NCCN 11th Annual Congress:
Hematologic Malignancies™

Patient Case Studies & Panel Discussion

Panelists: Jessica Altman, MD, *Robert H. Lurie Comprehensive Cancer Center of Northwestern University*; Ruben A. Mesa, MD, *Mayo Clinic Cancer Center*; Jerald P. Radich, MD, *Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance*

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Hematologic Malignancies™

CASE 1

Jessica K. Altman, MD

Robert H. Lurie Comprehensive Cancer Center of Northwestern University

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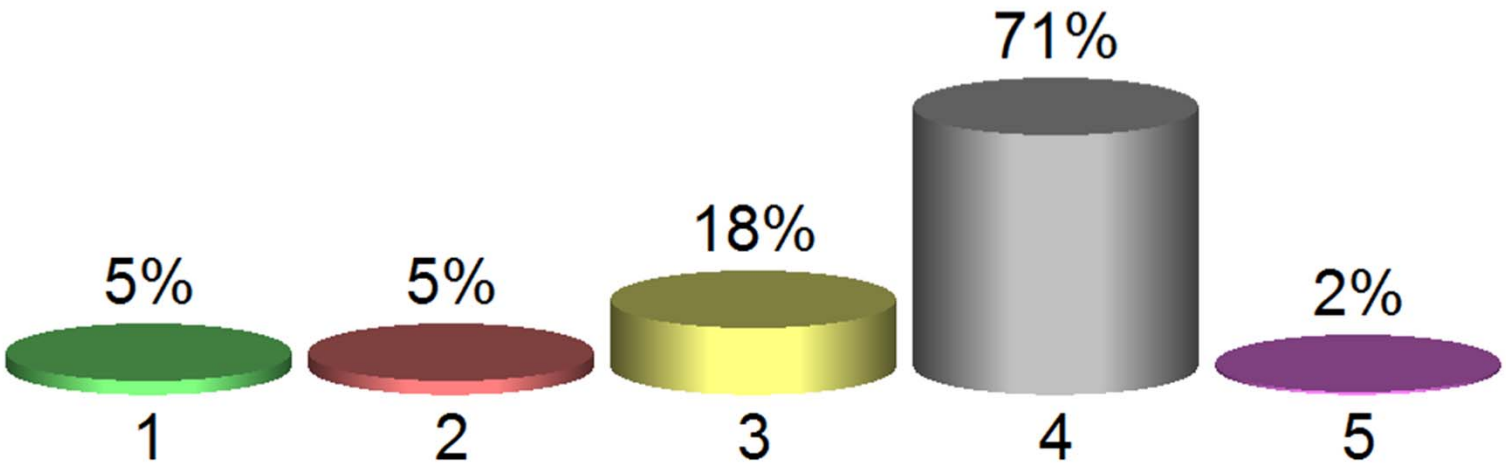
John W

- JW is a 76 yo male
- Extensive medical history:
  - 2011: prostate cancer, Gleason 3+3, continues on active surveillance
  - 2/12: EBV+ DLBCL. Stage IIIA. R-CHOP x 6 cycles 3/2012-6/2012
    - 25% reduction in cyclophosphamide and doxorubicin in cycles 5 and 6 due to grade 4 neutropenia
    - Course complicated by C difficile colitis and non-ST segment elevation myocardial infarction
  - 8/12: 3.5 x 2.5 x 0.5 cm infiltrating adenocarcinoma in Rt colon. R hemicolectomy; MSI high and therefore did not receive chemotherapy for stage II disease
- Developed progressive cytopenias and he is referred to you with WBC 3.0 K/uL, hgb 10.3 g/dL, plt 31 K/uL

Audience Polling Results

What is the diagnosis?

1. Marrow involvement of prostate cancer
2. DLBCL recurrence
3. de novo AML
4. therapy related myeloid neoplasm
5. autoimmune cytopenias



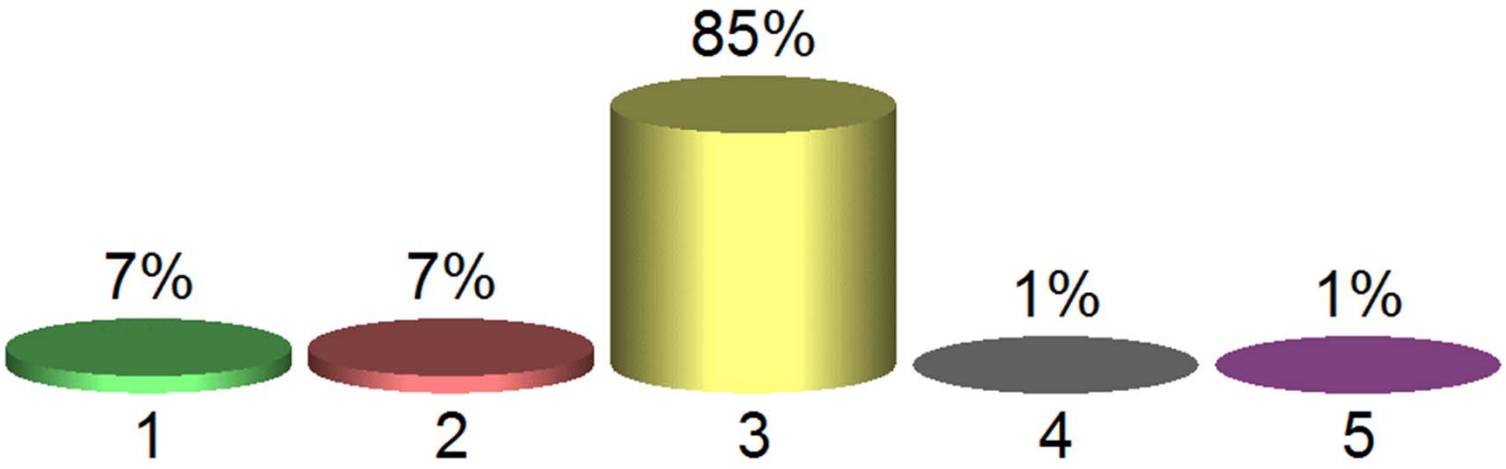
Marrow result

- Acute myeloid leukemia with dysplasia, extensively involving a hypercellular bone marrow
- Flow cytometric analysis reveals a dim CD45+ population that is CD33 dim, CD34+, CD117+, MPO+, CD13+, HLADR+, partial TdT+, partial CD7+, and negative for other lymphoid and monocytic markers

Audience Polling Results

What items do you consider important in determination of prognosis and treatment plan?

1. Cytogenetics and molecular features
2. Co-morbid medical problems and PS
3. Options 1 and 2
4. None of the above everyone will get 7+3
5. None of the above everyone will get HMA



More Data

Karyotype

- Clone 1: 46,XY,r(7)(p22q22)[5]
- Clone 2: 46,idem,t(8;12)(q13;p11.2)[9]
- NCA 1: 46,XY,-7,+22[1]
- Normal: 46,XY[5]

Molecular studies:

- FLT3, NPM1, kit, CEPBA negative
- IDH negative
- More extensive molecular profiling was not completed

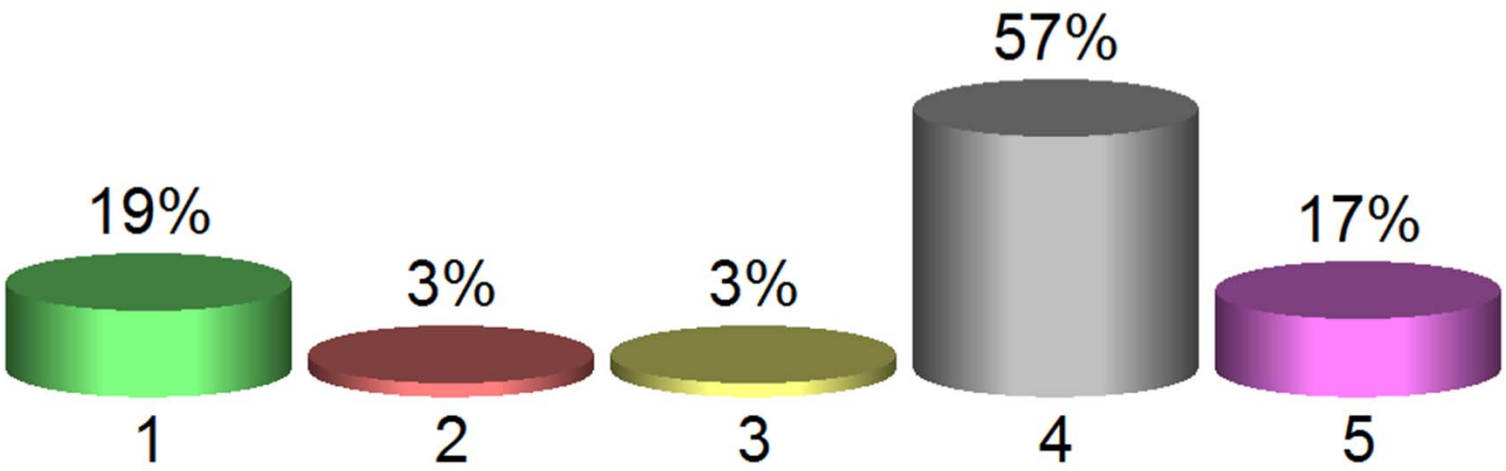
Normal creatinine, coags, bilirubin, transaminases, albumin, and uric acid

PS 2

Audience Polling Results

What Treatment Would You Recommend?

1. 7+3
2. Clofarabine
3. LDAC
4. 5-aza or Decitabine
5. Best supportive care

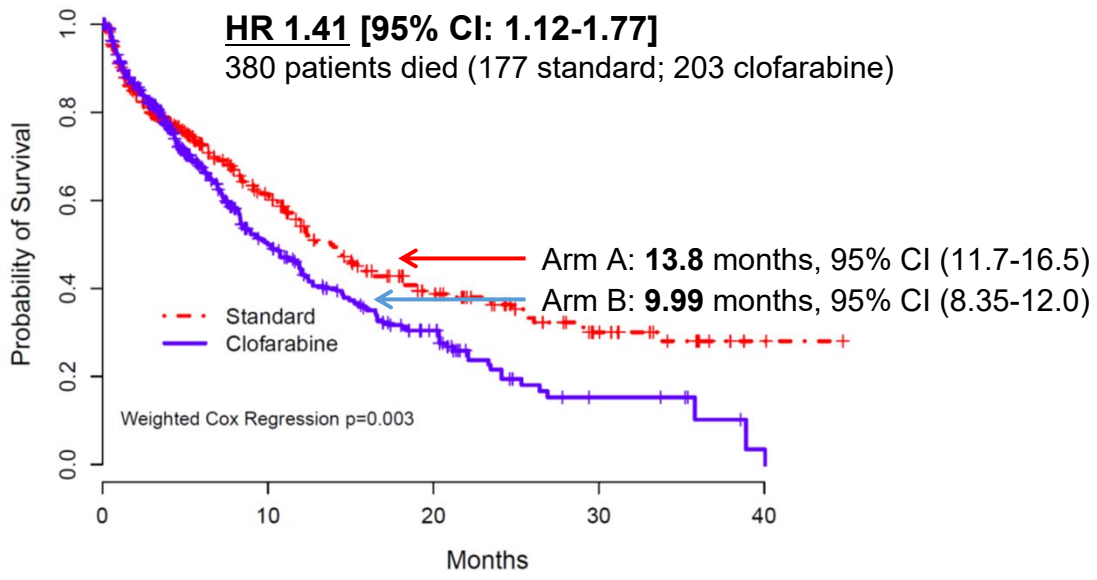


Musings about Treating the Older Adult with Intensive Chemotherapy

- 2-year survival of 15% to 20%
- The Swedish Acute Leukemia Registry: unselected cohort
  - 55% of patients 70-79 yrs of age had intensive treatment (44% of 75-79 yrs)
  - Half of those treated achieved complete remission
- Limitations to all of the risk algorithms
  - Some with both patient and disease specific factors but based on trials with patients receiving intensive chemo; HCT-CI; geriatric assessments: none widely accepted
- Patients with some disease characteristics are unlikely to benefit from intensive treatment (even if fit and desired) and therefore would rather offer a less intensive or investigational approach
  - Overexpression of the oncogene *EVI-1, ASXL1* gene mutations, biallelic *FLT3*-ITDs, *p53* gene mutations, and complex and/or monosomal karyotypes
  - Would consider intensive treatment only if HSCT is realistic

Löwenberg B, et al. *N Engl J Med 2009;361(13):1235-1248*
Juliusson, for the Swedish AML Group. *Blood* 2011 117:3473-3474
Ossenkoppele and Löwenberg *Blood* 2015 125:767-774

E2906: Phase III Randomized Trial of Clofarabine in Newly-Diagnosed AML in Adults 60 and Older:



Foran JM et al. ASH abstr# 217, 201

Azacitidine vs Conventional Care Regimens (CCR)

