

*Post-ASH
Tübingen
04.2.2009*

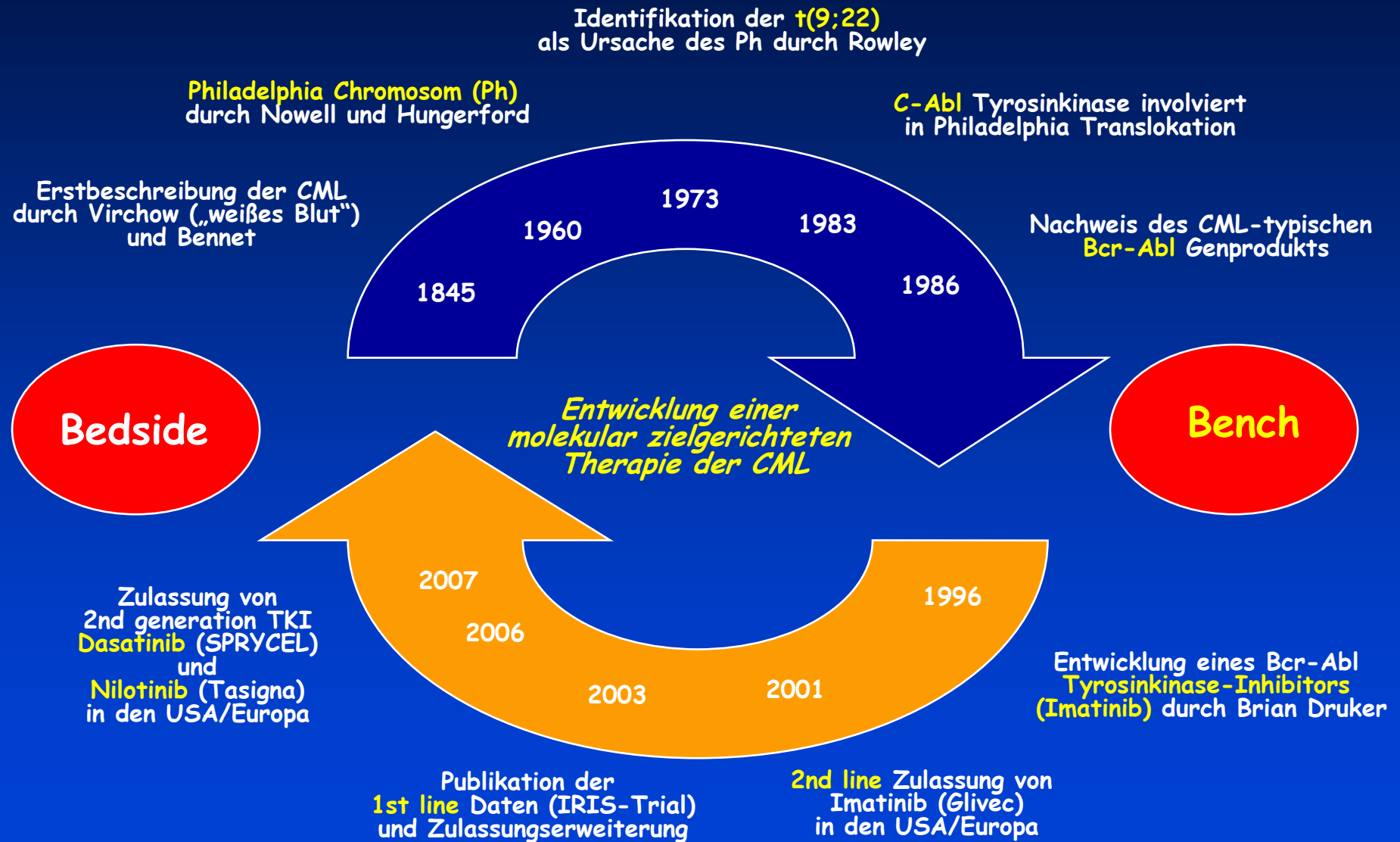
Chronisch myeloische Leukämie

Tim Brümmendorf

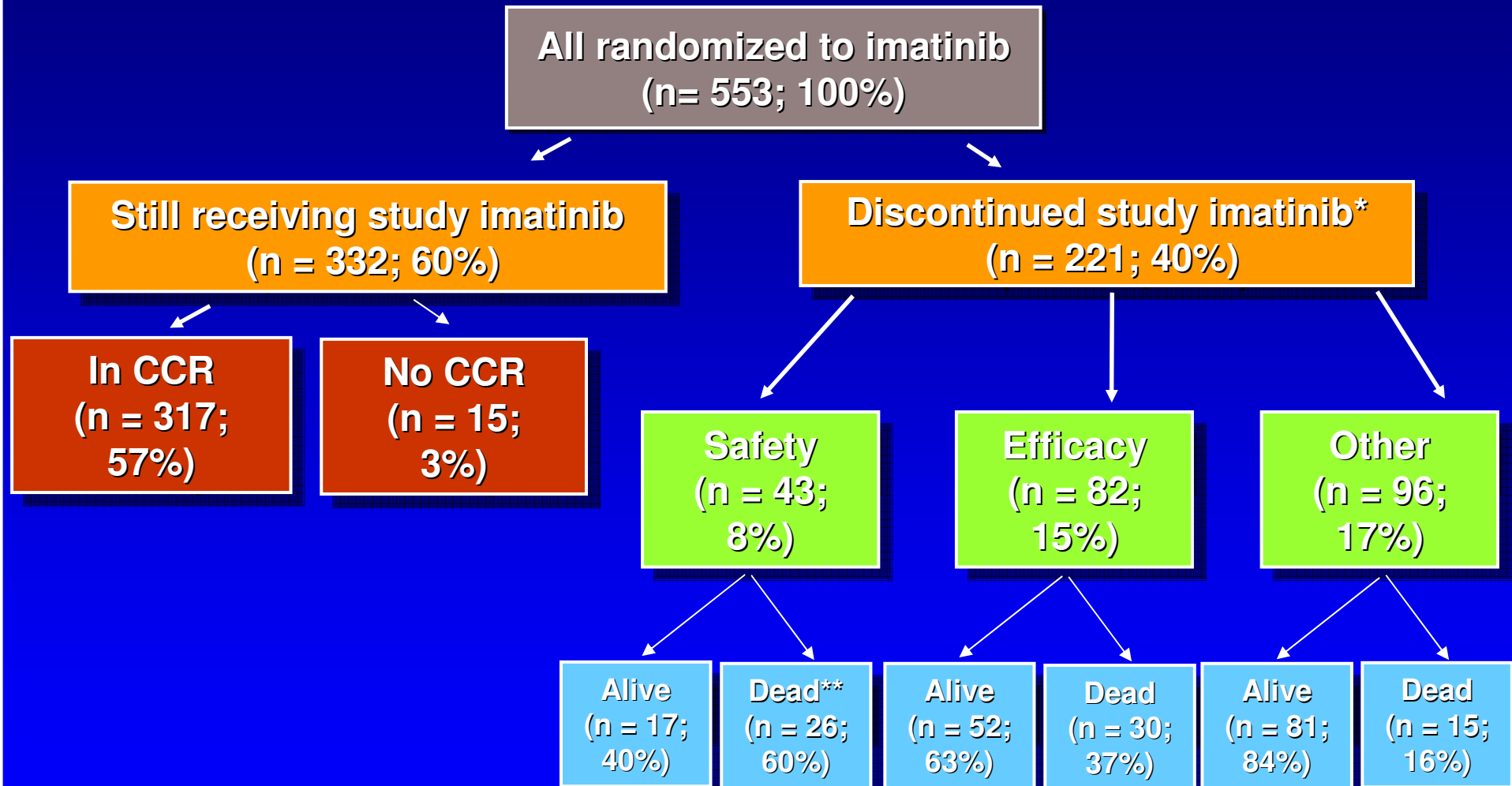
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„From bedside to bench and back“



What Happened To The Patients After 7 Years?

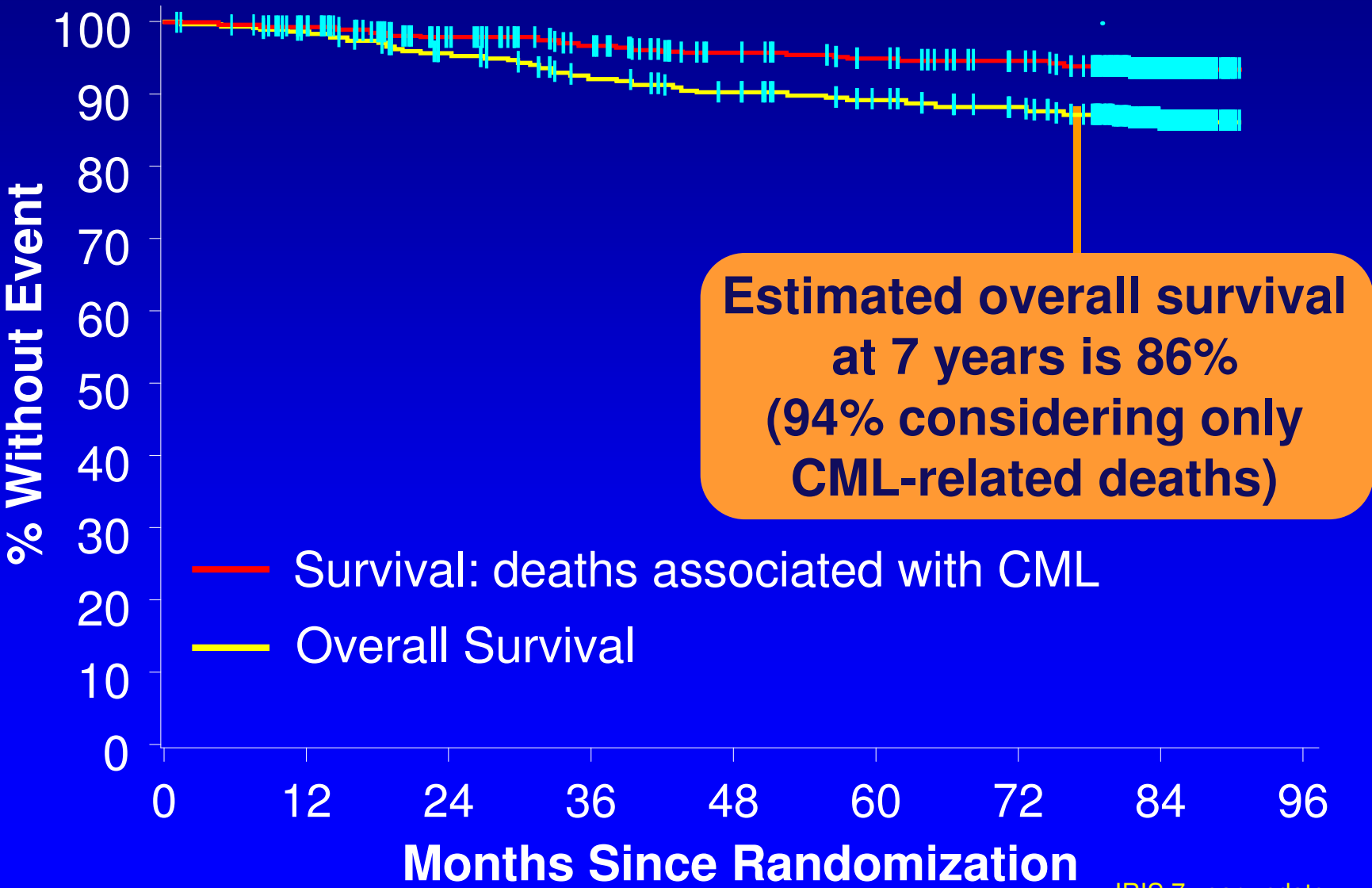


**Including primary discontinuation reason 'Death' (n=13)

*Patients may have continued imatinib off study.

