SPOTLIGHT ON CHRONIC MYELOID LEUKEMIA (CML)

Ehab Atallah, MD
Michael J. Mauro, MD
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LEUKEMIA & LYMPHOMA SOCIETY®

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WELCOMING REMARKS

SPOTLIGHT ON CHRONIC MYELOID LEUKEMIA (CML)

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Sr. Director, Education & Support
The Leukemia & Lymphoma Society

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DISCLOSURES

SPOTLIGHT ON CHRONIC MYELOID LEUKEMIA (CML)

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DISCLOSURES

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BMS *(Speaker Bureau);* Novartis, Pfizer, Takeda *(Consultant);* Novartis *(Grant Support)*; Novartis, Takeda *(Research Funding).*

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Astella, BerGen Bio, BMS, Curis, Gilead, Mayblytics and Novartis *(Consultant)*; Incyte *(Grant Support)*.

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Overview

- History of CML
- Choice of first line
- Second line therapy
- Future direction

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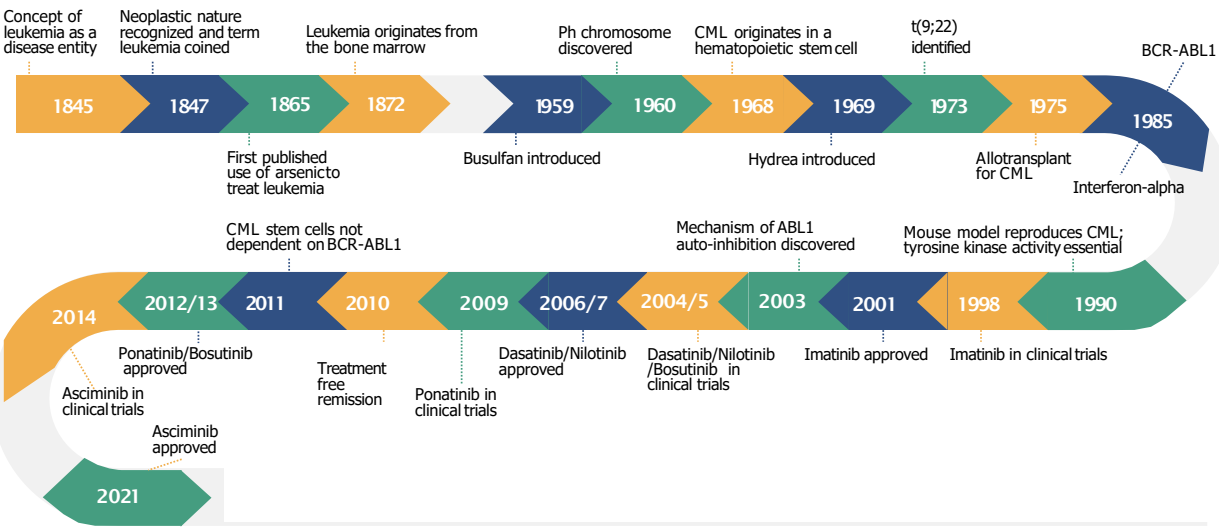

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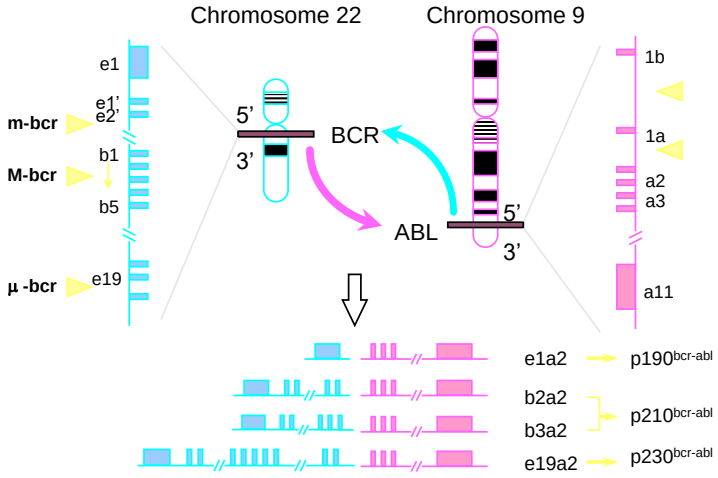
Patient # 1

- 40-year-old lady found to have an elevated WBC count on routine CBC
- Physical exam reveals splenomegaly ~ 6 cm below costal margin
- CBC:
  - WBC count: 50,000 cells/$mm^{3,}$ 2% blasts, 4% basophil, 80% neutrophils
  - Hemoglobin: 13 gm/dl
  - Platelet count: 443,000 cells/mm^3
- BM aspiration: hypercellular marrow (~100%) with 2% blasts
- Cytogenetics: Philadelphia chromosome in all 20 cells
- Risk Scores
  - Sokal: Low
  - Hasford: Low risk
  - EUTOS: Low risk

Questions

- What caused this? How common?
- What is the treatment?
- How long will I live?
- What is the response to treatment?
- How often will I be monitored?
- Will I stay on treatment forever?

The Philadelphia Chromosome



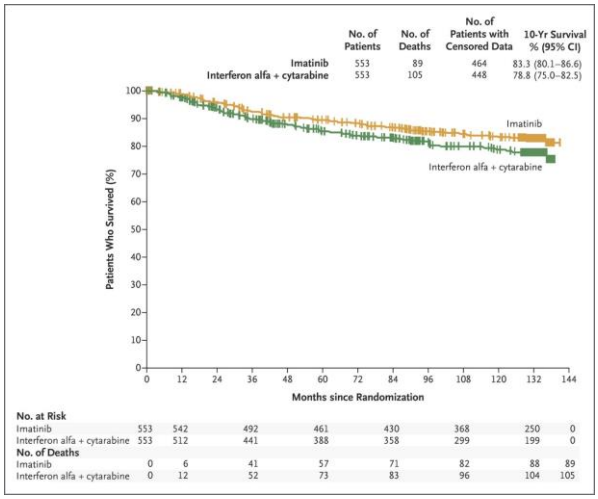
Natural History of CML

Chronic phase (CP)	Accelerated phase (AP)	Blast phase (BP)
Ph+	Cytogenetic changes Increasing blasts	
Median survival 3-5 years	12-24 mo	3-6 mo

Tyrosine Kinase Inhibitors Approved for the Treatment of Patients with Newly Diagnosed CML

- Imatinib 400 mg daily with food
- Nilotinib 300 mg twice daily without food
- Dasatinib 100 mg daily with or without food
- Bosutinib 400 mg daily with food

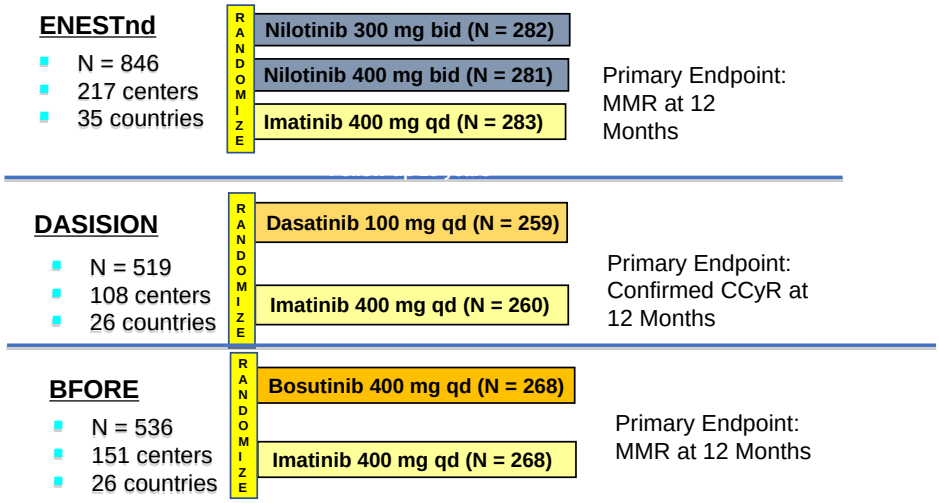
Overall Survival Rates Imatinib vs. Interferon



Hochhaus A et al. N Engl J Med 2017;376:917-927.

Second-Generation TKIs vs Imatinib

Treatment-Naïve Chronic Phase CML



MEDICAL COLLEGE OF WISCONSIN knowledge changing life

CCyR, complete cytogenetic response; MMR, major molecular response; TKI, tyrosine kinase inhibitor. Kantarjian et al. *JCO*. 2012;30(15 suppl): abstract 6509; Larson et al. *Leukemia* 2012;26(10):2197-2203. Cortes J et al. *JCO* 2018, 36, 231-237

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Imatinib (Gleevec®)

- MOA: BCR-ABL TKI (first generation)
- Dose: 400 mg PO daily <u>with food</u> and a full glass of water
- DLT: myelosuppression
- Other toxicities
  - GI (nausea, vomiting, diarrhea)
  - Edema
  - Transaminitis / hepatotoxicity
  - Rash, arthralgia, myalgia, fatigue, headache
- Clinical pearl – can take at dinnertime to help patient "sleep through nausea"

MEDICAL COLLEGE OF WISCONSIN knowledge changing life

Imatinib: Drug Information Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; 19 September 2016.

