NCCN 11th Annual Congress:
Hematologic Malignancies™

Does Generic Imatinib Change the Treatment Approach in CML?

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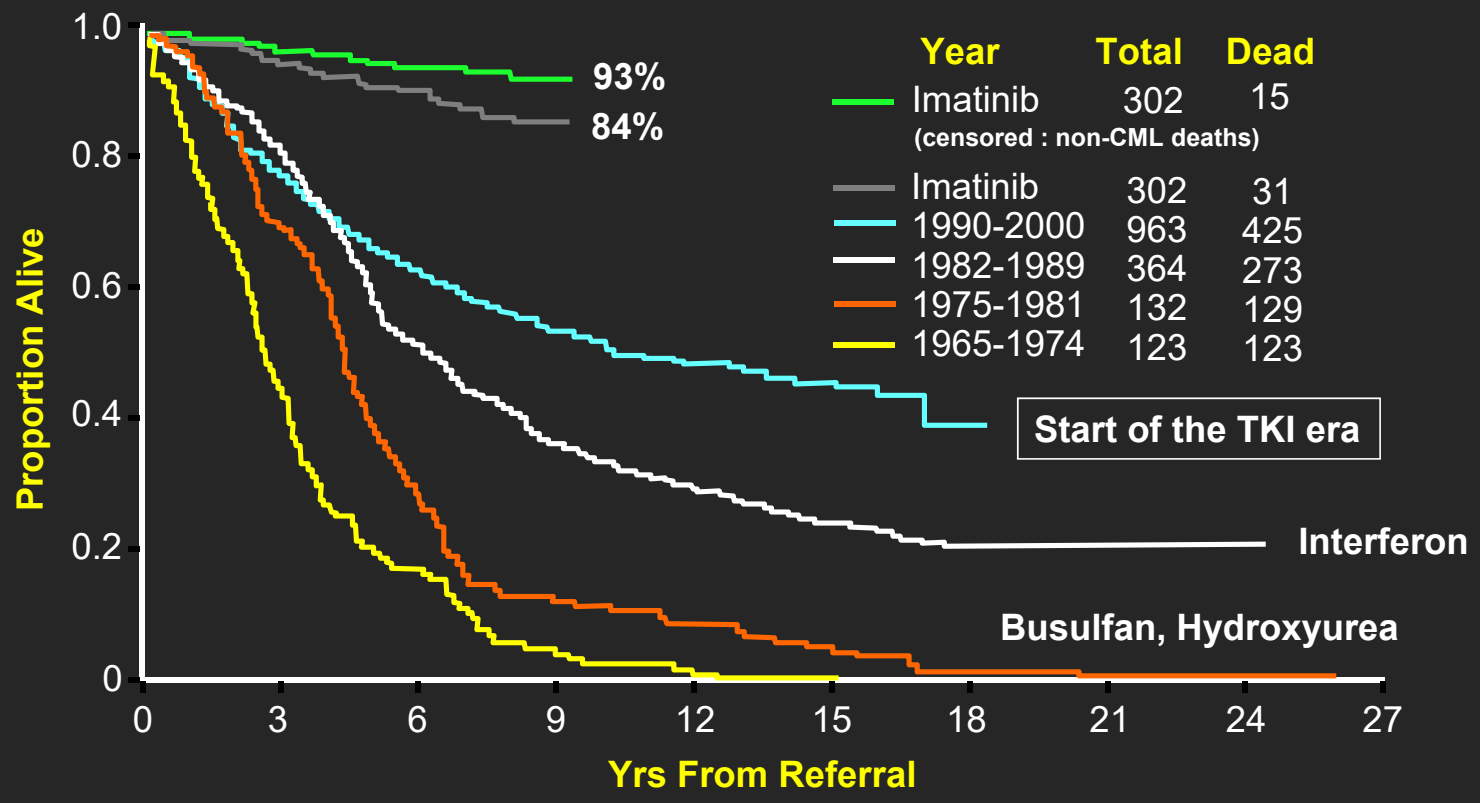
Educational Objectives

- Describe the current standard of care and the impact of generic imatinib for the management of newly diagnosed patients with CML.
- Identify the challenges associated with the selection of appropriate first-line TKI therapy for the management of patients with CML.

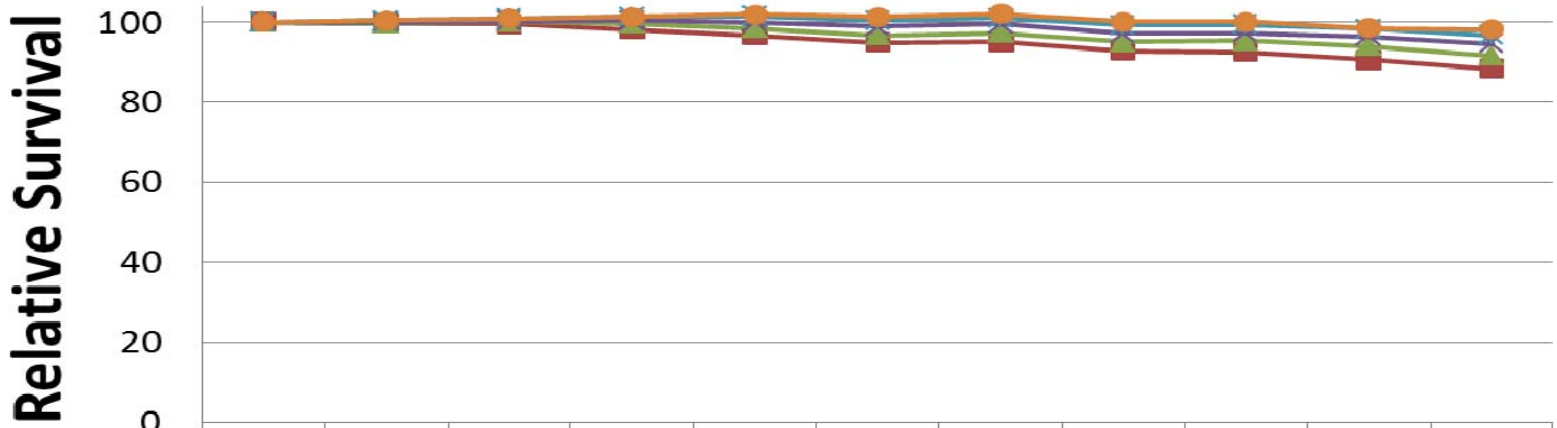
Survival in Early CP-CML



The University of Texas MD Anderson Cancer Center Database.

