Living with Chronic Myeloid Leukemia

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Disclosure

Michael Deininger, MD, PhD has affiliations with: Ariad, Bristol Myers Squibb, CTI BioPharma Corp., Gilead, Incyte, Novartis, and Pfizer.

LIVING WITH CHRONIC MYELOID LEUKEMIA

SOME GUIDANCE FOR PATIENTS AND CAREGIVERS

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CML Pioneers

Alfred Donné
1844

John Bennet
1845

Rudolf Virchow
1845

Outline

1. How CML is diagnosed
2. How CML is treated
3. How to deal with side effects
4. When can therapy be stopped?

CML Basics

- 1-1.5 cases/100,000 per year
- Median age > 60 years (developed world)
- More frequent in men (1.5-fold)
- Not heritable and no ethnic or racial differences
- Risk factor: radiation

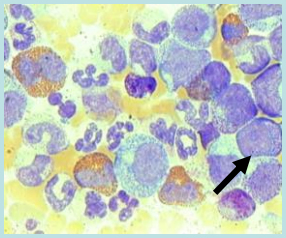
Chronic Myeloid Leukemia – A Typical Case

- A 38-year old sees his primary care provider because of night sweats, fatigue, weight loss and pain in his left belly
- Physical exam reveals a large spleen
- A complete blood count shows:

  Hemoglobin (red blood cells): slightly low

  White blood cells: much increased and with immature cells

  Platelets: increased



Initial Testing if CML is Suspected

The minimum needed

- History and physical: record spleen size
- Complete blood count and basic metabolic profile
- Bone marrow aspirate and biopsy
- Chromosome analysis of bone marrow cells

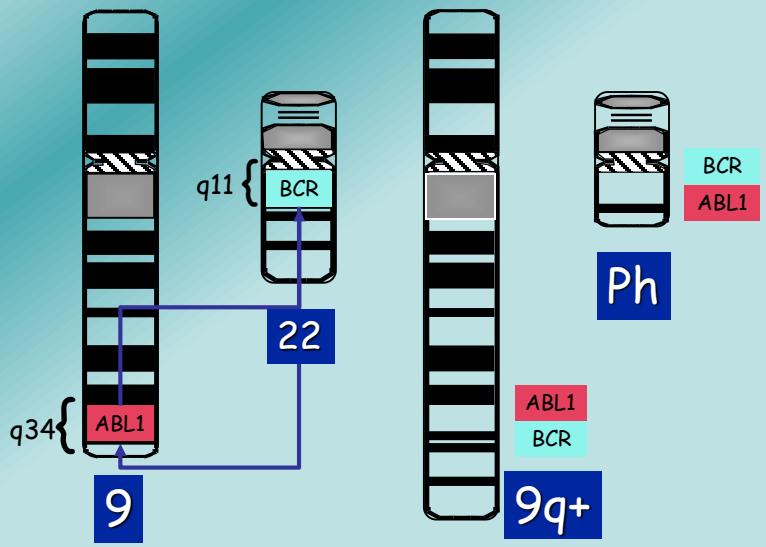
What establishes a diagnosis of CML

- The appearance of the blood smear and bone marrow is typical fro CML
- The bone marrow analysis shows the 'Philadelphia chromosome'
- Sometimes molecular tests are done or needed to establish the diagnosis

  FISH (Fluorescence in situ hybridization)

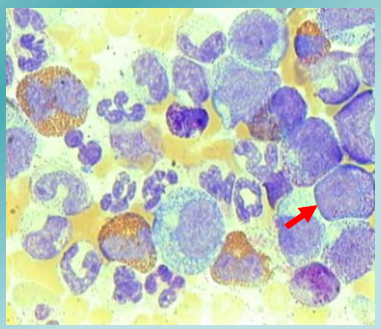
  PCR (Polymerase chain reaction)

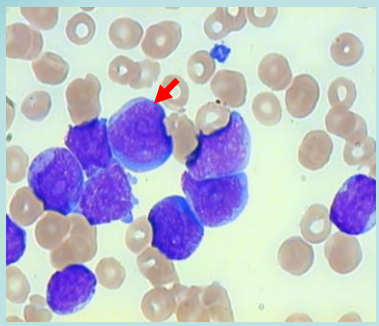
Philadelphia Chromosome: The Cause of CML



