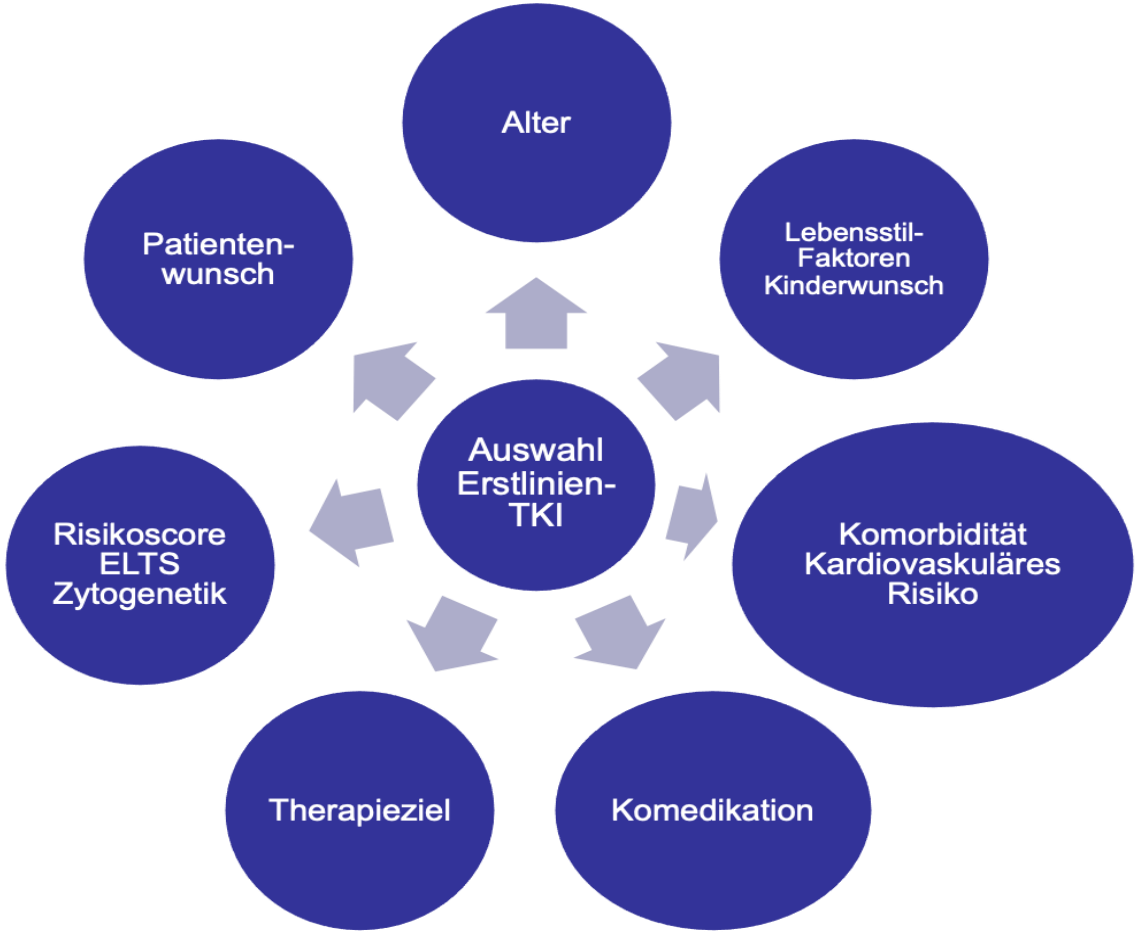
Auswahl der Erstlinientherapie



Imatinib	Nilotinib (Tasigna)	Dasatinib (Sprycel)	Bosutinib (Bosulif)
400 mg	2 x 300 mg	100 mg	400 / 500 mg

TKI Toxizitäten

	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	-	+	++	-	+++	?

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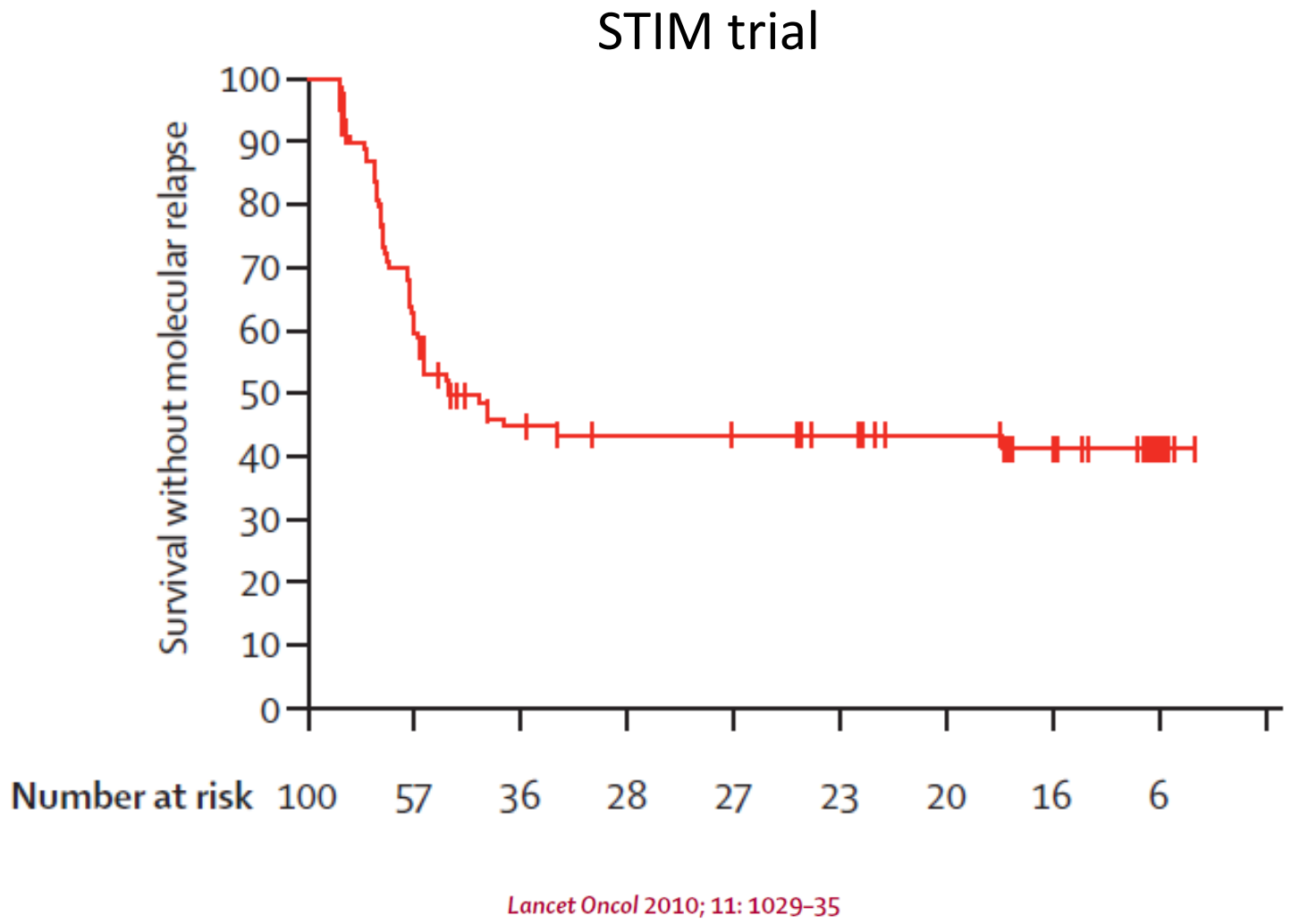
K Yoshifuji and K Sasaki: Front in Oncol 2022