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Dasatinib (Sprycel®)

- MOA: BCR-ABL TKI (second generation)
- Dose: 100 mg PO daily with or without food
- DLT: myelosuppression (thrombocytopenia)
- Other toxicities
  - Pleural effusions
  - Headache
  - Pulmonary hypertension
  - Rash, arthralgia, myalgia, fatigue, edema
- Clinical pearl – avoid PPIs and H2RAs (decrease absorption)

Dasatinib: Drug Information Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; 19 September 2016.

Nilotinib (Tasigna®)

- MOA: BCR-ABL TKI (second generation)
- Dose: 300 mg PO q12h <u>without food</u>
- DLTs: myelosuppression,
- Other toxicities
  - Hepatotoxicity
  - Electrolyte imbalances
  - Pancreatitis
  - Hyperglycemia
- Clinical Pearls
  - LOTS of DDIs – always screen!
  - Avoid PPIs and H2RAs (decrease absorption)
    - Not contraindicated

QT prolongation (BBW)

- Itching
- Rash, arthralgia, myalgia, fatigue, headache, edema
- Peripheral arterial occlusive disease

Nilotinib: Drug Information Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; 19 September 2016.

Bosutinib (Bosulif®)

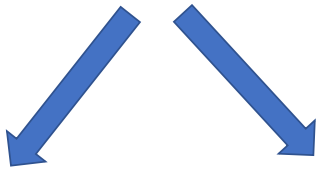
- MOA: BCR-ABL TKI (second generation)
- Dose: 400 mg daily with food
- Side effects:
  - Liver toxicity
  - Skin rash
  - Diarrhea
- Clinical Pearls
  - Diarrhea in first week. Usually resolves

Choice of Frontline TKI

- 2GTKI have faster deeper response
- 2GTKI have 2-3% less chance of progressing to AP/BC
- No difference in overall survival
- Choose based on:
  - Side effects and co-morbidities
  - Sokal score

2GTKI: Second generation TKI include dasatinib, bosutinib and nilotinib

Defining Response

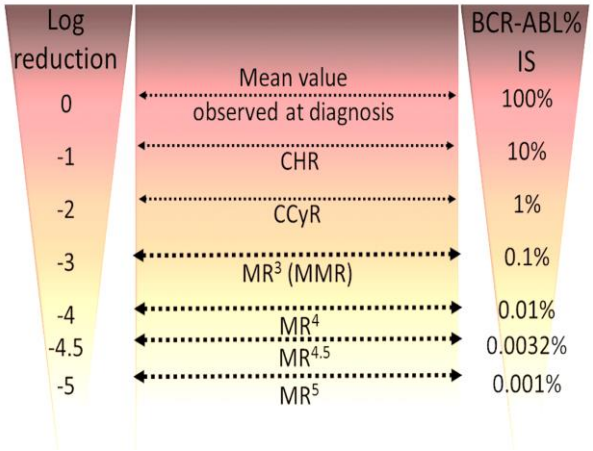


Depth of Response Duration of therapy

Depth of Response

Type of Response		Definition
CHR	Complete Hematologic Response	Normal differential, WBC, platelets ≤ ULN
MCyR	Major cytogenetic Response	0-35% Ph+ marrow metaphases
CCyR	Complete Cytogenetic Response	0% Ph+ marrow metaphases
MMR	Major Molecular Response	BCR-ABL/ABL ≤ 0.1% (International Scale)
UMR	Undetectable	Undetectable BCR-ABL (test of sensitivity ≥ 4.5 logs)

Depth of Response



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

NCCN Guidelines for Monitoring Response to TKI Therapy and Mutational Analysis

Test	Recommendation
BM Cytogenetics	• At diagnosis to establish disease • Failure to reach milestones • Any sign of loss of response (defined as hematologic or cytogenetic relapse)
QPCR using IS	• At diagnosis • Every 3 months after initiating treatment. After BCR-ABL1(IS) ≤1% (>0.1-1%) has been achieved, every 3 months for 2 years and every 3-6 months thereafter • ⬆ BCR-ABL transcript (1 log) w/ MMR, QPCR should be repeated in 1-3 months
BCR-ABL kinase domain mutation analysis	• Chronic phase -Failure to reach milestones -Any sign of loss of response -1-log increase in BC-ABL1 transcript levels and loss of MMR • Disease progression to accelerated or blast phase

QPCR, quantitative PCR; IS, international scale; MMR, major molecular response; BM bone marrow.

*FISH has been inadequately studied for monitoring response to treatment.

NCCN Guidelines. CML 3.2020. Available at www.NCCN.org. Accessed February 2020

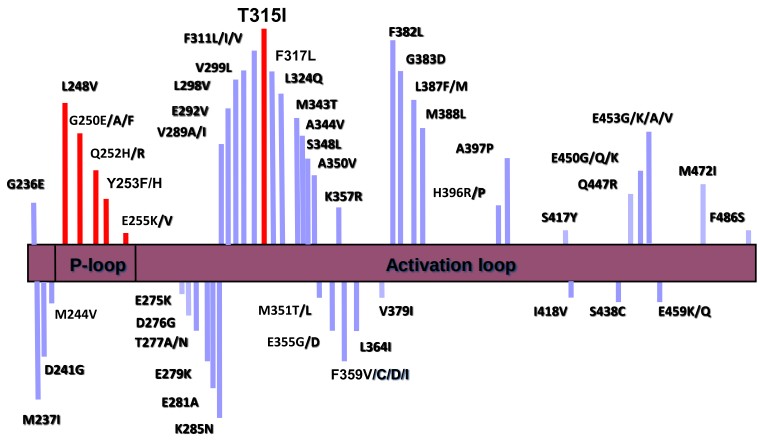
NCCN Response Guidelines for CP-CML

BCR::ABL1 (IS)	3 months	6 months	12 months[m]
>10%[n]	YELLOW	RED	
>1%–10%	GREEN		YELLOW
>0.1%–1%	GREEN		LIGHT GREEN
≤0.1%	GREEN		

NCCN Guidelines. CML V. 1 2023. Available at www.NCCN.org. Accessed September 2022

Resistance To First Line TKI

BCR-ABL Imatinib-Resistance Mutations



knowledge changing life

Height of the bars indicates frequency of mutation

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Activity of TKIs Against 18 Imatinib-Resistant BCR/ABL Mutants

		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

knowledge changing life

Redaelli S, et al. *J Clin Onc.* 2009;27(3):469-471.

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Second line TKI after imatinib failure

Drug	#	Imatinib Resistant (%)	Imatinib Resistant MCyR/CCyR (%)	Imatinib resistant 24 month PFS
Dasatinib*	387	74	55/44	75%
Nilotinib*	321	70	56/41	64%
Bosutinib**	288	69	54/41	73%

*Minimum follow up 24 months
**Median follow up 24 months

Mauro M et al. ASCO 2008. Abstract 7009. Kantarjian et al. Blood. 2011; 117: 1141-1145, Cortes JE et al. Blood. 2011;118:4567–4576, Giles FJ et al. Leukemia (2013) **27,** 107–112

Ponatinib in 2nd Generation TKI-Resistant CML and Ph+ ALL: PACE Trial

Patients with CML or Ph+ ALL resistant or intolerant to dasatinib or nilotinib or with emergent T315I mutation

Ponatinib 45 mg/day (n=444)

	CP-CML (N=270)		
	MCyR	**CCyR**	**MMR**
R/I to dasatinib or nilotinib	56%	48%	31%
T315I mutation	**72%**	**70%**	**58%**
Total	60%	54%	38%

T315I mutation: N= 64(24%)
≥ 3 prior TKIs: N=161 (60%)

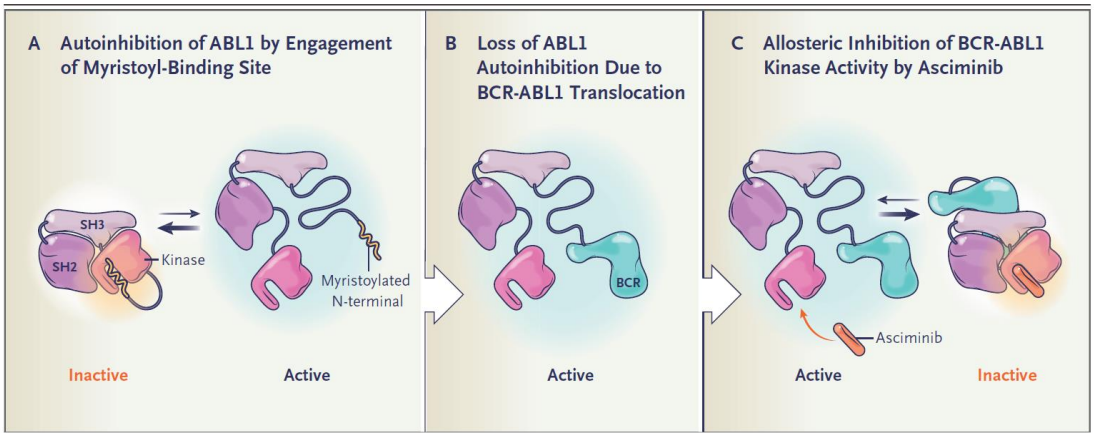
Cortes JE, et al. *ASH Annual Meeting Abstracts.* 2013: Abstract 650.

