Case Presentations 11:35-12:15

Ehab Atallah

knowledge changing life

MEDICAL COLLEGE OF WISCONSIN

Conflicts of Interest

- Research support: Novartis, Incyte, Takeda
- Speakers bureau: BMS, Abbvie
- Advisory board: Abbvie, Novartis,

OVERVIEW

- AML
  - AML therapy overview
  - Intensive chemotherapy
  - Azacitidine + venetoclax
  - AML with FLT3 mutation
  - AML with IDH1 mutation
- CML
  - Overview
  - Refractory CML
  - Treatment Free Remisson

Case Presentation

- 67 year old woman c/o easy bruising and fatigue
- Has PMH of diabetes, hypertension, COPD and obesity
- Has a very supportive family
- Labs:
  - WBC count: 50,000 cells/$mm^{3,}$ 60% blasts
  - Hemoglobin: 8.4 gm/dl
  - Platelet count: 36,000 cells/mm^3

BM biopsy/aspirate: Normal cytogenetics, myeloid malignancy panel pending

What is your treatment choice?

7 + 3 (Cytarabine + daunorubicin)

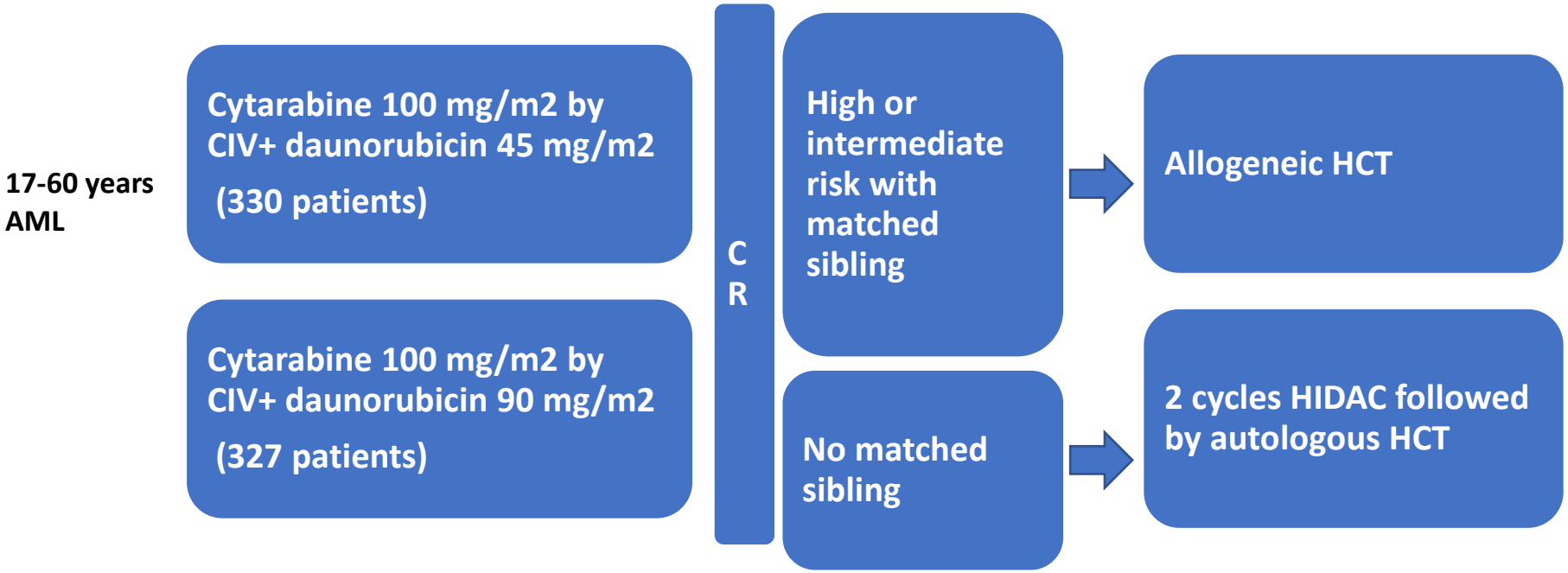
Azacitidine + venetoclax

CPX-351

Azacitidine

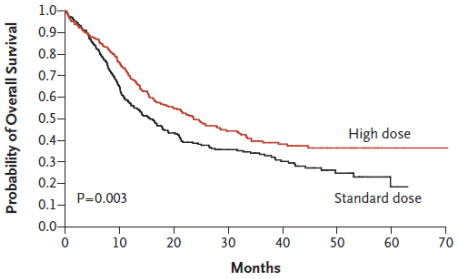
None of the above

High-Dose Daunorubicin in Patients with Acute Myeloid Leukemia



Fernandez et al. NEJM. September 24, 2009

High Dose vs. Standard Dose Daunorubicin Response and Survival

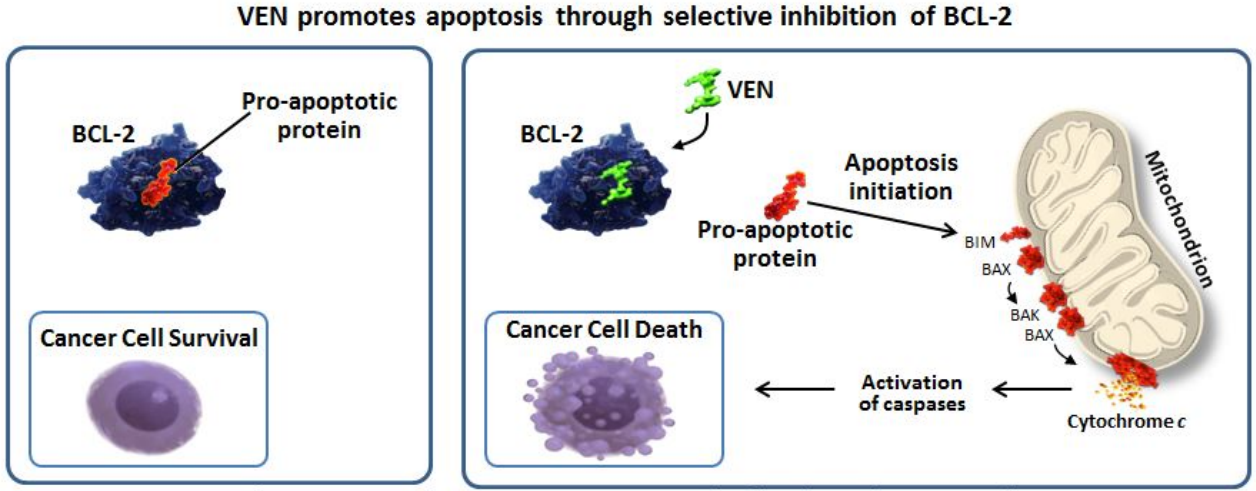


Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m^2/day)	330	199	131	15.7 mo
High dose (90 mg/m^2/day)	327	168	159	23.7 mo

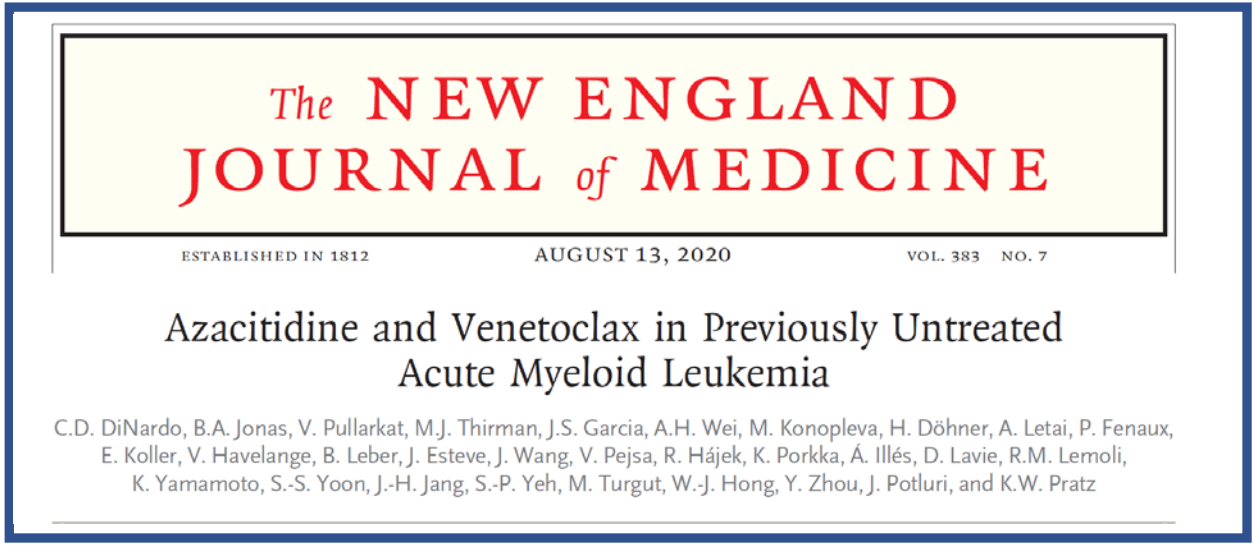
	CR	Median Survival	Mortality %
High dose	70.6%	23.7	5.5
Standard dose	57.3%	15.7	4.5

Fernandez et al. NEJM. September 24, 2009

Venetoclax Mechanism of Action



1. Leverson JD, et al. *Sci Transl Med* 2015; 7:279-40.
2. Czabotar OA, et al. *Nature Reviews* 2014;15:49-63.
3. Plati J, et al. *Integr Biol (Camb)* 2011;3:279–96.
4. Certo M, et al. *Cancer Cell*. 2006;9:351-65.
5. Souers AJ, et al. *Nat Med*. 2013;19:202-8.
6. Del Gaizo Moore V, et al. *J Clin Invest*. 2007;117:112-21.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 13, 2020 VOL. 383 NO. 7

Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia

C.D. DiNardo, B.A. Jonas, V. Pullarkat, M.J. Thirman, J.S. Garcia, A.H. Wei, M. Konopleva, H. Döhner, A. Letai, P. Fenaux, E. Koller, V. Havelange, B. Leber, J. Esteve, J. Wang, V. Pejsa, R. Hájek, K. Porkka, Á. Illés, D. Lavie, R.M. Lemoli, K. Yamamoto, S.-S. Yoon, J.-H. Jang, S.-P. Yeh, M. Turgut, W.-J. Hong, Y. Zhou, J. Potluri, and K.W. Pratz

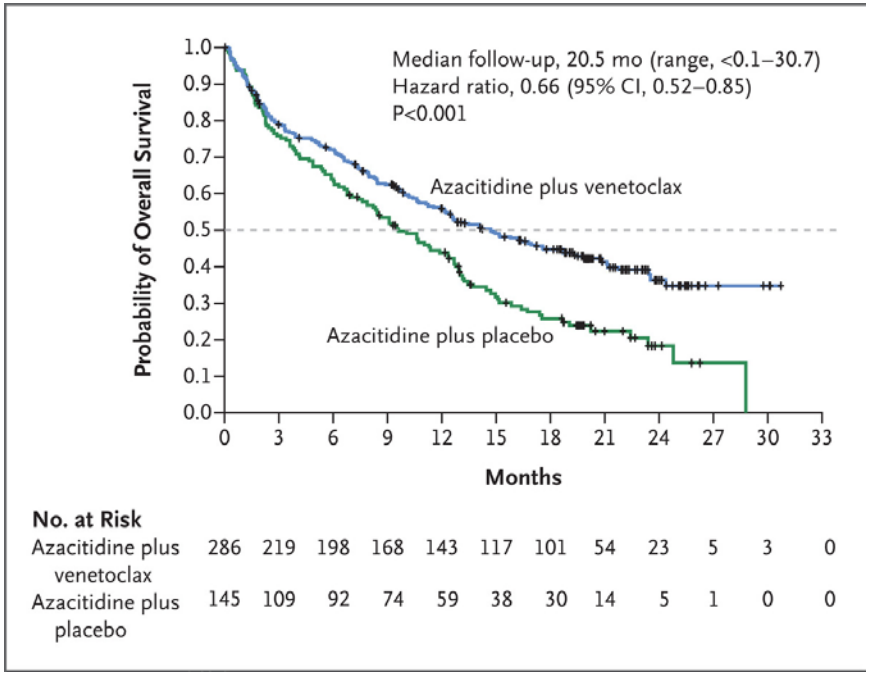
-≥18 years
-Untreated AML
-Ineligible for standard induction therapy
-Randomized 2:1
-N=431

Azacitidine 75 mg/m^2 x 7 days IV/SQ
+ venetoclax 400 mg daily
(after dose ramp up)
N=286

Azacitidine 75 mg/m^2 x 7 days IV/SQ
+ placebo
N=145

CD DiNardo et al. N Engl J Med 2020;383:617-629.

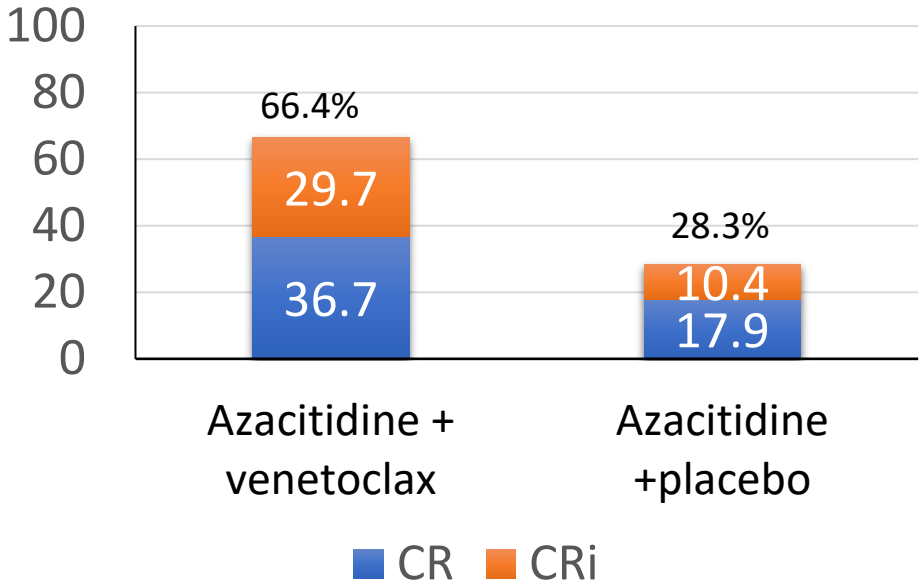
Overall Survival
Azacitidine + Venetoclax vs. Azacitidine



Median OS:
14.7 months vs. 9.6 months

CD DiNardo et al. N Engl J Med 2020;383:617-629.

