WELCOME & INTRODUCTIONS

Chronic Myeloid Leukemia (CML): Know Your Options

To register or to view the 'Save the Date' BCC schedule, visit www.LLS.org/bcc.

New York/New Jersey Blood Cancer Conference	**Pennsylvania Blood Cancer Conference**
New York Marriott Marquis New York, NY October 5, 2019	Double Tree Pittsburgh-Cranberry Mars, PA November 2, 2019

Program will begin shortly

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CHRONIC MYELOID LEUKEMIA: KNOW YOUR OPTIONS

Kendra Sweet, MD, MS
Assistant Member, Department of Malignant Hematology
Moffitt Cancer Center
Tampa, FL

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DISCLOSURES

Chronic Myeloid Leukemia (CML): Know Your Options

Kendra Sweet, MD, MS, has affiliations with Abbvie, Agios, Astellas, Bristol Meyer Squibb (*Advisory Board*); Pfizer, Stemline (*Consultant*); Incyte (*Grant Support*); Celgene, Jazz, Novartis (*Speakers Bureau*).

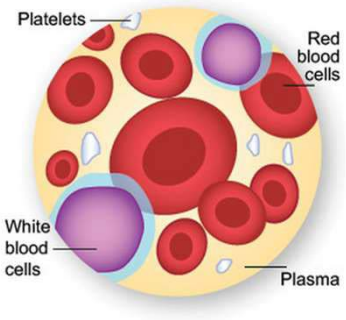
ABOUT BLOOD

Blood cells

- White blood cell (fights infection)
- Red blood cell (carries oxygen)
- Platelet (helps blood to clot)

Plasma

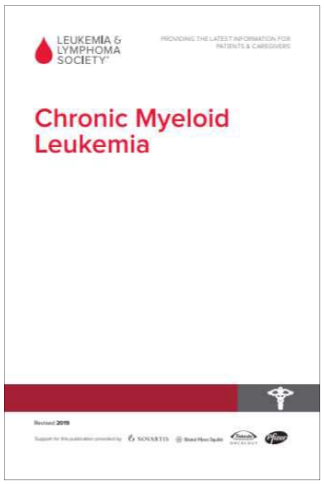
- The liquid part of the blood
- Mostly water
- Vitamins, minerals, proteins, hormones and other natural chemicals



Slide courtesy of the Leukemia and Lymphoma Society

WHAT IS LEUKEMIA?

Leukemia is a type of cancer of the bone marrow and blood.



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ABOUT CHRONIC MYELOID LEUKEMIA

- CML results from an acquired (not present at birth) genetic injury to the DNA of a single bone marrow cell.
- The mutated cell multiplies into many cells (CML cells).
- The result of the uncontrolled growth of CML cells in the bone marrow is an increase in the number of CML cells in the blood.

Slide courtesy of the Leukemia and Lymphoma Society

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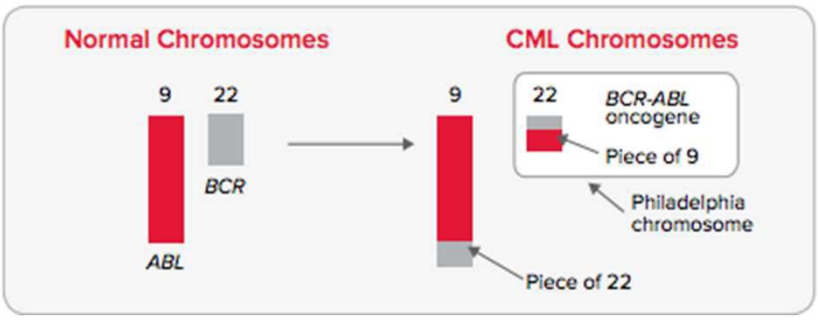
THE *BCR-ABL* CANCER-CAUSING GENE (ONCOGENE)



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CAUSES/RISK FACTORS

- Caused by an injury to the DNA of a single bone marrow cell
- Slight increase in risk from exposure to very high doses of radiation, such as an atomic bomb blast
- Slight increase in risk from high-dose radiation therapy for other cancers, such as lymphoma

Slide courtesy of the Leukemia and Lymphoma Society

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PHASES OF CML

There are 3 phases of CML:

- **Chronic phase**
  - less than 10% of the cells in the blood and bone marrow are immature white blood cells (blasts)
- **Accelerated phase**
  - the number of blast cells in the blood and/or marrow is higher than normal
- **Blast crisis phase**
  - the number of blast cells increases in both the blood and bone marrow

