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UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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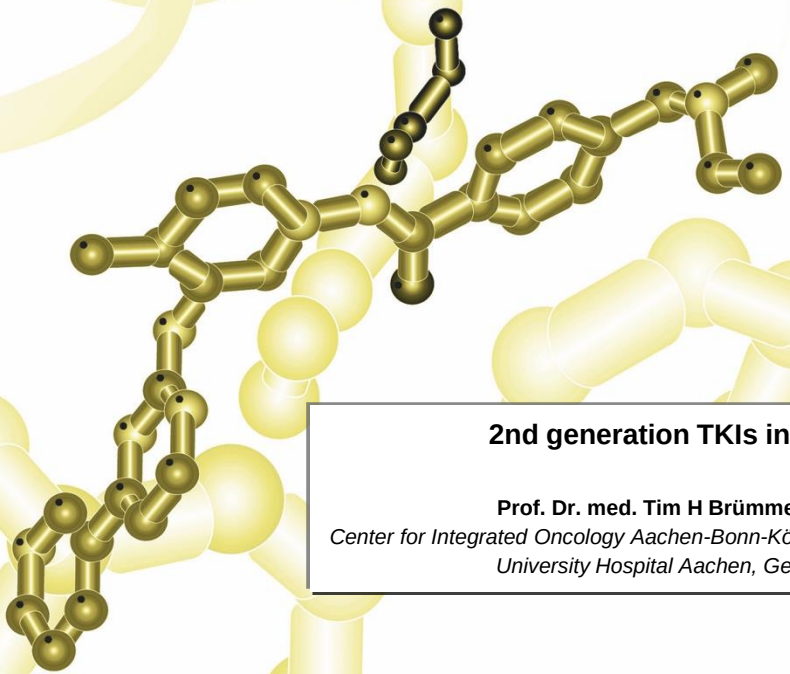


New Drugs in Hematology

President: Pier Luigi Zinzani
Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
January 15-17, 2024

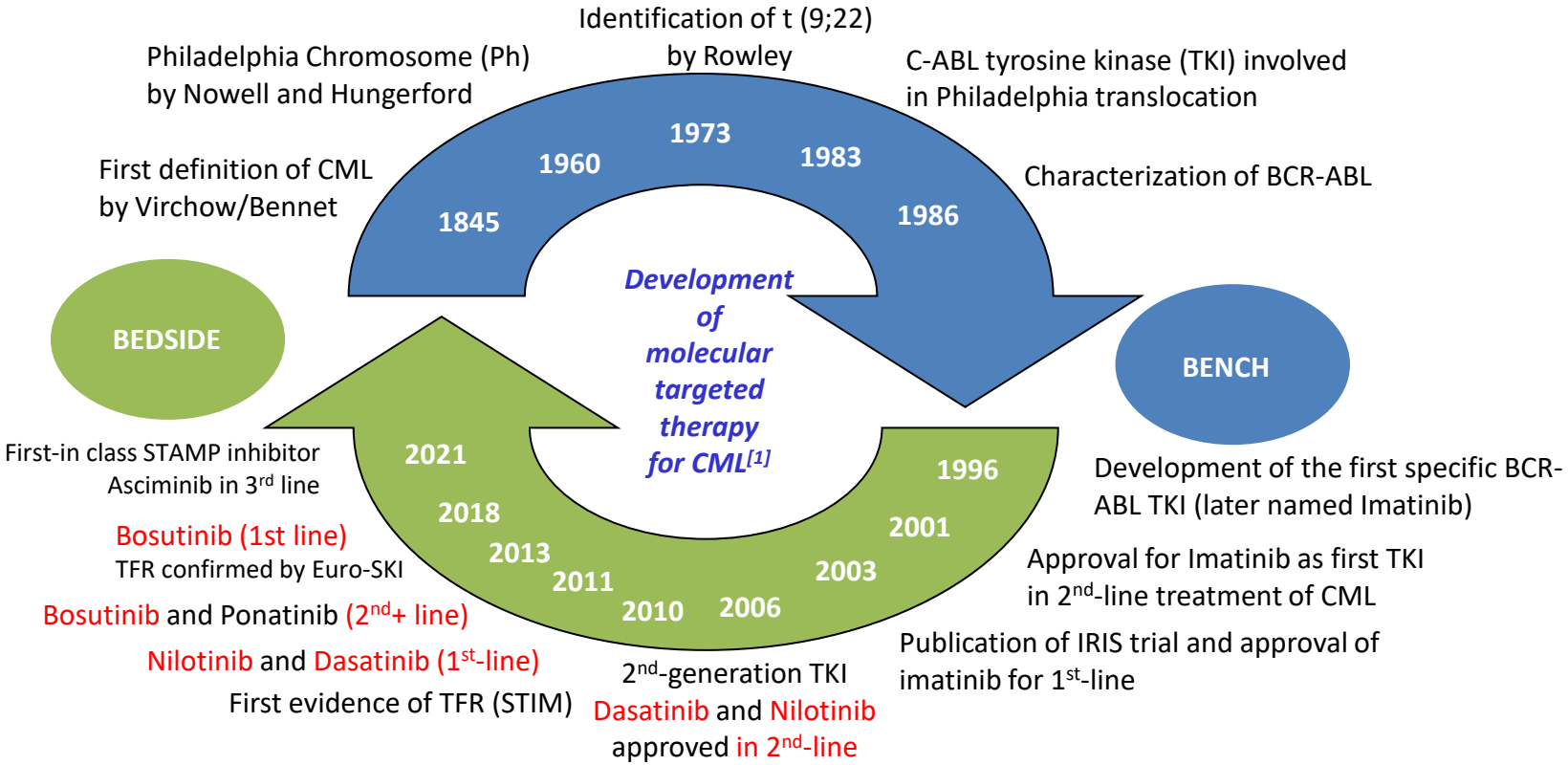
2nd generation TKIs in CML

Prof. Dr. med. Tim H Brümmendorf
Center for Integrated Oncology Aachen-Bonn-Köln-Düsseldorf (CIO^{ABCD})
University Hospital Aachen, Germany

Disclosures of Tim H. Brümmendorf

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Pfizer	x		x			x	
Novartis	x		x			x	
Gilead			x				
Ariad							x
Roche							x
Merck							x
RepeatDx	x						

Chronic Myeloid Leukemia (CML): A Model Disease in Oncology



Continously updated from:
Balabanov S. et al. ***Drug Discov Today Technol***. 2014;11:89
2nd generation TKI's indicated in red

CIO
Centrum für Integrierte Onkologie
Aachen Bonn Köln Düsseldorf

Structure, MoA and activity of approved BCR-ABL TKIs

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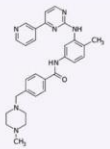
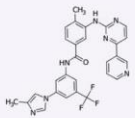
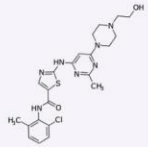
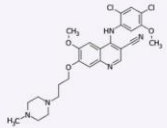
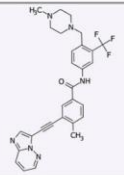
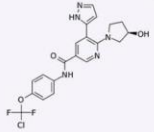
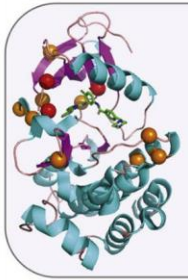
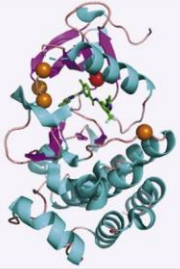
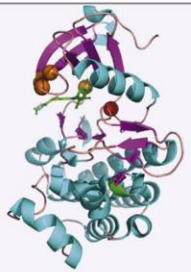
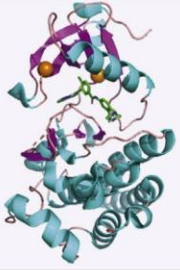
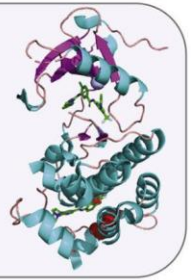
2nd generation TKI (2G TKI)

Inhibitor	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib
Chemical Structure						
Crystal Structure						
Binding Conformation	Inactive	Inactive	Active	Both	Inactive	Myristoyl Pocket
Resistance	Y253 Q252 E255 F317 T315 M351 M244 M355 L248 F359 G250 H396	T315 L248 Y253 E255 F359	T315 V299 F317	T315 V299 L248 G250 E255 F317		A337 W464 P465 V468 I502

Braun et al.
***Cancer Cell** 2020;*
37: 530-42

Challenges in the Treatment of CML in 2024

Background:

- Most patients with newly diagnosed CML are assumed to have a normal life expectancy

Challenges:

- Offering the perspective of a **treatment-free remission** (cure?) to as many patients as possible
- Prevention of and (in case it happens) improved treatment of:
  - **Disease progression** to AP/BC and
  - Development of **resistance** to TKI
- Improvement of **tolerability** and **adherence** to TKI
- **Eradication of leukemic stem cells** as a continued source of relapse/disease progression

Do 2nd generation TKIs improve treatment of CML over Imatinib ?