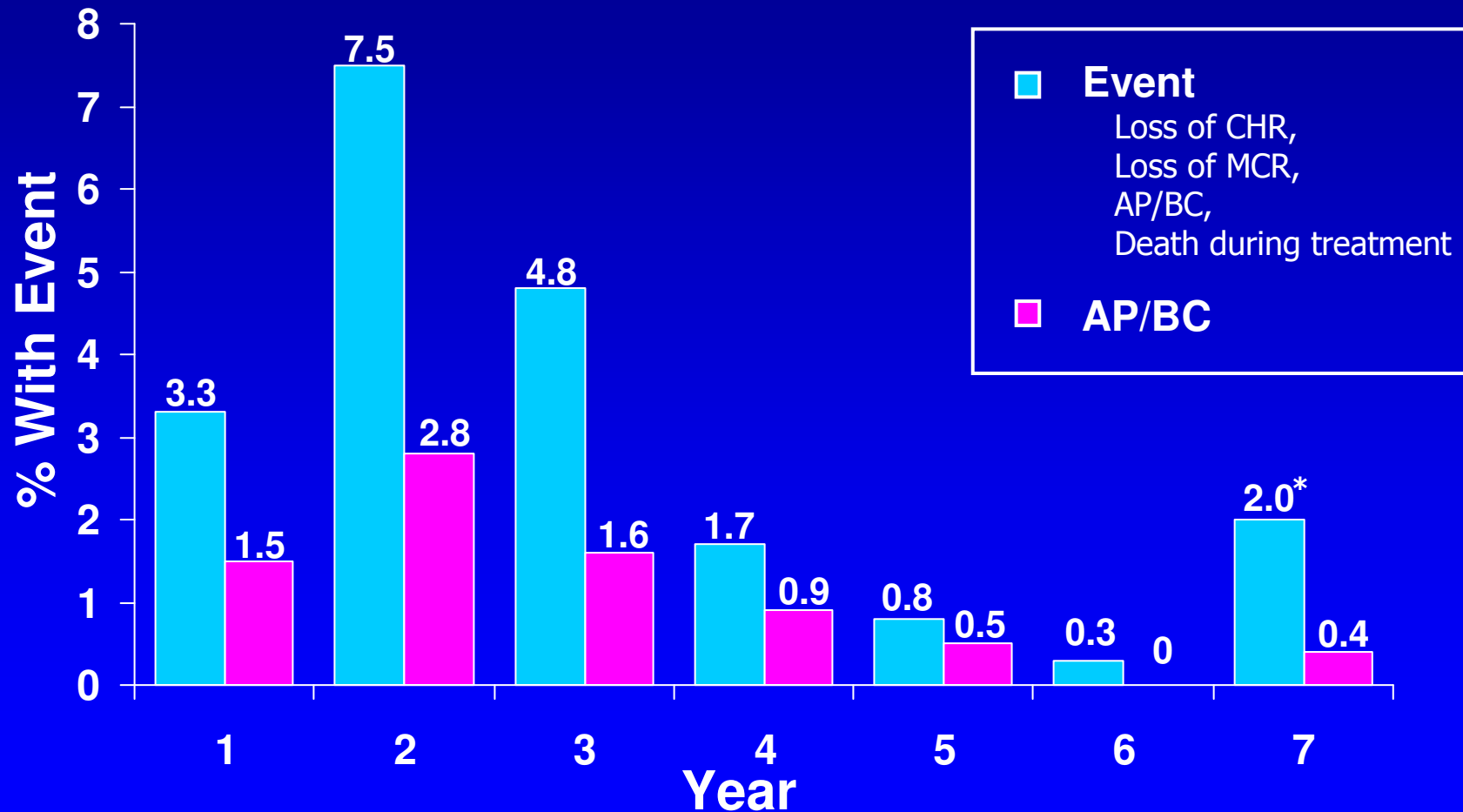
IRIS 7 year update

Overall Survival (ITT Principle): Imatinib Arm



Annual Event Rates: Imatinib Arm

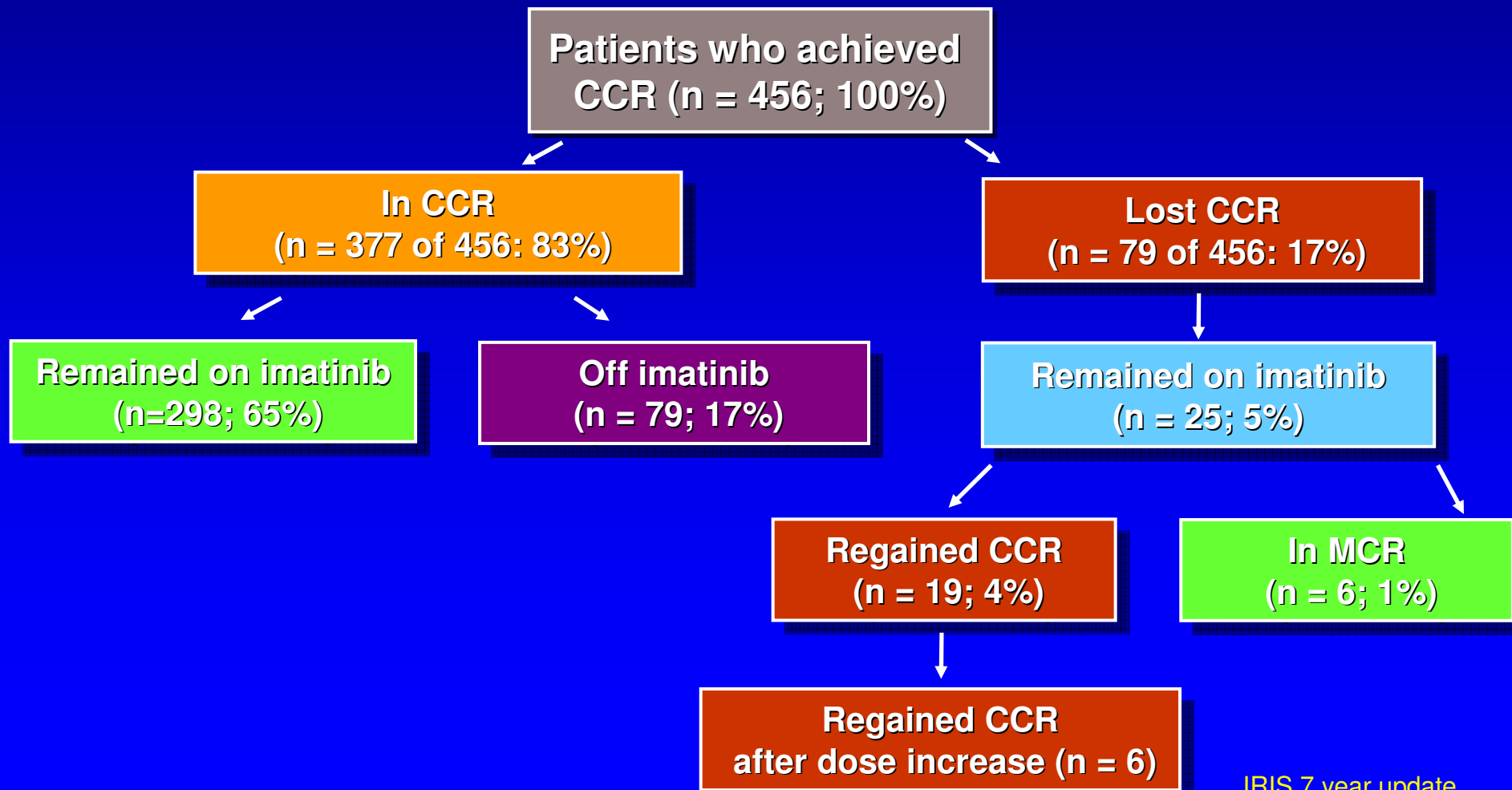
- KM estimated EFS at 7 years = 81%
- KM estimated rate without AP/BC at 7 years = 93%



*Total events (n=5) including loss of MCR (n=3) and deaths (n=2, one of which was coded as progression to AP/BC in a patient in CMR 6 months prior to death).

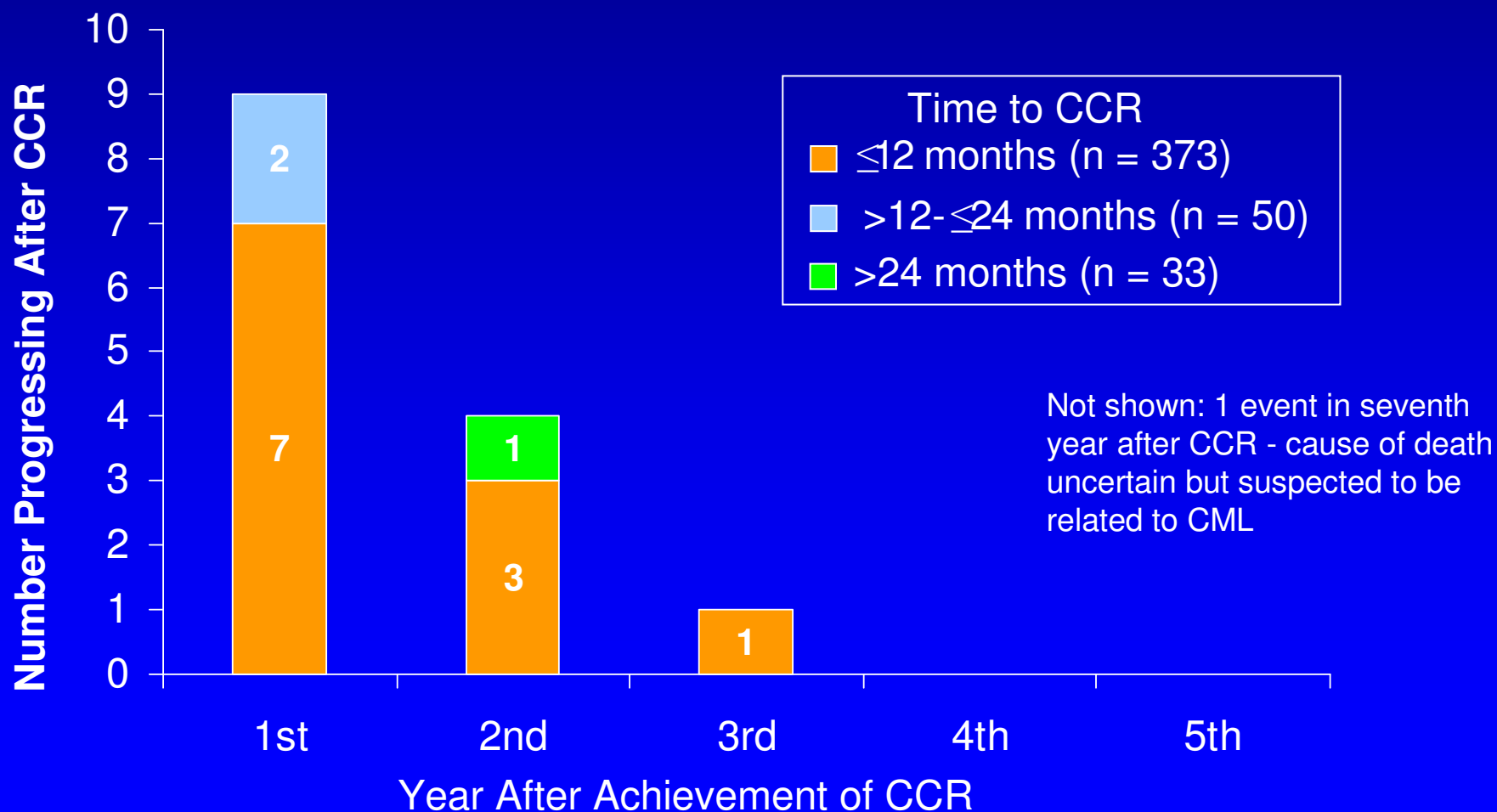
Durability of Cytogenetic Response

- 456 of 553 (82%) of first-line imatinib patients achieved CCR
- 317 (57%) patients randomized to imatinib remained on protocol and were in complete cytogenetic response (CCR)



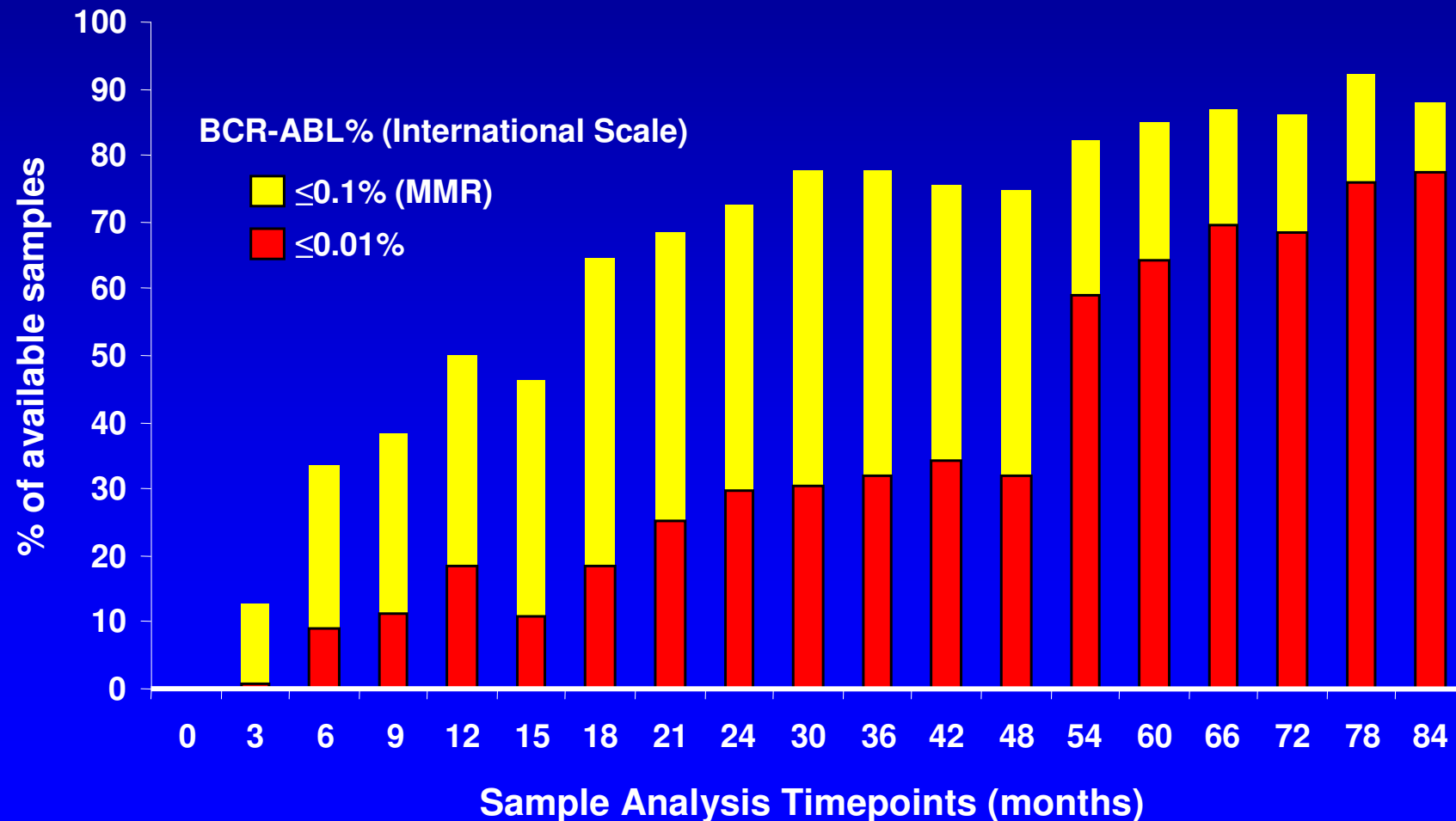
Rates of Progression in Patients After CCR

- Progression to AP/BC occurred in 15 (3%) of the 456 patients who had achieved a CCR
- Of 456 patients who achieved CCR, 10 (2%) died from CML



Molecular Response Rates

- Major molecular response (MMR) and the depth of molecular response increase over time