Slide courtesy of the Leukemia and Lymphoma Society

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CML TREATMENT GOALS

For people with **chronic phase CML**, the goals of treatment are to:

- Return blood counts to normal levels
- Kill cells that have the *BCR-ABL* gene
- Prevent progression to advanced phases of CML

For people with both **accelerated** and **blast crisis phases of CML** the goal of therapy is to:

- Kill cells that contain the BCR-ABL gene
- Return the disease to chronic phase

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COMMON MISCONCEPTIONS

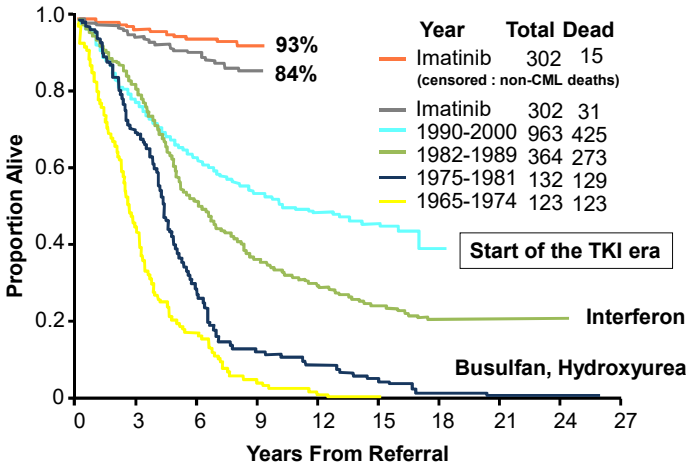
1. I must get to the point at which my PCR results are undetectable otherwise I am failing treatment
2. If I only miss a few doses of my TKI per month, that will be insignificant
3. I must remain on my TKI forever

MISCONCEPTION #1:

I must get to the point at which my PCR results are undetectable otherwise I am failing treatment

- Primary goal of treating chronic phase CML is preventing the progression to advanced phase CML
- Do not need to be undetectable to successfully prevent progression

SURVIVAL IN EARLY CP-CML



The University of Texas M.D. Anderson Cancer Center database.

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TYPES OF RESPONSE

Hematologic

- *Complete hematologic response (CHR)*
  - Blood counts completely return to normal
  - No blast cells in the peripheral blood
  - No signs/symptoms of CML (spleen returns to normal size)

Cytogenetic

- *Complete cytogenetic (CCyR)*
  - No Ph chromosomes detected
- *Partial cytogenetic response (PCyR)*
  - 1%-35% of cells have Ph chromosome

Slide courtesy of the Leukemia and Lymphoma Society

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TYPES OF RESPONSE

Cytogenetic (cont'd)

- *Major cytogenetic response*
  - 0%-35% of cells have Ph chromosome
- *Minor cytogenetic response*
  - More than 35% of cells have the Ph chromosome

Molecular

- *Complete molecular response (CMR)*
  - No BCR-ABL gene detectable
- *Major molecular response (MMR)*
  - At least a 3-log reduction in BCR-ABL levels or BCR-ABL 0.1%

Slide courtesy of the Leukemia and Lymphoma Society

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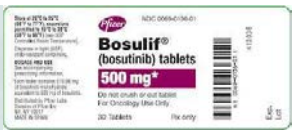
TREATMENT OPTIONS IN CML IN 2019

First Generation TKI
2001

Second Generation TKIs

2006

2007



2012

Third Generation TKI
2012

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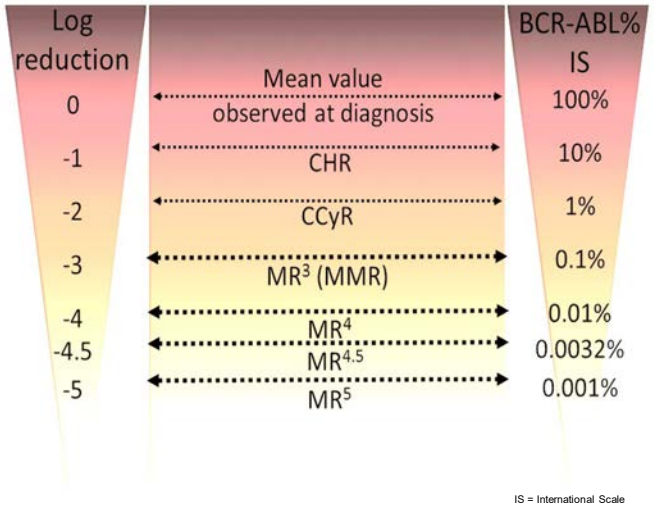
DEPTH OF RESPONSE