Relative Survival with TKI by Response to Rx

- **483 pts with CML Rx with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=111) or nilotinib (n=101)**
- 5-yr relative survival 94.8% **[92.1 - 97.4]**

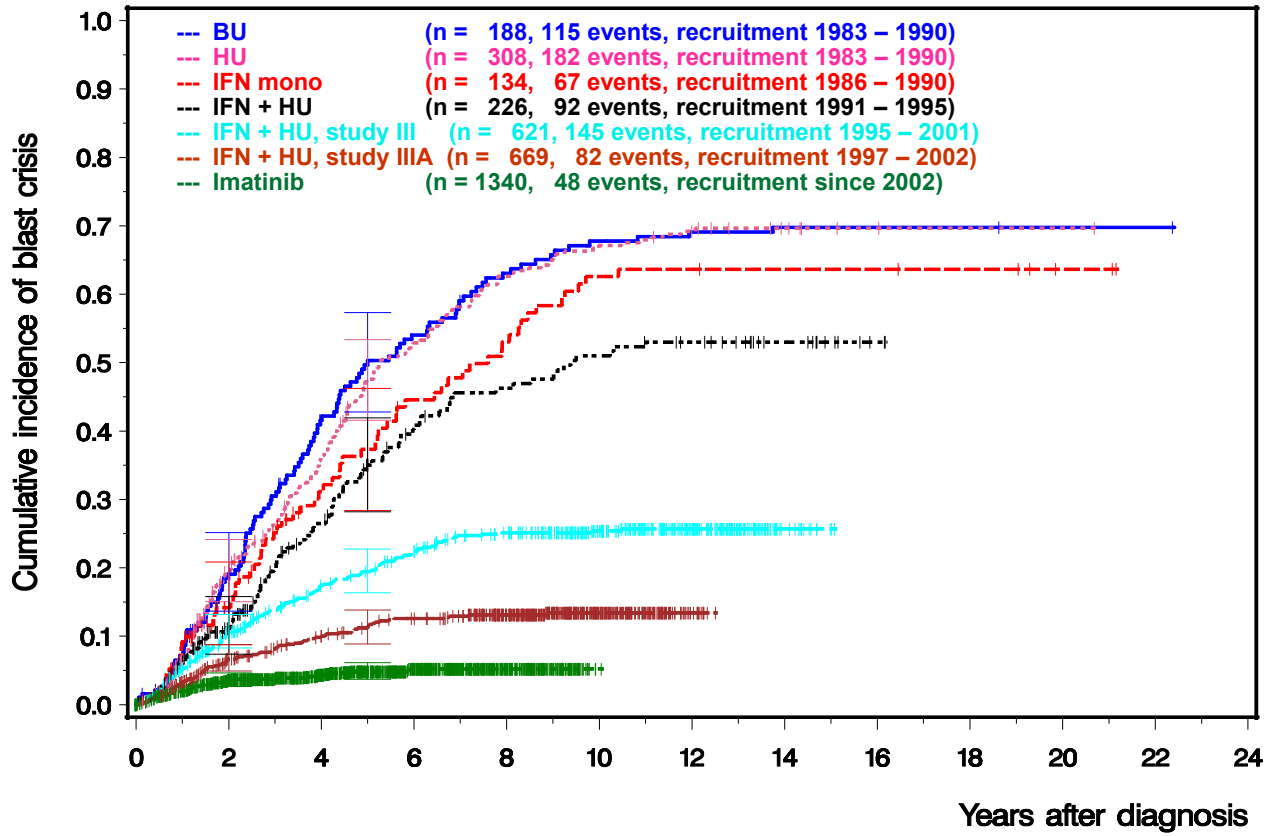


	0	12	24	36	48	60	72	84	96	108	120
All	100.0	99.6	99.5	98.2	96.7	94.8	95.0	92.7	92.5	90.6	88.3
CCyR	100.0	99.7	100.1	99.7	98.4	96.7	97.2	95.1	95.3	94.0	91.7
MMR	100.0	99.9	100.3	100.4	100.0	98.9	99.5	97.2	97.3	96.4	94.5
MR4.5	100.0	100.4	100.8	101.3	101.4	100.4	101.0	99.2	99.4	98.3	96.7
CMR	100.0	100.4	100.8	101.3	101.8	101.4	102.0	100.2	100.1	98.5	98.2

Month

Sasaki . Lancet Hematology 2: e186-193; 2015

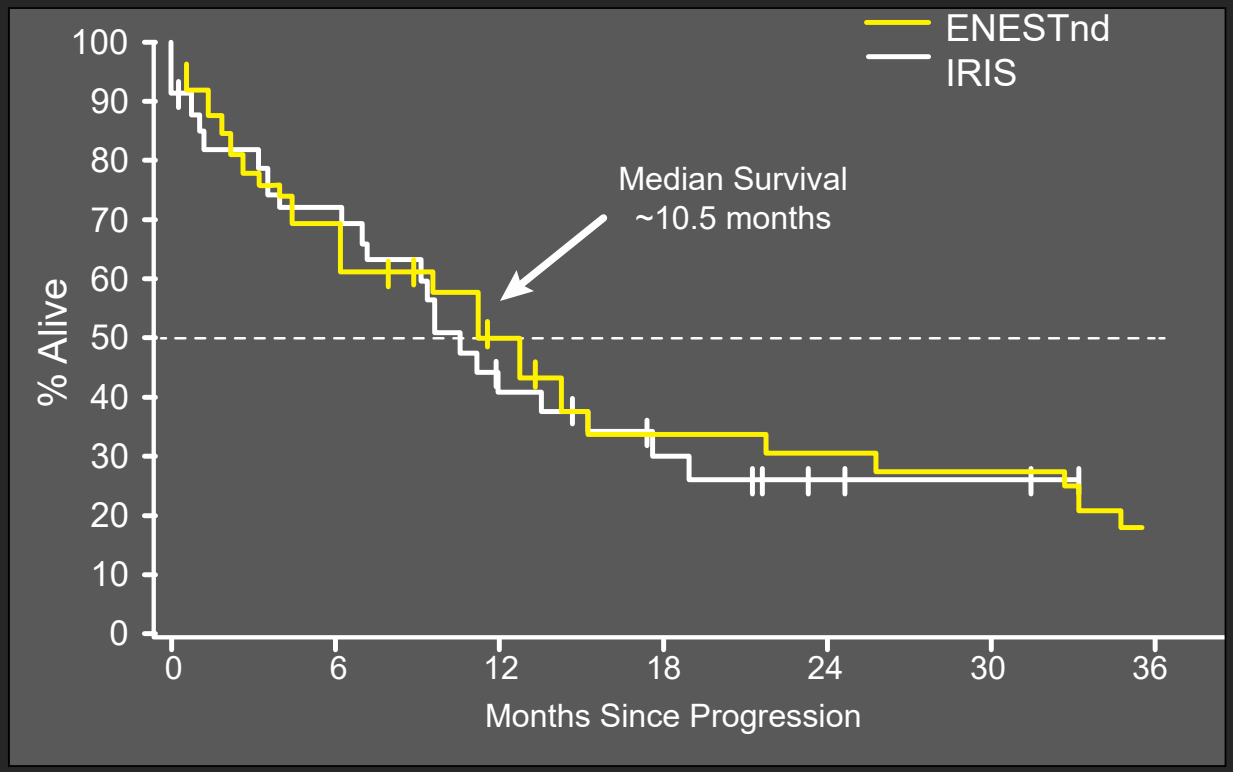
Prevention of blast crisis
Cumulative Incidences 1983 – 2013



German CML Study group, unpublished

OS After Progression to AP/BC in the ENESTnd and IRIS Trials

Progression during TKI therapy is not good



Larson RA, et al. *Leukemia*. 2012;26(10):2197-2203.