Response:
Azacitidine + Venetoclax vs. Azacitidine



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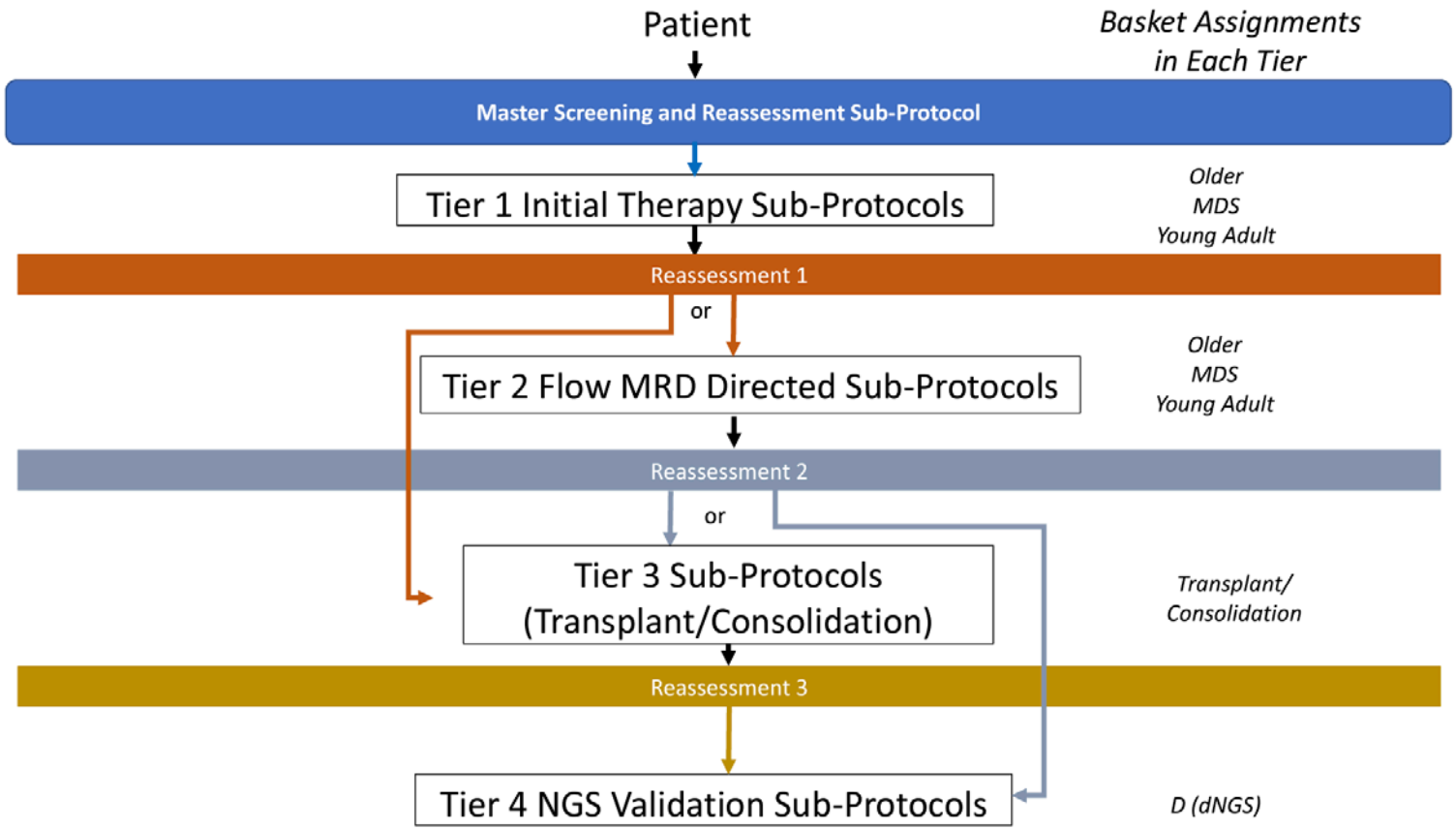
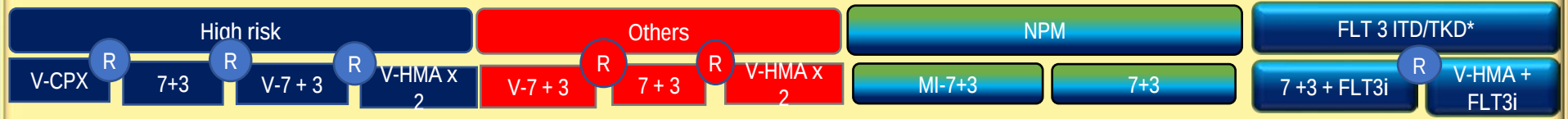

Patient
Basket Assignments in Each Tier
Master Screening and Reassessment Sub-Protocol
Tier 1 Initial Therapy Sub-Protocols
Older
MDS
Young Adult
Reassessment 1
or
Tier 2 Flow MRD Directed Sub-Protocols
Older
MDS
Young Adult
Reassessment 2
or
Tier 3 Sub-Protocols
(Transplant/Consolidation)
Transplant/
Consolidation
Reassessment 3
Tier 4 NGS Validation Sub-Protocols
D (dNGS)

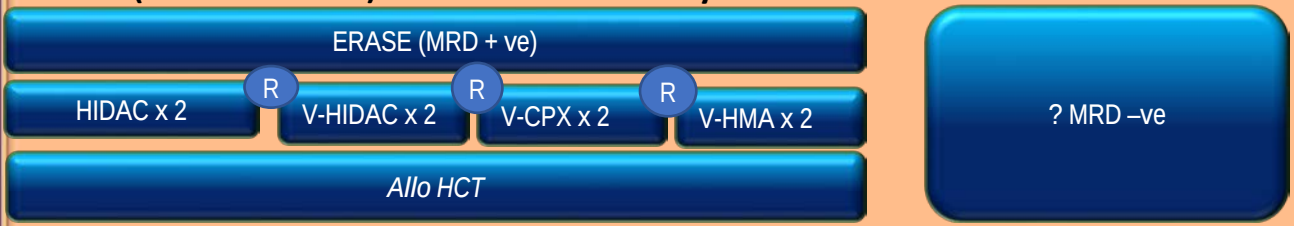
STEP1: Screening protocol — **Karyotyping, mutation analysis**

TIER 1: Separate arms/cassettes/protocols for each risk group (Investigational or SOC)



N=268 **N=153**

TIER 2 (after induction) MRD=MRD after 1st cycle



? MRD –ve

N=256

Tier 3: Early MRD detection and intervention

V=Venetoclax, HMA: Hypomethylating agents, FLT3i: FLT3 inhibitor, MI: Menin Inhibitor

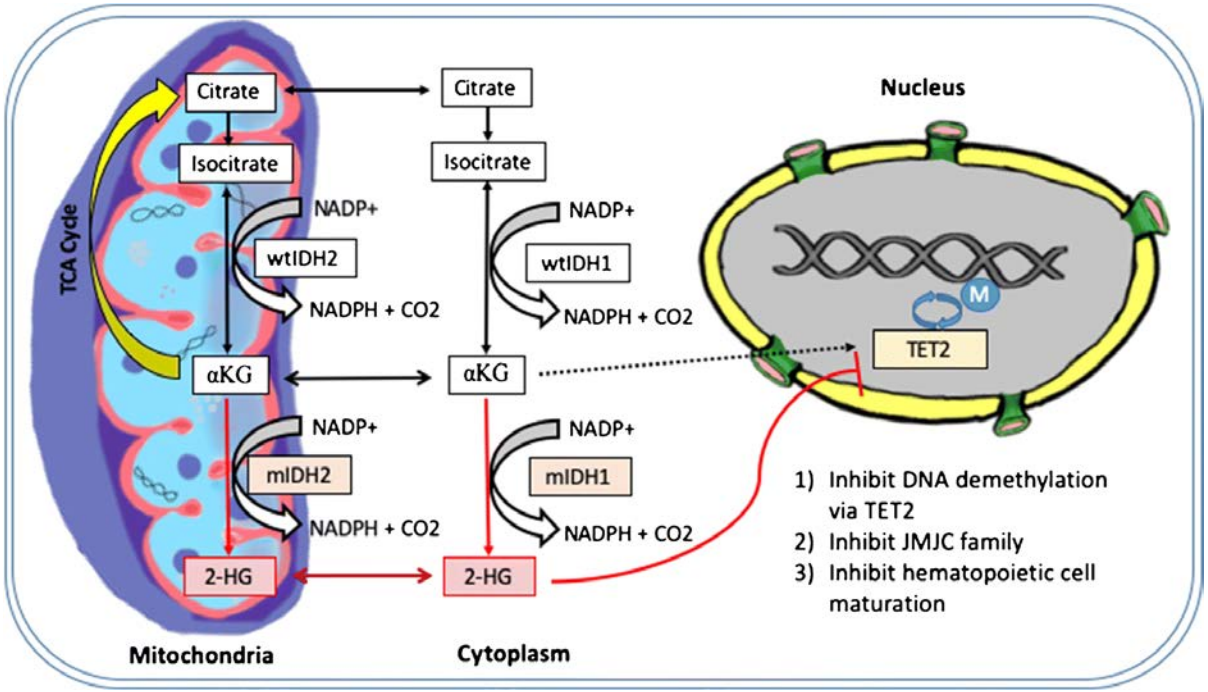
Patient presentation

- 76 year old woman, seeing you for a second opinion
- Presents with fatigue and easy bruising
- No significant PMH
- Exam: Has some bruising
- CBC:
  - WBC count: 50,000 cells/mm^3, 60% blasts
  - Hemoglobin: 8.4 gm/dl
  - Platelet count: 36,000 cells/mm^3
- IDH1 mutation on NGS

What is your treatment choice?

- Azacitidine
- Azacitidine + ivosidenib
- Azacitidine + ventoclax
- Ivosidenib
- None of the above

IDH-1 Mutation



McMurry, H.,. *Curr Hematol Malig Rep* **16**, 207–217 (2021)

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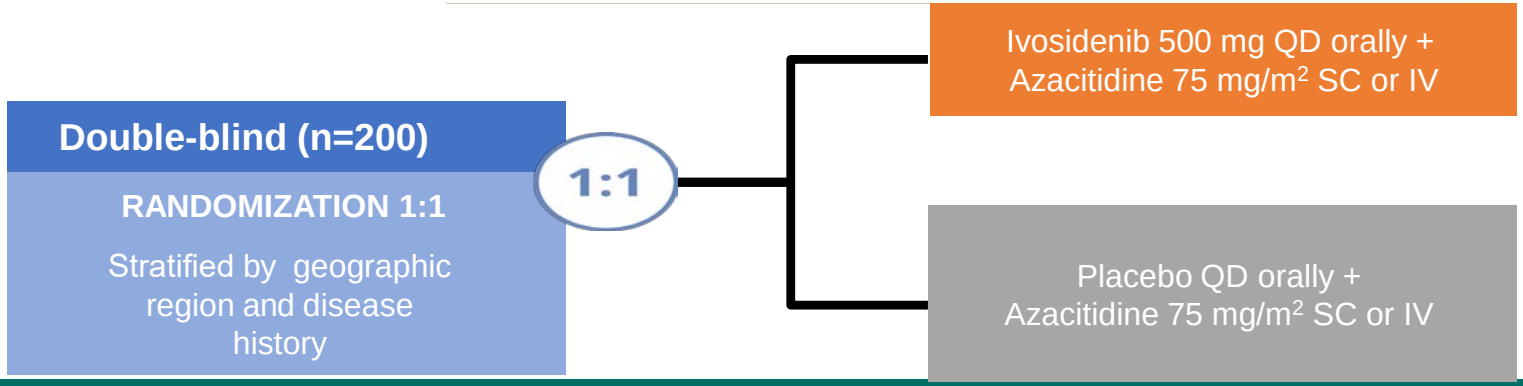
N=145

CD DiNardo et al. N Engl J Med 2020;383:617-629

ORIGINAL ARTICLE

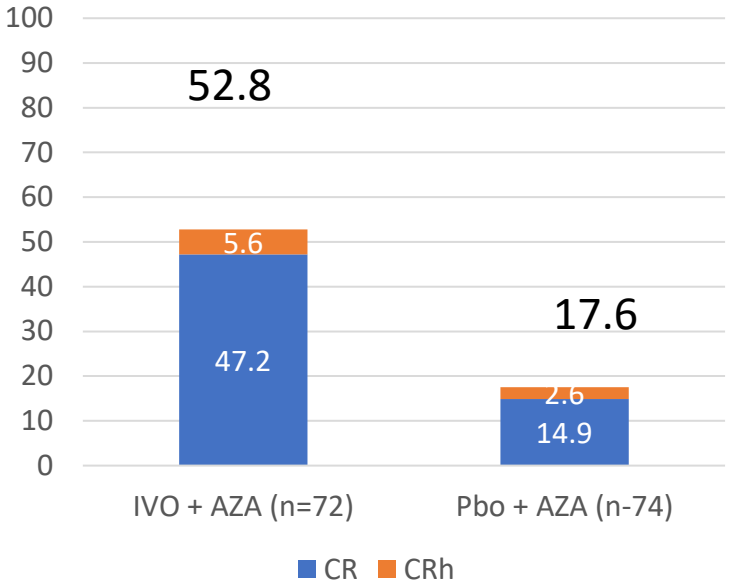
Ivosidenib and Azacitidine in *IDH1*-Mutated Acute Myeloid Leukemia

Pau Montesinos, M.D., Ph.D., Christian Recher, M.D., Ph.D., Susana Vives, M.D., Ewa Zarzycka, M.D., Jianxiang Wang, M.D., Giambattista Bertani, M.D., Michael Heuser, M.D., Rodrigo T. Calado, M.D., Ph.D., Andre C. Schuh, M.D., Su-Peng Yeh, M.D., Scott R. Daigle, M.S., Jianan Hui, Ph.D., Shuchi S. Pandya, M.D., Diego A. Gianolio, Ph.D., Stephane de Botton, M.D., Ph.D., and Hartmut Döhner, M.D.