See abstract 334 for complete data

IRIS 7 year update

IRIS SAEs in Years 6 and 7

- No unique, previously unreported AEs attributed to imatinib observed over the past 24 months
- In years 6 and 7, 13 SAEs with suspected relationship to imatinib were reported:
 - Congestive Heart Failure (n=3): all of the patients had pre-existing cardiac disease prior to study entry
 - Second malignancy (n=3)*
 - Myositis (n=1); elevated CK (n=1); multiple sclerosis (n=1)
 - Pancreatitis (n=1); vomiting (n=1)
 - Renal failure (n=1)
 - Dermatitis (n=1)

*With >400,000 patient years of estimated imatinib exposure, the analysis of clinical safety data from clinical trials and spontaneous reports did not provide evidence for an increased incidence of malignancies for patients treated with imatinib compared to that of the general population

Limitationen einer Imatinib-Therapie

- Eingeschränkte Effektivität in späten Erkrankungsstadien

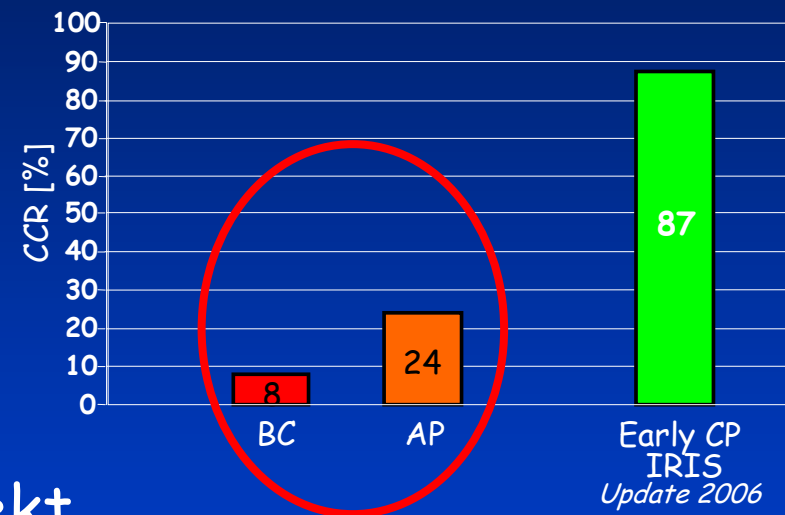
- Resistenzentwicklung

CP < AP < BC

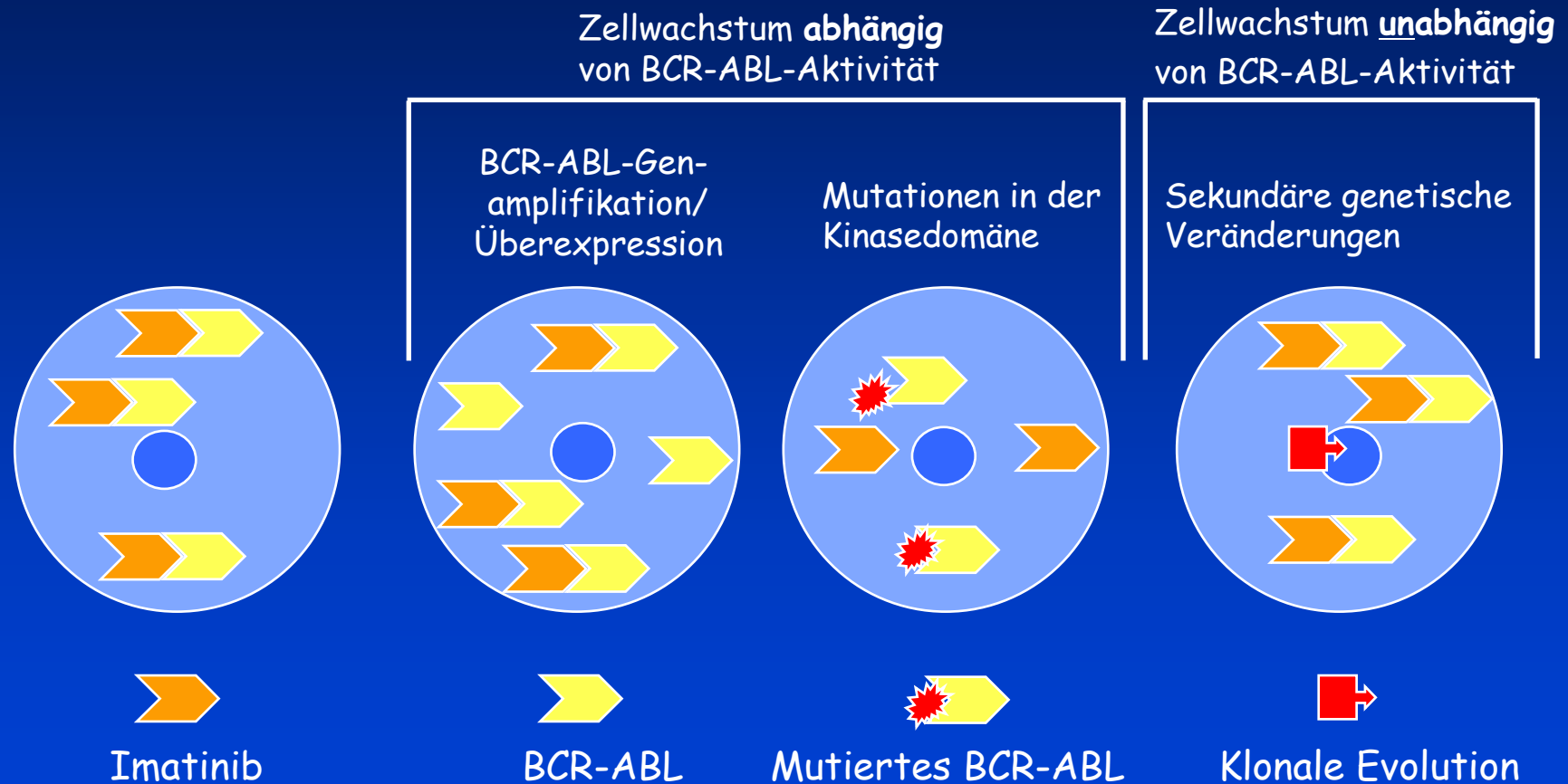
- Fehlender zytotoxischer Effekt auf ruhende Stammzellen

=> nach heutigem Kenntnisstand:

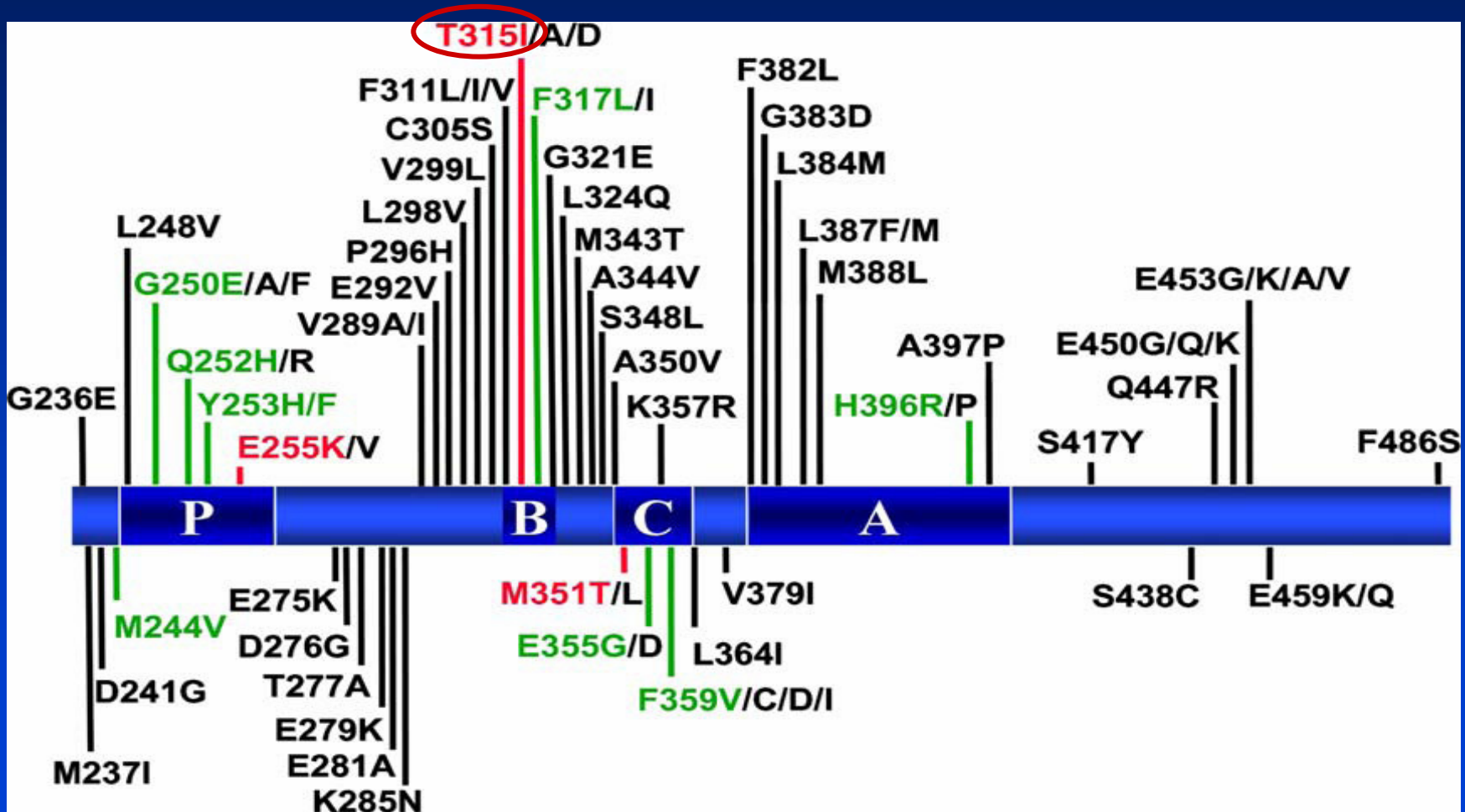
Vermutlich kein kurativer Therapieansatz !



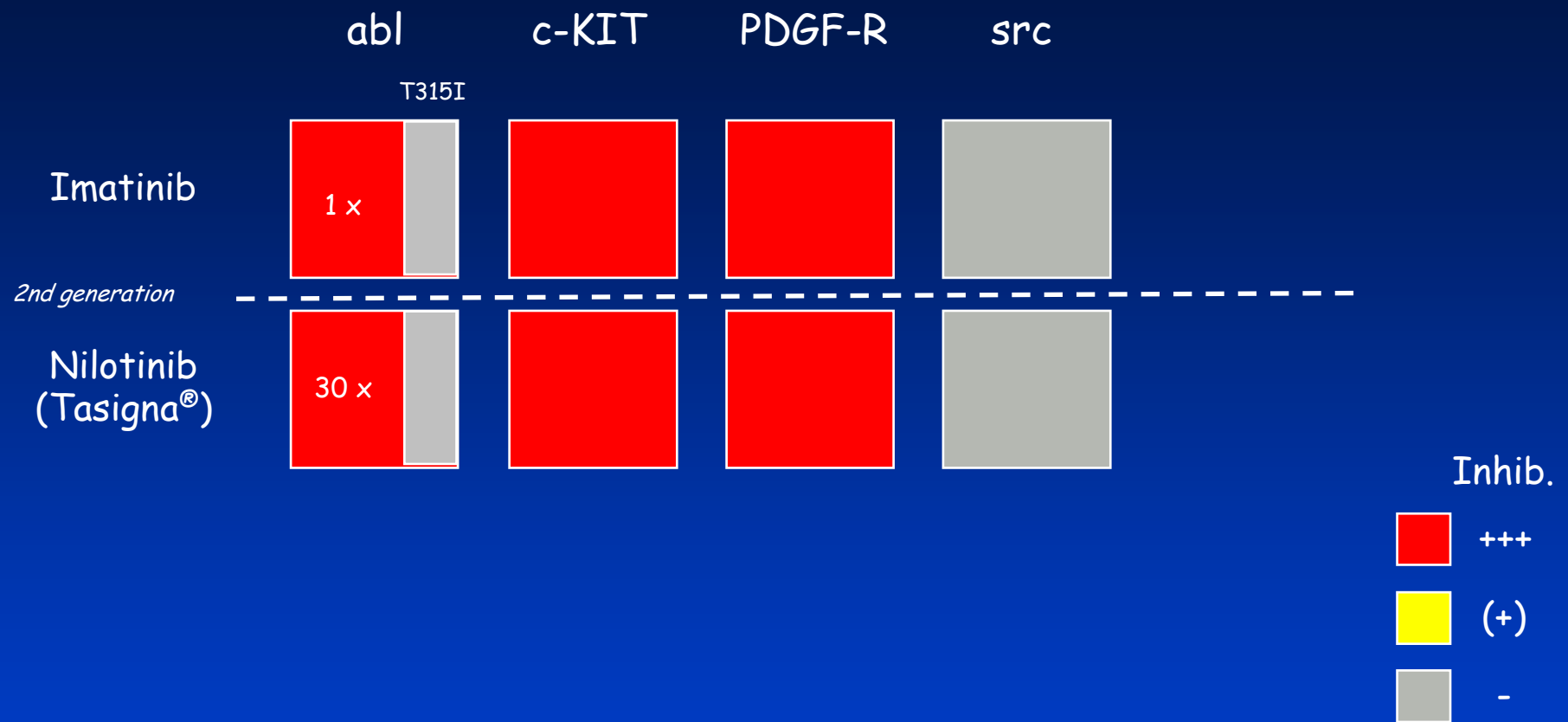
Mögliche Imatinib-Resistenzmechanismen



Map of *BCR-ABL* Kinase Domain Mutations Associated with Clinical Resistance to Imatinib