Absetzstudien bei Patienten jenseits MR4



Lancet Oncol 2010; 11: 1029–35

F Mahon et al.: Lancet Oncology 2010

Absetzstudien bei Patienten jenseits MR4

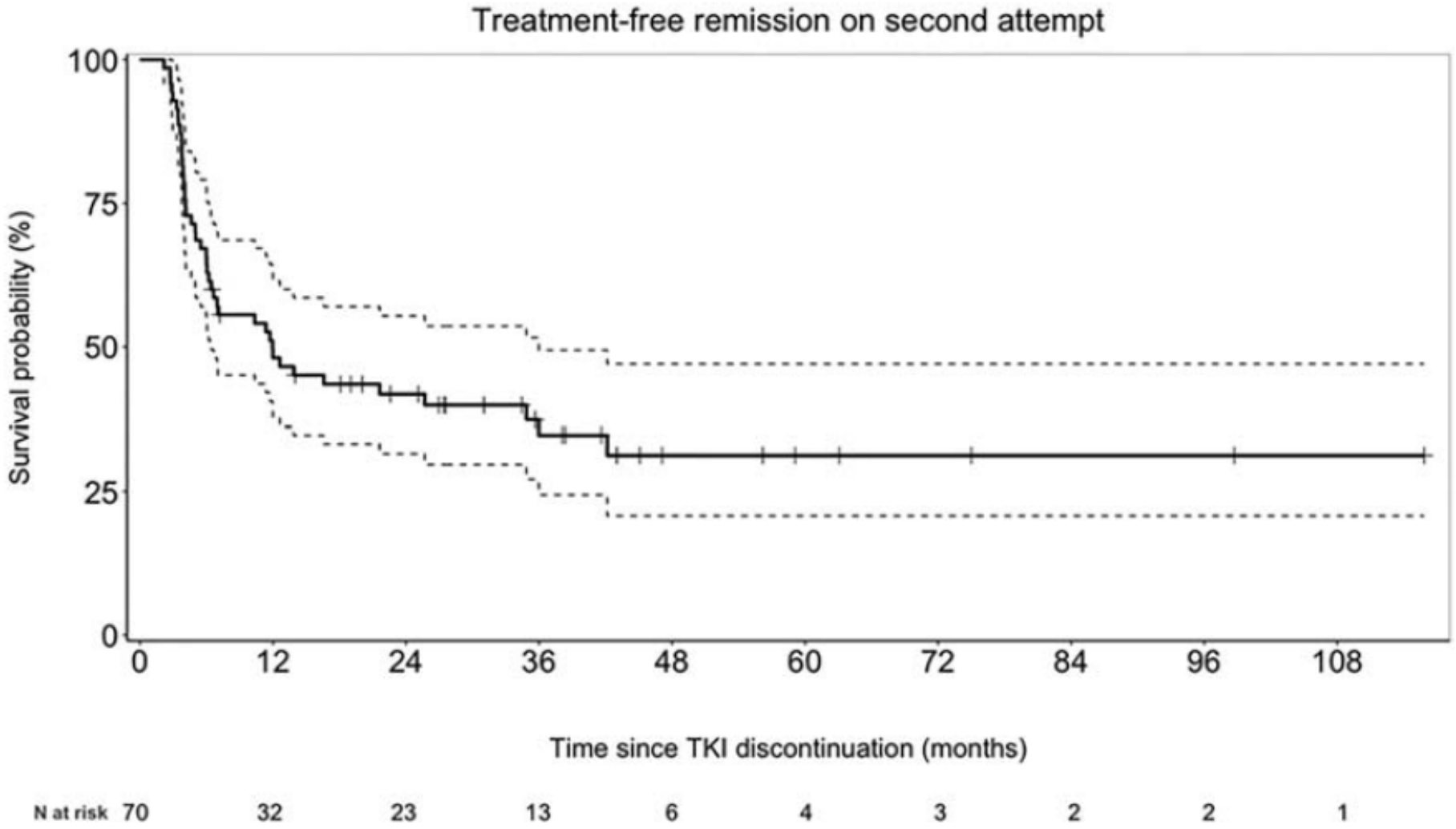
TABLE 1 | Participant characteristics and loss of major molecular response (MMR) rates.

References	Sample size	Male ratio (%)	Age	Sokal (%)			No. of patients with loss of MMR (%)			
				Low	Intermediate	High	3 months	6 months	12 months	24 months
Takahashi et al. (23)	43	44	57	25 (58.1)	15 (34.9)	3 (7)	4 (9.3)	11 (25.6)	14 (32.6)	17 (39.5)
Rousselot (22)	80	52	55	41 (51.3)	22 (27.5)	16 (20)	25 (31.3)	25 (31.3)	28 (35)	29 (36.3)
Mori et al. (21)	108	59	49	40 (37)	29 (26.9)	8 (7.4)	6 (5.6)	30 (27.8)	41 (38)	52 (48.1)
Lee et al. (14)	90	42	56	29 (32.2)	23 (25.6)	15 (16.7)	20 (22.2)	29 (32.2)	34 (37.8)	37 (41.1)
Ross et al. (15)	190	50	55	62 (32.6)	50 (26.3)	28 (14.7)	25 (13.2)	70 (36.8)	92 (48.4)	97 (51.0)
Rea et al. (17)	60	37	60	32 (53.3)	16 (17.8)	9 (15)	11 (18.3)	18 (30)	21 (35)	24 (40)
Takahashi (13)	68	62	55	51 (75)	6 (8.8)	11 (16.2)	9 (13.2)	19 (27.9)	22 (32.4)	24 (35.3)
Takahashi et al. (24)	78	58	57	44 (56.4)	17 (21.8)	16 (20.5)	NR	25 (32.1)	25 (32.1)	29 (37.2)
Saussele (10)	758	52	60	259 (34.2)	197 (26)	128 (16.9)	136 (17.9)	323 (42.6)	340 (44.9)	379 (50)
Mahon et al. (18)	126	44	56	NR	NR	NR	NR	NR	34 (26.9)	36 (28.5)

NR, not reported.