Therapy of CML in 2016

- **Frontline**
  - Imatinib 400 mg daily
  - Nilotinib 300 mg twice daily
  - Dasatinib 100 mg daily
- **Second/third line**
  - Nilotinib, Dasatinib, Bosutinib, Ponatinib
  - Omacetaxine
  - Allogeneic SCT
- **Other**
  - Decitabine, Interferon
  - Hydroxyurea, Cytarabine, combination of TKIs
  - Investigational agents, Clinical trials

How to decide on a TKI

- Treatment goals
  - Lengthen survival?
  - Prevent progression?
  - Complete molecular response/discontinuation?
- Co-morbidities (anticipated drug toxicity)
- Compliance (frequency of dose, restrictions)

Treatment goals in CML

Response goals

- Early molecular response
- CCyR
- Major molecular response
- Deep/complete MR

Why?

- Progression and survival
- Progression and survival
- "Safe haven"
- Discontinuation?

Somewhat bogus comparison of TKIs across randomized trials

Outcome, %	Dasatinib[1]	Nilotinib[2]	IM 400[1,2]
Discontinued	39	40	37/50
12-month CCyR	77	80	66/65
5-year MMR	76	77	64/60
5-year $MR^{4.5}$	42	54	33/31
3-month <10%	84	91	64/67
5-year AP/BC	5	4	7/8
5-year OS	91	94	90/92
5-year PFS	85	92	86/91

1. Cortes JE et al. *J Clin Oncol* 2016;34:2333-2340; 2. Hochhaus AE et al. *Leukemia* 2016;30:1044-1054.

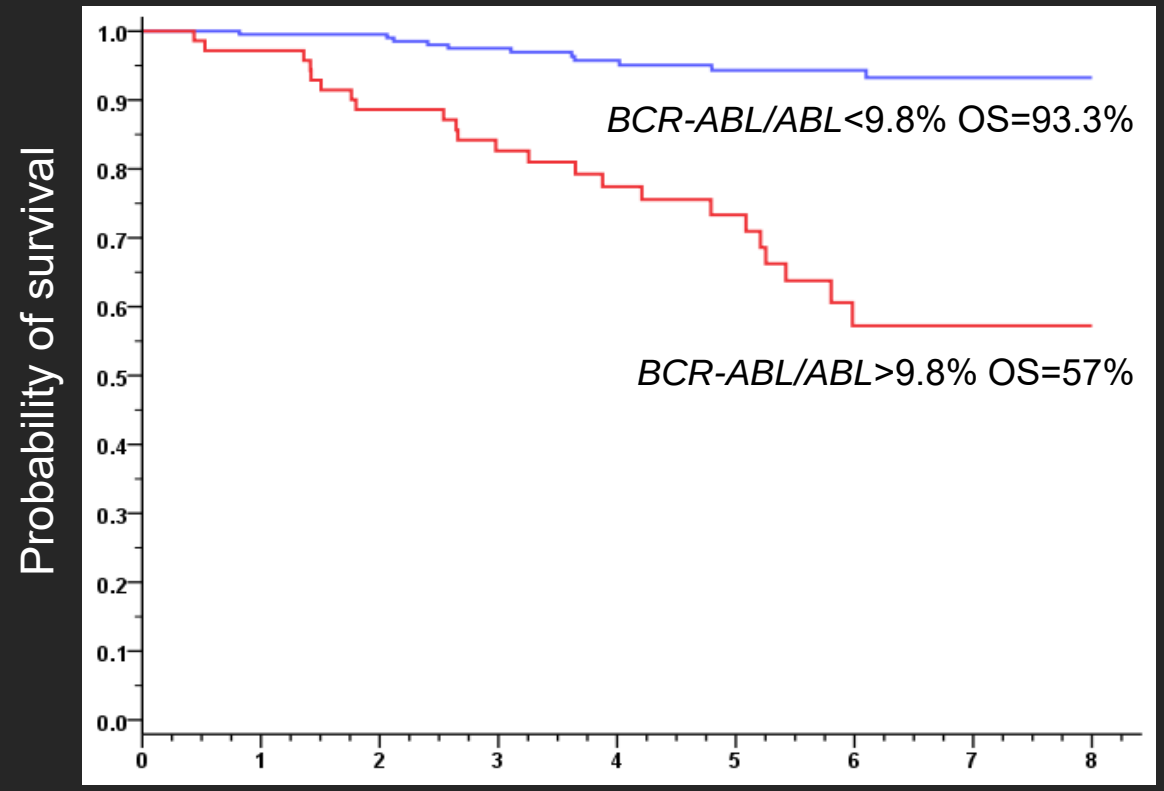
The Intergroup trials

Outcome	DAS[1]	IM 400	IM 800[2]	IM 400
CCyR	84	69	85	67
MMR	59	44	53	35
MR4.5	21	15	19	9
PFS	93	90	92	80
OS	97	97	95	90

1. Radich JP et al. *Blood* 2012;120:3898-3905;
2. Deininger MW et al. *Br J Haematol* 2014;164:223-232.

Survival Based on 3 Months of Molecular Response

Survival After Imatinib Therapy by Molecular Response Achieved at 3 Months



Marin D, et al. *J Clin Oncol*. 2012;30(3):232-238.

Importance of Testing at 3 Months

% Survival / TFS by Early Molecular Response

Study	QPCR <10%	QPCR >10%
Marin (8 year)	93	57
MD Anderson (10 year)	98	94
ENEST-nd	97	87
DASISION	97	86
BELA	98	88

TFS = transformation-free survival

Marin D, et al. *J Clin Oncol*. 2012;30(3):232-238; Jain P, et al. *Blood*. 2012;120:abstract 70; Hochhaus A, et al. *Blood.* 2012;120:abstract 167; Saglio G, et al. *Blood*. 2012;120:abstract 1675; Brummendorf T, et al. *Blood.* 2012;120:abstract 69.