Vascular Events
Restrictions with Ponatinib

- Serious adverse vascular events
  - Phase II: 24% (median treatment duration 1.3 years)
  - Phase I: 48% (median treatment duration 2.7 years)
- Due to the risk of life-threatening blood clots and severe narrowing of blood vessels, the FDA requested marketing and sales of ponatinib be suspended on October 31, 2013
  - Patients currently taking ponatinib who are not responding should discontinue treatment and discuss alternative options
  - Patients currently responding and whose benefits outweigh the associated risks should be treated under a single-patient IND application or expanded access
  - Do not initiate treatment with new patients unless there are no other treatment options and all other available therapies have failed

US Food and Drug Administration. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm373040.htm. Accessed November 2013.

Asciminib



Not FDA approved

Hughes et al. NEJM 2019

ASCEMBL

CML-CP previously treated with ≥2 TKIs

- N = 233
- Crossover allowed
- 2:1

RANDOMIZE

Asciminib 40 mg bid (N=157)

Bosutinib 500 mg qd (N = 76)

Primary Endpoint:
MMR at 12 Months

Results at 24 weeks

Asciminib vs. Bosutinib

MMR: 25.5% vs. 13.2%

MR^4: 10.8% vs. 5.3%

$MR^{4.5}$: 8.9% vs. 1.3%

CCyR: 40.8% vs. 24.2%

ASCEMBL-Side Effects

	Asciminib N (%)		Bosutinib N (%)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Headache	25 (16.0)	3 (1.9)	10 (13.2)	0
Diarrhea	18 (11.5)	0	54 (71.1)	8 (10.5)
Hypertension	18 (11.5)	9 (5.8)	3 (3.9)	3 (3.9)
Nausea	18 (11.5)	1 (0.6)	35 (46.1)	0
Fatigue	16 (10.3)	0	7 (9.2)	1 (1.3)
Nasopharyngitis	15 (9.6)	0	2 (2.6)	0
Rash	11 (7.1)	0	18 (23.7)	3 (3.9)
Vomiting	11 (7.1)	2 (1.3)	20 (26.3)	0
Abdominal pain	7 (4.5)	0	11 (14.5)	1 (1.3)

Rea et al. Blood 2021

Summary

- Many choices for frontline TKI
- Adherence to TKI important for optimal response
- Mutation analysis important at time of resistance/relapse

The H. Jean Khoury *Cure CML Consortium (HJKC3)*

"Galvanized by the spectacular collaboration created by the LAST study, the creation of a CML consortium was simply the next logical thing to do"
(1967-2017)

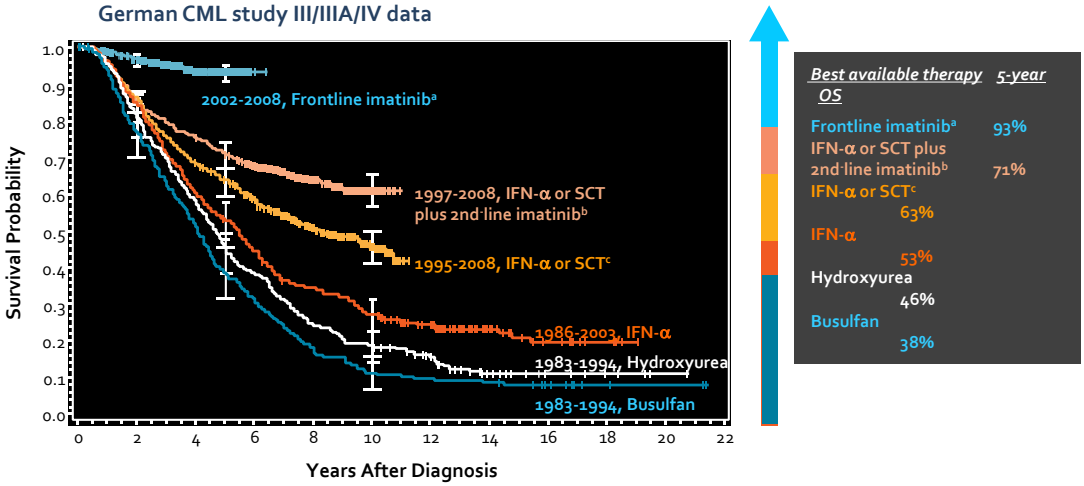
UCSF Helen Diller Family Comprehensive Cancer Center
EMORY WINSHIP CANCER INSTITUTE
DANA-FARBER CANCER INSTITUTE
AUGUSTA UNIVERSITY
MEDICAL COLLEGE OF WISCONSIN CANCER CENTER
FRED HUTCH CURES START HERE
Karmanos CANCER INSTITUTE
Weill Cornell Medicine Sandra and Edward Meyer Cancer Center
Memorial Sloan Kettering Cancer Center
UHN Princess Margaret Cancer Centre
OHSU
THE UNIVERSITY OF CHICAGO MEDICINE Comprehensive Cancer Center
ROSWELL PARK CANCER INSTITUTE
HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH
Duke Cancer Institute
MOFFITT CANCER CENTER

CML Clinical trials, Treatment Free Remission, Functional CURE!

Michael J. Mauro, MD
Leader, Myeloproliferative Neoplasms Program
Memorial Sloan Kettering Cancer Center
New York

CYCLE FOR SURVIVAL
MEMORIAL SLOAN KETTERING CANCER CENTER
FRED'S TEAM
IMAGINE A WORLD WITHOUT CANCER
CURE CML CONSORTIUM
THE NATIONAL CML SOCIETY
iCMLf International Chronic Myeloid Leukemia Foundation
LEUKEMIA & LYMPHOMA SOCIETY®
TEAM IN TRAINING
The Max Foundation
TEAM922
What is My PCR?
ASK ME
MyPCR.org

Imatinib changed the way we treated CML, Revolutionized the approach to cancer therapy, and was the beginning of a new era…



Adapted from Hehlmann R., German CML Study Group.

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Targeted Cancer Therapy: Then and Now

1998- the year STI571 (Gleevec) entered clinical trials:

- Avastin
- Tamoxifen
- Herceptin

2021

Targeted Drugs in Blood Cancer, 2021

Leukemia: Tretinoin (Vesanoid), imatinib mesylate (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), rituximab (Rituxan), alemtuzumab (Campath), ofatumumab (Arzerra), obinutuzumab (Gazyva), ibrutinib (Imbruvica), idelalisib (Zydelig), blinatumomab (Blincyto), venetoclax (Venclexta), ponatinib hydrochloride (Iclusig), midostaurin (Rydapt), enasidenib mesylate (Idhifa), inotuzumab ozogamicin (Besponsa), tisagenlecleucel (Kymriah), gemtuzumab ozogamicin (Mylotarg), rituximab and hyaluronidase human (Rituxan Hycela), ivosidenib (Tibsovo), duvelisib (Copiktra), moxetumomab pasudotox-tdfk (Lumoxiti), glasdegib maleate (Daurismo), gilteritinib (Xospata), tagraxofusp-erzs (Elzonris), acalabrutinib (Calquence)

Lymphoma: Ibritumomab tiuxetan (Zevalin), denileukin diftitox (Ontak), brentuximab vedotin (Adcetris), rituximab (Rituxan), vorinostat (Zolinza), romidepsin (Istodax), bexarotene (Targretin), bortezomib (Velcade), pralatrexate (Folotyn), ibrutinib (Imbruvica), siltuximab (Sylvant), idelalisib (Zydelig), belinostat (Beleodaq), obinutuzumab (Gazyva), nivolumab (Opdivo), pembrolizumab (Keytruda), rituximab and hyaluronidase human (Rituxan Hycela), copanlisib hydrochloride (Aliqopa), axicabtagene ciloleucel (Yescarta), acalabrutinib (Calquence), tisagenlecleucel (Kymriah), venetoclax (Venclexta), mogamulizumab-kpkc (Poteligeo), duvelisib (Copiktra), polatuzumab vedotin-piiq (Polivy), zanubrutinib (Brukinsa), tazemetostat hydrobromide (Tazverik), selinexor (Xpovio), tafasitamab-cxix (Monjuvi), brexucabtagene autoleucel (Tecartus), crizotinib (Xalkori), umbralisib tosylate (Ukoniq), lisocabtagene maraleucel (Breyanzi)

Multiple myeloma: Bortezomib (Velcade), carfilzomib (Kyprolis), panobinostat (Farydak), daratumumab (Darzalex), ixazomib citrate (Ninlaro), elotuzumab (Empliciti), selinexor (Xpovio), isatuximab-irfc (Sarclisa), *daratumumab and hyaluronidase-fihj (Darzalex Faspro)*, *belantamab mafodotin-blmf (Blenrep)*, *melphalan flufenamide hydrochloride (Pepaxto)*, *idecabtagene vicleucel (Abecma)*