CML Phases (Stages)

Chronic Phase → Blastic Phase





- Maturation lost
- Additional mutations
- Rapidly fatal

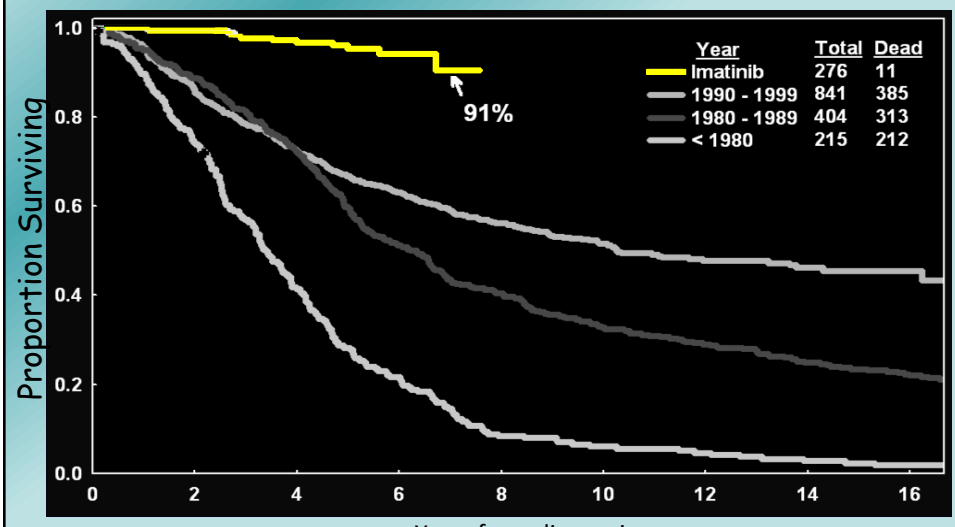
CML Therapy

Hydroxyurea: Only initially to lower the white blood cells

Tyrosine kinase inhibitors (TKIs): Long-term therapy

Stem cell transplant (TKIs): In case of TKI failure

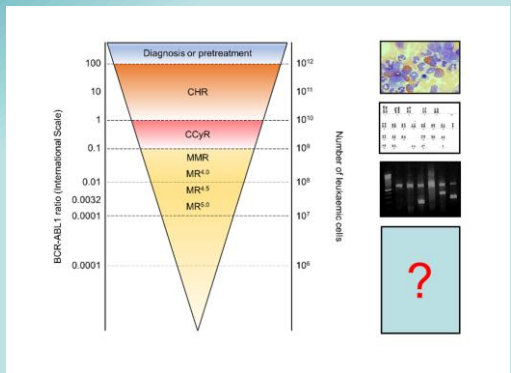
Imatinib Greatly Improved Survival in Chronic Phase CML



Kantarjian H, et al. Blood. 2012;119(9):1981

Disease Burden & Monitoring

Complete hematologic response: blood counts and spleen normal
Complete cytogenetic response: bone marrow chromosomes normal
Major molecular response: >1,000-fold reduction of CML cells
Deep molecular response: >10,000-fold reduction of CML cells



Recommended Monitoring

	At diagnosis	On therapy	At failure
Bone Marrow karyotyping	yes	At 3, 6, 12 months or until CCyR, then annually	yes
qPCR (blood) for BCR-ABL1(IS)	yes	Every 3 months until MMR, then every 3-6 months	yes
FISH	no	If CCyR documented and qPCR IS unavailable	no
BCR-ABL1 mutation screen	no	no	no

Baccarani et al. Blood. 2013;122(6):872-84.