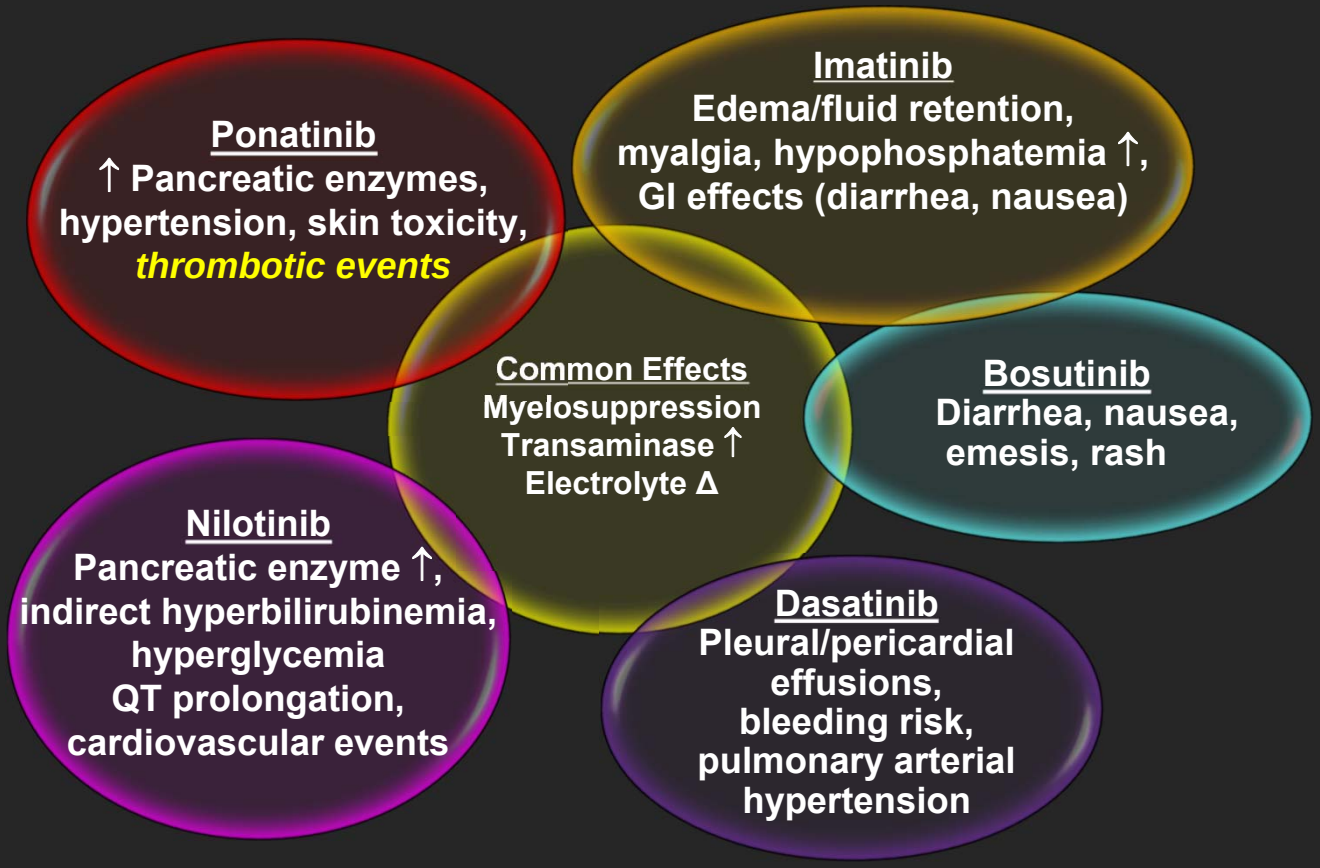
Outcome by Response at 3m and 6m

- 528 patients treated with imatinib
- 89/483 (18%) had *BCR-ABL* >10% at 3 months

Response		No.	% at 4 years			
3 month	6 month		Survival	PFS	FFS	MMR
≤10%	<1	342	97	97	87	88
≤10%	1-10	42	100	97	79	71
≤10%	>10	10	89	90	51	56
>10%	<1	18	100	100	76	88
>10%	1-10	36	100	94	79	69
>10%	**>10**	**35**	**74**	**69**	**11**	**3.3**

Branford S, et al. *Blood.* 2013;122:abstract 254.

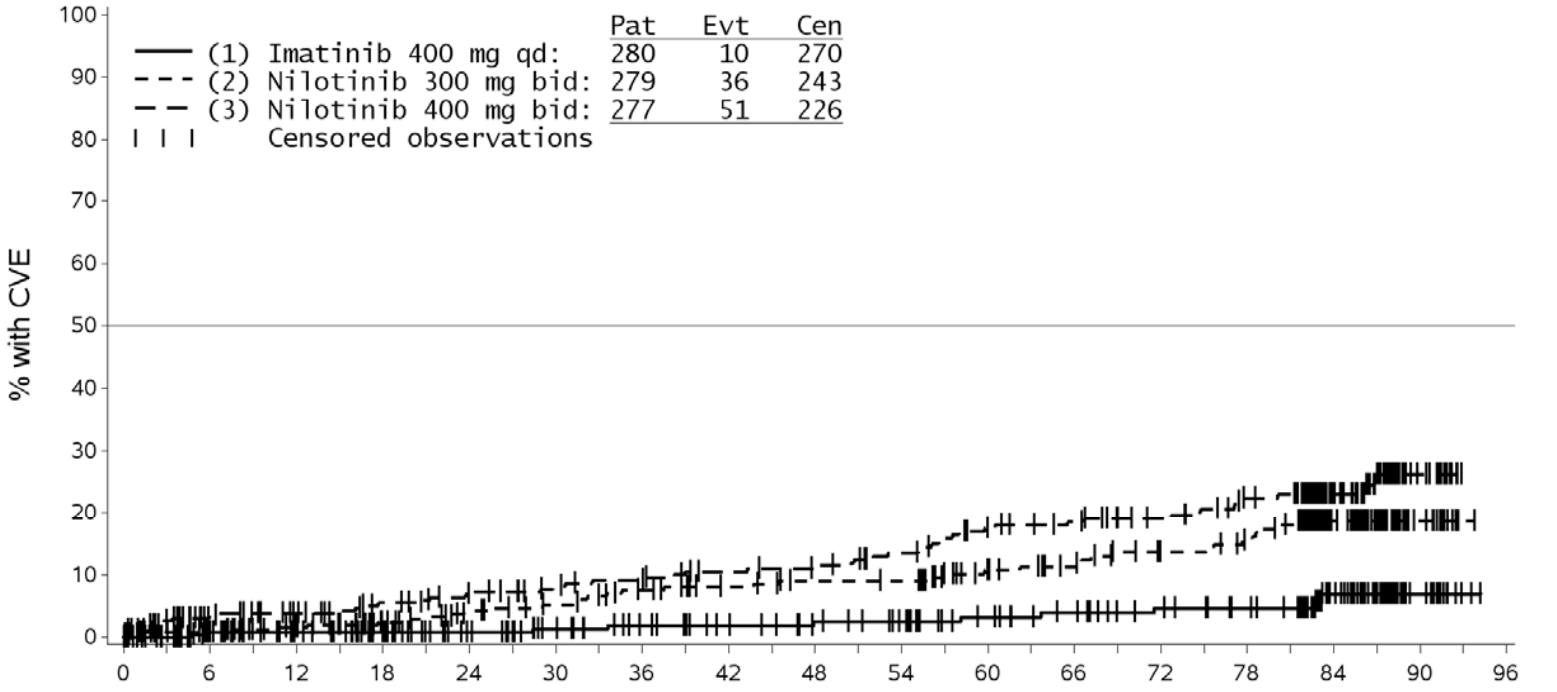
Treatment Options Based on Adverse Event Spectrum of TKIs in CML



Saglio G, et al. *N Engl J Med*. 2010;362(24):2251-2259; Kantarjian H, et al. *N Engl J Med*. 2010;362(24):2260-2270; Cortes JE, et al. *J Clin Oncol*. 2012;30(28):3486-3492; Kantarjian H, et al. *J Clin Oncol*. 2014;32(5 suppl):abstr 7081.

