



TSH MEETING 2025

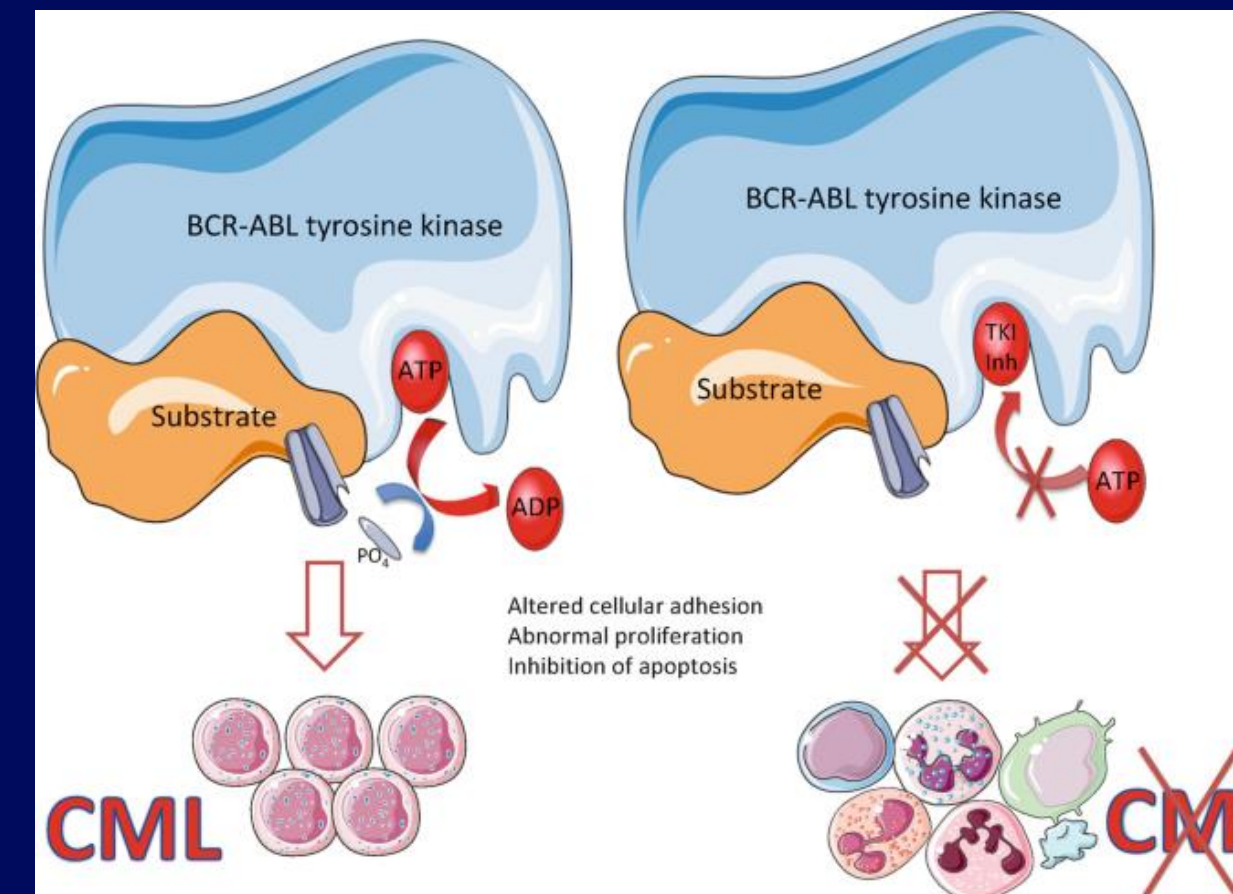
INTEGRATING EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES TO REAL PRACTICE

TKI SWITCHING IN CML PATIENT FROM PRACTICE GUIDELINE TO REAL LIFE

16 MAR 2025

TONTANAI NUMBENJAPON, M.D.

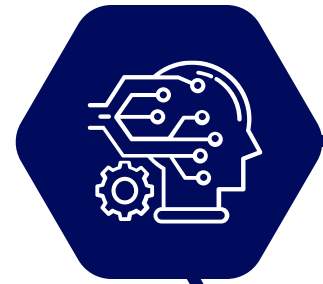
DEPUTY DIRECTOR, ARMY INSTITUTE OF PATHOLOGY AND DIVISION
OF HEMATOLOGY, DEPARTMENT OF MEDICINE, PHRAMONGKUTKLAO
HOSPITAL AND PHRAMONGKUTKLAO MEDICAL CENTER



Topic of presentation



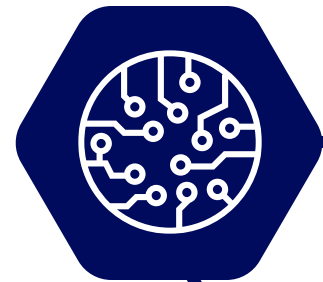
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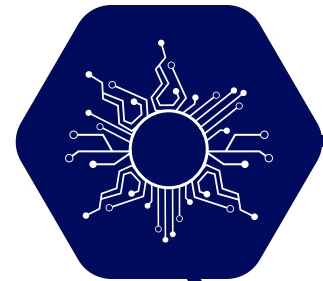
Baseline prognostic factors



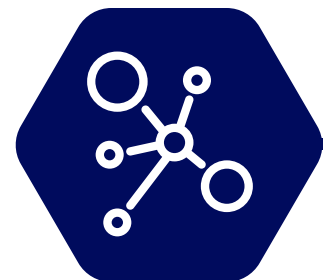
Treatment response monitoring



First-line treatment



Switching to $\geq 2^{\text{nd}}$ line TKI



AE management



Declaration

Disclosure

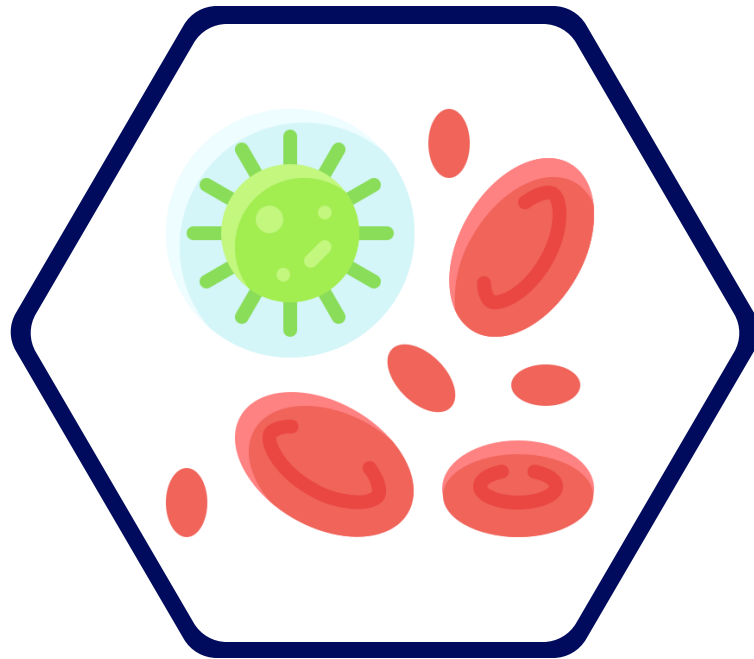
No conflict of interest



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Factors

CML management



Disease itself

Not 100% homogeneous

Risk score



Patient

Goal of treatment

Quality of life

Comorbidity

Adherence/compliance

Drug/food interaction



Physician

Monitoring

TKI switching

AE management

Fit patient

Goal of CML therapy in 2025



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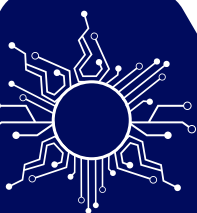
Achieve clinical, cytogenetic, and molecular remission



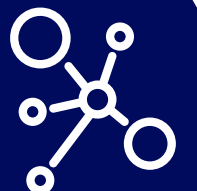
Maintain long-term disease control



Avoid progression to advanced disease



Optimize quality of life by limiting treatment-related toxicity



Achieve TFR

ELN and NCCN recommendation

Pretreatment laboratory evaluation for co-morbidities



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	Hematology	Blood chemistry/ Electrolyte/ FBS/Lipid	CXR	EKG	Viral hepatitis
At diagnosis	✓	✓	✓	✓	✓
At TKI switching	✓	Amylase/ Lipase (Nil, Pon)	✓	✓	✓

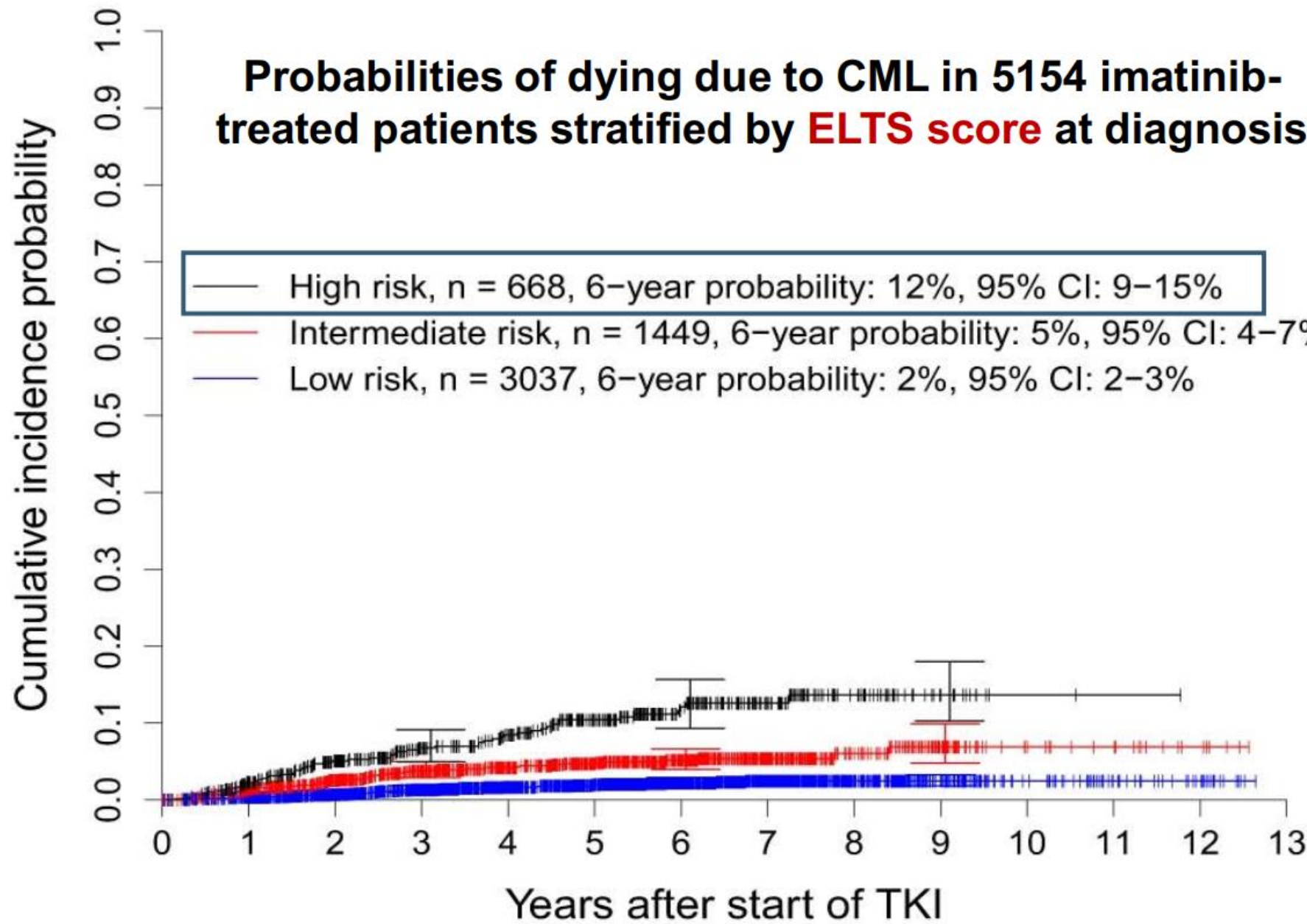
Sokal and ELTS risk scores (calculation and outcome)