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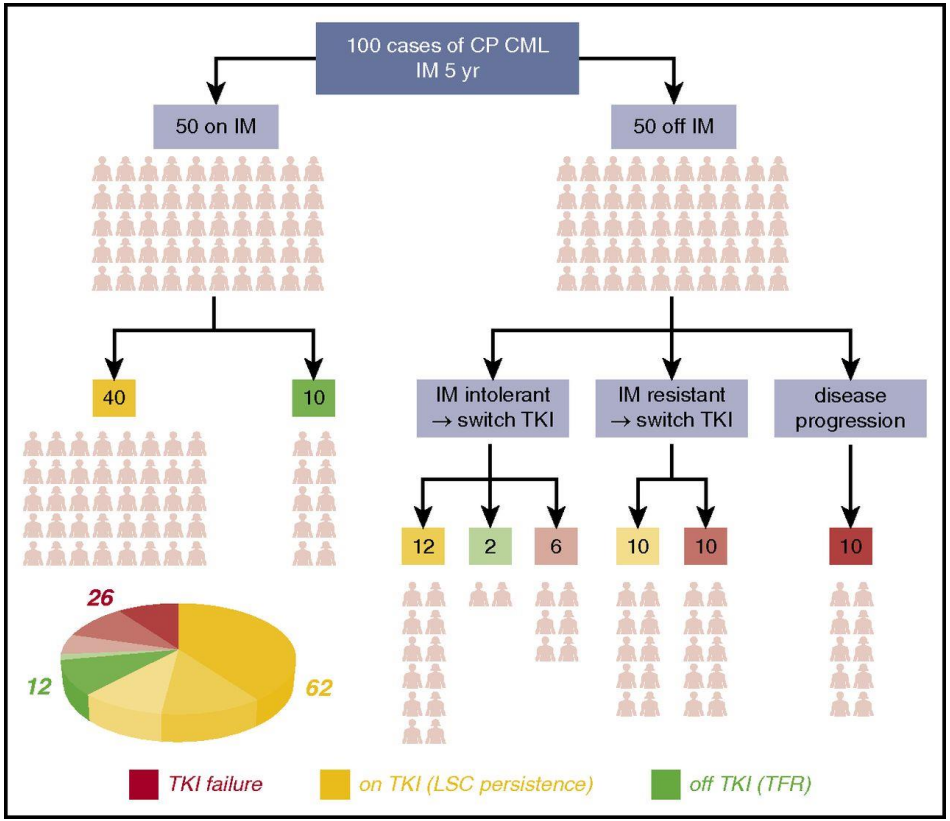
Do 2nd generation TKIs improve treatment of CML over Imatinib ?

If so, how to decide when to apply them and which one to choose ?

Treatment-free Remission (TFR) in CML First Line

TFR rates achieved with Imatinib in CP CML in First Line



Holyoake. Blood. 2017;129:1595.

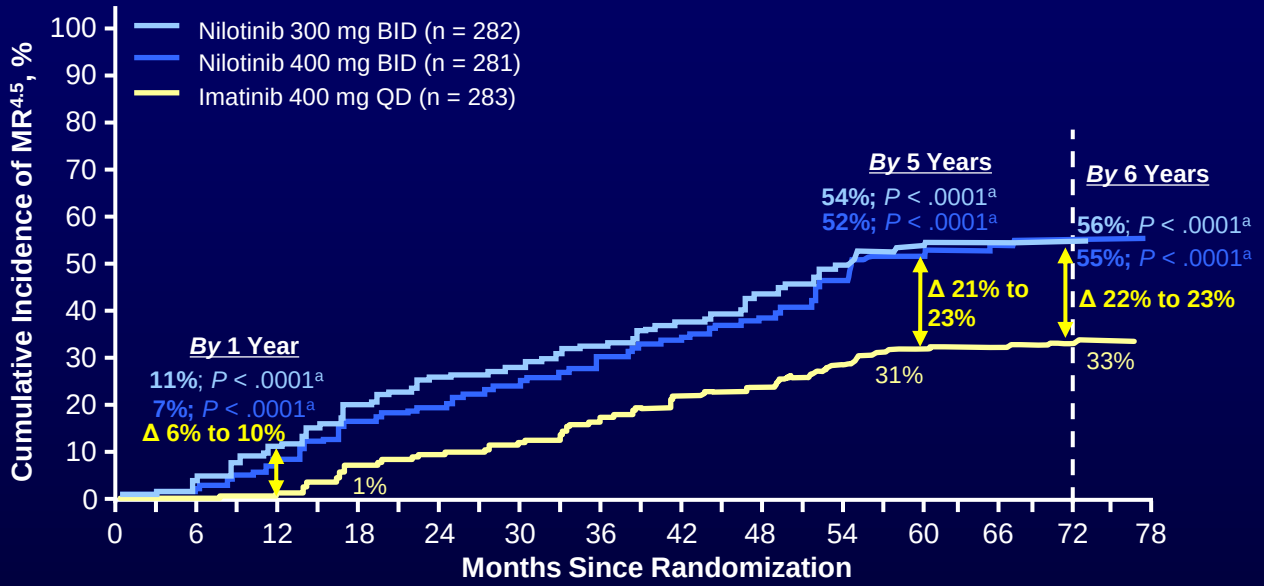
TFR rate (on the basis of 5 years from start of treatment !):

Imatinib first line (accord. to *Vetrie und Holyoake* ***(2017 !)***:

12 %

Can We Improve the Number of Patients Achieving TFR by Using 2nd Generation TKIs in First Line and/or by longer pretreatment period (duration of deep response)?