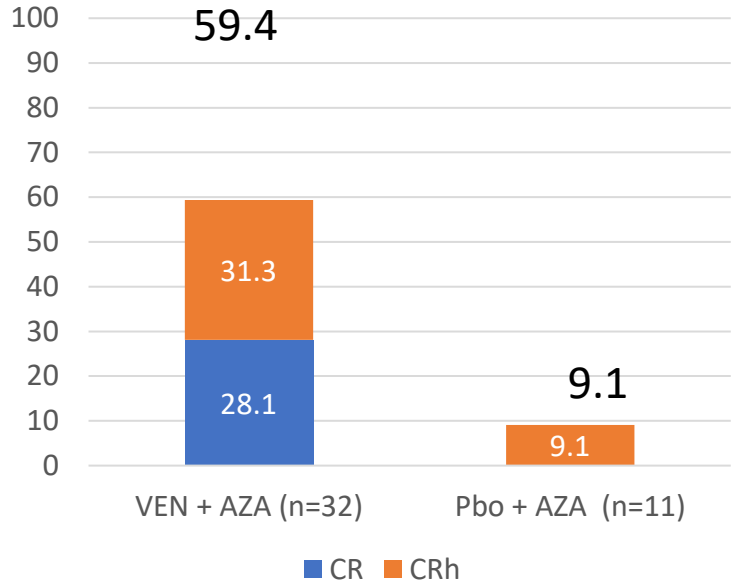


Response rate

Ivosidenib



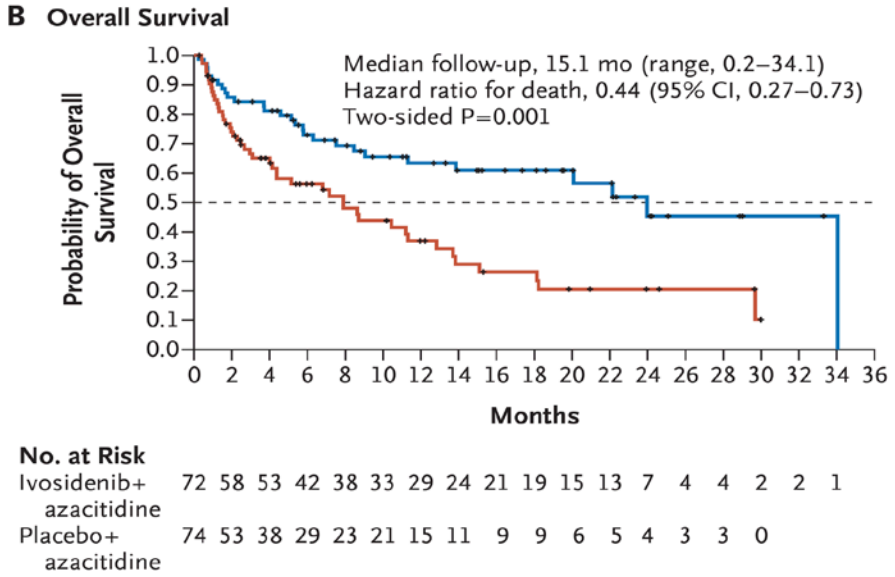
Venetoclax



Pollyea et al. *Blood* 2020; 136
Montesinos P, et al. . N Engl J Med. 2022 Apr 21;386(16):1519-1531

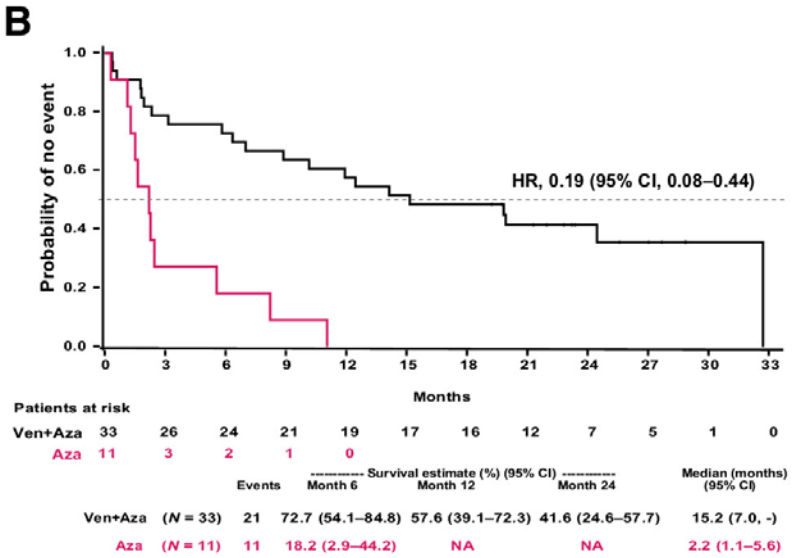
Overall Survival

Ivosidenib



Median OS, **24.0 months** vs **7.9 months**

Venetoclax



Median OS, **15.2 months** vs **2.2 months**

Pollyea et al. *Blood* 2020; 136
Montesinos P, et al. . N Engl J Med. 2022 Apr 21;386(16):1519-1531

Toxicity

Adverse events^, n (%)	VEN + AZA		PBO + AZA	
	All grade n=283	Grade 3/4 n=276	All grade n =144	Grade 3/4 n =136
Neutropenia	119 (42)	119 (42)	42 (29)	41 (29)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anemia	78 (28)	74 (26)	30 (21)	29 (20)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)

	IVO+AZA (n=71)		PBO+AZA (n=73)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	20 (28.2)	19 (26.8)	12 (16.4)	12 (16.4)
Febrile neutropenia	20 (28.2)	20 (28.2)	25 (34.2)	25 (34.2)
Anemia	22 (31.0)	18 (25.4)	21 (28.8)	19 (26.0)
Thrombocytopenia	20 (28.2)	17 (23.9)	15 (20.5)	15 (20.5)

Pollyea et al. *Blood* 2020; 136
Montesinos P, et al. . N Engl J Med. 2022 Apr 21;386(16):1519-1531

Newly Diagnosed-AML with IDH1

- Ivosidenib monotherapy (n=33)
  - CR rate was 30%, CR/CRh was 42.5%
  - median OS of 12.6 months
- Venetoclax + azacytidine:
  - CR+CRh: 59%
  - Median OS : 15.2 months
- Ivosidenib + azacitidine (n=72)
  - CR +CRh: 52.8%
  - Median OS: 24 months

Roboz, G. J. et al.. *Blood 2020;* **135**, 463–471
Pollyea et al. *Blood* 2020; 136
Montesinos P, et al. . N Engl J Med. 2022 Apr 21;386(16):1519-1531

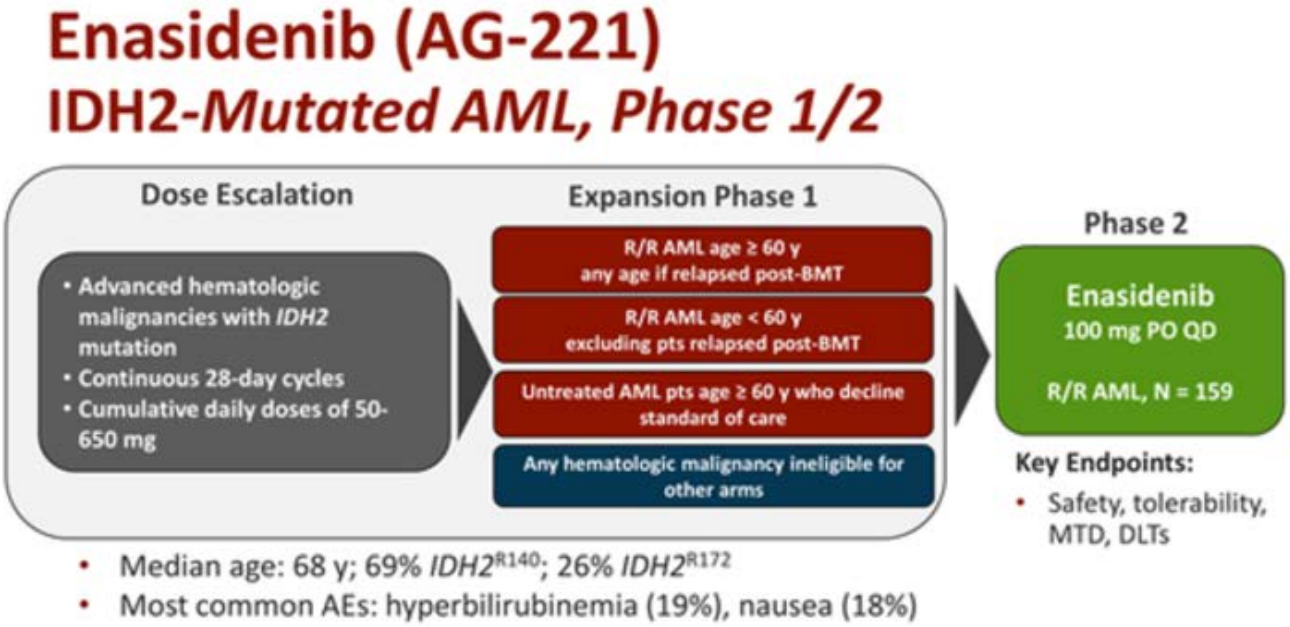
Ivosidenib-IDH 1 inhibitor-R/R AML

- Primary efficacy population=125 patients
- CR, CRh:30.4%
- The median DOR: 8.2 months
- Transfusion independence: 35%
- Adverse events:
  - QT prolongation
  - Differentiation syndrome
  - Anemia, thromobocytopenia

DiNardo et al. N Engl J Med. 2018 Jun 21;378(25):2386-2398

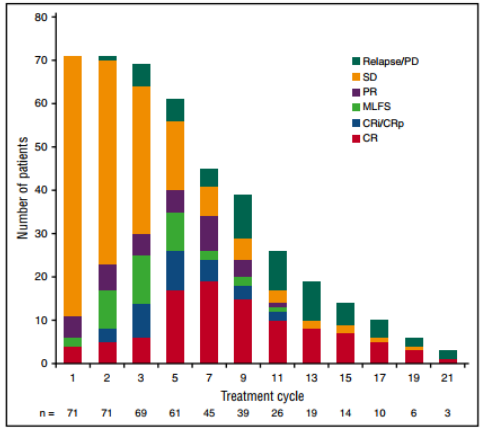
AML with IDH2 mutation

AML – New Treatment: Enasidenib

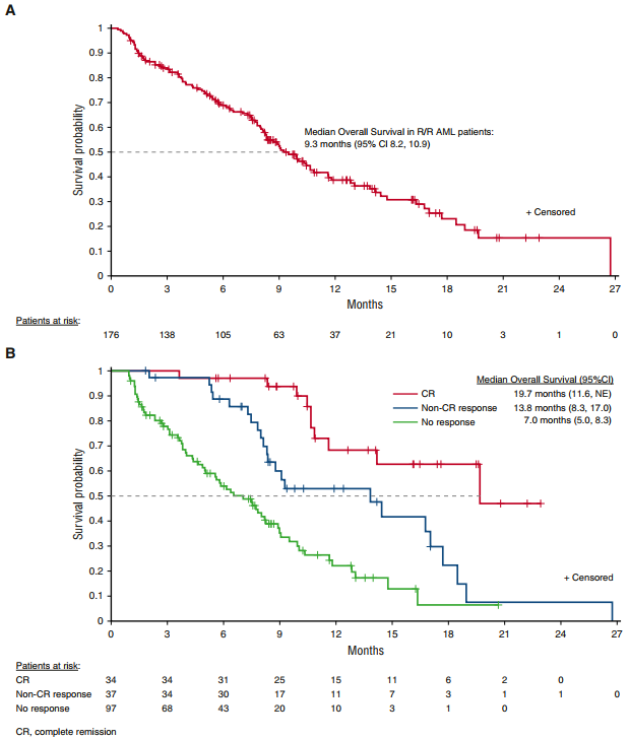


Stein EM. Blood. 2015; 126. Abstract 323.

Enasidenib-Response and Survival



Among 172 patients
- 71 patients responded
- Best response could take months to achieve



Stein EM. Blood. 2017; 130: 722-731.

Enasidenib-Adverse reactions

TEAE	Enasidenib 100 mg per day (n = 153)	
	No.	%
Hyperbilirubinemia	13	8
differentiation syndrome	11	7
Anemia	10	7
Thrombocytopenia	8	5
Tumor lysis syndrome	5	3
Decreased appetite	3	2

Patient presentation

- 76 year old man, seeing you for a second opinion
- Presents with fatigue and easy bruising
- No significant PMH
- Exam: Has some bruising
- CBC:
  - WBC count: 50,000 cells/$mm^{3,}$ 60% blasts
  - Hemoglobin: 8.4 gm/dl
  - Platelet count: 36,000 cells/mm^3
- FLT3 ITD mutation

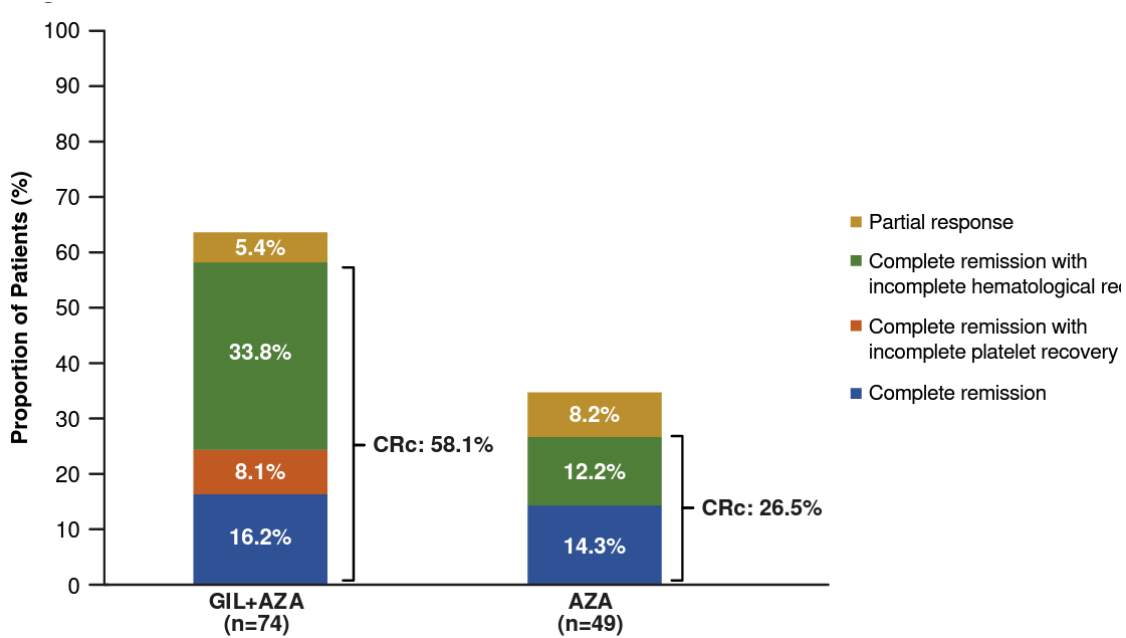
When poll is active, respond at **pollev.com/hematologyo105**