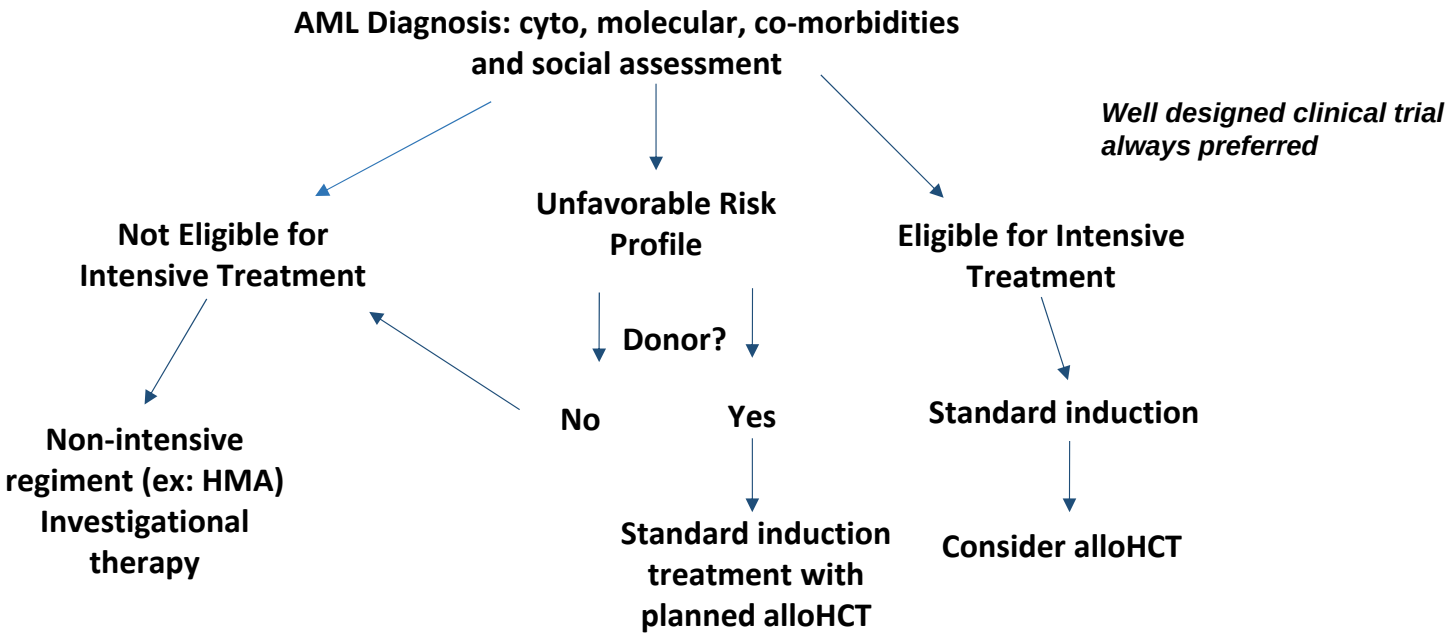
- Randomized phase 3 trial: 488 patients age ≥65 years with AML
- CCR (standard induction chemotherapy, low-dose ara-c, or supportive care only) preselected
- Patients were assigned 1:1 to azacitidine or CCR
- Median overall survival (OS) was increased with azacitidine vs CCR: 10.4 months (95% confidence interval [CI], 8.0-12.7 months) vs 6.5 months (95% CI, 5.0-8.6 months)
- One-year survival rates with azacitidine and CCR were 46.5% and 34.2%
- Particular AML genotypes, especially TET2 and DNMT3A mutations, may benefit from HMA

Dombret H, et al. *Blood.* 2015 Jul 16;126(3):291-9
Bejar R, et al. *Blood. Vol. 124.(17) 2014. p. 2705-2712*
Im AP, et al. *Leukemia 2014;28(9):1774-1783*

Back to John W

- He was treated on a phase 1b trial with HMA (decitabine) + ABT-199
- He entered CRi after 1 cycle of therapy and then CR after 2 cycles and has been maintained

A General Approach to the Older Adult w AML



In part adapted from: Ossenkoppele and Löwenberg *Blood* 2015 125:767-774

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CASE 2

Jerald P. Radich, MD

Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

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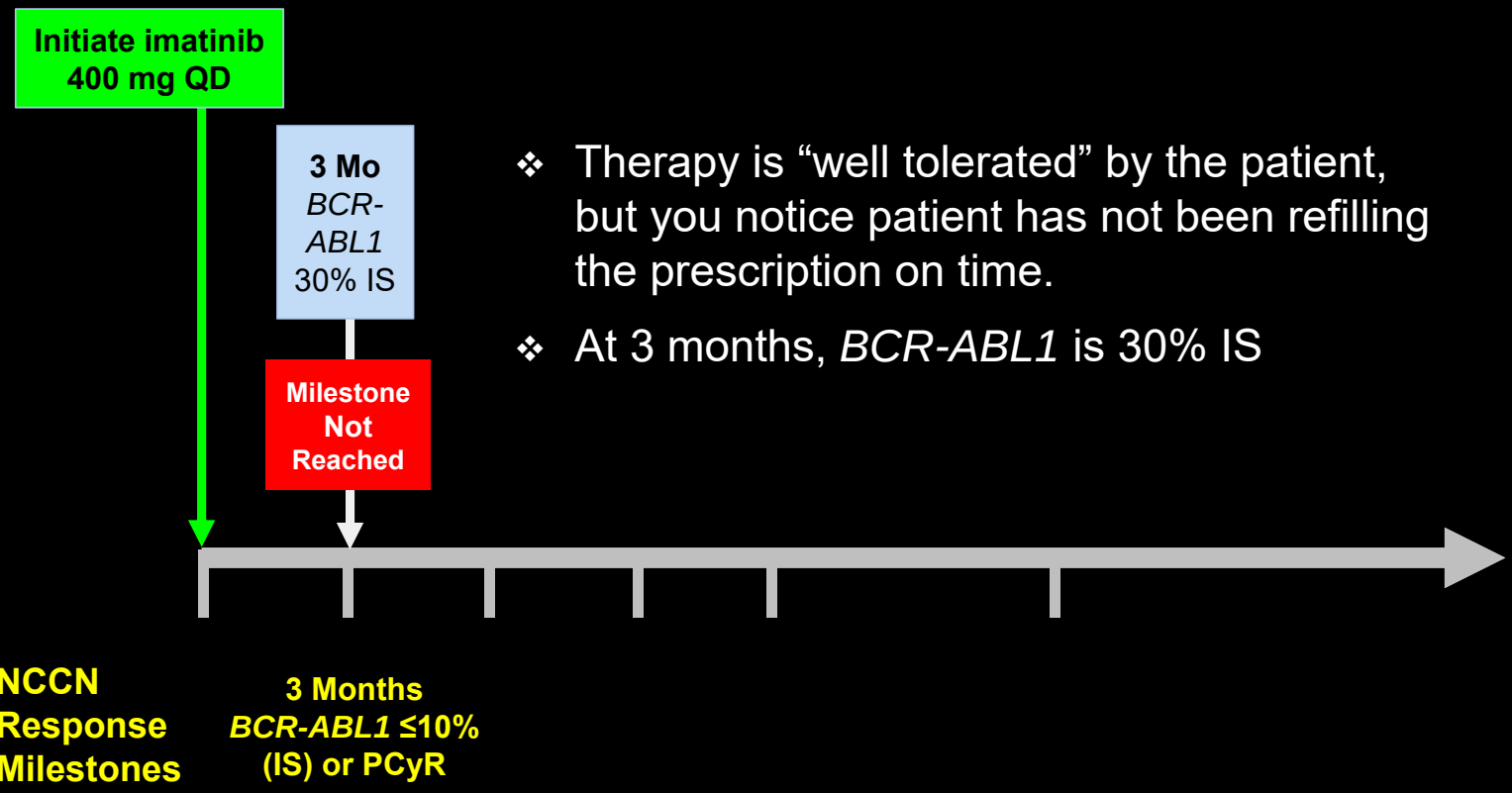
A Case

- 45-year-old male rodeo clown complains of fatigue and easy bruising (?). WBC 40,000k, diagnosed with CP-CML No significant comorbidities or medical history
- Physical exam reveals splenomegaly ~4 cm below costal margin
- CBC assessment
  - WBC count: 242,000 cells/$mm^{3,}$ 2% blasts, 3% basophil, 5% eosinophils; hematocrit: 38%; platelet count: 400,000 cells/mm^3
- BM aspiration shows hypercellular marrow (~100%) with 2% blasts
- Cytogenetics identify Ph chromosome in all 20 cells assessed: 46,XX, t(9;22)(q34;q11.2)
- BCR-ABL mRNA 94.2% by Q-RT-PCR
- Intermediate risk Sokal score

Timeline: Patient Monitoring and Treatment

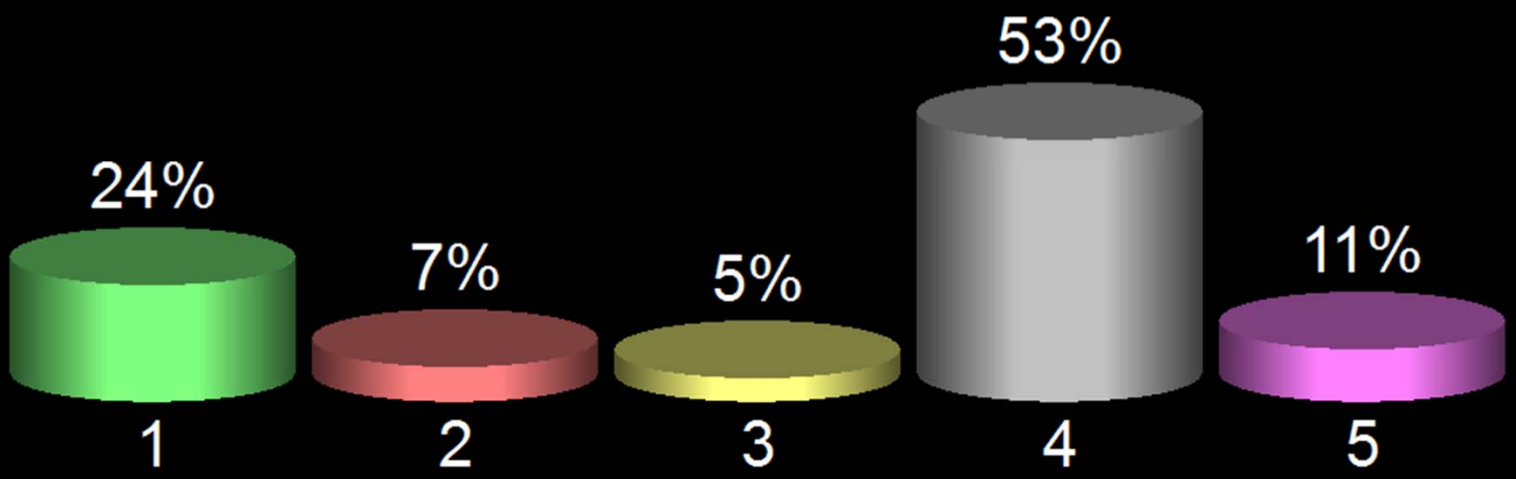


- Therapy is "well tolerated" by the patient, but you notice patient has not been refilling the prescription on time.
- At 3 months, *BCR-ABL1* is 30% IS

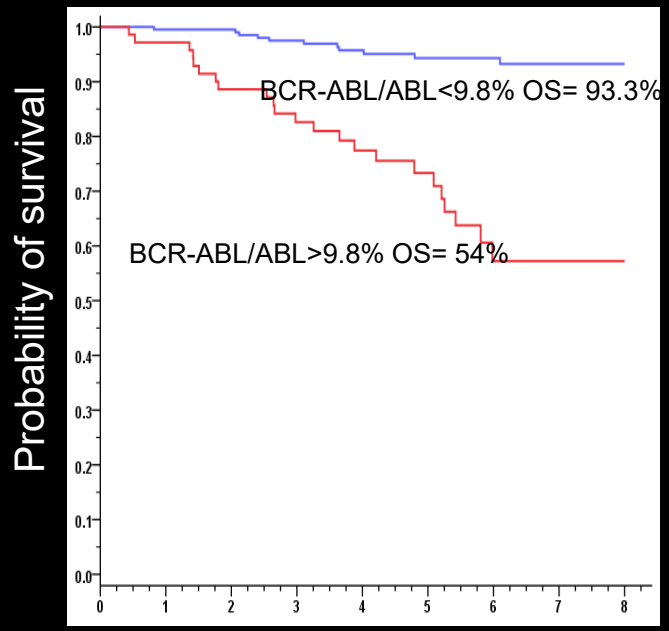
Audience Polling Results

Q1. What would you do?