Cumulative Incidence of MR$^{4.5}$ and Time to First MR$^{4.5}$

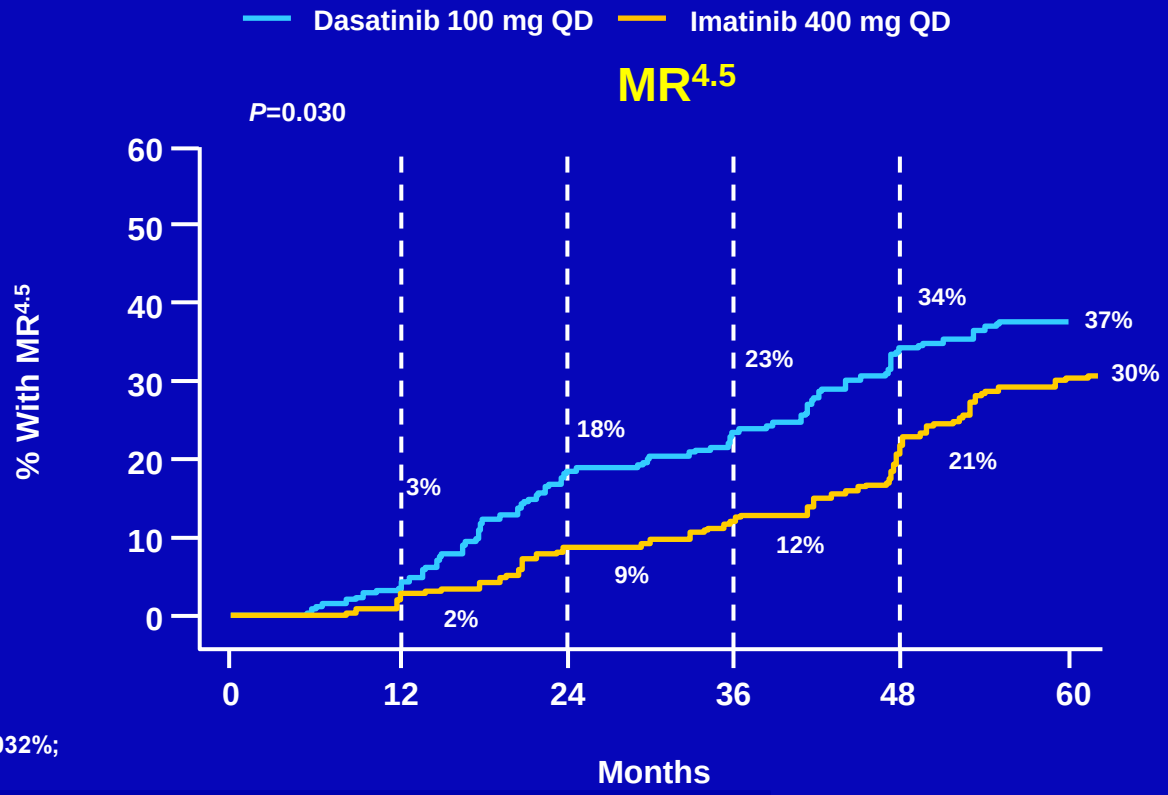


Treatment Arm	Kaplan-Meier Estimated Median Time to First MR$^{4.5}$, months	Hazard Ratio vs Imatinib (95% Confidence Interval)	*P* value[a]
Nilotinib 300 mg BID	45.5	2.0387 (1.5807-2.6295)	< .0001
Nilotinib 400 mg BID	49.8	1.7770 (1.3780-2.2915)	< .0001
Imatinib 400 mg QD	61.1	–	–

[a] *P* values are nominal, were provided for descriptive purposes only, and were not adjusted for multiple comparisons.

Hughes TP, et al. *Haematologica*. 2015;100:[abstract P228].

Cumulative Rate of MR$^{4.5}$

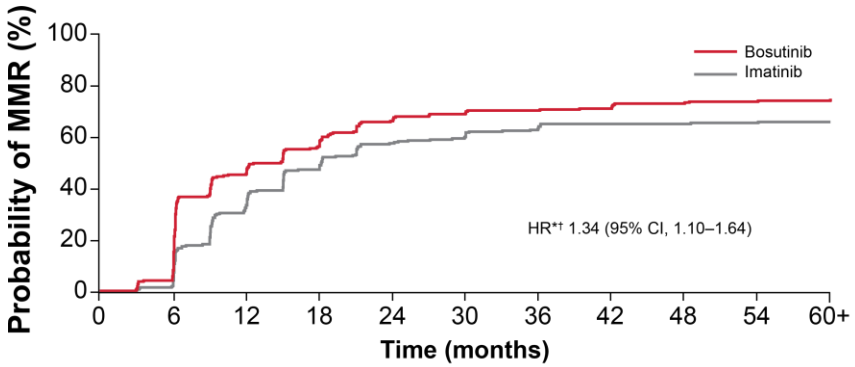


MR$^{4.5}$ = BCR-ABL (IS) ≤0.0032%;
IS = International Scale.

Molecular Response

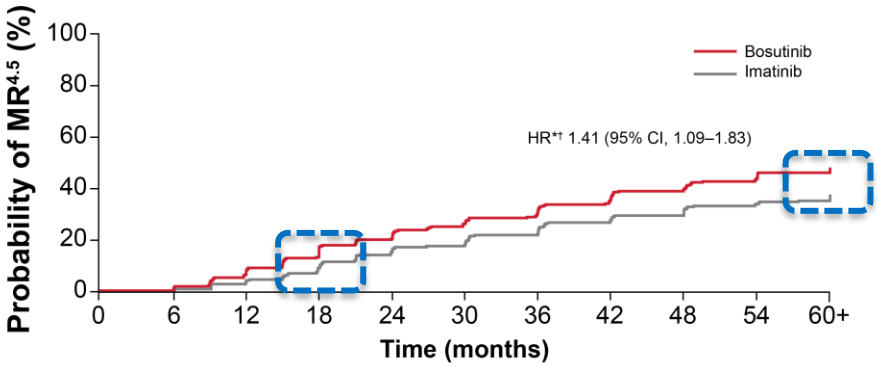
Cumulative response rates by 60 months, % (95% CI)*	Bosutinib n=268	Imatinib n=268	OR (95% CI)
MMR	73.9 (68.6–79.1)	64.6 (58.8–70.3)	1.57 (1.08–2.28)
MR^4	58.2 (52.3–64.1)	48.1 (42.2–54.1)	1.50 (1.07–2.12)
$MR^{4.5}$	47.4 (41.4–53.4)	36.6 (30.8–42.3)	1.57 (1.11–2.22)

Time to MMR



No. at risk											
Bosutinib	268	223	101	64	34	22	15	13	8	6	4
Imatinib	268	224	129	72	32	26	16	10	10	8	5

Time to $MR^{4.5}$



No. at risk											
Bosutinib	268	236	200	174	150	126	111	96	82	69	53
Imatinib	268	230	207	170	135	125	112	91	84	72	52

* Adjusted for Sokal risk group and region as determined at the time of randomization.

† From a proportional subdistributional hazards model adjusted for competing risk of treatment discontinuation without a response.

Ratios with 95% CIs excluding 1 are predictive (no adjustment for multiple comparisons). MMR: *BCR-ABL1* IS ≤0.1%. MR^4: *BCR-ABL1* IS ≤0.01%. $MR^{4.5}$: *BCR-ABL1* IS ≤0.0032%.

Deep molecular response of 1st vs. 2nd generation TKI

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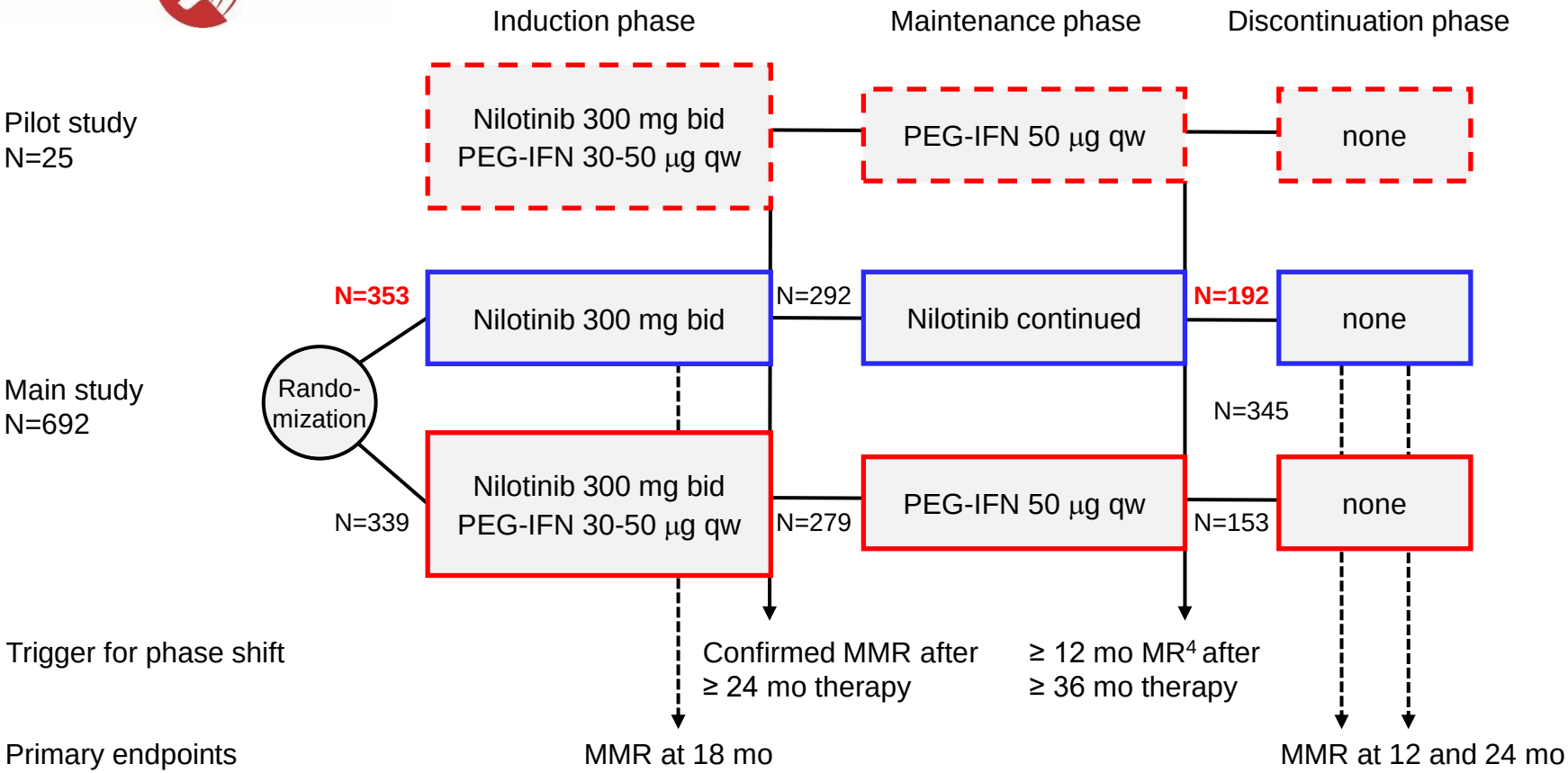
(CAVE ! Cross-trial comparison !)

