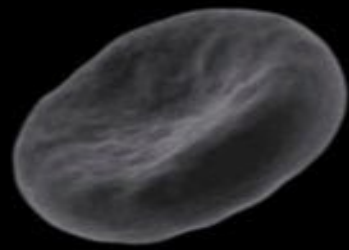
Translating CML Treatment-Free Remission (TFR) Data into Clinical Practice

GET Meeting 2019

Anthony Schwarer



Question 1

Have you attempted TFR in any CML patients?

1. yes
2. no

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Question 2

At what maintained level of bcr-abl are you comfortable at attempting TFR?

1. MR3.0 (0.1%)
2. MR4.0 (0.01%)
3. MR4.5 (0.0032%)
4. MR5.0 (0.001%)
5. <MR5.0 but still detectable
6. undetectable bcr-abl

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Question 3

How long should your patient maintain that level of bcr-abl before attempting TFR?

1. 1 yr
2. 2 yrs
3. 3 yrs
4. 4 yrs
5. 5 yrs

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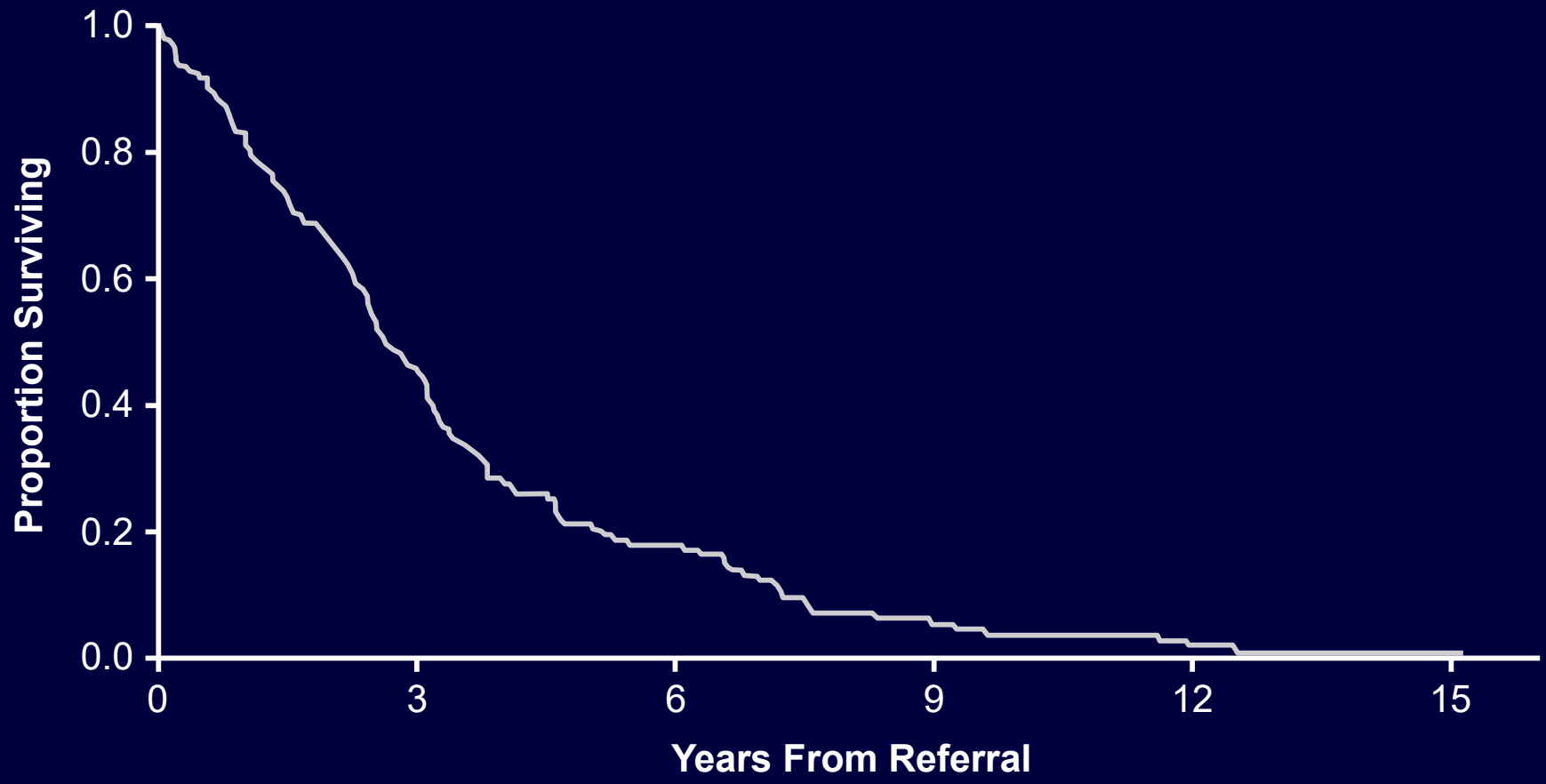
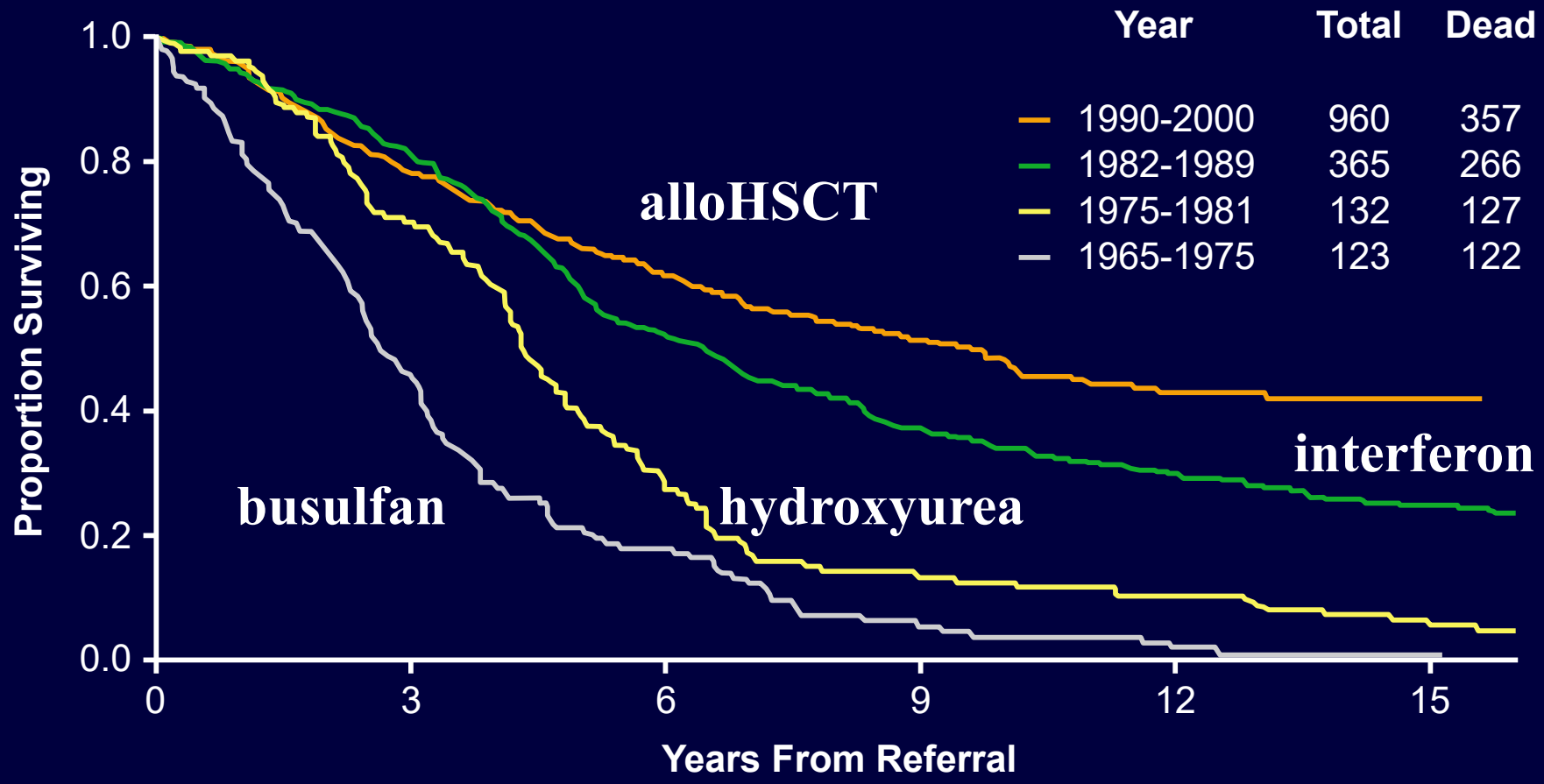
Survival in Early Chronic-Phase CML



