Chronic Myeloid Leukemia

BHS Course 2026

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1. Introduction

2. Diagnostic Workup

3. Treatment of CP: 1L and from 2L

4. Response Milestones

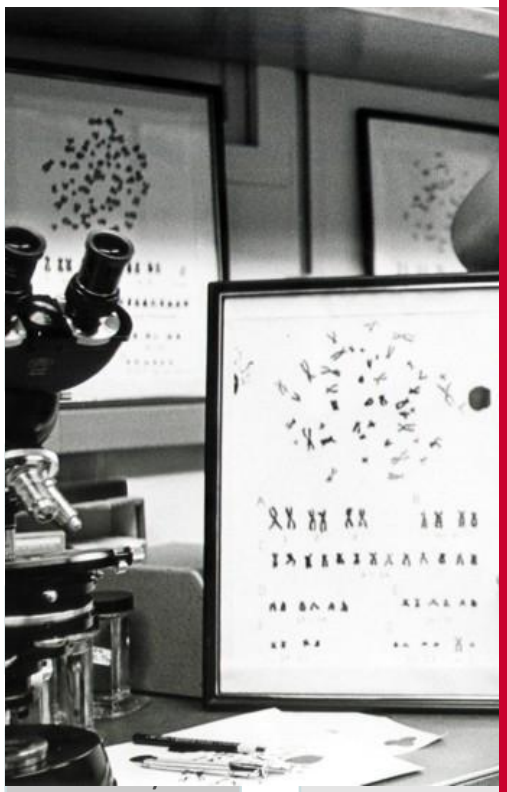
5. Others and Treatment Free Remission

1. Introduction

Date

Te

Treatment



J.V. Melo et al. 2007. Springer Science

1. Introductio

Epidemiology:

1. Annual **incider** … Median age at diagnosis 64yo

2. **Prevalence** ste … val

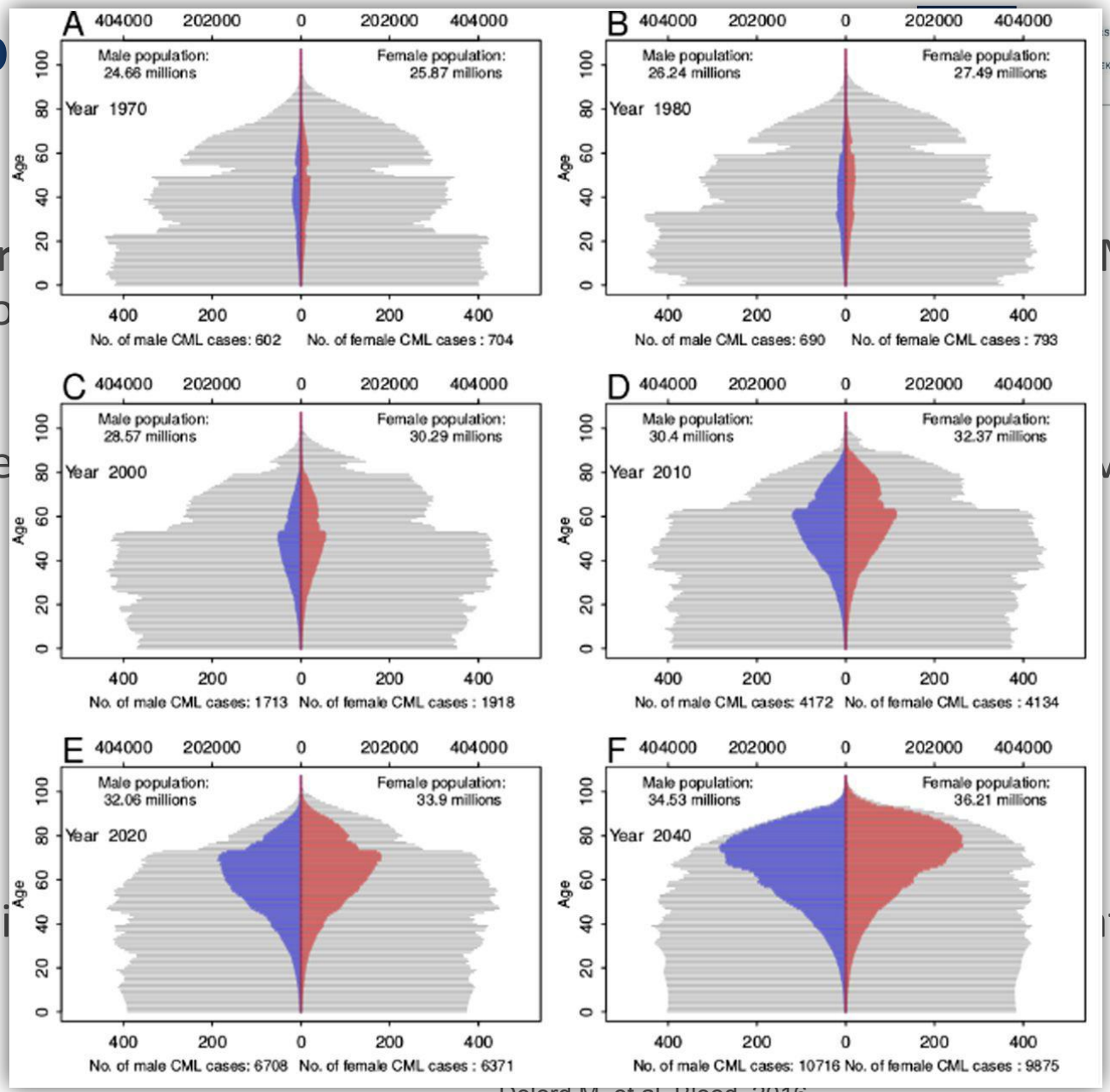
   US: 112.000 in

   France: 13.079

3. **Survival** in the

✔For CML-CP is only

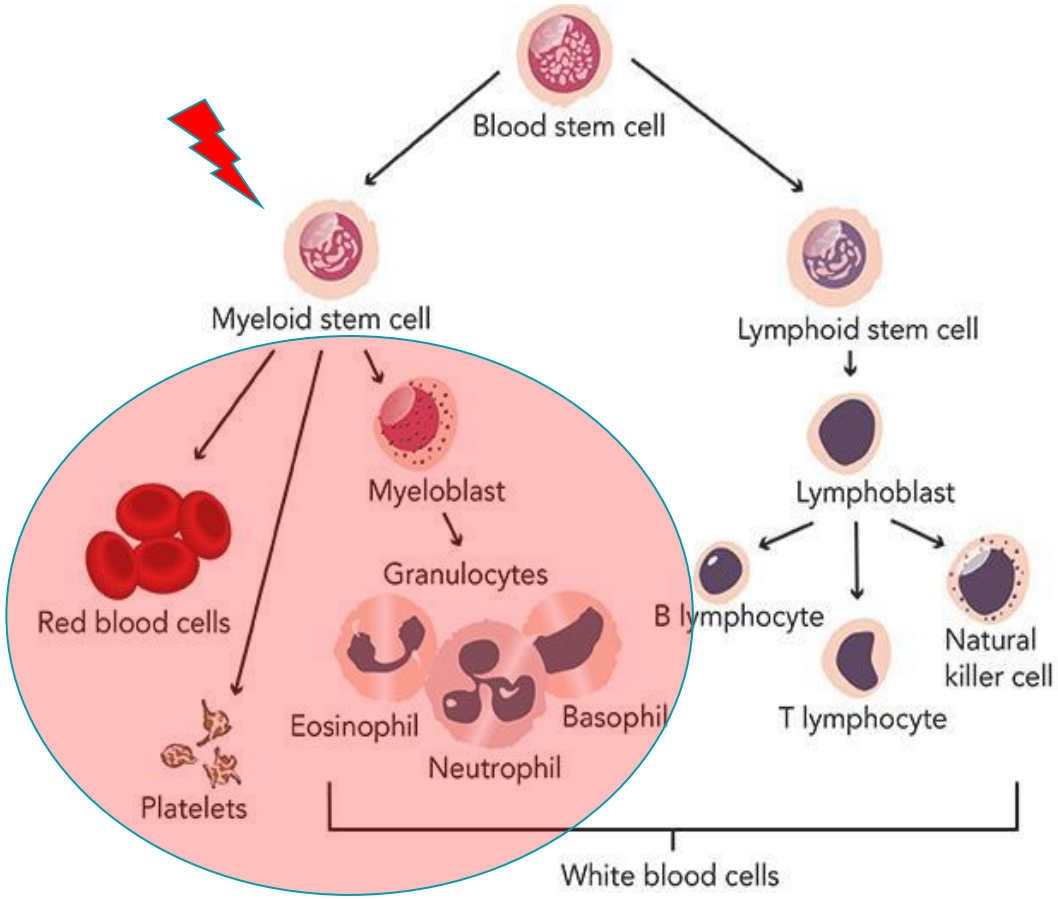
✔For CML-CP achievi … tion (4)

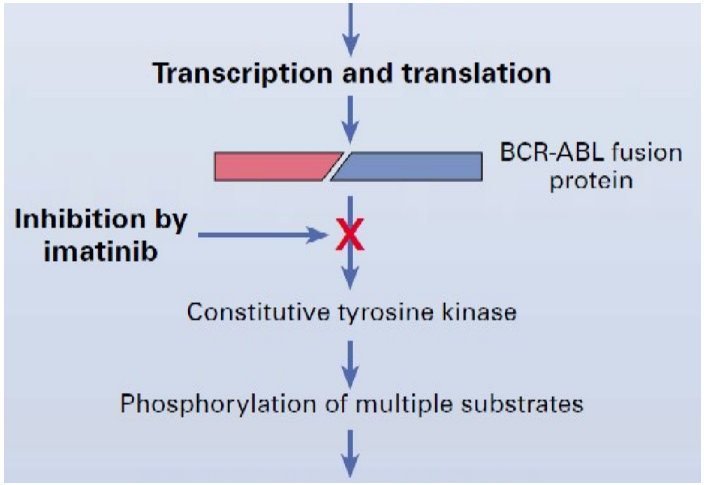


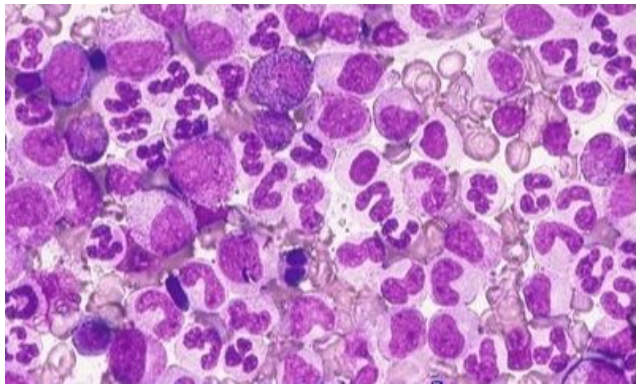
Delord M. et al. Blood, 2016
Sasaki K et al. Lancet Haematol, 2015

1. Introduction

Pathophysiology:







https://www.cancer.gov/publications/dictionaries/cancer-terms/def/philadelphia-chromosome

Savage DG et al. NEJM 2002

1. Introduction

Classification:

Table 1. WHO classification of myeloid neoplasms and acute leukemia

WHO myeloid neoplasm and acute leukemia classification	
Myeloproliferative neoplasms (MPN)	WHO 2022 [13]
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$	
Chronic neutrophilic leukemia (CNL)	
Polycythemia vera (PV)	
Primary myelofibrosis (PMF)	
PMF, prefibrotic/early stage	
PMF, overt fibrotic stage	
Essential thrombocythemia (ET)	
Chronic eosinophilic leukemia, not otherwise specified (NOS)	
MPN, unclassifiable	
Mastocytosis	
Myeloid/lymphoid neoplasms with eosinophilia and rearrange	
PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2	
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement	
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement	
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement	
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2	