1. Change to a "second generation" TKI
2. Keep the patient on IM 400 mg/d
3. Allogeneic transplant
4. Keep the patient on IM 400 mg/d if you think adherence was suboptimal
5. Increase to IM 800 mg/d

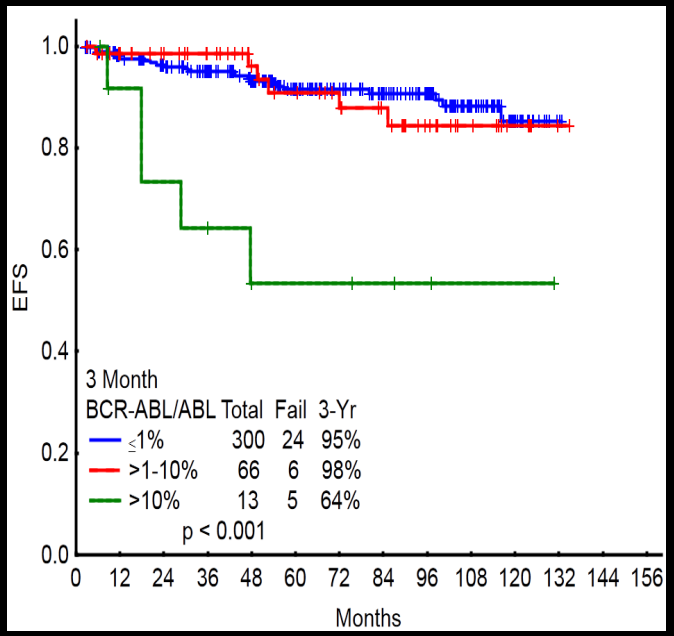


Outcome after TKI Therapy by Molecular Response Achieved at 3 Months



Time from onset of IM (years)

Marin et al, J Clin Oncol 2012;30:232-238



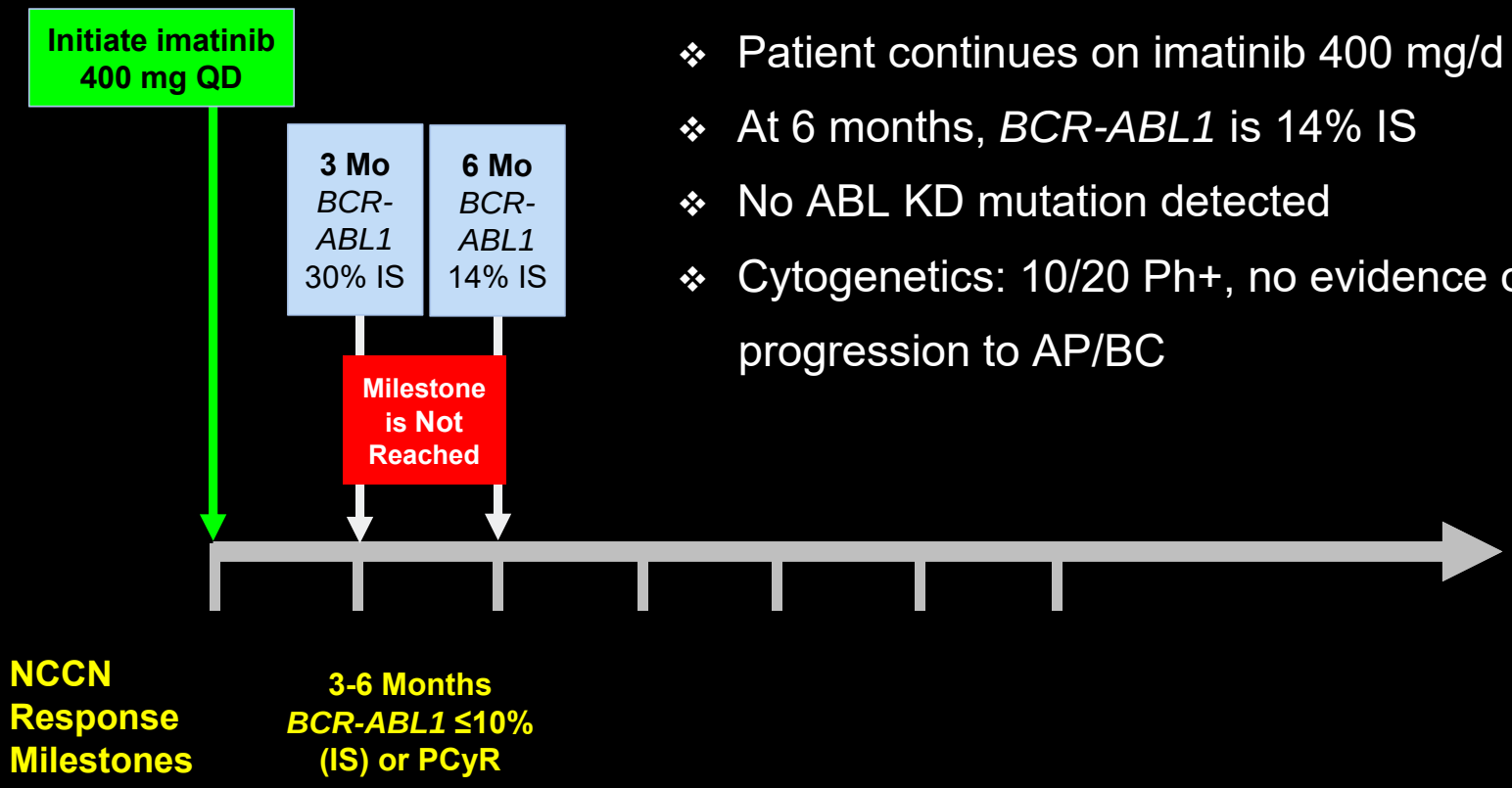
Time from onset of TKI (months)

Jain et al. Blood 2013;121:4867-4874.

Poor early molecular response

- Poor adherence
- Bad biology
- Often a mix a both
- *Patient does not fail therapy, therapy fails a patient*

Patient Monitoring and Treatment



- Patient continues on imatinib 400 mg/d
- At 6 months, *BCR-ABL1* is 14% IS
- No ABL KD mutation detected
- Cytogenetics: 10/20 Ph+, no evidence of progression to AP/BC

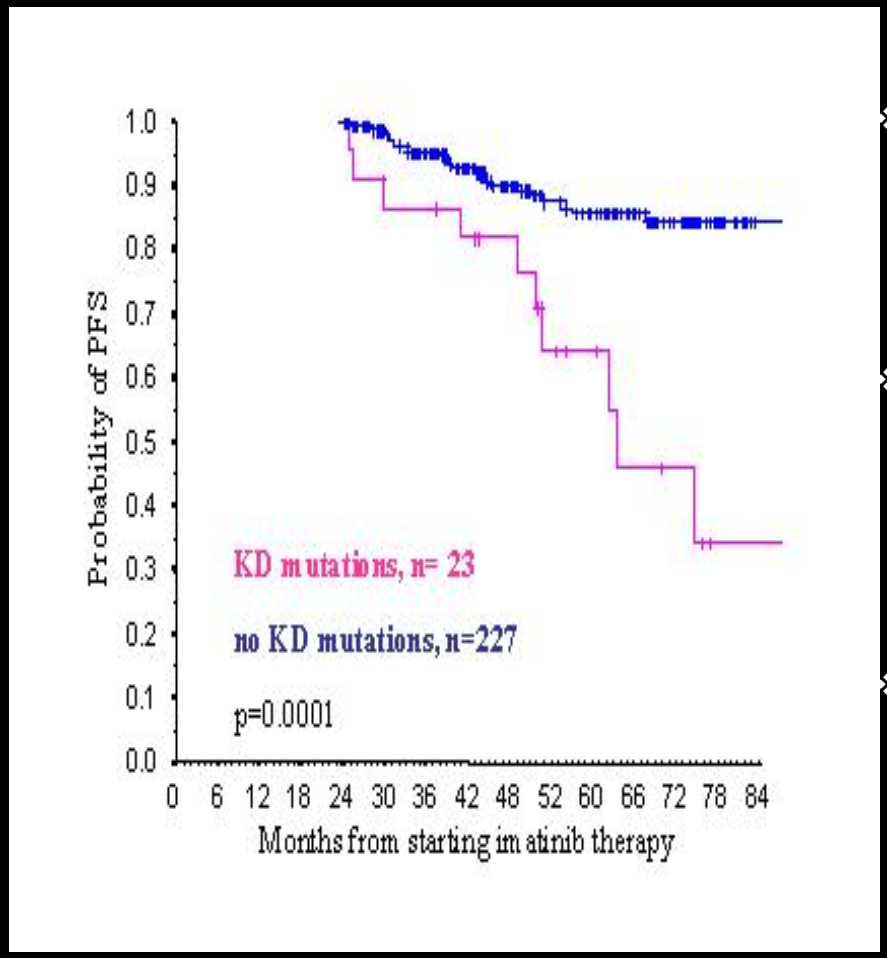
When to Consider Mutational Analysis

Recommendations on When to Perform Mutational Analysis	
ELN[1]	**NCCN[2]**

• **At diagnosis**
  • Only in AP/BC patients
• **During first-line imatinib therapy**
  • In case of failure
  • In case of an increase in *BCR-ABL* transcript levels leading to MMR loss
  • In any other case of suboptimal response
• **During second-line dasatinib or nilotinib therapy**
  • In case of hematologic or cytogenetic failure
	• *BCR-ABL1* >10% by [IS] or <PCyR at 3 and 6 months months
	• <CCyR or *BCR-ABL1* >1% [IS] at 12 months
	• Any sign of loss of response
	  • Defined as hematologic or cytogenetic relapse or 1-log increase in *BCR-ABL1* transcript levels and loss of MMR
	• Disease progression to AP or BP

1. Soverini S et al. *Blood.* 2011;118:1208-1215.
2. NCCN Guidelines Chronic Myelogenous leukemia V.1.2016.

KD mutations w/o other signs of resistance



- The detection of mutation antedates any documented rise in the transcript level by a median time of 9 months
- TKD mutations were the only independent predictor for loss of CCyR in patients who receive imatinib as first line therapy (n=204, RR=13.4, p<0.0001)
- TKD mutations were an independent predictor for PFS in CP population (n= 319, RR=2.3, p=0.01)

Khorashad et al J Clin Oncol 2008;26:4806-4813.

Activity of Bosutinib, Dasatinib, and Nilotinib 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

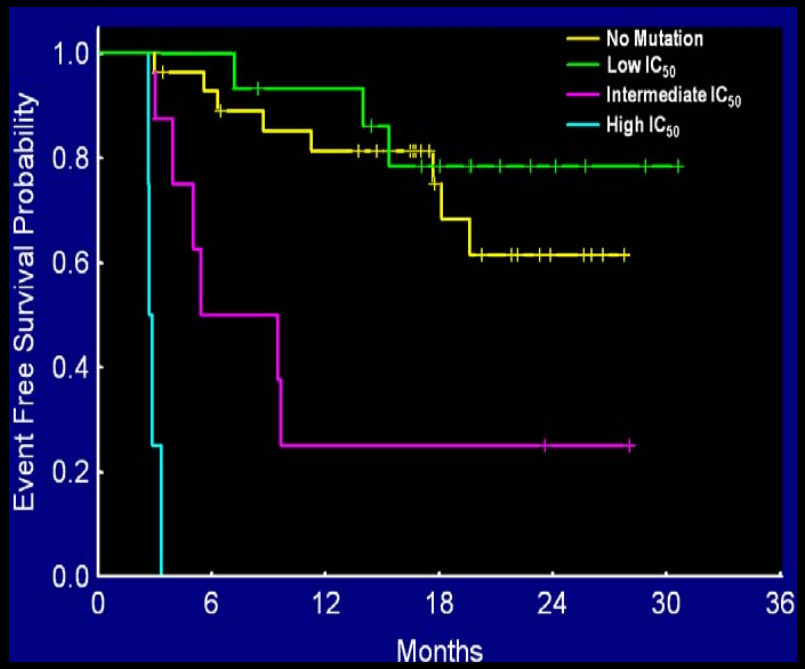
Sensitive	≤ 2
Moderately resistant	2.01–4
Resistant	4.01-10
Highly resistant	> 10

Redaelli et al, J Clin Oncol 2009;27:469-471.