IS = International Scale

Baccarani M et al. Am Soc Clin Oncol Educ Book. 2014:167-75

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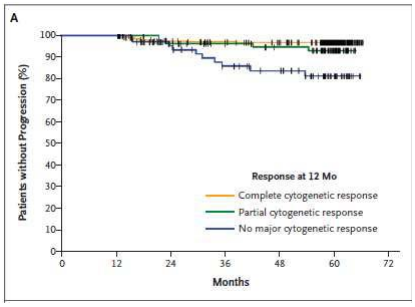
FIVE YEAR PROGRESSION TO ADVANCED PHASE CML BASED ON RESPONSE AT 12 MONTHS

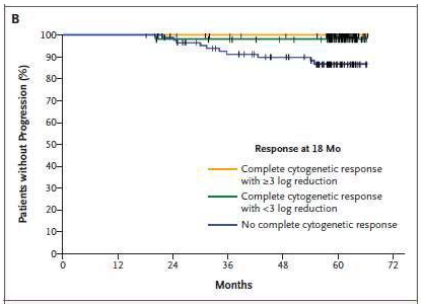


Five Year Freedom From Progression Based on 12 Month Response

CCyR – 97%
PCyR – 93%
No MCyR – 81%

Not significantly different

Significant difference



Five Year Freedom From Progression Based on 12 Month Reponse

CCyR and MMR – 100%
CCyR without MMR – 98%
No CCyR – 87%

Not significantly different

Significant difference

Druker B. NEJM 355;23 Dec 7, 2006 2408-17

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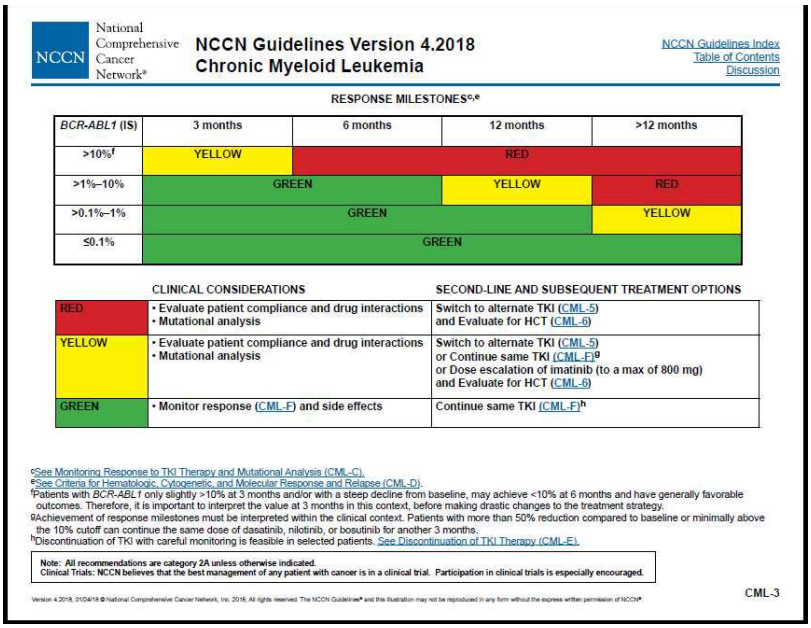

National Comprehensive Cancer Network

NCCN Guidelines Version 4.2018
Chronic Myeloid Leukemia

NCCN Guidelines Index
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Discussion

RESPONSE MILESTONES[c,e]

BCR-ABL1 (IS)	3 months	6 months	12 months	>12 months
>10%[f]	YELLOW	RED		
>1%–10%	GREEN		YELLOW	RED
>0.1%–1%	GREEN			YELLOW
≤0.1%	GREEN			

	CLINICAL CONSIDERATIONS	SECOND-LINE AND SUBSEQUENT TREATMENT OPTIONS
RED	• Evaluate patient compliance and drug interactions • Mutational analysis	Switch to alternate TKI (CML-5) and Evaluate for HCT (CML-6)
YELLOW	• Evaluate patient compliance and drug interactions • Mutational analysis	Switch to alternate TKI (CML-5) or Continue same TKI (CML-F)[g] or Dose escalation of imatinib (to a max of 800 mg) and Evaluate for HCT (CML-6)
GREEN	• Monitor response (CML-F) and side effects	Continue same TKI (CML-F)[h]