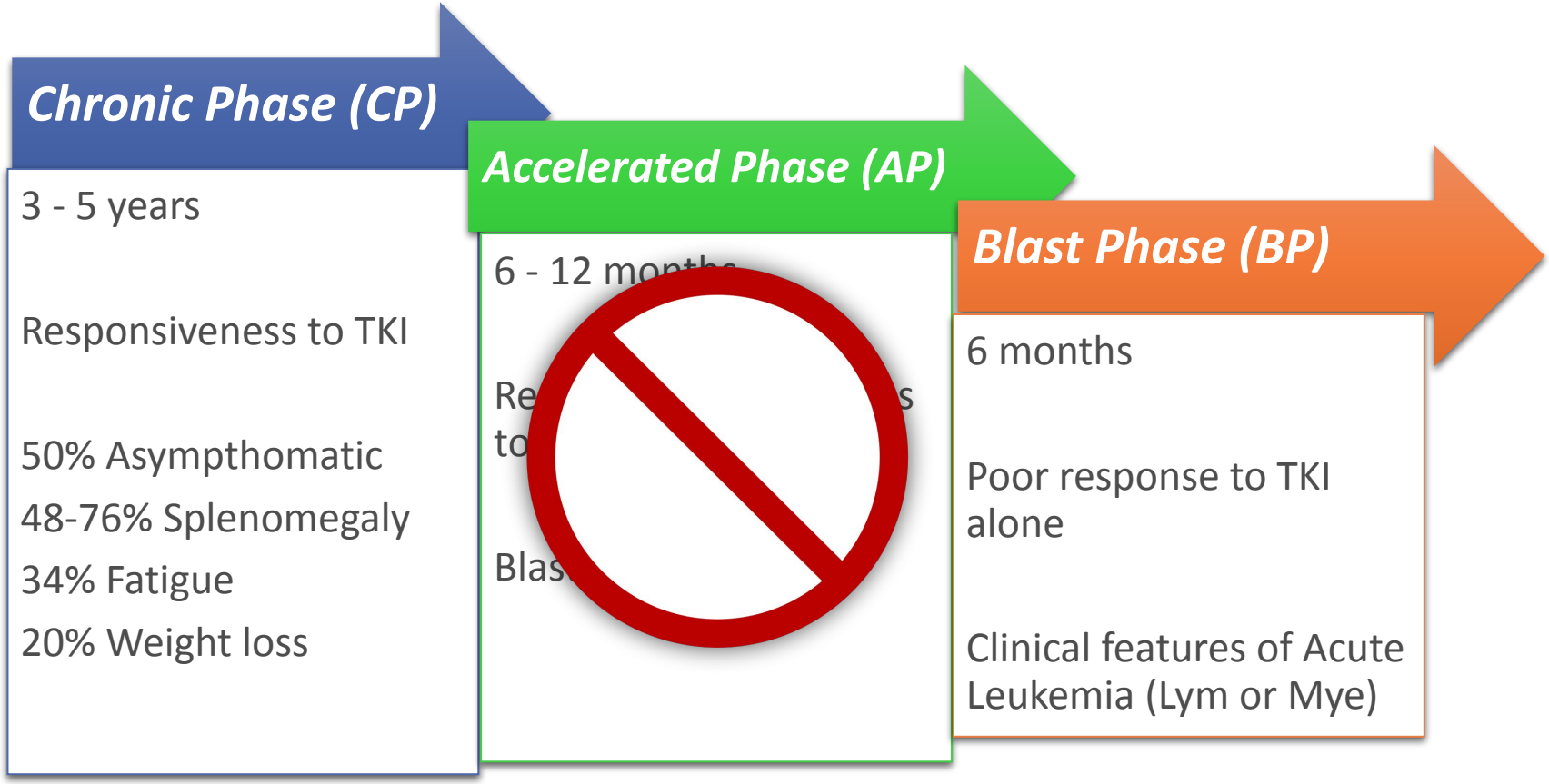
Table I. Staging of CML according to the ELN or WHO criteria (both can be used).[26,27]

Blasts (PB & BM) < 20% **High risk indicators** **At diagnosis** High ELTS score Blasts (PB & BM) 10–19% PB basophils ≥20% ACA: 3q26.2 rearrangements, -7, i(17q) & complex karyotype Clusters of small megakaryocytes with fibrosis **High risk indicators** **On treatment** No CHR on 1st line TKI Resistance to 2GTKI (unless due to a *BCR::ABL1* mutation) Development of ACA Compound mutations in *BCR::ABL1*	No longer exists	Blasts (PB or BM) ≥ 20% Extramedullary blast proliferation Bona fide lymphoblasts in PB or BM (even if <10%)

"major routes" abnormalities include :
trisomy 8, additional Ph (+der(22)t(9;22)(q34;q11) or ider(22)(q10)t(9;22)(q34;q11)), isochromosome 17, and trisomy 19.[2]

Arber DA et al. Blood, 2016
Benghiat et al. Belg J Hematol 2015

1. Introduction



Druker B et al. Chronic Leukemias 17th Edition. 2005

2. Diagnostic Workup

History

Comorbidities (CV, Pulmonary, Pancreatic, IBD), ESC Score, Comedications

Physical Examination

Splenomegaly (cm from costal border)

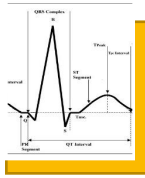
Blood

- FBC, Renal and Liver, Chol, Lipase, Glucose, HbA1c, β-HCG, FISH t(9;22), RT-PCR BCR-ABL

Bone Marrow

BM Aspiration: morphology (AP, BP!), karyotype (ACA!)

BM Biopsy: fibrosis, blasts clusters



Others

ECG + Hearth US + Chest X-Ray

Abdominal US, ABI +/- Carotid/Peripheral arteries US

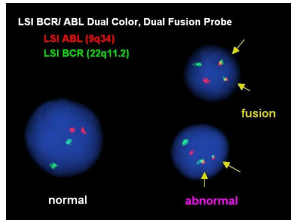
2. Diagnostic Workup

53yo male, 3 months history of fatigue and abdominal bloating

Hb 11.7 g/dL
WBC 89.0 x 10^9/L
PLTs 648 x 10^9/L
Neutrophils: 44.0 x 10^9
Lymphocytes: 3.7 x 10^9
Eosinophils: 2.1%
Basophils: 7.8%
Blasts: 1%

Suspicion of CML

Blood
FISH t(9;22)
24-48h



CML Confirmed!