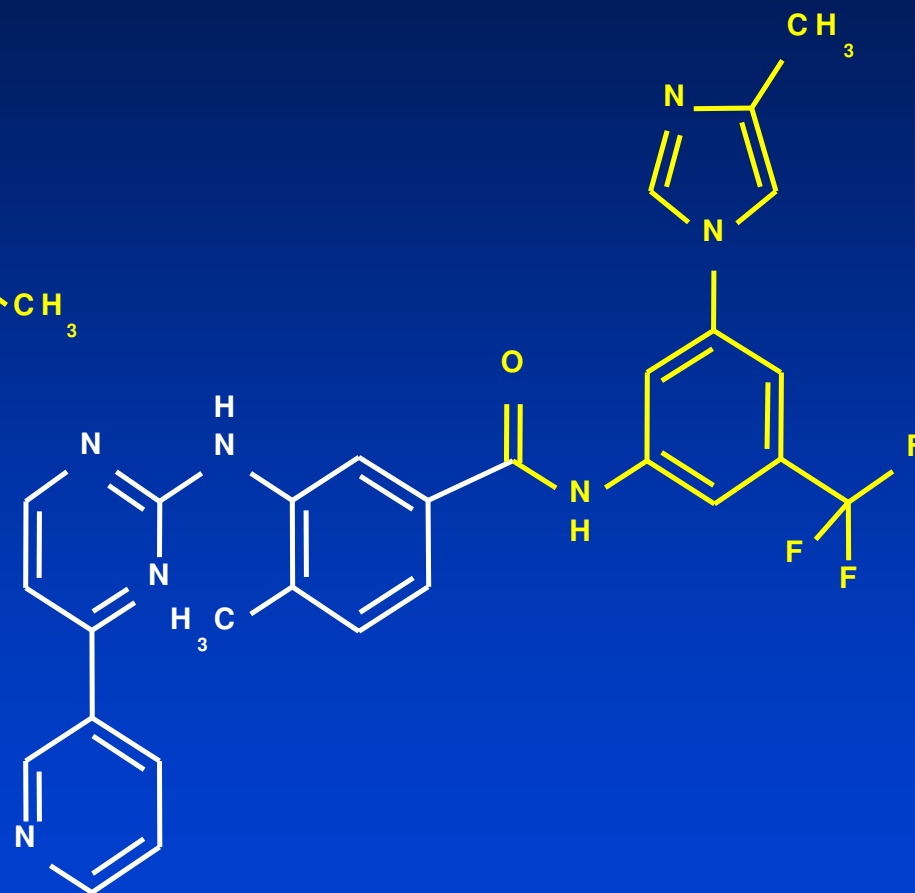
Zielstrukturen der (Tyrosin-)kinaseinhibitoren



Nilotinib in CML-CP. Chemical Structures

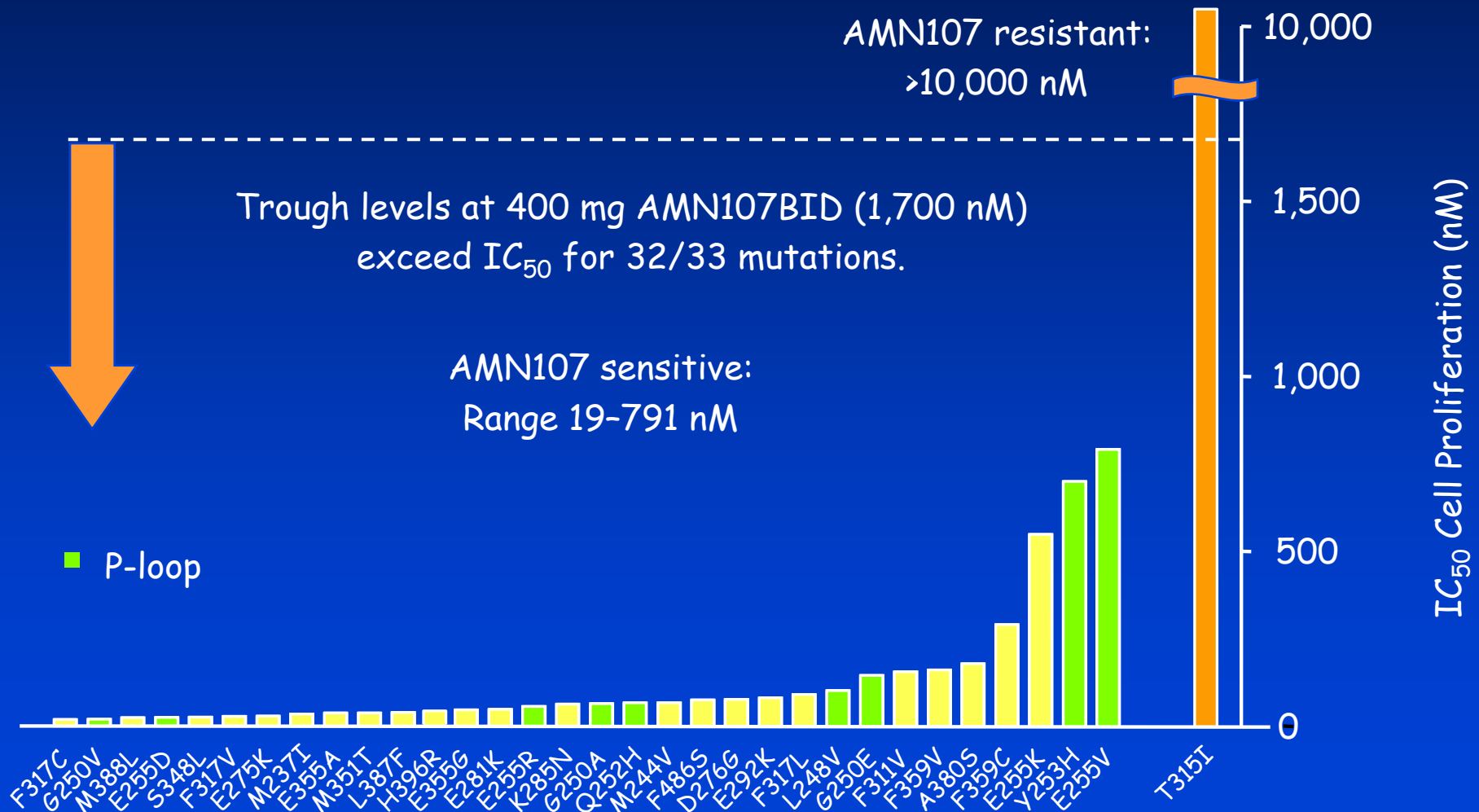


Imatinib



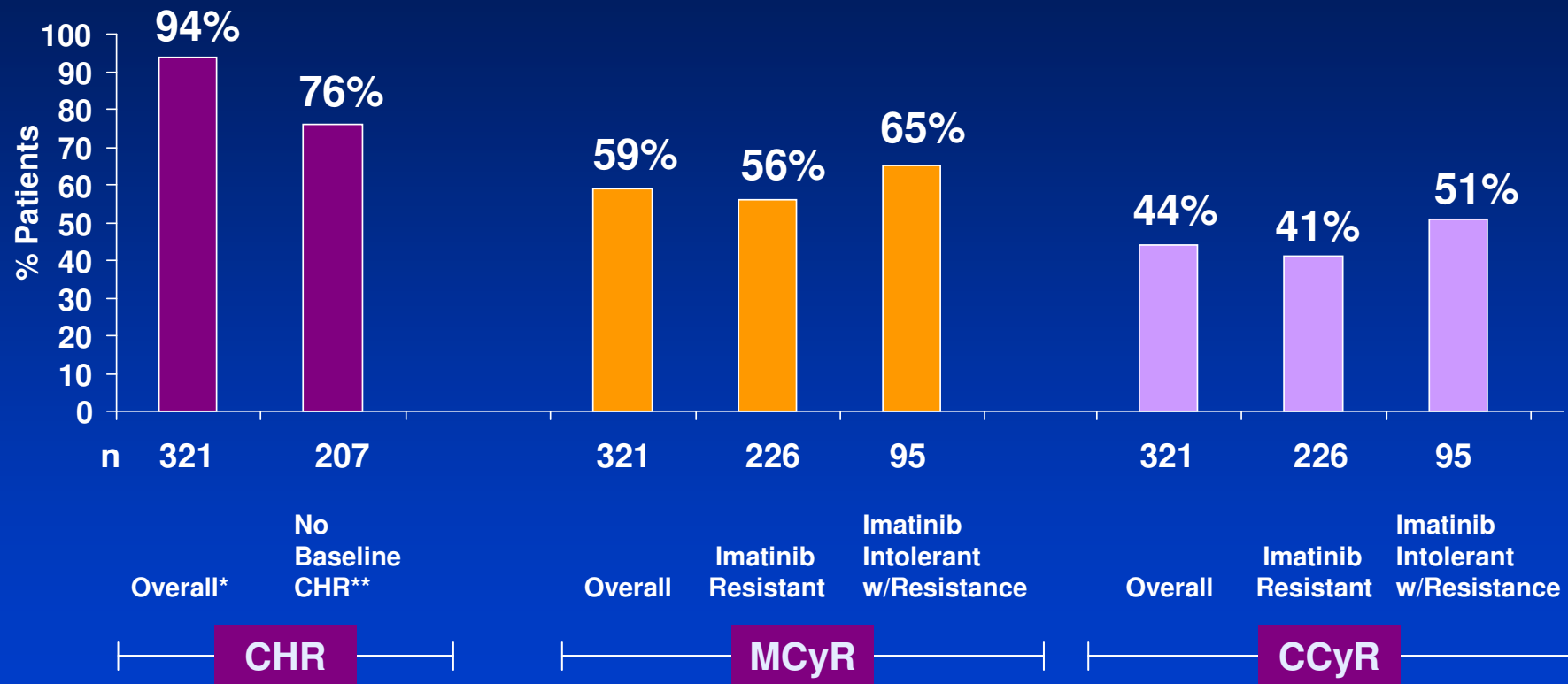
Nilotinib

AMN107 hemmt auch Imatinib-resistente Bcr-Abl-Mutationen



Nilotinib in CML-CP: response

Response in Patients with a Minimum Follow-up of 19 Months (N=321)

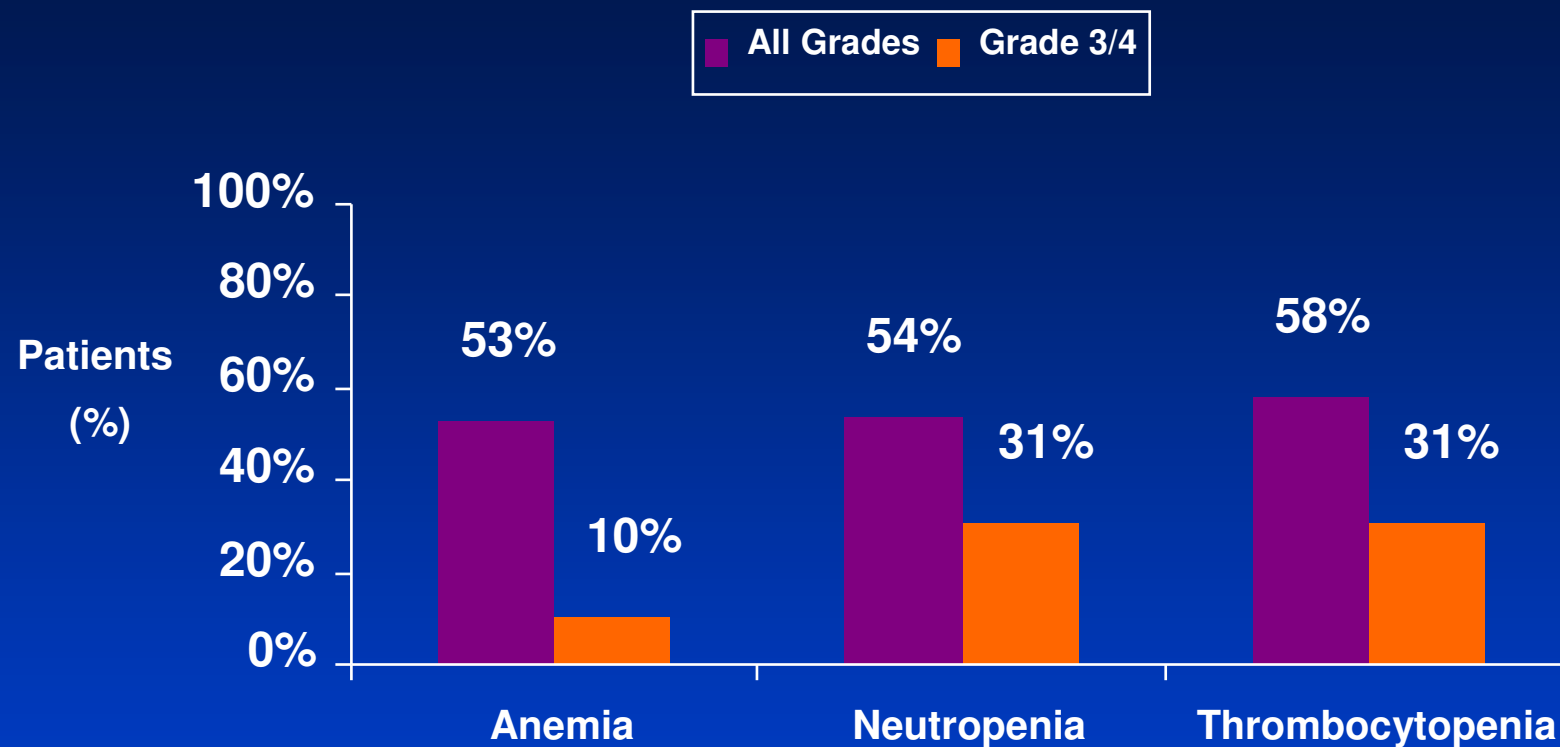


* Patients who achieved or maintained CHR

** Patients with no CHR at baseline

- The median time to CHR was 1.0 month in patients without CHR at baseline
- The median time to MCyR was 2.8 months

Nilotinib in CML-CP: Myelosuppression



Grade 3/4	8	15	22
Median duration (days)			
Grade 3/4	61	56	42
Median onset (days)			

* Most frequent newly occurring or worsening, regardless of causality

Nilotinib in CML-CP

Most Frequent (>10%) Drug-Related Nonhematologic Adverse Events (N=321)