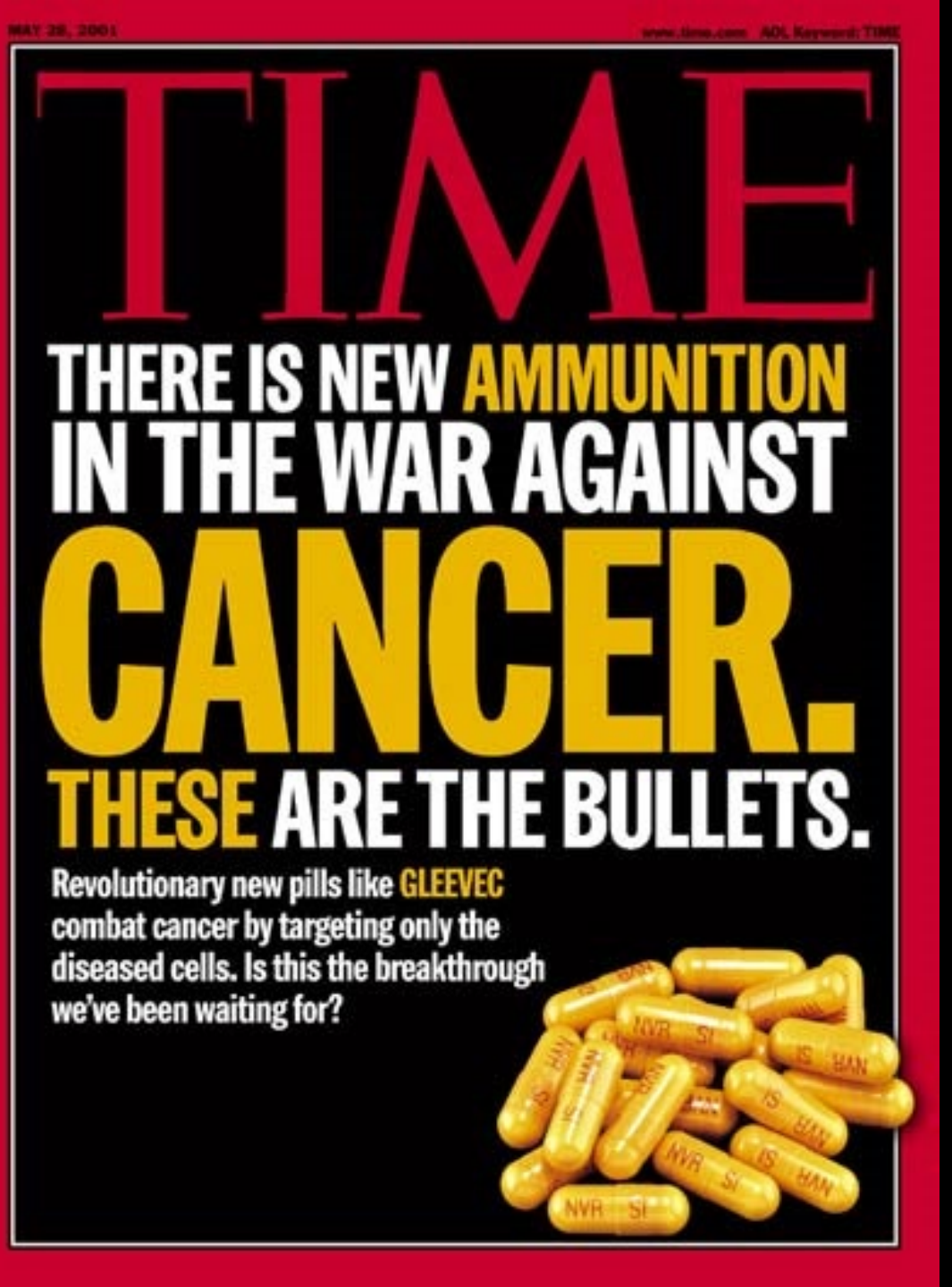
The University of Texas M. D. Anderson Cancer Center database.

Survival in Early Chronic-Phase CML

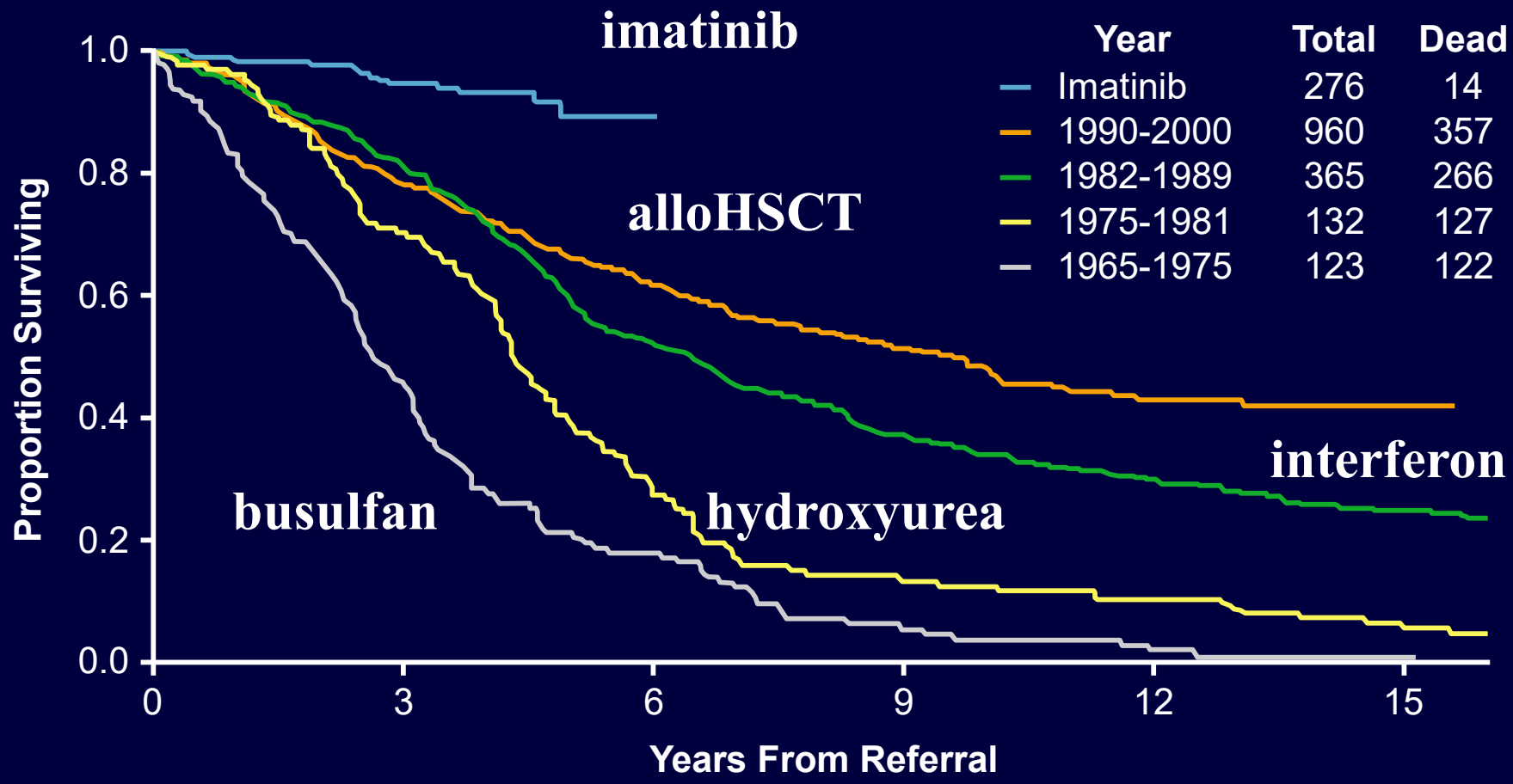


The University of Texas M. D. Anderson Cancer Center database.