[c] See Monitoring Response to TKI Therapy and Mutational Analysis (CML-C).
[e] See Criteria for Hematologic, Cytogenetic, and Molecular Response and Relapse (CML-D).
[f] Patients with *BCR-ABL1* only slightly >10% at 3 months and/or with a steep decline from baseline, may achieve <10% at 6 months and have generally favorable outcomes. Therefore, it is important to interpret the value at 3 months in this context, before making drastic changes to the treatment strategy.
[g] Achievement of response milestones must be interpreted within the clinical context. Patients with more than 50% reduction compared to baseline or minimally above the 10% cutoff can continue the same dose of dasatinib, nilotinib, or bosutinib for another 3 months.
[h] Discontinuation of TKI with careful monitoring is feasible in selected patients. See Discontinuation of TKI Therapy (CML-E).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CML-3

National Comprehensive Cancer Network CML Guidelines version 4.2018. www.nccn.org

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MISCONCEPTION #2:

If I only miss a few doses of my TKI per month, that will be insignificant

- The extent to which people adhere to the prescribed dosing schedule of oral anti-cancer therapy ranges from 16% - 100% depending on the specific treatment and method of assessment
- Many studies have looked at adherence to treatment and assessed the impact of missed doses on responses
- Data suggests that there is a significant decrease in the number of patients achieving deep molecular responses when adherence to treatment is <90%

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CORRELATION BETWEEN ADHERENCE RATE AND RESPONSE TO TREATMENT

Adherence is strongly associated with achievement of MMR, MR4.0 and CMR at 18 months and 6 years

Table 2. Six-Year Probability of MMR, 4-Log Reduction in Transcript Levels, and CMR and Degree of Adherence

		Six-Year Probability of Response					
		MMR		4-Log Reduction		CMR	
Adherence Rate (%)	No. of Patients	%	*P*	%	*P*	%	*P*
≥100	36	91.1	.01	79.9	.02	46.7	.02
≤ 99	51	58.6		38.6		22.7	
> 95	57	94.5	< .001	77.2	< .001	45.2	.002
≤ 95	30	29.3		15.0		8.2	
> 90	64	93.7	< .001	76.0	< .001	43.8	.002
≤ 90	23	13.9		4.3		0	
> 85	69	85.8	< .001	69.2	.001	40.8	.007
≤ 85	18	11.8		5.6		0	
> 80	75	81.2	.001	63.8	.005	37.1	.04
≤ 80	12	0		0		0	

NOTE. The median adherence rates for patients with a rate of ≤ 99%, ≤ 95%, ≤ 90%, ≤ 85%, and ≤ 80% were 93.5%, 81.7%, 76.0%, 73.9%, and 63.1%, respectively.
Abbreviations: MMR, major molecular response; CMR, complete molecular response.

Marin D. Journal of Clinical Oncology. Col 28;14. May 10, 2010. 2381-2388

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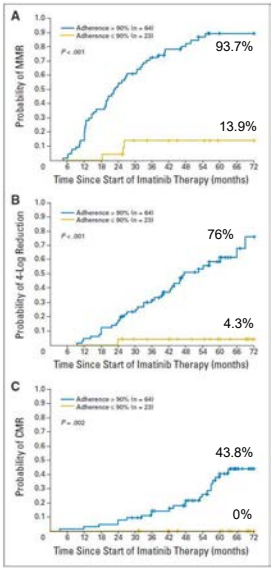
90% ADHERENCE IS SIGNIFICANT

- Analysis found only 2 factors predictive of response
  1. Adherence to treatment
  2. Levels of a drug transport molecule called OCT1
- More specific analyses found that adherence was the only predictive factor
- Adherence was significantly lower when the dose of imatinib was increased
- Adherence was significantly lower in younger patients compared to older patients
- No CMRs were observed when adherence was ≤90%.
- No MMRs were observed when adherence was ≤80%



Marin D. Journal of Clinical Oncology. Col 28;14. May 10, 2010. 2381-2388

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REASONS FOR NON-ADHERENCE

- A study of 413 patients found the primary drivers for adherence were social support and concomitant medication.
- The primary reason for non-adherence was lack of information provided to the patients about CML.