Myelodysplastic/myeloproliferative disorders: Imatinib mesylate (Gleevec), ruxolitinib phosphate (Jakafi), fedratinib hydrochloride (Inrebic)

Systemic mastocytosis: Imatinib mesylate (Gleevec), midostaurin (Rydapt)

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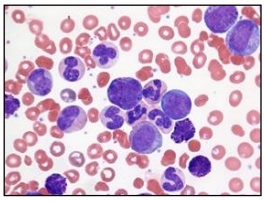
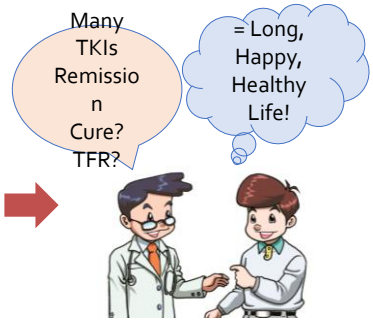
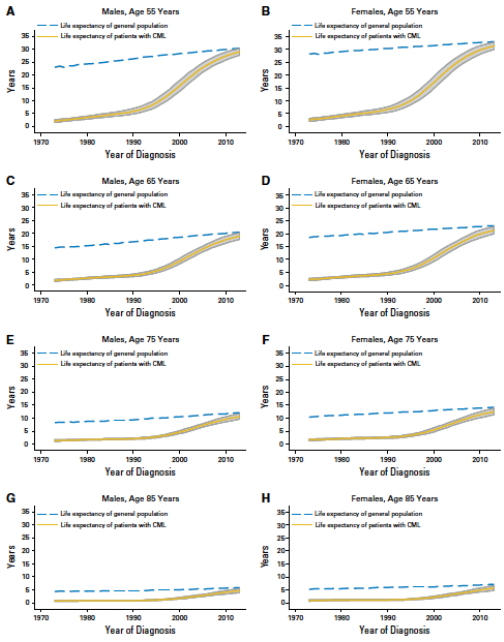
CML is an increasingly prevalent and survivable cancer







Bower H et al, *J Clin Oncol 34:2851-57, 2016.*

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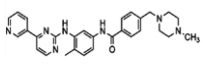
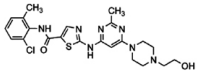
9 TKIs Approved Globally (6 in US); 'spoil of riches'!

1st Gen. TKI

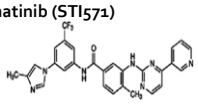


Imatinib (STI571) — 2001 Novartis (1st line)

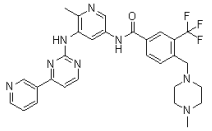
2nd Gen. TKIs



Dasatinib (BMS354825) — 2007/2010 BMS (1st, 2nd line)

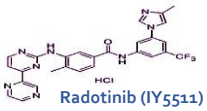


Nilotinib (AMN107) — 2007/2010 Novartis (1st, 2nd line)

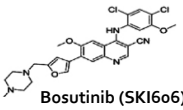


Flumatinib (HH-GV-678) — China only — 2019 Hansoh (1st line)

South Korea only

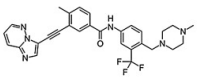


Radotinib (IY5511) — 2012/2015 IL-YANG: (1st, 2nd line)



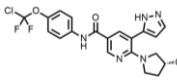
Bosutinib (SKI606) — 2012/2018 Pfizer (1st, 2nd/3rd line)

3rd Gen. TKI



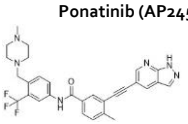
Ponatinib (AP24534) — 2012 Takeda (3rd line/T315I)

4th Gen. TKI 'STAMP'



Asciminib (ABL001) — 2021 Novartis (3rd line/T315I)

China only



Olverembatinib (HQP1351) — 2021 Ascentage (T315I)

1998 phase I study of imatinib (STI571): 54 patients
2007 pilot study to stop imatinib (STIM): 15 patients

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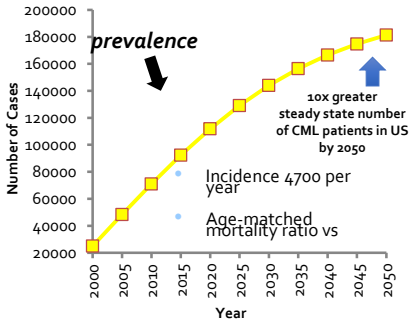
The Unmet Need: Increasing the CURE Fraction– *Treatment Free Remission*

- Number of people living with CML– CML survivors continues on increase (prevalence)
- Number of people achieving safe and stable remissions is very high
- Increasing guidelines and potential to plan ***deliberate, carefully monitored treatment cessation ('TFR')***



Huang et al, *Cancer* 118:3123-3127, 2012
Hochhaus A, et al, *Leukemia* 34(4):966-984, 2020

Table 7 Cumulative incidence of deep molecular response (MR^4 and $MR^{4.5}$) with imatinib, nilotinib, and dasatinib by 5 and 10 years.

Study		5 years (%)	10 years (%)
CML-Study IV[a], [36, 37]	Imatinib MR^4	68	81
	Imatinib $MR^{4.5}$	53	72
ENESTnd[b], [41, 52]	Nilotinib MR^4	66	73
	Nilotinib $MR^{4.5}$	54	64
	Imatinib MR^4	42	56
	Imatinib $MR^{4.5}$	35	45
Dasision[c], [40]	Dasatinib $MR^{4.5}$	42	NA
	Imatinib $MR^{4.5}$	33	NA

DMR rates of these trials cannot be directly compared owing to different methods of trial evaluation.

NA not available.

[a]Imatinib ($n = 1442$).

[b]Nilotinib 300 mg twice daily ($n = 282$), imatinib 400 mg daily ($n = 283$).

[c]Dasatinib 100 mg once daily ($n = 259$), imatinib 400 mg daily ($n = 260$).

'Functional Cure' Fraction

- ~75% Deep Remission
- ~35-40% successful TFR
- majority of patients thus remain on TKI…for now… but not for long?!

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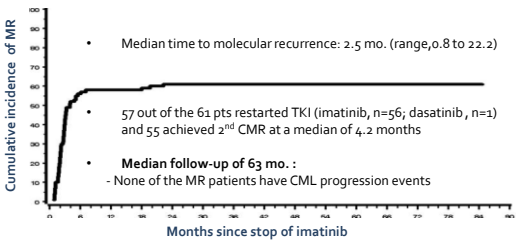
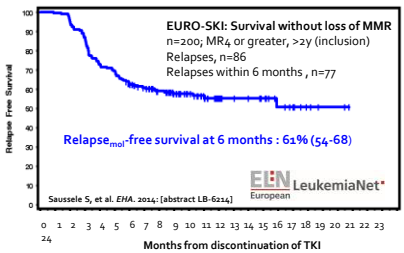


- Median time to molecular recurrence: 2.5 mo. (range,0.8 to 22.2)
- 57 out of the 61 pts restarted TKI (imatinib, n=56; dasatinib , n=1) and 55 achieved 2nd CMR at a median of 4.2 months
- **Median follow-up of 63 mo. :**
  - None of the MR patients have CML progression events



A Cancer Drug Gave Me This Life. Can I Survive Without It?

Since she was 23, Erin Zammett Ruddy has swallowed a daily pill to keep her leukemia at bay. Now she has a choice: stay the course or ditch the drug. Find out what she'll do next.

fantastic therapy + careful selection + good monitoring = fantastic outcomes…

'treatment free remission'

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One Woman's Story Says it All…..

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The Balance: TKIs have low (but not *NO)* toxicity…

Issue	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib	Asciminib
Dosing	QD/BID, with food	BID, without food (2h)	QD, w/ or w/o food	QD, with food	QD, w/ or w/o food	QD or BID, w/o food; dosing varies (T315I or not)
Long term safety	Most extensive	Extensive; Emerging toxicity	Extensive; Emerging toxicity	Extensive, No emerging toxicity	More limited but increasing; Emerging toxicity	Emerging; long phase I data (8y)
Heme toxicity	Intermediate	Least	Most severe; ASA-like effect; Lymphocytosis	~dasatinb in 2nd, 3rd line; ~nilotinib in 1st line	Thrombocytopenia ASA-like effect	Thrombocytopenia Neutropenia
Non-Heme toxicity	Edema, GI effects (diarrhea, nausea), Muscle cramps, ↓Phos	↑Lipase, ↑Bili, ↑Chol, ↑Glu, Fatigue, Musculo-skeletal symptoms Black box: QT prolongation	Headache (early/transient) Pleural / pericardial effusions	Diarrhea; Transaminitis	↑Lipase, Pancreatitis, Rash, Hypertension Black box: vascular occlusion, heart failure, and hepatotoxicity	↑Lipase, Pancreatitis, Hypertension, Hypersensitivity reaction, Possible cardiovascular adverse events
Special concern issues	Early question re: CHF ?late renal effects	Vascular events (ICVE, IHD, PAD)	?PAH (pulmonary arterial hypertension)	? Mild renal effects	Vascular events (ICVE, IHD, PAD, VTE)	Longer follow-up needed re: cardiovascular AEs