Bone Marrow Aspirate:
1. Morphology (CP, AP, BP)
2. Cytogenetics (ACA)

Bone Marrow Biopsy:
Fibrosis and Blasts Clusters

Blood
RT-PCR for BCR-ABL

Blood or Bone Marrow
BCR-ABL1 KD mutation testing at diagnosis **only for AP and BP**

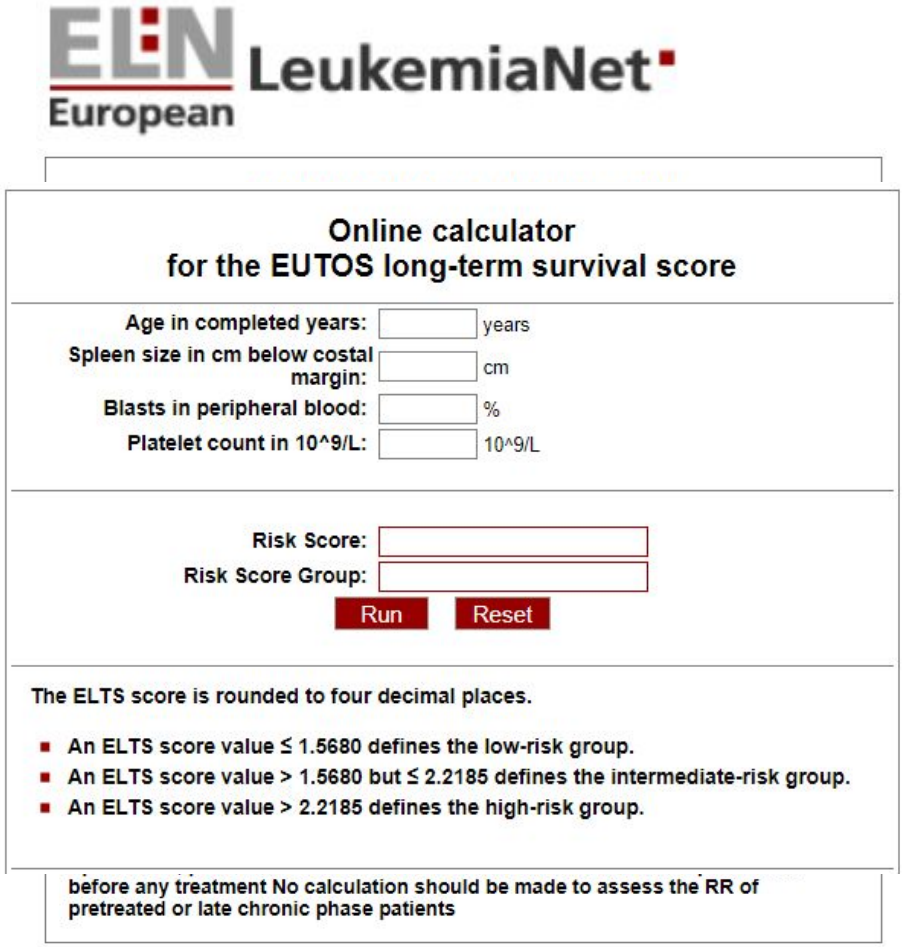
2. Diagnostic Workup

Risk Score Stratification History:

1. Sokal (1984, CHT Era)
2. Euro/Hasford (1998, IFN Era)
3. Eutos (2011, Imatinib Era)

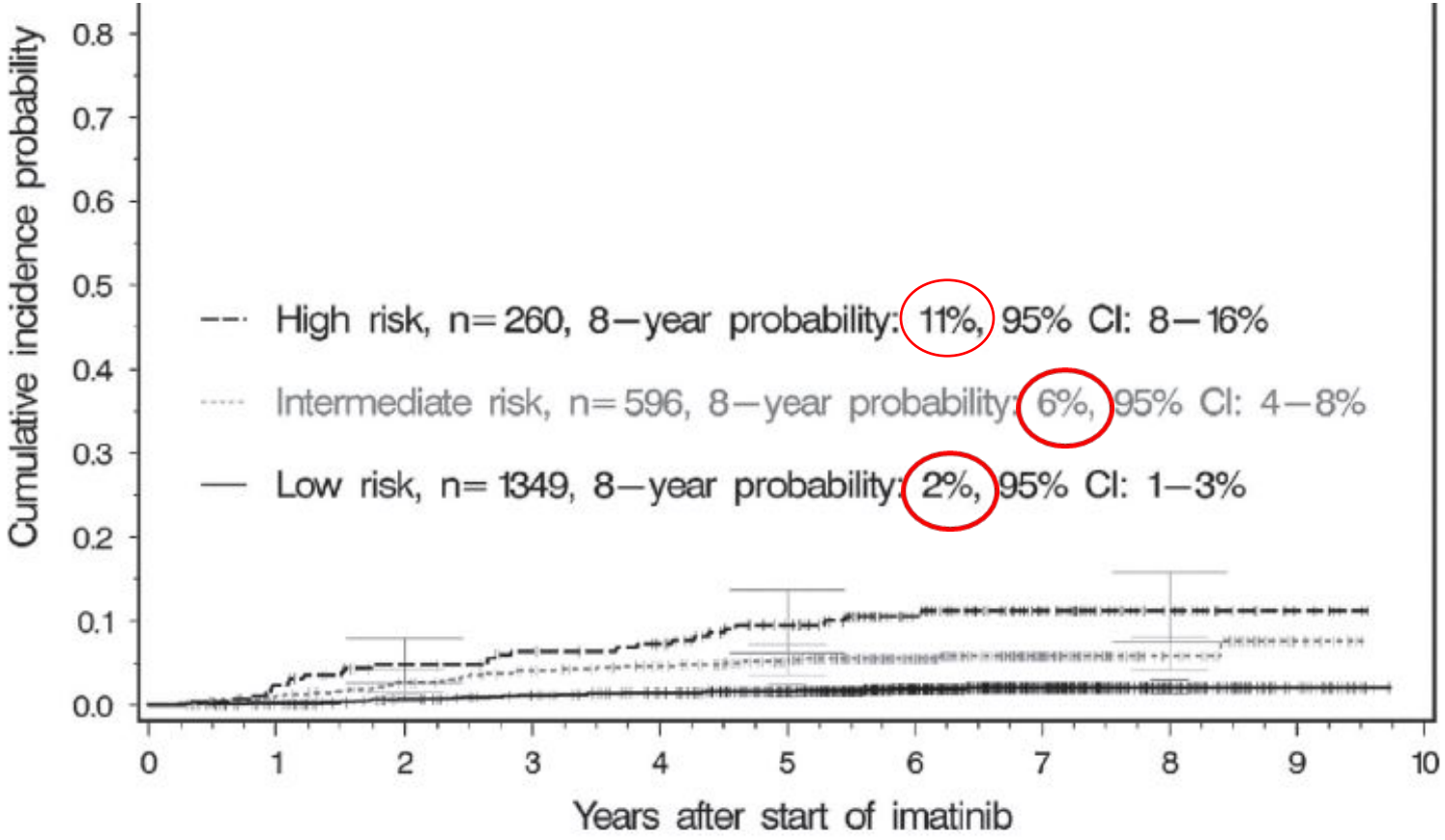
Risk Score Stratification Today:

1. ELTS (2015) : Superior prognostic discrimination of the probabilities of CML-related death and of overall survival



https://www.leukemia-net.org/content/leukemias/cml/euro__and_sokal_score/index_eng.html
https://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html

2. Diagnostic Workup



Pfirrmann M, Leukemia, 2015

3. Treatment of CP CML

1. First: Debulking Phase: Hydratation, Allopurinol, Hydroxyurea
2. Then:

ITK disponibles en 1L en Belgique, Apr 2026	Imatinib (Glivec)	Dasatinib (Sprycel)	Nilotinib (Tasigna)	Bosutinib (Bosulif)
Dosage	400 mg QD	100 mg QD	300 mg BID	400 mg QD
Common side effects	- Fluid retention - Muscle cramps - Gastrointestinal disorders	- Pleural effusion - Pulmonary hypertensions	- Diabetes - Hypercholesterolemia - Pancreatitis - Peripheral arterial disease	- Diarrhea - Hepatic toxicity
€ for 31 days of treatement (CBIP, April 2026)	856 €	1.431 €	1.109 €	1.284 €
18.5 years of treatment	190.000 €	317.700 €	246.200 €	285.000 €

3. Treatment of CP CML

How to choose the 1st line TKI in CP CML:

Disease Features:

1. ELTS Low Risk Vs Intermediate and High Risks
2. Presence of additional chromosomal abnormalities (ACA) at diagnosis > High Risk ELN2025
3. Signs of fibrosis

Patients Features:

1. Priority for DMR > TFR (Age)
2. Drug interactions
3. Comorbidities

3. Treatment of CP CML

Comorbidities:

Previous or Concomitant Diseases	Imatinib	Dasatinib	Nilotinib	Bosutinib	Ponatinib
Cardiovascular risk factors					
Peripheral arterial disease					
Arterial hypertension		Risk factor for pleural effusion			
Arteriosclerosis		Risk factor for pleural effusion			
Lung disease (e.g., pleural effusion, respiratory failure)					
Pulmonary arterial hypertension					
Pericarditis					
Autoimmune diseases		Risk factor for pleural effusion			
Hypercholesterolemia		Risk factor for pleural effusion			
Diabetes mellitus					
Pancreatitis					
Liver disease					
Diarrhoea / inflammatory bowel disease					
Renal failure					

No relevant restriction | With Limitation | Strong contraindication

CML=chronic myeloid leukemia; **ELN**=European LeukemiaNet; **TKI**=tyrosine kinase inhibitor. Adapted from ELN Guidelines updated March 3rd 2020

1. Hochhaus A, et al. Leukemia. 2020;34(4):966-984.

https://www.pfizerpro.ie/product/bosulif/chronic-phase-cp/eln-guidelines-2020 adapted from Claudiani S, Apperley JF. *Hematology Am Soc Hematol Educ Program* 2018; 2018:161–7

3. Treatment of CP CML

Pros and Cons of 1st Line 2nd Generation TKI

Pros

- Faster and deeper MR
- Reduce risk of early progression and CML-related death
- Increased number of patients achivieng criteria for TFR

Cons

- No Improvement in OS
- Appear to be associated with more long term toxicities
- Costs

3. Treatment of CP CML : 2nd line

Always ask yourself: **why a 2nd line**?

- 2nd line for **intolerance/AE** > Try supportive measures
- 2nd line for **ELN Failure (or Warning)** > First check adherence. Then Drugs interactions. Then Mutation Analysis and Bone Marrow aspiration for Karyotype.

How to chose the 2nd line TKI in CML:

- **Disease Features**:
  - Mutational Analysis of BCR-ABL KD

- **Patients Features**:
  - Comorbidities
  - Drug interactions

Apperley J et al. Leukemia 2025

3. Treatment of CP CML: 2nd line

Mutational Analysis of BCR-ABL KD

When?

BCR-ABL1 KD mutation testing by Sanger or NGS is indicated in CP CML in patients with a "warning" or "failure" or progression to AP or BP.

From Where?