Text **HEMATOLOGYO105** to **22333** once to join

What therapy would you choose for this patient

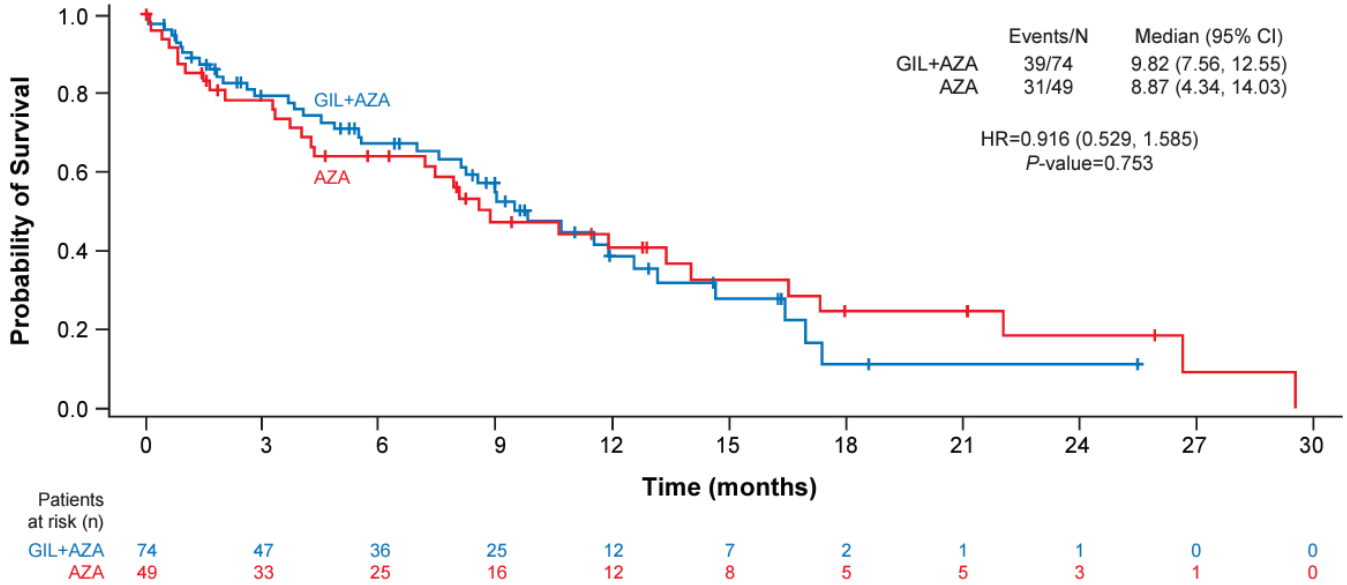
- Azacitidine
- Azacitidine + venetoclax
- Azacitidine + giltretinib
- Azacitidine + venetoclax + giltretinib
- None of the above

Response-GIL+AZA vs AZA



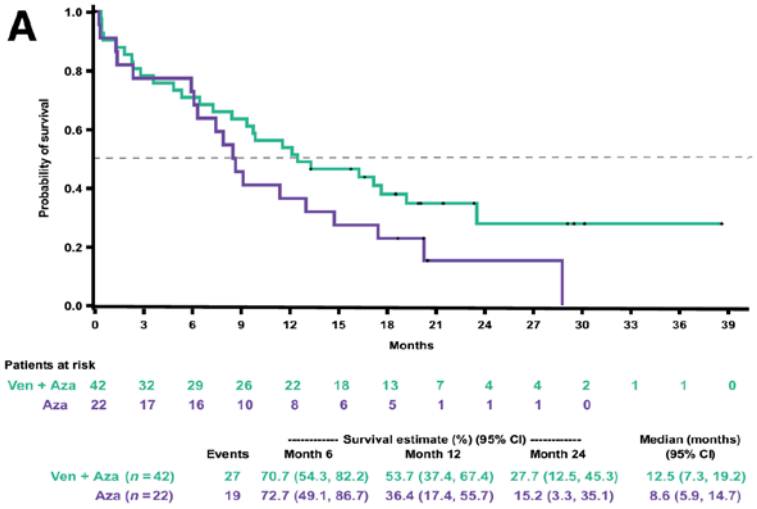
Wang E et al. Blood 2022

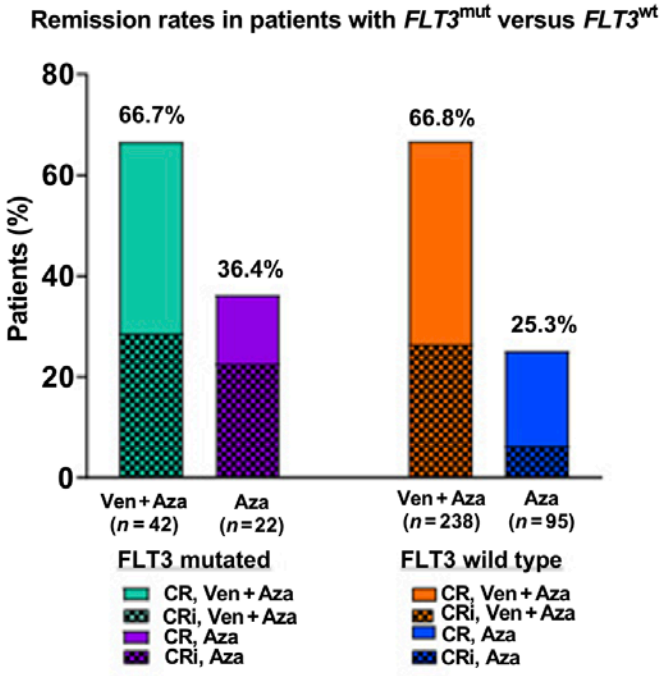
Overall Survival-GIL + AZA vs. AZA



Wang E et al. Blood 2022

FLT3-AML- Azacitidine + Venetoclax vs. Azacitidine





Konopleva et al. Clinical Cancer Research. July 2022

Combine all Three

- Decitabine 10 + venetoclax + FLT3i
- Twelve patients
- ORR:
  - CRc rate was 92%
  - MRD negativity by FCM: 56% and by
  - MRD negativity by PCR/NGS in 91% of responders
- NPM (50%), IDH1/2 (33%)

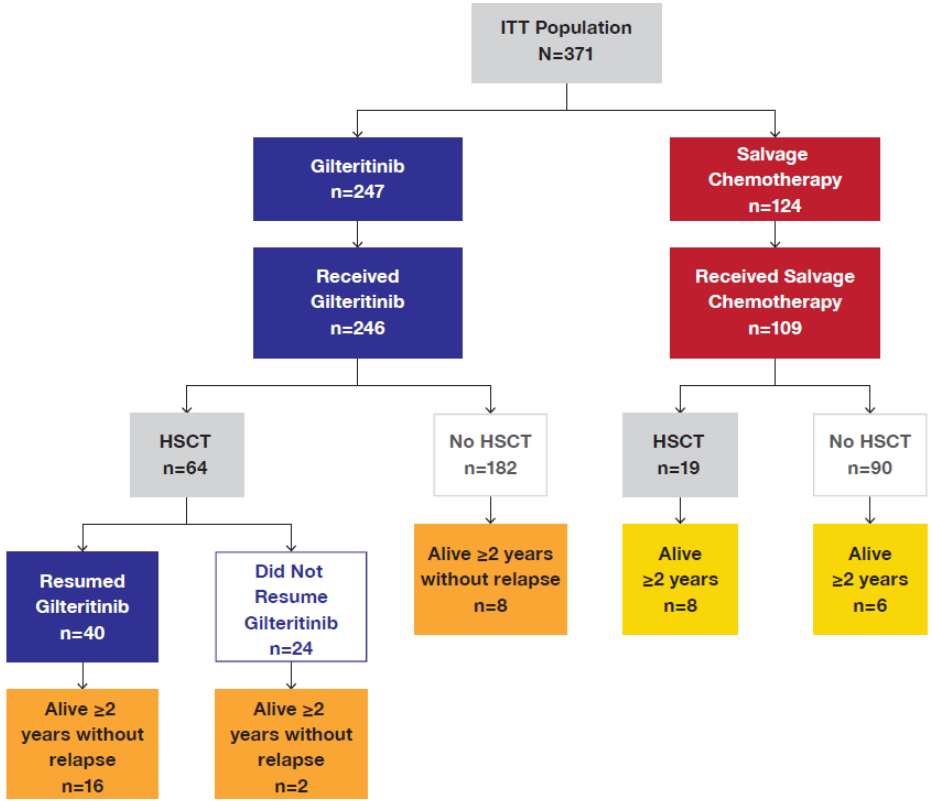
Gilteritinib in R/R AML

Follow-up of Patients With *FLT3*-Mutated Relapsed or Refractory AML in the Phase 3 ADMIRAL Trial

- Masahiro Onozawa[1]; Alexander E. Perl[2]; Richard A. Larson[3]; Nikolai A. Podoltsev[4]; Stephen Strickland[5] ; Eunice S. Wang[6] ; Ehab Atallah[7]; Gary J. Schiller[8]; Giovanni Martinelli[9]; Andreas Neubauer[10]; Jorge Sierra[11]; Pau Montesinos[12]; Christian Recher[13]; Sung-Soo Yoon[14]; Naoko Hosono[15]; Shigeru Chiba[16]; Hee-Je Kim[17]; Nahla Hasabou[18]; Qiaoyang Lu[18]; Ramon Tiu[18]; Mark J. Levis[19]

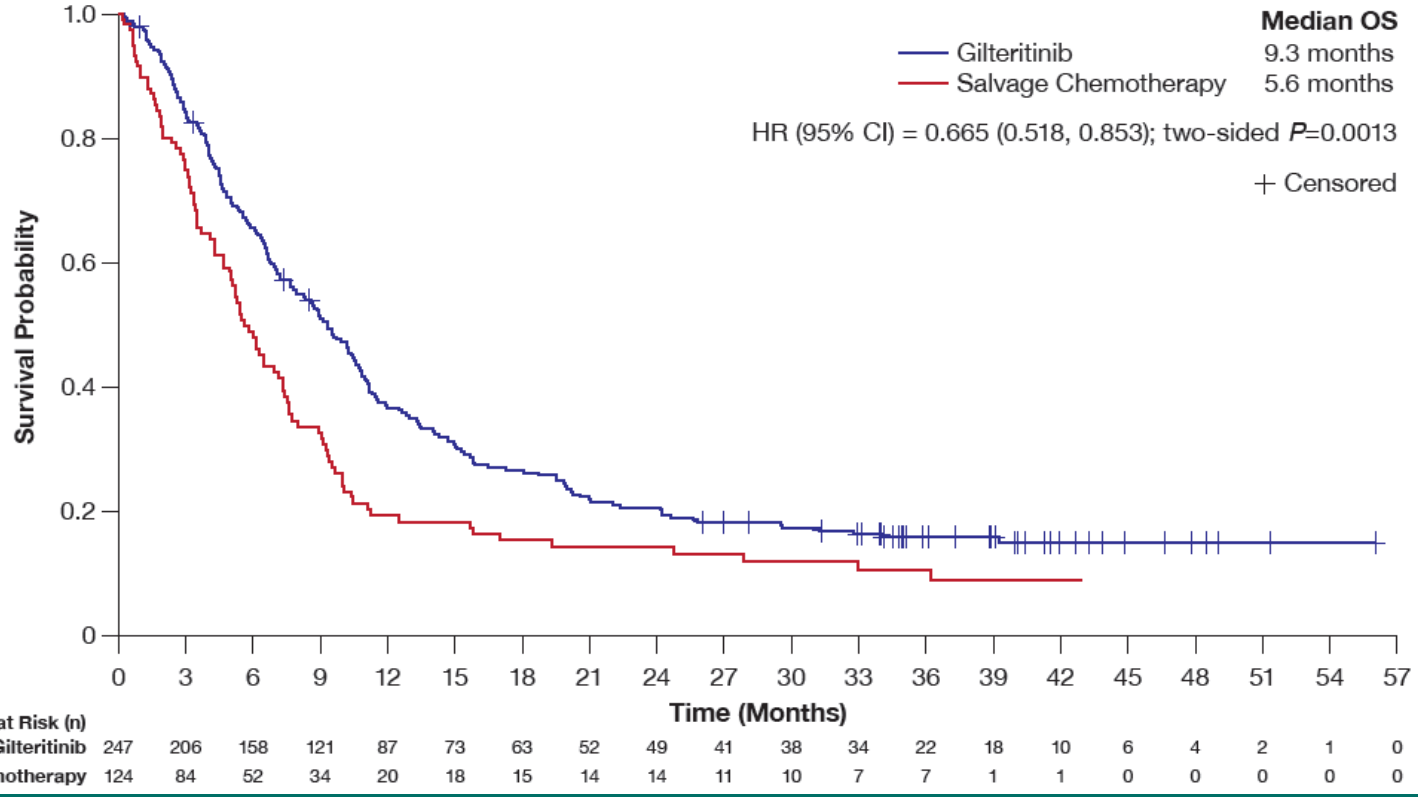
[1]Hokkaido University, Sapporo, Japan; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]University of Chicago, Chicago, IL, USA; [4]Yale School of Medicine, New Haven, CT, USA; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]Cancer Center - Froedtert Hospital, Milwaukee, WI, USA; [8]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [9]IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" – IRST S.r.l., Meldola, Italy; [10]Universitätsklinikum Giessen und Marburg GmbH, Marburg, Germany; [11]Hospital de la Santa Creu I Sant Pau and Josep Carreras Leukemia Research Institute, Barcelona, Spain; [12]University Hospital La Fe, Valencia, Spain; [13]Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse Oncopole, Université de Toulouse 3 Paul Sabatier, Toulouse, France; [14]Seoul National University Hospital, Seoul, Republic of Korea; [15]University of Fukui, Fukui, Japan; [16]Department of Hematology, University of Tsukuba, Tsukuba, Japan; [17]Catholic Hematology Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [18]Astellas Pharma US, Inc., Northbrook, IL, USA; [19]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