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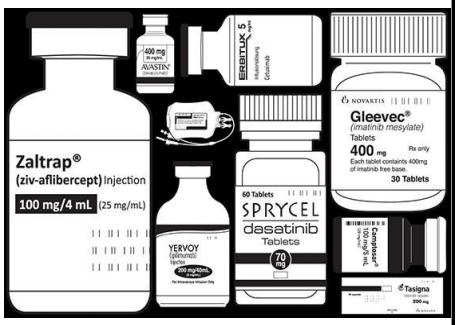
Financial Toxicity of Current TKI Therapy Paradigm

- Global access to care and TKI therapy *varies very widely*
- Limited generic options (imatinib (global), dasatinib (ex-US))
- Paradigm shift between 'lifelong' and defined duration therapy would be remarkably less



The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts

Experts in Chronic Myeloid Leukemia

Kantarjian H. *Blood* 121: 4439-4442, 2013

As a group of more than 100 experts in chronic myeloid leukemia (CML), we draw attention to the high prices of cancer drugs, with the particular focus on the prices of approved tyrosine kinase inhibitors for the treatment of CML. This editorial addresses the multiple factors involved in cancer drug pricing and their impact on individual patients and health care policies, and argues for the need to (1) lower the prices of cancer drugs to allow more patients to afford them and (2) maintain sound long-term health care policies. (*Blood.* 2013;121(22):4439-4442)

Kantarjian H. *Blood* 121: 4439-4442, 2013
Hall S, *New York Magazine*, Published 10/20/13

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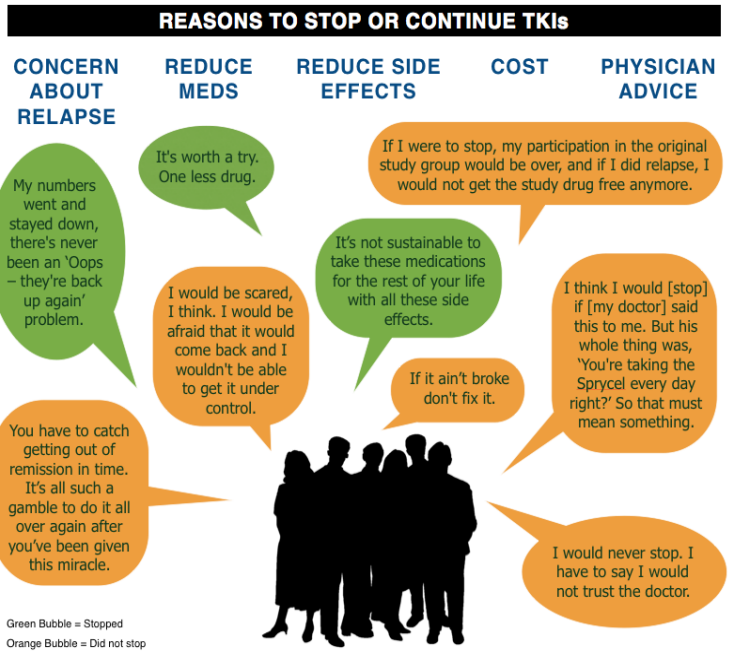
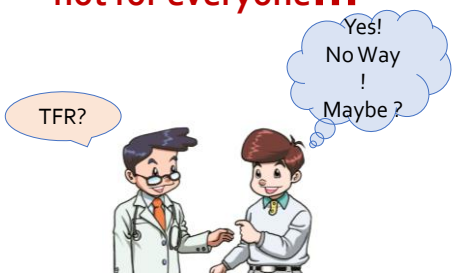


Treatment Free Remission: not for everyone…



Patient Characteristics (N=22)	N (%)
Men	9 (40%)
Age 65+	5 (23%)
Ever on imatinib	18 (82%)
Years on TKI, median (range)	6.75 (2-15)
Discussed stopping with doctor	18 (82%)
Stopped TKI	11 (50%)
Do not want to stop TKI	11 (50%)

Courtesy of Kathryn Flynn. ESH 2016

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Treatment Free Remission, Here and Across the Pond

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2021
Chronic Myeloid Leukemia

'Treatment Free Remission'

DISCONTINUATION OF TKI THERAPY

General Considerations

- **Discontinuation of TKI therapy appears to be safe in select CML patients.**
- **Consultation with a CML specialist to review the appropriateness for TKI discontinuation and potential risks and benefits of treatment discontinuation, including TKI withdrawal syndrome.**
- **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.**
- **Consultation with an NCCN Panel member or center of expertise is recommended in the following circumstances:**
  - **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 3 months following treatment reinitiation.**
- **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 for at least 3 years.[1,2]**
- **Prior evidence of quantifiable *BCR-ABL1* transcript.**
- **Stable molecular response (MR4; *BCR-ABL1* ≤0.01% IS) for ≥2 years, as documented on at least 4 tests, performed at least 3 months apart.[2]**
- **Access to a reliable qPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤0.0032% IS) and that provides results within 2 weeks.**
- **Monthly molecular monitoring for the first 6 months following discontinuation, bimonthly during months 7–12, and quarterly thereafter (indefinitely) for patients who remain in MMR (MR3; *BCR-ABL1* ≤0.1% IS).**
- **Prompt resumption of TKI within 4 weeks of a loss of MMR with monthly molecular monitoring until MMR is re-established, then every 3 months thereafter is recommended indefinitely for patients who have reinitiated TKI therapy after a loss of MMR. For those who fail to achieve MMR after 3 months of TKI resumption, BCR-ABL1 kinase domain mutation testing should be performed, and monthly molecular monitoring should be continued for another 6 months.**

[1] The feasibility of treatment-free remission (TFR) following discontinuation of bosutinib or ponatinib has not yet been evaluated in clinical studies. It is reasonable to assume that the likelihood of TFR following discontinuation would be similar irrespective of TKI in patients who have achieved and maintained deep molecular response (MR4.0; ≤0.01% *BCR-ABL1* IS) for ≥2 years, based on the extrapolation of findings from the studies that have evaluated TFR following discontinuation of imatinib, dasatinib, or nilotinib.
[2] Data from the EURO-SKI study suggest that MR4.0 (*BCR-ABL1* ≤0.01% IS) for 3 years or more was the most significant predictor for successful discontinuation of imatinib. Total duration of imatinib therapy for at least 6 years was also predictive of successful discontinuation (Saussele S, Richter J, Guilhot J, et al. Lancet Oncol 2018;19:747-757).

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.

ELN European LeukemiaNet

Table 8 Requirements for tyrosine kinase inhibitor discontinuation.

Mandatory:

- CML in first CP only (data are lacking outside this setting)
- Motivated patient with structured communication
- Access to high quality quantitative PCR using the International Scale (IS) with rapid turn-around of PCR test results
- Patient's agreement to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter.

Minimal (stop allowed):

- First-line therapy or second-line if intolerance was the only reason for changing TKI
- Typical e13a2 or e14a2 BCR–ABL1 transcripts
- Duration of TKI therapy >5 years (>4 years for 2GTKI)
- Duration of DMR (MR^4 or better) >2 years
- No prior treatment failure

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 $MR^{4.5}$

NCCN CML Guidelines, Version 3.2021, Accessed with permission, www.nccn.org 5/1/2021
Hochhaus A, et al, *Leukemia* 34(4):966-984, 2020

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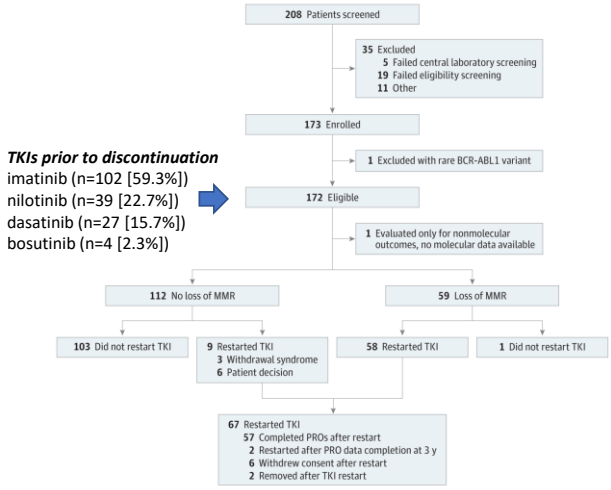
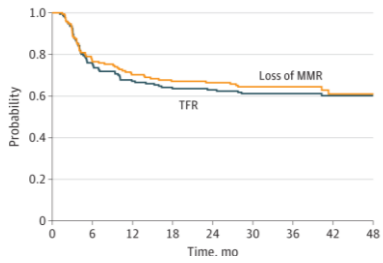
Treatment Free Remission (TFR):
Khourv Cure CML Consortium / The LAST Study

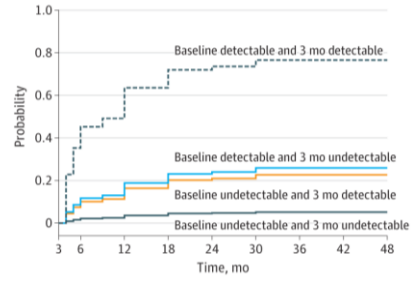


TKIs prior to discontinuation
imatinib (n=102 [59.3%])
nilotinib (n=39 [22.7%])
dasatinib (n=27 [15.7%])
bosutinib (n=4 [2.3%])