Blood or Bone Marrow

BCR-ABL	Imatinib IC50 range (nM)	Bosutinib IC50 range (nM)	Dasatinib IC50 range (nM)	Nilotinib IC50 range (nM)	Ponatinib IC50 range (nM)
ongemuteerd	260-678	41,6	0,8-1,8	<10-25	0,5
M244V	1.600-3.100	147,4	1,3	38-39	2,2
L248V	1.866-10.000	NB	9,4	49,5-919	5
G250E	1.350->20.000	179,2	1,8-8,1	48-219	4,1
Q252H	734-3.120	33,7	3,4-5,6	16-70	2,2
Y253F	>6.400-8.953	40	6,3-11	182-725	2,8
Y253H	>6.400-17.700	NB	1,3-10	450-1.300	6,2
E255K	3.174-12.100	394	5,6-13	118-566	14
E255V	6.111-8.953	230,1	6,3-11	430-725	16-36
D276G	1.147	25	2,6	35,3	NB
E279K	1.872	39,7	3	36,5-75	NB
V299L	540-814	1.086	15,8-18	23,7	4
F311L	480-1.300	NB	1,3	23	NB
T315I	>6.400->20.000	1.890	137->1.000	697->10.000	6-11
T315A	125	NB	760	NB	1,6
F317L	810-7.500	100,7	7,4-18	39,2-91	1,1-4
F317V	500	NB	NB	350	10
M351T	880-4.900	29,1	1,1-1,6	7,8-38	1,5
E355G	NB	NB	NB	NB	NB
F359V	1.400-1.825	38,6	2,2-2,7	91-175	4-10
V379I	1.000-1.630	NB	0,8	51	NB
L384M	674-2800	19,5	4	39-41,2	NB
L387M	1.000-1.100	NB	2	49	NB
H396R	1.750-5.400	33,7	1,3-3	41-55	4
H396P	850-4.300	18,1	0,6-2	41-43	1,1
E459K	NB	NB	NB	NB	5
F486S	2.728-9.100	96,1	5,6	32,8-87	NB
	Plasmaspiegel				
C_{min}	2.062±1.334	268 (30-1.533)	5,5±1,4	1.923±1.233	64,3±29,2
C_{max}	4.402±1.272	392 (80-1.858)	133±73,9	2.329±772	145,4±72,6

Soverini et al. J Hematol Oncol. 2019

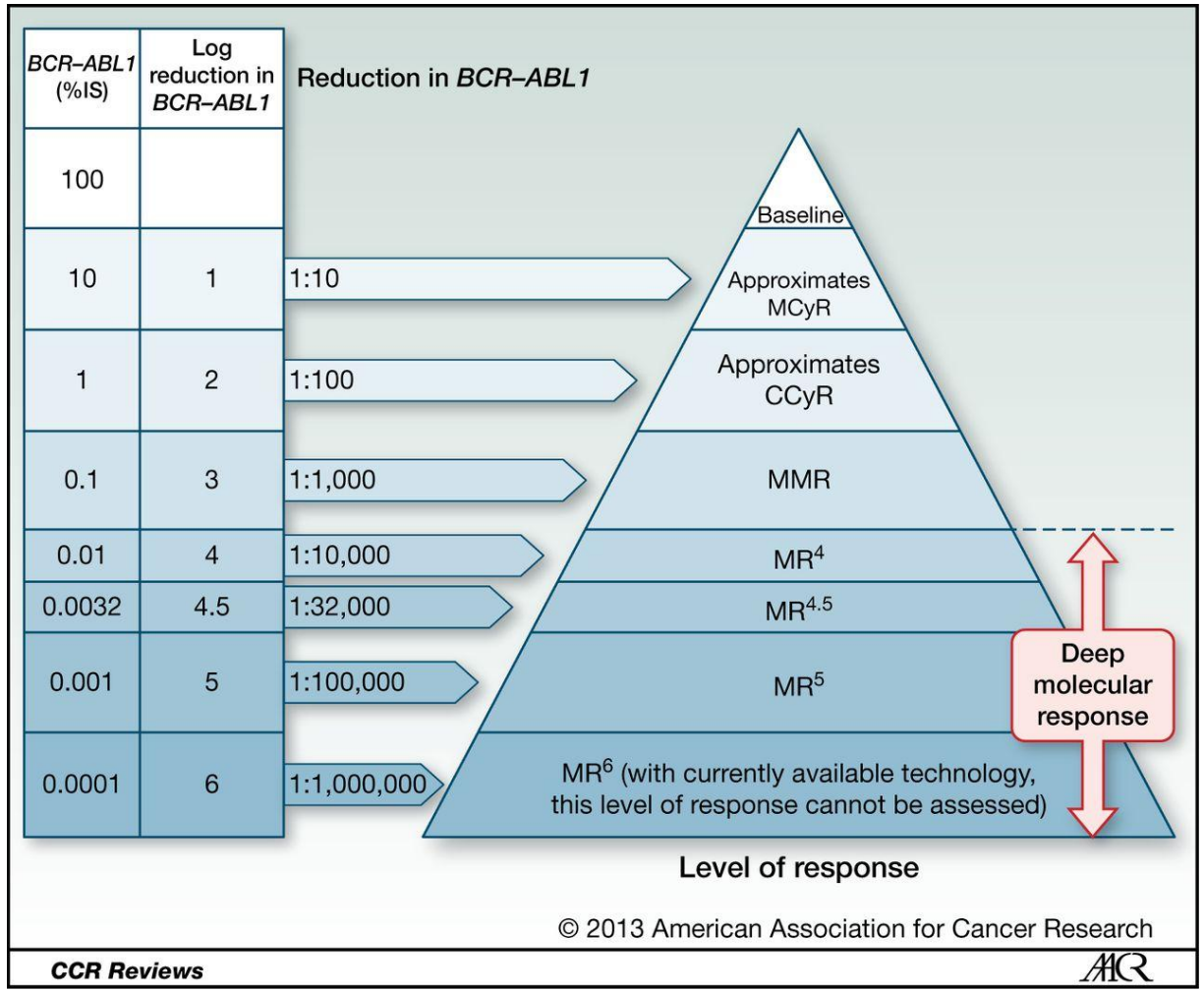
3. Treatment of CP CML: from 2nd line

TKI available from 2Lin CP CML in Belgium, Oct 2022	Imatinib (Glivec)	Dasatinib (Sprycel)	Nilotinib (Tasigna)	Bosutinib (Bosulif)	Ponatinib (Iclusig, from 3L)	Asciminib (Scemblix, from 3L)
Dosage	400–800 mg/jour	100 mg/jour	400 mg 2x/jour	500 mg/jour	15–45 mg/jour	40 mg BID
Common Side Effects	Fluid retention Muscle cramps Gastrointestinal disorders	Pleural effusion Pulmonary hypertensions	Diabetes Hypercholesterolemia Pancreatitis Peripheral arterial disease	Diarrhea Hepatic toxicity	Hypertension Peripheral arterial disease Arterial thrombosis Hepatic toxicity	Thrombocytopenia Increased lipase levels
€ for 31 days of treatement (CBIP, April 2026)	856 - 1712 €	1431 €	1596 €	1605 €	2649 - 4268 €	4273 €