	@5 years						*@3 months*		
	MMR			**MR$^{4.5}$**			**EMR** (≤10%)		
	2ndgen	IM	ΔMMR	2ndgen	IM	ΔMR$^{4.5}$	2ndgen	IM	ΔEMR
DAS vs IM	**76%**	64%	12%	**42%**	33%	9%	**84%**	64%	20%
NIL vs IM	**77%**	60%	17%	**54%**	31%	23%	**91%**	67%	24%
BOS vs IM	**74%**	65%	9%	**47%**	37%	10%	**75%**	57%	18%

Hochhaus et al. ENESTnd. LEUKEMIA 2016
Cortes et al. DASISION. JCO 2016
Brümmendorf et al. BFORE. LEUKEMIA 2022

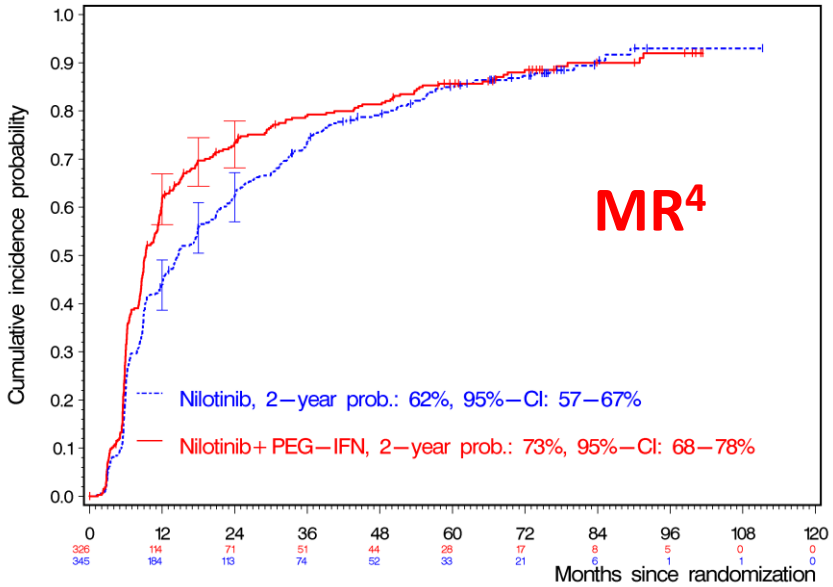
TIGER STUDY

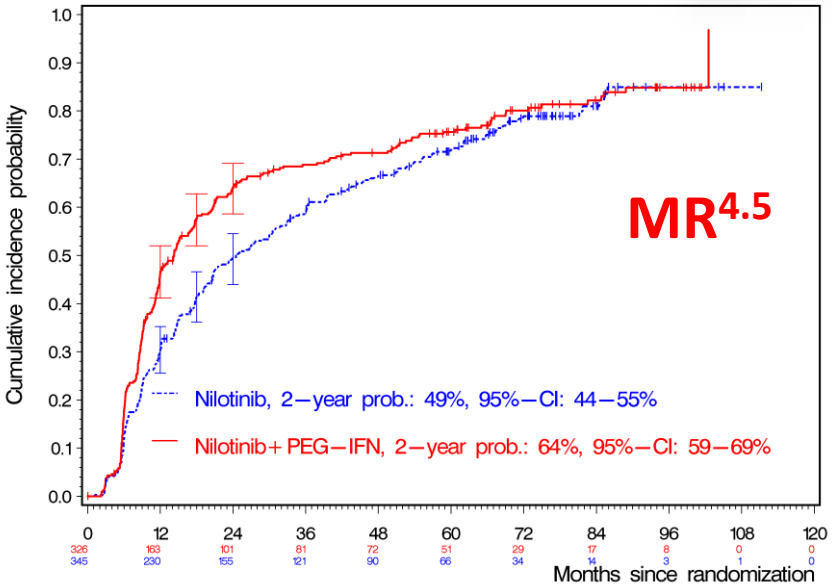
N=717 (Median follow up 6.4 years)



modified from: Hochhaus A. et al., ASH 2023: #446: Treatment Free Remission after Nilotinib Plus Peg-Interferon Alpha Induction and Peg-Interferon Alpha Maintenance Therapy for Newly Diagnosed Chronic Myeloid Leukemia Patients; The Tiger Trial

Cumulative incidences of DMR



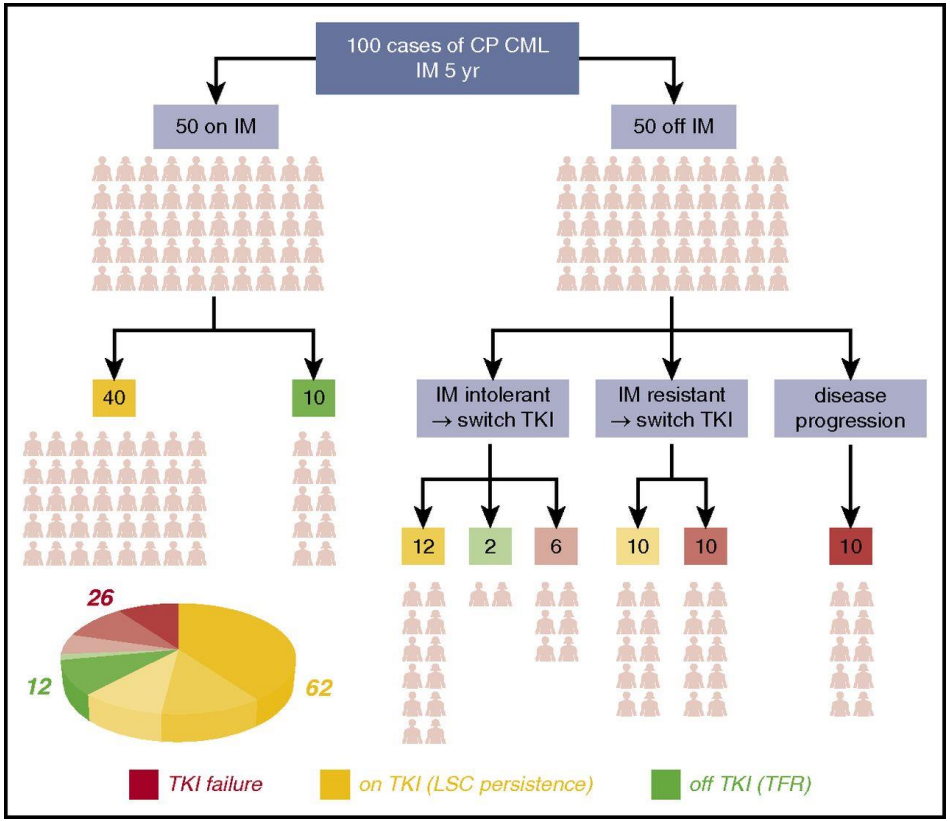


192/353 patients i.e. 54.3 % of all patients included in the Nilotinib monotherapy arm could discontinue treatment of which TFR* was successfully achieved in 53%

*discontinuation criteria: minimum of 3 years of therapy and a minimum of 1 year in MR^4

modified from: Hochhaus A. et al., ASH 2023: #446: Treatment Free Remission after Nilotinib Plus Peg-Interferon Alpha Induction and Peg-Interferon Alpha Maintenance Therapy for Newly Diagnosed Chronic Myeloid Leukemia Patients; The Tiger Trial

TFR rates achieved with Imatinib or Nilotinib in CP CML in First Line



Holyoake. Blood. 2017;129:1595.