Score	Calculation		Definition of risk groups			
Sokal	Exp 0.0116 × (age-43.4) +0.0345 × (spleen-7.51) +0.188 × [(platelet count/700) ² -0.563] +0.0887 × (blood blasts-2.10)		Low risk: <0.8 Intermediate-risk: 0.8–1.2 High-risk: >1.2			
ELTS	0.0025 × (age/10) ³ +0.0615 × spleen size +0.1052 × peripheral blood blasts +0.4104 × (platelet count/1000) ^{-0.5}		Low risk: <1.5680 Intermediate risk:1.5680–2.2185 High-risk: >2.2185			
	Low		Intermediate		High	
n = 5154	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
%	38	55	38	28	23	13
10-year OS	89%	88%	81%	79%	75%	68%
6-year LRD*	3%	2%	4%	5%	8%	12%



*Leukemia related death

EUTOS Long-Term Survival (ELTS) score



Recommended
by ELN

1. Better at identifying patients at risk of dying of CML
2. Classifies fewer patients as high-risk
3. Newer model recently proposed also includes genetic features

Variables: age, spleen size (cm) below the costal margin, peripheral blood blasts, and platelet count



Case

A 37-yo male with progressive LUQ discomfort and splenomegaly (7 cm) for 6 mo



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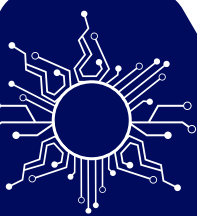
Hb 12 g/dL, WBC 200,800/ μ L, N 51%, L 11%, band 4%, M 1%, E 1%, Baso 2%, meta 8%, myelo 14%, pro 7%, blast 1%, platelet 257,000/ μ L



BM hypercellularity 3+, myeloblast 2%, no increased fibrosis



BM cytogenetic analysis: Ph' chromosome + and no ACA



Sokal risk score: low (0.56), ELTS risk score: low (1.4721)



Initial treatment: hydroxyurea

ELN and NCCN recommendation

Laboratory test for CML diagnosis and monitoring

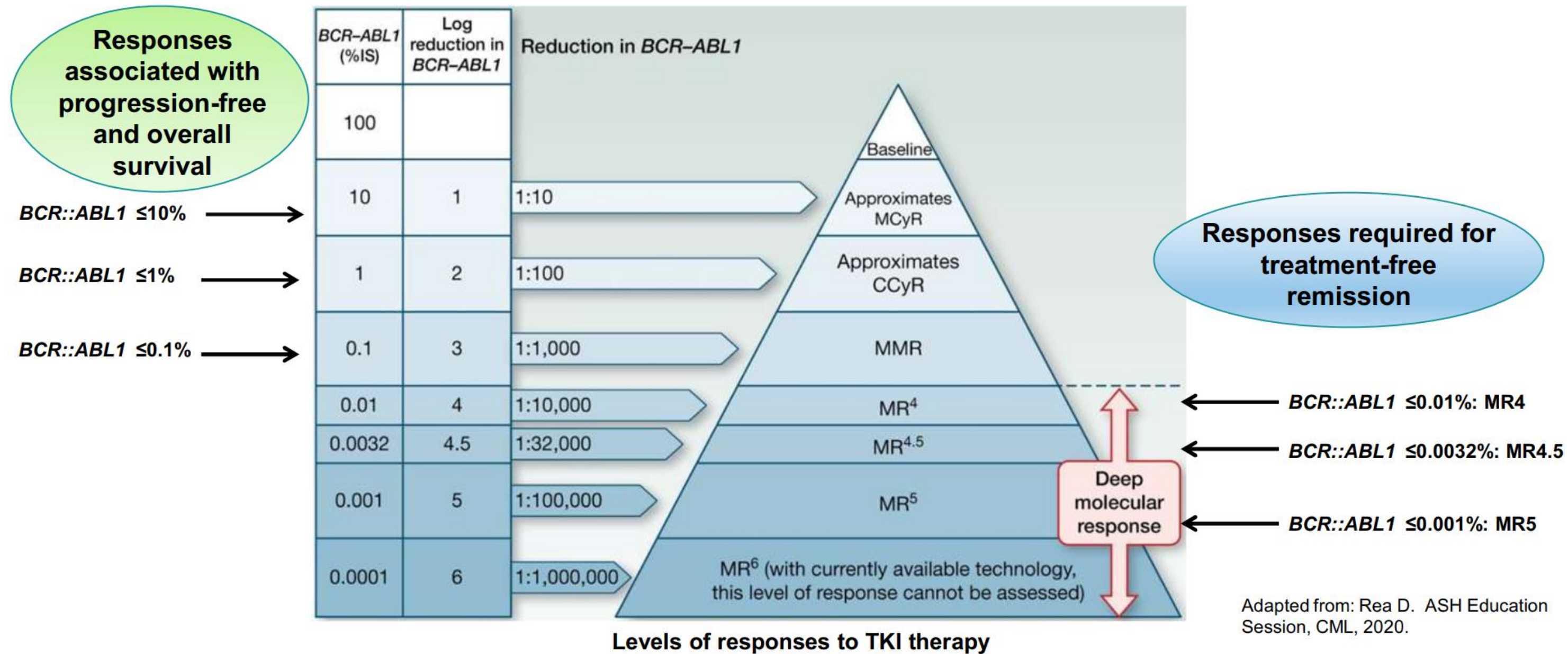


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	Cytogenetic	Interphase FISH	RT-PCR	RQ-PCR	TKD Mutation
At diagnosis	✓	✓	✓	✗	✗
Monitoring	✓ Overt relapse/ progression	✗	✗	✓	✓ Fail to reach ELN response mile stone

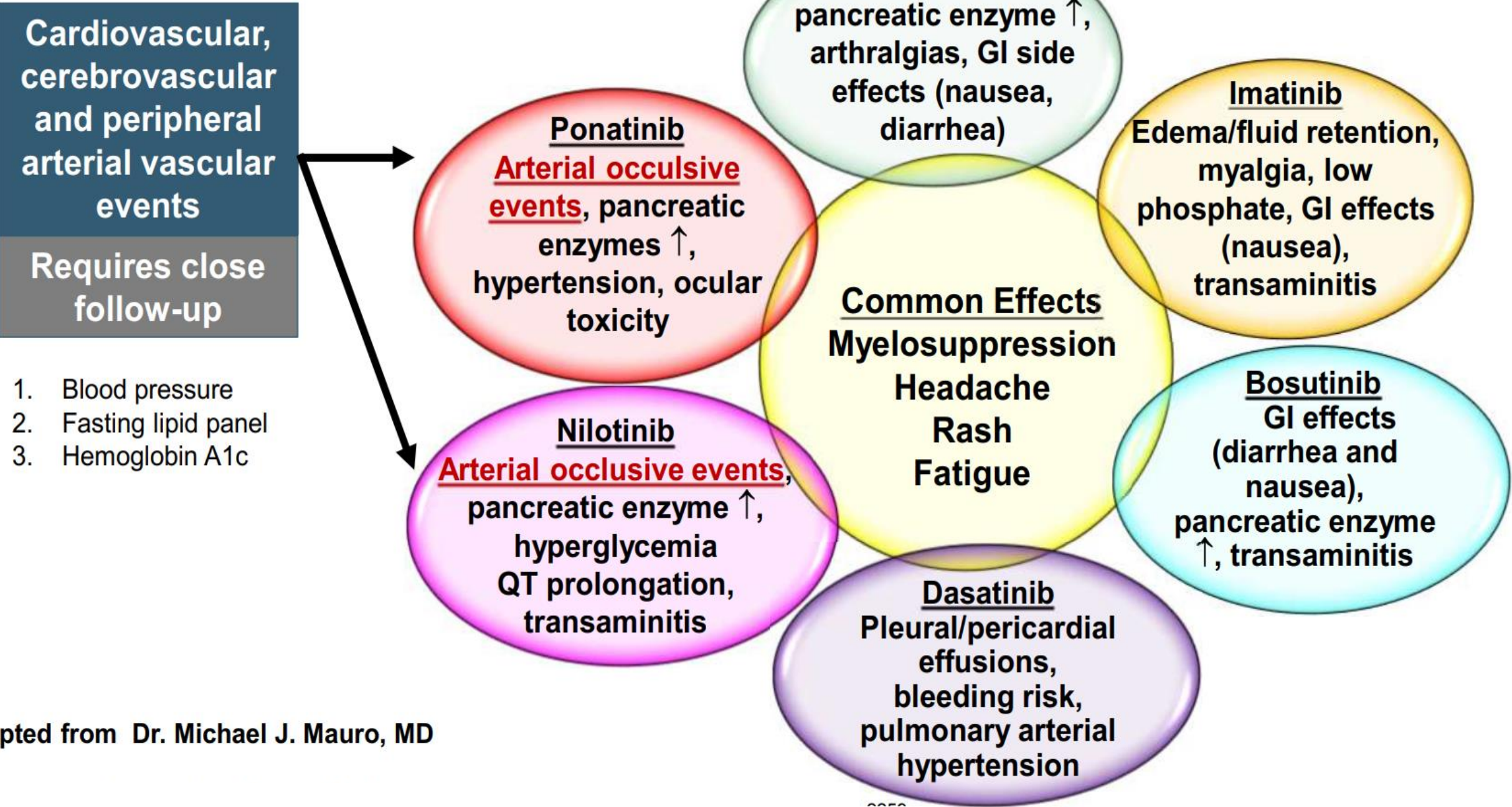
Treatment response monitoring milestones