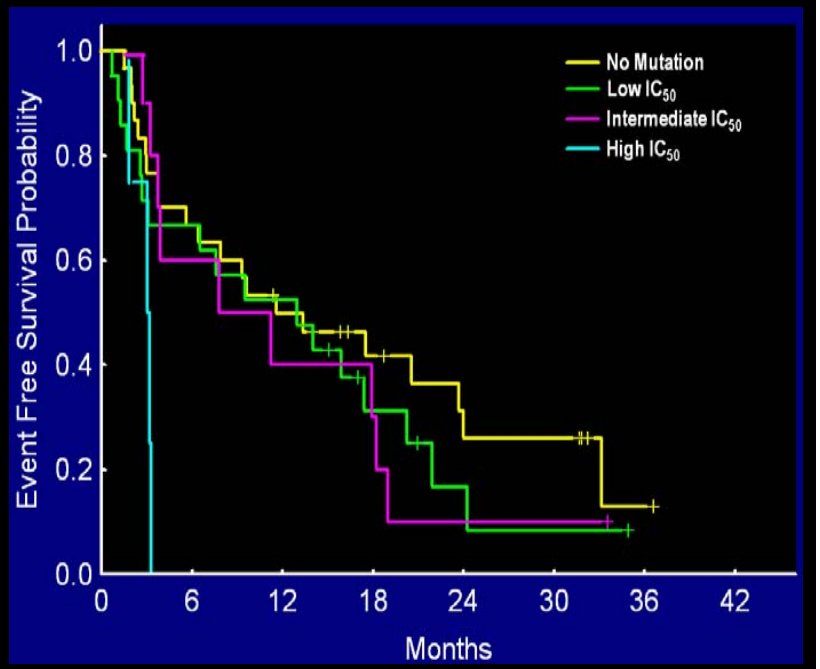
CCyR by Mutations in CML Treated with 2nd Generation TKI after IM Failure

- 86/169 (51%) pts treated had mutation
  - CP 30/59 (51%), AP 41/71 (58%), BP 15/39 (38%)
- Mutations classified based on IC_{50}
- Better response if low IC_{50} in CP and AP, not BP

Chronic Phase



Accelerated Phase

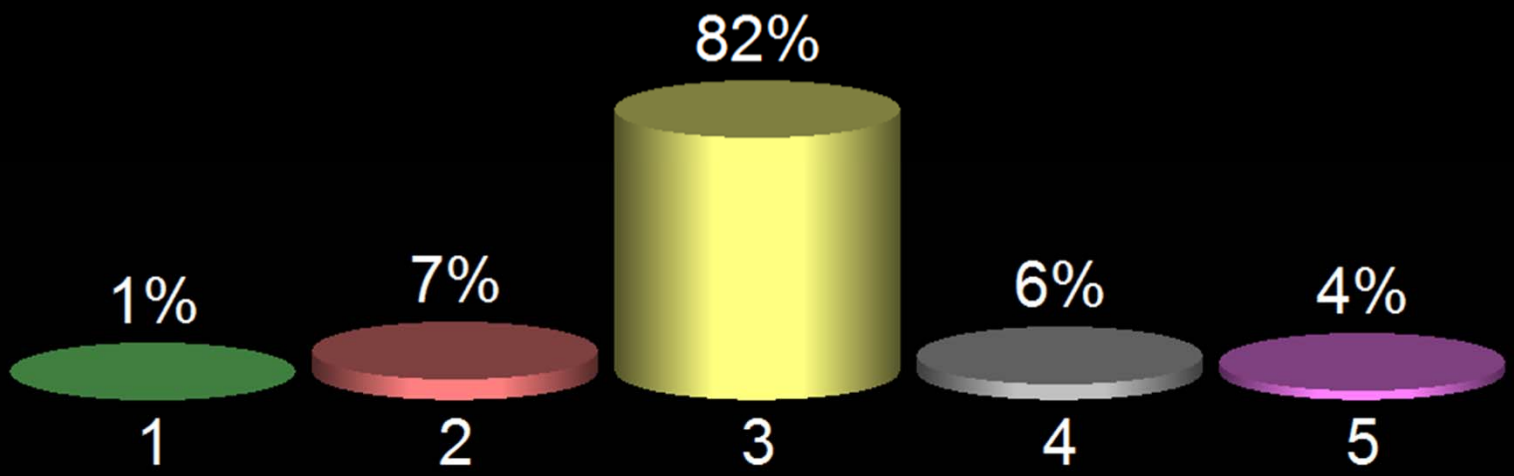


Jabbour et al, Blood 2009;14: 2037-43

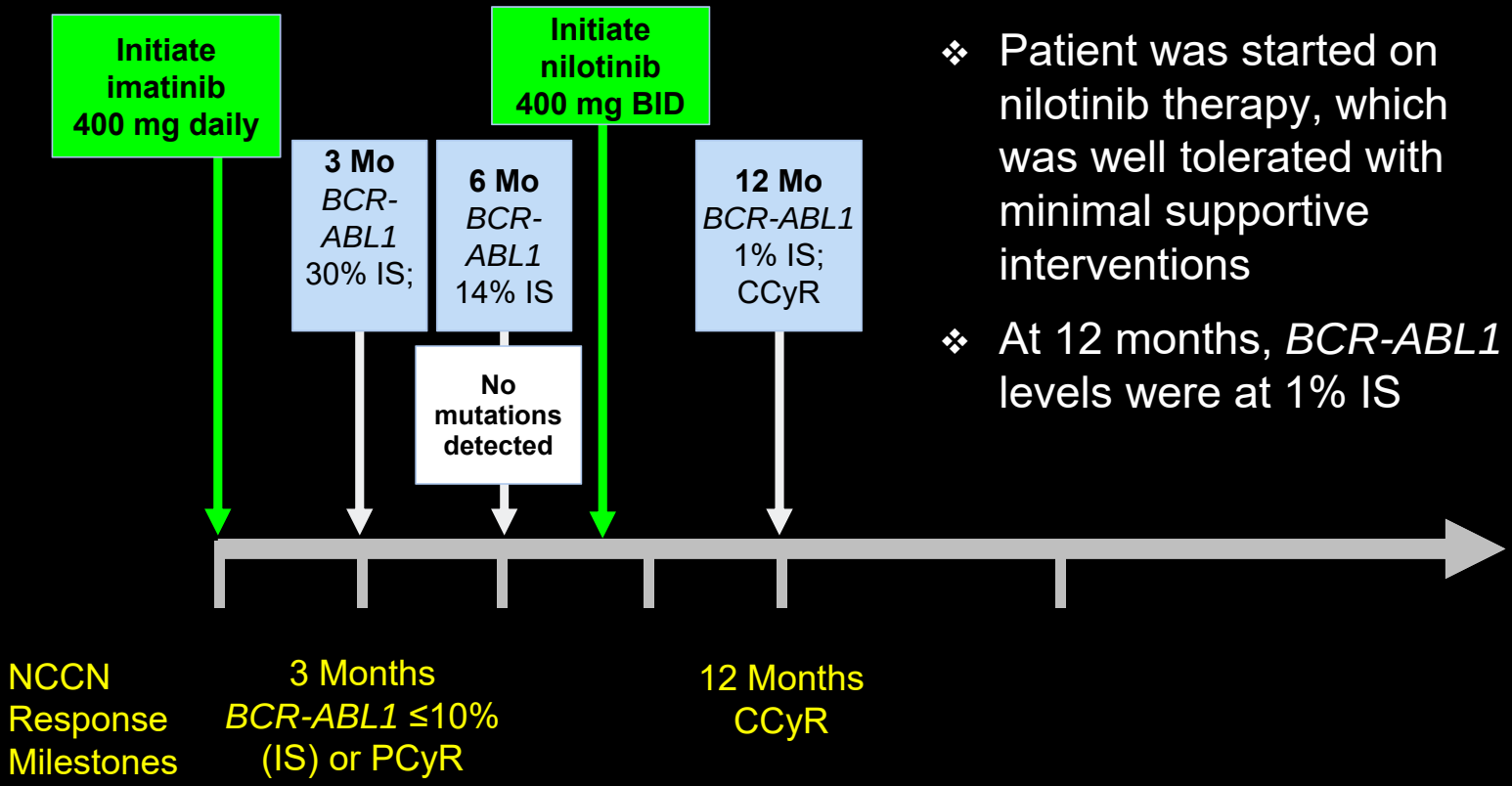
Audience Polling Results

Q2. Now what?

1. Stubbornly hold the line
2. Increase IM dose
3. Change to nilotinib, dasatinib, bosutinib
4. Allogeneic transplantation
5. Change to ponatinib



Patient Monitoring and Treatment



- Patient was started on nilotinib therapy, which was well tolerated with minimal supportive interventions
- At 12 months, *BCR-ABL1* levels were at 1% IS

Response and PFS with 2nd-Generation TKIs in Imatinib-Resistant CP-CML

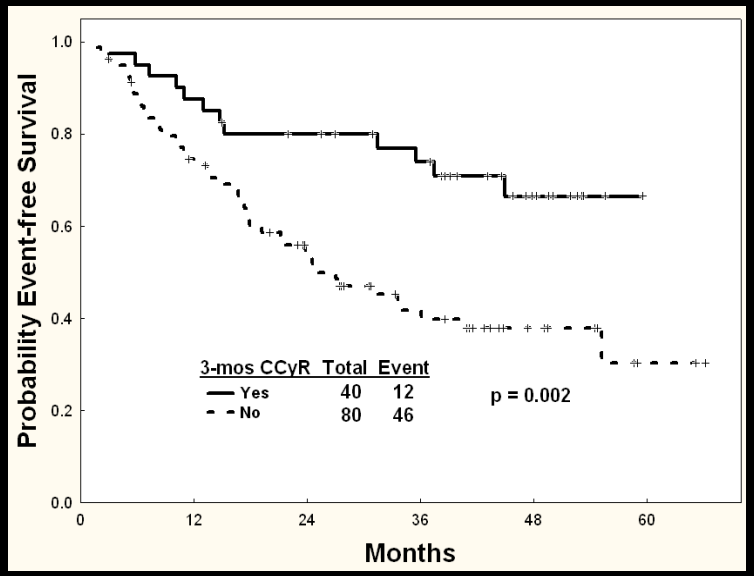
	Dasatinib[1,2]	Nilotinib[3]	Bosutinib[4]
Number of pts	167*	226	200
Follow-up	Minimum 24 mo	Minimum 24 mo	Median 24 mo
MCyR	63% at 24 mo*	56% at 24 mo	33% at 6 mo
CCyR	50% at 24 mo*	41% at 24 mo	23% at 6 mo
PFS at 24 mo, %	80*	64*	73

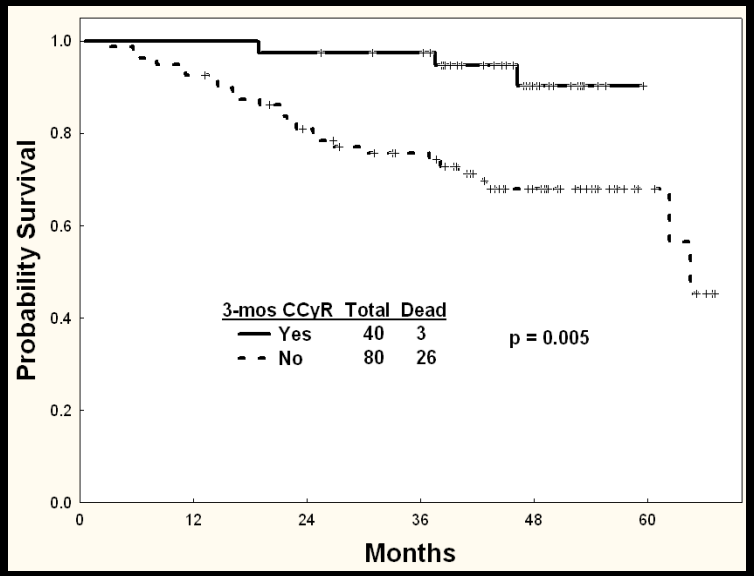
*Includes imatinib-intolerant patients.

1. Dasatinib Official prescribing information. November 2012.
2. Shah NP, et al. J Clin Oncol. 2010;28:15s (abstract 6512).
3. Kantarjian HM et al. *Blood*. 2011;117:1141-1145.
4. Cortes JE et al. *Blood* 2011;118:4567-4576.