TFR rate (on the basis of 5 years from start of treatment !):

Imatinib first line (accord. to *Vetrie und Holyoake* ***(2017 !)***:

12 %

TFR rate (>3 years of treatment and >1 year of MR^4):

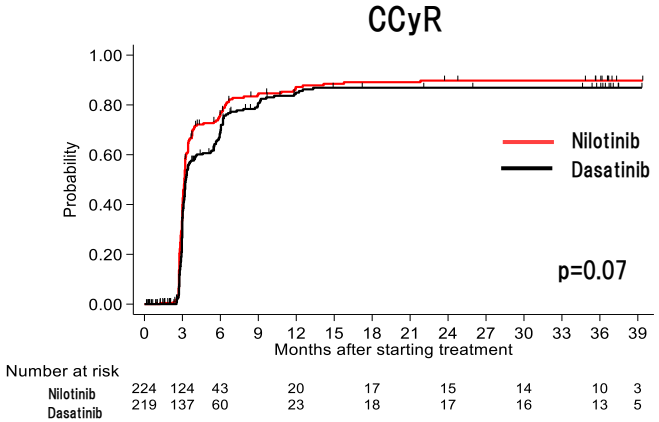
Nilotinib first line (accord. to *Hochhaus et al. TIGER-Study* ***(2023 !)***:

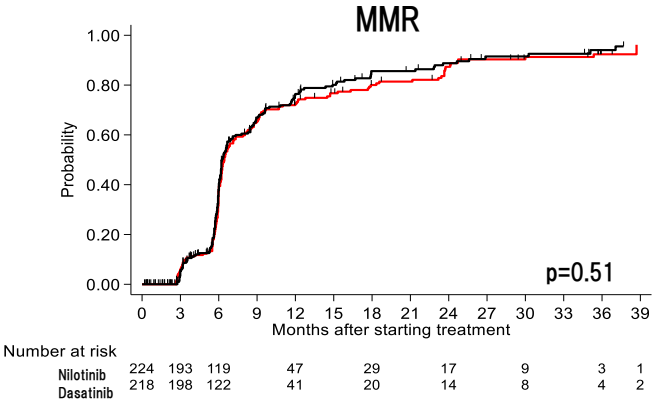
29 %

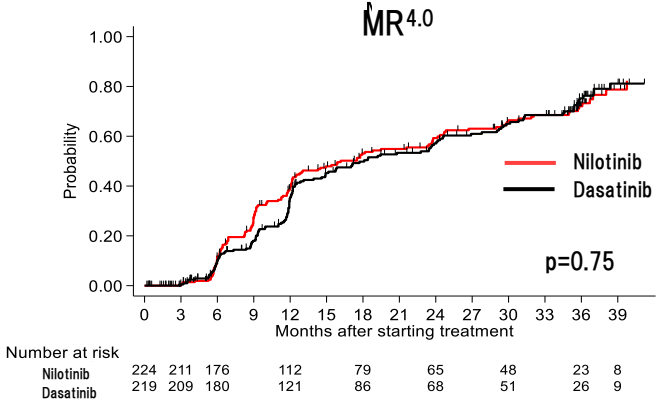
Times to Cytogenetic and Molecular Responses

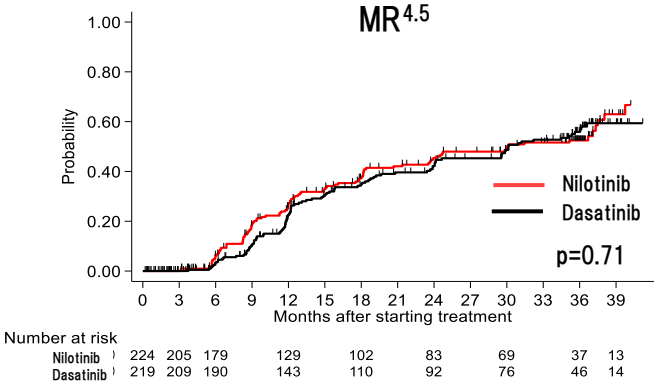
(Per-protocol population Japanese study)

Kaplan-Meier Method









Matsumura *et al.*
ASH 2020

Flumatinib Versus Nilotinib for Newly Diagnosed CP CML

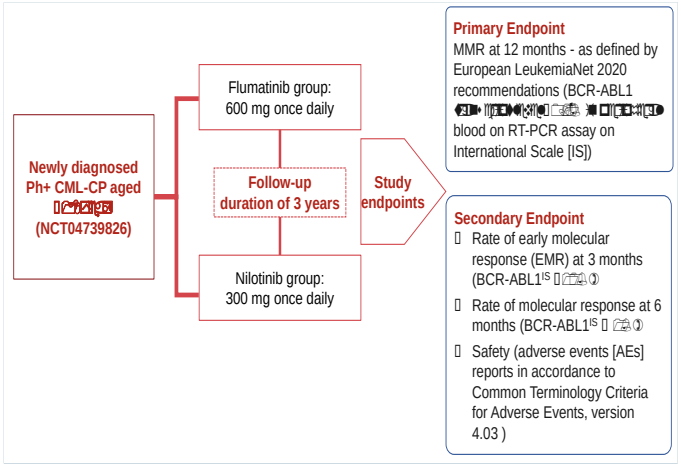
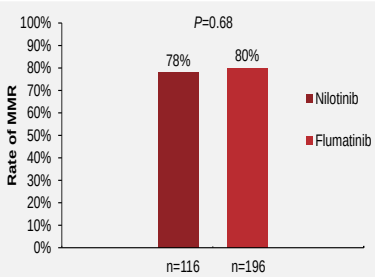
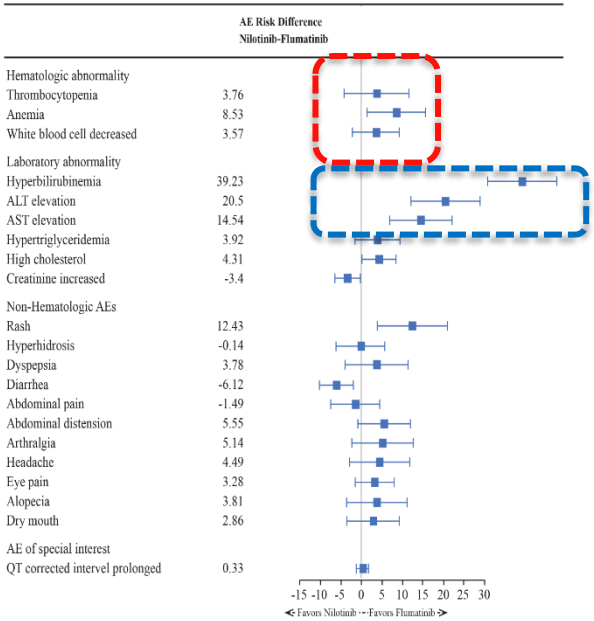


Figure 1: Rate of MMR at 12 months in nilotinib and flumatinib groups



Group	Number of patients	Total number of patients	MMR (BCRABL IS≤0.1%)
Nilotinib	90	116	0.78
Flumatinib	156	196	0.80

Figure 1: Forest plot showing the risk difference of adverse events between Flumatinib and Nilotinib



Treatment of CML in 2nd+ line following Imatinib

Response in Patients With a Minimum Follow-Up of 24 Months (N = 321)