Chen K-K, Du T-F, Yang W. Frontiers in Oncology. 2019

Zweiter Absetzversuch

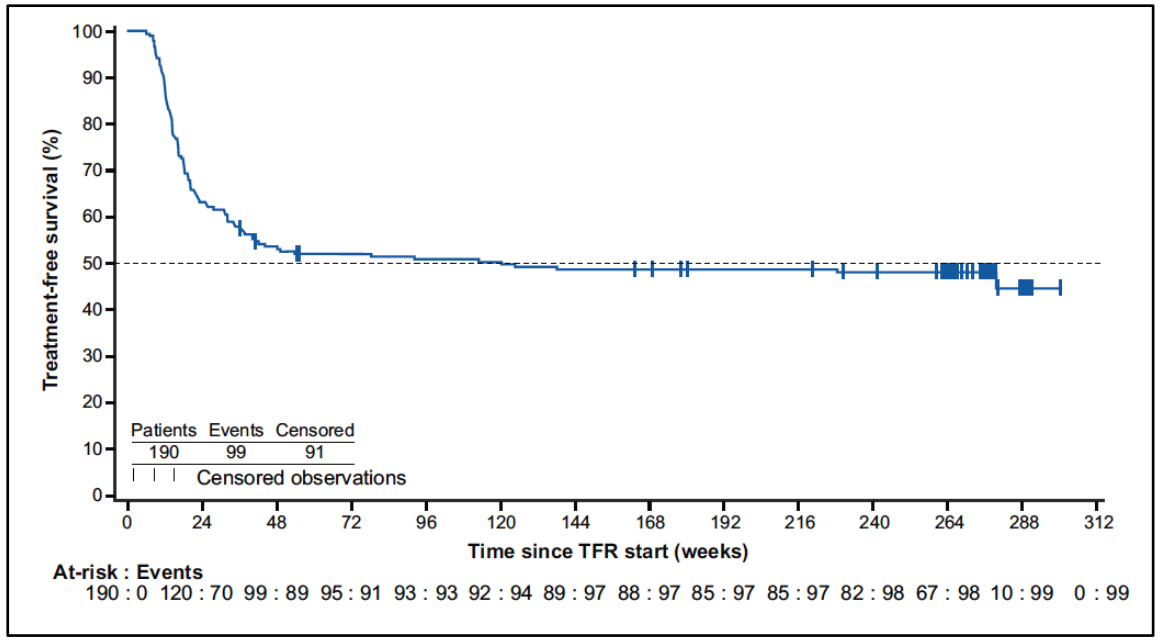


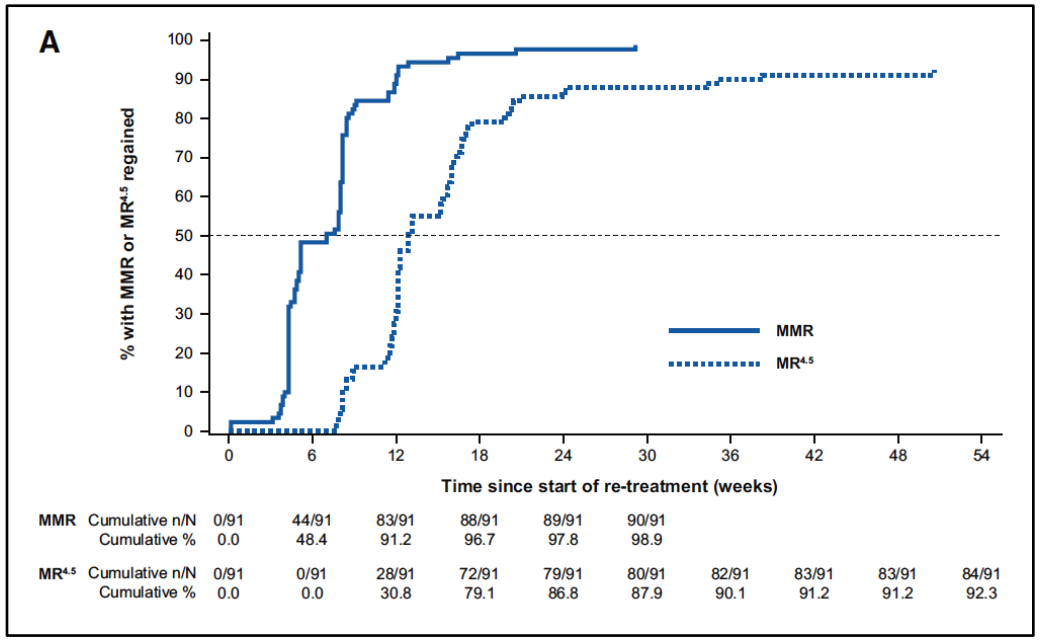
L Legros et al.: Cancer 2017

Absetzstudien bei Patienten mit 2nd Gen TKI

Therapiefreie Zeit:

ENESTfreedom Studie: 5-Jahres-follow-up





Radich JP. et al, Leukemia. 2021

Erstlinienstudien

WHO Clasification 2022

Leukemia www.nature.com/leu

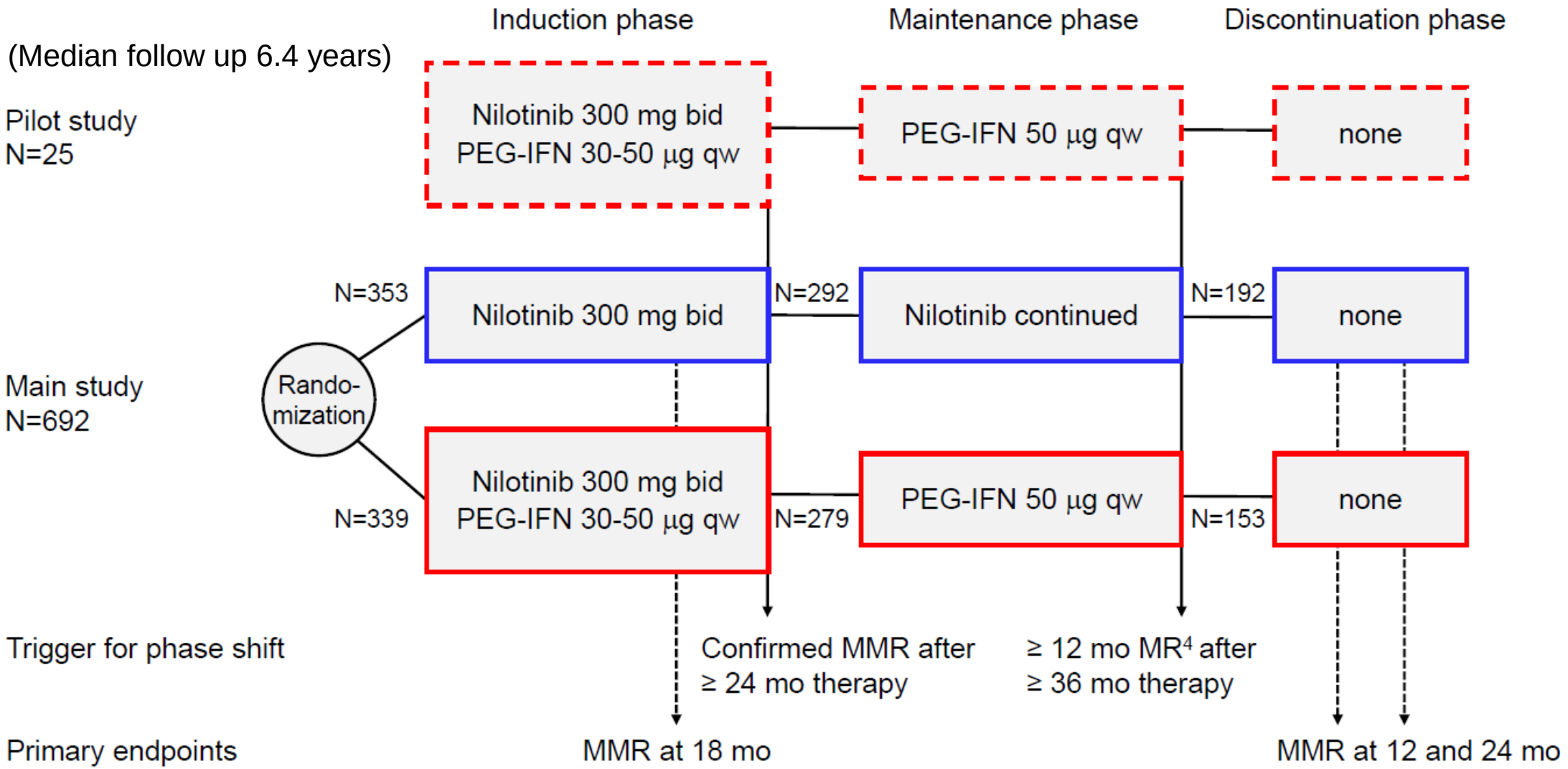
REVIEW ARTICLE OPEN

The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

CML is 80–90% [10, 11]. The designation of AP has thus become less relevant, where resistance stemming from *ABL1* kinase mutations and/or additional cytogenetic abnormalities and the development of BP represent key disease attributes [12, 13]. Accordingly, AP is omitted in the current classification in favour of an emphasis on high risk features associated with CP progression and resistance to TKI. Criteria for BP include: (1) ≥20% myeloid blasts in the blood or bone marrow; or (2) the presence of an extramedullary proliferation of blasts; or (3) the presence of increased lymphoblasts in peripheral blood or bone marrow. The