Predictors of Outcome to 2nd Line TKI in CML

- 123 patients treated with dasatinib (n=78) or nilotinib (n=45) after imatinib failure
- Median follow-up 76 months (range, 25-109)
- MCyR 63%, CCyR 59%, 3-year EFS 53%, 3-year OS 84%
- 3-month CCyR 33%



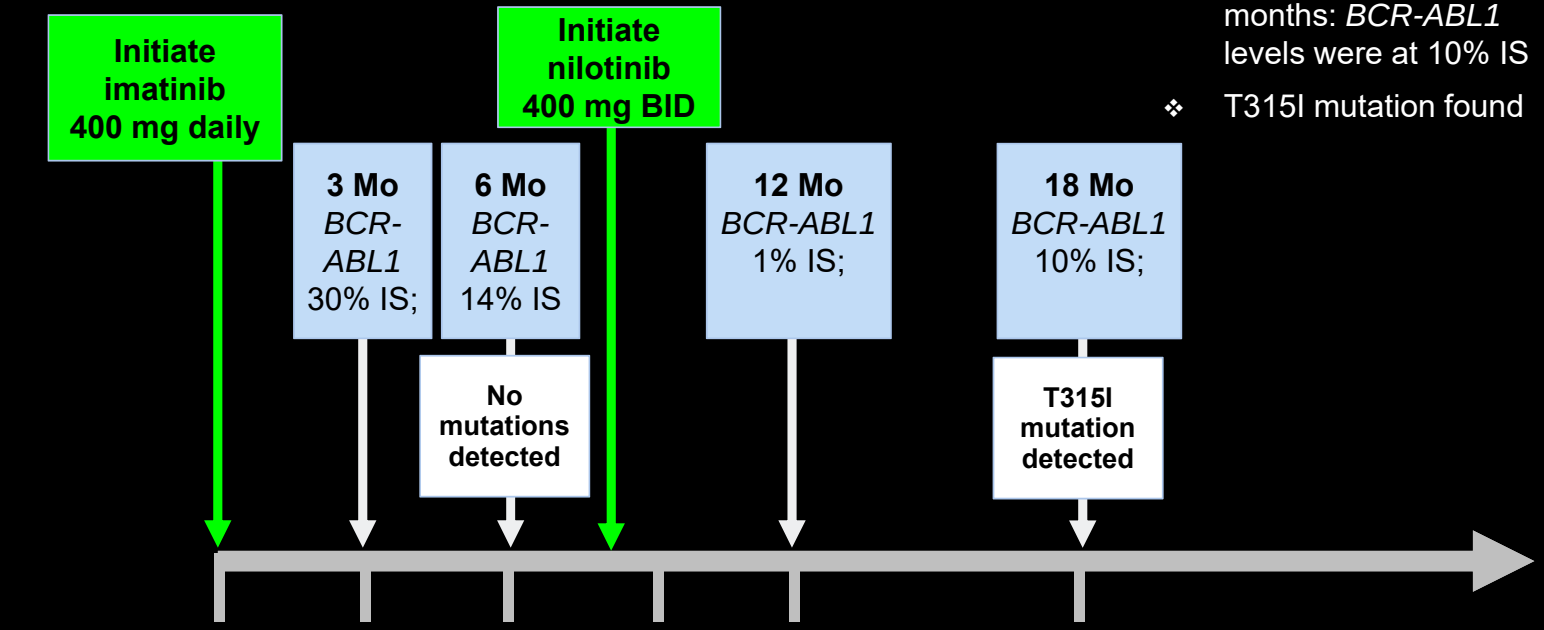


- *MVA: 3-mo CCyR only factor independently associated with EFS (p<0.001) and OS (p=0.03)*

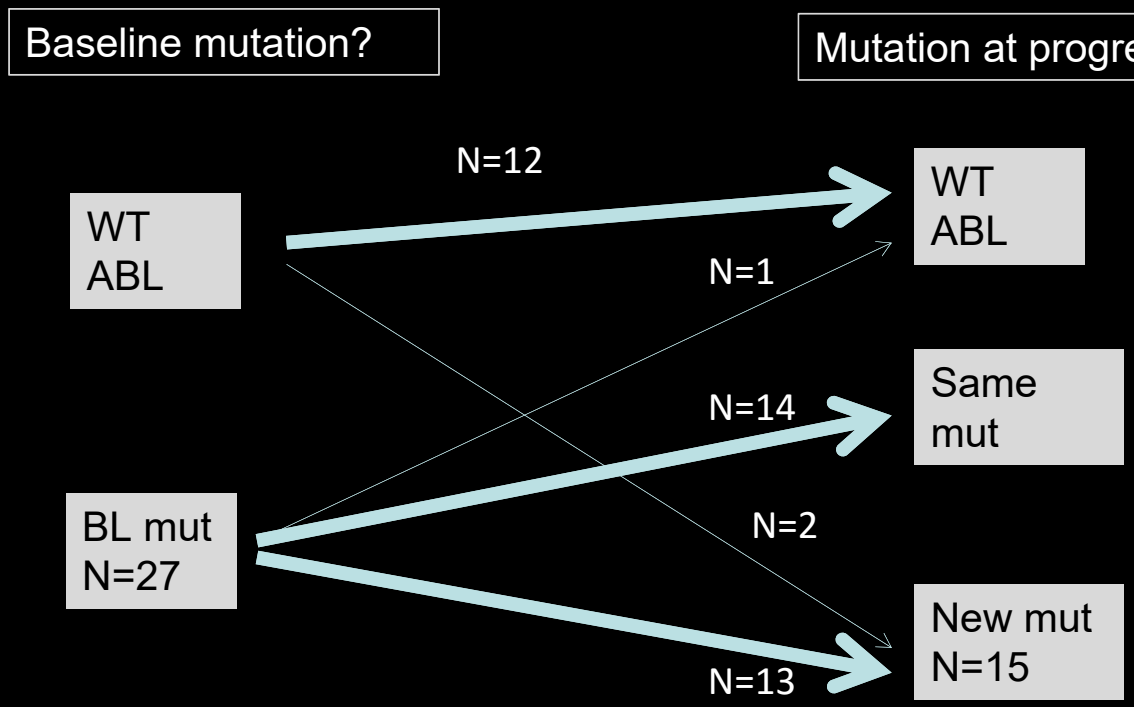
Jabbour et al. Blood. 2010;116: Abstract 2289. Jabbour et al. Clin Lymphoma Myeloma Leuk. 2013;13:302-306

Patient Monitoring and Treatment

- Pt. lost response at 18 months: *BCR-ABL1* levels were at 10% IS
- T315I mutation found



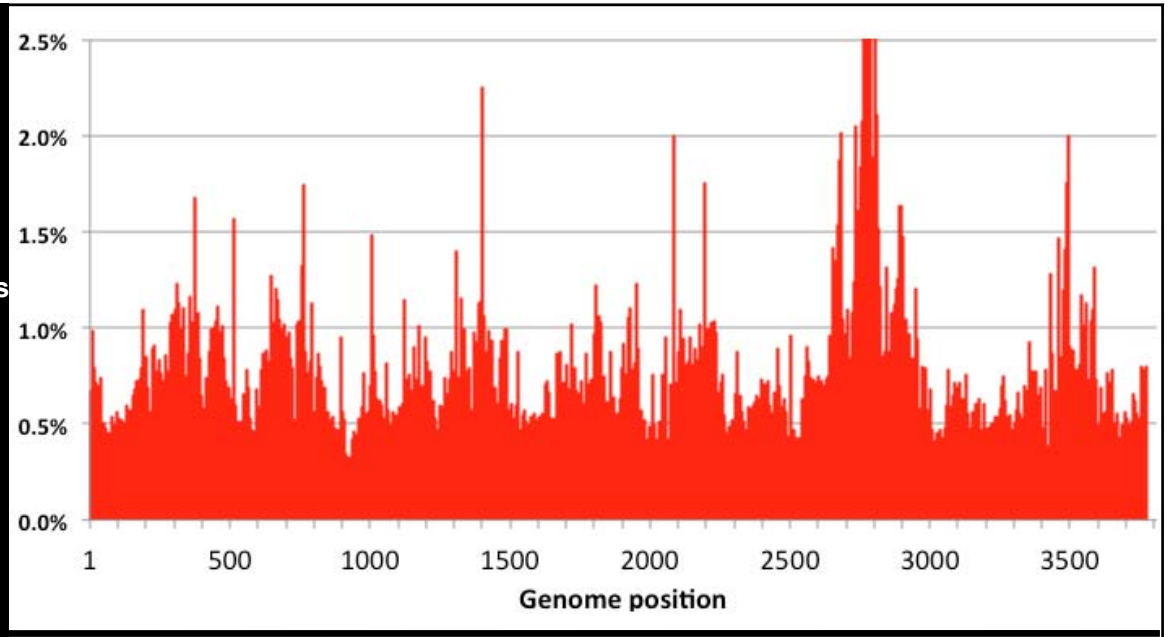
Patterns of mutation after salvage Rx



- Patients who do not have baseline mutations rarely progress with newly detected mutations
- Patients who have baseline mutations rarely progress in the absence of a mutation, either the same baseline or newly detectable mutation.

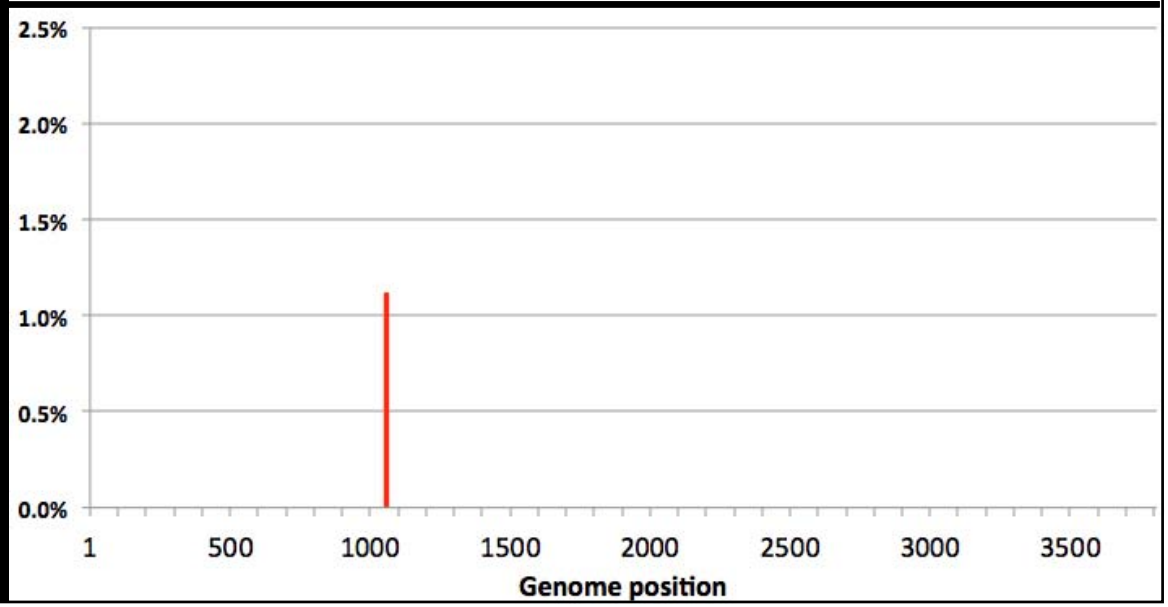
Conventional next-generation sequencing:

Artifactual errors obscure low-level variants.



Duplex Sequencing:

Errors are removed, revealing a single true mutation.



Schmitt MW et al.
Nature Methods (2015).

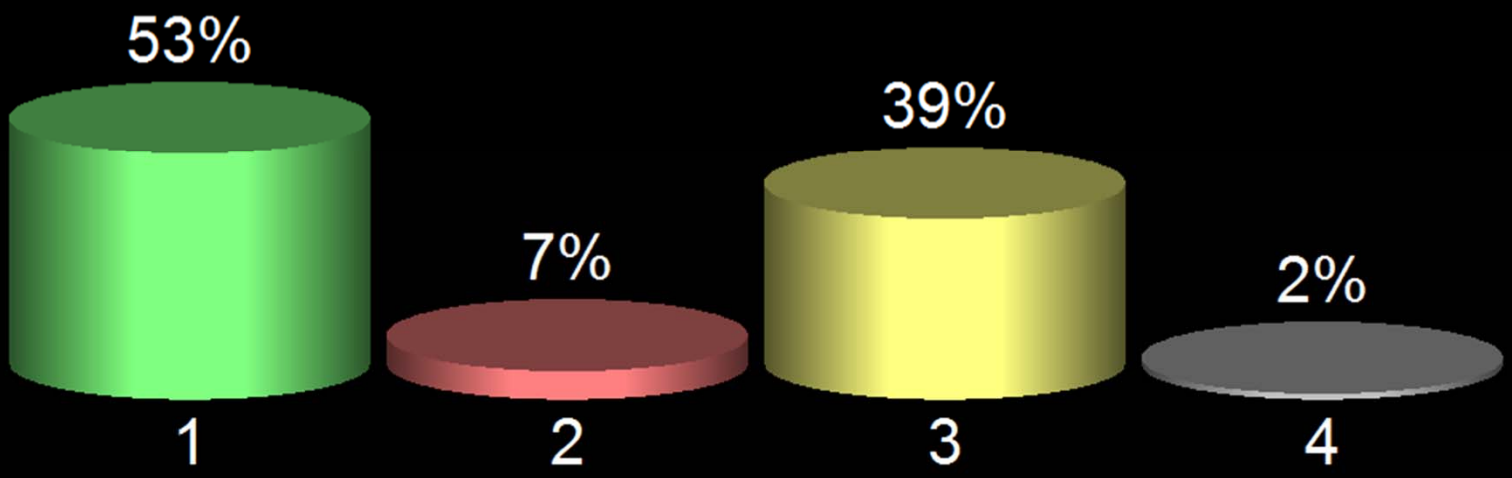
Competing subclones during CML treatment

Schmitt MW et al. PNAS (2012)