Therapeutic Milestones

Month		Optimal	Warning	Failure
3	ELN	Ph+≤35% or BCR-ABL1<10%	Ph+ 65-95% or BCR-ABL1>10%	No CHR or Ph+>95%
	NCCN	Ph+≤35% or BCR-ABL1≤10%	NA	Ph+>35% or BCR-ABL1>10%
6	ELN	Ph+0% and/or BCR-ABL1<1%	Ph+1-35% and/or BCR-ABL1 1-10%	Ph+>35% and/or BCR-ABL1 >10%
	NCCN	Ph+≤35% or BCR-ABL1≤10%	NA	Ph+>35% or BCR-ABL1>10%
12	ELN	BCR-ABL1 <0.1%	BCR-ABL1 0.1-1%	Ph+ >0% BCR-ABL1 >1%
	NCCN	Ph+ 0%	NA	Ph+ >0%

Baccarani et al. Blood. 2013;122(6):872-84. Radich et al. J Natl Compr Canc Netw. 2014;12(11):1590-610

CML Therapy – Available TKIs

Generic name	Brand name	Generation	Indication
Imatinib	Gleevec	1	First line
Dasatinib	Sprycel	2	First line & imatinib resistance
Nilotinib	Tasigna	2	First line & imatinib resistance
Bosutinib	Bosulif	2	Imatinib resistance
Ponatinib	Iclusig	3	If other TKIs are not indicated

It can be necessary to switch from one TKI to another because of side effects.

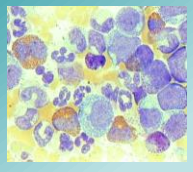
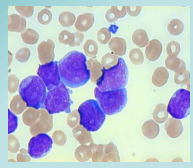
I've been diagnosed with CML. Which TKI should my doctor pick?

Things to consider

- Am I in the chronic phase?
- Am I in the chronic phase, but high risk?
- What other medical conditions do I have?
- What is my lifestyle?

High Risk CML

1. Chronic phase but aggressive with immature cells, high platelet count, big spleen.
2. Accelerated phase or blastic phase

- Treatment must be with a 2-generation TKI
- Stem cell transplant may be necessary
- Early referral to a center is important

Past Medical History

	IM	NIL	DAS	BOS	PON
Diabetes					
POAD					
CHF					
Prolonged QT					
PHT					
GI Bleeding					
IBS					
Pancreatitis					
Impaired LF					
Thrombembolism					

Problems Potential

- Low
- Somewhat elevated
- Elevated
- Typically contraindicated

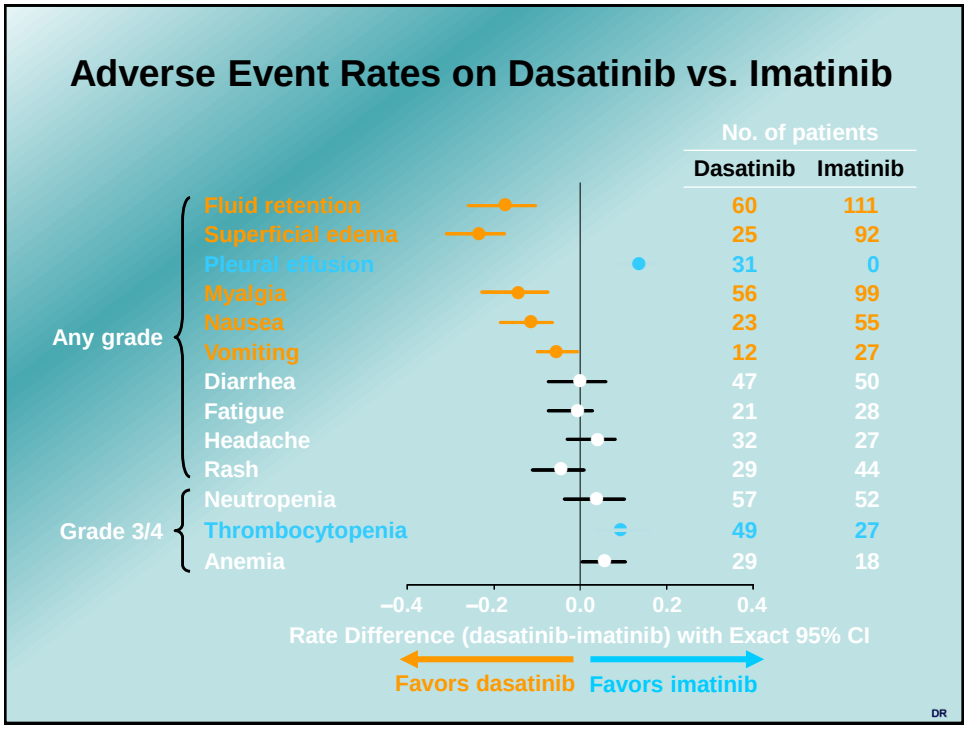
- Few absolute contraindications
- Many better or worse picks
- Clinical judgment crucial

Side Effects of TKI Therapy

Things to consider

- Prior to imatinib average survival with drug therapy was 5 years.
- Stem cell transplant can cause severe side effects or even death.
- All TKIs have side effects.
- Supportive care can frequently mitigate side effects.
- For the provider it's very important to understand which symptoms are related to the TKI and which are not.