28 May 2001

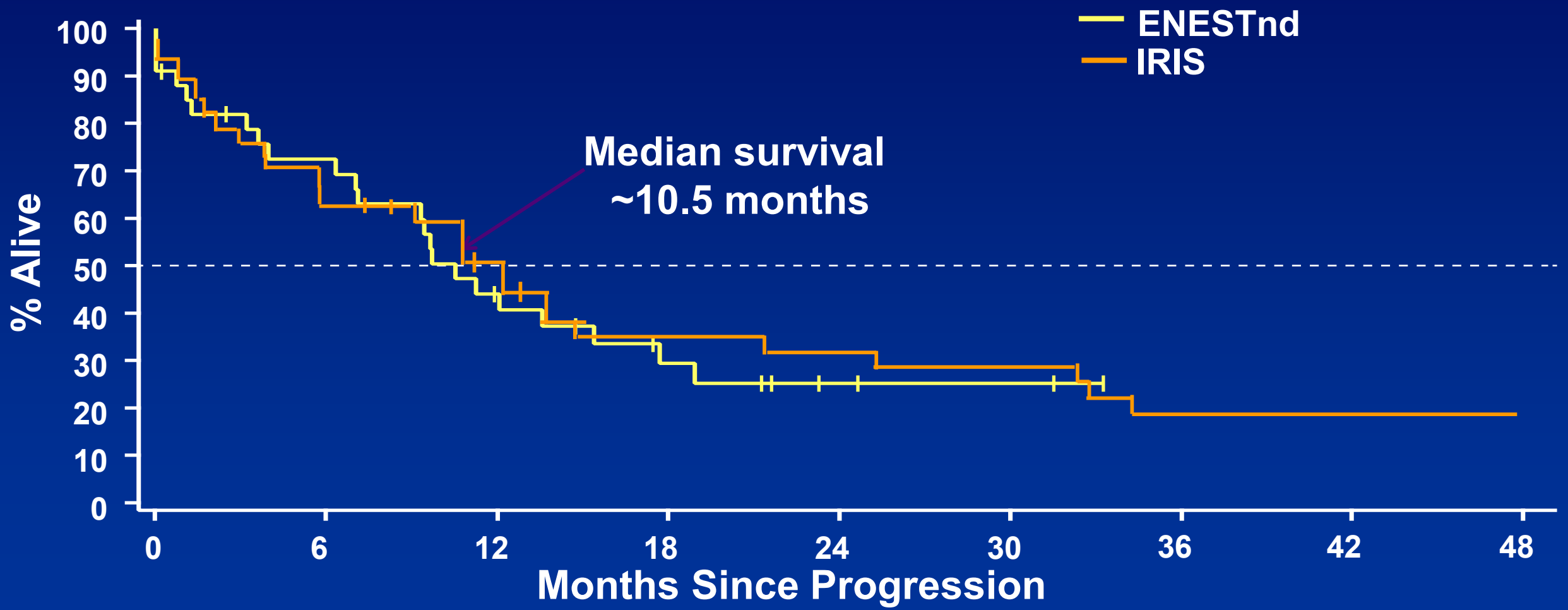

MAY 28, 2001
TIME
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER.
THESE ARE THE BULLETS.
Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

Survival in Early Chronic-Phase CML



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

Survival After Progression to AP/BC



Data cutoff: 27Jul2011.

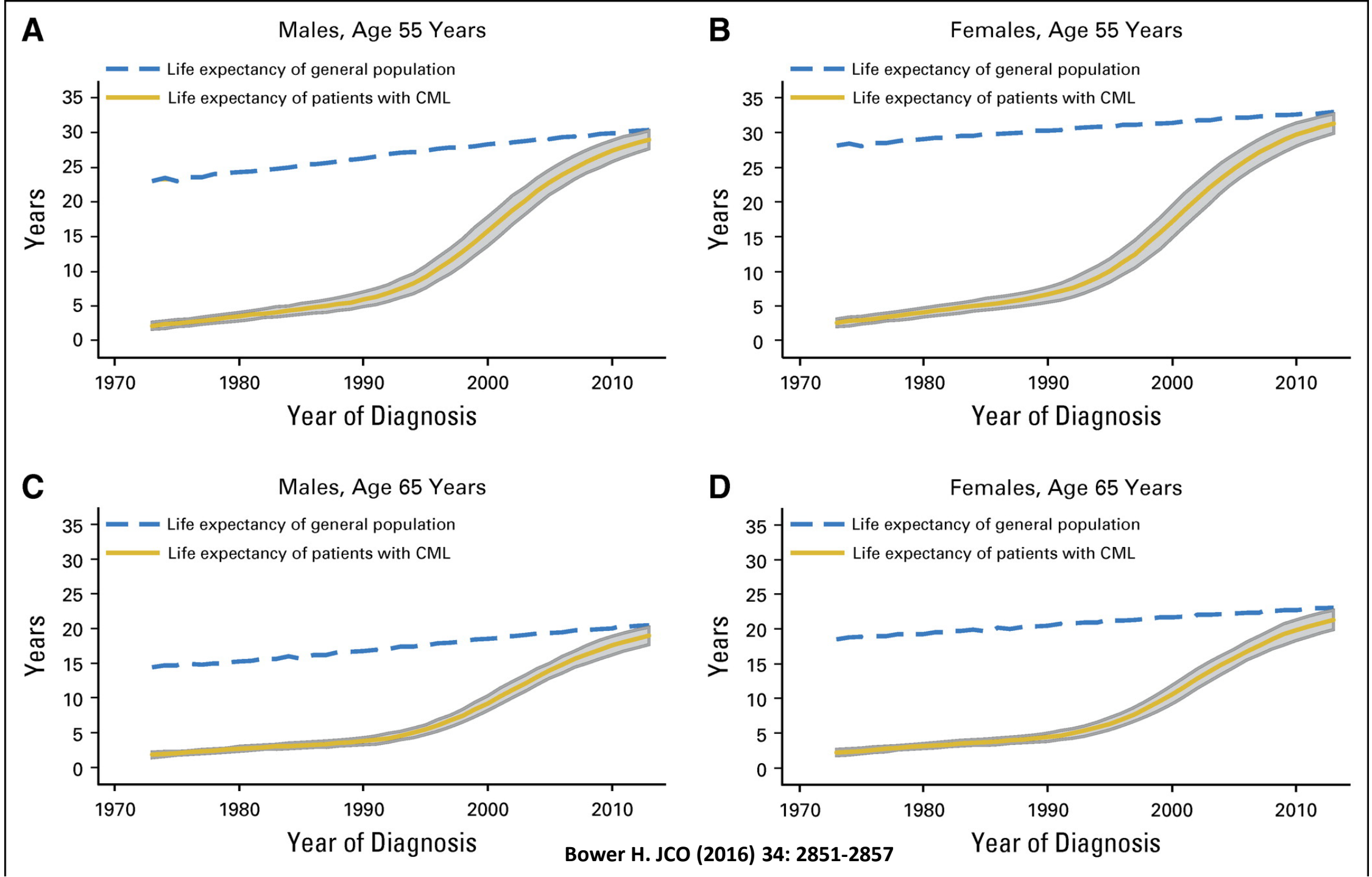
Clark RE, et al. *Haematologica*. 2012;97(s1):237 [abstract 0583].

Bosutinib (not currently available in Australia)

Ponatinib (for resistant CML)

Radotinib (Korea)

Asciminib (ABL001) – in trials



Bower H. JCO (2016) 34: 2851-2857

Should Treatment-Free Remission (TFR) be a goal?