Probability of molecular relapse-free survival and TFR



Landmark analysis of MRec probability at 3 mo



- TFR success rate was 60.8%
- Treatment free remission (TFR) feasible after any available front-line TKI
- PCR status at baseline and 3mo predictive

Atallah E et al, *JAMA Oncol.* 2021;7(1):42-50

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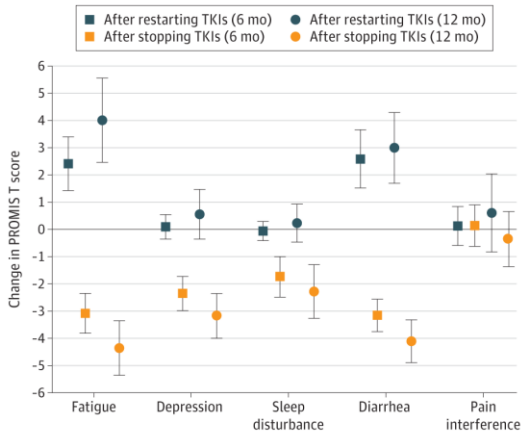
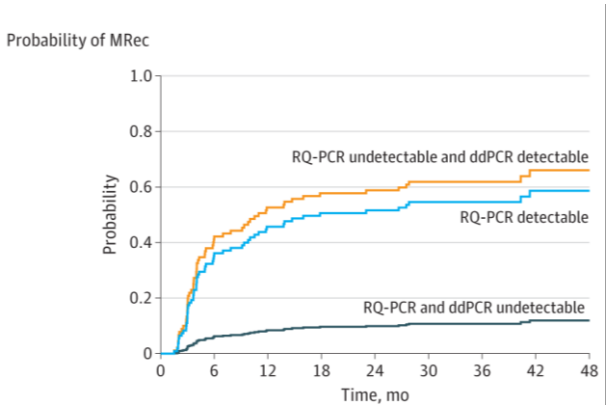
TFR: patient reported adverse events, and alternate PCR strategies in the LAST Study





- AEs from TKIs clearly improve
- Digital Drop PCR (ddPCR) may add predictive value

Atallah E et al, *JAMA Oncol.* 2021;7(1):42-50

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Do Adverse Events Occur With TKI *Withdrawal?*

N=200; 222 AEs in 98 patients were reported

57 AEs in 31 patients were related to treatment stop, no grade 4

	Patients All Grade (n)	Patients Grade 3 (n)	AEs All Grade (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.

Tyrosine kinase inhibitor withdrawal syndrome: a matter of c-kit ?
Response to Richter et al.
Ph. Rousselot et al.

Mahon FX et al, Blood 2014 124:151

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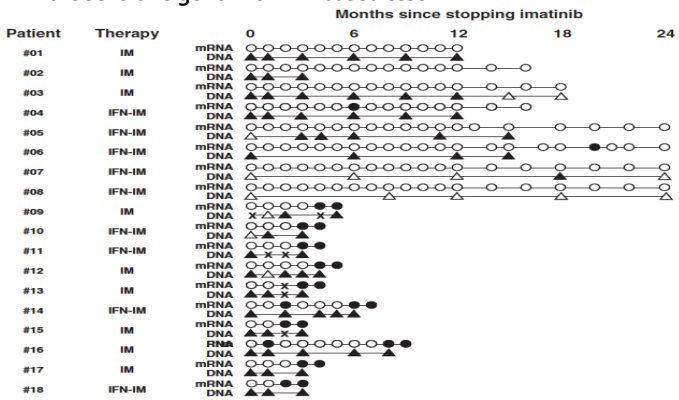
What is really happening with TFR?

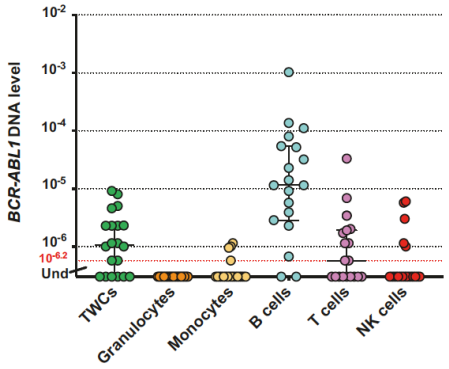
Patients in long term deep remission (successful 'TFR') commonly have evidence of BCR-ABL when assessed with a more sensitive genomic DNA based test



Ten patients with loss of CMR had rising gDNA PCR levels, whereas a generally stable gDNA level was detectable in 7/8 patients with sustained CMR (follow-up 12-41 months)

Ross et al, Leukemia 2010

Subset analysis shows BCR-ABL DNA may arise from lymphocyte fractions, not myeloid compartment



Patients in TFR, repeatedly not detected (UMR4.5), including 6 'negative' unfractionated samples, have BCR-ABL DNA in subset analyses, often lymphocyte fractions

Pagani IS, et al. *Leukemia* 2020

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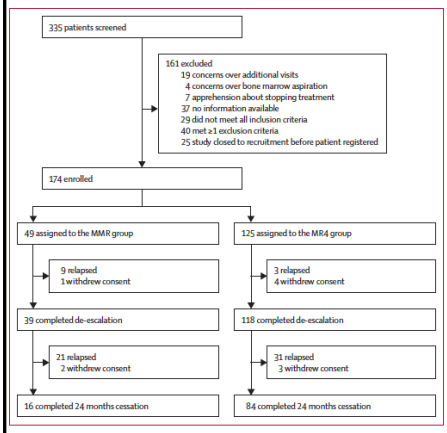
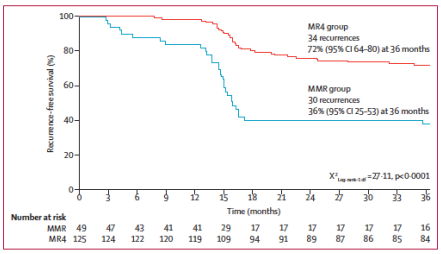
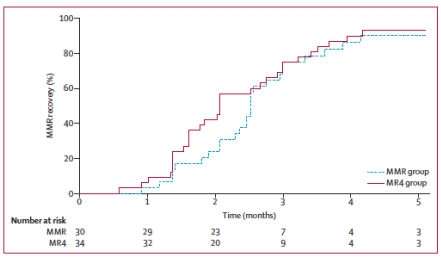
Maybe we should not go 'cold turkey': UK DESTINY Study: De-escalation of TKI *Prior to TFR*



Imatinib -> 200 mg
Nilotinib -> 200 bid
Dasatinib -> 50 mg





- De-escalation may yield a higher fraction of successful TFR candidates
- Caution regarding TFR for patents in MMR only

	HR (95% CI)	p value
Characteristic (univariate)		
Molecular group MR4 (vs MMR)	0·29 (0·18–0·48)	<0·0001
Age	0·99 (0·97–1·01)	0·19
Male sex (vs female)	0·70 (0·43–1·14)	0·15
Medication imatinib	1·60 (0·73–3·52)	0·23
ECOG score	0·83 (0·37–1·83)	0·64
Time on TKI therapy	0·94 (0·87–0·99)	0·082
Time in MMR	0·92 (0·83–1·03)	0·13
MR4.5 at entry	0·43 (0·26–0·72)	0·00099
Characteristic (multivariable)		
Molecular group MR4	0·27 (0·16–0·44)	<0·0001
Time on TKI	0·92 (0·86–0·99)	0·021

Where relevant, the HR refers to the probability of recurrence for the named parameter relative to the alternative (eg, MR4 *vs* MMR, male *vs* female, or imatinib *vs* other entry drugs). HR=hazard ratio. MR4=deep molecular response (BCR-ABL1:ABL1 ratio <0·01%). MMR=major molecular response (BCR-ABL1:ABL1 ratio consistently <0·1%). ECOG=Eastern Cooperative Oncology Group. TKI=tyrosine kinase inhibitor.

Table 1: **Univariate and multivariable analysis of various parameters' associations with molecular recurrence**

Clark RE et al; *Lancet Haematol.* 2019 Jul;6(7):e375-e383.

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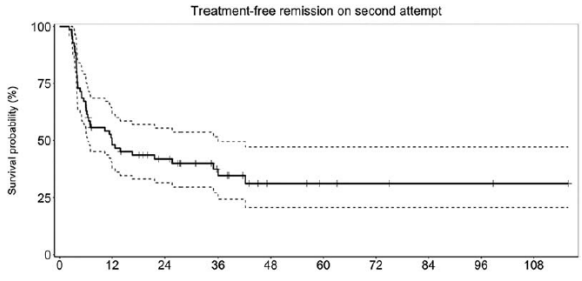

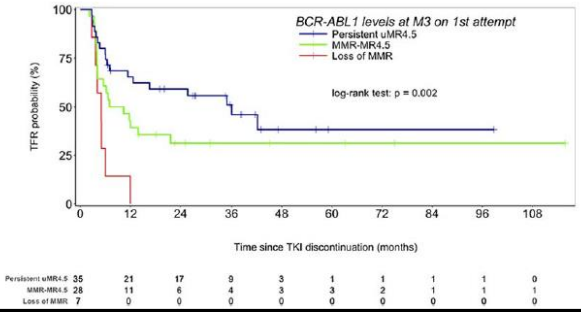

Do we have only one shot at this?