Hematologic, cytogenetic and molecular



Common and unique TKI toxicities

Imatinib/nilotinib/dasatinib/bosutinib/ponatinib/asciminib



Adapted from Dr. Michael J. Mauro, MD



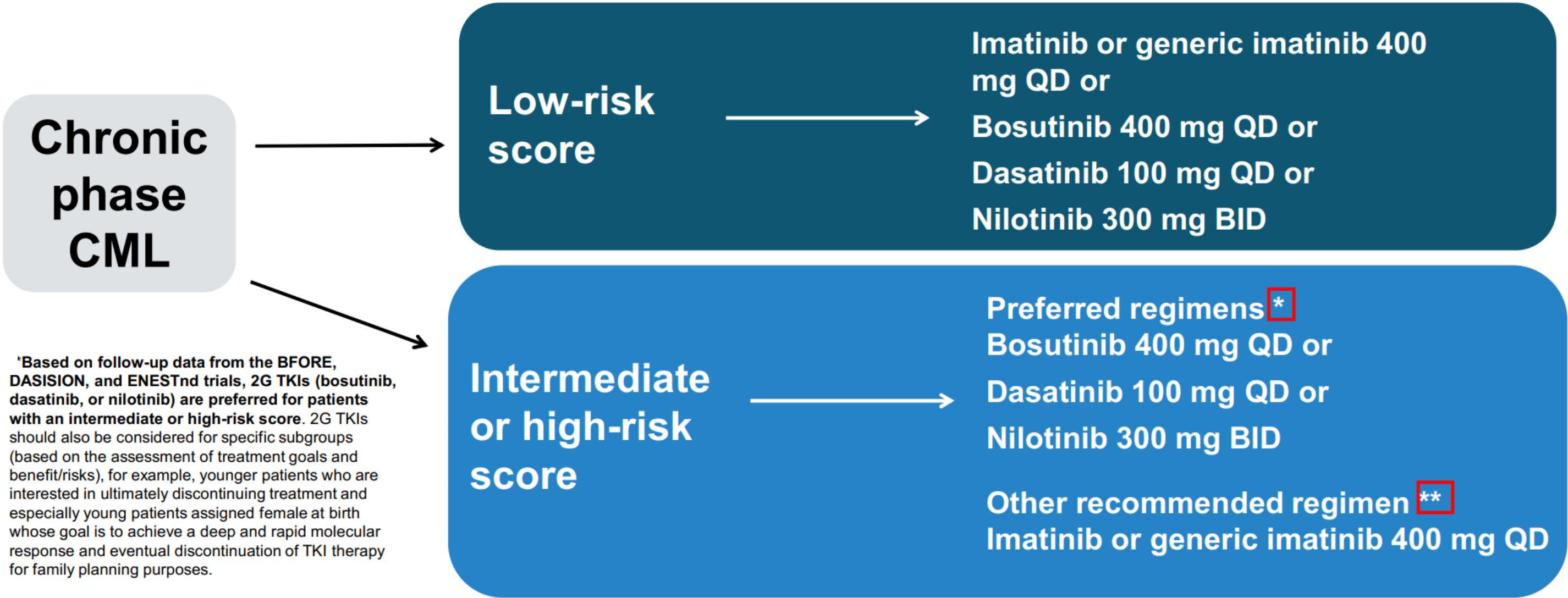
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First-line therapy for CML-CP



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Risk stratify: Sokal, Hasford, and EUTOS long-term survival (ELTS) scores



*Based on follow-up data from the BFORE, DASISION, and ENESTnd trials, 2G TKIs (bosutinib, dasatinib, or nilotinib) are preferred for patients with an intermediate or high-risk score. 2G TKIs should also be considered for specific subgroups (based on the assessment of treatment goals and benefit/risks), for example, younger patients who are interested in ultimately discontinuing treatment and especially young patients assigned female at birth whose goal is to achieve a deep and rapid molecular response and eventual discontinuation of TKI therapy for family planning purposes.

** Imatinib may be preferred for older patients with comorbidities such as cardiovascular disease

Clinical trial, if available can be considered for all patients

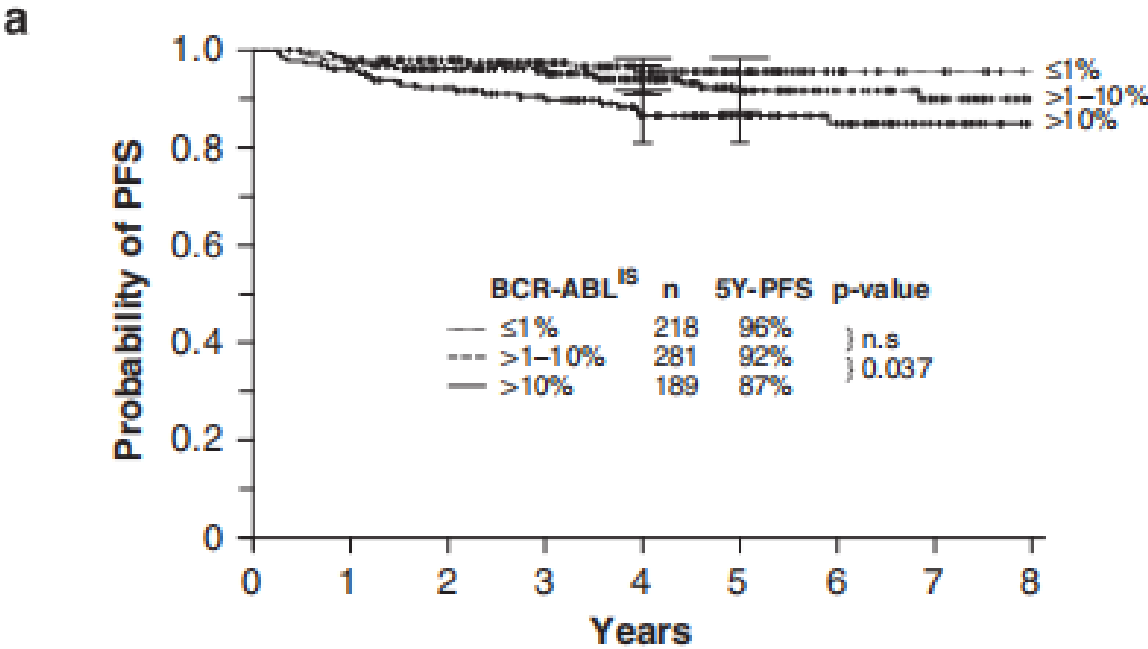
ELN 2020 recommends any one of imatinib, nilotinib, dasatinib and Bosutinib

Outcomes

Patients grouped according to molecular response and cytogenetic response at 3 months

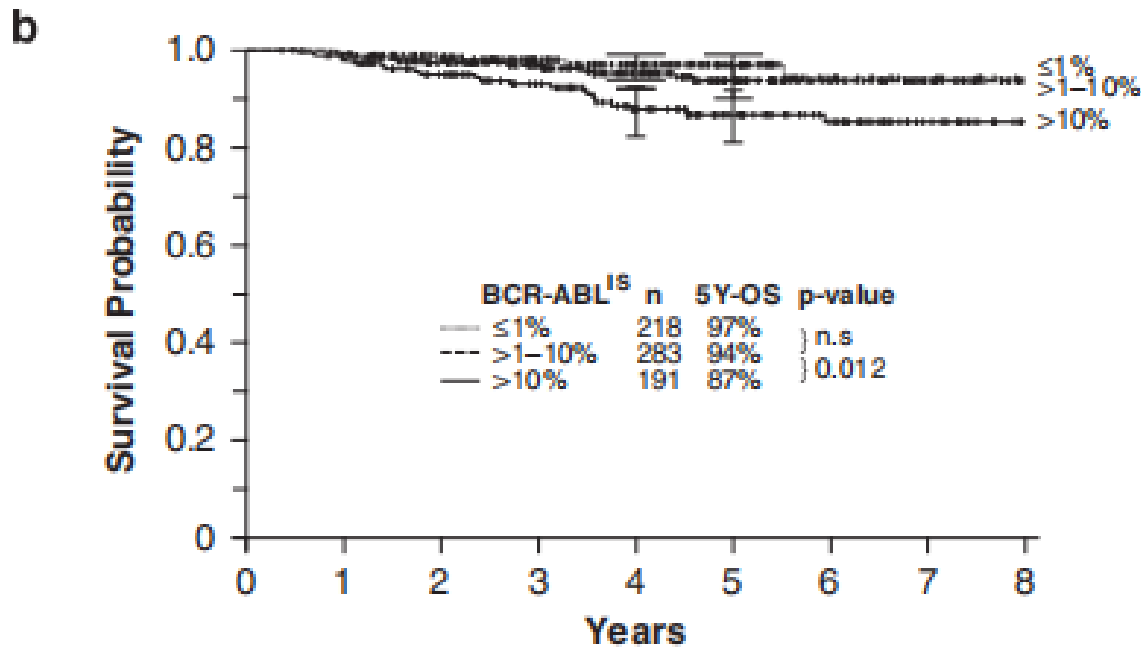


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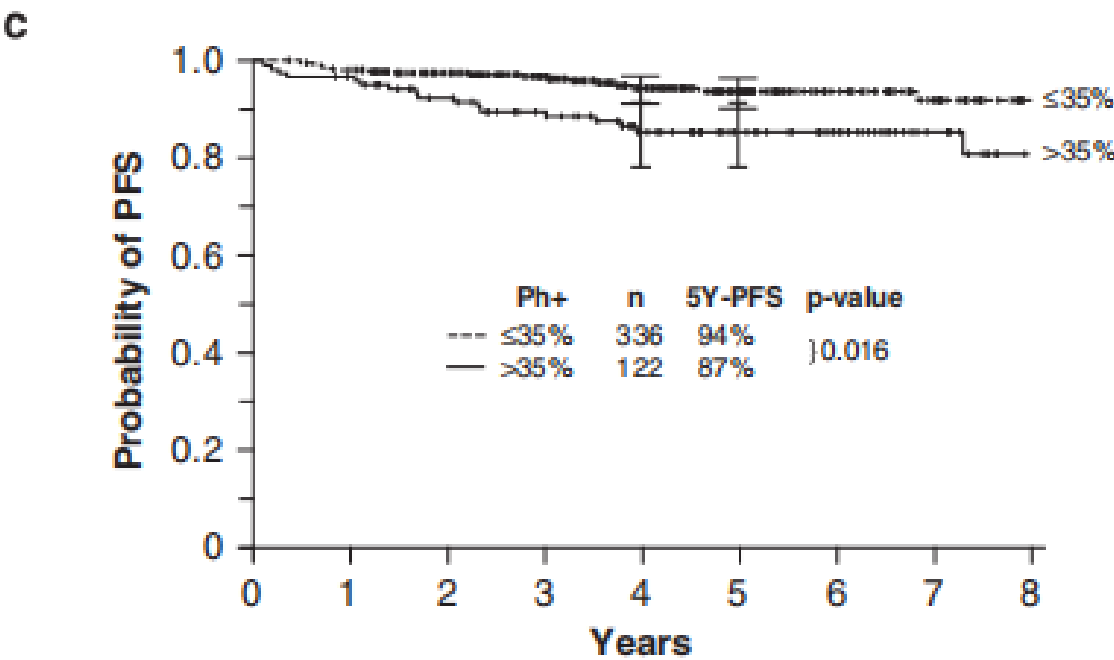
Patients at risk (n)