Patient disposition by treatment received



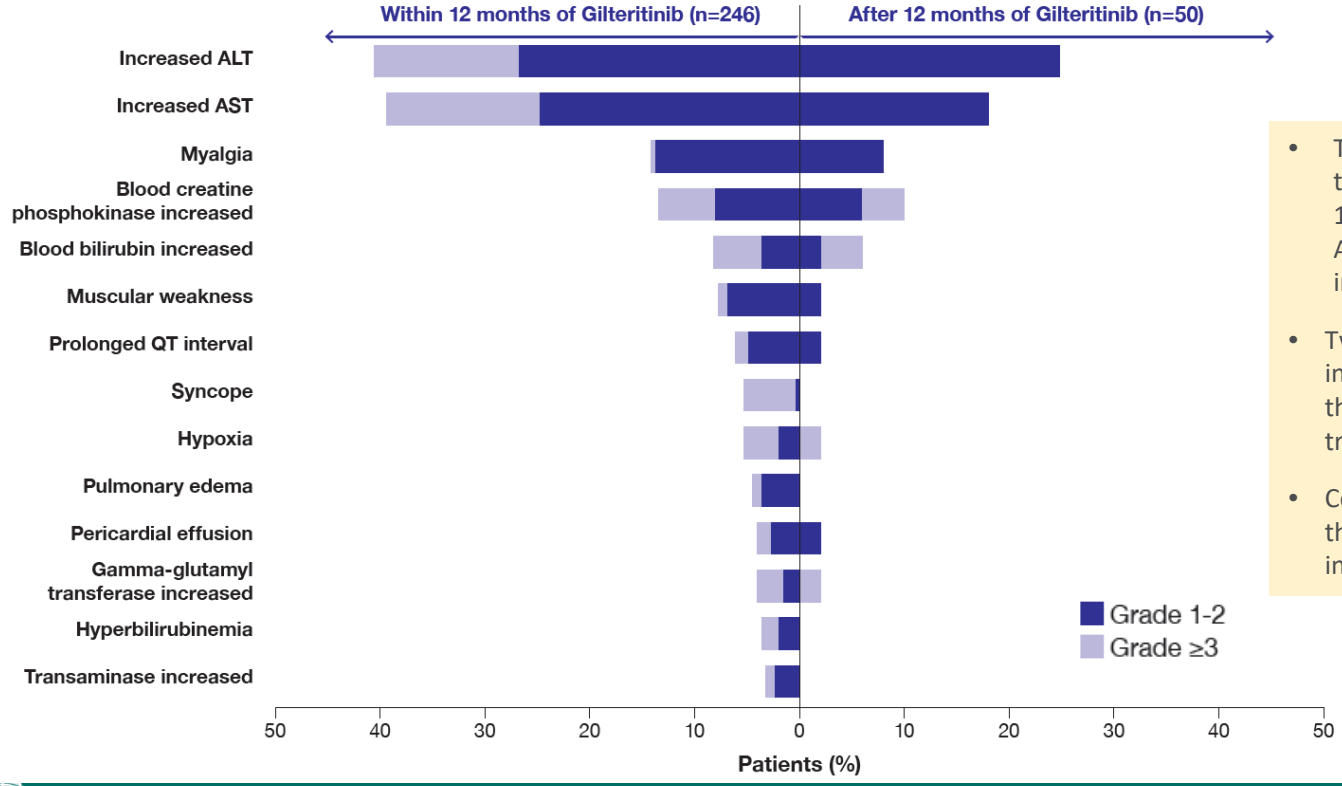
- Overall, 26 patients in the gilteritinb arm were alive without relapse for ≥2 years
- Of the 26 patients in the gilteritinib arm living without relapse for ≥2 years, 16 remained on gilteritinib therapy

Overall Survival in R/R *FLT3*$^{mut+}$ AML Patients: ITT population



Abbreviations: CI, confidence interval; *FLT3*$^{mut+}$, *FLT3*-mutation–positive; HR, hazard ratio; ITT, intention-to-treat; OS, overall survival; R/R, relapsed or refractory.

Adverse Events of Interest During and After First Year of Gilteritinib Therapy



- The most common AEIs in patients treated with gilteritinib during Years 1 and 2 of treatment were increased ALT and AST levels (mostly grade 1/2 in severity)
- Twelve patients experienced increased ALT/AST levels during Year 1 that persisted in Year 2 of gilteritinib treatment.
- Compared with Year 1 of gilteritinib therapy, Year 2 saw a decline in the incidence of AEIs

Abbreviations: AEIs, adverse events of interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Summary

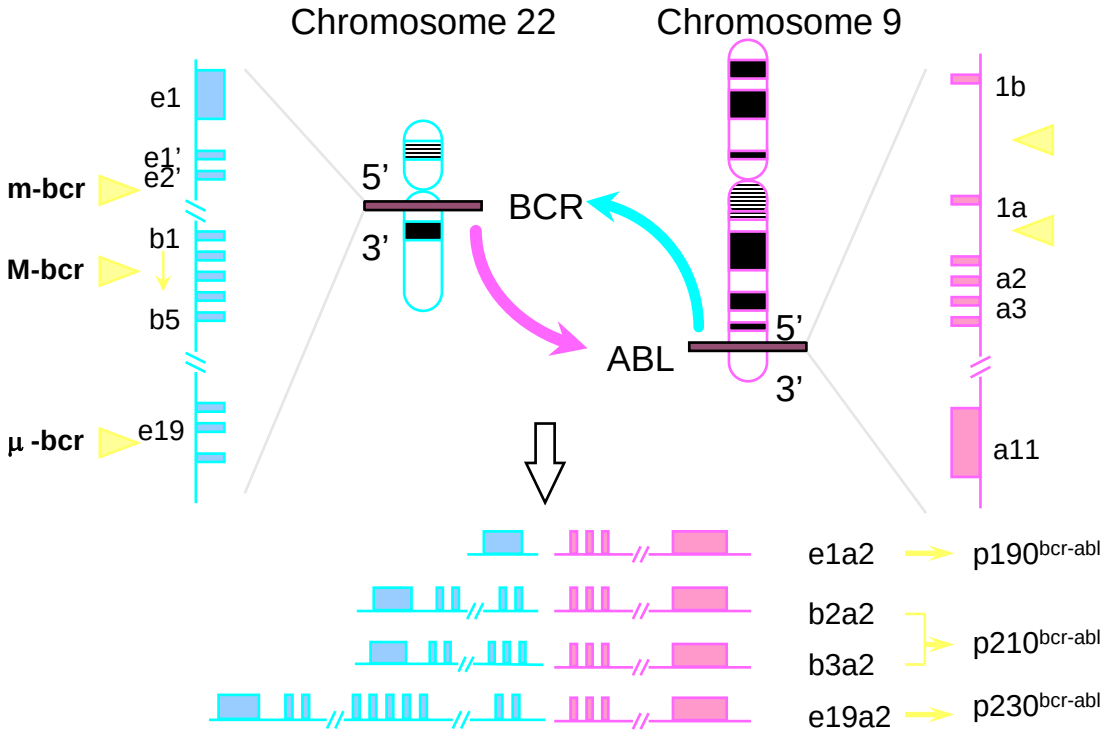
- Eligibility for intensive chemotherapy is the first decision in magament algorithm
- Cooperative group studies will evaluate the role of high intensity vs. low intensity therapy in Myelomatch
- For older patients not candidates for intensive chemotherapy decision based on mutation analysis

Chronic Myeloid Leukemia

Overview

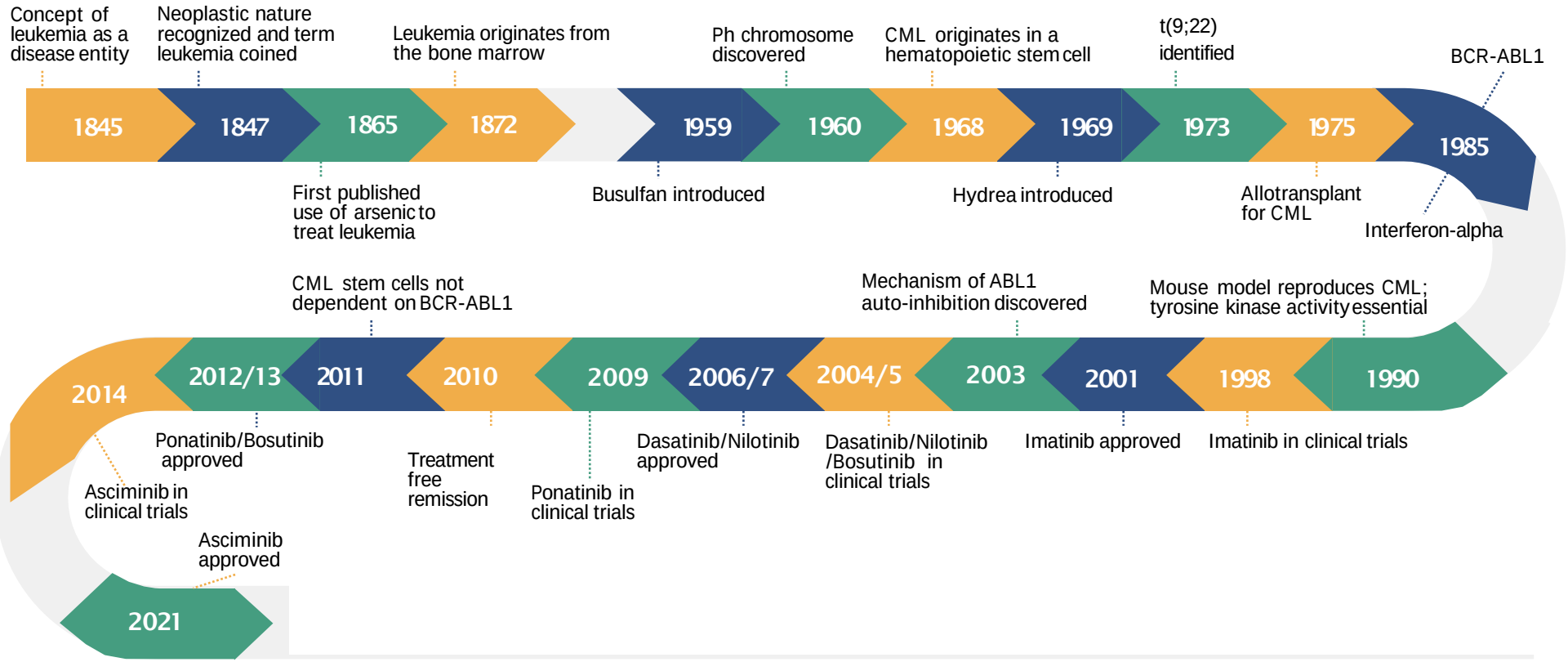
- CML
  - Background
  - Management of patients with refractory disease
  - Treatment Free Remission

The Philadelphia Chromosome



Natural History of CML

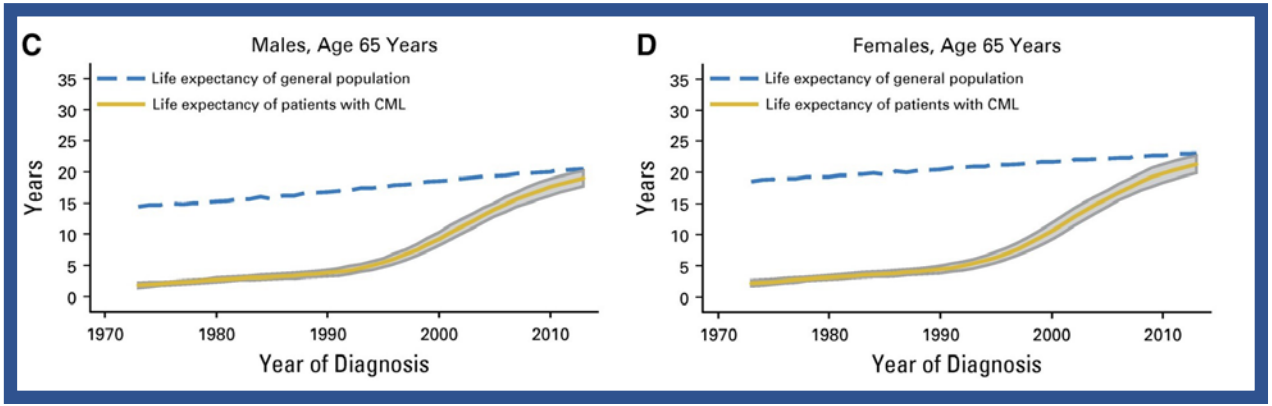
Chronic phase (CP)	Accelerated phase (AP)	Blast phase (BP)
Ph+	Cytogenetic changes Increasing blasts	
Median survival 3-5 years	12-24 mo	3-6 mo


Concept of leukemia as a disease entity
Neoplastic nature recognized and term leukemia coined
Leukemia originates from the bone marrow
Ph chromosome discovered
CML originates in a hematopoietic stem cell
t(9;22) identified
BCR-ABL1
1845
1847
1865
1872
1959
1960
1968
1969
1973
1975
1985
First published use of arsenic to treat leukemia
Busulfan introduced
Hydrea introduced
Allotransplant for CML
Interferon-alpha
CML stem cells not dependent on BCR-ABL1
Mechanism of ABL1 auto-inhibition discovered
Mouse model reproduces CML; tyrosine kinase activity essential
2014
2012/13
2011
2010
2009
2006/7
2004/5
2003
2001
1998
1990
Ponatinib/Bosutinib approved
Asciminib in clinical trials
Treatment free remission
Ponatinib in clinical trials
Dasatinib/Nilotinib approved
Dasatinib/Nilotinib /Bosutinib in clinical trials
Imatinib approved
Imatinib in clinical trials
Asciminib approved
2021

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

Life Expectancy of Patients with CML



Patients of all ages diagnosed with CML will lose < 3 life-years as a result of CML

Bower et al. J Clin Oncol.2016 Aug 20;34(24):2851-7

Life Expectancy of Patients with CML

Leukemia (2020) 34:333–335
https://doi.org/10.1038/s41375-019-0699-y

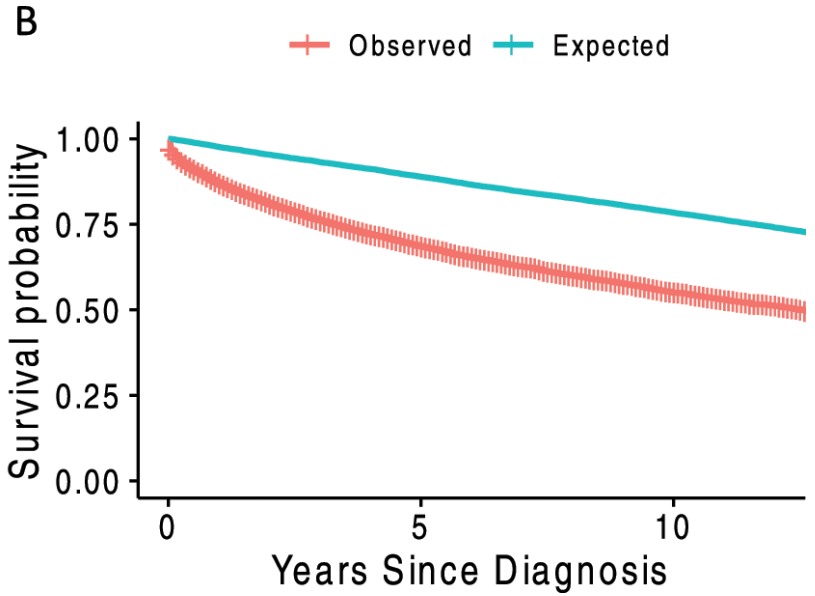
EDITORIAL

Chronic myelogenous leukemia

Do persons with chronic myeloid leukaemia have normal or near normal survival?