ENESTnd-CV Events

Figure 14.3.1-1.2 (Page 1 of 5)
Kaplan-Meier estimate of time to first cardiovascular event
Safety population
All CVEs



At-risk : Events									
(1) 280 : 0	227 : 2	196 : 2	173 : 4	159 : 5	141 : 6	125 : 8	67 : 10	0 : 10
(2) 279 : 0	240 : 4	208 : 10	191 : 17	177 : 20	158 : 23	139 : 28	71 : 36	0 : 36
(3) 277 : 0	232 : 10	209 : 17	196 : 22	185 : 26	161 : 39	145 : 42	70 : 49	0 : 51

/report/pgm_saf/ttcve.sas 27NOV2015 12:08 (Cut-Off 17JUL2015)

Hochhaus AE et al. *Leukemia* 2016;30:1044-1054

Arteriothrombotic Events With TKI

	Imatinib (%)	Other TKI (%)
ENESTnd	3	10-16
DASISION	2	5
BELA*	1 (8)	1 (11)
EPIC	2	8
PACE* (Ponatinib)		13 (27)
Bosutinib, phase 2 Trial		6

* Exposure adjusted. Actual rate in parenthesis

Larson R, et al. *Blood.* 2014;124:abstract 4541; Cortes J, et al. *Blood.* 2014;124:abstract 152; Lipton J, et al. *Blood.* 2014;124:abstract 519; Cortes J, et al. *J Clin Oncol.* 2014;21(5s):abstract 7060.

Compliance to Imatinib

(Adagio Study)

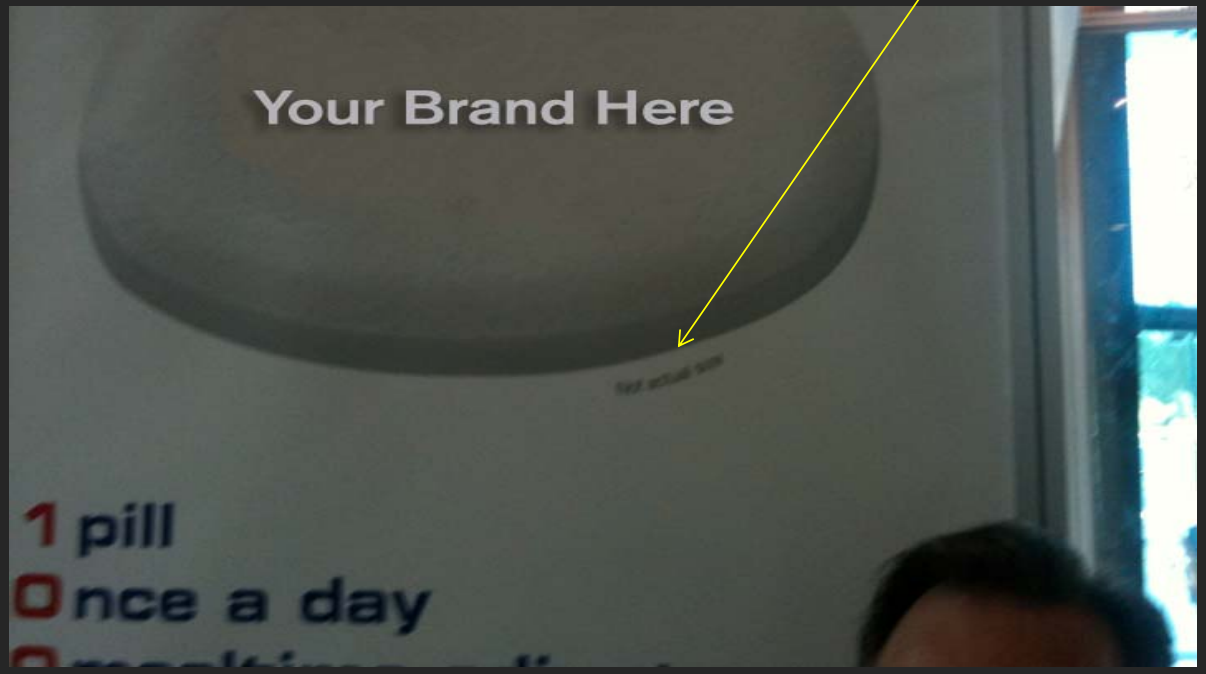
Actual Imatinib Taken (assessed by pill count)	n	%
As prescribed	23	14.2
>the prescribed dose	24	14.8
<prescribed dose	115	71.0

NCCN recommends evaluating compliance whenever a milestone is not achieved.

Noens L, et al. *Blood.* 2009;113:5401-5411; NCCN Guidelines. Chronic Myelogenous Leukemia. Version 1.2016.