BCR-ABL ^{IS}	≤1%	>1-10%	>10%
n	210	272	178
184	132	197	156
90	148	131	104
55	100	75	



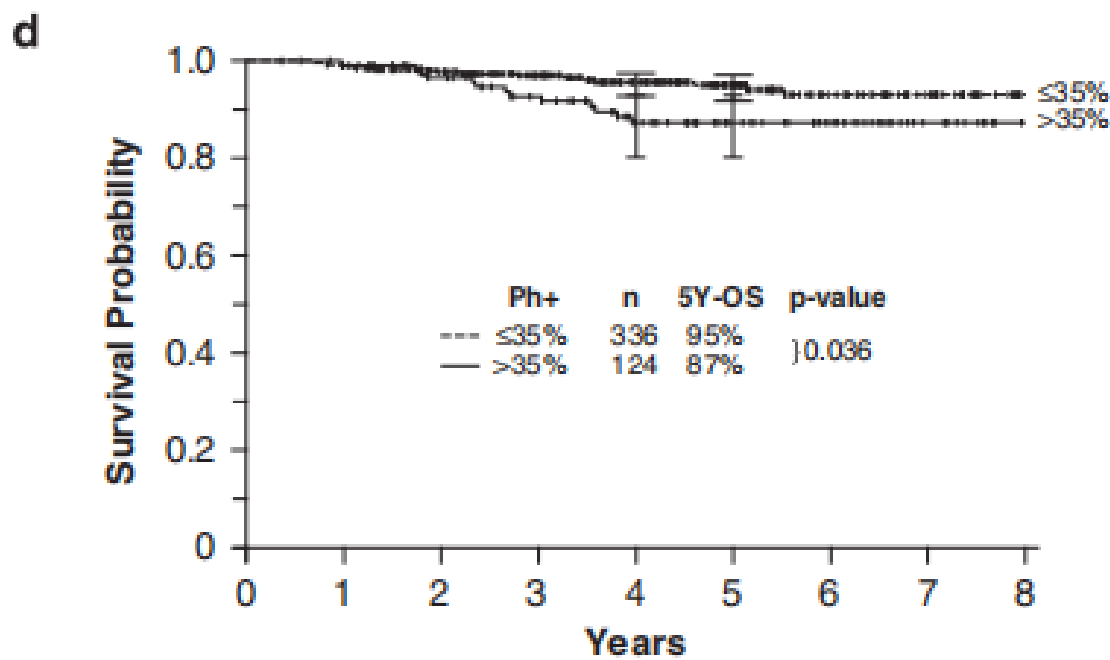
Patients at risk (n)

BCR-ABL ^{IS}	≤1%	>1-10%	>10%
n	213	278	184
185	202	161	136
91	152	106	
56	104	76	



Patients at risk (n)

Ph+	≤35%	>35%
n	324	118
285	235	104
174	91	70
123	52	

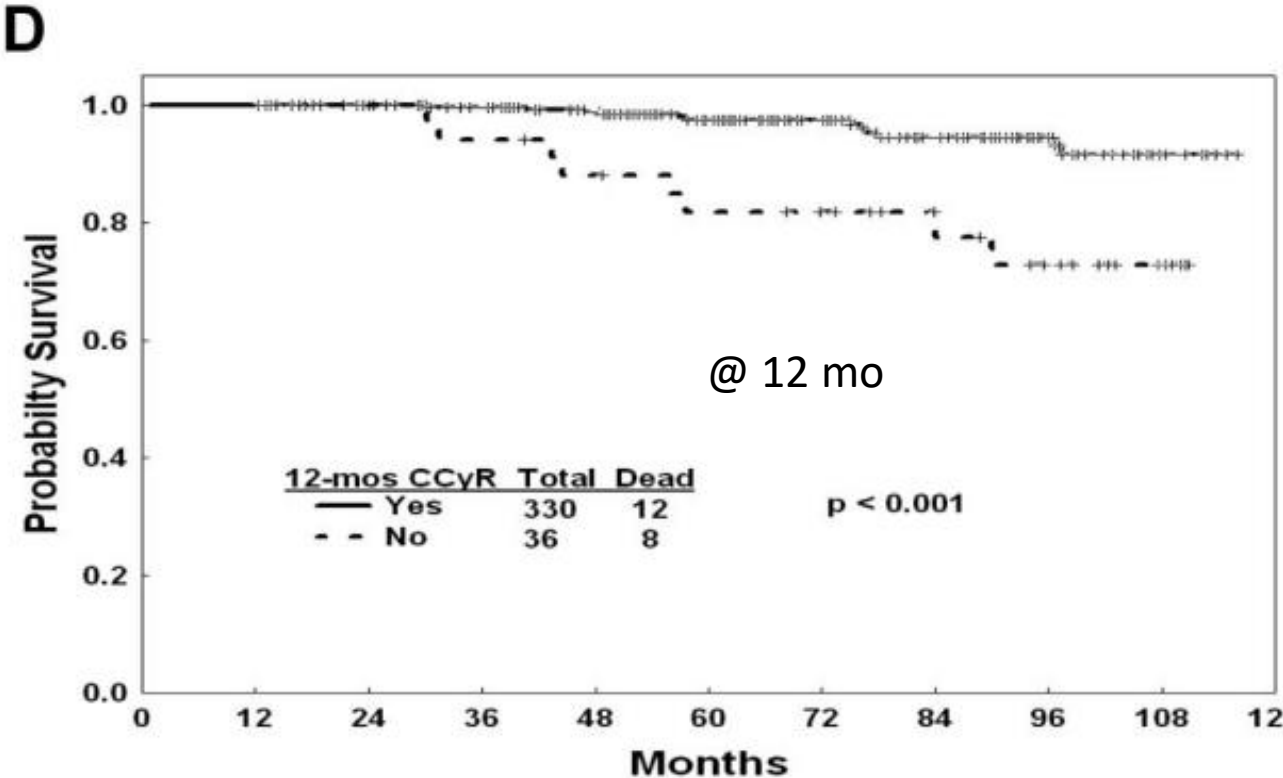
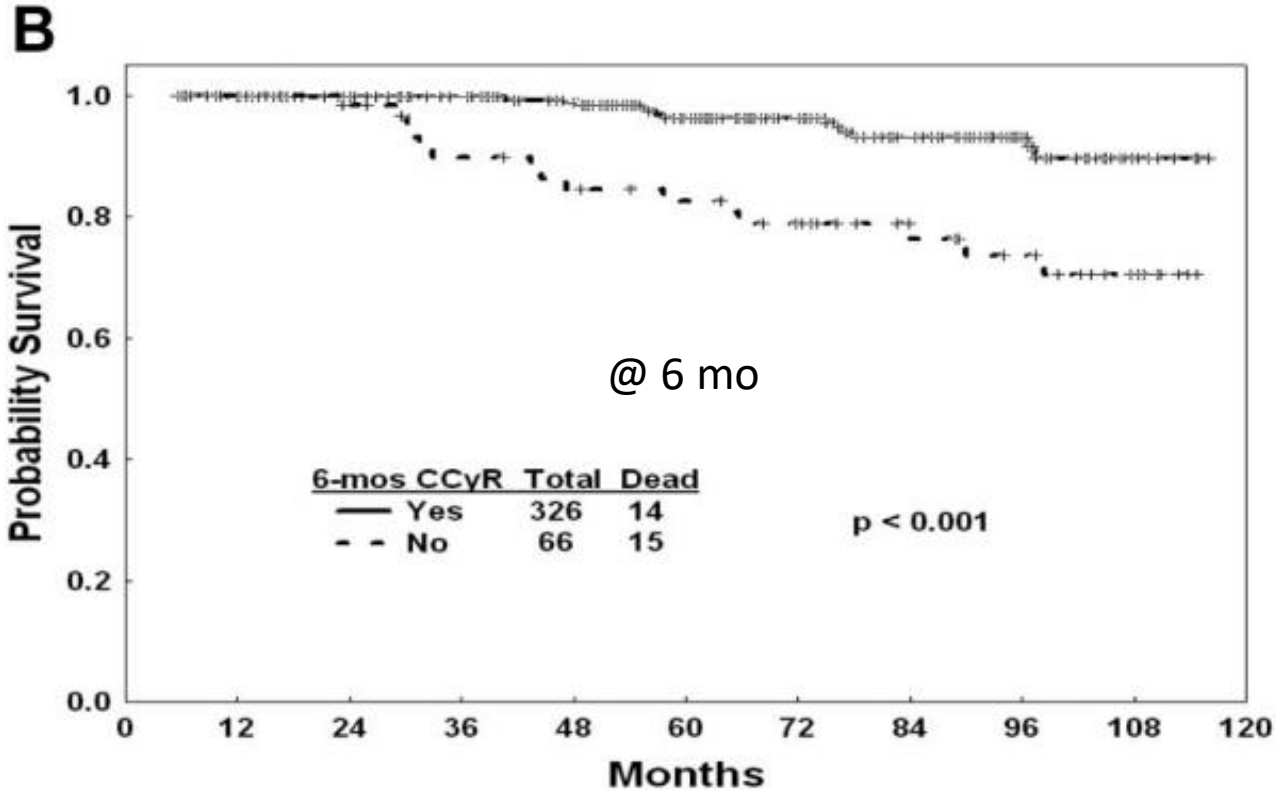
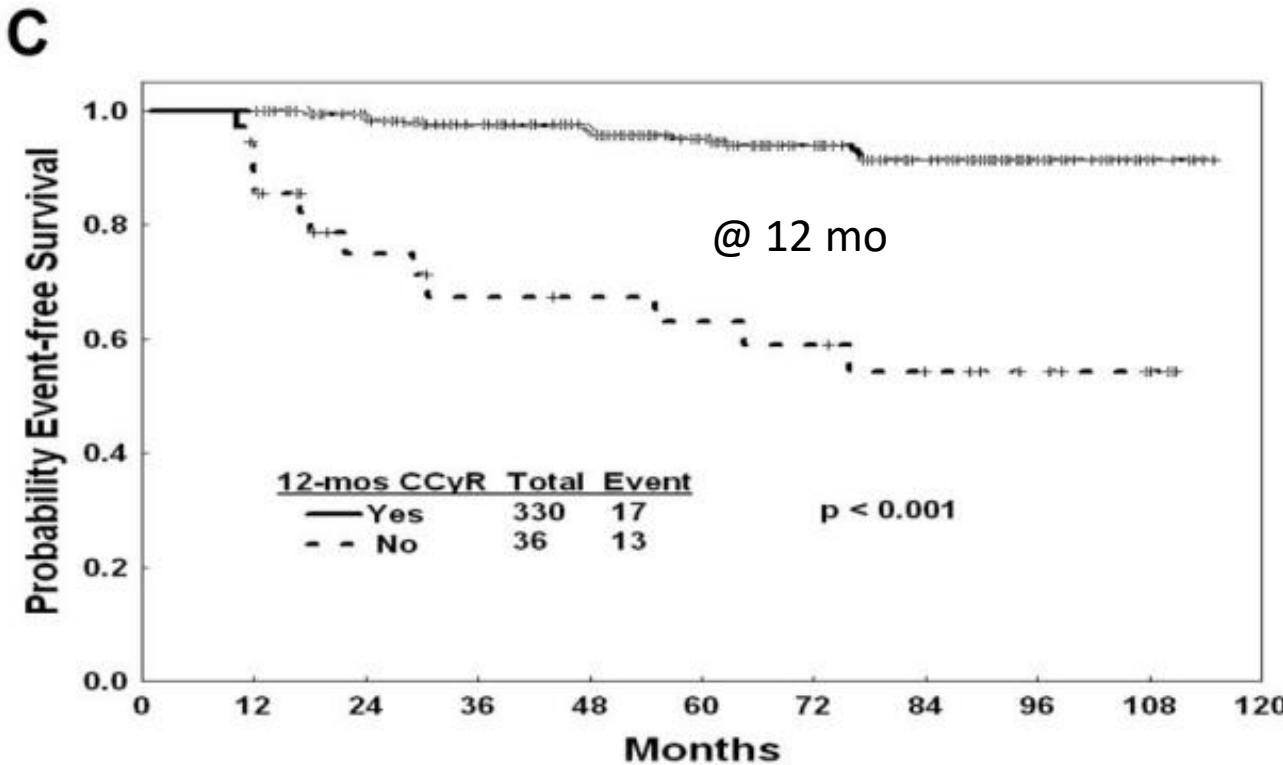
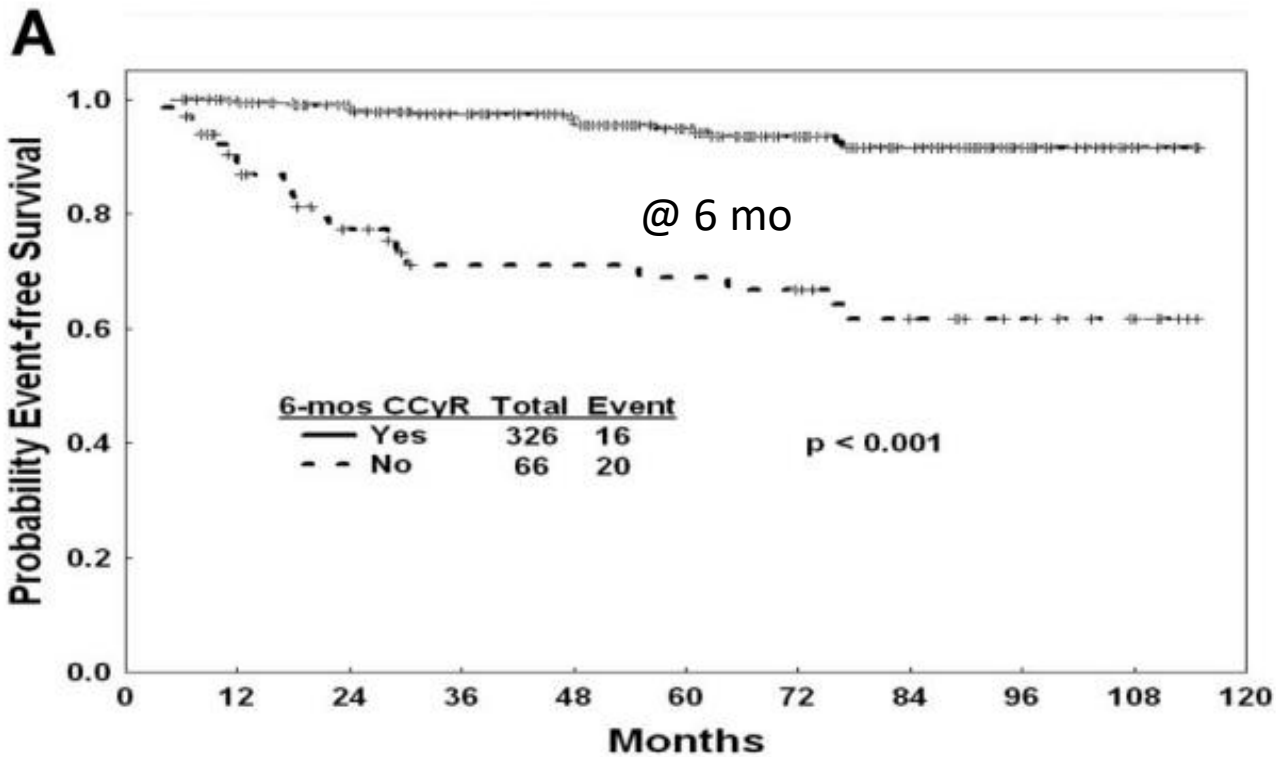