4. Response Milestones

Table Xb. Definitions of responses and monitoring.[2]

Response	Definitions	Monitoring**
Hematologic- Complete (CHR)	Platelet count < 450x10⁹/L WBC count < 10 x 10⁹/L No immature granulocytes Basophils < 5% Non palpable spleen	Every 15 days until CHR has been confirmed then every 3 months or as required.
Cytogenetic*		
Complete (CCyR)	No Ph+ metaphases	At 3, 6 and every 6 months until a CCyR has been confirmed. Once a CCyR is achieved, FISH on blood cells can be used. If an adequate molecular monitoring can be assured, cytogenetics can be spared after achievement of CCyR. Cytogenetics is required only in case of failure, unexplained cytopenias and if molecular testing is not available.
Partial (PCyR)	1-35% Ph+ metaphases	
Minor	36-65% Ph+ metaphases	
Minimal	66-95% Ph+ metaphases	
None	> 95% Ph+ metaphases	



Mahon FX, Clin Cancer Res. 2014
Benghiat et al. Belg J Hematol 2015

Table 4. Response milestones for 1st, 2nd and 3rd line TKI expressed as BCR::ABL1^{IS}.

	Favorable Low risk of developing resistance: treatment switch unnecessary	Warning Possible risk of developing resistance: treatment switch may become necessary	Unfavorable High risk of developing resistance: treatment switch preferred
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%-established resistance
12 months	≤0.1%	>0.1–1%	>1% (1–10%—see text for other considerations)
At any time	≤0.1%	>0.1–1% loss of ≤0.1% (MMR)	Loss of a previous response, resistant *BCR::ABL1* mutations, high-risk ACA

Apperley J et al. Leukemia 2025

5. Others and Treatment Free Remission

- **PEG-IFNalpha-2a and -2b (Pegasys, Besremi):** pregylated form of the treatment of choice in the pre-TKI era.

✔Still some cases of DMR and TFR after IFN treatment.

✔Combination trial with TKI investigational for faster and possibly more DMR > more TFR

✔Can be considered for CML female patients while in pregnancy

✔Currently very limited acces in Belgium (solidarity fund)

Lipton H et al. Leuk Lymphoma, 2007

5. Others and Treatment Free Remission

Accelerated Phase (AP) CML:

1. **AP at diagnosis** should be trea -risk patient, becoming eligibl allo-SCT if the response is not KIs
2. **Progression to AP** during treatme uld immediately be considered f

Chronic phase (CP)
High risk indicators
At diagnosis
High ELTS score
Blasts (PB & BM) 10–19%
PB basophils ≥20%
ACA: 3q26.2 rearrangements, -7, i(17q) & complex karyotype
Clusters of small megakaryocytes with fibrosis
High risk indicators
On treatment
No CHR on 1st line TKI
Resistance to 2GTKI (unless due to a *BCR::ABL1* mutation)
Development of ACA
Compound mutations in *BCR::ABL1*

3. **High Risk CML**: may benefit from more potent drugs and closer monitoring.

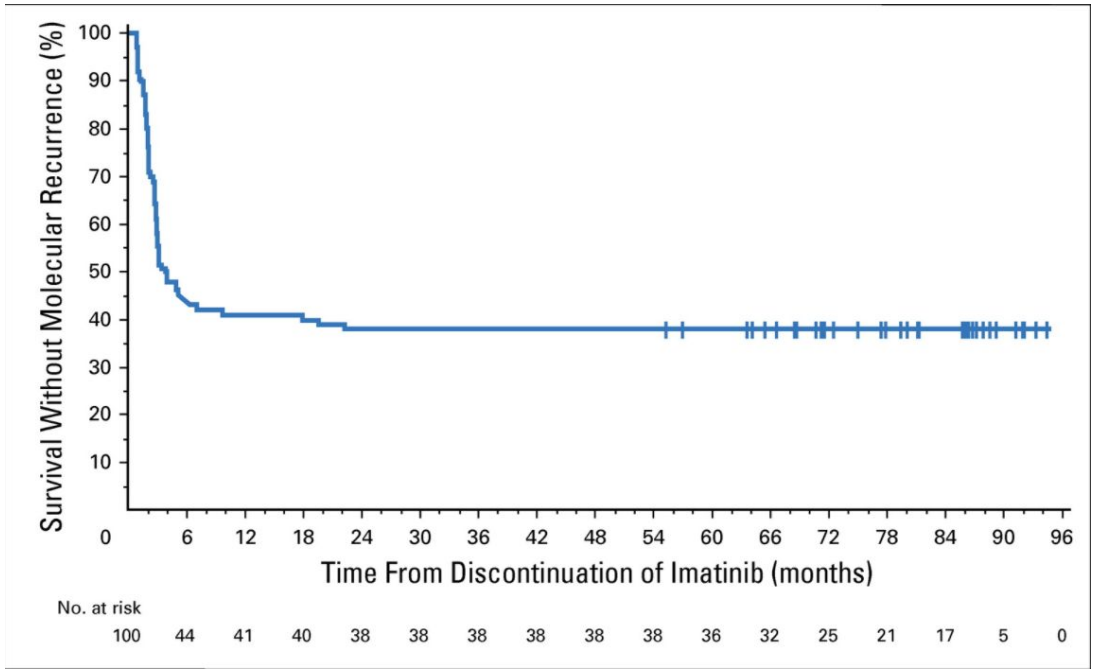
4. **Blasts Phase (BP) CML**: can be lymphoid or myeloid.
   - **Lymphoid**: treat with ALL Like Protocols + TKI + AlloSCT
   - **Myeloid**: treat with AML Like Protocols + TKI + AlloSCT