Efficace F. British Journal of Cancer 2010 107(6):904-909

PATIENT-DRIVEN SURVEY ON TKI ADHERENCE

- **2546 people with CML worldwide**
  - 32.7% were highly adherent
  - 46.5% were moderately adherent
  - 20.7% were in the low adherence group
- **Men were significantly more adherent than women**
- **Older patients were significant more adherent than younger patients**
- **Adherence was higher during the first year after diagnosis and declined over time**
- **Only requiring one pill per day led to better adherence**
- **Side effect management resulted in better adherence**
  - Not the fact of having side effects, but the quality of side effect management
- **Feeling well informed about CML by their doctor**

Geissler J. J Cancer Res Clin Oncol 2017 143:1167-1176

PATIENT EDUCATION

- **Satisfaction with the information provided by the CML doctor correlated with adherence rates**
  - Information provided about the risks of non-adherence did not influence adherence
  - General information about the diagnosis and treatment was significant
- **This suggests that merely instructing patients rather than informing and empowering them is not beneficial to improving adherence and therefore improving responses**

Geissler J. J Cancer Res Clin Oncol 2017 143:1167-1176

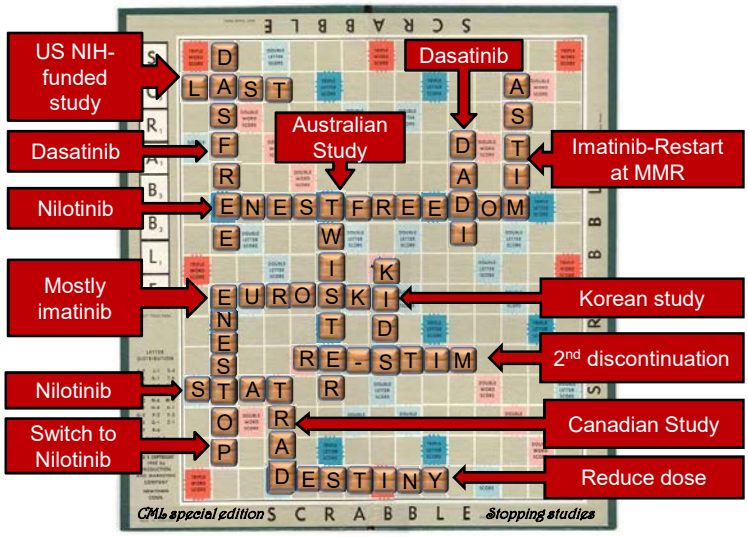
DOCTOR-PATIENT RELATIONSHIP

- This speaks to the importance of a good doctor-patient relationship
- Patients need to feel comfortable with their doctor and feel as if they can openly ask questions and explain their concerns

Geissler J. J Cancer Res Clin Oncol 2017 143:1167-1176

MISCONCEPTION #3:
I Must Remain on My TKI Forever

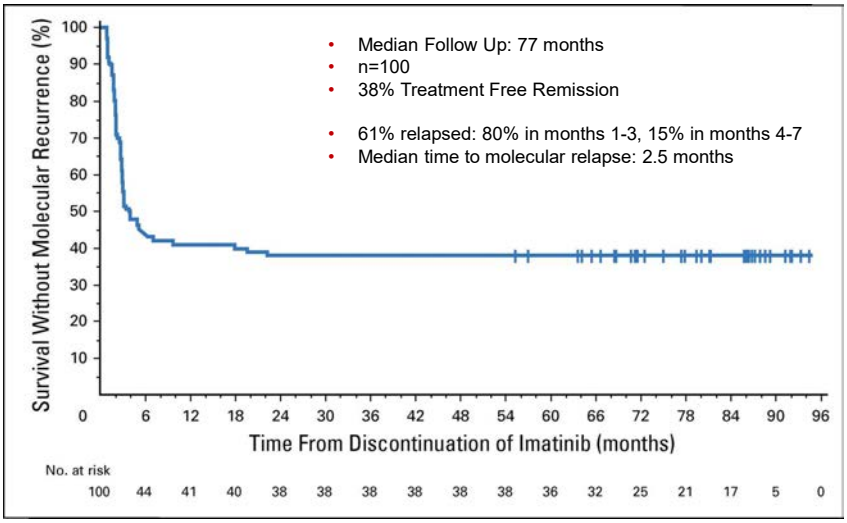
- **Many studies have been done asking the question "can TKIs ever be stopped in people with CML?"**
  - The short answer is YES!!
- **First treatment free remission (TFR) study was the STIM1 trial in France**