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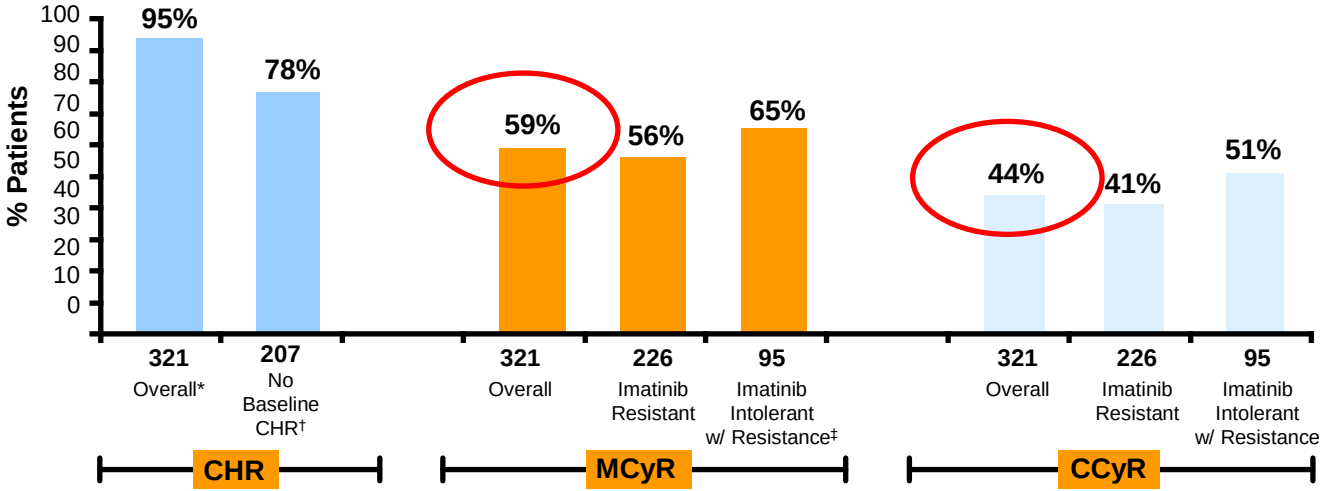

CCyR, complete cytogenetic response; **CHR**, complete hematologic response; **MCyR**, major cytogenetic response.

* Patients who achieved (without baseline CHR) or maintained CHR (had CHR at study entry).
† Patients with no CHR at baseline.
‡ See definition of imatinib-intolerant with resistance in the Methods sections.

- The overall rate of major molecular response (MMR) at 24 months was 38% for all patients with post-baseline PCR data available and baseline CHR (n = 105)

*24 months update: Kantarjian et al. **Blood.** 2009;114:464. Abstract #1129*
*(6 months data published in: Kantarjian et al. **Blood** 2007;110: 3540-3546)*

Dasatinib 100 mg QD in CP-CML (034): 4-year follow-up

Best overall response

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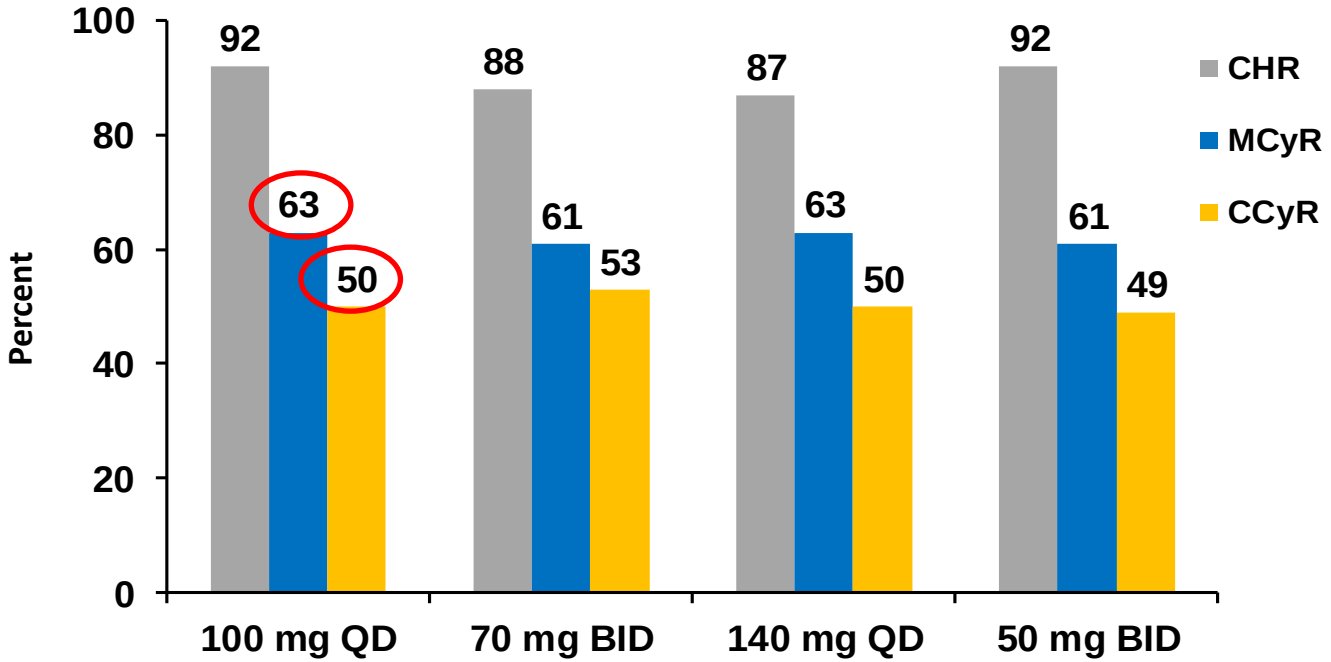

[a]CHR and CyR were last assessed at 24 months (per protocol)
Patients with Ph(–) BCR-ABL(+) disease (n=14) are excluded from CyR rates

presented at ASCO 2010
Shah NP, et al.: ***Haematologica.*** *2010 Feb; 95(2): 232–240.*

Bosutinib in 2nd line treatment following Imatinib
Study 200: Efficacy summary
(median follow-up of 54.8 months)

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Table 2. Efficacy outcomes at two and five years.

Parameter	IM-R (n=195)		IM-I (n=89)		Total (n=284)	
	Year 2	Year 5	Year 2	Year 5	Year 2	Year 5
Response,*† n. of evaluable patients (%) [95% CIs]						
Cumulative MCyR	102/182 (56) [48.5–63.4]	107/182 (59) [51.3–66.0]	49/80 (61) [49.7–71.9]	49/80 (61) [49.7–71.9]	151/262 (58) [51.4–63.7]	156/262 (60) [53.3–65.5]
Cumulative CCyR	79/182 (43) [36.1–50.9]	88/182 (48) [40.9–55.9]	41/80 (51) [39.8–62.6]	42/80 (53) [41.0–63.8]	120/262 (46) [39.7–52.0]	130/262 (50) [43.4–55.8]
Cumulative MMR	42/127 (33) [25.0–42.0]	57/127 (45) [36.1–54.0]	20/70 (29) [18.4–40.6]	25/70 (36) [24.6–48.1]	62/197 (31) [25.1–38.5]	82/197 (42) [34.7–48.8]

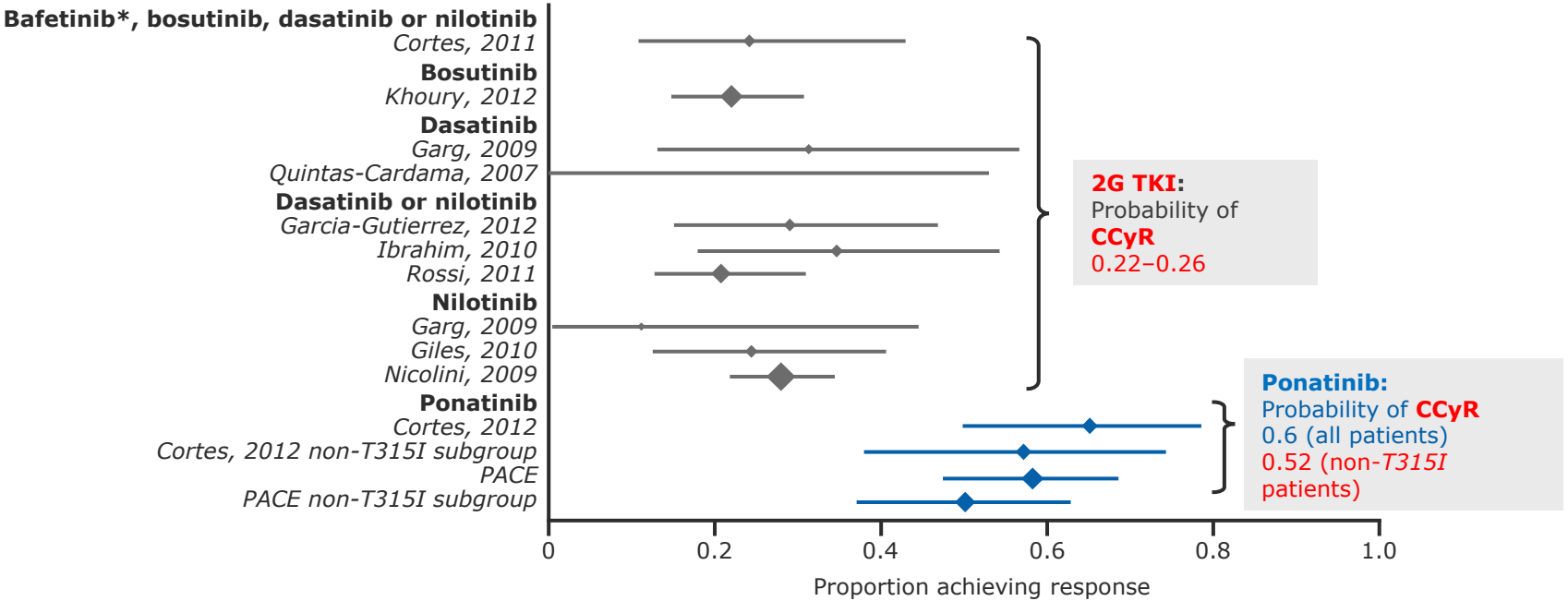
CI, confidence interval; CML, chronic myeloid leukemia; CCyR, complete cytogenetic response; IM-I, imatinib intolerant, IM-R; imatinib resistant; KM, Kaplan–Meier; MCyR, major cytogenetic response; PD, progressive disease