Avoid rapid switching from one TKI to the next or you may quickly run out of options.



ENESTnd: Nilotinib vs Imatinib in CML-CP

Study Drug-Related Non-Laboratory Adverse Events (≥ 10% in Any Group)

% of Patients Treated	Nilotinib 300 mg BID n = 279		Nilotinib 400 mg BID n = 277		Imatinib 400 mg QD n = 280	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	14	< 1	21	1	34	0
Diarrhea	8	< 1	7	0	26	1
Vomiting	5	0	9	1	18	0
Peripheral edema	5	0	6	0	15	0
Facial edema	< 1	0	2	0	11	< 1
Eyelid edema	< 1	0	2	< 1	16	< 1
Periorbital edema	< 1	0	1	0	14	0
Muscle spasms	8	0	7	< 1	27	< 1
Rash	32	< 1	37	3	13	2
Headache	14	1	22	1	9	< 1
Pruritus	16	< 1	13	< 1	6	0
Alopecia	9	0	13	0	5	0
Myalgia	10	< 1	10	0	11	0
Fatigue	11	0	9	< 1	10	< 1

- At the 24-month data cut-off, one patient in the imatinib arm had a QTcF > 500 msec but no patient in any of the nilotinib arms had a QTcF > 500 msec
- No patients in the study had a decrease in LVEF < 45%

Data cut-off: 20Aug2010

Hughes TP, et al. ASH 2010. Abstract 207.

Survival on Imatinib and Nilotinib at 6 Years

	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg QD (n = 283)
Total deaths on study, n[a]	21	11	23
KM-estimated 6-year OS on study (95% CI), %	91.6 (88.0-95.1)	95.8 (93.4-98.2)	91.4 (88.0-94.7)
Hazard ratio vs imatinib (95% CI)	0.8934 (0.4944-1.6143)	0.4632 (0.2258-0.9503)	–
Nominal *P* value vs imatinib	.7085	.0314	–
Deaths due to advanced CML, n	6	4	16
KM-estimated 6-year freedom from death due to advanced CML (95% CI), %	97.7 (96.0-99.5)	98.5 (97.1-100)	93.9 (91.0-96.8)
Hazard ratio vs imatinib (95% CI)	0.3694 (0.1445-0.9440)	0.2433 (0.0813-0.7279)	–
Nominal *P* value vs imatinib	.0302	.0061	–

Larson RA, et al. *Blood*. 2014:[abstract 4541].

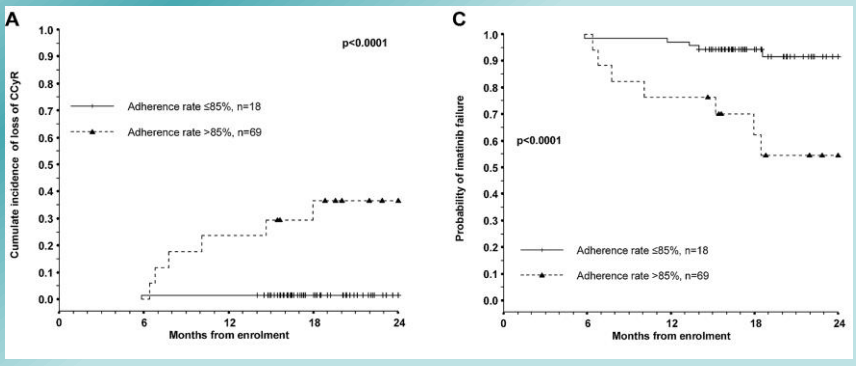
Survival on Imatinib vs. Dasatinib at 5 Years

	Dasatinib 100 mg QD (n=259)	Imatinib 400 mg QD (n=260)	Hazard ratio (95% CI)
Total number of deaths,[a] n	26	26	–
Estimated 5-year OS,[a] % (95% CI)	90.9 (86.6-93.8)	89.6 (85.2-92.8)	1.01 (0.58-1.73)
Estimated 5-year PFS,[a] % (95% CI)	85.4 (80.3-89.2)	85.5 (80.4-89.4)	1.06 (0.68-1.66)

[a]On study treatment and in follow-up after discontinuation of randomized treatment.
CI = confidence interval; OS = overall survival; PFS = progression-free survival.