> 2000 patients enrolled on stopping studies

Slide borrowed from Ehab Atallah, MD, Medical College of Wisconsin

LONG TERM FOLLOW UP FROM STIM



- Median Follow Up: 77 months
- n=100
- 38% Treatment Free Remission

- 61% relapsed: 80% in months 1-3, 15% in months 4-7
- Median time to molecular relapse: 2.5 months

Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

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OUTCOMES IN PATIENTS WITH MOLECULAR RELAPSE

Table 2. MR Patient's Disposition, Treatment, and Molecular Status at the Last Date of Follow-Up

Patient Disposition and Treatment	Patients (n = 61) No.	%	No. of Molecular Responses at Last Available Evaluation ≥ MR4.5	≥ MMR to < MR4.5	< MMR
Alive with TKI therapy	43	70.5	34	6	3
Imatinib	31	50.8	28	2	1
Dasatinib	7	11.4	3	3	1
Nilotinib	4	6.5	3	1	0
Bosutinib	1	1.6	0	1	0
Alive without TKI therapy	14	22.9	10	3	1
Second or third TKI discontinuation*	9	14.7	8	1	0
Discontinuation for TKI-related AE	2	3.2	0	1	1
Without any TKI resumption	3	4.9	2	1	0
Death	4†	6.5	2	2	0

Abbreviations: AE, adverse event; MMR, major molecular response; MR, molecular response; MR4.5, molecular response 4.5-log; TKI, tyrosine kinase inhibitor.
*Twenty-one patients who had achieved a second sustained undetectable molecular residual disease (UMRD) of at least 1 year had a second treatment discontinuation as previously described.[21] Of those patients, 13 had MR leading to treatment resumption, and eight were free from MR with a median follow-up of 11.6 months (range, 0.9 to 21.4 months) after second imatinib discontinuation and without TKIs at last follow-up. Among the 13 MR patients, four achieved a third sustained UMRD and one experienced a third treatment discontinuation without molecular recurrence at the last date of follow-up.
†One patient died as a result of pleural mesothelioma while receiving imatinib. The remaining three patients discontinued TKI therapy because of worsening concomitant disease leading to death (one patient case each of cerebral hemorrhage, metastatic gastric adenocarcinoma, and acute renal failure).

- 57/61 relapsed pts restarted TKIs
- 55 achieved second undetectable status – median time 4.3 months
- No progression to AP/BP
- 14 now alive and off TKIs – 10 in MR4.5
- 4 deaths – none CML related

Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

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MULTIVARIATE ANALYSIS FROM STIM

Two factors predictive of molecular relapse

1. High-risk Sokal score at diagnosis
   - HR 2.22
   - 95% CI 1.11-4.42
   - P=0.024
2. Imatinib duration ≥58.8 months prior to discontinuation
   - HR 0.54
   - 95% CI 0.32-0.92
   - P=0.024

Etienne G. Journal of Clinical Oncology 35, no. 3 (January 2017) 298-305

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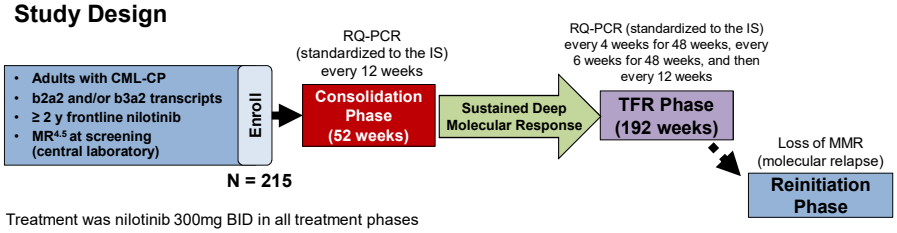
ENESTFREEDOM

Enrollment and Inclusion Criteria	
Total enrollment	n=215
Minimum treatment duration required prior to discontinuation	≥3 years frontline nilotinib
Minimum response required prior to discontinuation	Sustained $MR^{4.5}$ for at least 1 year

- 37.9% of nilotinib 300mg BID treated patients on ENESTnd met the inclusion criteria for attempting TFR on ENESTfreedom