Gambacorti-Passerini C et al. ***Haematologica*** *2018;103:1298–1307*

Treatment of CML in 2nd line following 2nd generation TKI

Comparing the effectiveness of sequential 2G TKI use versus switch to ponatinib after 2G TKI failure

Proportion of CP-CML patients who achieve a CCyR (after failure of ≥1 2G TKI and ≥2 prior TKI therapies):



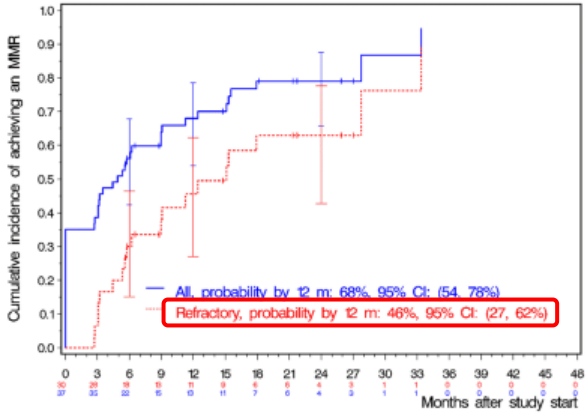
The size of the diamonds in the figure represents the number of patients; the length of the lines shows the 95% confidence intervals.
*Bafetinib is not approved for the treatment of patients with CML; treatment only in the context of clinical studies.

2G, second generation; CCyR, complete cytogenetic response; CP-CML, chronic phase, chronic myeloid leukaemia; TKI, tyrosine kinase inhibitor.

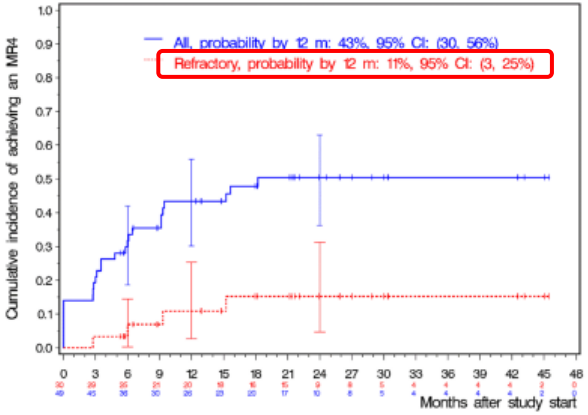
Lipton JH, et al. *Leuk Res.* 2015;39:58–64.

Bosutinib run-in dosing following 2nd generation TKI failure:
The German CML-7 (BODO) trial: *Efficacy*

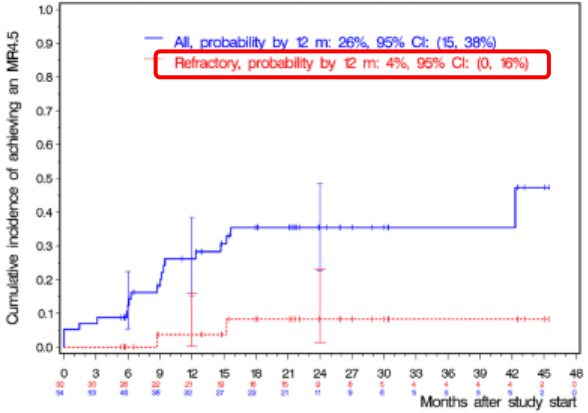
MM



MR4



MR4.



- Probability of **MMR after 24 months of therapy was 79%** (95% CI: 65.8% to 87.5%)
  - 6 out of 7 previously **intolerant** patients achieved MMR or better
  - 30 **refractory** patients (19 refractory; 11 refractory and intolerant) **without baseline MMR**:
    → **19 (53%) patients achieved MMR or better** (2 patients with MR4.5; 2 with MR4 and 15 MMR)

Isfort et al. ***Ann Hematol*** *102:2741-52 (2023)*

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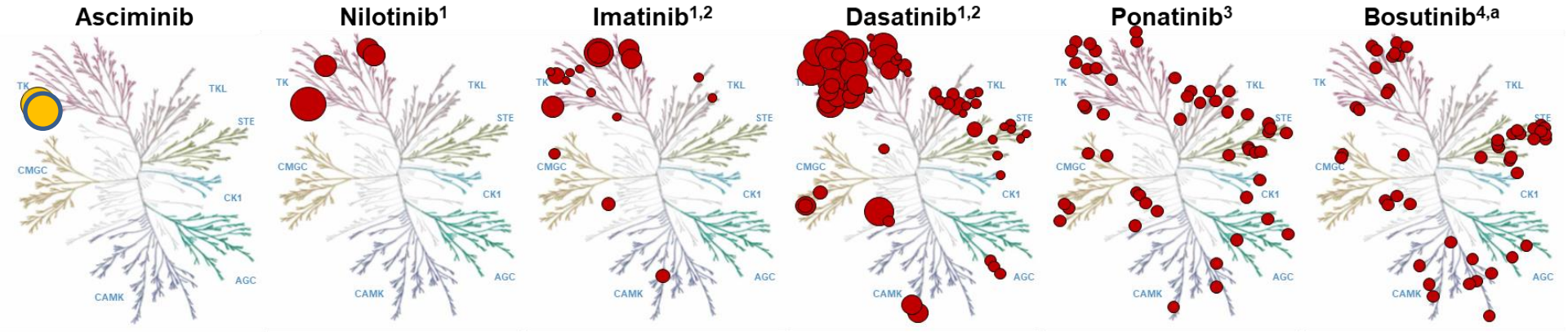
Tolerability of TKIs:

- spectrum of organs affected
- on vs. off target effects
- confounding factors
- dose-dependency
- reversability
- kinetics

Role of Comorbidities:

… and the **Patient's Perspective**:

Selectivity of BCR::ABL-Inhibitors



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.

Side effects of TKIs approved for treatment of CML

	Imatinib		Dasatinib		Nilotinib		Bosutinib		Ponatinib	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Fatigue	++++	+	+++	+	++++	-	NR	NR	++++	++
Rash	++++	++	+++	+	++++	-	++++	++	++++	++
Headache	+++	-	++++	-	++++	-	++++	++	++++	++
Myalgia and arthralgia	+++++	-	++++	-	NR	NR	++	-	++++	++
Bone pain	+++	++	NR	NR	NR	NR	++	-	NR	NR
Diarrhoea	++++	++	++++	+	+++	+	+++++	++++	NR	NR
Nausea	++++	-	++++	-	+++	+	++++	++	++++	+
Vomiting	+++	-	+++	-	++	-	++++	++	NR	NR
Abdominal pain	++	-	NR	NR	NR	NR	++++	++	++++	+++
Pancreatitis	+	+	NR	NR	++	++	NR	NR	+++	+++
Bleeding events (GI, CNS)	+	+	++	++	++	+	NR	NR	NR	NR
Oedema	++++	++	++++	++	+++	-	+++	++	NR	NR
Pleural effusion	++	+	++++	++	++	+	NR	NR	NR	NR
PAH	NR	NR	+	+	NR	NR	NR	NR	NR	NR
QT prolongation	+	NK	++	NK	++	NK	NR	NR	NR	NR
Hypertension	NR	NR	NR	NR	NR	NR	NR	NR	+++	++
PAOD	-	-	NR	NR	++	++	NR	NR	++++	++++
Elevated lipase	++++	+++	NG	-	++++	+++	++++	+++	++++	++++
Elevated ALT	++++	++	NG	+	+++++	+++	+++++	++++	++++	++
Low phosphate	+++++	++++	NG	+++	++++	+++	++++	++	NR	NR
Raised glucose	-	-	-	-	++++	+++	-	-	NR	NR
Anaemia	+++++	+++	+++++	++++	++++	++	+++++	+++	+++	+++
Neutropenia	+++++	++++	+++++	++++	++++	+++	++++	++++	++++	++++
Thrombocytopenia	+++++	++++	+++++	++++	++++	+++	++++++	++++	++++	++++
Abn platelet function	++++	NK	++++	NK	-	-	++++	NK	NR	NR
LGL expansion	NR	NR	++++	NK	NR	NR	NR	NR	NR	NR