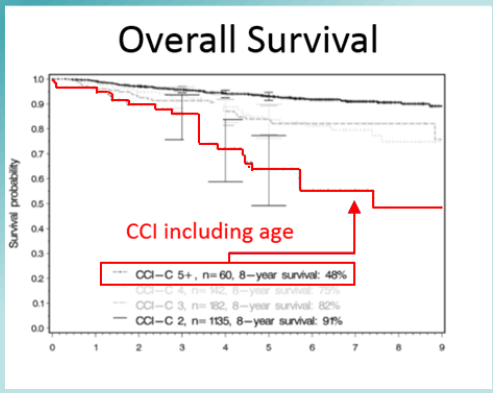
Cortes JC, et al. *Blood*. 2014

Adherence to Therapy is Crucial For Avoiding Failure



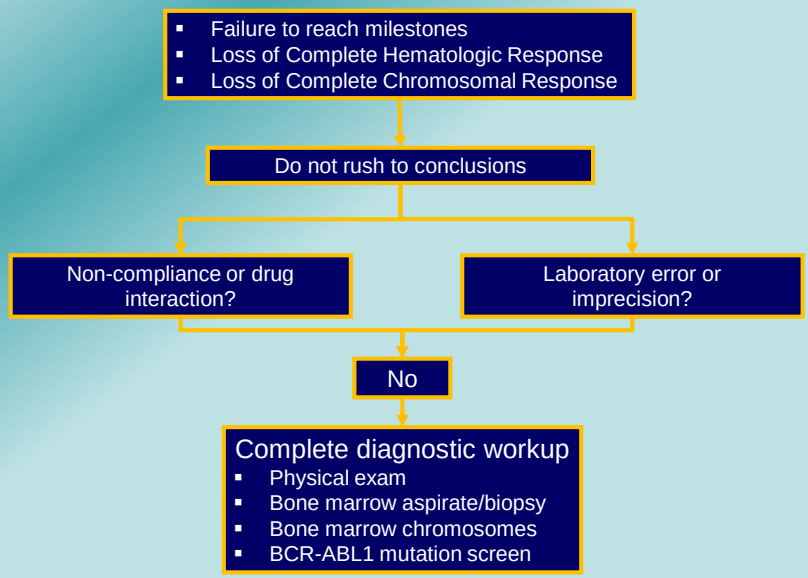
Amr R. Ibrahim et al. Blood 2011;117:3733-3736

Well-managed CML Impacts Survival Less Than Comorbidities



Saussele et al. Blood. 2015;126(1):42-9

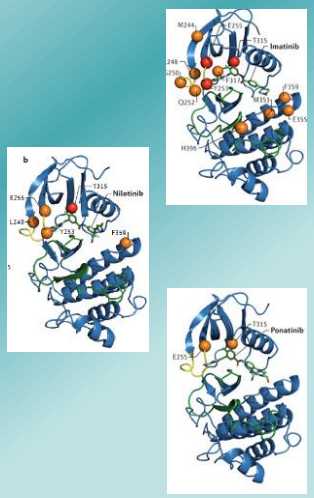
Recognizing Therapy Failure



Factors Influencing Selection of Salvage Therapy

- Disease phase (chronic or blastic)
- BCR-ABL1 mutation analysis
- Previous treatment history
- Past medical history