A pill a day keeps the CML at bay

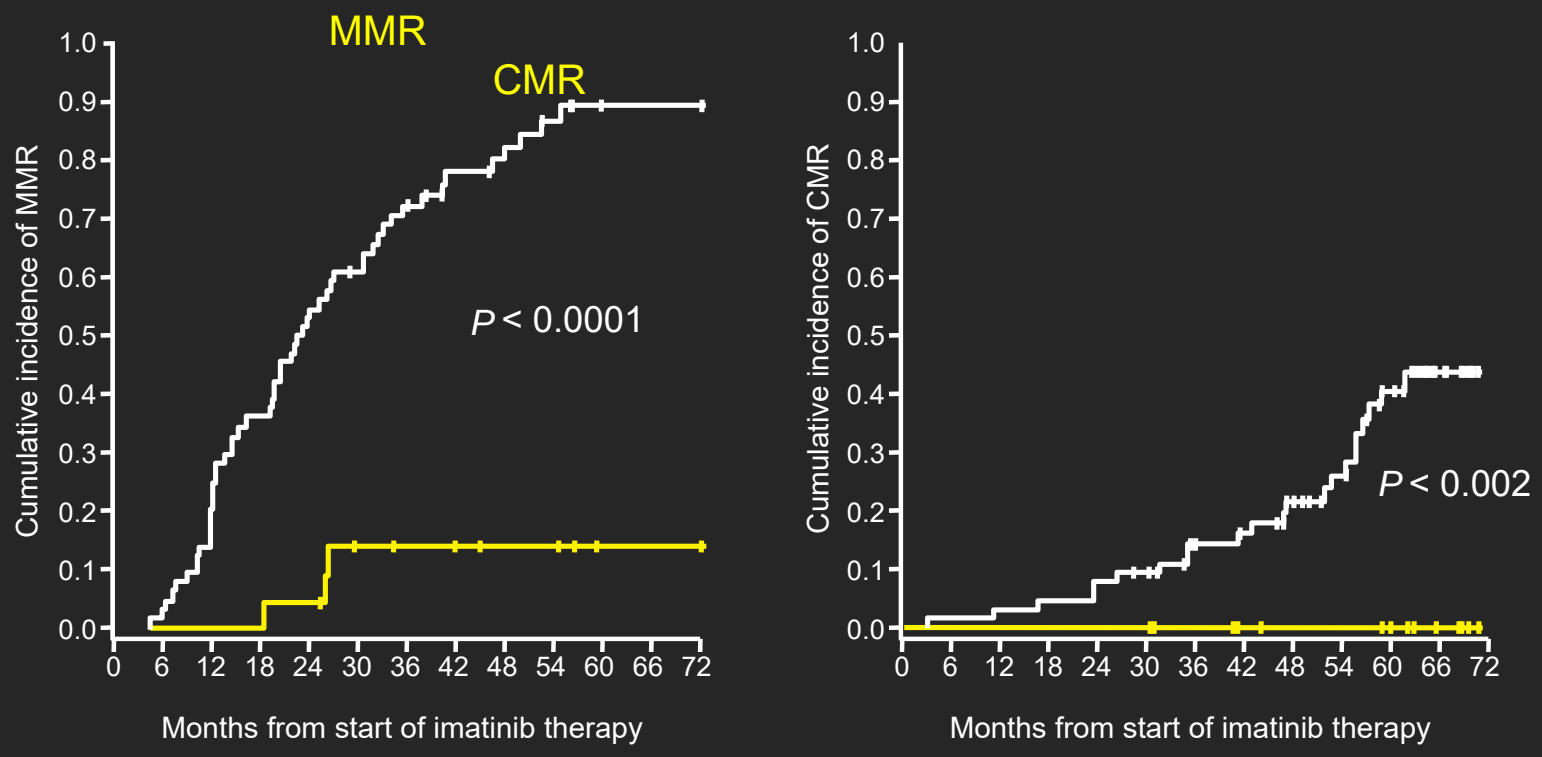
"Not actual size."



Forehead, Dr. Timothy Hughes

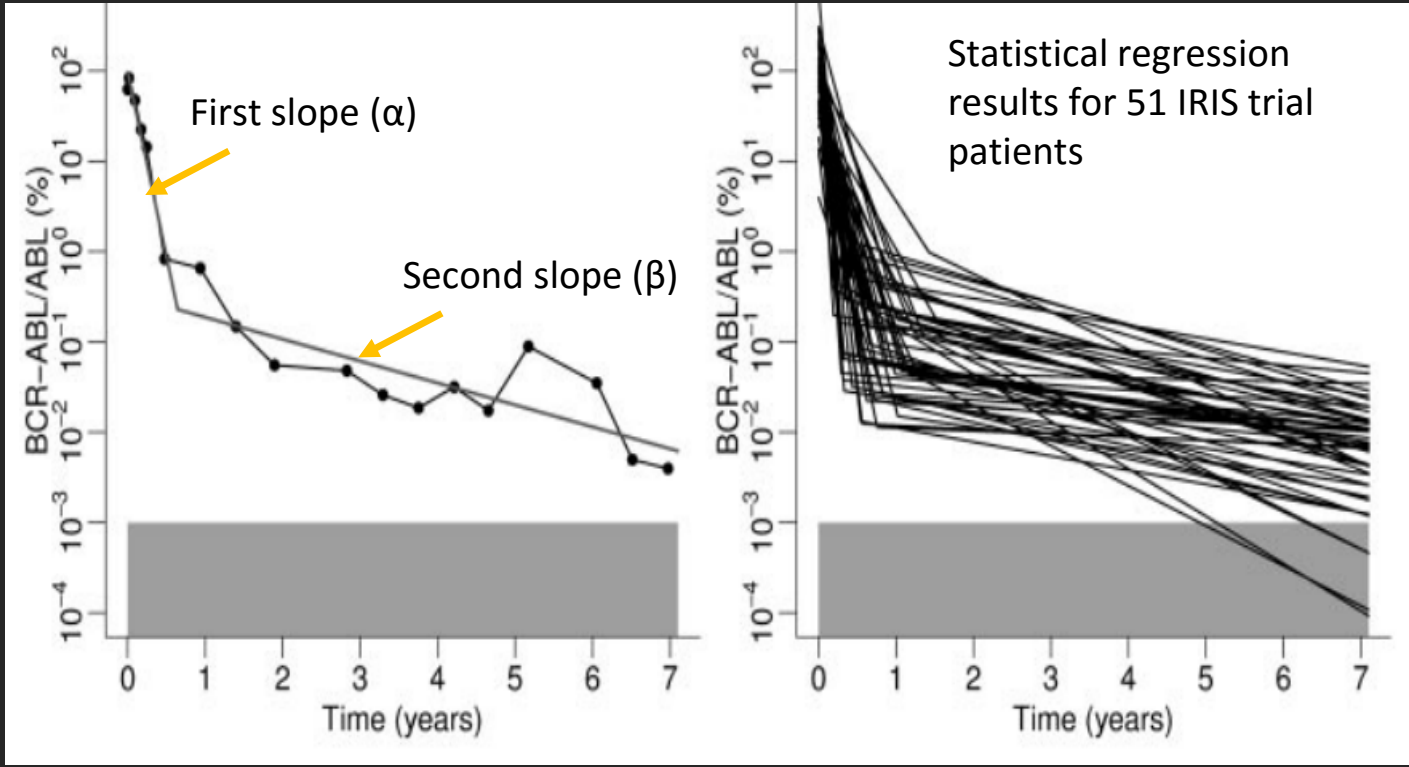
Take these and call me in the morning

Adherence and Molecular Response



Bazeos A, et al. *Blood.* 2009;114:abstract 3290; Ibrahim AR, et al. *Blood.* 2011;117:3733-3736.