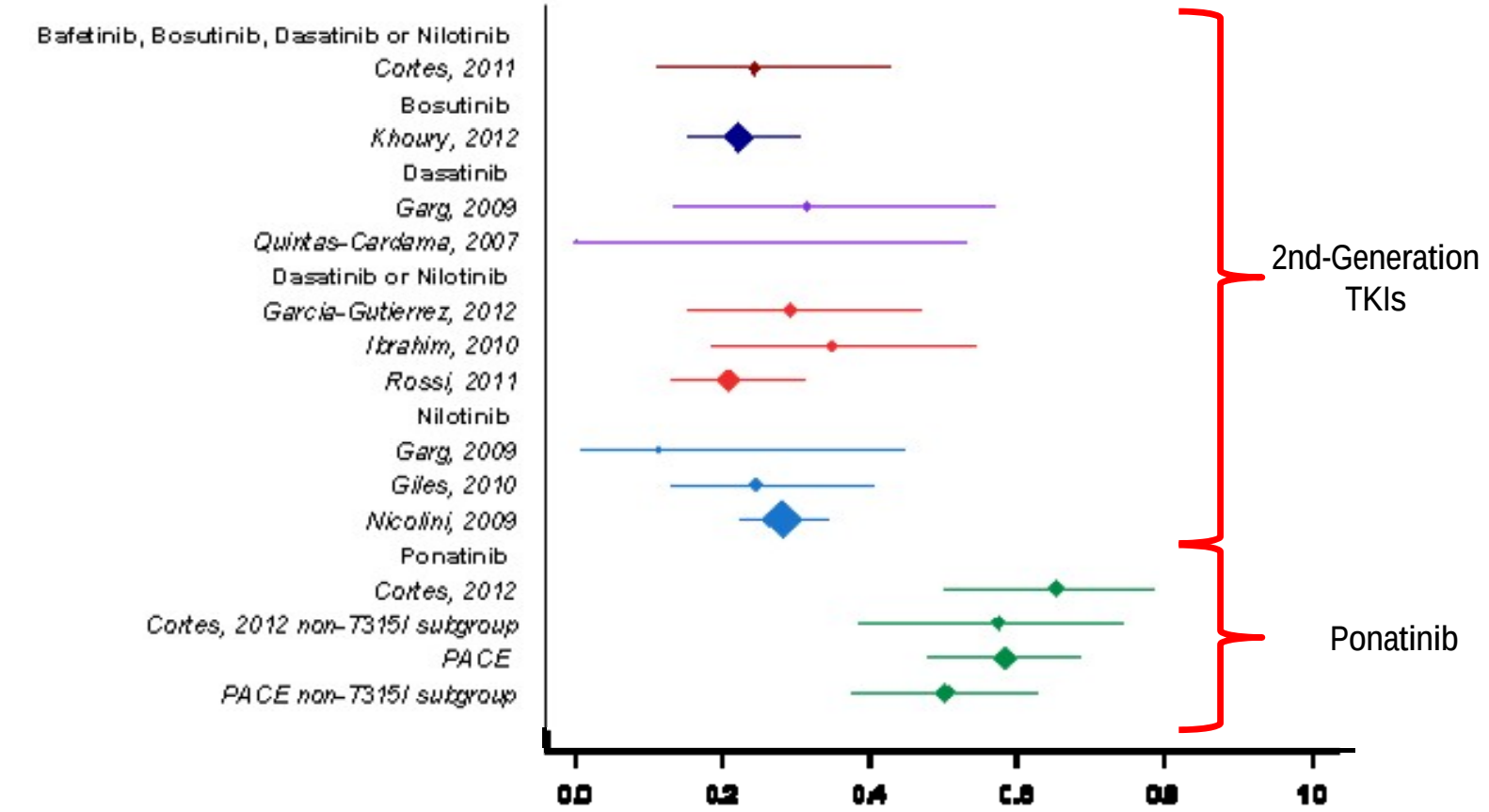
Audience Polling Results

Q3. Now what?

1. Change to ponatinib
2. Change to bosutinib
3. Allogeneic transplantation
4. Change to omacetaxine

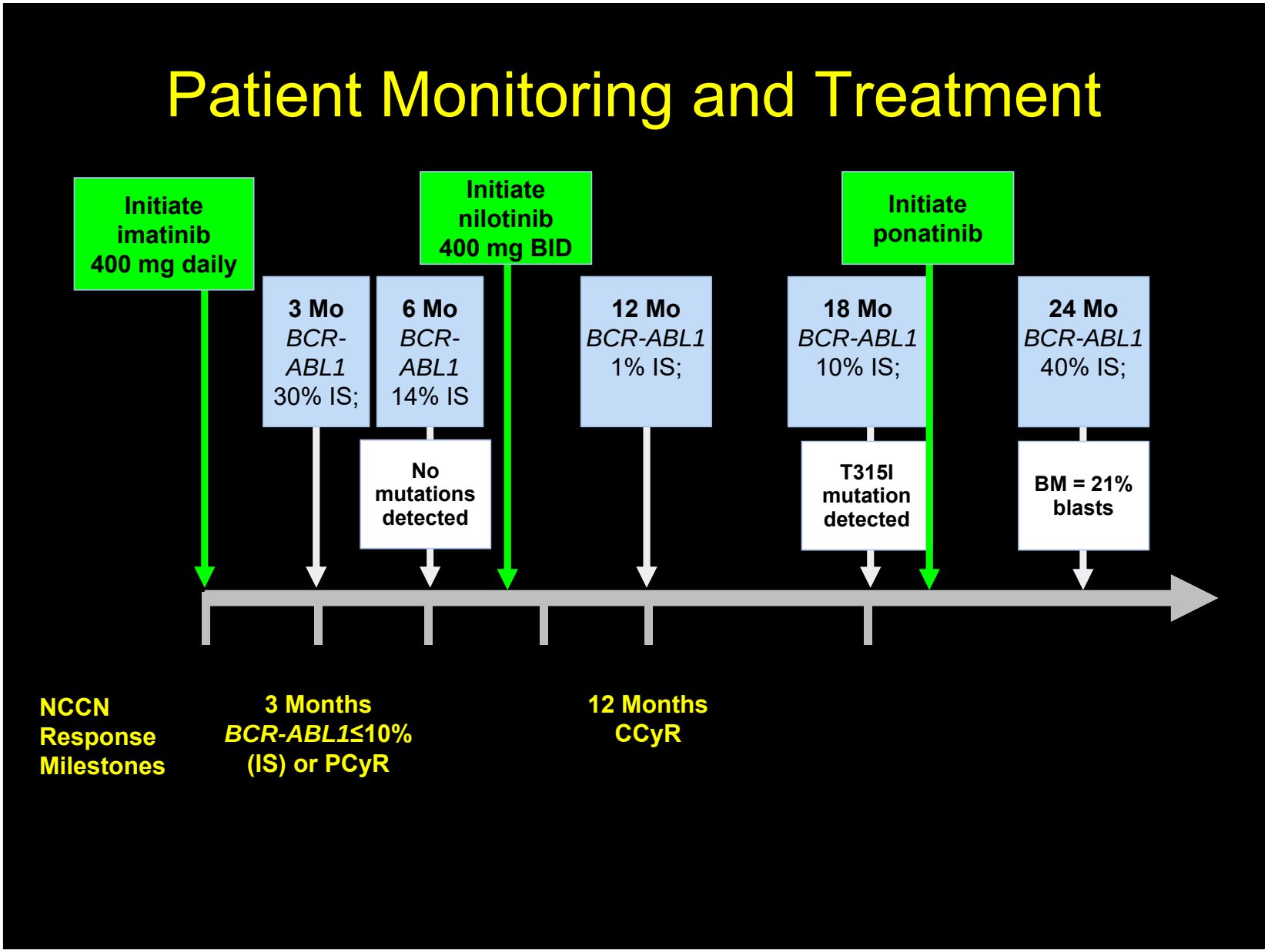


CCyR Rates After 2nd-Gen TKI Failure



Lipton J, et al. ASH 2013. Abstract 4010.

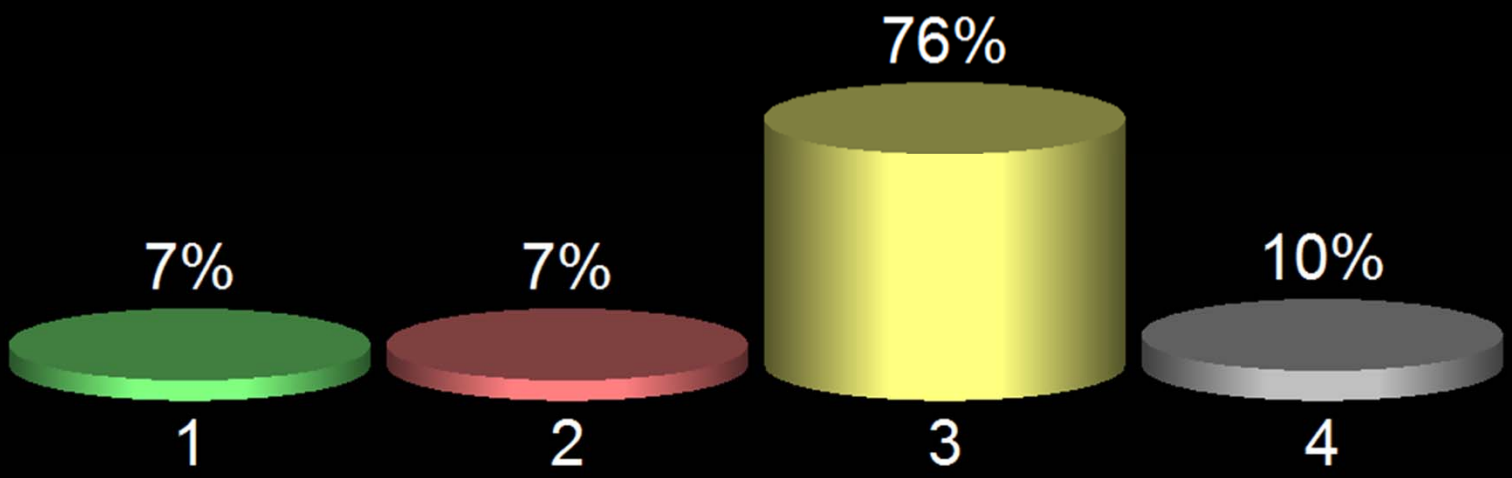
Patient Monitoring and Treatment



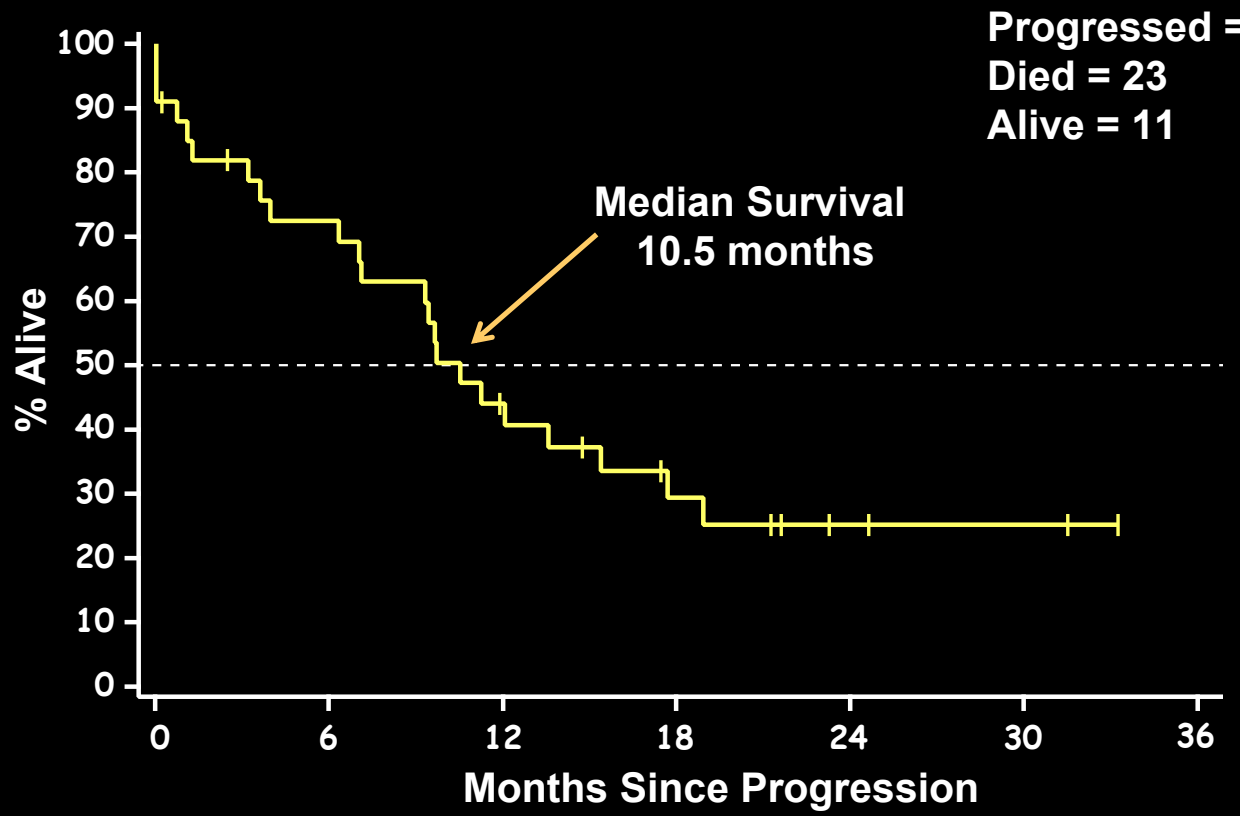
Audience Polling Results

Q4. Uh oh. Now what do you do?