Patients at risk (n)

Ph+	≤35%	>35%
n	327	121
286	236	108
177	72	
126	53	

Outcomes

Patients grouped according to cytogenetic response at 6,12 months



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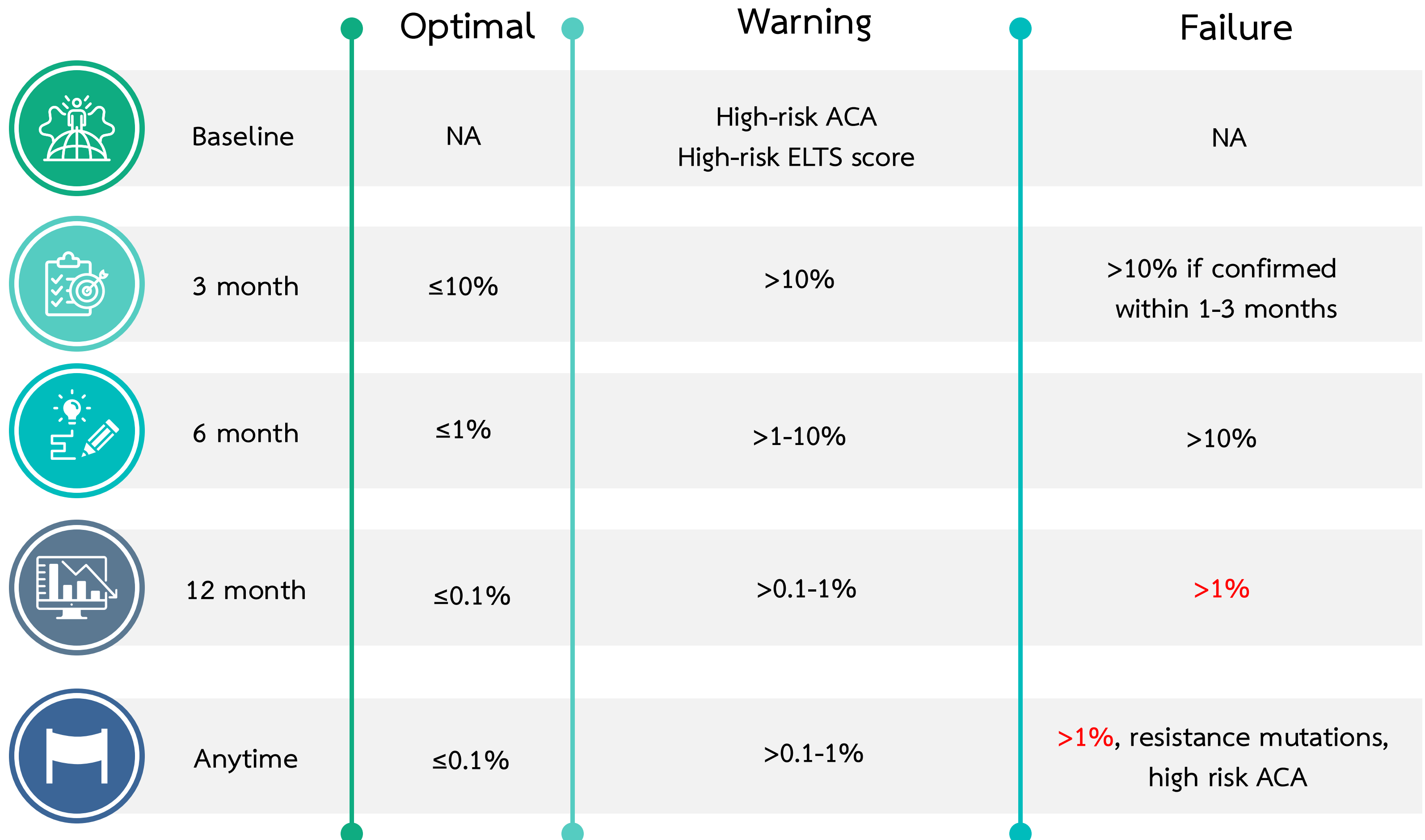
**European LeukemiaNet Recommendations for
the Management of Chronic Myeloid Leukemia (CML)**

Response definitions for any TKI **first line**,
and 2nd line in case of intolerance, all patients (CP, AP, and BC)

Time	Optimal response	Warning	Failure
Baseline		High risk Major route CCA/Ph+	
3 mos.	BCR-ABL ^{IS} ≤10%* Ph+ ≤35% (PCyR)	BCR-ABL ^{IS} >10%* Ph+ 36-95%	No CHR* Ph+ >95%
6 mos.	BCR-ABL ^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL ^{IS} 1-10%* Ph+ 1-35%	BCR-ABL ^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL ^{IS} ≤0.1%* (MMR)	BCR-ABL ^{IS} 0.1-1%*	BCR-ABL ^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

Response milestones for CML expressed as *BCR-ABL1/ABL1* on the IS (ELN 2020)



For patients aiming at TFR, the optimal response (at any time) is $BCR-ABL1 \leq 0.01\%$ (MR4). A change of treatment may be considered if MMR is not reached by 36–48 months. NA not applicable, ACA additional chromosome abnormalities in Ph+ cells, ELTS EUTOS long term survival score. aLoss of MMR ($BCR-ABL1 > 0.1\%$) indicates failure after TFR

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

Response milestones for CML expressed as *BCR-ABL1/ABL1* on the IS (NCCN v.3 2025)

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NCCN Guidelines Version 3.2025 Chronic Myeloid Leukemia

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EARLY TREATMENT RESPONSE MILESTONES [CRITERIA FOR RESPONSE AND RELAPSE](#)

<i>BCR::ABL1</i> (IS)	3 months	6 months	12 months ⁿ
>10% ^o	YELLOW	RED	
>1%–10% ^p	GREEN		ORANGE
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

COLOR	CONCERN	CLINICAL CONSIDERATIONS ^r	RECOMMENDATIONS ^{r,i}
RED	TKI-resistant disease ^q	- Evaluate patient adherence and drug interactions Consider <i>BCR::ABL1</i> kinase domain mutational analysis^s - Consider bone marrow cytogenetic analysis to assess additional chromosomal abnormalities (ACAs)	Switch to alternate TKI (CML-5) (other than imatinib) and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance ^q	- Evaluate patient adherence and drug interactions Consider <i>BCR::ABL1</i> kinase domain mutational analysis^s	Switch to alternate TKI (CML-5) or Continue same TKI ^o
ORANGE **NEW**	Possible TKI resistance ^q	- Evaluate patient adherence and drug interactions Consider <i>BCR::ABL1</i> kinase domain mutational analysis^s - Consider bone marrow cytogenetic analysis to assess for CCyR at 12 mo	Consider switch to alternate TKI ^p (CML-5) or Continue the same TKI if CCyR is achieved
LIGHT GREEN	TKI-sensitive disease	- Evaluate patient adherence and drug interactions - If treatment goal is long-term survival: ≤1% optimal - If treatment goal is treatment-free remission: ≤0.1% optimal	- If optimal: continue same TKI - If not optimal: shared decision-making with patient^{q,t}
GREEN	TKI-sensitive disease	- Evaluate patient adherence and drug interactions - Monitor response (CML-G)	Continue same TKI ^u

[Footnotes on CML-3A](#)

Note: All recommendations are category 2A unless otherwise indicated.