Adverse Event	All Grades (%)	Grades 3/4 (%)
Rash	31	2
Pruritis	26	<1
Nausea	25	<1
Fatigue	20	1
Headache	18	2
Diarrhea	12	2
Vomiting	13	<1
Constipation	13	<1

- Severe nonhematologic AEs are infrequent on nilotinib therapy

Cross-Intolerance Between Nilotinib & Imatinib

Nilotinib Cross Intolerance in Patients with Imatinib Intolerance- Nonhematologic AEs					
Reason for Imatinib Intolerance	Imatinib Intolerant* Grade 3/4 AE or persistent Grade 2 AE	Grade 3/4 AE or persistent grade 2 AE on nilotinib [†]	Grade 3/4 AE on nilotinib [‡]	AE that led to dose reduction of nilotinib	D/C nilotinib due to AE
	n (%)	n (%)	n (%)	n (%)	n (%)
CML-CP	N = 95[§]				
Non-hematologic AEs	60 (63)	4 (4)	1 (1)	0 (0)	0 (0)
Rash/Skin	28 (29)	0 (0)	0 (0)	0 (0)	0 (0)
Fluid Retention	18 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	12 (13)	3 (3)	1 (1)	0 (0)	0 (0)
ALT elevations	3 (3)	1 (1)	0 (0)	0 (0)	0 (0)
AST elevations	4 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia/arthralgia	10 (11)	0 (0)	0 (0)	0 (0)	0 (0)
CML-AP	N = 27[§]				
Nonhematologic AEs	15 (56)	0 (0)	0 (0)	0 (0)	0 (0)
Rash/Skin	5 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Fluid Retention	5 (19)	0 (0)	0 (0)	0 (0)	0 (0)
Diarrhea	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)
ALT elevations	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)
AST elevations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Myalgia/arthralgia	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)

* Patients with multiple reasons for imatinib intolerance are counted for each reason category

[†] Number of imatinib-intolerance patients who experienced the same grade 3/4 AEs, or grade 2 AEs persisting for more than 30 days, that caused imatinib intolerance during nilotinib therapy

[‡] Number of imatinib-intolerant patients who experienced the same grade 3/4 AEs that caused imatinib intolerance during nilotinib therapy

[§] Includes patients (8 CML-CP; 3 CMNL-AP) with unusual symptoms during imatinib therapy; none of these patients discontinued nilotinib due to the same AE

Jabbour et al. Blood. 2008;112(11):Abstract 3215. Poster presentation at ASH 2008

Cross-Intolerance Between Nilotinib & Imatinib

Nilotinib Cross-Intolerance in Patients with Imatinib Intolerance - Hematologic AEs					
Reason for Imatinib Intolerance	Imatinib Intolerant* Grade 3/4 AE or persistent grade 2 AE	Grade 3/4 AE or persistent grade 2 AE on nilotinib [†]	Grade 3/4 AE on nilotinib [‡]	AE that led to dose reduction of nilotinib	D/C nilotinib due to AE
	n (%)	n (%)	n (%)	n (%)	n (%)
CML-CP	N = 95[§]				
Hematologic AEs	30 (32)	19 (20)	17 (17)	12 (13)	7 (7)
Anemia	3 (3)	1 (1)	1 (1)	0	0
Neutropenia	9 (10)	5 (5)	5 (5)	2 (2)	0
Thrombocytopenia	25 (26)	16 (17)	14 (15)	10 (11)	7 (7)
CML-AP	N = 27[§]				
Hematologic AEs	9 (33)	4 (15)	4 (15)	3 (11)	0
Anemia	1 (4)	1 (4)	0	0	0
Neutropenia	3 (11)	2 (7)	2 (7)	2 (7)	0
Thrombocytopenia	6 (22)	2 (7)	2 (7)	1 (4)	0

Zielstrukturen der (Tyrosin-)kinaseinhibitoren

	abl	c-KIT	PDGF-R	src
	T315I			
Imatinib	1 x	+++	+++	-
<i>2nd generation</i>				
Nilotinib (Tasigna®)	30 x	+++	+++	-
Dasatinib (Sprycel®)	325 x	+++	+++	+++

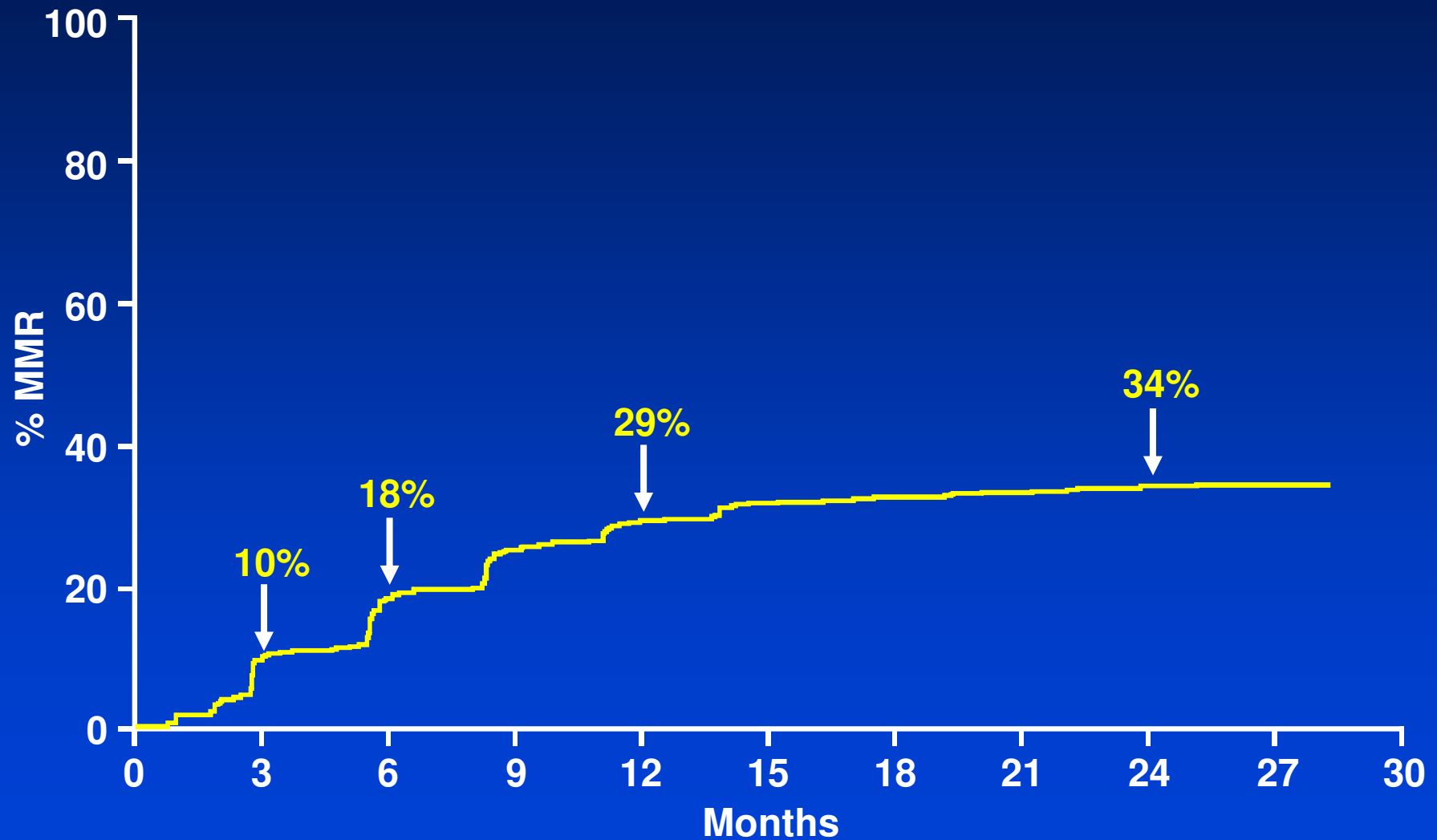
Inhib.
+++
(+)
-

Methods: patients and treatment

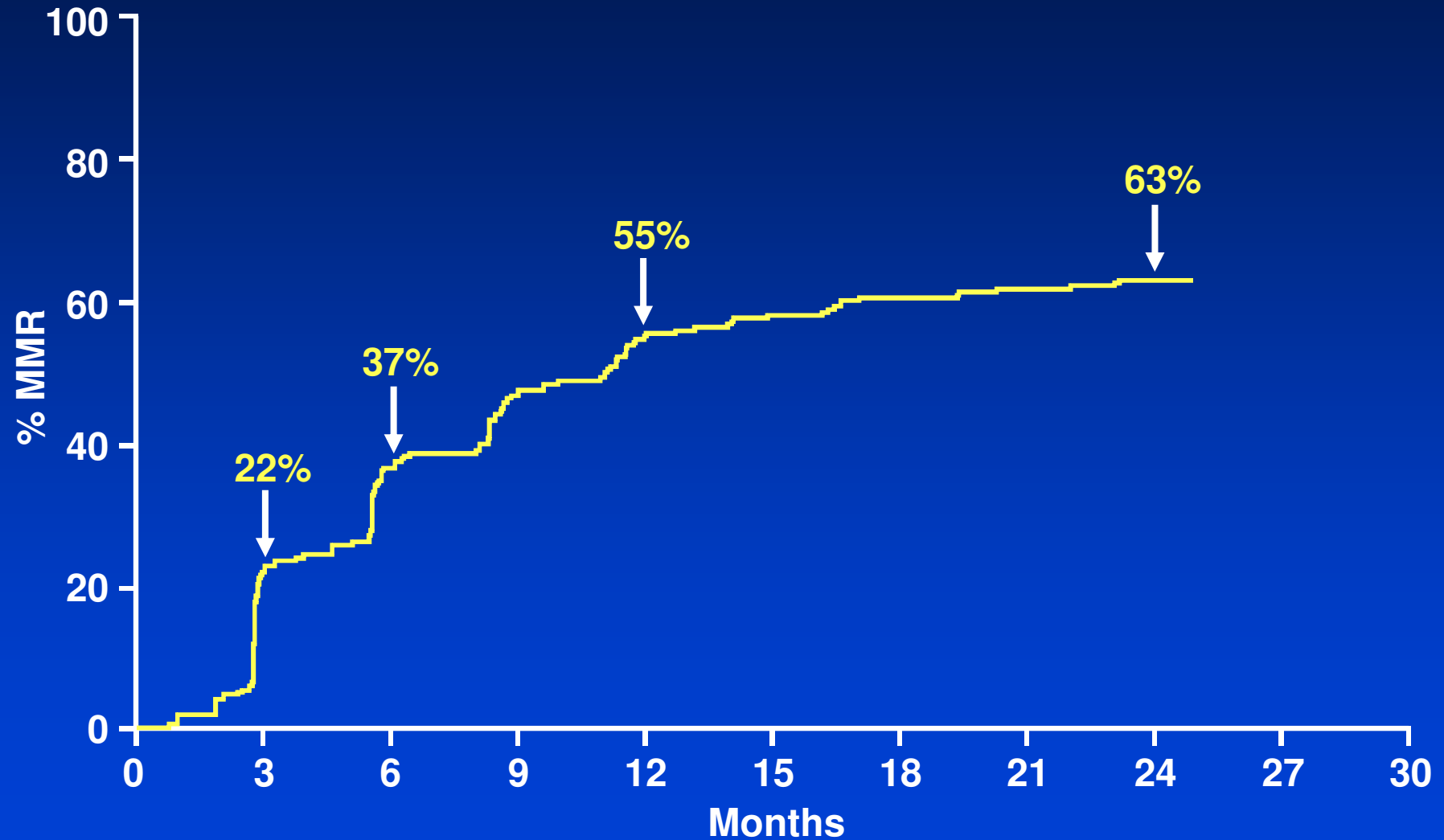
Study	Disease phase	Eligibility following imatinib treatment	Dasatinib treatment	n
CA180-013 (START-C) ²	CML-CP	Resistance or intolerance	70 mg BID	387
CA180-017 (START-R) ³	CML-CP	Resistance	70 mg BID	101
CA180-034 ⁴	CML-CP	Resistance, suboptimal response, or intolerance	100 mg once daily 70 mg BID 140 mg once daily 50 mg BID	165 167 163 167
Total				1,150

Minimum follow-up 24 months in all three studies (last patient first visit to database lock)