1. Start HLA typing and search for a donor
2. Change to bosutinib
3. Allogeneic transplantation (you already did #1!)
4. Change to omacetaxine

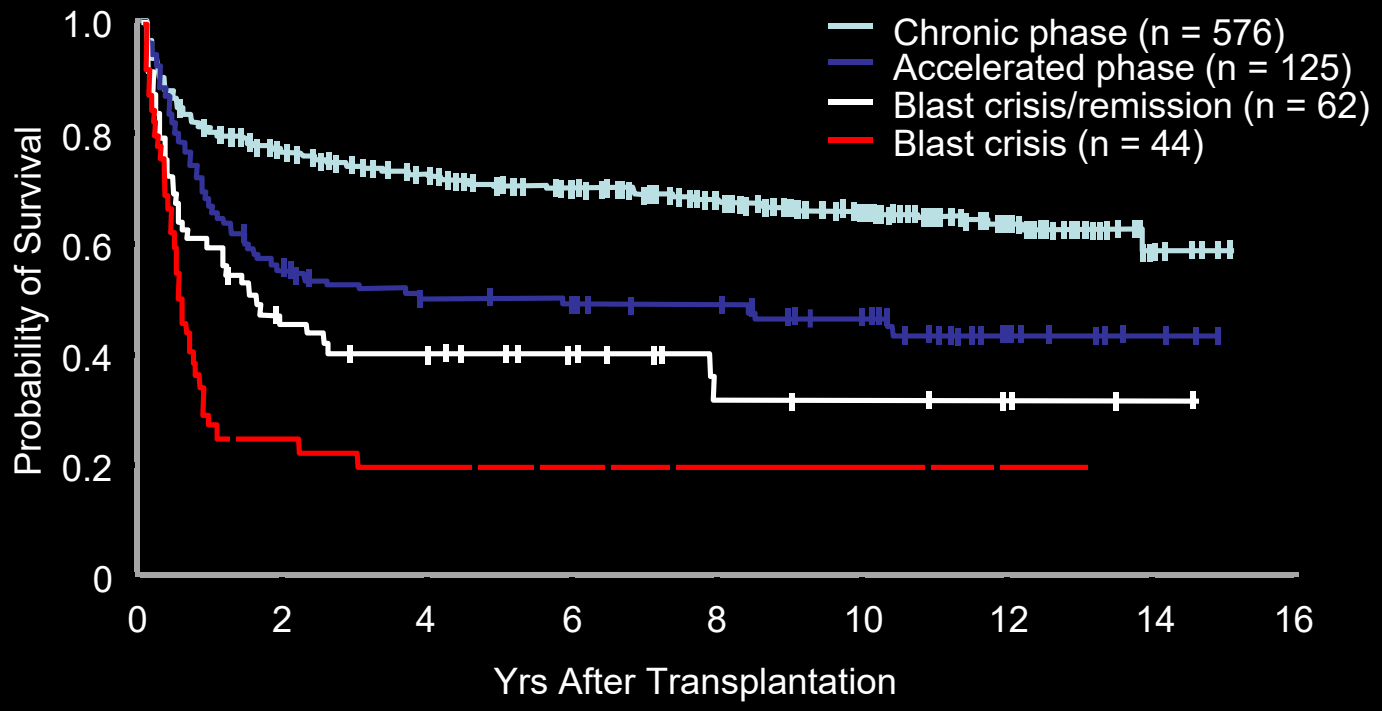


Survival After Progression to AP/BP (ENESTnd)



Saglio et al, 2011.

CML Survival After Allogeneic HCT (FHCRC)



Patients receiving allografts at the Fred Hutchinson Cancer Research Center from 1995 to the present. Figure is courtesy of Dr. Ted Gooley.

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CASE 3

Ruben A. Mesa, MD
Mayo Clinic Cancer Center

National Comprehensive Cancer Network®

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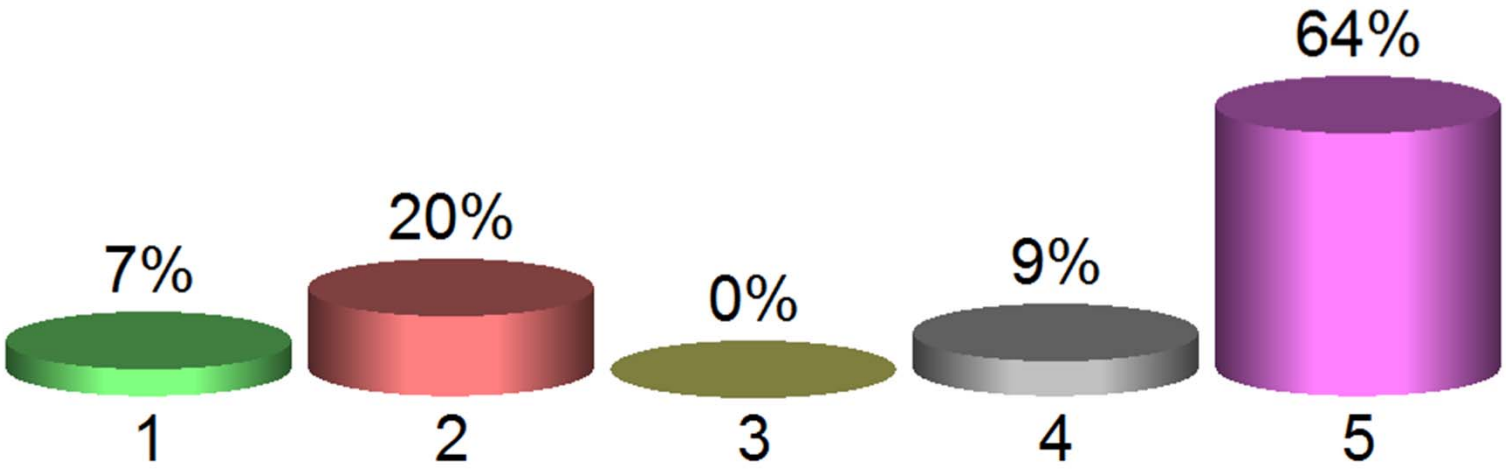
“Incidental” JAK2 Clone

- Question 1: What is threshold for JAK2-positive?
- Question 2: Where do we see JAK2 mutation where an MPN does not seem obvious?

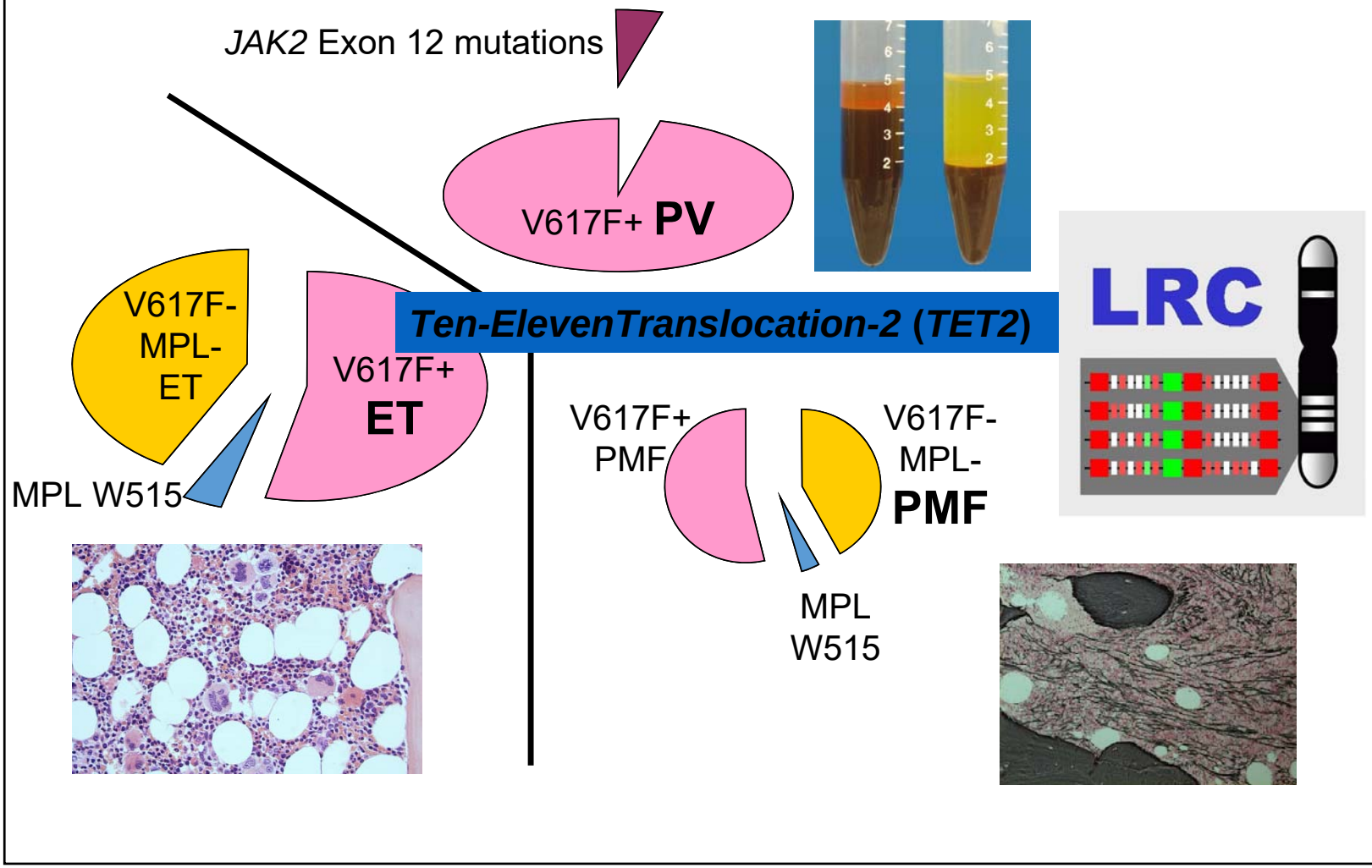
Audience Polling Results

Q1: What do you consider a "positive" JAK2 Mutation test?

1. JAK2 V617F mutated - allele burden 0.1%
2. JAK2 V617F mutated - allele burden 10%
3. CALR mutation
4. JAK2 Exon 12 mutation
5. All of the above



MPNs – new era in pathogenesis



What is JAK2 Positive?

- Mayo Medical Laboratory (mayomedicallaboratories.com)
- David Viswanatha, MD Source
  - Detection threshold 0.06%
  - Low Level positive 0.05% - 0.1% - still somewhat equivocal
  - 0.1% - 1% Low level but seem truly MPN positive when compared to marrow findings
  - Above 0.5-1.0% Likely ChiP or low level MPN almost certain
  - Can be positive in CHiP (much less common than DNMT3a)
- Wu et. al. (Applied IHC and MM 2015)
  - 1697 sequential JAK2 tests (2.6% were “low” (0.2% - 5%: 62% <1%))
  - Only 8/45 found to have an MPN

MDS somatic mutation profile

= mRNA splicing
= epigenetic/chromatin remodeling
= transcription factors
= cohesins

= activated kinases or RAS pathway
= DNA repair & mutation surveillance
= other / function unknown

Courtesy of D. Steensma, MD

Scaled by square root of frequency. Created by DPS and R Bejar.

Mutation frequency data source: Haferlach T et al *Leukemia* 2014.