Study Design



Treatment was nilotinib 300mg BID in all treatment phases

Hochhaus A. ASCO Annual Meeting 2016. Abstract #7001

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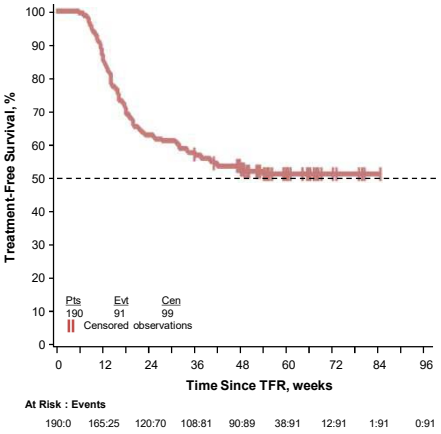
PRIMARY ENDPOINT AND TREATMENT-FREE SURVIVAL

Kaplan-Meier Estimated Treatment-Free Survival[a]



- 190 patients entered the TFR phase
- 51.6% of patients (95% CI, 44.1-58.9%) remained in TFR after 48 weeks

[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to accelerated phase/blast crisis, or death due to any cause.

Hochhaus A. ASCO Annual Meeting 2016. Abstract #7001

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LAST

Life After Stopping TKIs

The LAST study is a national study examining discontinuation in the US

Patients were enrolled from December 2014 through December 2016

Atallah E. European School Of Hematology iCMLf Annual Meeting. 2017

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STUDY DEMOGRAPHICS

Characteristic	N=173
Number Screened	208
Number Enrolled	173
Male/Female	83 (48%)/90 (52%)
Median TKI Duration	79 months (51-117)
TKI	
Imatinib	104 (60%)
Nilotinib	39 (23%)
Dasatinib	26 (15%)
Bosutinib	4 (2%)
Median Follow Up	12.3 mos (0.9-27)

Atallah E. European School Of Hematology iCMLf Annual Meeting. 2017

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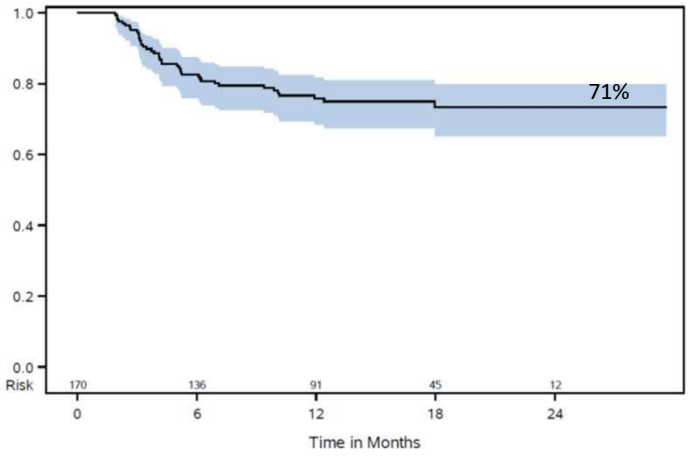
MOLECULAR RECURRENCE FREE SURVIVAL



Molecular recurrence free survival: 71% (based on study criteria)
Treatment free remission: 65% (based on number who restarted drug)

Atallah E. European School Of Hematology iCMLf Annual Meeting. 2017

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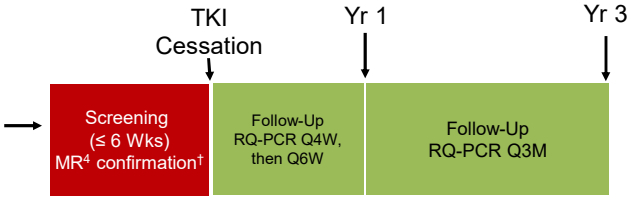
EURO-SKI: STUDY DESIGN

CML pts receiving TKI for ≥ 3 yrs with deep MR* for ≥ 1 yr and no history of TKI failure (N = 755*)



*In primary analysis of 868 preregistered pts.
†MR^4, defined as detectable BCR-ABL ≤ 0.01%, or undetectable BCR-ABL in samples with ≥ 10,000 ABL or ≥ 24,000 GUS transcripts, respectively.

Primary endpoint: molecular recurrence (BCR-ABL > 0.1%, i.e., loss of MMR)

- Largest TFR study to date
- Goal was to establish criteria for TKI discontinuation

Sauselle S, et al. ASH 2017. Abstract 313.

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Slide credit: clinicaloptions.com 37

EURO-SKI: PATIENT POPULATION

- **N = 821 pts recruited**
  - Male: 52%
  - Median age: 60 yrs (range: 19-90)
  - 448 imatinib treated patients
- **N = 755 included in MRFS analysis**
  - MMR loss after TKI cessation: n = 371 (49%)
  - TKI restarted in MMR: n = 13 pts
  - Death in MMR: n = 4 pts

Sauselle S, et al. ASH 2017. Abstract 313.