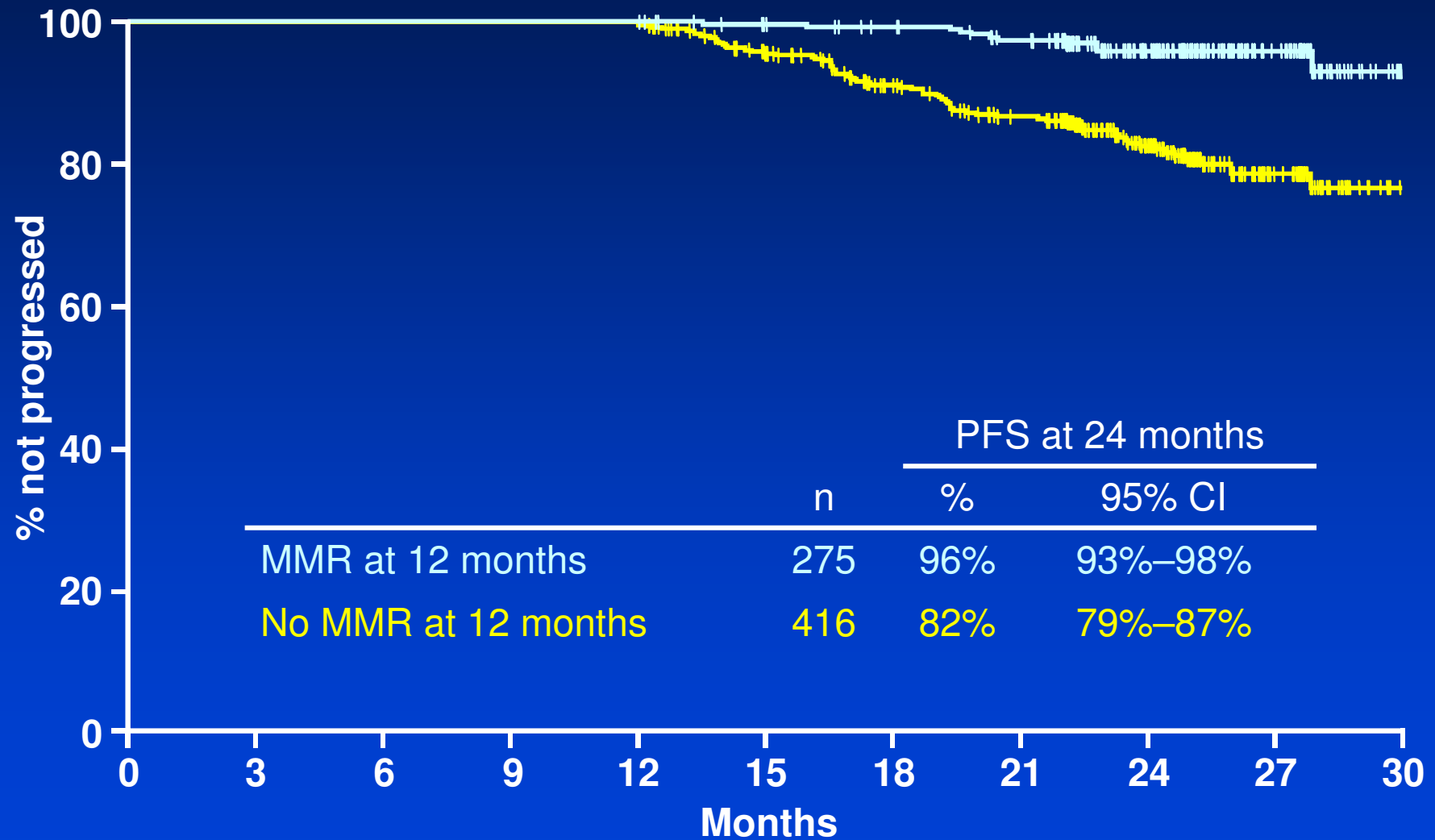
Time to MMR: patients with resistance or suboptimal response to imatinib (n=829)



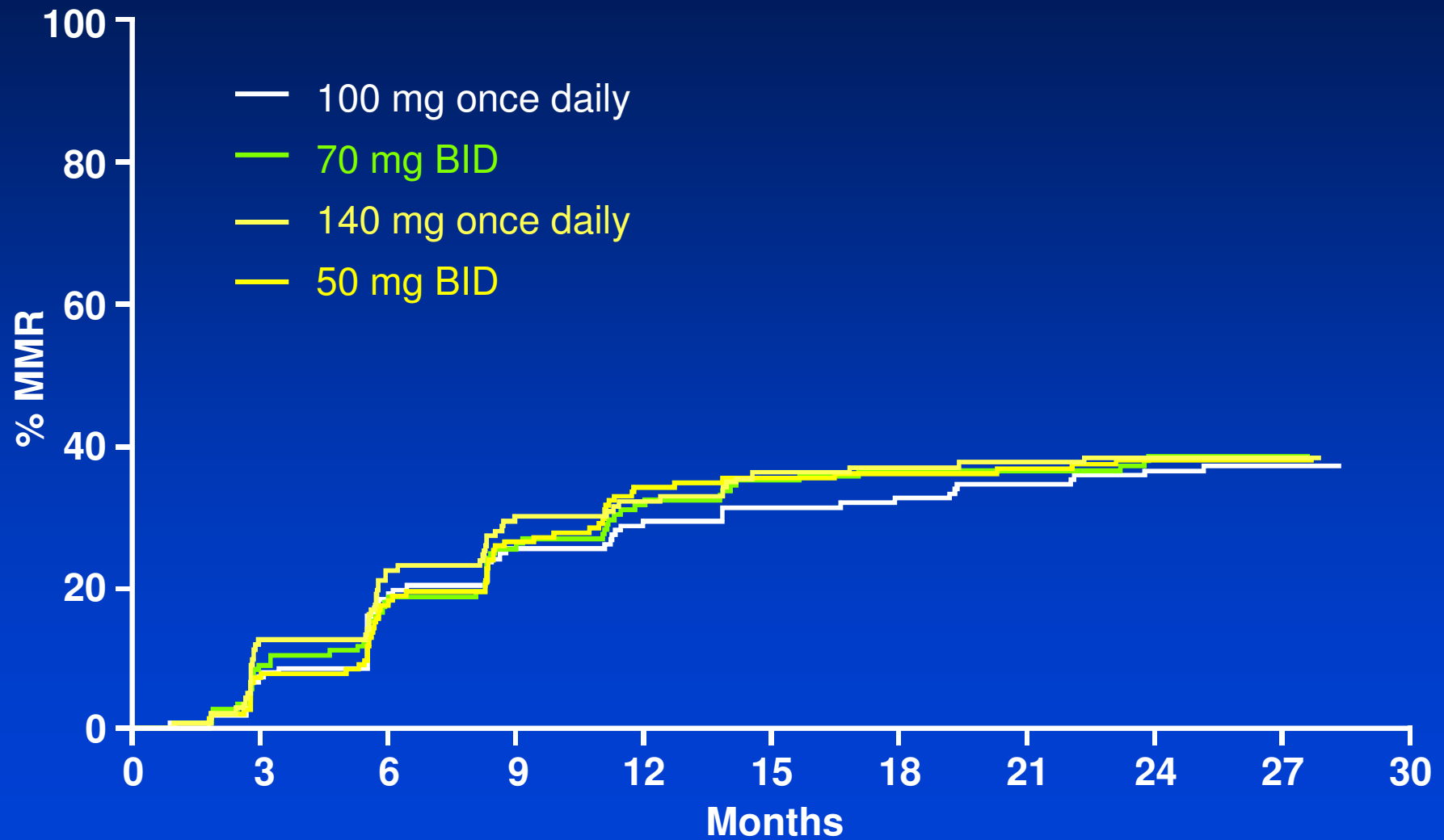
Time to MMR: patients with intolerance to imatinib (n=238)



Landmark analysis of PFS according to MMR at 12 months



Time to MMR (034 study)

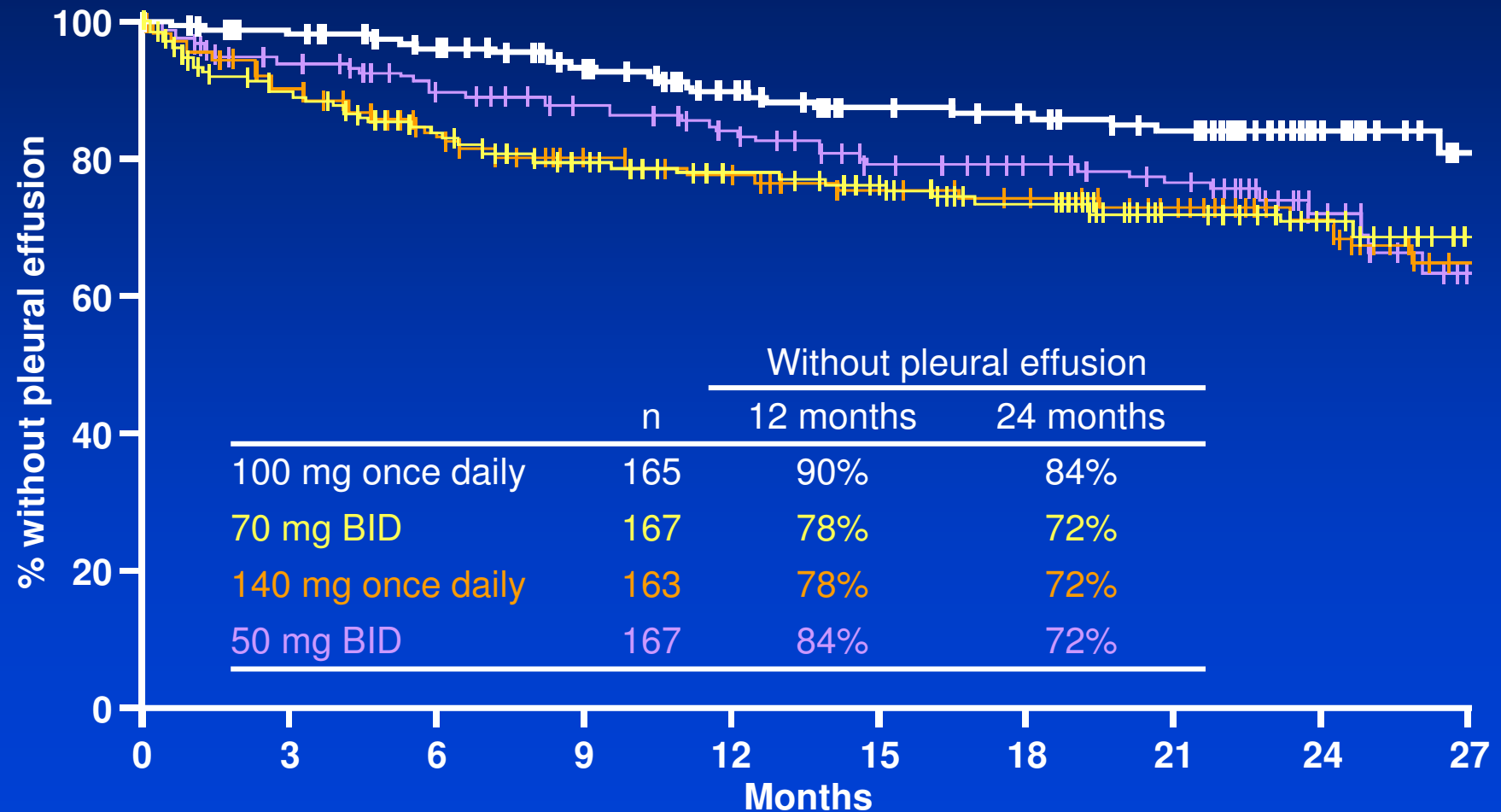


Dasatinib in 2nd line CML in CP: 100 mg QD compared to 70 mg BID

	Patients (%)		P-value
	100 mg QD	70 mg BID	
CHR	92	89	0.379
MCyR	64	58	0.300
CCyR	46	50	0.440
Progression-free survival	91	84	0.032
Pleural effusion	10	18	0.058
Neutropenia	34	43	0.112
Thrombocytopenia	22	38	0.004
CHF	0	4	0.015
Dose interruption	58	71	0.012
Dose reduction	33	57	<0.001
Discontinuation	22	32	0.049
Discontinuation due to toxicity	6	15	0.012

Dasatinib 100 mg once daily minimizes pleural effusion

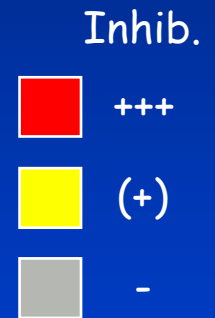
Time on dasatinib treatment without pleural effusion (any grade)



Kimmo Porkka, Abstract 3242, ASH 2008

Zielstrukturen der (Tyrosin-)kinaseinhibitoren

	abl	c-KIT	PDGF-R	src
	T315I			
Imatinib	1 x	+++	+++	-
<i>2nd generation</i>				
Nilotinib (Tasigna®)	30 x	+++	+++	-
Dasatinib (Sprycel®)	325 x	+++	+++	+++
SKI-606 (Bosutinib)	100 x	(+)	(+)	+++



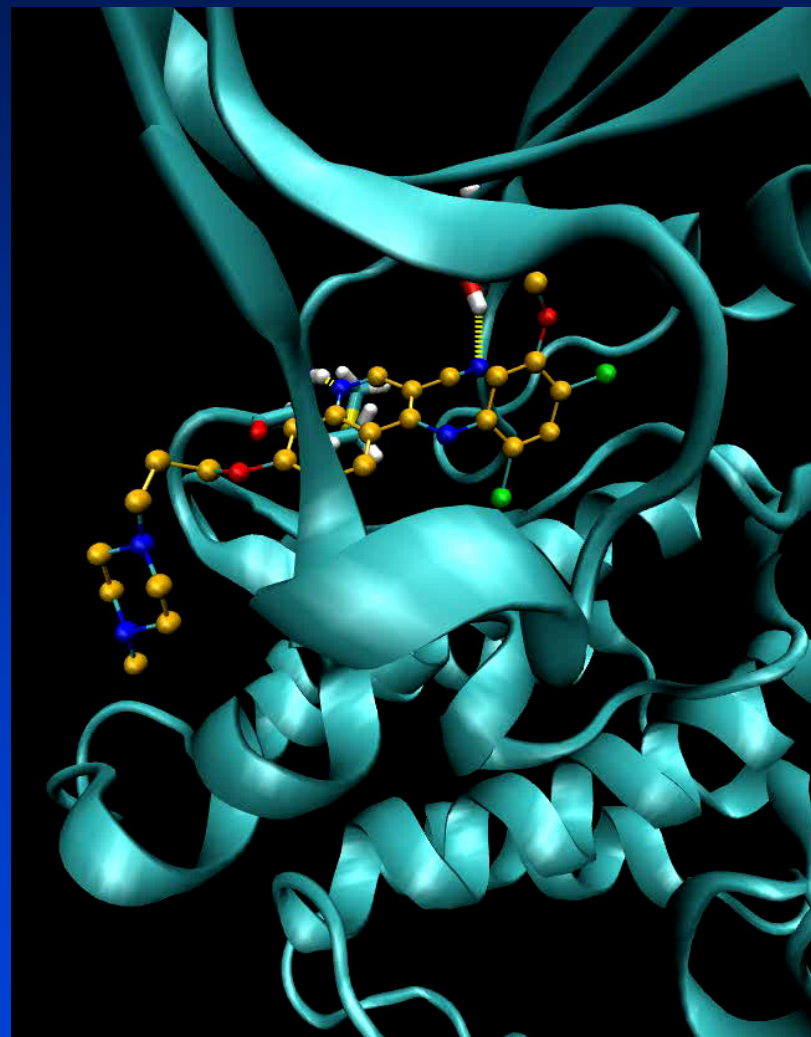
Bosutinib - A Dual Inhibitor of Src and Abl Kinases



Src Enzyme (Elisa) $IC_{50} = 1.2 \text{ nM}$
Src Enzyme (Lance) $IC_{50} = 3.8 \text{ nM}$
Abl Enzyme $IC_{50} = 1.4 \text{ nM}$

K562 Cell $IC_{50} = 20 \text{ nM}$
KU812 Cell $IC_{50} = 4.3 \text{ nM}$

Boschelli et al. *J Med Chem.* 2005
Golas et al. *Cancer Res.* 2003
Golas et al. *Cancer Res.* 2005
Gontarewicz et al. *Blood* 2008



Puttini et al. *Cancer Res* 2006; 66: 11314-22
Courtesy of L Scapozza and A Shaheen, University of Geneva,
Switzerland

Bosutinib in CP CML

Response (Imatinib Resistant*)

Median duration of treatment: 7 months

Response	N / N evaluable** (%)
<hr/>	
Hematologic	
Overall	60 / 69 (87)
Complete	56 / 69 (81)
Cytogenetic	
Major	45 / 101 (45)
Complete	32 / 101 (32)
Molecular	
Major	28 / 67 (42)
Complete	15 / 67 (22)

*Patients had no prior exposure to kinase inhibitors other than imatinib.