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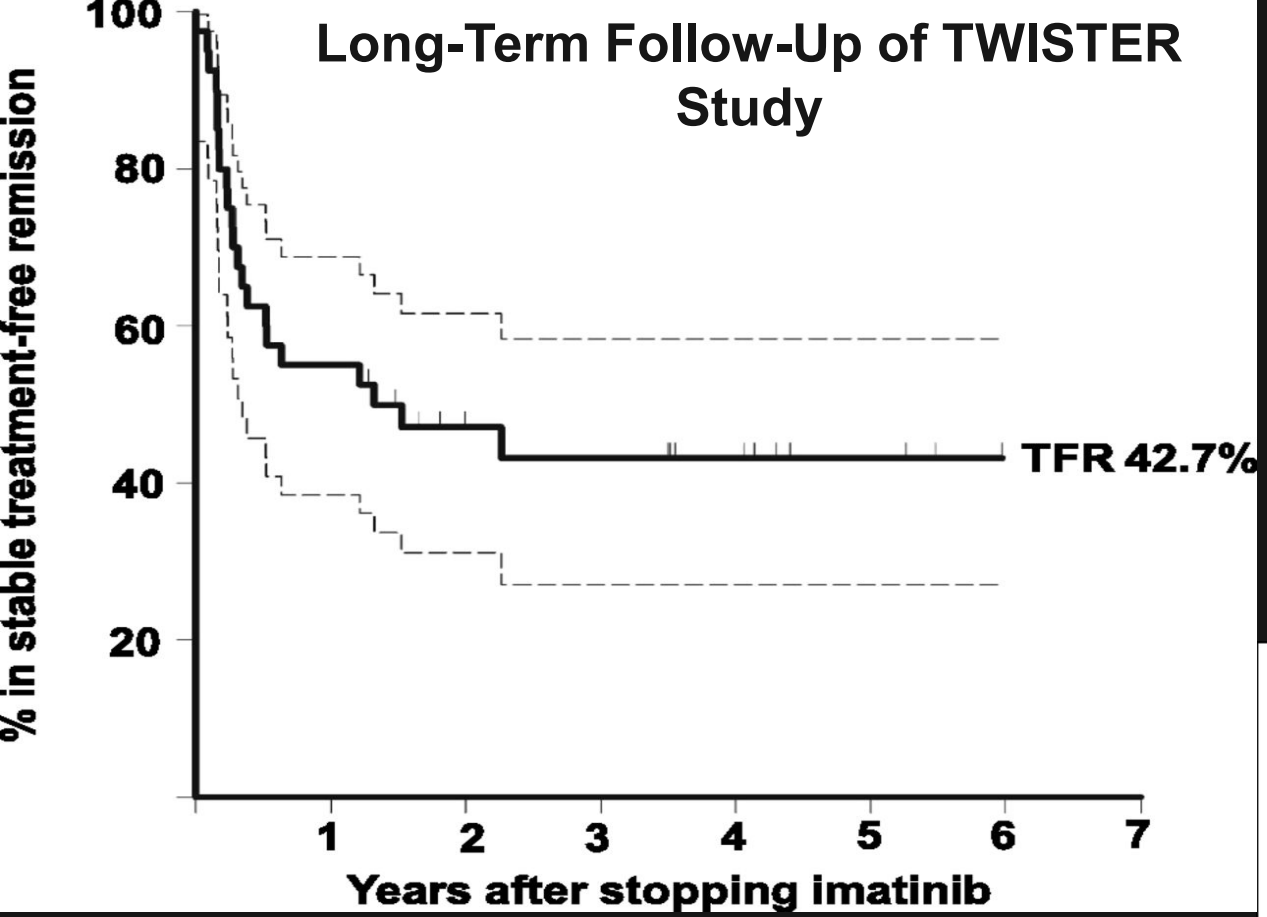


Etienne G, et al. JCO (2017) 35:298-305

Ross DM, et al. Blood (2013) 122:515-522

CML-CP patients on imatinib with persistently undetectable bcr-abl for >2 yrs

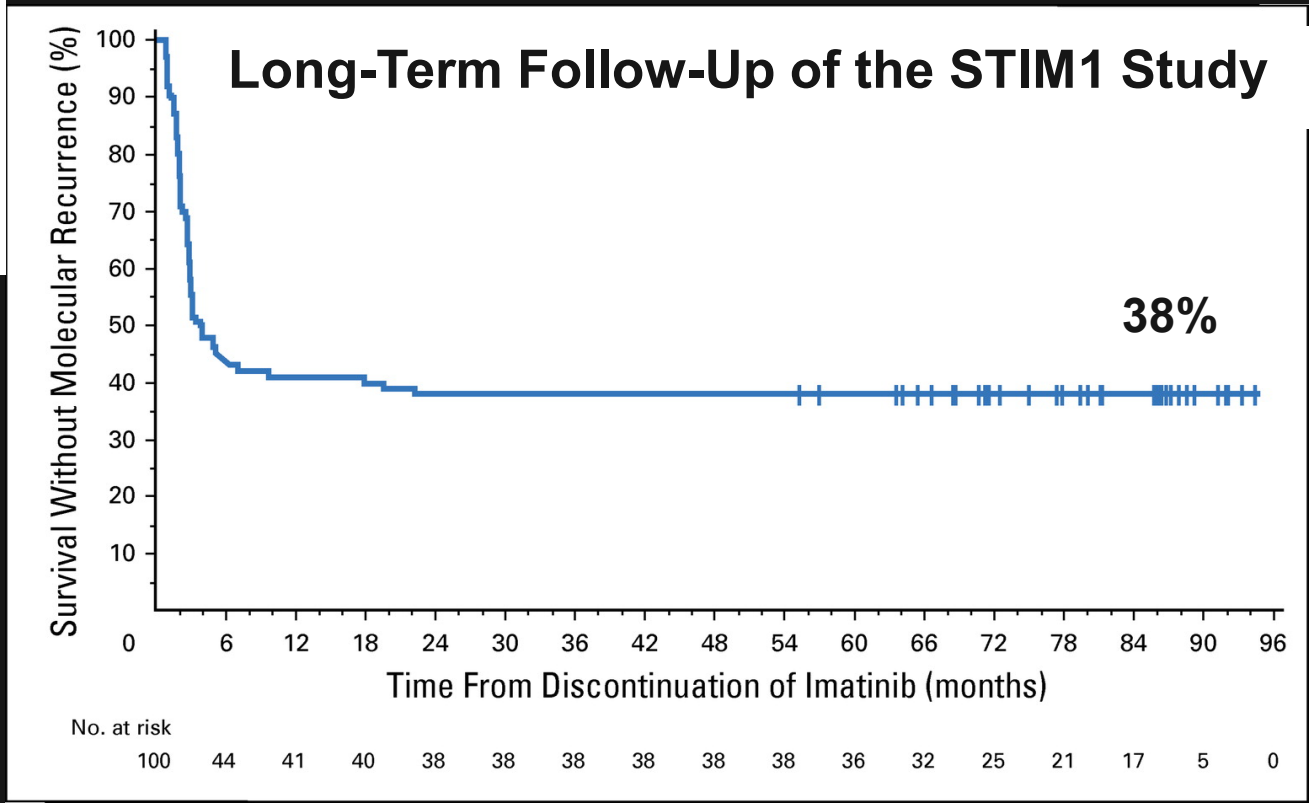


Table 1. Summary of TKI discontinuation trials and retrospective series

Study	# Pts	1st-line TKI	2nd-line/ consolidation TKI	Median duration TKI (years)	Stable DMR at STOP	Median duration DMR (years)	Retreatment criteria	Follow-up (years)	Time TFR (years)	Rate TFR (%)
A-STIM [6]	80	I (100%)		6.58	UMRD	3.42	> MMR	2.58	2	64
DADI [7]	63	I (100%)	D (100%)	6.83	0.0069%[IS]	NR	> 0.0069%[IS]	1.67	1	48
DASFREE [23]	84	I (85%),D	D (100%)	5.91	MR4.5	NR	> MMR	NR	1	49
Destiny* [15, 29]	117	I (84%), D (8%), N (4%)		6.80	MR4.0*	NR	> MMR	NR	2	77
D-STOP [19]	54	I (61%), D (39%)	D (100%)	7.66	UMRD	4.25	> MR4.0	1.5	1	62.9
ENESTfreedom [22]	190	N (10							1.85	48.9
ENESTop [16]	126	I (10							1.85	53.2
Euro-Ski [21]	750	I (94							2	51
Ginema [26]	293	I (72							1	68
Hovon [12]	15	I (10							2	33
ISAV [9]	112	I (10							3	51.9
Japan [28]	43	I (10							5	47
Keio [20]	53	I (91							2	52.8
KID [8]	90	I (100%)		6.73	UMRD	3.32	> MMR × 2	2.22	2	58.5
Korea [27]	24	I (67%), D (21%), B (12%)		6.42	UMRD	4.16	> MMR	3.04	2	59.7
LAST [14]	173	I (60%), N (23%), D (15%), B (2%)		6.58	MR4.0	NR	> MMR	1.025	1	60
MDA** [25]	27	I (77%), D (11%), N (6%), B (6%)		8.0	UMRD	5.25	> UMRD	1.33	1.5	59
NILst [17]	87	I/N	N (100%)	8.6	MR4.5	2–12 Y	> MR4.5 × 2	1.11	1	58.9
STAT2*** [24]	73	I/N	N (100%)	8.52	MR4.5	2[SG1], 2.58[SG2]	> MR4.5 × 2	NR	1	67.9
STIM1 [4]	100	I (100%)		4.9	UMRD	3.03	> UMRD × 2, > MMR	6.42	5	38
STIM123 [11]	68	I (100%)		8.125	MR4.5	4.5	> MMR	NR	1	67.6
STIM-Pilot [5]	12	I (100%)		3.75	UMRD	2.67	> UMRD × 2	1.5	1.5	50
STOP 2G-TKI [10]	60	D/N 1st L 13.3%, 2nd L 66.7%, 3rd L 20%		6.3	UMRD	2.42	> MMR	3.92	4	53.6
TRAD [18]	123	I (100%)		9.16	MR4.5	NR	> MR4 × 2, > MMR	NR	1	57.5
Twister [13]	40	I (100%)		5.92	UMRD	2.5	> UMRD × 2, > MMR	3.5	2	47.1