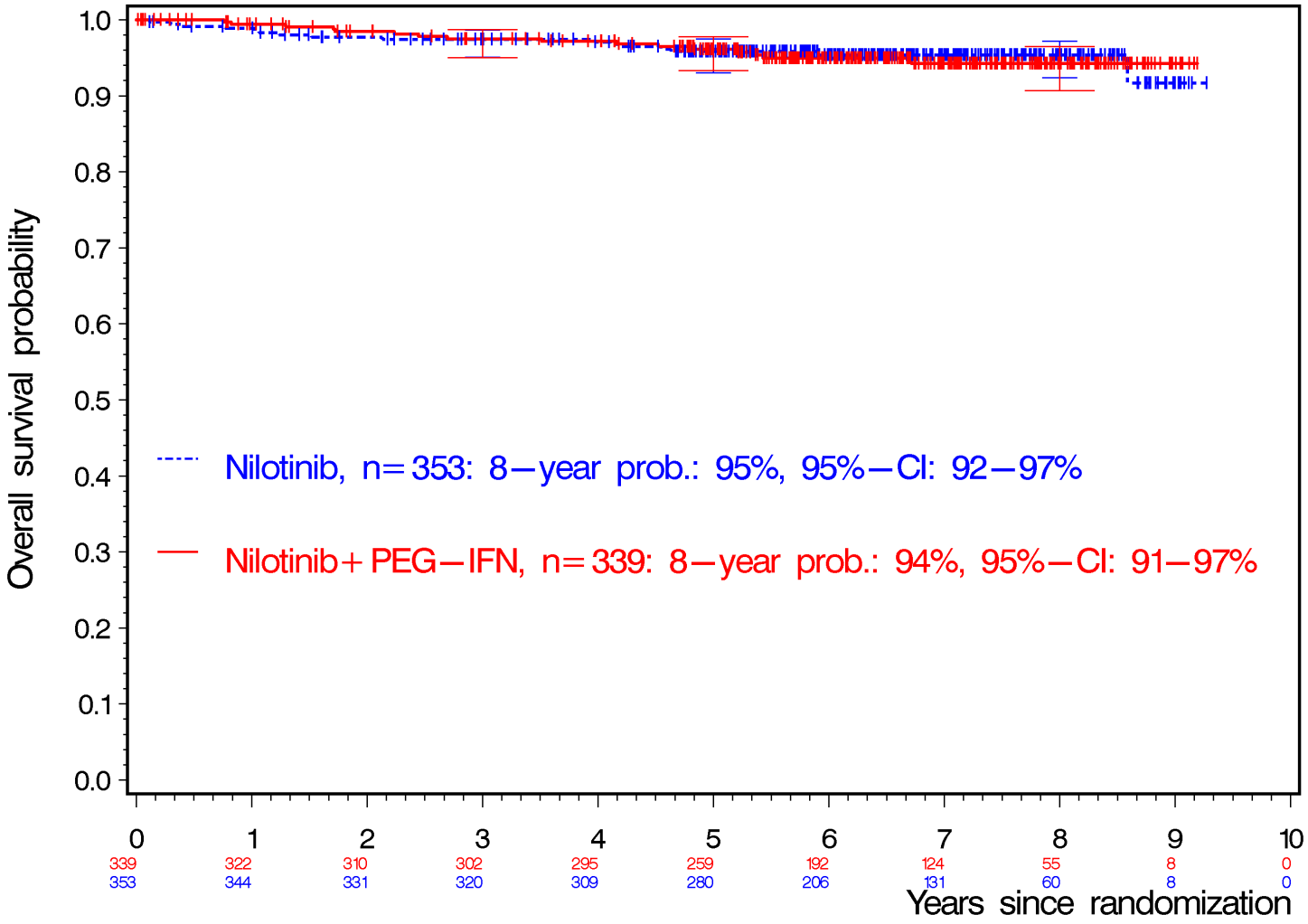
TIGER TRIAL

N=717 (Median follow up 6.4 years)



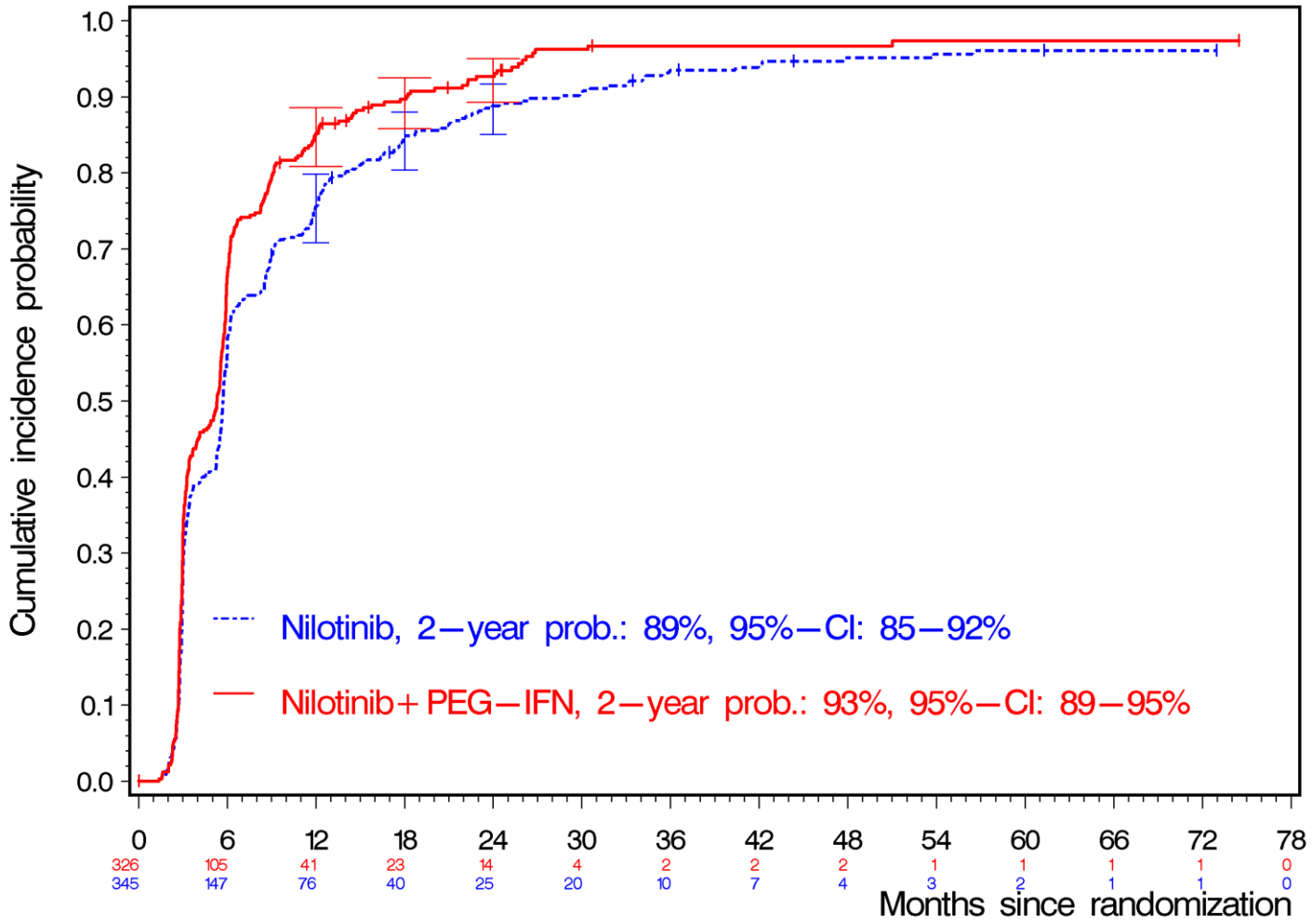
TIGER TRIAL

Overall survival by randomized therapy



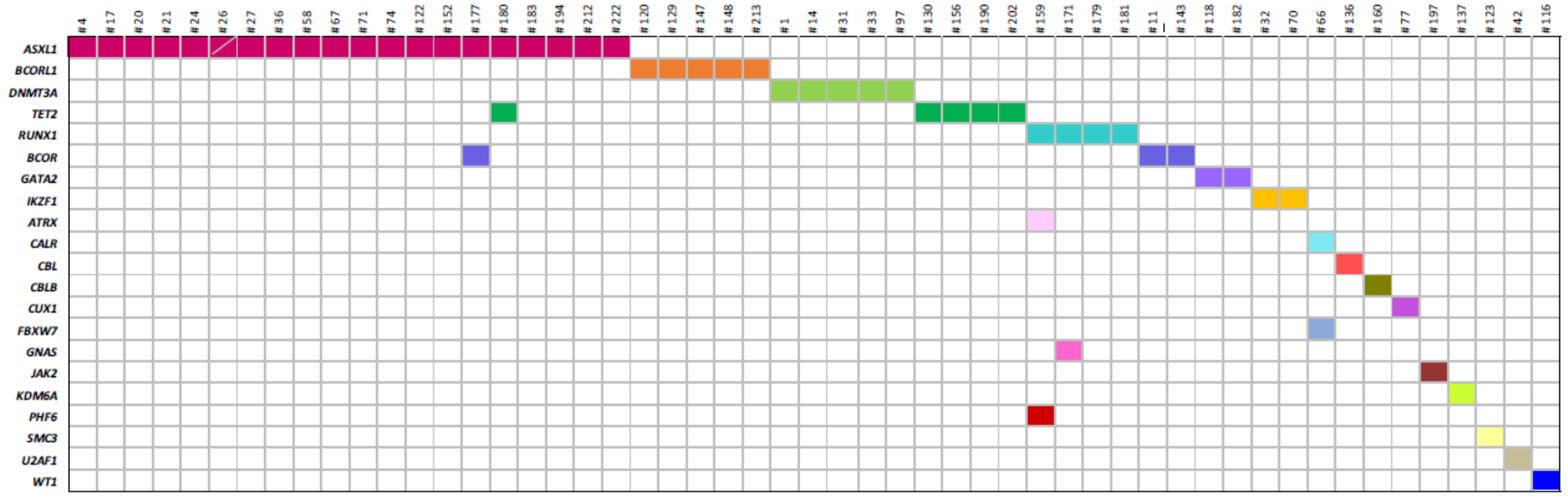
TIGER TRIAL

Cumulative incidence of MMR



TIGER TRIAL

T Ernst: ASXL1 Mutations Predict Inferior Molecular Response to Nilotinib Treatment in Newly Diagnosed Patients with Chronic Myeloid Leukemia in Chronic Phase



- Mutations in 24% (53/222) CML patients at diagnosis
- *ASXL1* being most commonly affected (n=20)
- Most patients only have one mutation in addition to *BCR::ABL1*
- Median age of affected patients: 54 years (range 19-78 years)