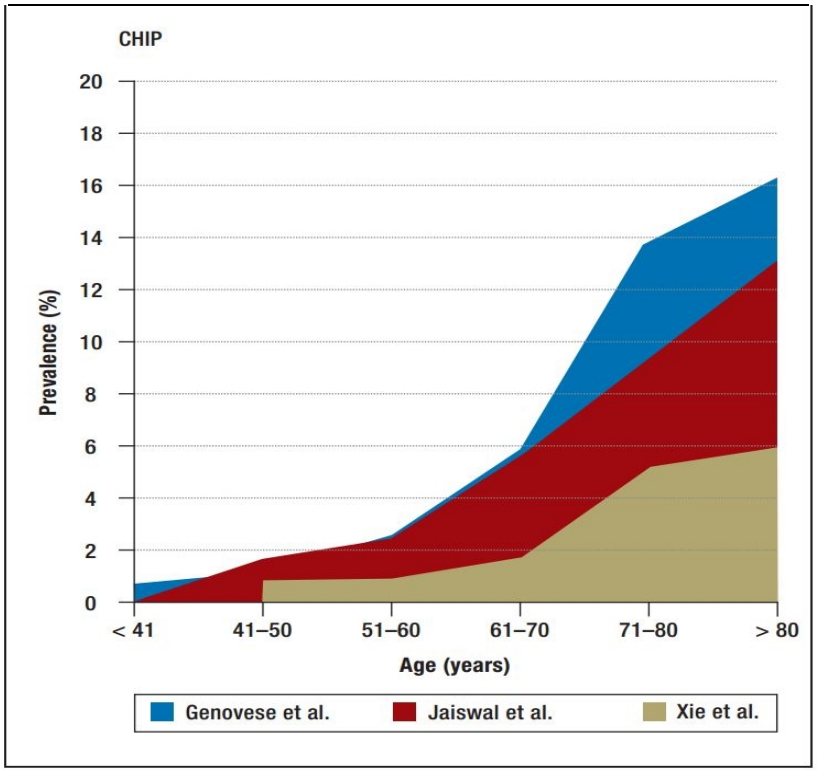
Clonal Hematopoiesis of Indeterminate Potential (CHIP) (aka Age Related Clonal Hematopoiesis (ARCH)

Features:

- Absence of definitive morphological evidence of a myeloid neoplasm or other clonal hematological disorder
- Presence of a somatic mutation associated with myeloid neoplasia (e.g., *DNMT3A, TET2, SF3B1*)
- Variant allele frequency (VAF) of 2% or above (otherwise everyone would have CHIP)
- *Odds of progression are ~0.5-1% per year*

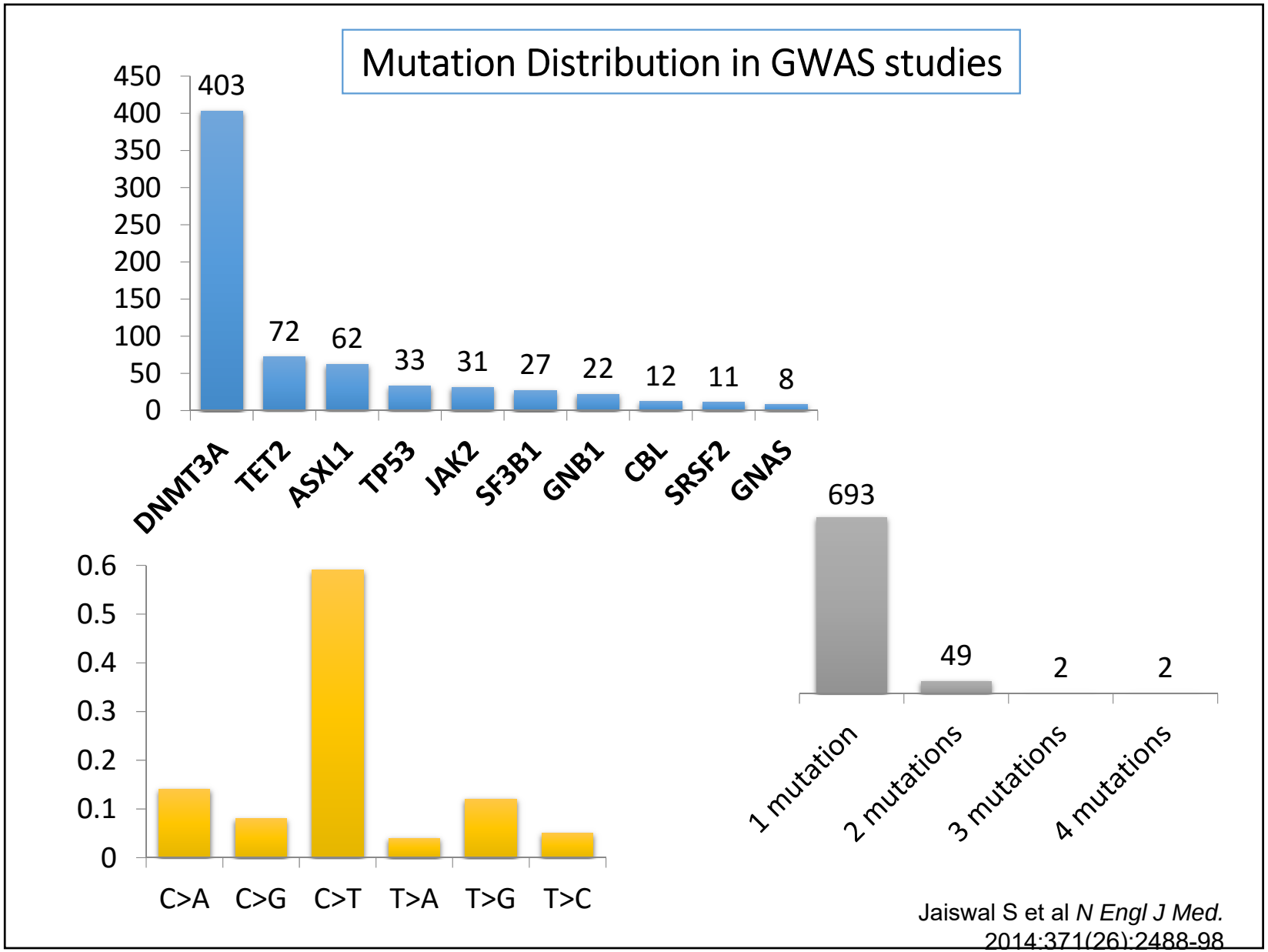
Steensma DP et al *Blood* 2015;126(1):9-16.

Prevalence of Mutations by Age



Age-related prevalence of CHIP (7–9)
CHIP, clonal hematopoiesis of indeterminate potential

Heuser M et al *Dtsch Arztebl Int* 2016; 113(18): 317-22



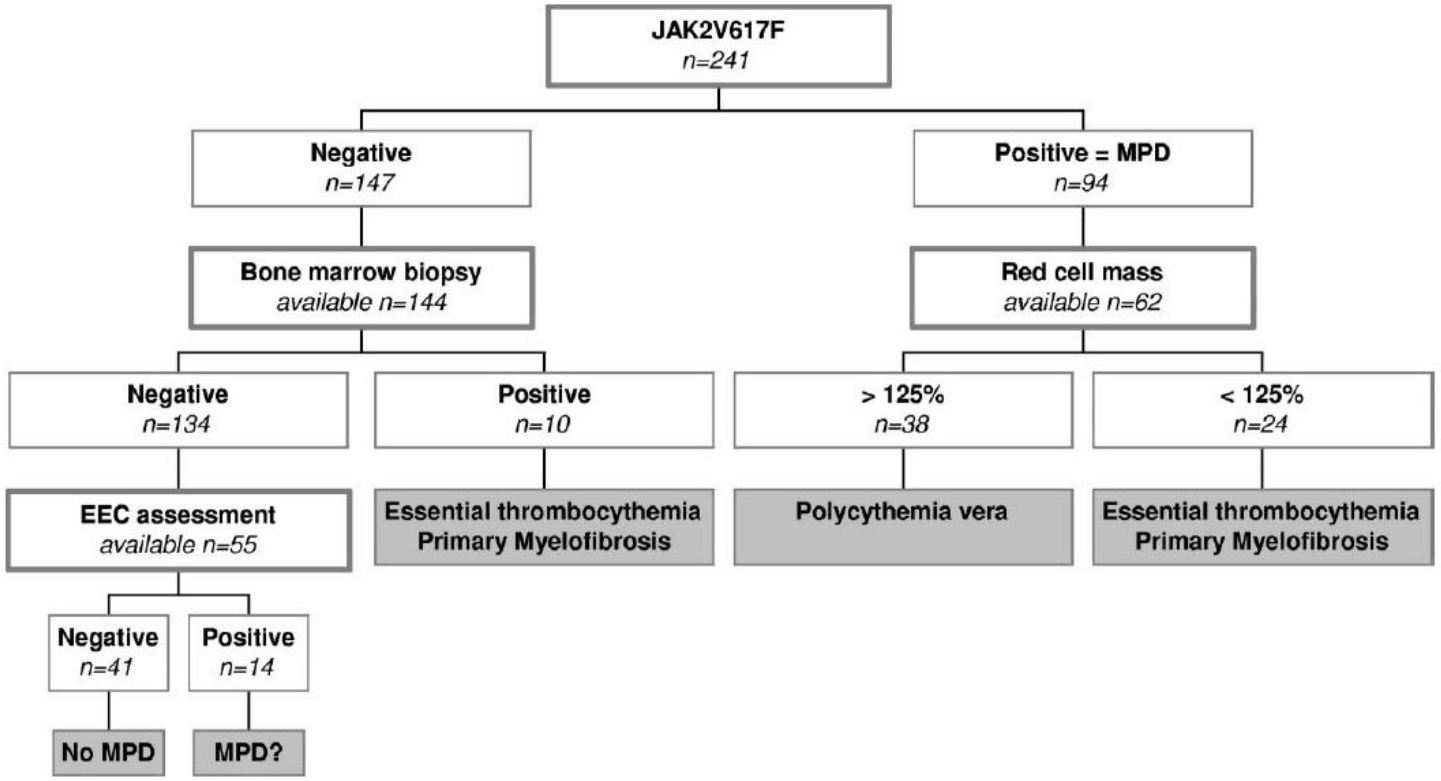
Case

- 47-year-old female presents with abdominal pain and bloating. Evaluation in Emergency Department demonstrates hepatomegaly, elevated transaminases, and hepatic vein thrombosis (Budd Chiari Syndrome). Spleen noted 5cm BLCM.
- Labs
  - Hemoglobin 13.7 g/dL
  - Leukocytes 8.5 x 10(9)/L
  - Platelets 333 x 10(9)/L
  - EPO 12 mU/ml (normal)
  - JAK2 V617F (15% allele burden)

Case Continued

- Bone Marrow
  - Does not meet WHO diagnosis of any specific MPN
  - Marrow is slightly hypercellular, some increased megakaryocytes with clustering
  - Scant reticulin fibrosis 0-1+
  - Karyotype 46, XX [20]

The impact of *JAK2* and *MPL* mutations on diagnosis and prognosis of splanchnic vein thrombosis: a report on 241 cases

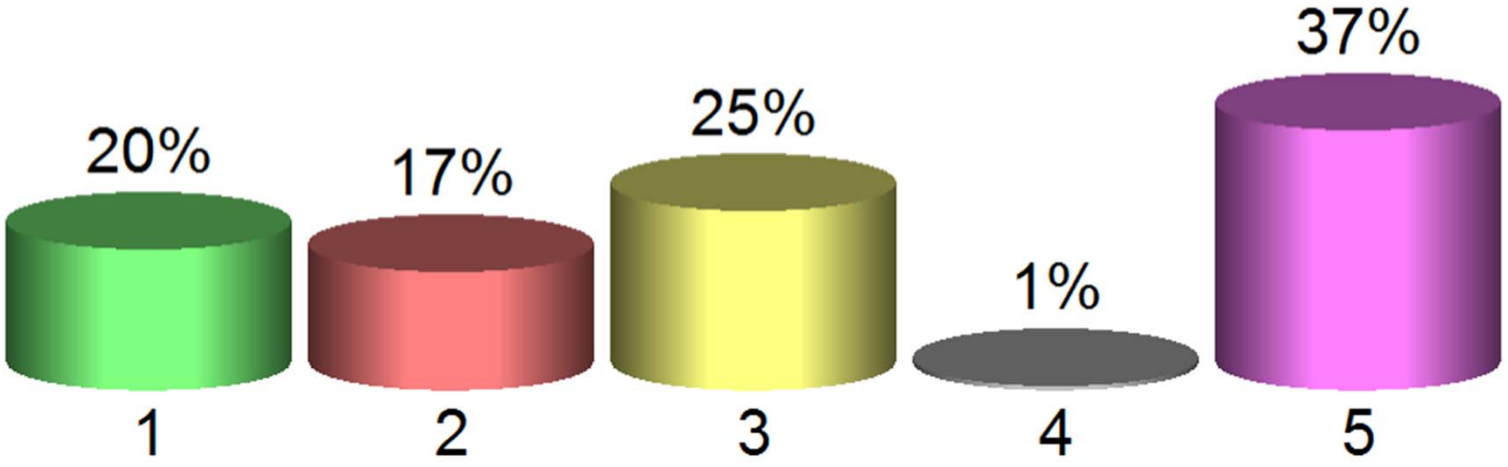


Kiladjian et. al. Blood 2008;111(10):4922-

Audience Polling Results

Q2: In setting of JAK2 mutated splanchnic vein thrombosis with no elevation in blood counts, what would be your management?

1. Warfarin alone
2. Warfarin plus aspirin
3. Warfarin +/- ASA; as well as hydroxyurea
4. Warfarin +/- ASA; as well as pegylated interferon
5. Warfarin +/- ASA; as well as ruxolitinib



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