Tomas Radivoyevitch[1] · Davis Weaver[2] · Brian Hobbs[1] · Jaroslaw P. Maciejewski[1] · Rudiger Hehlmann[3] · Qian Jiang[4] · Andreas Hochhaus[5] · Robert Peter Gale[6]

Received: 13 October 2019 / Revised: 14 November 2019 / Accepted: 12 December 2019 / Published online: 20 December 2019



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
- Starts dasatinib 100 mg daily

Initial Response

Depth

Duration

Response Monitoring-BCR::ABL1 by PCR

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%,	>1%, resistance mutations, high-risk ACA

Hochhaus A et al. Leukemia 2020

Continue follow up-3 months

Patient results

BCR::ABL1: 12%

	Optimal	Warning	Failure
3 months	≤10%	>10%	>10% if confirmed within 1–3 months

Continue follow up-6 months

Patient results

BCR::ABL1: 12%

BCR::ABL1: 8%

	Optimal	Warning	Failure
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%

Continue follow up-12 months

Patient results

BCR::ABL1: 12%

BCR::ABL1: 8%

BCR::ABL1: 6%

	Optimal	Warning	Failure
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%

What would you do next for this patient?

Assess adherence, check BCR::ABL1 mutation and bone marrow biopsy and switch to another TKI based on mutation analysis

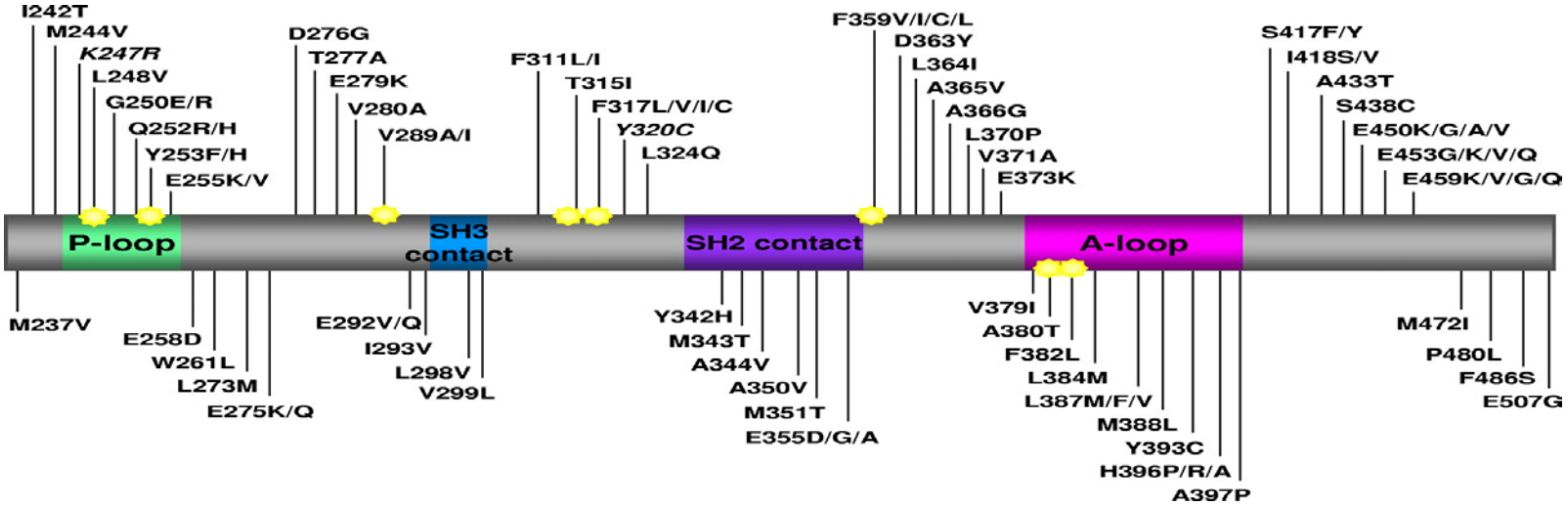
Continue close observation

Call Ehab Atallah at 262-744-9174 or email at eatallah@mcw.edu

None of the above

- Patient is adherent to medications
- BM biopsy:
  - Blasts 2%
  - No other cytogenetic abnormalities
- BCR::ABL1 mutation analysis:
  - T315I mutation

BCR-ABL kinase domain mutation



Simona Soverini,et al. Blood, 2011

Choice of TKI

Mutations poorly sensitive to dasatinib	V299L, T315I, T315A, F317L, F317V, F317I, F317C
Mutations poorly sensitive to nilotinib	Y253H, E255K, E255V, T315I, F359V, F359I, F359C
Mutations poorly sensitive to bosutinib	E255V, E255K, V299L, T315I
Mutations poorly sensitive to ponatinib	T315M, T315L

Soverini et al. *J Hematol Oncol* **12**, 131 (2019).

What would you next for this patient

Start ponatinib 15 mg daily

Start ponatinib 30 mg daily and reduce to 15 mg daily once in MMR

Start ponatinib 45 mg daily and reduce to 15 mg daily once in MMR

Asciminib 200 mg twice daily

Asciminib 40 mg twice daily

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%)

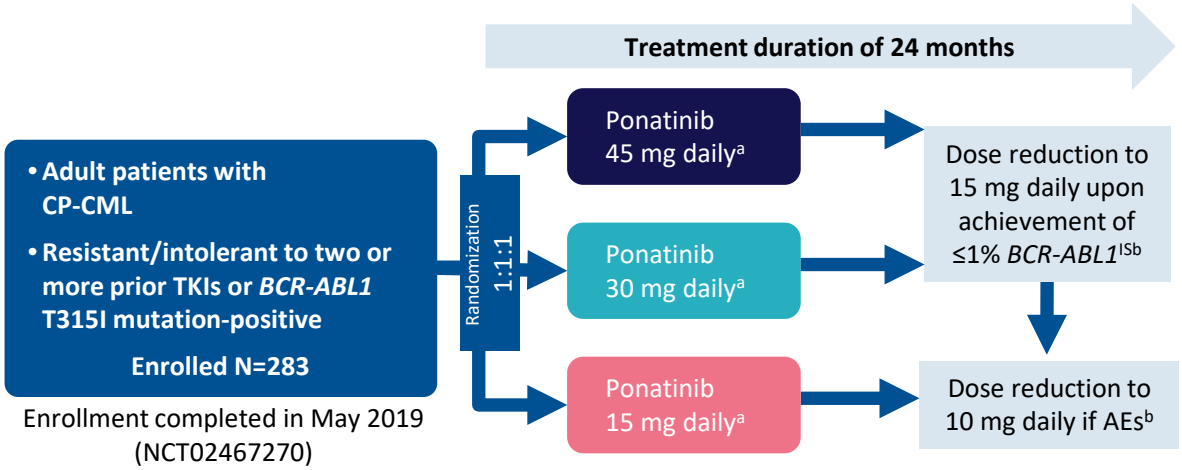
Cortes JE, et al. *ASH Annual Meeting Abstracts.* 2013: Abstract 650.

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.

OPTIC (Optimizing Ponatinib Treatment In CP-CML): Ongoing, Multicenter, Randomized Phase 2 Trial



Enrollment completed in May 2019 (NCT02467270)

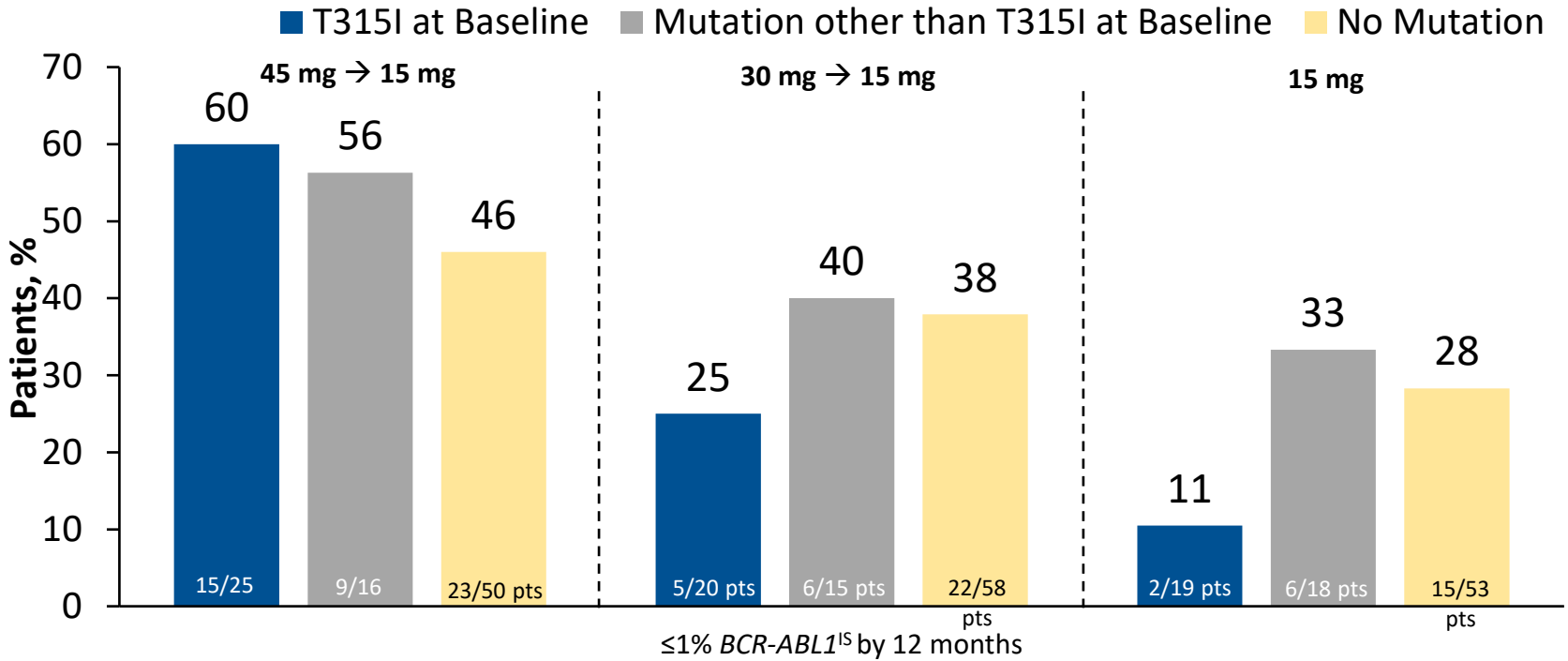
Primary endpoint[c]
≤1% *BCR-ABL1*[IS] ***at*** 12 months

- Statistical analysis
  - N ≥92 patients/cohort distinguished a favorable ≤1% *BCR-ABL1*[IS] rate of 35% from a null/uninteresting rate of 20% with a nominal 80% power and one-sided type I error rate of 0.0083 (exact binomial test)

- Median (range) duration of follow-up: 32 months (1–57)
- Minimum follow-up (date last patient was randomized to data cutoff date [5/31/20]): 12.8 months

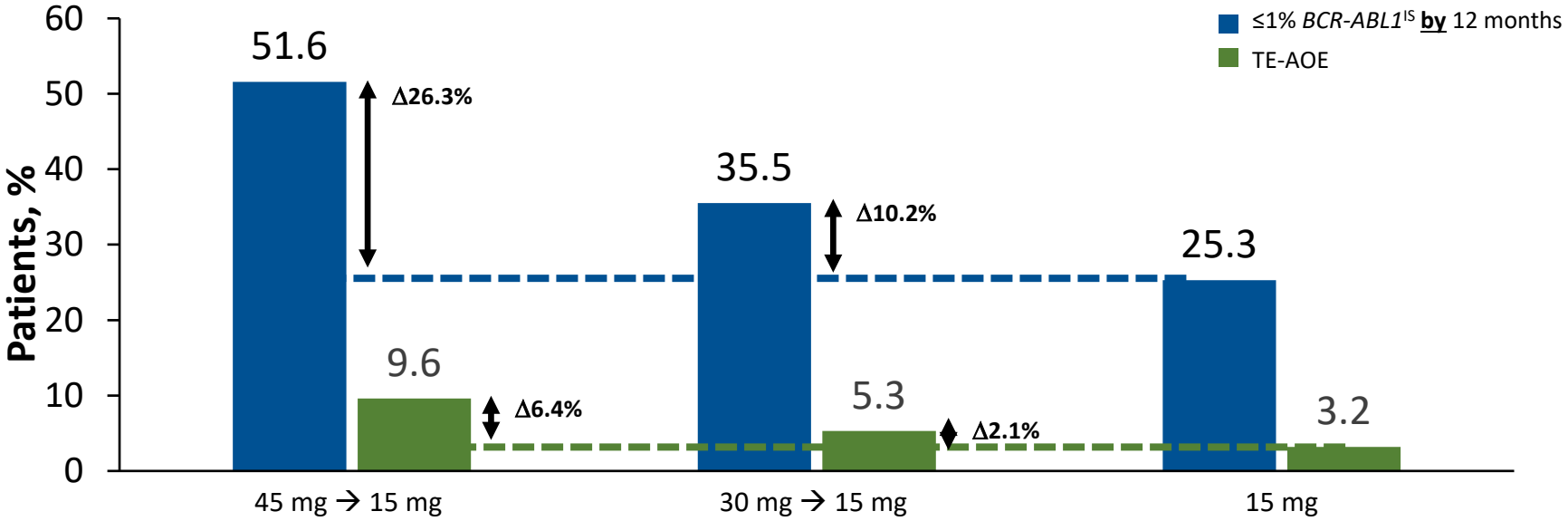
AE, adverse event; CML, chronic myeloid leukemia; CP, chronic phase; IS, International Scale; MCyR, major cytogenetic response; MMR, major molecular response.
[a]Dose reductions due to AEs were permitted.
[b]Escalation to the starting dose allowed for patients who lost their response following dose reduction; no dose escalation allowed beyond starting dose.
[c]Key secondary endpoints: MMR rate at 12 and 24 months, MCyR rate by 12 months, duration of MMR, and safety across the 3 doses.