Statistical model of CML response



Roeder et al, *Blood* 2013;121:378-384

Results from mathematical model for IRIS trial and CML IV trial

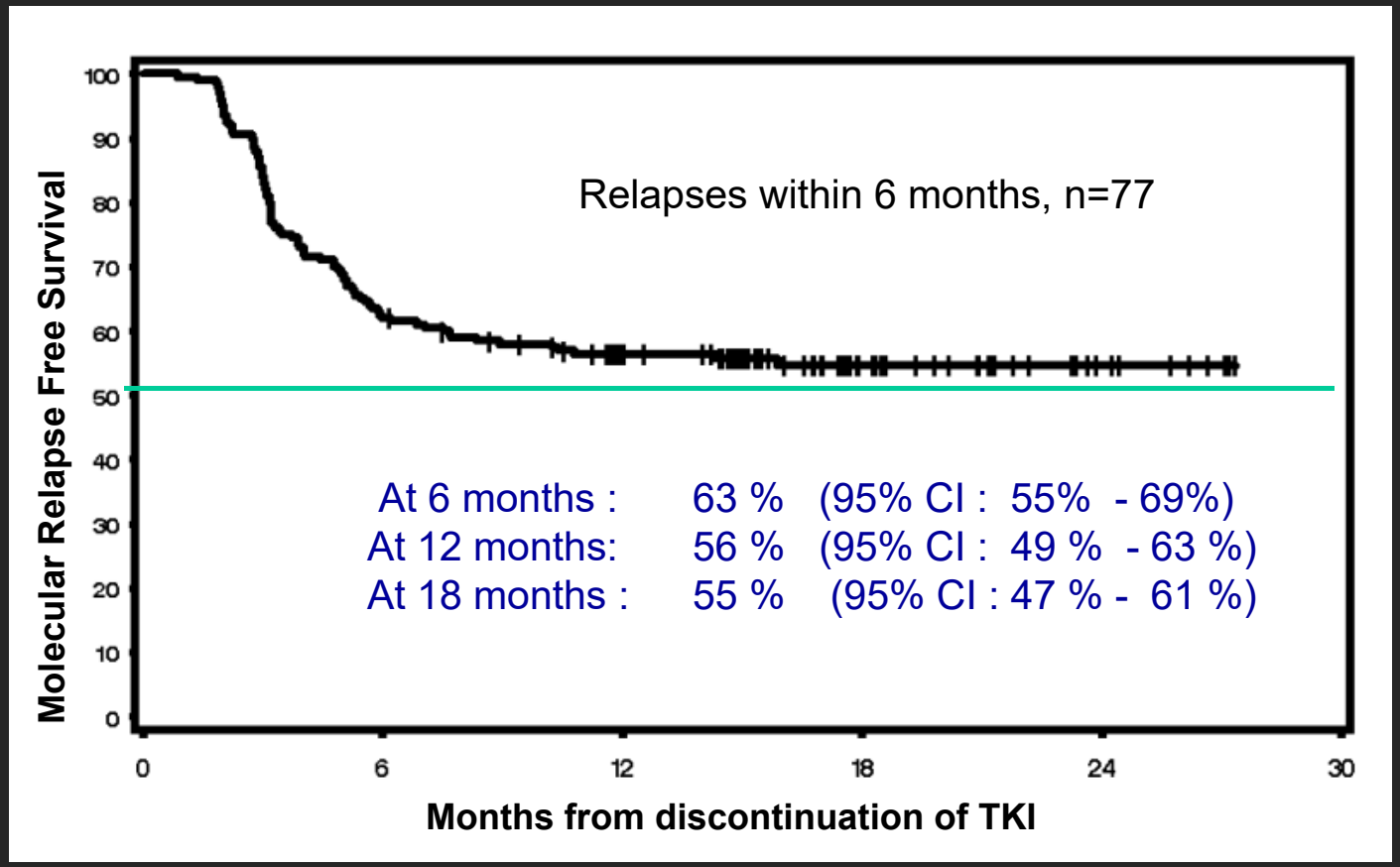
Time to complete eradication of MRD	48.9 y (28-112)/ 32.8 y (18-176)
Treatment time to 4.0 log reduction ($MR^{4.0}$)	6.5 y (5.0-9.7)/ 5.3 y (4.5-9.2)
Treatment time to 4.5 log reduction ($MR^{4.5}$)	10.7 y (7.7-13)/ 9.1 y (6.9-13)
Cumulative cure rate after 15 y of treatment	14%/16%
Cumulative cure rate after 30 y of treatment	31%/42%

Roeder et al, *Blood* 2013;121:378-384

EURO-SKI

Molecular relapse free survival

200 interim patients – overtime, loss MMR=89



Mahon et al. *Blood (ASH 2014)*;124:Abstract#151.

TKI Discontinuation trials in CML--Update

Study	TKI	No. Patients	% off TKI (at X year)	Comment
STIM 1	IM	100	38 (5)	
STIM 2	IM	220	51 (2)	
ASTIM	IM	-	61 (3)	Rx for loss of MR 3
STIK 2/DADI	NIL or DAS	52/63	48-50 (2-4)	Rx for loss of MR 4
EURO—SKI	Any	750	50 (2.5)	
ENEST-Freedom	NIL	190	50 (1)	
ENESTop	IM->NIL	126	58 (1)	

Rousselot P. *J Clin Oncol* 32: 424-431; 2014. Imagawa J. *Lancet Haematol*. 2015;2(12):e528-35:e528-e535; 2015
Hughes TP, Ross DM. Moving treatment-free remission into mainstream clinical practice in CML. Blood 2016;128:17-23.

CML Frontline Rx

- IM = 2nd generation in OS
- "Deep MR" 2nd gen TKI > IM
  - ~40% 2nd gen; 25% IM
  - 25%->40% if switch IM->2nd gen (equally durable?)
- Discontinuation equally successful all TKIs
- Imatinib = 2nd generation TKIs in lower risk CML
- Second generation TKIs > IM in progression (and high risk?) CML?
- Long-term toxicities (vascular) 2nd gen. TKI > IM

CML Frontline Rx

Generic IM

- Generics = branded IM in potency and toxicity
- ~$800,000/QALY for 2nd generation TKIs vs imatinib
- Sun now on 6 m exclusivity clock
  - Generally 70-90% of branded
- Expected price drop
  - Med. ~40% of branded
  - ~15% of branded if > 3 generics
  - In Canada, generics 15-25% of branded

Padula. *JNCI* 2016;Mar 4;108(7). Kantarjian. *Lancet Oncology* 13: May 2016.
Chhatwal. *Cancer* 121:3372;2015; McDougall JNCCN 14:2016

Issues with using generic IM (gIM)

- gIM good for cost-effective, long term use
- But, 2nd gen. TKI better at preventing AP/BC
- 2nd gen. TKI better at deep remissions
  - *Cost savings with discontinuation?*
- Could a cost-effective strategy be hi dose IM?