Pts number of patients, *TKI* tyrosine kinase inhibitor, *DMR* deep molecular response, *TFR* treatment-free remission, *I* imatinib, *D* dasatinib, *N* nilotinib, *B* bosutinib, *UMRD* undetectable molecular residual disease, *MR* molecular response, *MMR* major molecular response, *IS* international standard, *NR* not reported

*MR4 subgroup

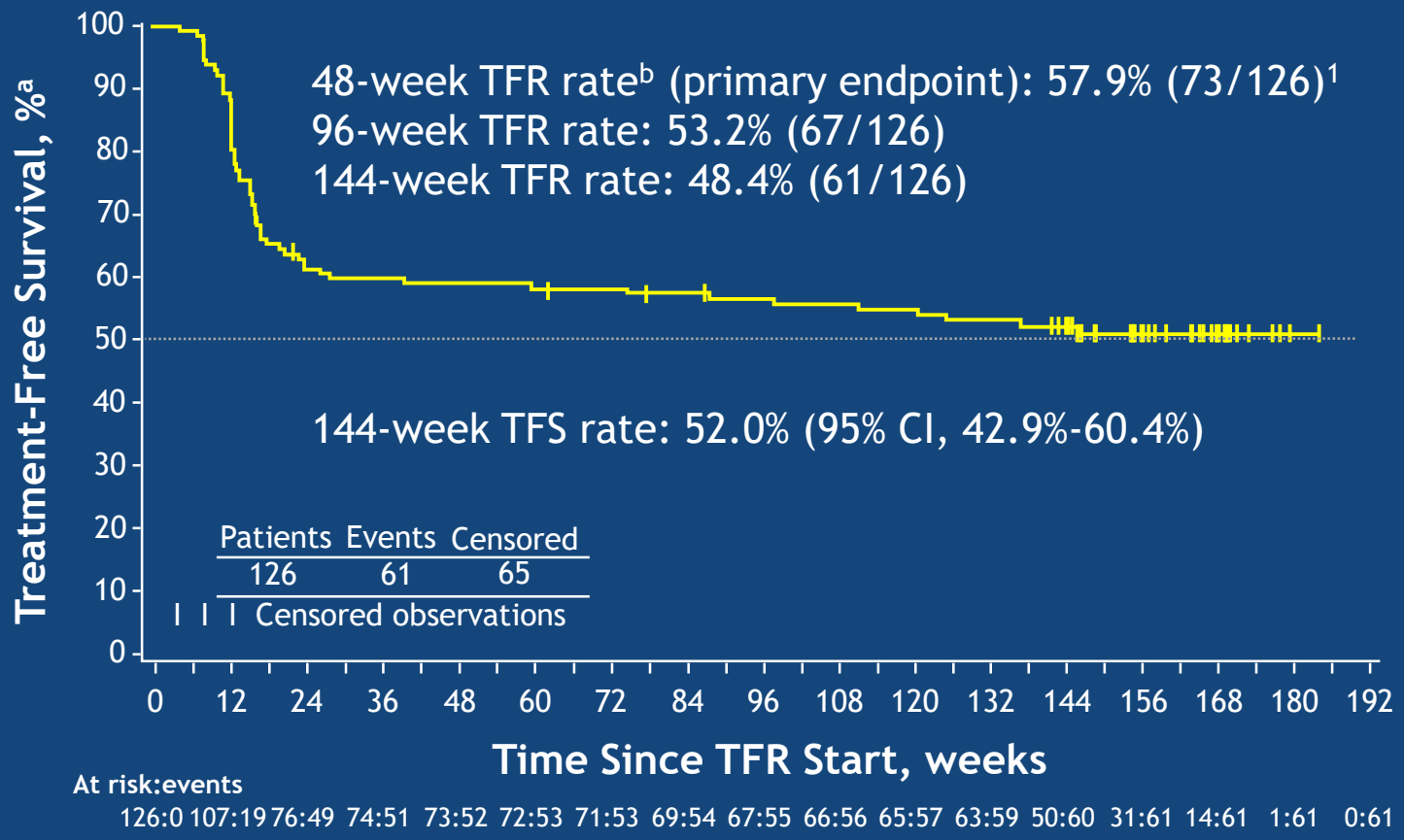
**UMDR subgroup

***Median duration TFR from weighted average of SG1[A] and SG2[AA] patient groups

Durable TFR rates of 40-60%

Laneuville P. Curr Treat Options in Oncol (2018) 19:15

ENESTop Study TFR (nilotinib)



TFR rate at 144 weeks was 48.4% (61/126)

Of 67 patients in TFR at 96 weeks, 6 were no longer in the TFR phase at 144 weeks

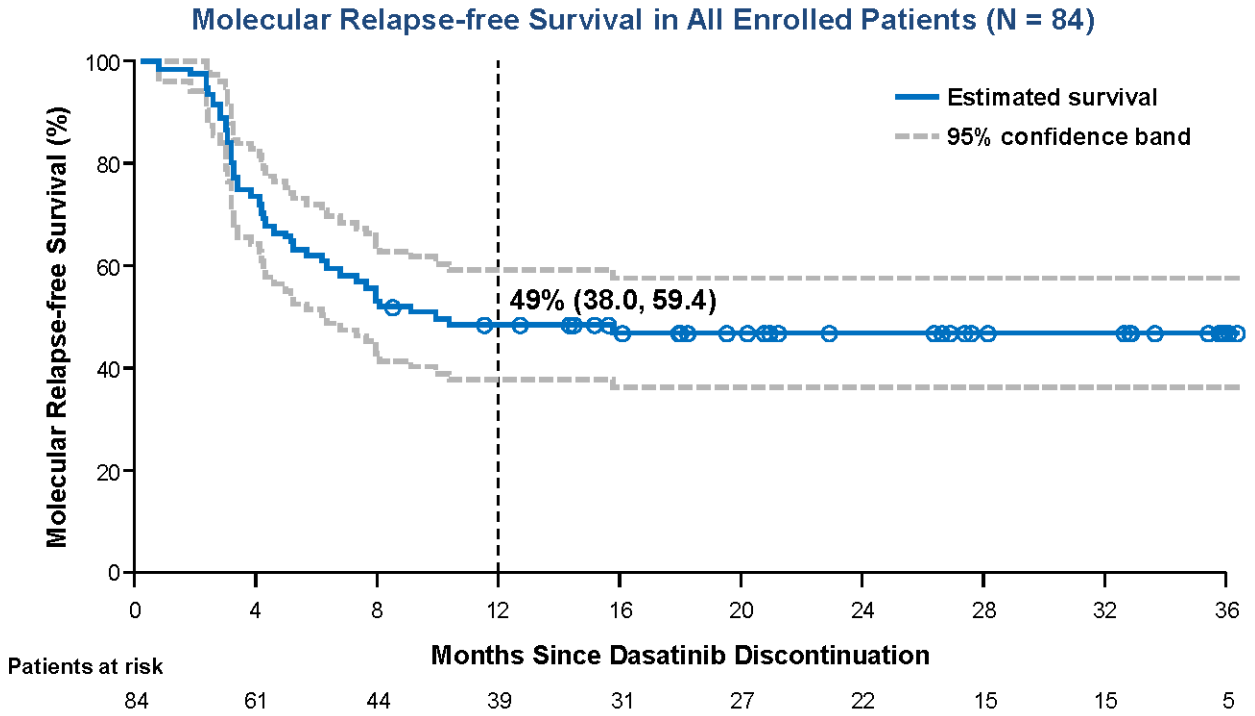
- 3 had confirmed loss of MR^4 at 108, 120, and 144 weeks, respectively
- 2 died (respiratory failure and arthritis bacterial, respectively; neither lost $MR^{4.5}$ during TFR)
- 1 discontinued the study due to patient decision while in $MR^{4.5}$

A total of 61 of 126 patients had TFS[a] events by the 144-week data cutoff, including 9 reported after the 48-week data cutoff[c]

AP/BC, accelerated phase/blast crisis; TFS, treatment-free survival. [a] Defined as the Kaplan-Meier estimate of the time from the start of TFR until the earliest of any of the following: loss of MMR, confirmed loss of MR^4, treatment reinitiation due to any cause, progression to AP/BC, or death due to any cause. [b] Defined as the proportion of patients without loss of MMR, confirmed loss of MR^4, or treatment reinitiation. [c] At the 48-week data cutoff, all patients had completed ≥ 48 weeks of TFR, restarted nilotinib, or discontinued the study. 1. Mahon FX, et al. *Ann Intern Med*. 2018;168:461-470.