Resistance Due to BCR-ABL1 Point Mutations



Imatinib

Nilotinib
Bosutinib
Dasatinib

Ponatinib

TKI Resistance

Single BCR-ABL1 Mutants

T315I

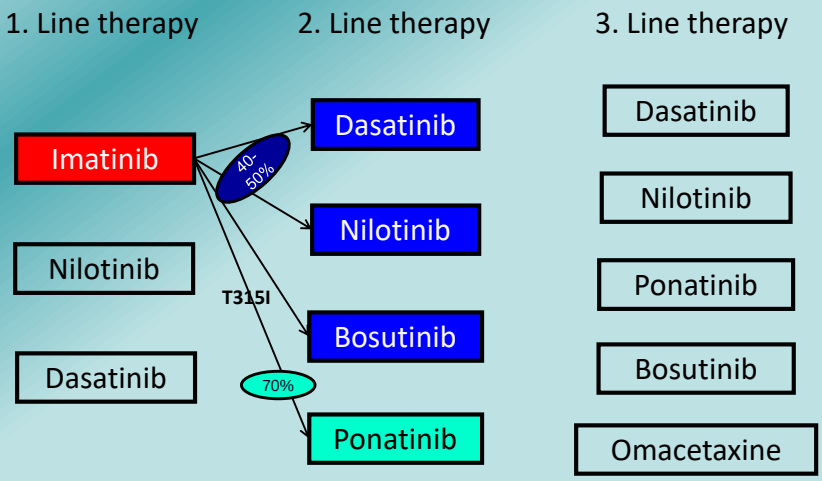
Relatively resistant
Completely resistant

O'Hare et al. Nat Rev Cancer. 2012;12(8):513-26

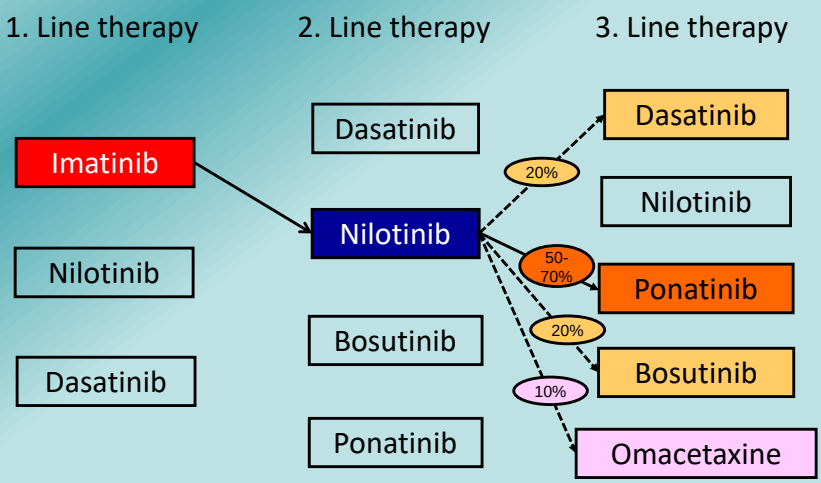
Second Line Therapy: Treatment History is Important

1. Line therapy	2. Line therapy	3. Line therapy
Imatinib	Dasatinib	Dasatinib
Nilotinib	Nilotinib	Nilotinib
Dasatinib	Bosutinib	Ponatinib
	Ponatinib	Bosutinib
		Omacetaxine

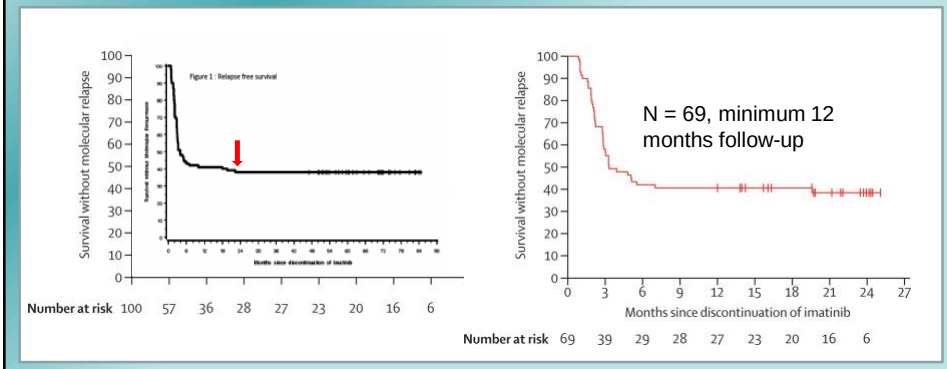
Treatment History and Salvage Therapy – Likelihood of a Complete Chromosomal Response