≤1% *BCR-ABL1*^{IS} Response Rate by 12 Months[a] by T315I Baseline Status



[a]Patients on study who had not reached 12 months were excluded from the denominator.

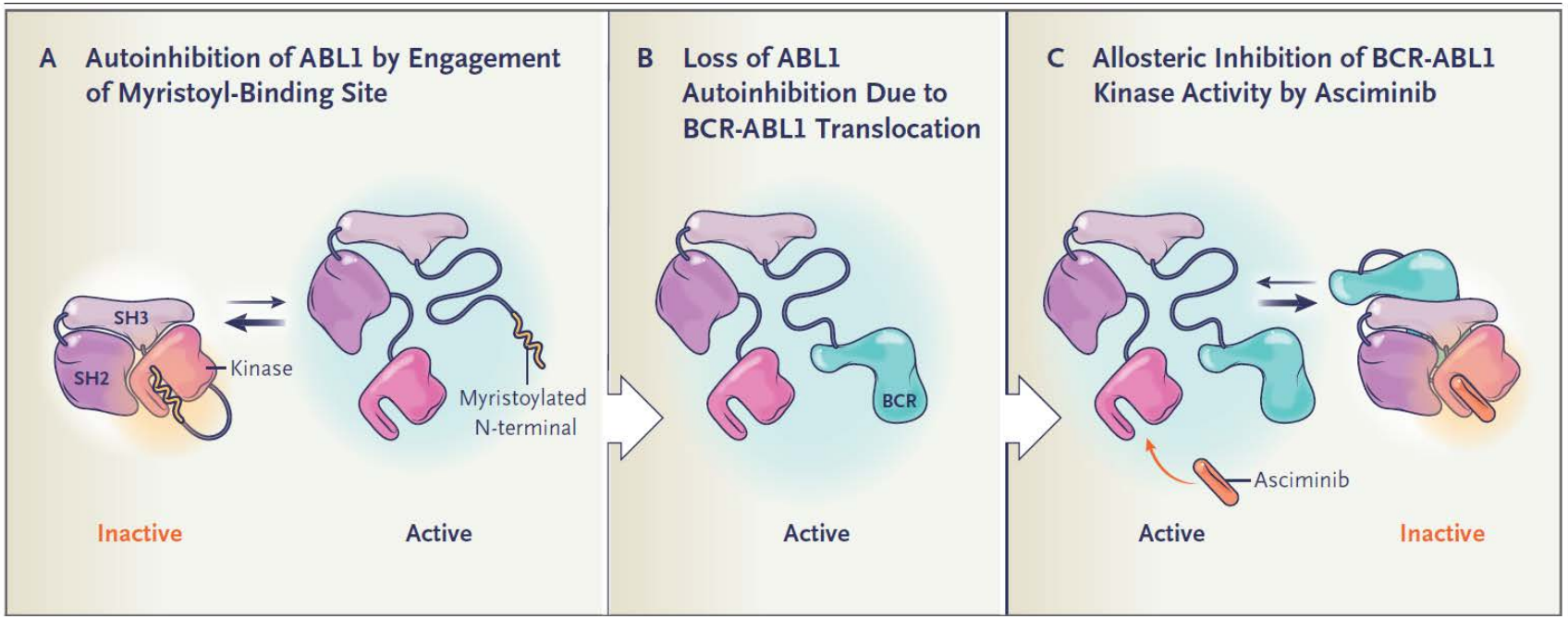
Overall Safety and Efficacy by Starting Dose



- The percentage of patients with ≤1% *BCR-ABL1*^{IS} decreased with decreasing doses
- The incidence of TE-AOEs decreased with decreasing doses

TE-AOE, treatment-emergent arterial occlusive event

Asciminib



Specifically Targeting the ABL Myristoyl Pocket (**STAMP**) **inhibitor**

CML-T315I

Ponatinib

	Phase I + PACE N(%)
Time	Not reported
N	76
CCyR	55(72)
<1%	

Asciminib

	Ponatinib Pretreated	Ponatinib Naive	All
Time	By week 96		
N	26	19	45
CCyR			
<1%	10 (47.6)	13 (81.3)	23 (62.2)

Mauro et al. *Blood* 2014; 124 (21): 4552.
Hughes TP, et al. Poster presented at: EHA2022; June 9-12, 2022; Abstract P704.

CML-T315I

Ponatinib

	Phase I + PACE N(%)
Time	Not reported
N	76
CCyR	55(72)
<1%	
<0.1%	46(61)
<0.01%	32(42)
<0.0032%	25(33)

Asciminib

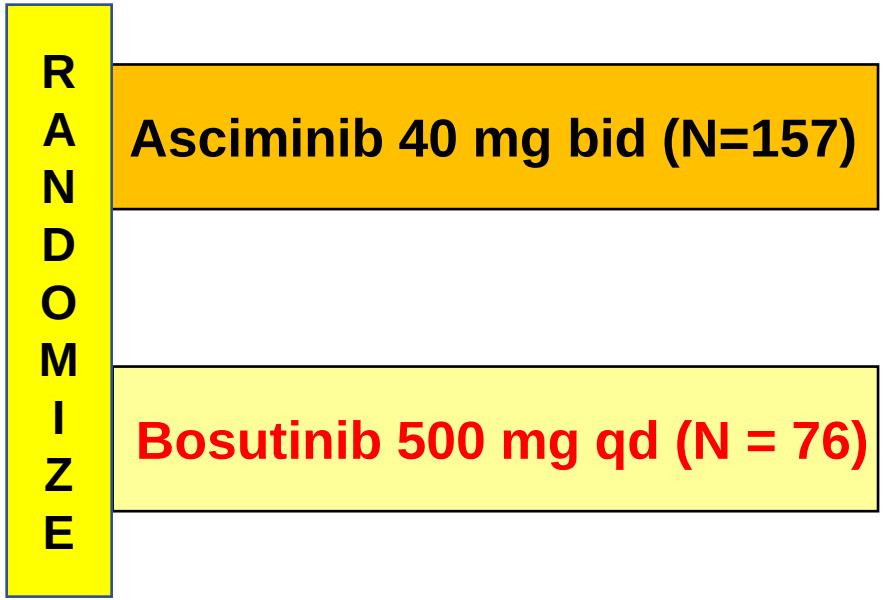
	Ponatinib Pretreated	Ponatinib Naive	All
Time	By week 96		
N	26	19	45
CCyR			
<1%	10 (47.6)	13 (81.3)	23 (62.2)
<0.1%	9 (34.6)	13 (68.4)	22 (48.9)
<0.01%	NR	NR	14 (28.9)
<0.0032%	NR	NR	11 (24.4)

Mauro et al. *Blood* 2014; 124 (21): 4552.
Hughes TP, et al. Poster presented at: EHA2022; June 9-12, 2022; Abstract P704.

ASCEMBL

CML-CP previously treated with ≥2 TKIs

- N = 233
- Stratified by MCyR
- Crossover allowed for lack of efficacy
- 2:1
- No T315I or V299L



Primary objective:
MMR at week 24

Rea et al. Blood 2021

ASCEMBL-Asciminib vs. Bosutinib

	24 weeks	96 weeks
MMR:	25.5% vs. 13.2%	37.6% vs. 15.8%
MR^4:	10.8% vs. 5.3%	17.2% vs. 10.5%
$MR^{4.5}$:	8.9% vs. 1.3%	10.8% vs. 5.3%
$BCR::ABL1^{IS}$ ≤1%:	44.4% vs. 20.8%	45.1% vs. 19.4%

Adverse Events-Asciminib vs. Bosutinib

	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)

Occurring in ≥10% of patients on either arm

Rea et al. Blood 2021

Adverse Events-Asciminib vs. Bosutinib

	Asciminib		Bosutinib	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Thrombocytopenia	45 (28.8)	34 (21.8)	14 (18.4)	7 (9.2)
Neutropenia	34 (21.8)	28 (17.9)	16 (21.1)	11 (14.5)
Anemia	15 (9.6)	2 (1.3)	6 (7.9)	3 (3.9)
Increased ALT	6 (3.8)	1 (0.6)	21 (27.6)	11 (14.5)
Increased AST	6 (3.8)	1 (0.6)	16 (21.1)	5 (6.6)

Occurring in ≥10% of patients on either arm

- Rea et al. Blood 2021

Summary

- Patients with CML have an excellent survival
- Always assess adherence and mutational status in patients who do not respond
- Both asciminib and ponatinib are FDA approved for the therapy of patients with T315I mutation or in patients who have received ≥ 2 TKIs

Patient Case

- 54 year old gentleman with chronic phase CML on TKI therapy, is in the office to discuss treatment discontinuation.
- He has been on TKI therapy for 5 years
- BCR::ABL1 levels in last 2 years:
  - 0.008
  - 0.000
  - 0.006
  - 0.000
  - 0.000
  - 0.004

It is safe to go ahead and stop therapy

True

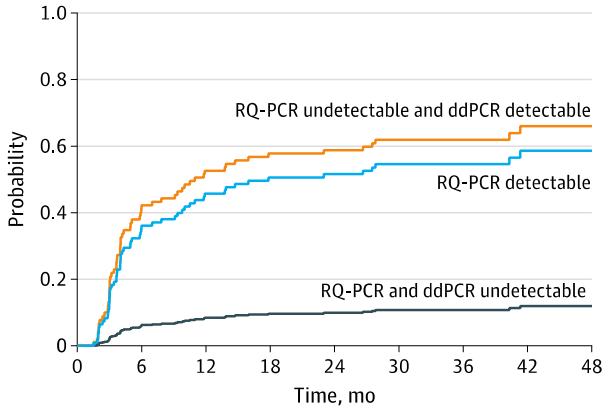
False

Who Can be Considered For Stopping TKIs?

- Chronic phase CML
- Duration of TKI: at least 3 years
- Duration of low level BCR-ABL by PCR: 1-2 years
- Depth of response: at least MR^4 (BCR::ABL1 <0.01%)
- Involved patient
- Multi-team approach

Ross DM, et al. ASH Annual Meeting abstracts 2013., Mahon FX et. ASH Annual Meeting abstracts 2016, Pfirrmann M et al. ASH Annual Meeting abstracts 2016, Choi SY et al. ASH Annual Meeting abstracts 2013., Rousselot P et al JCO 2013, Atallah et al. JAMA oncology 2020

B Probability of MRec



No. at risk

RQ-PCR and ddPCR undetectable	87	76	71	70	68	63	30	13	8
RQ-PCR undetectable and ddPCR detectable	56	32	25	21	20	19	18	5	1
RQ-PCR detectable	28	16	15	14	14	13	6	3	1

JAMA Oncology | Original Investigation

Assessment of Outcomes After Stopping Tyrosine Kinase Inhibitors Among Patients With Chronic Myeloid Leukemia

A Nonrandomized Clinical Trial

Ehab Atallah, MD; Charles A. Schiffer, MD; Jerald P. Radich, MD; Kevin P. Weinfurt, PhD; Mei-Jie Zhang, PhD; Javier Pinilla-Ibarz, MD; Vamsi Kota, MD; Richard A. Larson, MD; Joseph O. Moore, MD; Michael J. Mauro, MD; Michael W. N. Deininger, MD; James E. Thompson, MD; Vivian G. Oehler, MD; Martha Wadleigh, MD; Neil P. Shah, MD, PhD; Ellen K. Ritchie, MD; Richard T. Silver, MD; Jorge Cortes, MD; Li Lin, MS; Alexis Visotcky, MS; Arielle Baim, BA; Jill Harrell, BS; Bret Helton, BS; Mary Horowitz, MD; Kathryn E. Flynn, PhD

Why consider stopping?

TKI therapy is associated with reduced QOL

High cost to patient and society

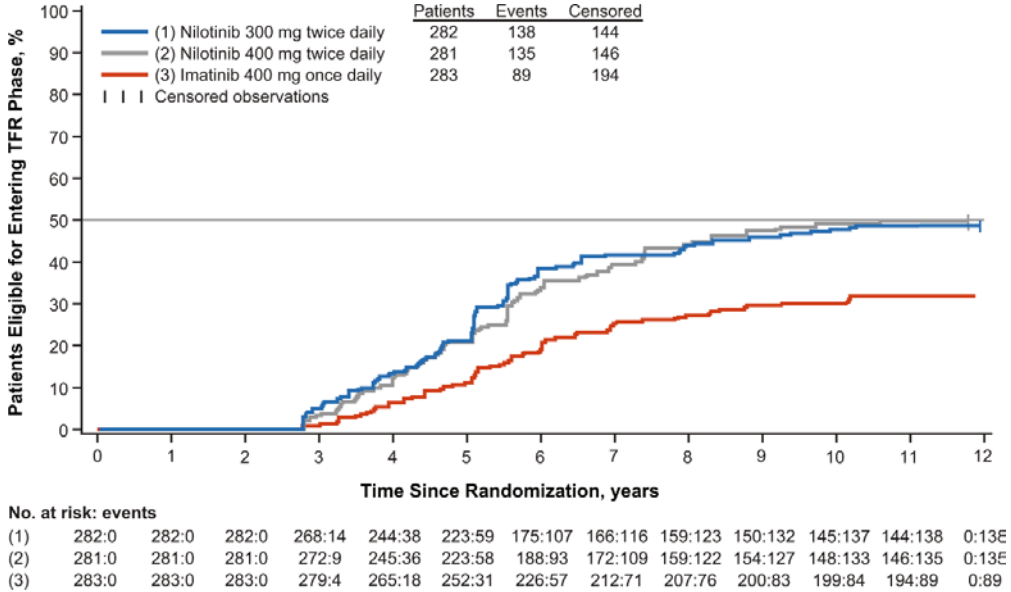
Some patients may not require lifelong TKIs

Children and adolescents:

- Substantial growth abnormalities
- Effect on pregnancy/fertility
- Cardiovascular toxicity and thyroid dysfunction

Efficace F et al. Blood 2011
Experts in CML. Blood 2013, Mahon FX, et al. Lancet Oncol. 2010

TFR Eligibility-ENESTnd



	Nilotinib 300 mg BID	Imatinib 400 mg QD
5 year	20.9%	11%
10 year	48.6%	29.7%

Kantarjian et al. Leukemia 2021

Continue

- Patient stopped therapy
- How should this patient be monitored?