DASFREE Study (dasatinib)

Molecular Relapse-free Survival

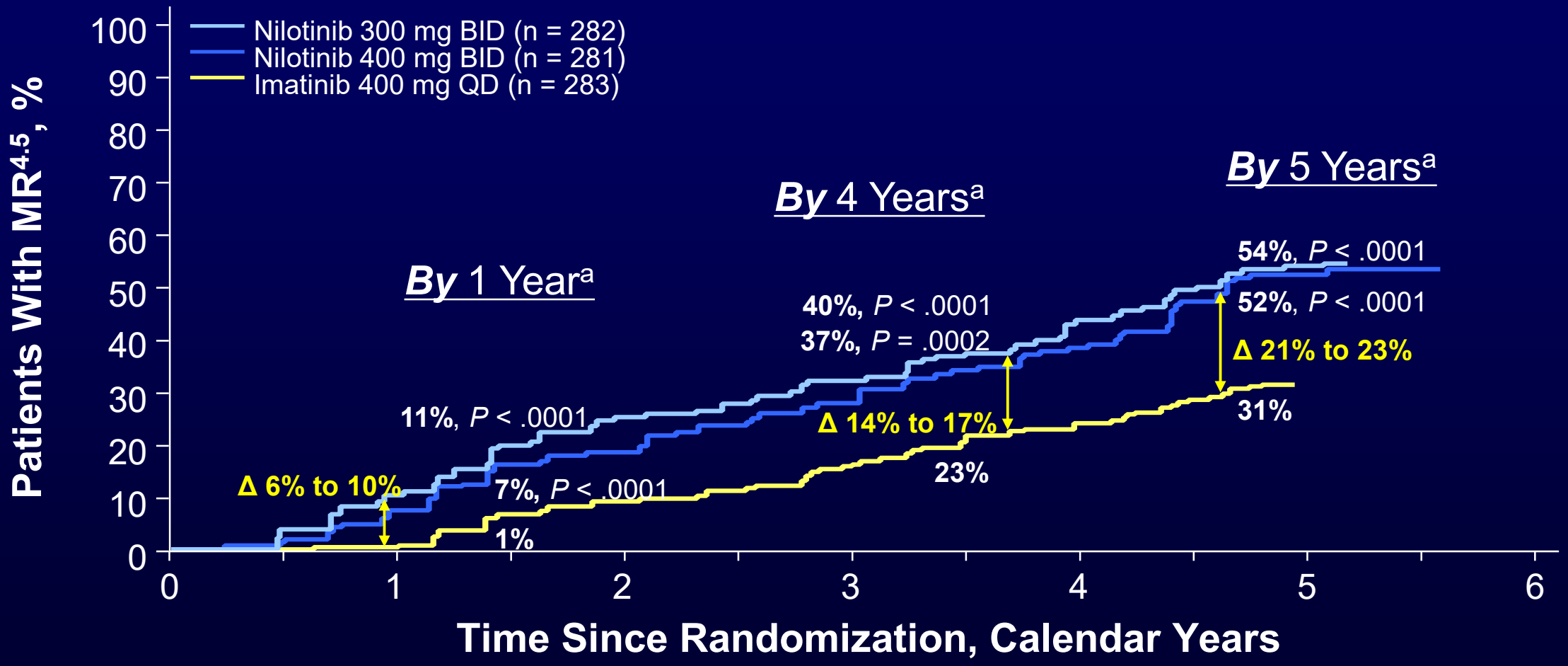


	MRFS, % (95% CI)
Patients on first-line dasatinib (n = 37)	54 (38.0, 70.1)
Patients on subsequent lines of dasatinib (n = 47)	45 (30.2, 58.7)
Resistant (n = 25)	44 (24.5, 63.5)
Intolerant (n = 18)	50 (26.9, 73.1)

- No patients lost CCyR or CHR; no transformation events or deaths were observed

CI = confidence interval; CCyR = complete cytogenetic response; CHR = complete hematologic response; MMR = major molecular response; MRFS = molecular relapse-free survival.

Cumulative Incidence of $MR^{4.5}$



$MR^{4.5}$, molecular response ≥ 4.5-logs ($BCR\text{-}ABL^{IS}$ ≤ 0.0032%).

[a] Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

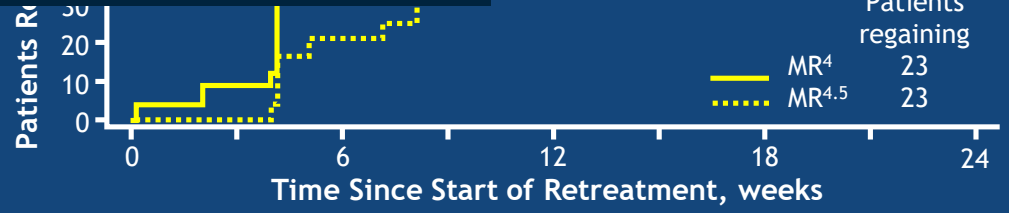
Data cutoff: May 22, 2013

Response to Nilotinib Reinitiation (ENESTop Study)

- 58 patients reinitiated nilotinib due to confirmed loss of MR^4 (n = 24) or loss of MMR (n = 34)
  - 54 patients (93.
  - Median time to
    and 13.1 weeks
  - Of 54 patients v
    42 (77.8%) mair
- Among 24 patien
  due to confirmed loss of MR^4, 23 (95.8%) regained MR^4 and $MR^{4.5}$
  - The remaining patient had only 1.1 weeks of follow-up after treatment reinitiation

"Only a single patient has died to date after transforming to advanced phase disease in >2500 patients reported"

eatment in Patients
ned Loss of MR^4



MR^4	Cumulative n/N:	0/24	11/24	20/24	23/24	
	Cumulative %:	0.0	45.8	83.3	95.8	
$MR^{4.5}$	Cumulative n/N:	0/24	5/24	15/24	22/24	23/24
	Cumulative %:	0.0	20.8	62.5	91.7	95.8

Should Treatment-Free Remission (TFR) be a goal?

1. TFR is safe

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Cardiotoxicity of the cancer therapeutic agent imatinib mesylate

Kerkela R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, Walters B, Shevtsov S, Pesant S, Clubb FJ, Rosenzweig A, Salomon RN, Van Etten RA, Alroy J,Durand JB, Force T.

Nat Med. 2006 Aug;12(8):908-916. Epub 2006 Jul 23.

Imatinib treatment duration is related to decreased estimated glomerular filtration rate in chronic myeloid leukemia patients

Marcolino MS, Boersma E, Clementino NC, Macedo AV, Marx-Neto AD, Silva MH, van Gelder T, Akkerhuis KM, Ribeiro AL.