Landmark phase III trials of frontline TKIs

Treatment	Longest F/U (year)	CCyR (%)	MMR (%)	<i>BCR::ABL1</i> <10% at 3 mos (%)	EFS/PFS (%) (AP/BP transformation, %)	OS (%)
		At 10 years				
IRIS Imatinib (n = 553) IFN-α+low-dose cyta (n = 553)	11	92 (76 @ 18 mo) NA (14 @ 18 mo)	93 NA		80 NA	83 79
		At 2 years	At 5 years			
DASISION Dasatinib (n = 259) Imatinib (n = 260)	5	86 82	76 64	84 64	85 (4.6) 86 (7.3)	91 90
		At 2 years	At 10 years			
ENEST-nd Nilotinib 300 mg (n = 282) Nilotinib 400 mg (n = 281) Imatinib (n = 283)	10	87 85 77	78 80 63	91 89 67	86 (4.1) 90 (2.7) 87 (9.2)	88 90 88
		At 2 years	At 5 years			
BFORE Bosutinib 400 mg (n = 268) Imatinib (n = 268)	5	83 77	74 65	81 61	93 (2.2) 91 (2.6)	95 95

O’Brien SG, et al. N Engl J Med 2003;348:994-1004. Hochhaus A, et al. N Engl J Med 2017;376:917-27. Shah NP, et al. Science 2004;305:399-401. Kantarjian H, et al. N Engl J Med 2010;362:2260-70. Kantarjian HM, et al. Blood 2012;119:1123-9. Jabbour E, et al. Blood 2014;123:494-500. Sasaki K, et al. Cancer 2016;122:238-48. Weisberg E, et al. Cancer Cell 2005;7:129-141. Saglio G, et al. N Engl J Med. 2010;362:2251-59. Kantarjian HM, et al. Clin Lymphoma Myeloma Leuk. 2024;24:285-97. Cortes JE, et al. J Clin Oncol 2018;36:231-7.



Case

A 56-year-old male CML-CP (low Sokal/ELTS risk) with 1st line IM

	13/7/48 (1st Dx)	14/7/48-12/2/56 7 yr 7 m	13/2/56	2/5/56 @3 m of IM	24/7/56 @6 m of IM	19/11/56 @9 m of IM	6/2/57 @12 m of IM	6/3/57 @13 m of IM
Treatment	HU 1500 mg/d	HU 1000-1500 mg/d	Start IM 400 mg/d	IM 400 mg/d	IM 400 mg/d	IM 400 mg/d	IM 400 mg/d	IM 400 mg/d Apply for NIL approval
Adverse event	-	-	-	Gr. 1 anemia	Gr. 1 anemia	Gr. 1 anemia	Gr. 1 anemia	Gr. 1 anemia
Best response	-	CHR	N/A	@ 3 mo: %BCR-ABL/ABL (IS) = 9.85%	@ 6 mo: %BCR-ABL/ABL (IS) = 2.69%	@ 6 mo: %BCR-ABL/ABL (IS) = 0.495%	@ 12 mo: %BCR-ABL/ABL (IS) = 2.24%	@ 13 mo: %BCR-ABL/ABL (IS) = 1.07%

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6 mos.	BCR-ABL ^{IS} <1%* Ph+ 0% (CCyR)	BCR-ABL ^{IS} 1-10%* Ph+ 1-35%	BCR-ABL ^{IS} >10%* Ph+ >35%
12 mos.	BCR-ABL ^{IS} ≤0.1%* (MMR)	BCR-ABL ^{IS} 0.1-1%*	BCR-ABL ^{IS} >1%* Ph+ >0%
Then, and at any time	MMR or better	CCA/Ph- (-7, or 7q-)	Loss of CHR Loss of CCyR Loss of MMR, confirmed** Mutations CCA/Ph+

*and/or **in 2 consecutive tests, of which one ≥1% IS: BCR-ABL on International Scale

TKI failure/intolerance

Switching to subsequent TKI



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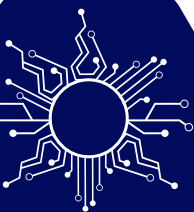
Check patient's adherence



Check how patient takes the medication



Check possible drug/food interactions



Evaluate previous TKI associated AE and co-morbidities



Check possible *BCR::ABL1* mutation

Characteristics of each TKI

Dosing, food interactions and baseline kidney/liver dysfunction

TKI	Dosing frequency and timing in relation to food	Dose adjustments for baseline kidney/liver dysfunction	Food interaction (induction of CYP 3A4)	Food interaction (inhibition of CYP 3A4)
Imatinib	Daily with food	Yes (kidney, liver)	St John's wort ↓imatinib exposure	Grape fruit/Licorice ↑imatinib exposure
Nilotinib	Twice daily without food	Yes (liver)	St John's wort ↓nilotinib exposure	Grape fruit/Licorice ↑nilotinib exposure
Dasatinib	Daily with or without food	No	St John's wort ↓dasatinib exposure	Grape fruit/Licorice ↑dasatinib exposure
Bosutinib	Daily with food	Yes (kidney, liver)	St John's wort ↓bosutinib exposure	Grape fruit/Licorice ↑bosutinib exposure
Ponatinib	Daily with or without food	Yes (liver)	St John's wort ↓ponatinib exposure	Grape fruit/Licorice ↑ponatinib exposure
Asciminib	Daily or twice daily without food	No	St John's wort ↓asciminib exposure	Grape fruit/Licorice ↑asciminib exposure



Drug interactions

Drugs/ Supplements	Change in TKI Level					
	Asciminib	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
Proton Pump Inhibitors (PPIs) • Lansoprazole • Rabeprazole • Esomeprazole • Omeprazole • Pantoprazole	No major interaction	Decrease in exposure	Decrease in exposure	No major interaction	Decrease in exposure	Minor decrease in exposure
Histamine 2 Receptor Antagonists (H2RAs) • Famotidine • Ranitidine • Nizatidine	No major interaction	Decrease in exposure; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after taking bosutinib	Decrease in exposure; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after taking dasatinib	No major interaction	Decrease in exposure; AVOID; If absolutely necessary consider once-daily H2RA ≥2 hours after or ≥10 hours before taking nilotinib	No major interaction
Antacids	No major interaction	Decrease in exposure if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking bosutinib	Decrease in exposure if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking dasatinib	No major interaction	Decrease in exposure if concomitant; Use antacids at least 2 hours before or at least 2 hours after taking nilotinib	No major interaction
Antidepressants • Fluoxetine • Bupropion • Citalopram	No major interaction	Minor increase in exposure; QTc monitoring	Minor increase in exposure; QTc monitoring	Minor increase in exposure; QTc monitoring	AVOID if possible due to cumulative QTc prolongation risk	Minor increase in exposure; QTc monitoring
Cardiovascular Medications • Amiodarone • Diltiazem • Verapamil • Simvastatin	No major interaction	Increase in exposure and arrhythmia risk; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure and arrhythmia risk; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure; Strongly consider alternative cardiac medication or TKI dose adjustment	Increase in exposure and arrhythmia risk; AVOID	Increase in exposure; Strongly consider alternative cardiac medication or TKI dose adjustment

Drug interactions

Drugs/Supplements	Change in TKI Level					
	Asciminib	Bosutinib	Dasatinib	Imatinib	Nilotinib	Ponatinib
Anti-infectives • Azole Antifungals ▸ Fluconazole ≥200 mg ▸ Voriconazole ▸ Itraconazole ▸ Posaconazole ▸ Isavuconazole • Clarithromycin • Telithromycin • Ritonavir	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment	Increase in exposure; Strongly consider alternative anti-infective or TKI dose adjustment
Anti-infectives • Fluoroquinolones ▸ Levofloxacin ▸ Moxifloxacin ▸ Ciprofloxacin	No major interaction	QTc monitoring	QTc monitoring	No major interaction	Use with caution	No major interaction
Herbal Supplements ^{3,4} • Curcumin (Turmeric) • Ginkgo Biloba • Green Tea Extract	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation	Increase in exposure; Strongly consider supplement discontinuation
Herbal Supplements ^{3,4} • St. John's Wort	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID	Decrease in exposure; AVOID



Warnings about supplements and drug interactions

You might be asked to stop taking or avoid certain herbal supplements when on a systemic therapy. Some supplements can affect the ability of a drug to do its job. This is called a drug interaction.

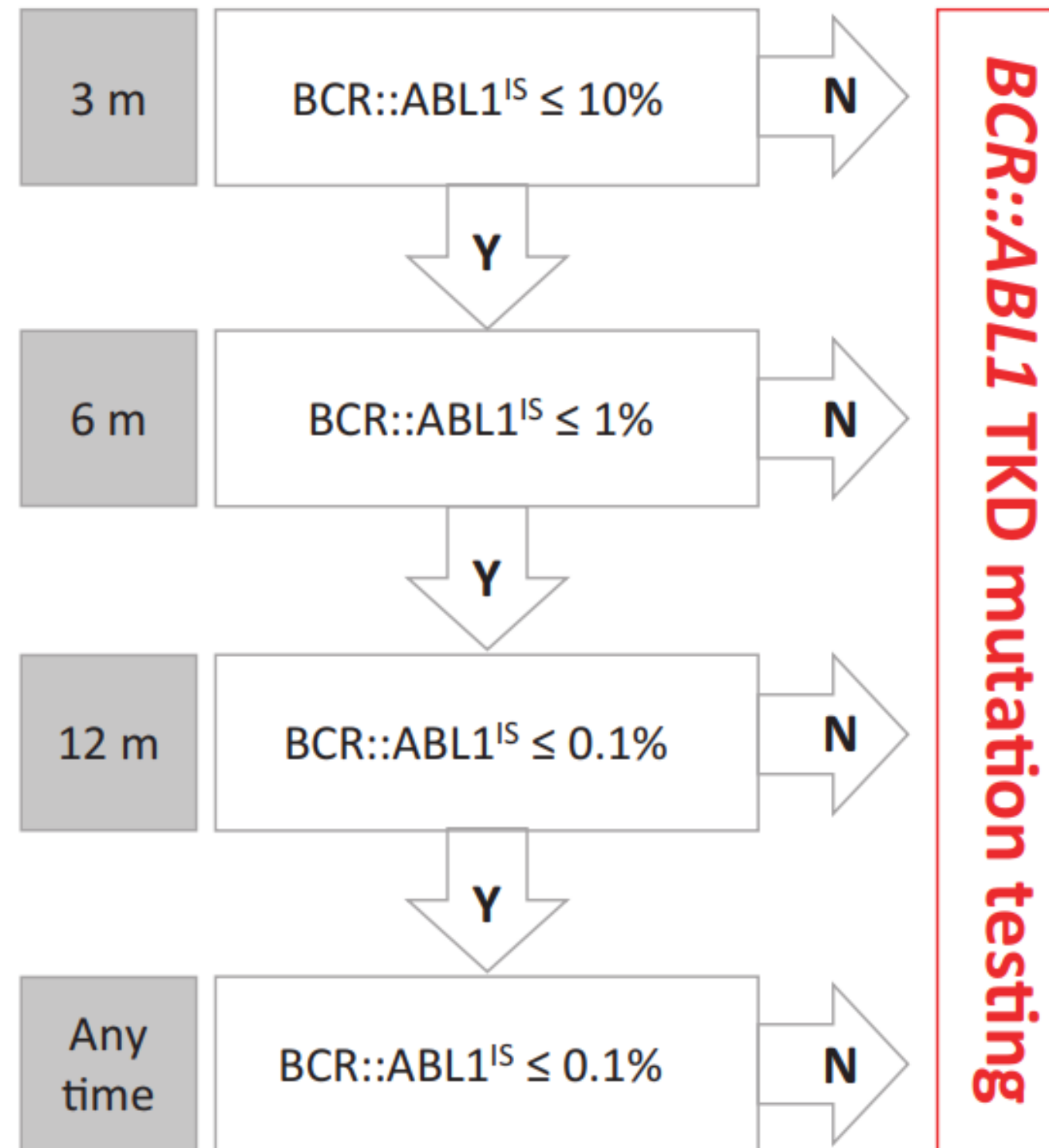
It is critical to speak with your care team about any supplements you may be taking. Some examples include:

- Turmeric
- Ginkgo biloba
- Green tea extract
- St. John's Wort
- Antioxidants

Certain medicines can also affect the ability of a drug to do its job. Antacids, heart or blood pressure medicine, and antidepressants are just some of the medicines that might interact with a systemic therapy or supportive care medicines given during systemic therapy. Therefore, it is very important to tell your care team about any medicines, vitamins, over-the-counter (OTC) drugs, herbals, or supplements you are taking.