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Slide credit: clinicaloptions.com 38

EURO-SKI: MOLECULAR RECURRENCE-FREE SURVIVAL

Month	Pts at Risk, n	MRFS, % (95% CI)
6	457	61 (58-65)
12	396	55 (51-58)
18	333	52 (49-56)
24	219	50 (47-54)
36	31	47 (43-51)

Sauselle S, et al. ASH 2017. Abstract 313.

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OUTCOME OF SELECT DISCONTINUATION STUDIES

Study	#	TKI	RFS % (years)
STIM1	100	IFN/Imatinib	38 (7)
TWISTER	40	Imatinib	45 (3.5)
STIM2*	124	Imatinib	46 (2)
Euro-SKI	750	Imatinib	52 (2)
Dasfree	130	Dasatinib	63 (1)
ENESTfreedom	190	Nilotinib	52 (4)
LAST	173	Imatinb/Das/Nil/Bos	66 (1)

*No prior therapy with IFN, **21 patients had prior HCT, Das: Dastainib, Nil: Nilotinib, Bos: Bosutinib

Etienne G et al. J Clin Oncol.2017
Ross et al. Blood 2013 122:515-522
Mahon FX, *et al.* ASH Annual Meeting abstracts 2013
Mahon FX, *et al.* ASH Annual Meeting abstracts 2016
Shah N et al. ASH Annual Meeting abstracts 2016
Hochhaus A et al. ASH Annual Meeting abstracts 2016
Atallah E et al. ASH Annual Meeting abstracts 2017

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Chronic Myeloid Leukemia

NCCN Guidelines Index
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Discussion

DISCONTINUATION OF TKI THERAPY[1]

- Discontinuation of TKI therapy appears to be safe in select CML patients.
- Clinical studies that have evaluated the safety and efficacy of TKI discontinuation have employed strict eligibility criteria and have mandated more frequent molecular monitoring than typically recommended for patients on TKI therapy.
- Some patients have experienced significant adverse events that are believed to be due to TKI discontinuation.
- Discontinuation of TKI therapy should only be performed in consenting patients after a thorough discussion of the potential risks and benefits.
- Outside of a clinical trial, TKI discontinuation should be considered only if ALL of the criteria included in the list below are met.

Criteria for TKI Discontinuation

- Age ≥18 years.
- Chronic phase CML. No prior history of accelerated or blast phase CML.
- On approved TKI therapy (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) for at least three years.
- Prior evidence of quantifiable *BCR-ABL1* transcript.
- Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least four tests, performed at least three months apart.
- Access to a reliable qPCR test with a sensitivity of detection at least MR4.5 (BCR-ABL1 ≤ 0.0032% IS) and provides results within 2 weeks.
- Monthly molecular monitoring for one year, then every 6 weeks for the second year, and every 12 weeks thereafter (indefinitely) is recommended for patients who remain in MMR (MR3; *BCR-ABL1* ≤0.1% IS) after discontinuation of TKI therapy.
- Prompt resumption of TKI within 4 weeks of a loss of MMR with molecular monitoring every 4 weeks until MMR is re-established, then every 12 weeks thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after three months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another six months.
- Consultation with a CML Specialty Center to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.
- Reporting of the following to a member of the NCCN CML panel is strongly encouraged:
  - Any significant adverse event believed to be related to treatment discontinuation.
  - Progression to accelerated or blast phase CML at any time.
  - Failure to regain MMR after three months following treatment reinitiation.

[1]See full prescribing information for nilotinib: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022068s026lbl.pdf

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CML-E

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Q&A SESSION

Chronic Myeloid Leukemia (CML): Know Your Options

- **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.

FREE LLS EDUCATION & SUPPORT RESOURCES

- **Information Specialists**

  Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.
  - **EMAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572
- **Additional Information about Leukemia:**
  - www.LLS.org/leukemia
- **Education Booklets:**
  - www.LLS.org/booklets
- **Telephone/Web Programs:**
  - www.LLS.org/programs
- **Weekly CML Online Chat:**
  - www.LLS.org/chat

LLS EDUCATION & SUPPORT RESOURCES

- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

- **Free Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

- **What to Ask**

  Questions to ask your treatment team: www.LLS.org/whattoask

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support

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THANK YOU

We have one goal: A world without blood cancers

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