Ann Oncol 2011 Sep;22(9):2073-9

Immune Function Effects

Hearing Impairment

Fertility

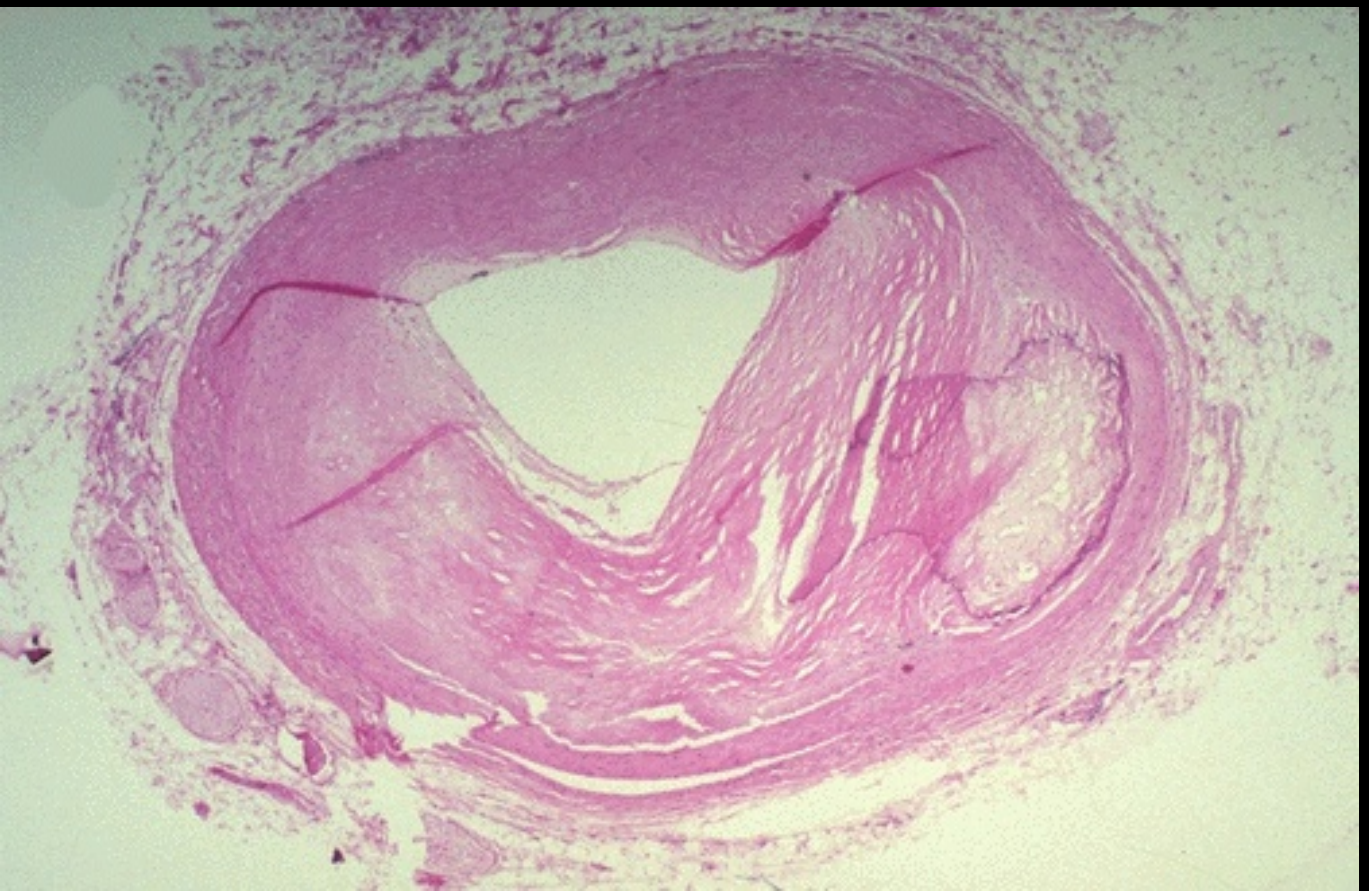
Altered bone and mineral metabolism in patients receiving imatinib mesylate

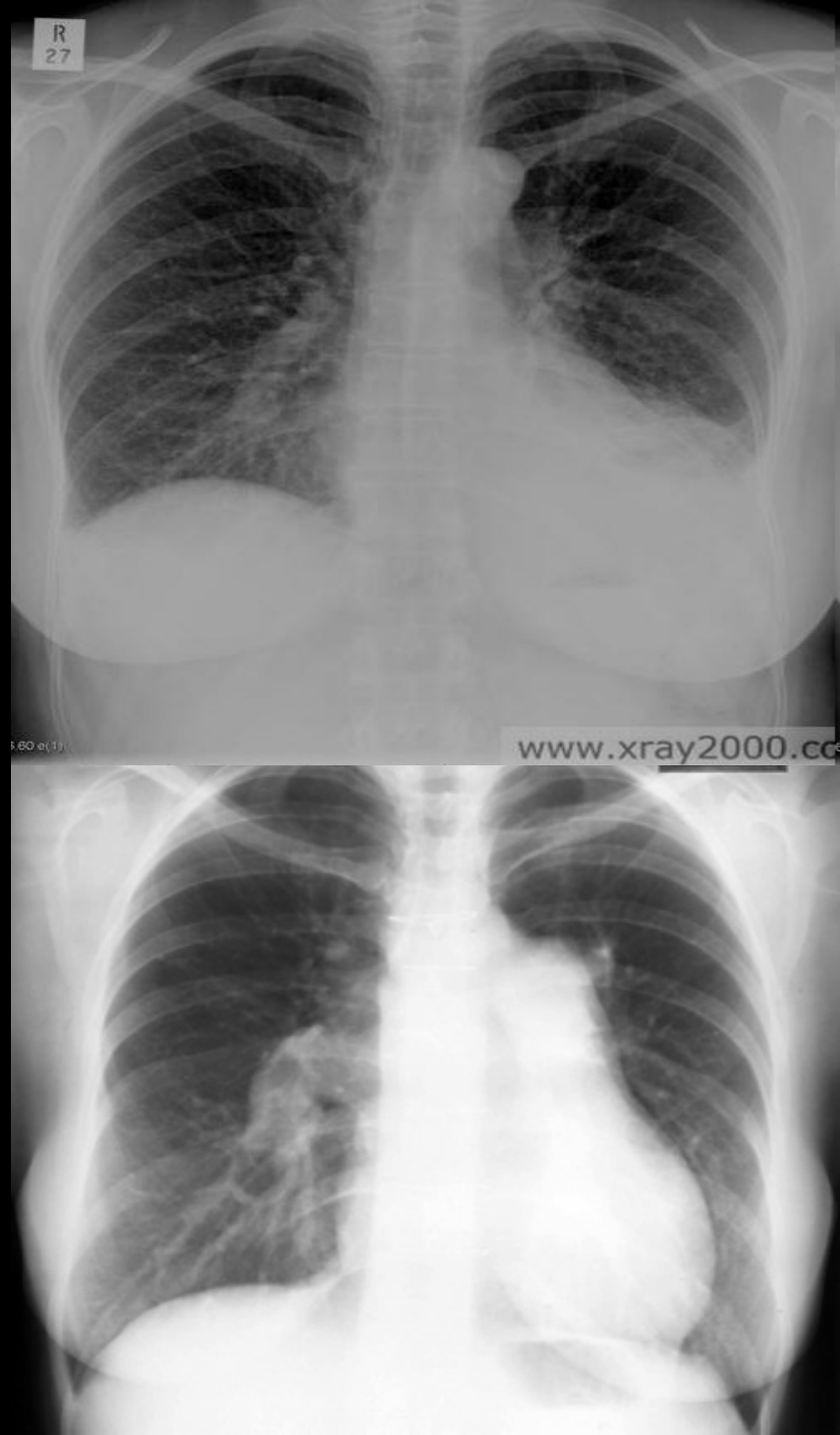
Berman E, Nicolaides M, Maki RG, Fleisher M, Chanel S, Scheu K, Wilson BA,

Heller G, Sauter NP.

N Engl J Med. 2006 May 11;354(19):2006-13

Avoid Long-term Complications





Should Treatment-Free Remission (TFR) be a goal?

1. TFR is safe
2. Long-term side-effects avoided

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TKIs are teratogenic

(not mutagenic)

Should Treatment-Free Remission (TFR) be a goal?

1. TFR is very safe
2. Long-term side-effects avoided
3. The next generation

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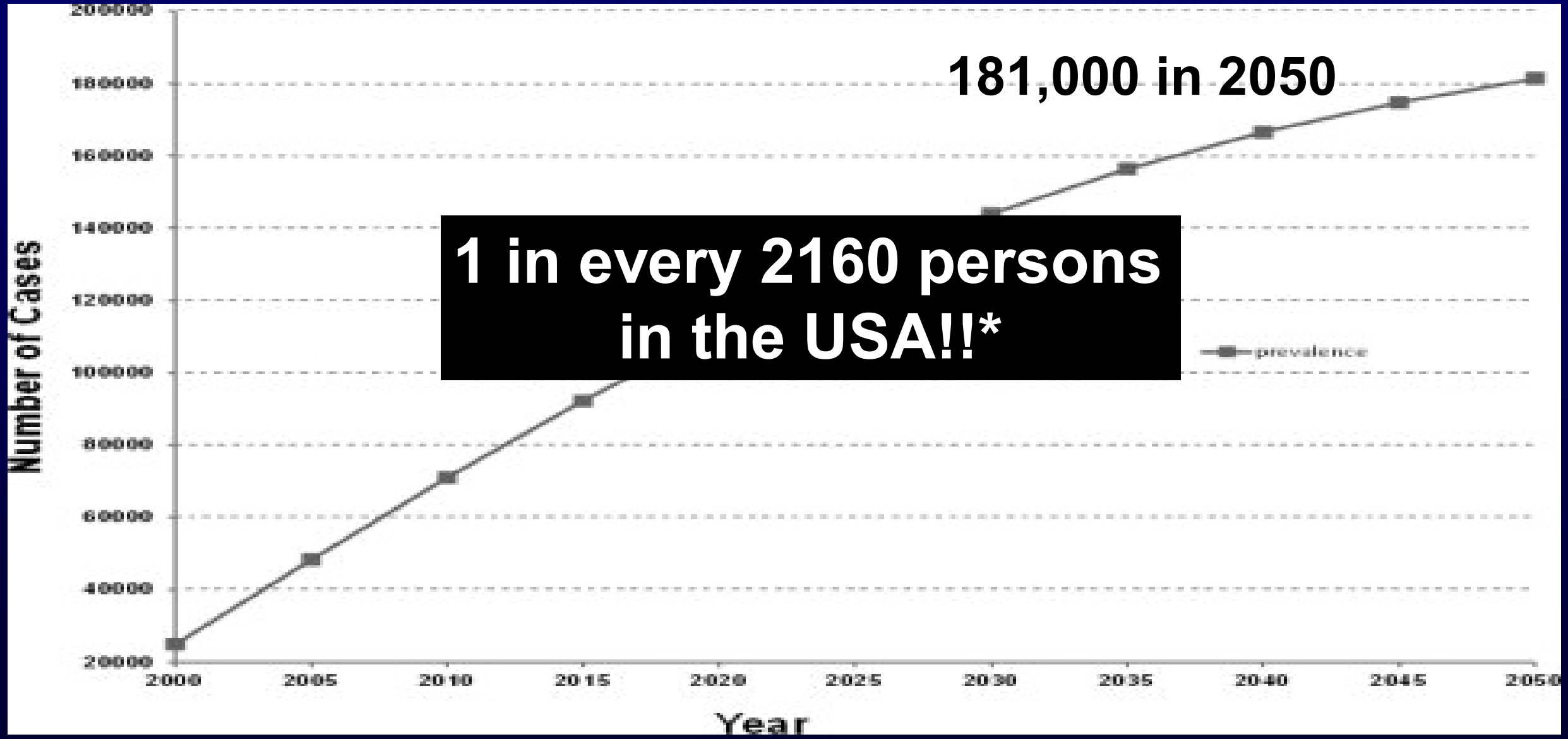
Prevalence and plateau prevalence of chronic myeloid leukemia in the era of TKIs