Data derived from studies of first line use with the exception of ponatinib (so far used only as second or subsequent line) and rare events such as PAH, PAOD, and abnormal platelet function.[72,74,75,82,83,86,92,93] +=<1% of patients. ++=1–5%. +++=5–10%. ++++=10–50%. +++++=50–100% =specifically reported as absent. NR=not reported. GI=gastrointestinal. PAH=pulmonary arterial hypertension. NK=effect of side-effect not known. PAOD=peripheral arterial occlusive disease. NG=data not given. ALT=alanine transaminase. Abn=abnormal. LGL=large granular lymphocytes.

Table 4: **Most frequently reported side-effects of tyrosine-kinase inhibitors**

Non-hematological side effects:

Mostly assumed to be due to ***off-target effects***

Hematological side effects:

Mix of ***on-target-effect*** *(BCR-ABL,* ***early****) and* ***off-target effects*** *(c-kit, PDGFR a.o.,* ***chronic****)*

reviewed in:
Apperley JF. *Lancet 2015, 385 (9976),1447-59*

TKI intolerance is a common reason for discontinuing CML therapy

- Although AEs may be adequately managed by dose reductions/interruptions in TKI trials, many patients discontinue therapy due to intolerance[1-10]
- Real-world data has shown that more than 1 in 5 patients discontinue TKI due to intolerance, with similar rates observed with imatinib and 2nd-generation TKIs[11]

Trial	Follow-up	TKI	Discontinuation	Discontinuation due to AEs	Discontinuation due to disease progression
1L					
IRIS[1]	5 years	Imatinib	28%	4%	NR
ENESTnd[2,a]	5 years	Nilotinib	31.6%-37.0%	12.1%-19.9%	0.7%-1.4%
DASISION[3]	5 years	Dasatinib	100/259 (39%)	21%[b]	11%
BELA[4]	2 years	Bosutinib	37%	24%	4%
BFORE[5]	12 months	Bosutinib	22%	13.8%	0.4%
2L					
2101[6]	48 months	Nilotinib	69.8%	20.6%	29.9%
CA180-034[7,c]	7 years	Dasatinib	78%-85%[d]	24%-31%	16%-26%
Study 200[8]	9 years	Bosutinib	86%	26%	19%
BYOND[9]	25.9 months	Bosutinib	15/46 (32.6%)	10/46 (21.7%)	0
≥3L or T315I					
Study 200[8]	8 years	Bosutinib	93%	30%	21%
PACE[10,e]	5 years	Ponatinib	NA[f]	21%	11%
BYOND[9]	24.2 months	Bosutinib	28/61 (45.9%)	16/61 (26.2%)	0

Cross-trial comparisons are not appropriate. Comparisons of treatments should be made only based on direct head-to-head clinical trials.

AE, adverse event; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.
[a] Discontinuation due to AEs/abnormal laboratory values for nilotinib 300 mg twice daily and 400 mg twice daily doses. [b] Includes patients who discontinued due to intolerance and AEs unrelated to study drug. [c] Discontinuations due to drug-related AEs. [d] Most patients discontinued due to "Other", as they moved off study and on to commercial dasatinib. [e] Included patients that received ponatinib in ≥3L or had a T315I mutation. [f] The study was closed at the time of data analysis and therefore total discontinuation rates weren't reported.

1. Druker BJ, et al. *N Engl J Med.* 2006;355:2408-2417. 2. Hochhaus A, et al. *Leukemia.* 2016;30:1044-1054. 3. Cortes JE, et al. *J Clin Oncol.* 2016;34:2333-2340. 4. Brümmendorf TH, et al. *British Journal of Haematology.* 2015;168:69-81. 5. Cortes JE, et al. *J Clin Oncol.* 2018;36:231-237. 6. Giles FJ, et al. *Leukemia.* 2013;27:107-112. 7. Shah NP, et al. *Am J Hematol.* 2016;91:861-874. 8. Cortes JE, et al. Presented at EHA25 Virtual, 2020. Abstract EP766. 9. Hochhaus A, et al. *Leukemia.* 2020;34:2125-2137. 10. Cortes JE, et al. *Blood.* 2018;132:393-404. 11. Geelen IGP, et al. *Haematologica.* 2017;102:1842-1849

By direct comparison *in first line,* 2nd generation TKIs compared to Imatinib

Do **consistently lead to**:

- Higher and earlier cumulative rates of EMR, MMR, MR4 and MR4.5
- Lower failure rates due to inefficacy
- Different (and narrower) spectrum of resistance-conferring BCR::ABL mutations
- Higher frequency of patients to become eligible for TFR (earlier)

but so far **fail to achieve:**

- Improved survival
- Neither improved tolerability (neither short-/long-term, low grade chronic nor acute tox.) nor adherence
- Favourable relapse rates following TFR compared to Imatinib (?!)

Take-home and discussion points:

Each 2nd generation TKI for CML has a **unique non-hematological side effect spectrum** regarding

- Organ system predominanty affected
- Kinetics, reversibility and dose-dependency
- confounding factors (e.g. BMI, co-medications …)

Given that existing 2nd generation TKIs seem equieffective in 1st line and 2nd line treatment post Imatinib, the choice of the individual compound can be based mostly on

- **side effect profile** of the TKI as well as
- the patients' **comorbidities** and expected **adherence**
- **emergent mutations** (applies to 2nd+ line only)

2nd+ line therapy post 2nd generation TKIs requires **careful weighing of reasons** including:

- resistance vs. intolerance**,** mutational spectrum, available allo SCT options, comorbidities, treatment line and patient preference before decision **between 2nd vs. 3rd gen TK**I is made

Expect to change once Asciminib being approved in earlier treatment lines (-> ASC4START/-FIRST)

*Thanks particularly to the **Uniklinik Aachen CML/MPN group:***

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- Susanne Isfort
- Anna Doleschal

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In direct comparison *in first line,* 2nd generation TKIs compared to Imatinib

Do consistently lead to:

- Higher cumulative rates of EMR, MMR, MR4 and MR4.5
- Earlier responses
- Higher frequency of patients to become eligible for TFR approaches (earlier)
- Lower failure rates due to inefficacy
- Different spectrum of resistance conferring BCR::ABL mutations

Fail to achieve:

- Higher frequency of TFR eligible patients actually staying in sustained TFR (?)
- Improved adherence
- Improved tolerability (neither short-term, long-term, low grade chronic nor acute tox.)
- Improved survival
- Better adherence

Why use 2nd generation TKIs in 1st line ?

Take-home and discussion points:

- Each 2nd generation TKI for CML has a **unique spectrum** of
  - Organ system predominance
  - Kinetics and reversibility
  - confounding effects for and
  - dose-dependency **of non-hematological side effects**
- Choice of 2nd generation TKIs in 1st line and 2nd line treatment post Imatinib can be based mostly on
  - **emergent mutations**
  - **side effect profile** of the TKI as well as
  - the patients' **comorbidities** and expected **adherence**
- 2nd line therapy post 2nd generation TKIs (!) requires **careful weighing of reasons including:**
  - resistance vs. intolerance**,** mutational spectrum, available allo SCT options, comorbidities, patient preference before decision **between 2nd vs. 3rd gen TKI** is made,
- Expect to change once Asciminib being approved in earlier treatment lines (-> ASC4START/-FIRST)