Experience with 2nd TFR: RE-STIM

- 64% failure (loss of MMR), median 5.3mo
- TFR rates:
- 48% @12mo, 42% @24mo, 35% @36mo
- No POD
- Molecular relapse speed predictive:
- 24mo TFR rate 72 *vs* 36% (DMR@3mo w/1st TFR, Y/N)

Legros et al, *Cancer* 2017;123:4403-10.

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Experience with Second TFR:RE-STIM

TABLE 2. Potential Predictive Factors of Treatment-Free Remission by Univariable Cox Regression Model Analysis

Variable	No. of Patients	HR	95% CI	*P*
Age at second discontinuation: < 60 vs > 60 y	70	1.00	0.97-1.02	.760
Sokal risk score	69			
Low and intermediate	60	1.00	—	
High	9	1.96	0.88-4.36	.100
Prior exposure to IFN	70			
No	51	0.93	0.49-1.74	.814
Yes	19			
TKI duration at first discontinuation: < 59 vs > 59 mo	70	1.00	0.99-1.01	.692
uMR4.5 duration at first discontinuation: < 32 vs > 32 mo	70	1.00	0.98-1.02	.905
TKI type at first attempt	70			
Imatinib	60	1.00	—	
Dasatinib and nilotinib	10	1.92	0.88-4.19	.102
First discontinuation molecular criteria	70			
1 y ≤ uMR4.5 < 2 y	20	1.00	—	
uMR4.5 ≥ 2 y	50	1.77	0.89-3.50	.102
Time to uMR4.5 loss from first TKI discontinuation	70			
<3 mo	35	1.00	—	
>3 mo	35	2.02	1.10-3.70	.024
Time to uMR4.5 loss from first TKI discontinuation	70			
<6 mo	59	1.00	—	
>6 mo	11	2.77	1.08-7.13	.035
Reason for first TKI re-challenge	70			
uMR4.5 loss	28	1.00	—	
MMR loss	42	1.43	0.76-2.66	.264
First TKI-free duration: < 5 vs > 5 mo	70	0.91	0.82-1.01	.084
Switch from imatinib to 2G TKI after first discontinuation	60			
No	52	1.08	0.54-2.13	.831
Yes	8			
Second TKI duration at second discontinuation: < 32 vs > 30 mo	70	1.00	0.98-1.02	.670
Total TKI duration at second discontinuation: < 103 vs < 103 mo	70	1.00	0.99-1.01	.420
Second uMR4.5 duration at second discontinuation: < 25 vs > 25 mo	70	1.00	0.98-1.03	.903
Total uMR4.5 duration at second discontinuation: < 68 vs > 68 mo	70	1.00	0.98-1.01	.577

40% w/o MMR loss

Abbreviations: 2G, second-generation; CI, confidence interval; HR, hazard ratio; IFN, interferon; MMR, major molecular response; TKI, tyrosine kinase inhibitor; uMR4.5, undetectable molecular disease.

Legros et al, *Cancer* 2017;123:4403-10.

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Thank you for your attention!

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Clinical Trials Within the Cure CML Consortium

Kendra Sweet, MD
Associate Member
Malignant Hematology
Moffitt Cancer Center

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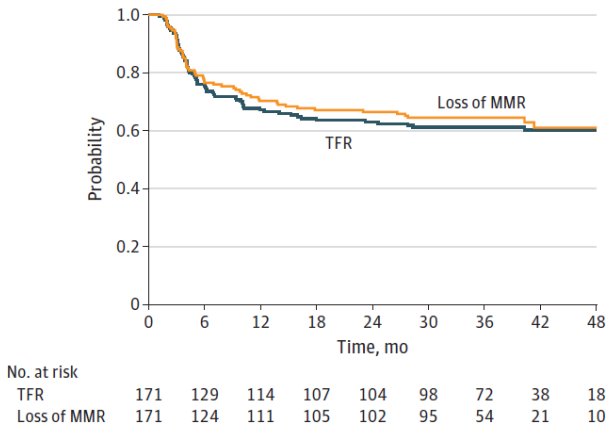
Life After Stopping TKI (LAST) Study

- Enrolled 172 patients from 14 US sites
- Primary endpoint: molecular recurrence defined as loss of MMR and patient reported outcomes
- Minimum f/u 3 years
- 65.5% remained in MMR
- 60.8% achieved TFR



Atallah, E. JAMA Oncology.

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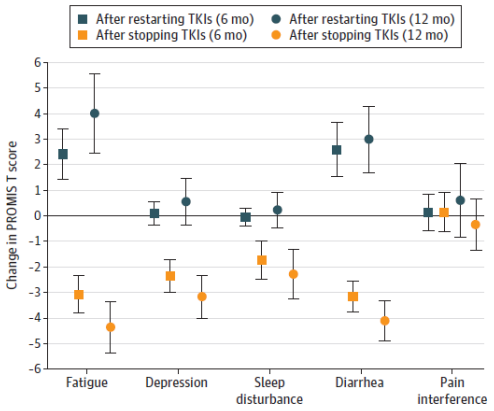
Patient Reported Outcomes with TFR

- 112 patients in TFR at 12 mos
- 80.4% with clinically meaningful improvement in fatigue
- 87.5% with clinically meaningful improvement in diarrhea
- 21.4% with clinically meaningful improvement in sleep disturbance
- 4.5% with clinically meaningful improvement in pain interference

Figure 3. Mean Changes in Patient-Reported Outcomes After Tyrosine Kinase Inhibitor (TKI) Discontinuation and TKI Restart at 6 and 12 Months



Vertical lines indicate 95% CIs. PROMIS indicates Patient-Reported Outcomes Measurement Information System.

Atallah, E. JAMA Oncology.

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Is Stopping TKI Realistic?

50% achieve MR4 or MR 4.5

50% restart TKI

70-80% of newly diagnosed patients with CML will need long term TKI therapy

Slide courtesy of Ehab Atallah

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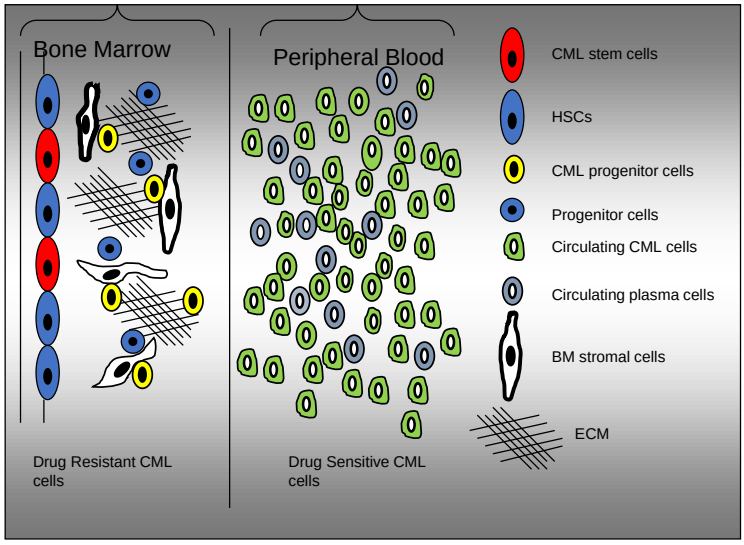
Residual Disease in CML:
BCR-ABL Independent Mechanism



Nair RR et al (2010) Biochem. Pharmacol.

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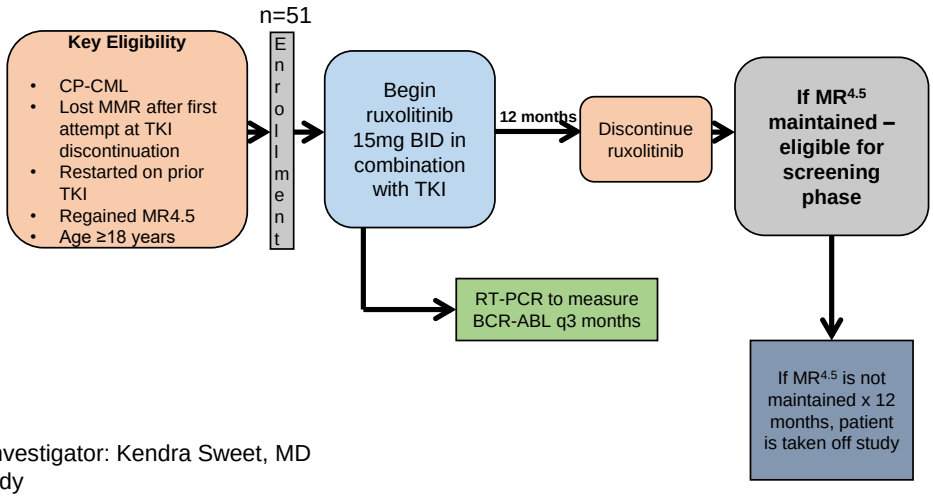
Phase II Trial for Second TFR with the J. Khoury Cure CML Consortium