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T Ernst et al. ASH 2022

TIGER TRIAL

Mutation dynamics: pattern I (eradication)

Patient	Gene	Mutation	Diagnosis	Month 12	Month 24	Month 36
#4	*ASXL1*	Y591X	6.6	0	0	0
#17	*ASXL1*	S1064EfsX23	41.3	0	0	0
#20	*ASXL1*	R693X	5.7	0	0	0
#21	*ASXL1*	L775X	38	0	10.6	21.6
#24	*ASXL1*	Q757X	34	0	0	0
#26	*ASXL1*	A752LfsX20	9.9	0	0	0
#27	*ASXL1*	R1068X	5	0	0	0
#36	*ASXL1*	E635RfsX15	11.3	(2.7)	0	0
	ASXL1	Q1039X	12.5	(2.3)	0	0
#58	*ASXL1*	L775X	10.7	0	0	0
#67	*ASXL1*	E850X	45	0	0	0
#71	*ASXL1*	C856X	38	0	0	0
#74	*ASXL1*	R693X	40.7	0	0	0
#11	*BCOR*	N1459S	51.4	0	0	0
#77	*CUX1*	I1092NfsX14	38.3	0	0	0
#1	*DNMT3A*	Y197X	46.8	0	0	0
#66	*FBXW7*	R465H	7.9	0	0	0
#32	*IKZF1*	C203VfsX14	39.2	0	0	0
#70	*IKZF1*	R143W	6.8	0	0	0
#42	*U2AF1*	R156H	27.1	0	0	0

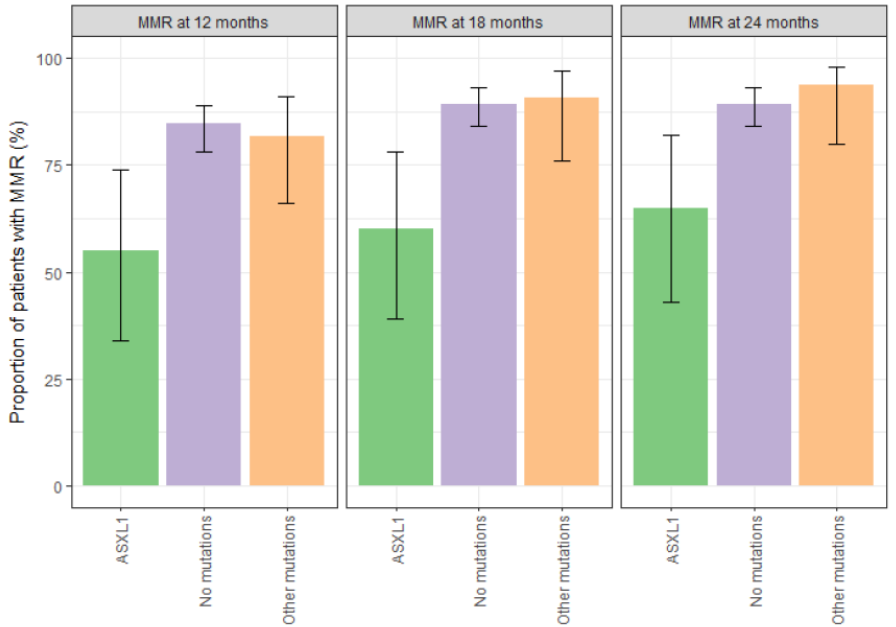
Variant allele frequency (%)

Mutation dynamics: pattern II (persistence)

Patient	Gene	Mutation	Diagnosis	Month 12	Month 24	Month 36
#66	*CALR*	E398_N400del	36.6	43.4	42.9	43.7
#14	*DNMT3A*	S786X	43.4	23.7	23.2	26.4
#31	*DNMT3A*	Q696X	48.7	(2.6)	(3.4)	(2.4)
#33	*DNMT3A*	K744del	46.9	(4.6)	7.5	8.7
#97	*DNMT3A*	N797D	47	22.4	20.0	19.9

Variant allele frequency (%)

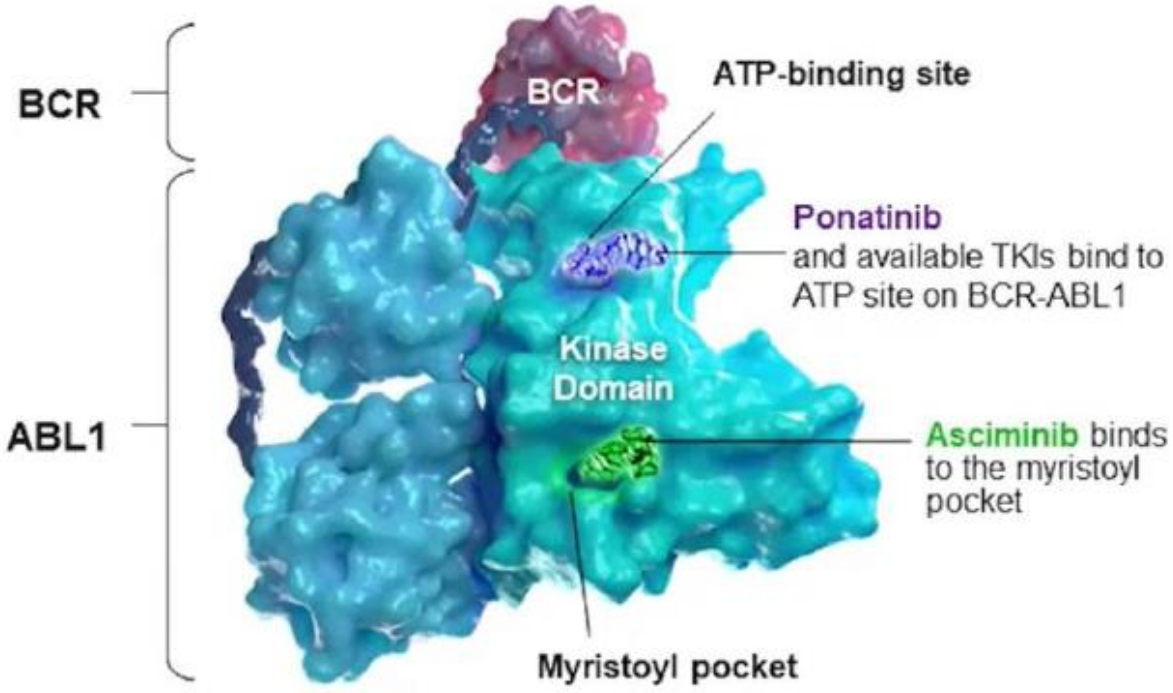
Mutations versus Response



T Ernst et al. ASH 2022

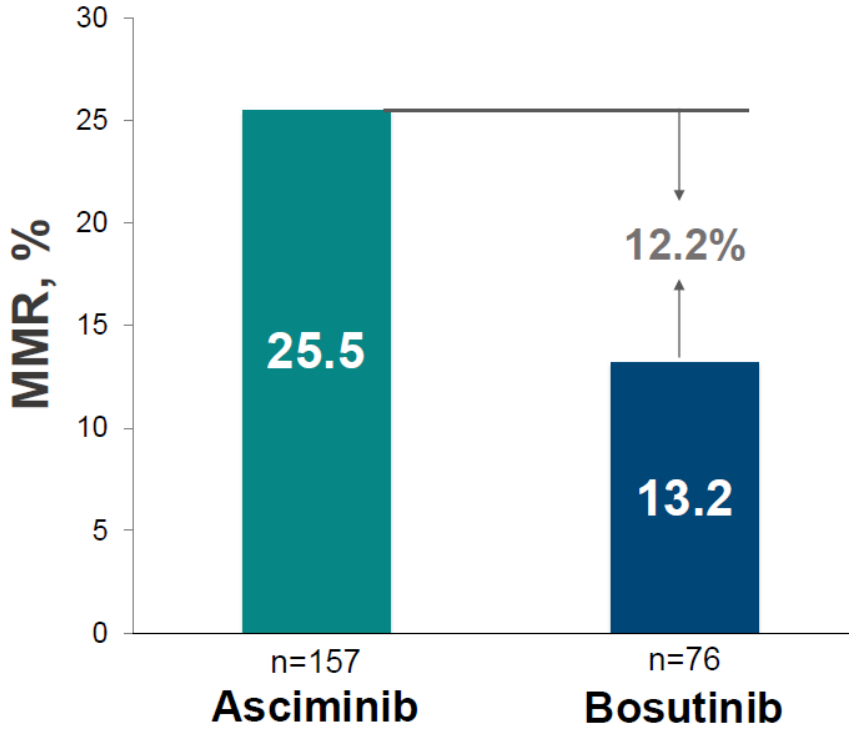
Neue Substanzklasse:

Die ASCEMBL-Studie führte zur Zulassung von Asciminib (First-in-Class-STAMP-Inhibitor) bei CML



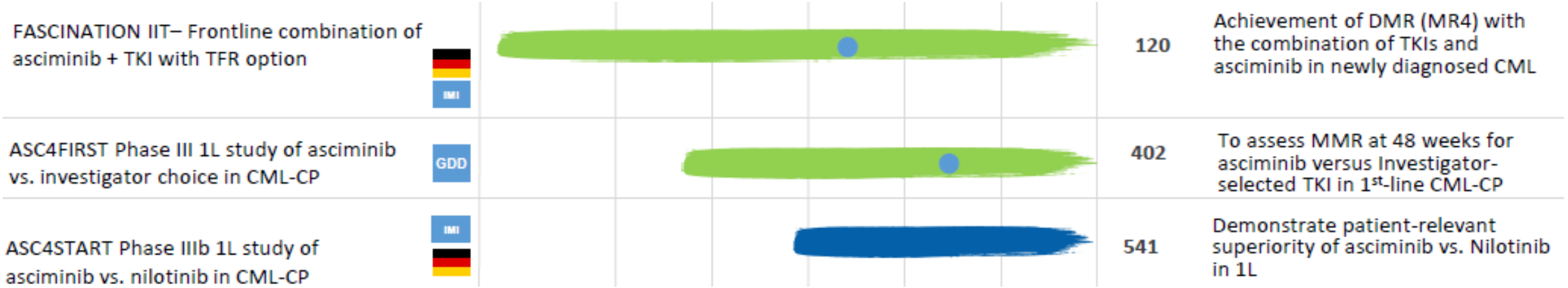
STAMP: (Specifically Targeting the ABL Myristoyl Pocket)

Primary endpoint: MMR @ 25 weeks



Hochhaus A et al., 62nd ASH 2020

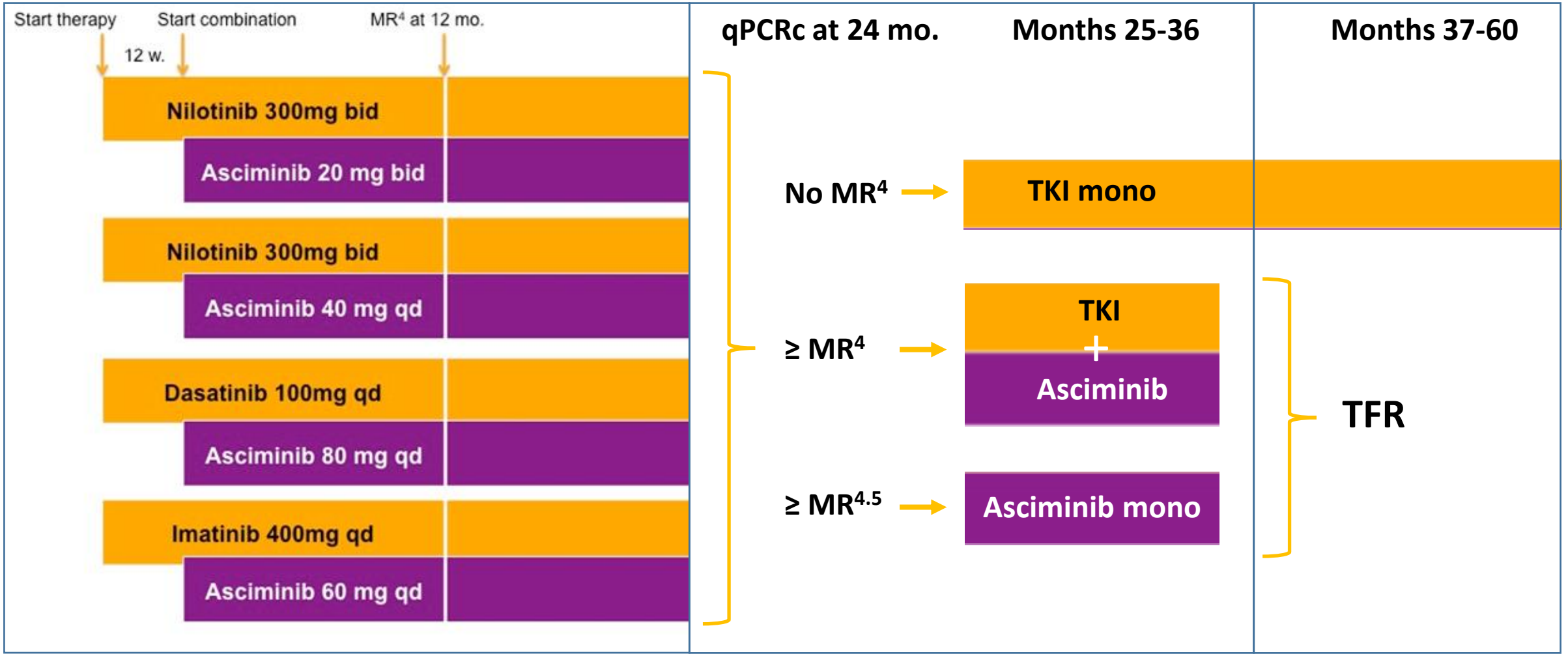
Aktuelle Asciminib 1–L Studien in Deutschland



a Novartis data on file
ClinicalTrials.gov Identifier NCT-No.: https://www.clinicaltrials.gov/

FASCINATION

Study design



FASCINATION

Endpoints

<u>The primary endpoint of this study is:</u>

- Rate of MR^4 at month 12

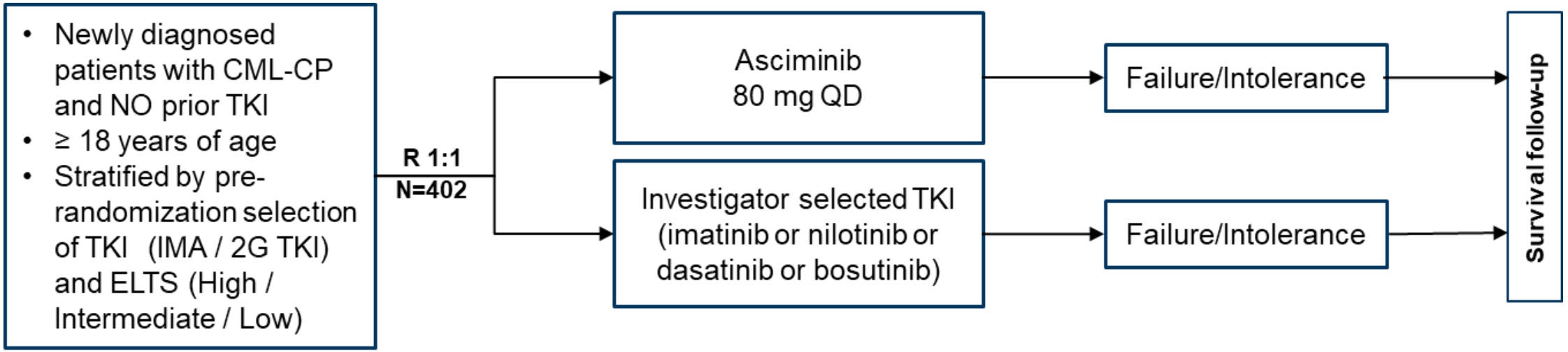
<u>The secondary endpoints of this study are:</u>

- Rate of MR^4 at month 24 and 36
- Maintenance of $MR^{4.5}$ during asciminib monotherapy in months 24 to 36
- Achievement and durability of TFR in months 37 to 60
- Incidence of adverse events grade 1-5
- Quality of life
- Progression-free survival, overall survival

ASCIMINIB TRIALS

Study Design

A phase III, multi-center, open-label, randomized study of oral asciminib versus Investigator selected TKI in patients with newly diagnosed Philadelphia Chromosome Positive Chronic Myelogenous Leukemia in Chronic Phase



QD, once daily; CML, chronic myeloid leukemia; CP, chronic phase; 2G: 2nd generation; IMA, Imatinib; R, randomized; ELTS, EUTOS Long-term survival; TKI, tyrosine kinase inhibitor

Data on file. Study Protocol No. CABL001J12301 Clinical Trial Protocol. Novartis Pharmaceuticals Corp.