How should this patient be monitored?

Monthly with BCR::ABL for three years

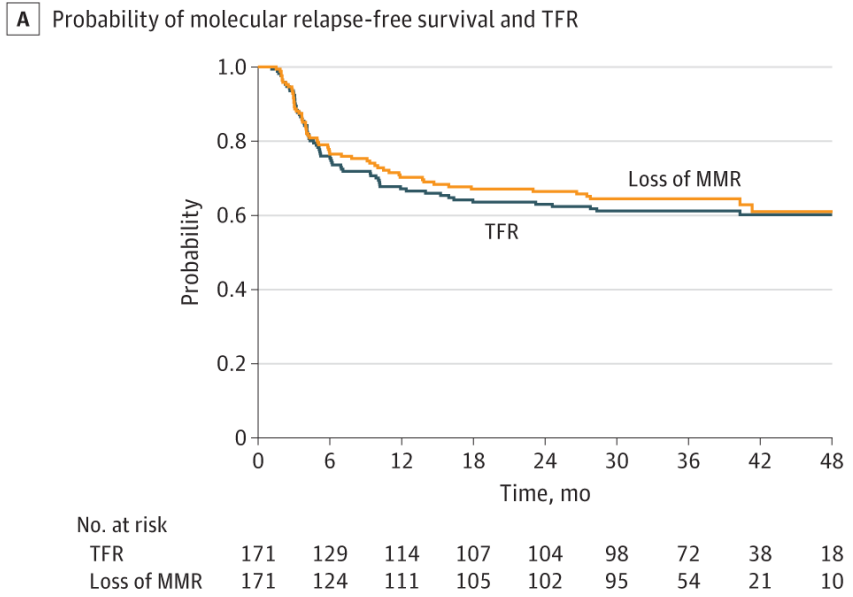
BCR::ABL every 3 months x 3 years then stop

Bone marrow biopsy every 3 monsth for one year, then PCR for BCR::ABL every 3 months

PCR for BCR::ABL monthly for 6 months, every 2 months for 6-12 months and every 3 months forever

Monitoring

- Monthly for first 6-12 months
- Every 2 months for 18-24 months
- Every 3 months thereafter



Atallah et al. JAMA Oncology 2021

When would you restart treatment for this patient

BCR::ABL >0.001

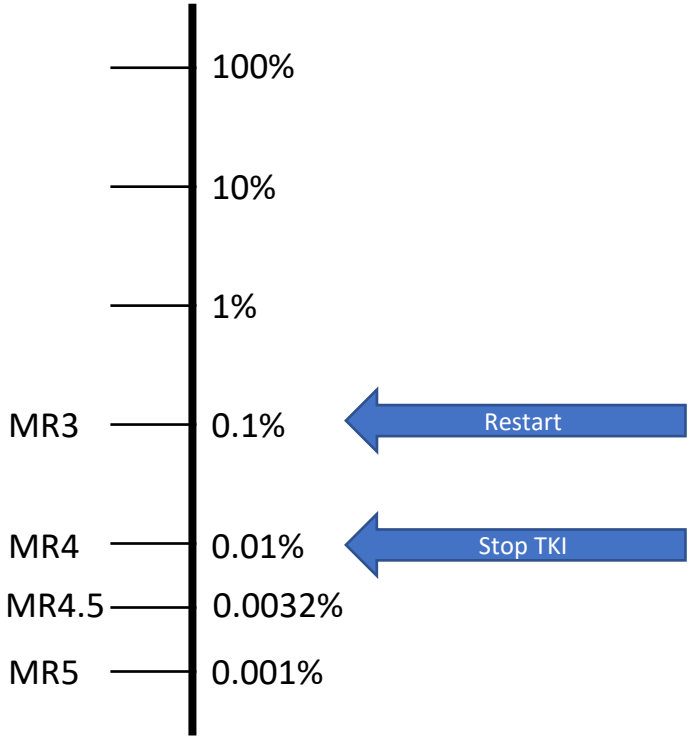
BCR::ABL >0.01

Any detectable level

You are crazy. Why did you stop treatment

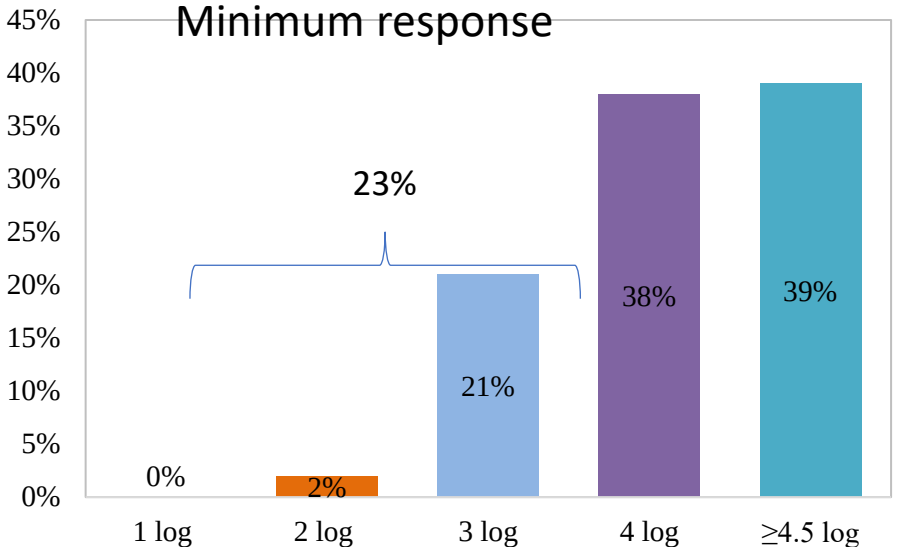
None of the above

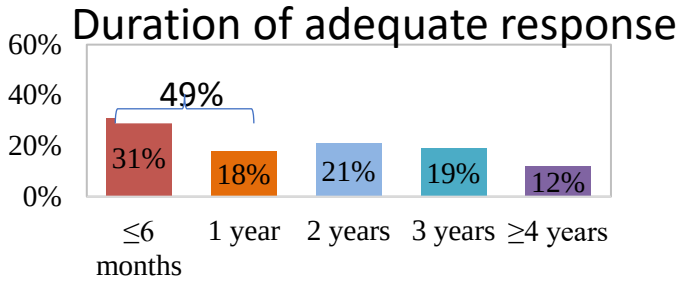
Restart-Loss of MMR

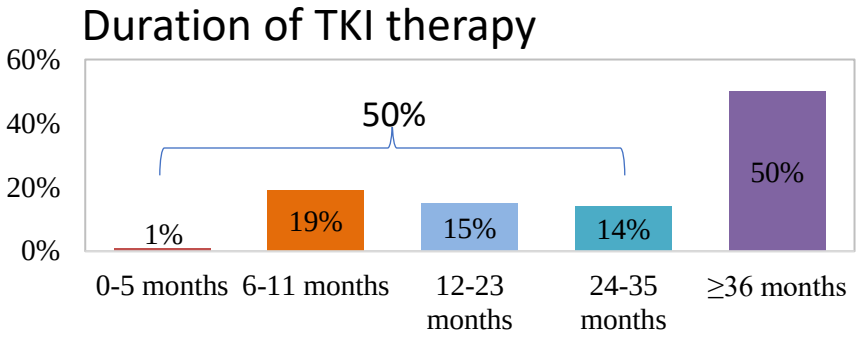


Ross DM, et al. ASH Annual Meeting abstracts 2013, Mahon FX, *et al.* ASH Annual Meeting abstracts 2013, Mahon FX, *et al.* ASH Annual Meeting abstracts 2016, Atallah E et al. JAMA oncology 2020, Choi SY et al. ASH Annual Meeting abstracts 2013., Rousselot P et al JCO 2013

Discontinuation Patterns in US







Outcome of Select Discontinuation Studies

Study	N	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	84	Dasatinib	46 (2)
ENESTfreedom	190	Nilotinib	52 (4)
LAST	173	Imatinib/Das/Nil/Bos	61 (3)

N: number of patients, IFN: Interferon, TKI: Tyrosine kinase inhibitor, RFS: Relapse free survival,
*No prior therapy with IFN, 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. Leuk Lymph 2020, Hochhaus A et al. ASH Annual Meeting abstracts 2016, Atallah E et al. JAMA oncology 2020

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

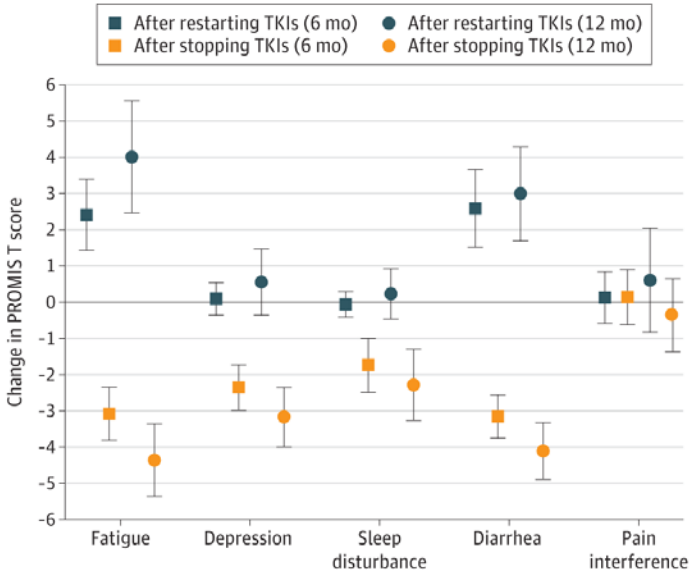
TKI Discontinuation Side Effects

- TKI withdrawal syndrome:
  - Musculoskeletal pain/joint pain
  - 30% of patients
  - Median duration 6 months
  - Less likely to relapse
- Increased Anxiety
- More frequent monitoring

Lee et al. Haematologica. 2016 Jun;101(6):717-23.
Richter et al. J Clin Oncol. 2014;32(25):2821–2823.

Benefits of Treatment Free Remission

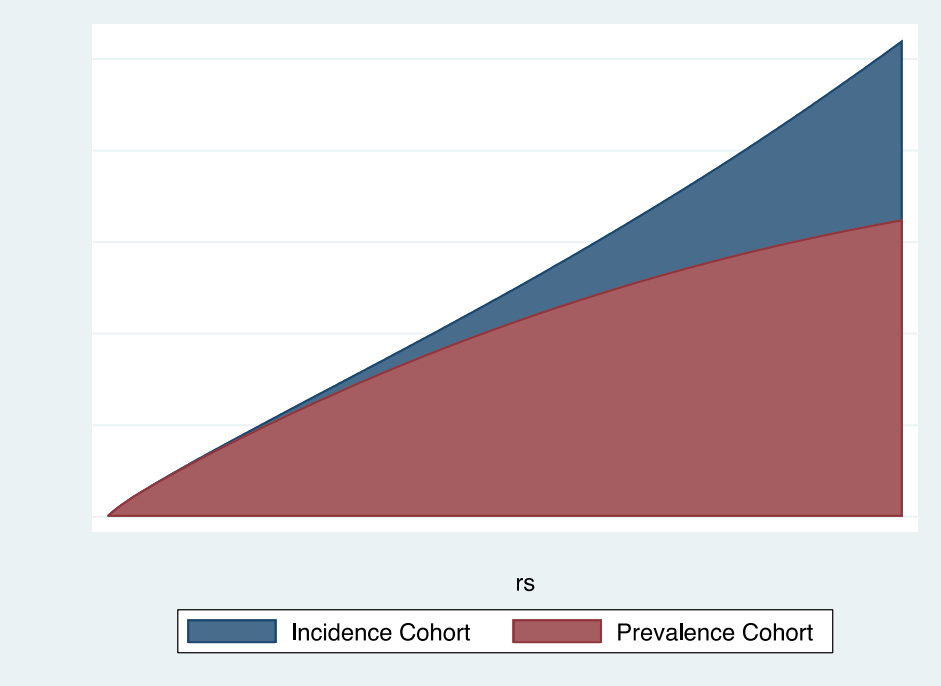
Improved Quality of Life after Discontinuation



Mean Changes in Patient-Reported Outcomes After Tyrosine Kinase Inhibitor (TKI) Discontinuation and TKI Restart at 6 and 12 MonthsVertical lines indicate 95% CIs. PROMIS indicates Patient-Reported Outcomes Measurement Information System.

Atallah et al. JAMA Oncology 2021

Cost Savings



$50 billion over 30 years

$50,000,000,000

Slide courtesy of Aaron Winn, PhD. Unpublished data

Summary

- TFR is safe and feasible in a select group of patients
- Close monitoring is required
- QOL does improve after successful TFR
- Multiple studies aiming at deeper remission and increasing rate of TFR are ongoing

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"

HJKC3 CML Studies:

Frontline therapy
- Asciminib ± Nilotinib

Attempt second treatment free remission
- Ruxolitinib
- Asciminib

UCSF Helen Diller Family Comprehensive Cancer Center
EMORY WINSHIP CANCER INSTITUTE
JOHNS HOPKINS MEDICINE THE SIDNEY KIMMEL
DANA-FARBER CANCER INSTITUTE
GEORGIA CANCER CENTER AUGUSTA UNIVERSITY
MEDICAL COLLEGE OF WISCONSIN CANCER CENTER
City of Hope
FRED HUTCH CURES START HERE
BARBARA ANN Karmanos CANCER INSTITUTE Wayne State University
Cleveland Clinic Taussig Cancer Institute
Weill Cornell Medicine Sandra and Edward Meyer Cancer Center
1884
UHN Princess Margaret Cancer Centre
THE UNIVERSITY OF CHICAGO MEDICINE Comprehensive Cancer Center
OHSU HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH
ROSWELL PARK CANCER INSTITUTE
Duke Cancer Institute
MOFFITT CANCER CENTER