Treatment History and Salvage Therapy – Likelihood of a Complete Chromosomal Response



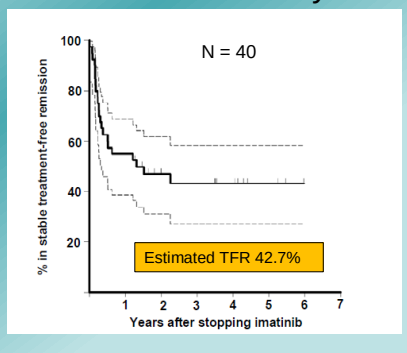
Treatment-Free Remission (TFR)



Mahon et al. Lancet Oncol. 2010;11(11):1029-35

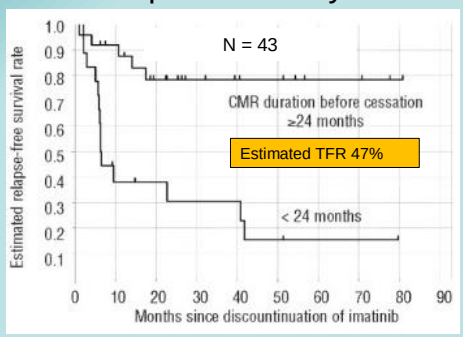
Maintenance of Deep Molecular Response After TKI Discontinuation in ~ 40% of Patients

Australian Study



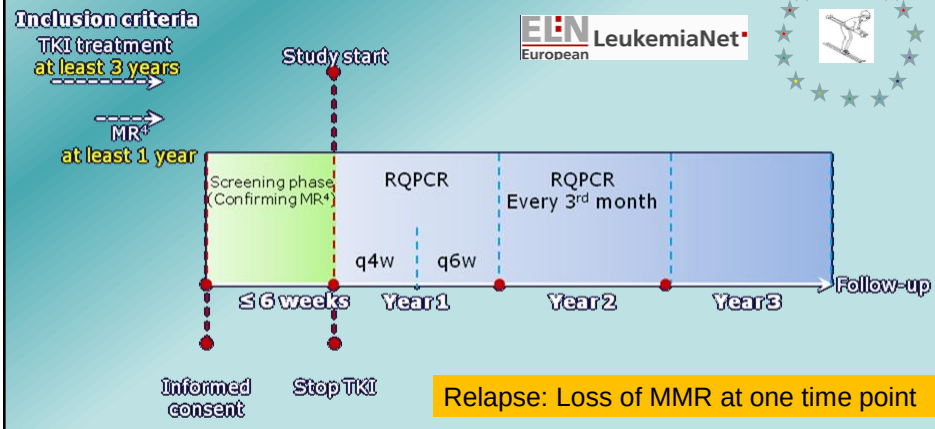
Ross et al. Blood. 2013;122(4):515-22

Japanese Study



Takahshi et al. Haematologica. 2012;97(6):903-6

EuroSKI Study

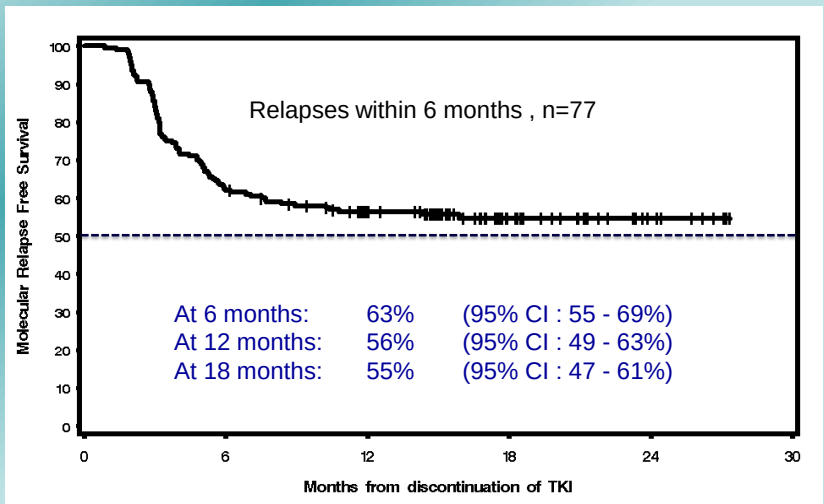


Relapse: Loss of MMR at one time point

Mahon et al. Blood 2014;124:812 (abstract)