Bring a list with you to every visit.

Recommendation to perform *BCR::ABL* KD mutation testing (ELN 2023)



Treatment recommendation based on *BCR::ABL* mutation profile

THERAPY	CONTRAINDICATED MUTATIONS ^{aa}
Asciminib	A337T, P465S, M244V, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L ^{bb}
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I
Ponatinib or allogeneic HCT	None ^{cc}



		IC ₅₀ fold increase (WT = 1)			
		Bosutinib	Imatinib	Dasatinib	Nilotinib
	Parental	38.31	10.78	> 50	38.43
	WT	1	1	1	1
P-LOOP	L248V	2.97	3.54	5.11	2.80
	G250E	4.31	6.86	4.45	4.56
	Q252H	0.81	1.39	3.05	2.64
	Y253F	0.96	3.58	1.58	3.23
	E255K	9.47	6.02	5.61	6.69
	E255V	5.53	16.99	3.44	10.31
C-Helix	D276G	0.60	2.18	1.44	2.00
	E279K	0.95	3.55	1.64	2.05
ATP binding region (drug contact sites)	V299L	26.10	1.54	8.65	1.34
	T315I	45.42	17.50	75.03	39.41
	F317L	2.42	2.60	4.46	2.22
SH2-contact	M351T	0.70	1.76	0.88	0.44
Substrate binding region (drug contact sites)	F359V	0.93	2.86	1.49	5.16
A-LOOP	L384M	0.47	1.28	2.21	2.33
	H396P	0.43	2.43	1.07	2.41
	H396R	0.81	3.91	1.63	3.10
	G398R	1.16	0.35	0.69	0.49
C terminal lobe	F486S	2.31	8.10	3.04	1.85
Sensitive		≤ 2			
Moderately resistant		2.01-4			
Resistant		4.01-10			
Highly resistant		> 10			

Case

A 56-year-old male CML-CP (low Sokal/ELTS risk) with 1st line IM

	8/10/57 @ 20 m of IM	11/3/58 – 16/3/58	25/3/58	29/4/58	24/11/58 @ 9 m of Nil	9/3/59 @12 m of Nil	1/9/59 @18 m of Nil	12/1/60-20/8/62 @>18 m of Nil
Treatment	IM 400 mg/d Due to not NIL approval	Switched to Nil 800 mg/d Due to failure Hold Nil 10 d	NIL 400 mg/d Due to AEs	NIL 800 mg/d	NIL 800 mg/d	NIL 800 mg/d	NIL800 mg/d	NIL800 mg/d
Adverse event	Gr. 1 anemia	Gr.1 anemia Gr. 2 MP rash	Gr.1 anemia Gr. 2 MP rash	Gr. 1 anemia Gr. 2 MP rash	Gr. 1 anemia Gr. 2 MP rash	Gr. 1 anemia Gr. 2 MP rash	Gr. 1 anemia Gr. 2 MP rash Metabolic syndrome	Gr. 1 anemia Gr. 2 MP rash Metabolic syndrome
Best response	@ >18 m: %BCR- ABL/ABL (IS) = 1.09%	N/A	N/A	N/A	@ 9 m: %BCR-ABL/ABL (IS) = 0.10%	@ 12 mo: %BCR-ABL/ABL (IS) = 0.10%	@ 18 mo: %BCR-ABL/ABL (IS) = 0.04%	@ >18 mo: %BCR-ABL/ABL (IS) = 0.01-0.05%

Management

TKI associated hematological AEs

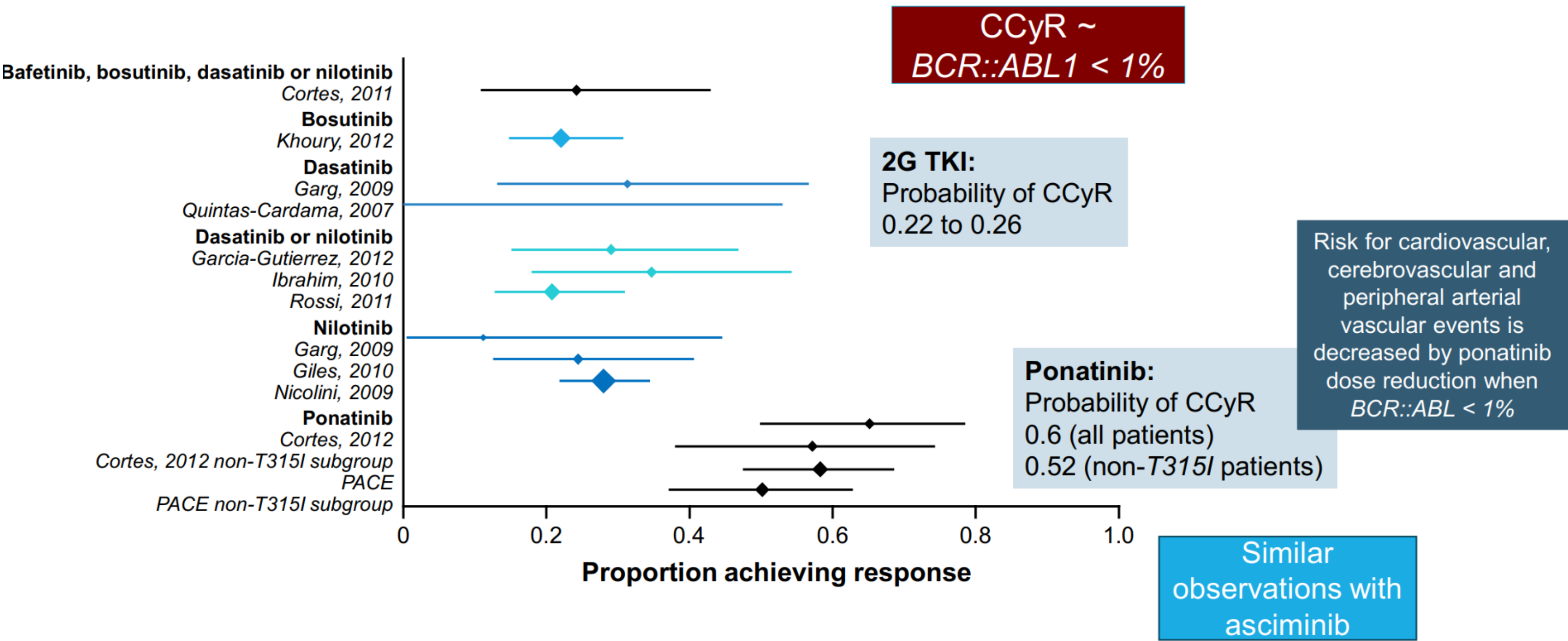
	Imatinib 400 mg OD	Nilotinib 300-400 mg BID	Dasatinib 100-140 mg OD	Ponatinib 45 mg OD
Stop treatment	Until ANC > 1,000-1,500/uL and /or platelet > 50-75,000/uL			
Re-treatment	Resume the same dose in the 1st episode, 300 mg OD in the 2nd episode	Resume the same dose in the 1st episode if recovery in 2 weeks, 400 mg OD otherwise	Resume the same dose in the 1st episode if recovery in 1 week, 80 mg OD in 2nd episode and 50 mg OD in 3rd episode	Resume the same dose in 1st episode, 30 mg OD in 2nd episode and 15 mg OD in 3rd episode

TKI	Common adverse events	Toxicity to watch for	Prohibitive toxicity	Lowest dose range
Imatinib	Rash, fluid retention, edema, weight gain, musculoskeletal aches, diarrhea, skin depigmentation	Renal toxicity	Neurotoxicity	100-200 mg OD
Nilotinib	Rash, headaches, increased bilirubin, impaired glycemic control, dyslipidemia	Renal toxicity, pancreatitis, worsening diabetes	Arterio-occlusive and vaso-occlusive events	200 mg OD - 200 mg BID
Dasatinib	Pleural effusion, cytopenia	Pulmonary hypertension, systemic hypertension	>1 episode of pleural effusion, pulmonary hypertension	20-50 mg OD
Bosutinib	Gastrointestinal toxicity (diarrhea/colitis), renal dysfunction, liver dysfunction	Enterocolitis	Enterocolitis	100-200 mg OD
Ponatinib	Rash, hypertension	Pancreatitis, hepatic toxicity	Arterio-occlusive and vaso-occlusive events; refractory hypertension	15 mg OD

TKI switching

3rd G therapy is optimal choice after 2nd G resistance/intolerance

Proportion of patients achieving CCyR (post 2G TKI setting)



HEMATOLOGY
Phramongkutklao Hospital

TKI switching

2nd and 3rd generation therapy selection based on co-morbidities and risks

History with prior TKI or co-morbidity	Preferred TKI	Less preferred TKI
Diabetes	Dasatinib, bosutinib, asciminib	Nilotinib
Pulmonary disease/PAH	Bosutinib, nilotinib, asciminib	Dasatinib
GI issues	Nilotinib, dasatinib, asciminib	Bosutinib
Cardiovascular	Bosutinib	Nilotinib, (asciminib??)
Peripheral arterial disease	Bosutinib (dasatinib?)	Nilotinib
Liver	Dasatinib	Bosutinib
Renal	Nilotinib, dasatinib, asciminib	Bosutinib

Case

A 56-year-old male CML-CP (low Sokal/ELTS risk) with 1st line IM

	22/8/62	11/12/62	15/7/63-10/11/63	11/11/63-7/12/64	8/12/64-19/2/68
Treatment	Switched to DAS 100 mg/d Due to unresloved Gr. 2 MP rash	DAS 100 mg/d	DAS 100 mg/d Furosemide + steroid	DAS 70 mg/d Furosemide + steroid	DAS 35 mg/d Furosemide + steroid
Adverse event	-	-	Gr. 1 pleural effusion	Gr. 2 pleural effusion	Gr. 2 pleural effusion
Best response	N/A	@ 3 mo: %BCR-ABL/ABL (IS) = 0.02	N/A	N/A	@ 12 mo: %BCR-ABL/ABL (IS) = 0.005

TKI	Common adverse events	Toxicity to watch for	Prohibitive toxicity	Lowest dose range
Imatinib	Rash, fluid retention, edema, weight gain, musculoskeletal aches, diarrhea, skin depigmentation	Renal toxicity	Neurotoxicity	100-200 mg OD
Nilotinib	Rash, headaches, increased bilirubin, impaired glycemic control, dyslipidemia	Renal toxicity, pancreatitis, worsening diabetes	Arterio-occlusive and vaso-occlusive events	200 mg OD - 200 mg BID
Dasatinib	Pleural effusion, cytopenia	Pulmonary hypertension, systemic hypertension	>1 episode of pleural effusion, pulmonary hypertension	20-50 mg OD
Bosutinib	Gastrointestinal toxicity (diarrhea/colitis), renal dysfunction, liver dysfunction	Enterocolitis	Enterocolitis	100-200 mg OD
Ponatinib	Rash, hypertension	Pancreatitis, hepatic toxicity	Arterio-occlusive and vaso-occlusive events; refractory hypertension	15 mg OD