Blast phase (BP)
Blasts (PB or BM) ≥ 20%
Extramedullary blast proliferation
Bona fide lymphoblasts in PB or BM (even if <10%)

Apperley J et al. Leukemia 2025

5. Others and Treatment Free Remission

TFR: remaining in a DMR without treatment



STIM Trial

EURO-SKY Trial

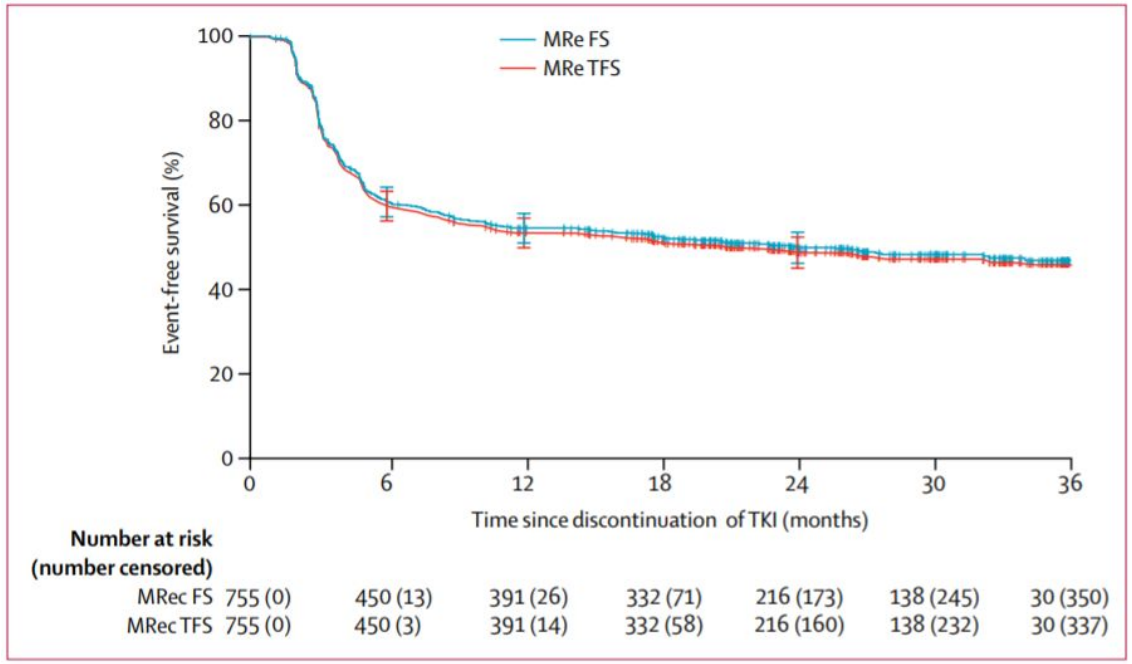


Figure 3: **MReFS and MReTFS after TKI discontinuation**
Bars at 6, 12, and 24 months indicate the upper and lower limits of the 95% CIs. MReFS=molecular relapse
survival. MReTFS=molecular relapse-free and treatment-free survival. TKI=tyrosine kinase inhibitor.

Etienne G et al JCO 2017
Saussele S. et al. Lancet Oncol. 2018

5. Others and Treatment Free Remission

Table 6. Guidance for attempts at treatment discontinuation.

Requirements for tyrosine kinase inhibitor discontinuation in CP CML.	
Mandatory:	CML in first CP only (data are lacking outside this setting).
	Motivated patient with structured communication.
	Access to high quality molecular monitoring using the International Scale (IS) with rapid turn-around of results. In case of atypical transcripts in laboratories with a high standard of quantification.
	Patient's agreement to more frequent monitoring after stopping treatment.
Minimal (stop allowed):	First-line therapy, second-line if the reasons for switch were intolerance or resistance due to a mutation sensitive to another TKI.
	Typical e13a2 or e14a2 *BCR::ABL1* transcripts. In case of atypical transcripts in laboratories with a high standard of quantification.
	Duration of TKI therapy >5 years (>4 years for 2GTKI).
	Duration of DMR (MR^4 or better) >2 years.
Optimal (stop recommended for consideration):	Duration of TKI therapy >5 years.
	Duration of DMR >3 years if MR^4.
	Duration of DMR >2 years if $MR^{4.5}$.
Procedures after stop:	Molecular monitoring 6 to 8 weekly for the first 6 months, 2 monthly for months 6–12, and every 3–6 months thereafter. Monitoring should increase in frequency if there is an increase in *BCR::ABL1* transcript levels.
	Restart TKI-therapy if MMR is lost.
	If TKI-therapy is restarted monitor 4-6 weekly until MMR is regained and then every 3 months until MR^4 is regained.

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5. Others and Treatment Free Remission

Pregnancy and CP CML

- **Male Patients**: imatinib, bosutinib, dasatinib, or nilotinib, safe. Few data for ponatinib. No data for Asciminib.

- **Female Patients**: TKIs teratogenic, especially in 1st trimester.
- **Discontinue TKI at confirmation of pregnancy!**
- Different scenarios (*planned pregnancy, unplanned pregnancy, diagnosis of CML while pregnant*)
  1. Patient in DMR: consider TFR is applicable
  2. Patient in MMR: unlikely to need treatment before reaching pregnancy term
  3. Patient needing a treatment: IFN, if rapid progression or loss of CHR Imatinib 400mg QD or Nilotinib 400mg QD from W16 of pregnancy

- No brest-feeding while on TKI!

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Key Messages

- Survival in CML-CP achieving CCyR or better it is similar to that of general population in the TKI era

- Choice of TKI must be guided by disease features and comorbidities

- **“2026” goals:**

1. *Assuring normal life expectancy to as many patients as possible*
2. *Increasing number of TFR: sparing toxicities for the patient, and reducing economic burden for the society*
3. *Correct approach to 1L 2G TKI Failure and advanced phases*
4. *To allow and properly manage pregnancy in CML*

- Unmet need in CML in 2026: Resistance to a 2G TKI without mutations, T315I mutation, TKI Multi-intolerant patients

Merci België

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