ASCIMINIB TRIALS

ASC4FIRST

Sites in Germany

Universitätsklinikum Jena Prof. Dr. med. Andreas Hochhaus (LKP)
Universitätsmedizin Mannheim Prof. Dr. med. Susanne Saussele
Universitätsklinikum Aachen Prof. Dr. med. Tim Brümmendorf
Universitätsklinikum Frankfurt Dr. Fabian Lang
Charité Berlin Prof. Dr. Philipp David Immanuel le Coutre
UKSH Campus Lübeck Prof. Dr. Nikolas von Bubnoff

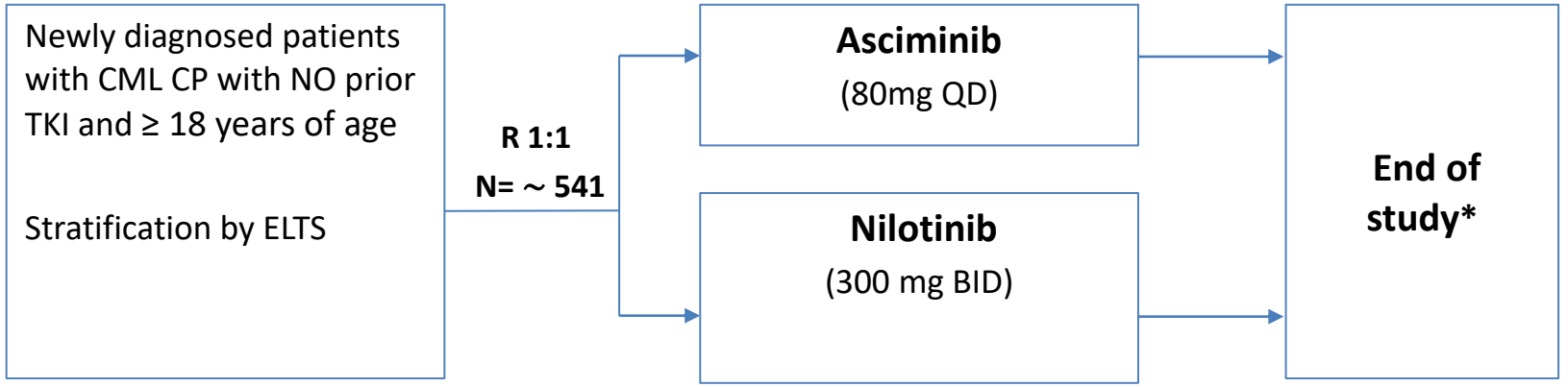
CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

CABL001J12302: Phase IIIb 1L study Asciminib vs. Nilotinib

ASCIMINIB TRIALS

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.

German Sites

PI Name	Stadt
Crysandt	Aachen
Hirschbühl	Augsburg
Schöndube	Bad Saarow
Kiani	Bayreuth
Le Coutre	Berlin
Teichmann	Bonn
Bormann	Bremen
Hänel	Chemnitz
Illmer	Dresden
Brückl	Erlangen
Goethert	Essen
Lang	FFM
Becker	Freiburg
Jäkel	Halle
Schafhausen	Hamburg
von der Heyde	Hannover
Sauer	Heidelbrg
Hochhaus	Jena
Franke	Leipzig
Von Bubnoff	Lübeck
Jentsch-Ullrich (tbc)	Magdeburg
Saussele	Mannheim
Burchert	Marburg
Herhaus	München
Schmidt	München
Gaska	Paderborn
Schenk	Regensburg
Möhle	Tübingen
Stegelmann	Ulm
Nusch	Velbert
Bumm	Würzburg

Allocation & Milestones

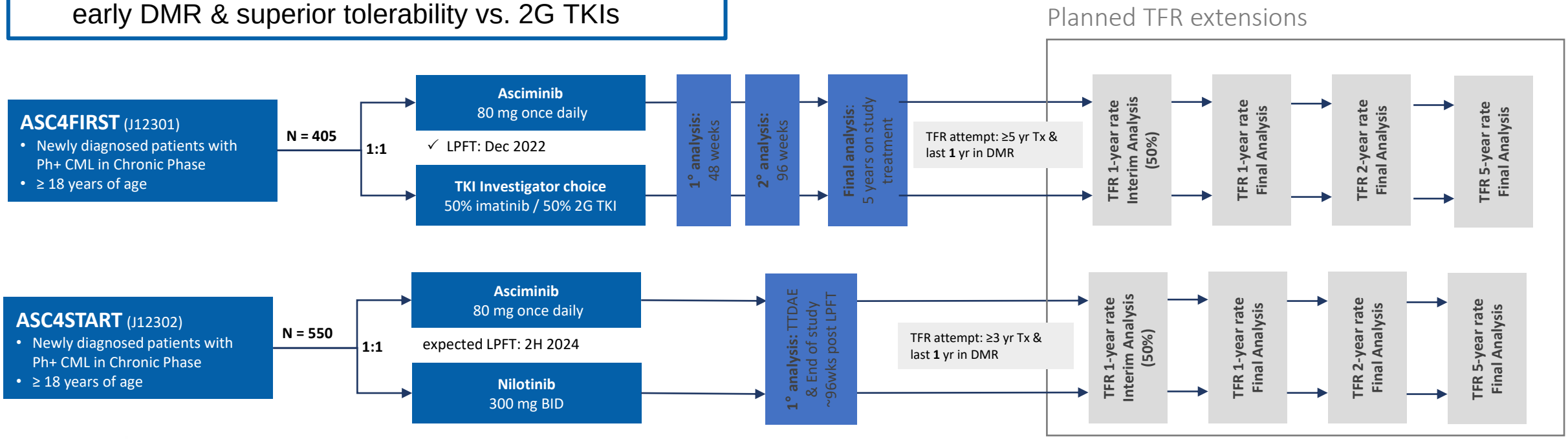
Patient	~541
Initiated Sites	31/31 in DEU
FPFV	21.11.2022
FPFT	28.11.2022

Stand: 11.09.2023

Treatment Free Remission – 1L CML

Situation:
- TFR is an important treatment objective in 1L with data available for 2G TKIs
- Current asciminib 1L Ph3 studies are not generating TFR outcome data
- Early data from ASCEND indicate potential for higher overall TFR success rates based on high early DMR & superior tolerability vs. 2G TKIs

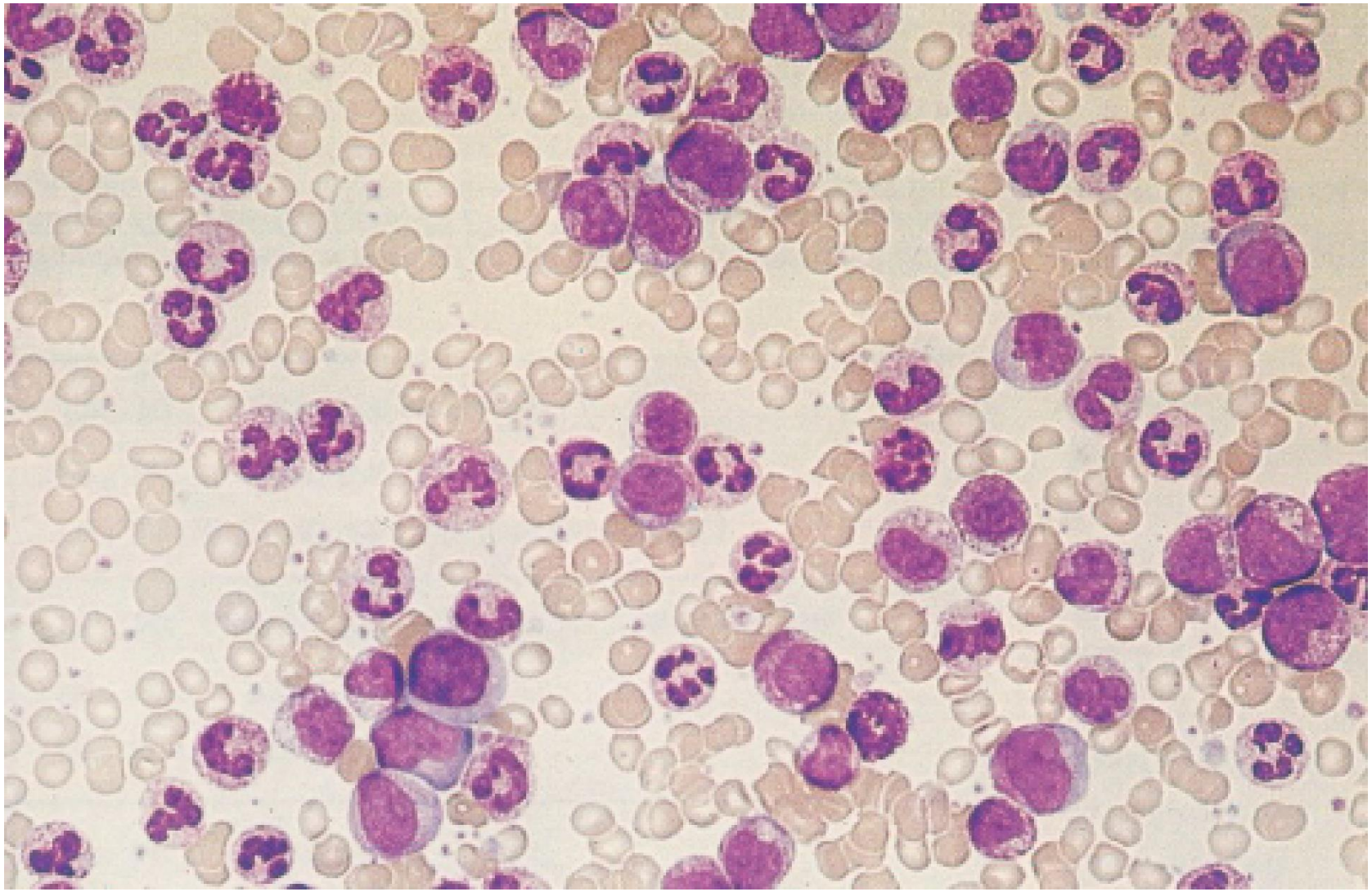
Plan to address:
- 1L Ph3 ASC4FIRST & Ph3b ASC4START ongoing
- Amend both studies for TFR extension
  - ≥5 yrs (FIRST) / ≥3 yrs (START) Tx, randomized
- TFR data: eligibility, 1,2,5-yr outcome, overall success
- ASC4FIRST TFR-amendment pending HA feedback