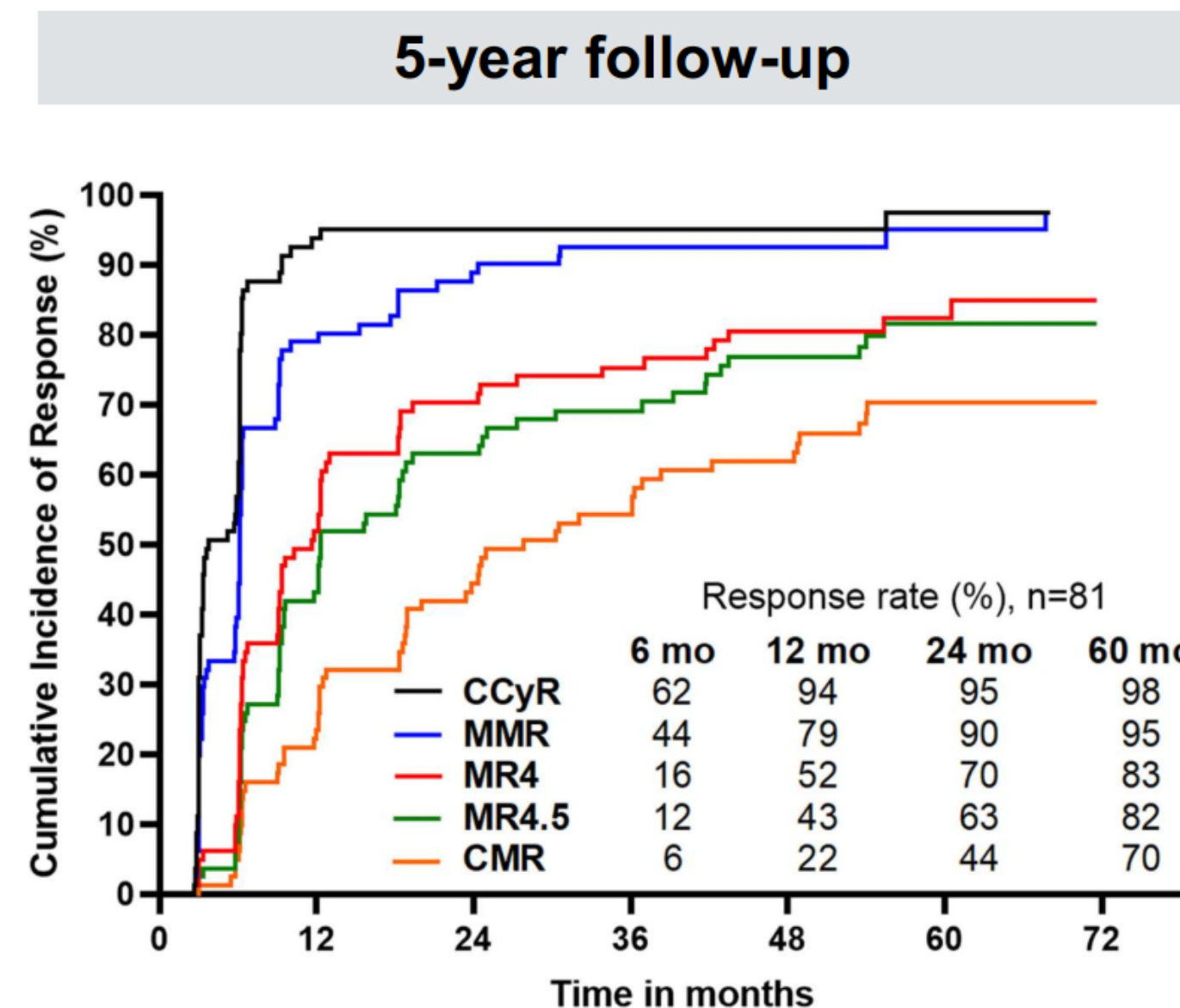
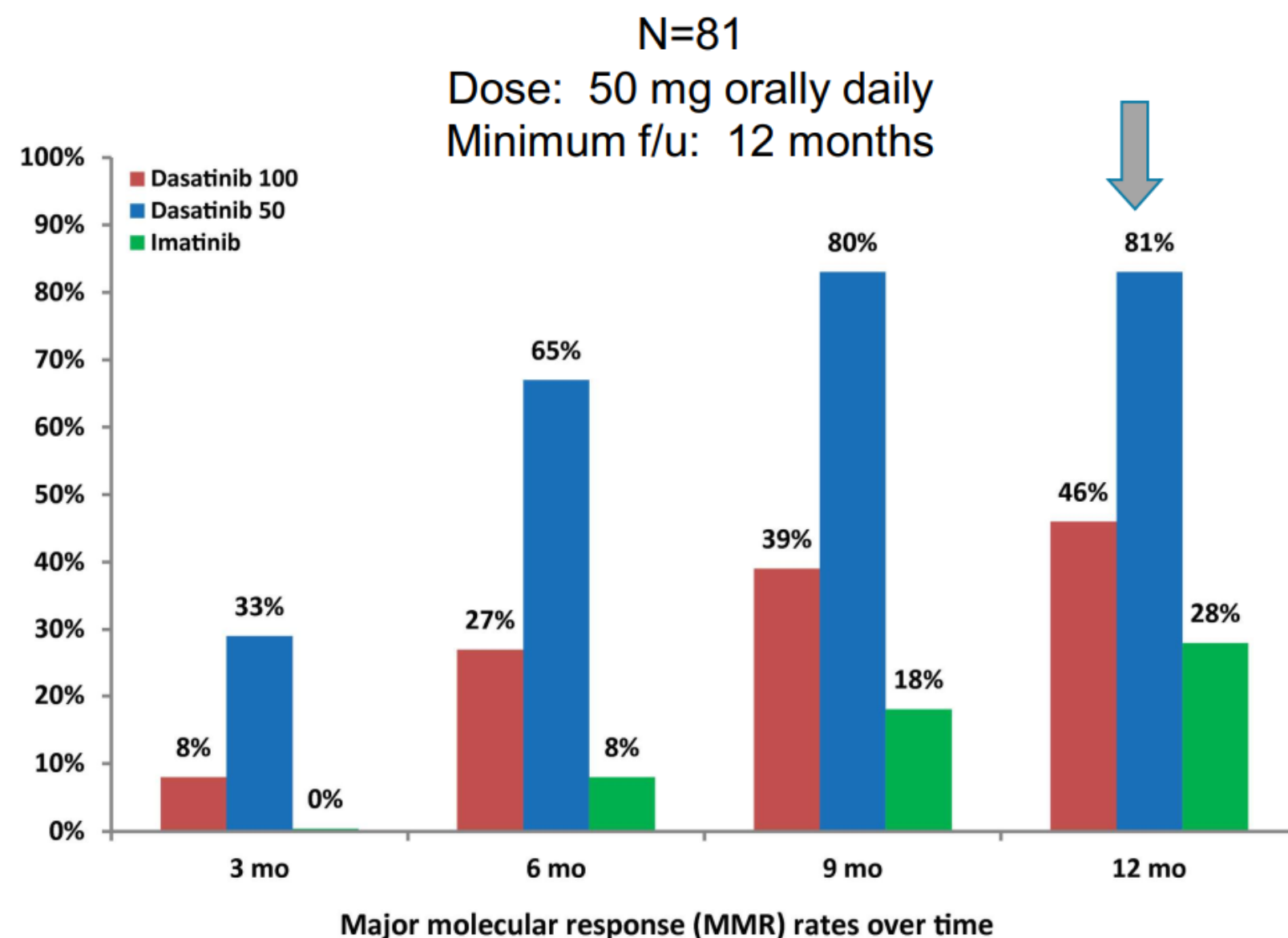
DAVLEC trial

Very low-dose 20 mg/d dasatinib in newly diagnosed elderly CML-CP

- Phase II Japanese trial (n = 52) aged >70 years, median F/U 1 year
- Starting dose 20 mg/d
- If optimal response at 3, 6, and 9 mos and AEs $\leq$ Gr. 2 the same dose was continued
- If suboptimal response and AEs $\leq$ Gr. 2, the dose was increased by 20 mg/d
- Once a dose reduction had been made because of a Gr. $\geq$ 3 AEs, there were no further dose increases
- Treatment was discontinued if assessed as failure (disease progression to AP/BP)
- Gr. 3-4 AEs: 12 (23%)
- MMR at 12 mo: 31 (60%)

1st line low-dose dasatinib

Low-dose dasatinib in CML-CP to mitigate AEs



- All Gr. pleural effusion (13%) and Gr. 3-4 pleural effusion (2%)*
- Rate of failure due to resistance (5%) and intolerance (5%)
- 5-y OS 96% and 5-y PFS 90%

*At standard dose dasatinib all Gr. Pleural effusion at 5 y is 37%.

Summary of 2nd line TKI after imatinib resistance

TKI	Nilotinib	Dasatinib	Bosutinib
Follow-up (mos)	≥48	72	≥108
CHR (%)	77	89	86
MCyR (%)	59	59	60
CCyR (%)	45	44	48
MMR (%)	N/A	40–43 [*]	46
PFS rate (%)	4-year, 57	6-year, 48–56 [*]	NA
OS rate (%)	4-year, 78	6-year, 76	9-year, 74

^{*}At different dasatinib dosing, ranging from 70 mg daily to 140 mg daily.

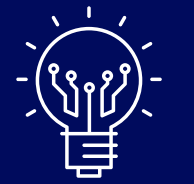
Summary of 3rdG TKIs in CML-CP post-2+TKIs failure

TKI	Ponatinib (PACE)	Ponatinib (OPTIC)			Asciminib (ASCEMBL)
		45–15 mg	30–15 mg	15 mg	
Follow-up (mos)	57	48			
MCyR (%)	60	50	33	44	NA
CCyR (%)	54	60	41	40	40
MMR (%)	40	34	25	23	38
DMR (MR4.5) (%)	24	NA	NA	NA	11
PFS rate (%)	5-year, 53	4-year, 72	4-year, 63	4-year, 64	2-year, 94
OS rate (%)	5-year, 73	4-year, 88	4-year, 86	4-year, 86	2-year, 97

Conclusions



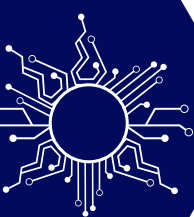
An optimal response milestone for each patient is not need to be the same



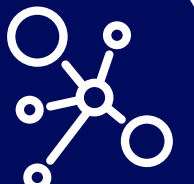
Before switching TKI due to intolerance, we should check patient's adherence, drug/food interaction and co-morbidities



Before switching TKI due to failure, we should check patient's adherence, drug/food interaction, co-morbidities and mutation



Dose adjustment and resume of TKI after AE should be made step by step.



Low-dose dasatinib should be considered as 2nd-3rd-line TKI in Thailand

Thank you