Recurrence-Free Survival

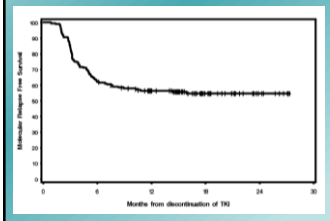
200 interim patients – overtime, loss MMR=89

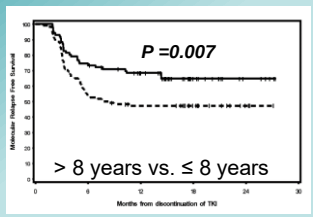


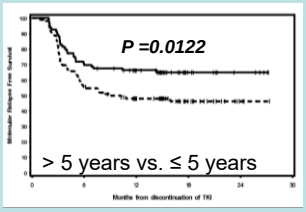
Mahon et al. Blood 2014;124:812 (abstract)

Longer Duration of Imatinib Exposure and of Deep Molecular Response Predict TFR

200 interim patients – overtime, loss MMR=89







Mahon et al. Blood 2014;124:812 (abstract)

Factors Associated with TFR in Various Studies

- Exposure to IFN-α
- Low Sokal risk
- Longer TKI treatment duration
- Longer duration of deep response

Mahon et al. Blood 2014;124:812 (abstract)

Withdrawal Syndrome Accompanies TKI Discontinuation in Some Patients

EuroSKI:

- 222 AEs in 98 patients reported
- 57 AEs in 31 patients were related to treatment stop, no grade 4

	Patients Grade 1-4 n	Patients Grade 3 n	AEs Grade 1-4 n	AEs Grade 3 n
Musculoskeletal pain, joint pain, arthralgia	23	3	39	6
Other (sweating, skin disorders, folliculitis, depressive episodes, fatigue urticaria, weight loss)	8	0	18	3

- Musculoskeletal pain in CML patients after discontinuation of imatinib: a tyrosine kinase inhibitor withdrawal syndrome? J. Richter et al. J Clin Oncol. 2014 Sep 1;32(25):2821-3
- The Life After TKI Study (LAST; NCT02269267) will specifically look into this
- Patients with chronic myelogenous leukemia may not want to discontinue tyrosine kinase inhibitor therapy (#1584, poster, Saturday)

ELN European LeukemiaNet

Treatment-Free Remission – When is it Safe to Try?

Patients who progressed to accelerated or blastic phase or became resistant to a TKI at any time are not candidates.

Otherwise patients considered for TRF must

1. Have completed at least 3 years of TKI therapy.
2. Have maintained a deep molecular response for the past 2 years.
3. Have had dense PCR monitoring for the past 2 years (at least every 3 -4 months).
4. Be willing to have frequent (initially monthly) lab monitoring
5. Be willing to go back on therapy if they relapse.

Prior consultation of or referral to a CML center or consultation is recommended.

Summary

- Patients with well-managed chronic phase CML can expect a normal life span.
- Dasatinib, nilotinib and imatinib are acceptable options for frontline therapy of chronic phase.
- Dasatinib and nilotinib should be considered in patients with high risk chronic phase CML.
- In case of side effects, try to manage with supportive care and/or dose reductions, before switching to another TKI.

Summary (continued)

- Failure of first line TKI therapy is a significant event and needs careful workup and a decisive management strategy.
- Progression to accelerated or blastic phase should trigger a referral to a center
- Treatment free remission is safe only if attempted in the right patients and with proper monitoring; consultation of a center is recommended.

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

UNIVERSITY OF UTAH SCHOOL OF MEDICINE Department of Medicine

Q&A Session

Ask a question by phone:

- Press star (*) then the number 1 on your keypad.

Ask a question by web:

- Click “Ask a question”
- Type your question
- Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

- **What to ask:** Questions to ask your treatment team: **www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/booklets**
- **Past CML education programs: www.LLS.org/programs**
- **Financial Assistance Program for CML patients: www.LLS.org/cml**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL: infocenter@LLS.org**
  - **TOLL-FREE PHONE: (800) 955- 4572**