Treatment Phase



Principal Investigator: Kendra Sweet, MD
HJKC3 study

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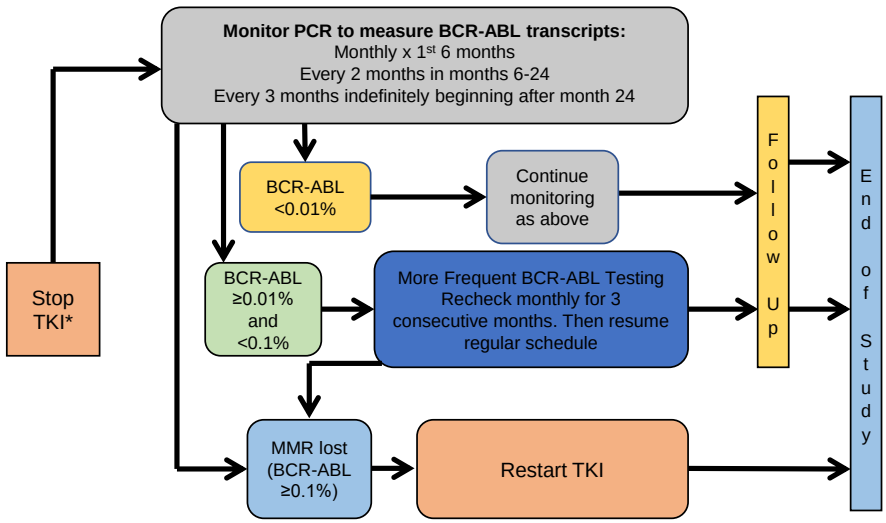
Treatment Free Remission Phase



Primary endpoint: TFR rate at 12 months
Will be open at 8 CML Consortium sites
Planned enrollment: 51
Current enrollment: 19

* Beginning day 1 of TFR Phase

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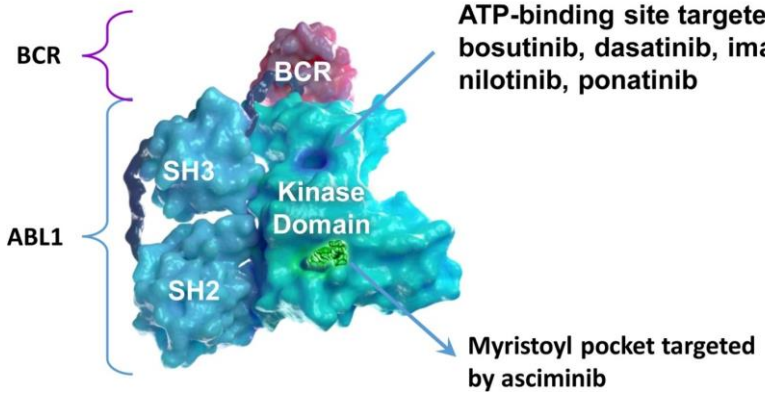
How is Asciminib Different?

Assembled inactive conformation ABL1



Manley P. Leukemia Research. Vol 98, Nov 2020 Pg 1-11.

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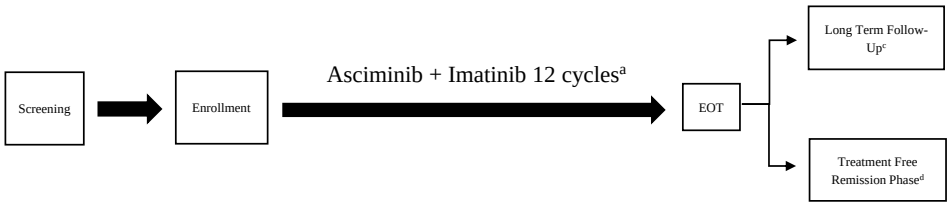
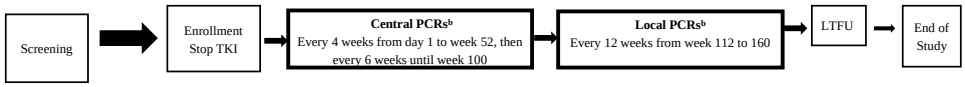
Second TFR trial
Asciminib + Imatinib

Combination Phase



Treatment Free Remission (TFR) Phase



Principal Investigator: Michael J. Mauro, MD
HJKC3 study

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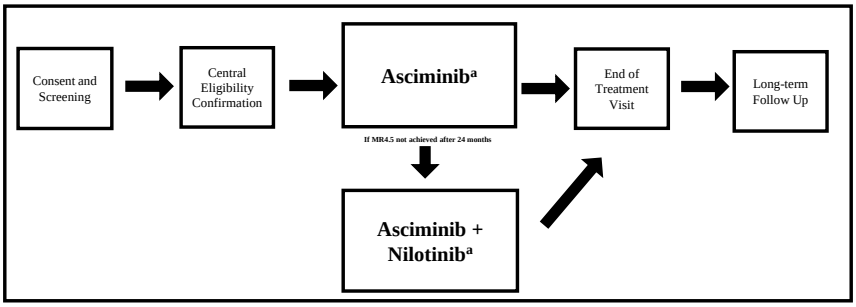
Frontline Asciminib ± Nilotinib



a. Patients will discontinue study treatment if they experience disease progression, or unacceptable toxicity. In addition, eligible patients may discontinue study treatment for elective treatment discontinuation of asciminib and, if applicable, nilotinib (eligible if sustained MR4.5 for at least 2 years), after four years of single agent asciminib, or two years of combination therapy (asciminib and nilotinib).

Principal Investigator: Jorge Cortes, MD
HJKC3 study

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ASK A QUESTION

SPOTLIGHT ON CHRONIC MYELOID LEUKEMIA (CML)

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.

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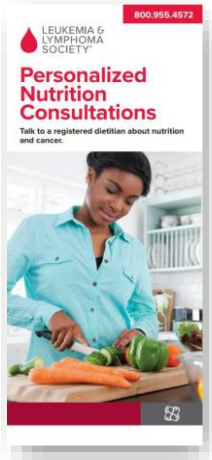
LLS EDUCATION & SUPPORT RESOURCES

HOW TO CONTACT US:

To contact an **Information Specialist** about disease, treatment and support information, resources and clinical trials:

Call: (800) 955-4572
Monday to Friday, 9 a.m. to 9 p.m. ET
Chat live online: www.LLS.org/InformationSpecialists
Monday to Friday, 10 a.m. to 7 p.m. ET
Email: www.LLS.org/ContactUs
All email messages are answered within one business day.

CLINICAL TRIAL SUPPORT CENTER
Work one-on-one with an LLS Clinical Trial Nurse Navigator who will help you find clinical trials and personally assist you throughout the entire clinical-trial process.
www.LLS.org/Navigation



NUTRITION CONSULTATIONS
Our registered dietitian has expertise in oncology nutrition and provides free one-on-one consultations by phone or email.
www.LLS.org/Consult.

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LLS EDUCATION & SUPPORT RESOURCES

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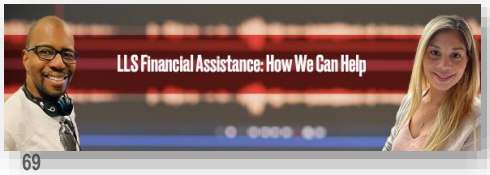
Online Chats are free, live sessions, moderated by oncology social workers. To register for one of the chats below, or for more information, please visit **www.LLS.org/Chat**

Education Videos

View our free education videos on disease, treatment, and survivorship. To view all patient videos, please visit **www.LLS.org/EducationVideos**



Patient Podcast

The Bloodline with LLS is here to remind you that after a diagnosis comes hope. To listen to an episode, please visit **www.TheBloodline.org**

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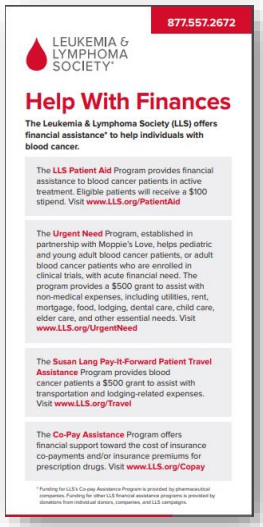
LLS EDUCATION & SUPPORT RESOURCES



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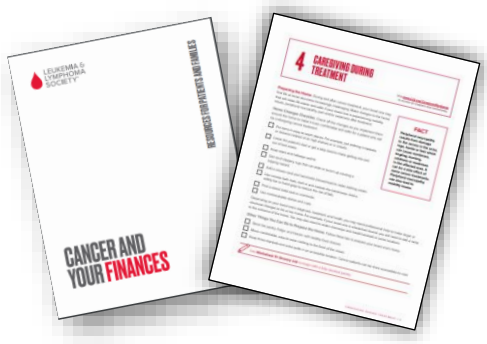
The Leukemia & Lymphoma Society (LLS) offers the following financial assistance programs to help individuals with blood cancers: www.LLS.org/Finances



To order free materials: **www.LLS.org/Booklets**

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THANK YOU
We have one goal: A world without blood cancers
LEUKEMIA & LYMPHOMA SOCIETY®