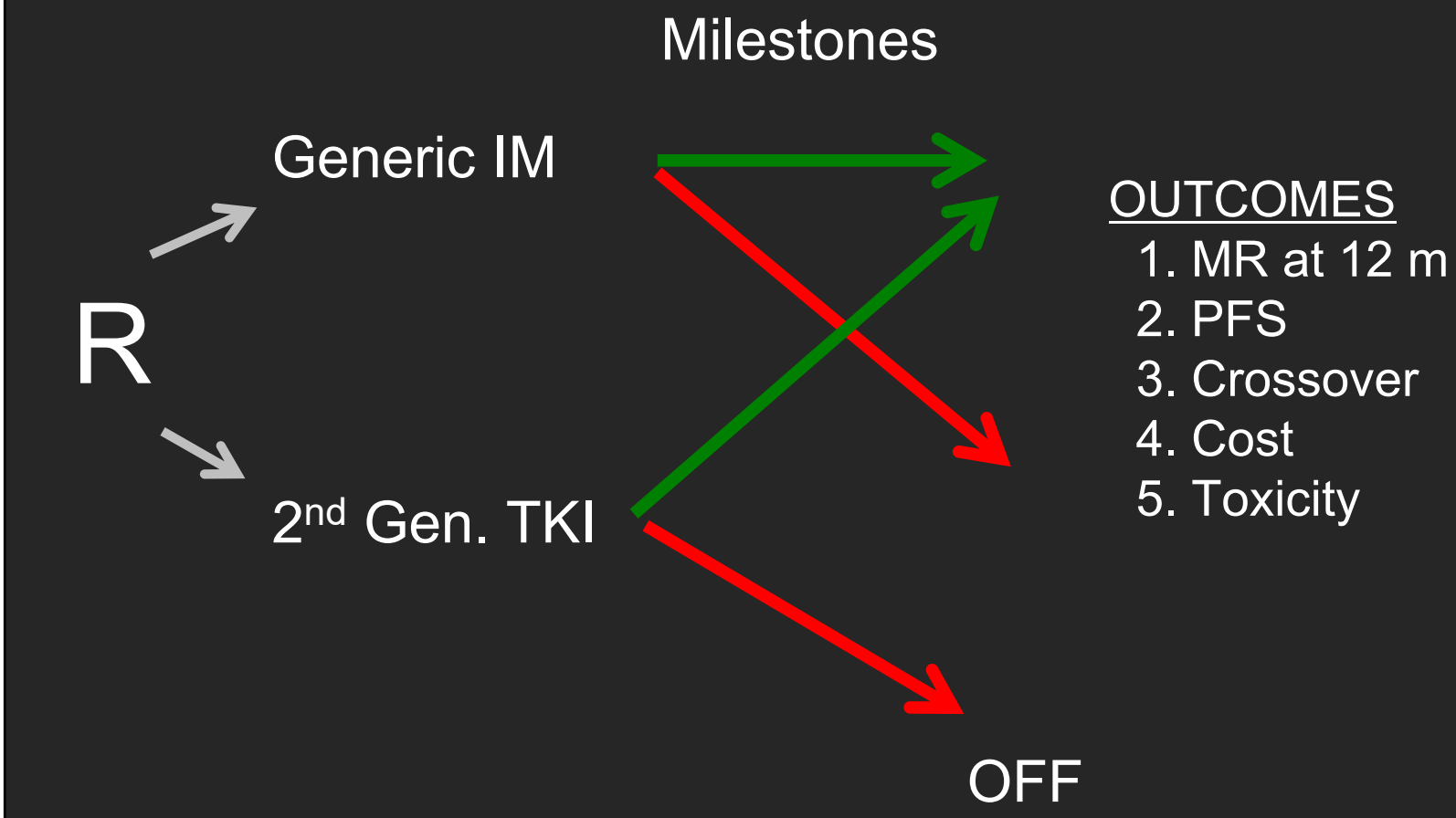
Best use of gIM should be guided by treatment goals?

Costs of Treatment-free remission (TFR)

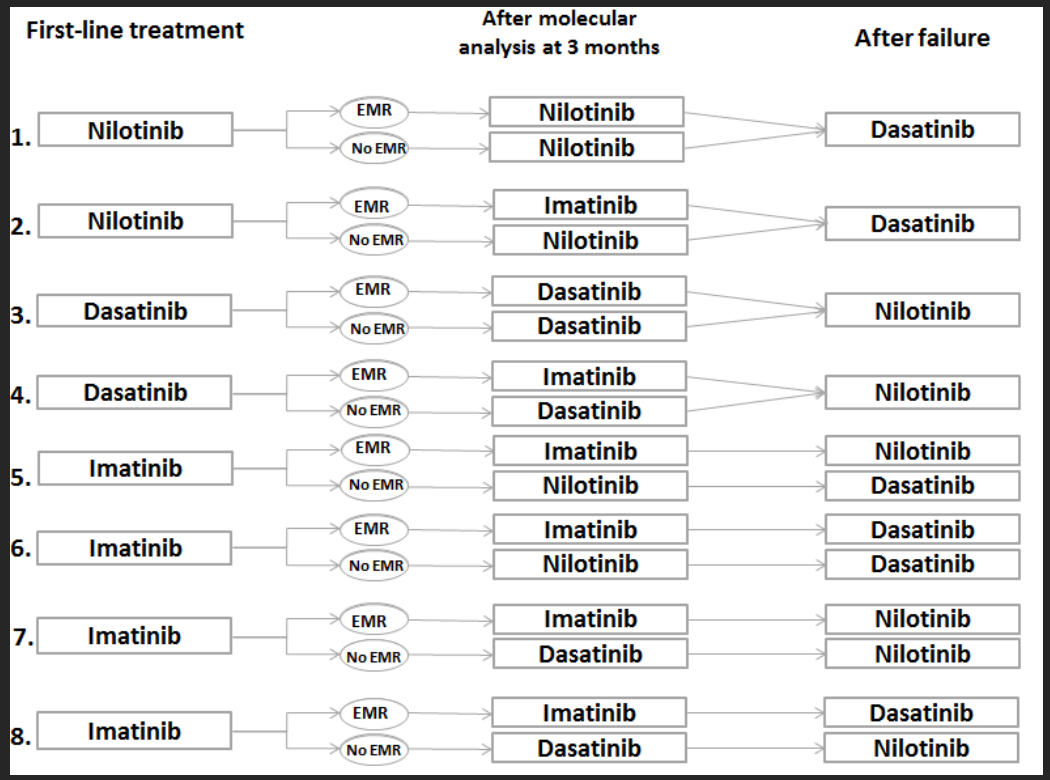
be careful what you ask for…

- TKI
  - 3 years of Rx and 2 years CMR @ $100,000/year
  - Say 40% get qualifying CMR
  - Say 50% stay in TFR after discontinuation
  - $2,500,000 patient-TFR
- Transplant
  - Transplant and 3 years chronic GVHD $1,000,000
  - Survival 85%
  - TFR rates 90%
  - $1,310,000 patient-TFR

The great unfunded trial



Simulation of this trial



"Winner" (of QALY) is 2nd generation TKI, then IM
Haven't built discontinuation into model yet.
Stay tuned.

Rochau, submitted, 2016

What do you want from life?*

WE WANT…

- Cheap meds!
- To not have an MI.
- To prevent blast crisis.
- A CMR and TKI discontinuation.
- Want cake, eat it too.

THUS, WE WILL…

- Use generic IM.
- Exercise! And generic IM.
- Use second gen. TKI.
- Use second gen. TKI.
- High dose IM?

* With apologies to *The Tubes*, circa 1975

CML Therapy in 2016-my guess

- Generic IM for low and intermediate risk
- Generic IM for older, sicker patients
- Second generation TKIs for higher-risk Sokal
  - until CCyR or MMR, then -> generic IM
  - Indefinitely if nervous
- Second generation TKIs for younger patients in whom Rx discontinuation is important

NCCN Member Institutions