**Patients with complete hematologic (N = 41), cytogenetic (N = 4) or molecular (N = 3) responses at baseline are not counted as evaluable for that response.

*Brümmendorf et al ASCO 2008
Cortes et al. ASH 2008*

Bosutinib in CP CML Response (Imatinib Intolerant*)

Response	N / N evaluable** (%)
Hematologic	
Overall	27 / 33 (82)
Complete	27 / 33 (82)
Cytogenetic	
Major	23 / 45 (51)
Complete	18 / 45 (40)
Molecular	
Major	15 / 38 (39)
Complete	12 / 38 (32)

*Patients had no prior exposure to kinase inhibitors other than imatinib.

**Patients with complete hematologic (N = 14), cytogenetic (N = 6) or molecular (N = 4) responses at baseline are not counted as evaluable for that response.

Bosutinib in CP CML Response (Imatinib Exposed, Dasatinib Resistant)

Median duration of treatment: 7 months

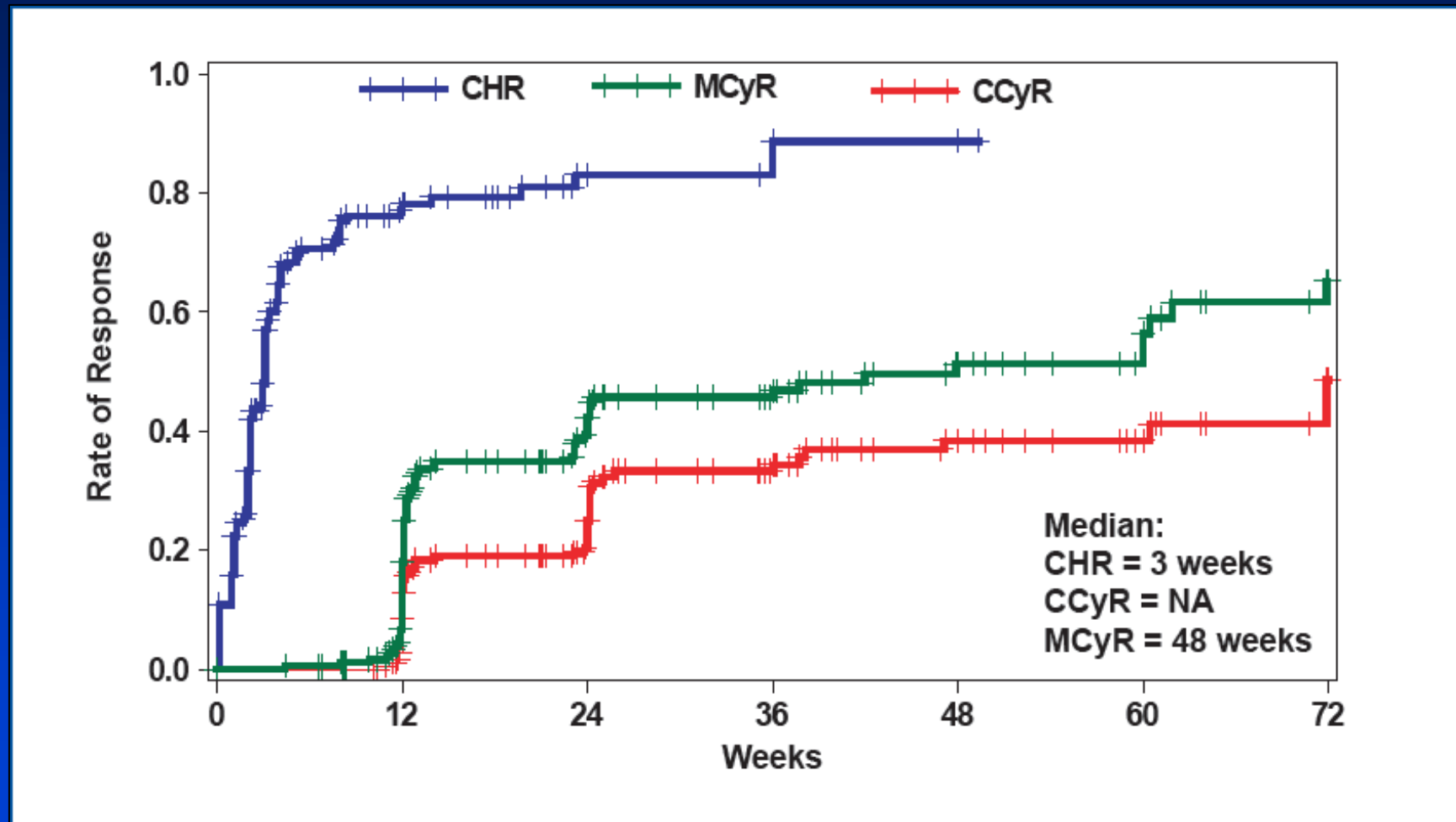
Response	N / N evaluable* (%)
Hematologic	
Overall	10 / 14 (71)
Complete	10 / 14 (71)
Cytogenetic	
Major	4 / 16 (25)
Complete	2 / 16 (13)
Molecular	
Major	1 / 14 (7)
Complete	0 / 14 (0)

*Patients with complete hematologic (N = 5), cytogenetic (N = 1) or molecular (N = 0) responses at baseline are not counted as evaluable for that response.

*Brümmendorf et al ASCO 2008
Cortes et al. ASH 2008*

Bosutinib in CP CML

Time to Response



Source: Cortes et al. Efficacy and Safety of Bosutinib in Patients with CP Ph+CML with Resistance or Intolerance to Imatinib
American Society of Hematology, December 6-9, 2008

Bosutinib in CP CML

Hematologic Laboratory Abnormalities (N=321)

Event	No. (%) Grade 3/4
Thrombocytopenia	68 (21)
Neutropenia	39 (12)
Anemia	19 (6)

Bosutinib in CP CML

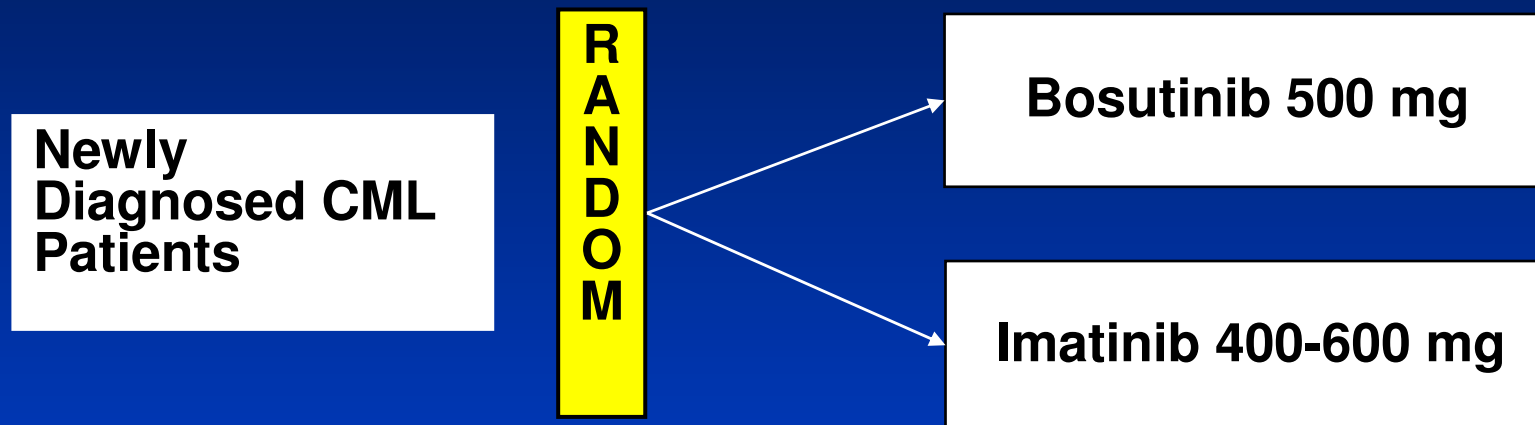
Response by Mutation Status

- Mutations in 44 of 104 (42%) patients tested
- 18 different mutations in 44 patients
- F317L (n = 6), G250E (n = 6), T315I (n = 5), F359V (n = 5), L248V (n = 3), Y253H (n = 3), M351T (n = 3), H396P (n = 2) and F486S (n = 2).

Mutation type	Response, N / N evaluable* (%)	
	CHR	MCyR
P-loop	4/5 (80)	4/8 (50)
Non-P-loop	15/21 (71)	12/30 (40)
No Mutation	27/30 (90)	25/48 (52)

*Patients with complete hematologic (P-loop = 3, non-P-loop = 6, no mutation = 15) or cytogenetic (non-P-loop = 1, no mutation = 6) responses at baseline are not counted as evaluable for that response.

Ongoing Phase 3 Trial Newly-diagnosed Chronic Phase CML Patients



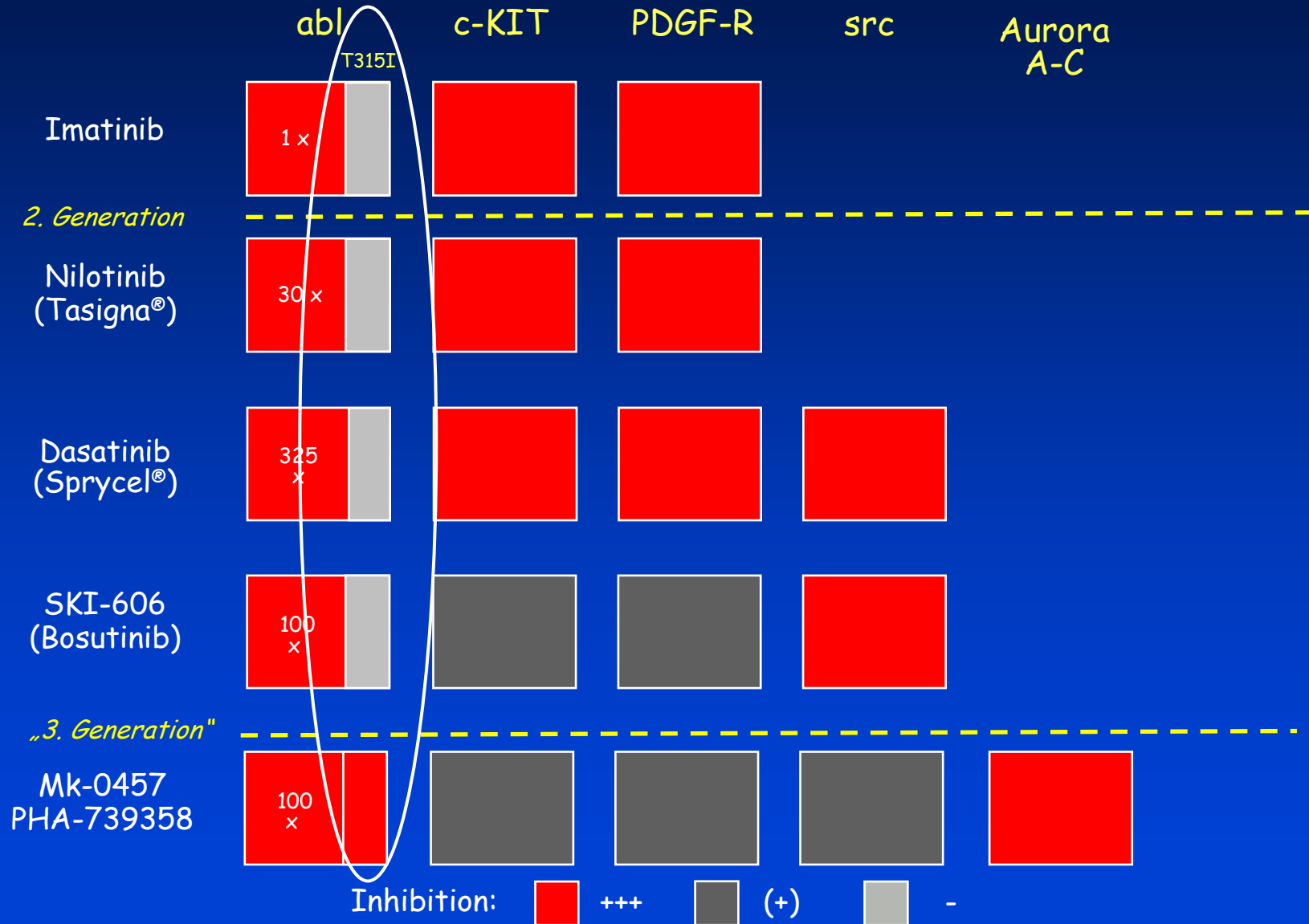
1° endpoint

- CCyR rate at 1 year: 65% vs 80%
- 412 patients (90% power)

2° endpoints:

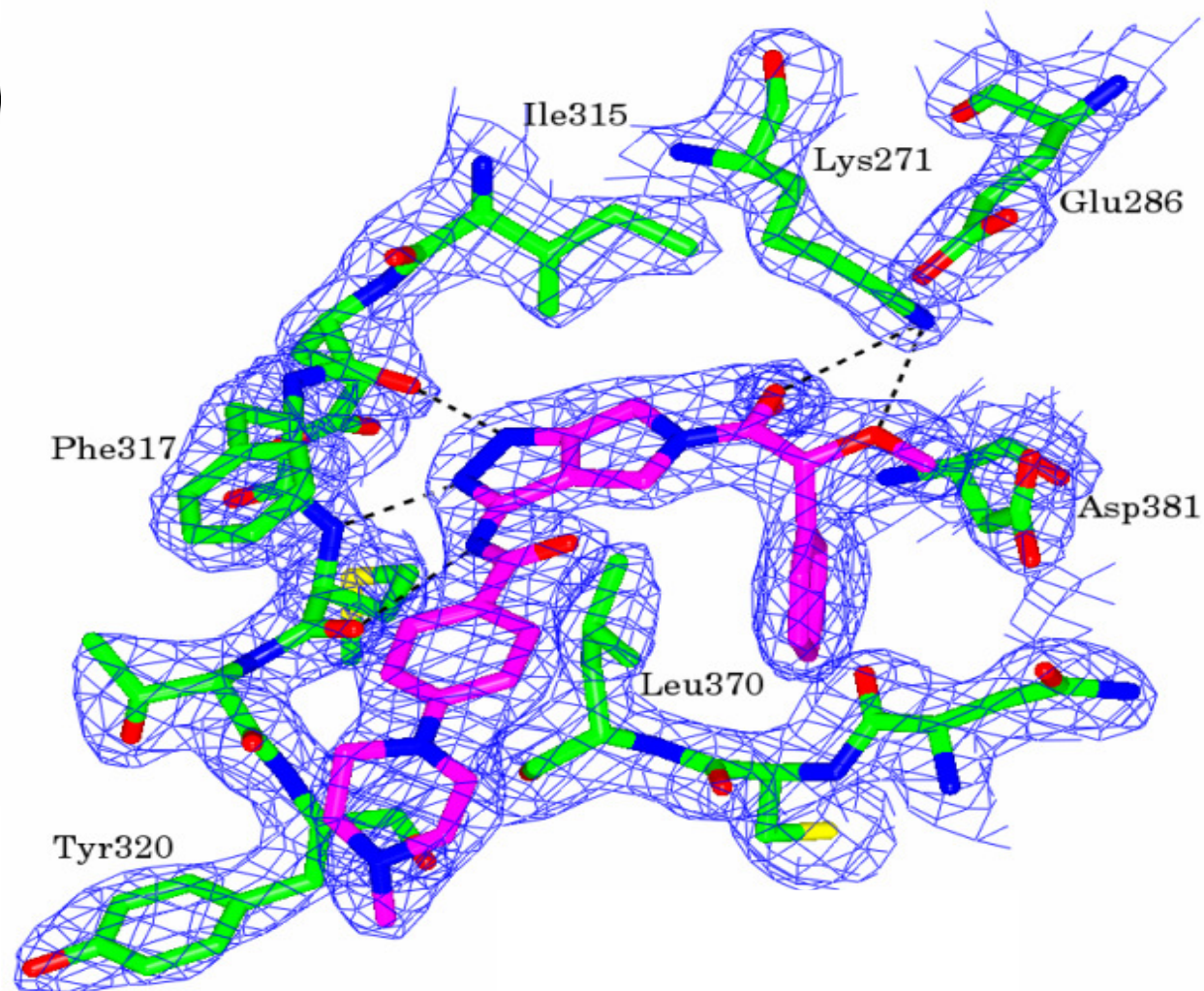
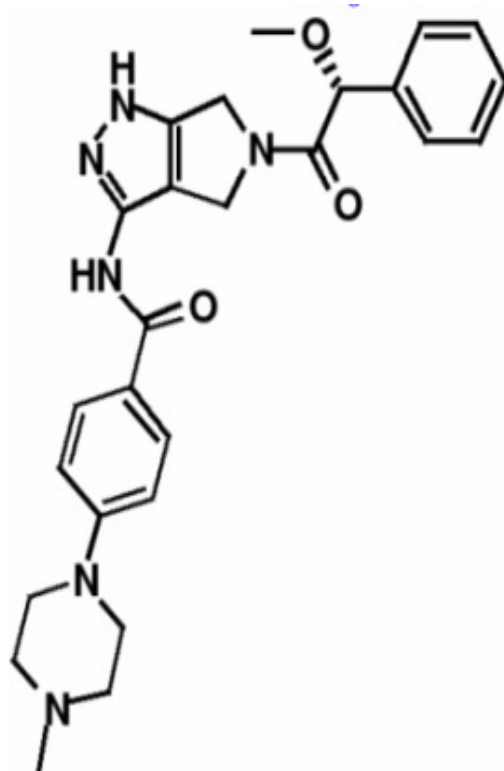
- MMR at one year
- Time to and duration of CCyR, MMR, and CHR
- Analyze differences based on Sokal
- Compare safety

Targets of selected Bcr-Abl TKI





Strukturelle Basis für die Wirkung von PHA-739358 auf die Imatinib-resistente Mutante T315I

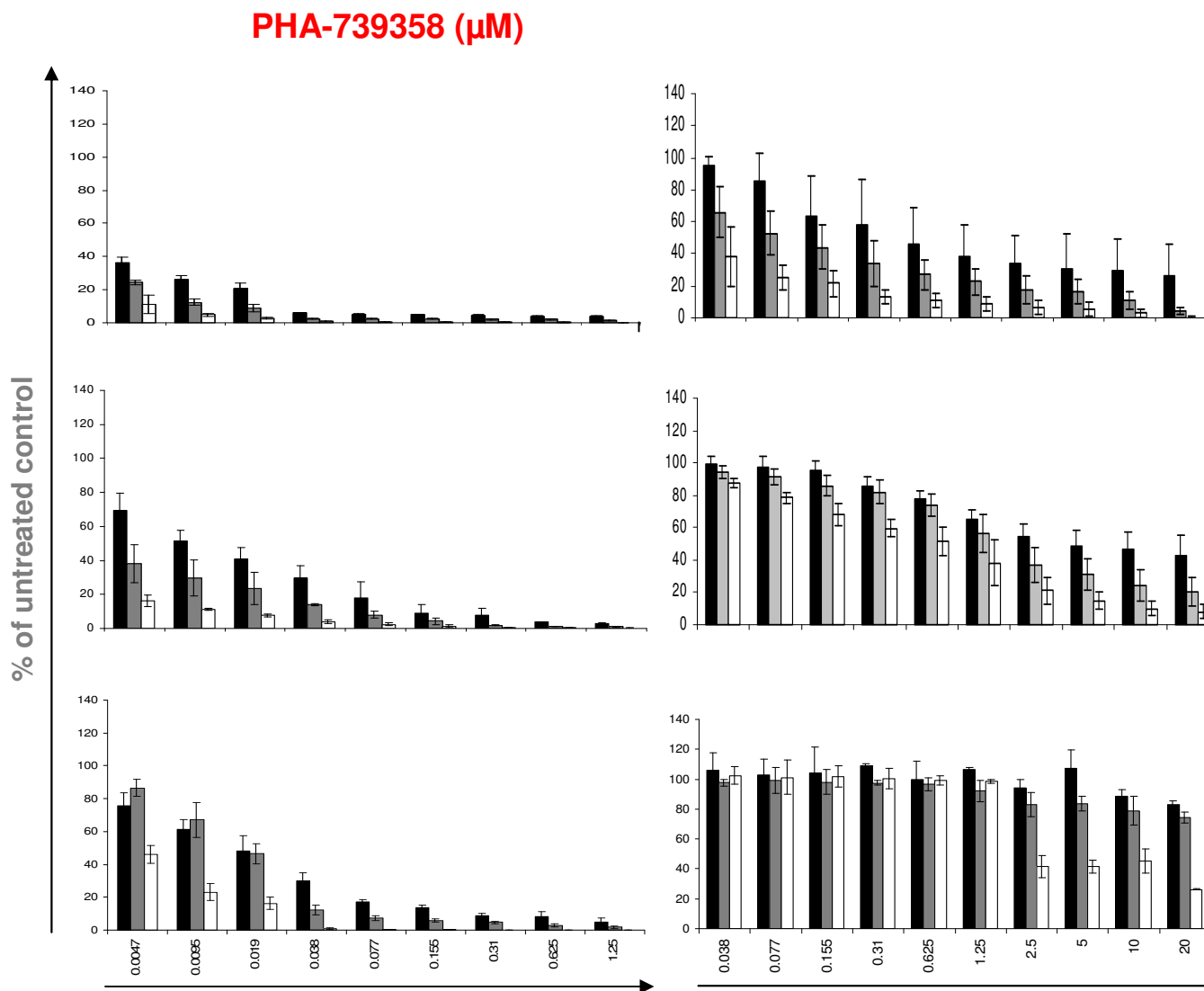




untreated
CP-CML
n=4

IM-resistant
BC-CML
n=3

IM-resistant
BC-CML
(T315I)
n=1



PHA-739358 in clinical trials

#1030:

■ Phase II: n=7 (1 CP, 1 AP, 5 BC); T315I-mutation: 6/7

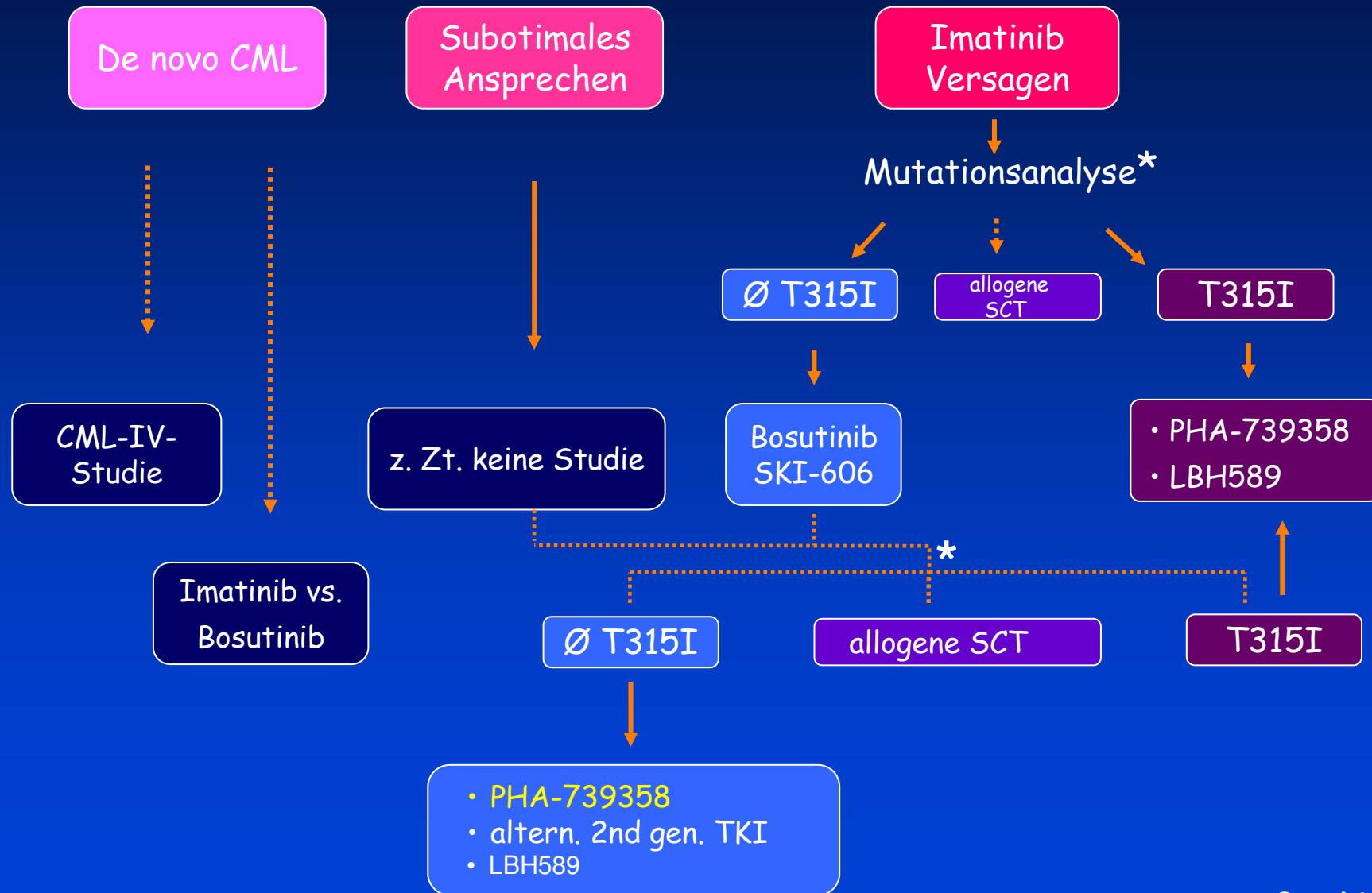
- Treatment: 250/ 330 mg/qm/d d 1,8, 15 repeat d28
- Results: → CHR (2/7) - subsequently one CCyR, one minor CR
→ no response in BC!
- Toxicity: Grade 4 Neutropenia 1/7
- Pharmacokinetic: sufficient blockade of Aurora Kinase and BCR-ABL @ 330mg/qm

#1042:

PHA-739358 is also active in CD34+ CML cells derived from patients in BC ex vivo

Aktuelle klinische Studien bei der CML

Klinik für Hämatologie und Onkologie, UCCH





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Melanie Braig
Ute Brassat
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Vera Bargsten
Joanna Schmid
Imke Rohe
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Christian Stender

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- *Roggenbuck-Stiftung*

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Bristol Myers Squibb
Wyeth Pharma
Nerviano MS

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