Vielen Dank!

cml@charite.de

Hyperleukozytose & Linksverschiebung



TIGER TRIAL

Risk scores	Total (N=692)	Nilotinib-Monotherapy (N=353)	Nilotinib + PEG-IFNα (N=339)
EUTOS-Score[1] %			
High risk	13	14	13
Low risk	87	86	87
ELTS-Score[2] %			
High risk	10	9	11
Intermediate risk	29	32	27
Low risk	60	59	62

[1] Hasford et al., Blood. 2011;118:686-92
[2] Pfirrmann et al., Leukemia. 2016;30:48-56

TIGER TRIAL
First primary endpoint, molecular result 18 months after randomization

Probability of MMR at 18 months:

An interval of 16.5 to 19.5 months for estimation of MMR probability was allowed.

For 605 of 677 randomized patients with normal transcript type, data was available.

For all 605 evaluable patients, the probability of MMR **at** 18 months was 84% (95%-CI: 81-87%),

509 patients with MMR.

Nilotinib (n=313):

Probability of MMR **at** 18 months 81% (95%-CI: 76-85%), 253 with MMR

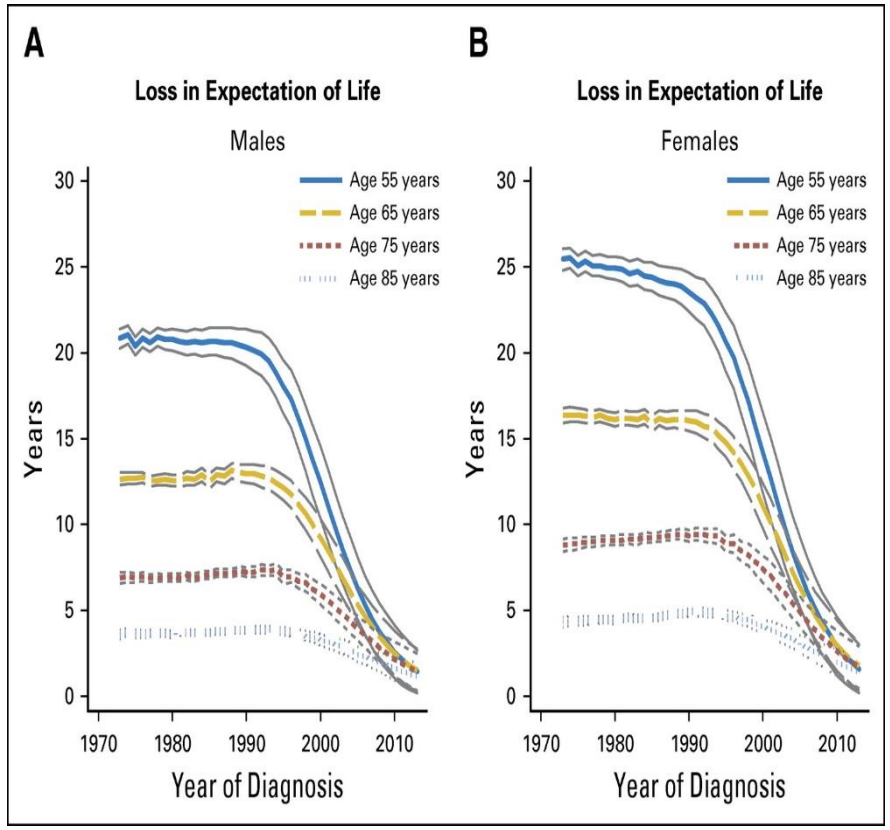
Nilotinib + IFN (n=292):

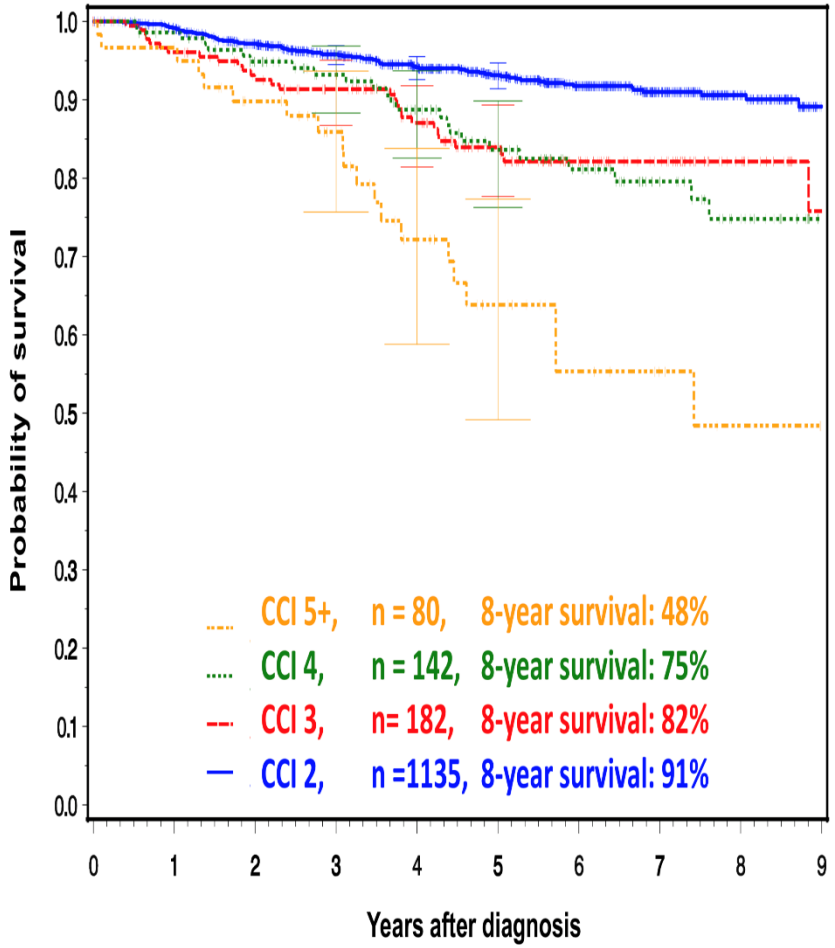
Probability of MMR **at** 18 months 88% (95%-CI: 83-91%), 256 with MMR

MMR proportions were compared with the uncorrected chi-square test without risk group stratification (**p=0.0214**).

This would have led to a rejection of null hypothesis 1, however, confirmatory testing had already been performed in 2019 and at this time, hypothesis 1 could not be rejected.

Erkrankungsprognose





Bower H, et al., J Clin Oncol. 2016
Saussele S. et al., Blood. 2015