Huang X, Cortes J, Kantarjian H. Cancer. (2012) 118:3123

*392 million population in 2050

Cost Per Year of TKIs from Dept of Health & Aging Website

- **Imatinib 400 mg per day $22,074 per yr**
- **Imatinib 600 m**
- **Nilotinib 300 mg BD $51,077 per yr**
- **Dasatinib 100 mg per day $51,648 per yr**

~$400,000,000 per year in Australia

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Should Treatment-Free Remission (TFR) be a goal?

1. TFR is very safe
2. Long-term side-effects avoided
3. The next generation
4. The Government would be grateful

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TFR for CML patients – TFR4CML A Global online survey for treatment free remission

CML Advocates Network

http://bit.ly/TFRCML

“CML advocate groups consider TFR of the utmost importance”

https://www.facebook.com/groups/CMLTFR

Should Treatment-Free Remission (TFR) be a goal?

1. TFR is very safe
2. Long-term side-effects avoided
3. The next generation
4. The Government would be grateful
5. Patients want TFR

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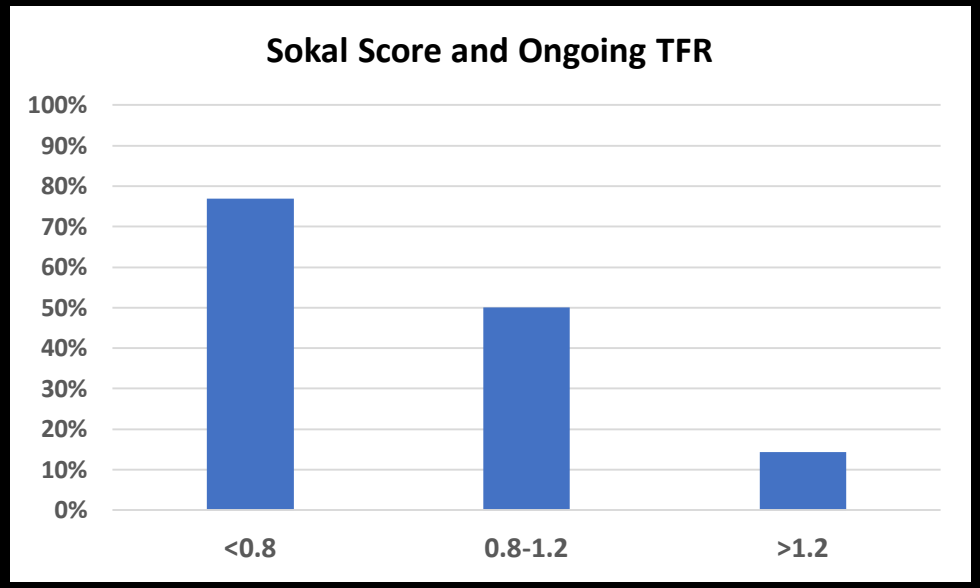
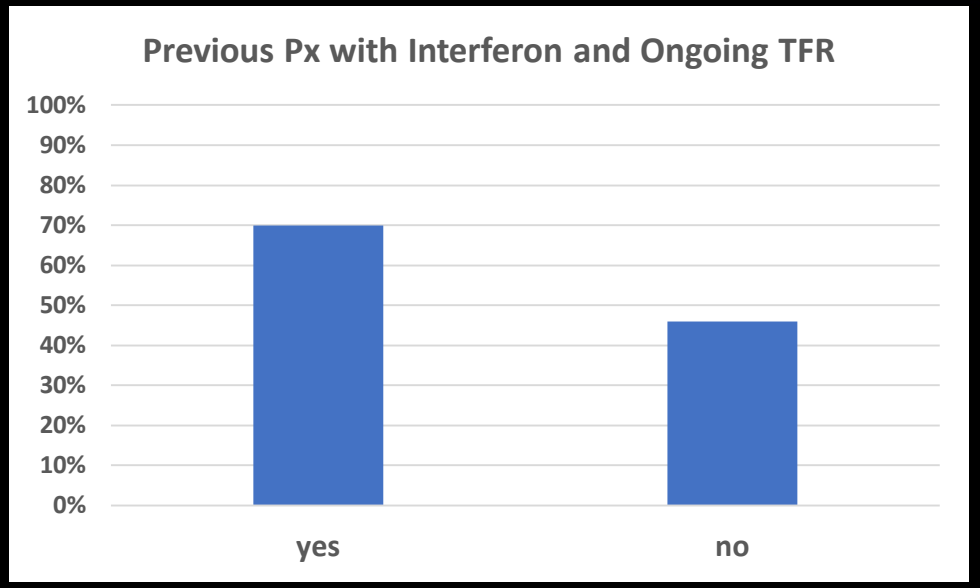
The Patients on My Books Attempted TFR

- **34 (26%) patients - $MR^{4.5}$ for at least >2yrs**

TKI prior to TFR	TFR attempted	TFR ongoing	TFR failed
imatinib	14	9	5
nilotinib	7	5	2
dasatinib	11	3	8
ponatinib	2	0	2
		17 (50%)	17 (50%)
Duration of TFR (range)		4.5 yrs (1.3-11.9 yrs)	3.7 mths (2-18 mths)

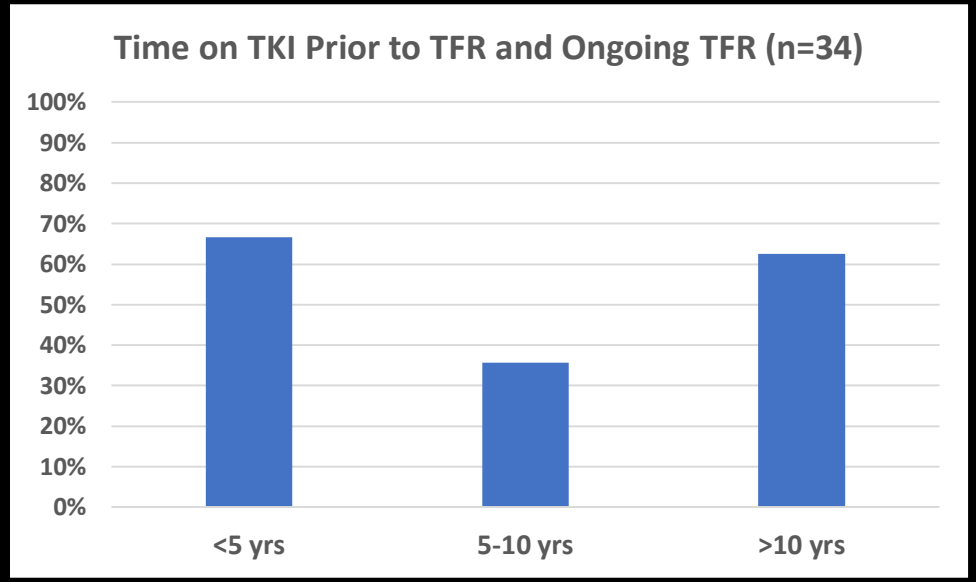
Prognostic Factors of My Cohort (n=34)



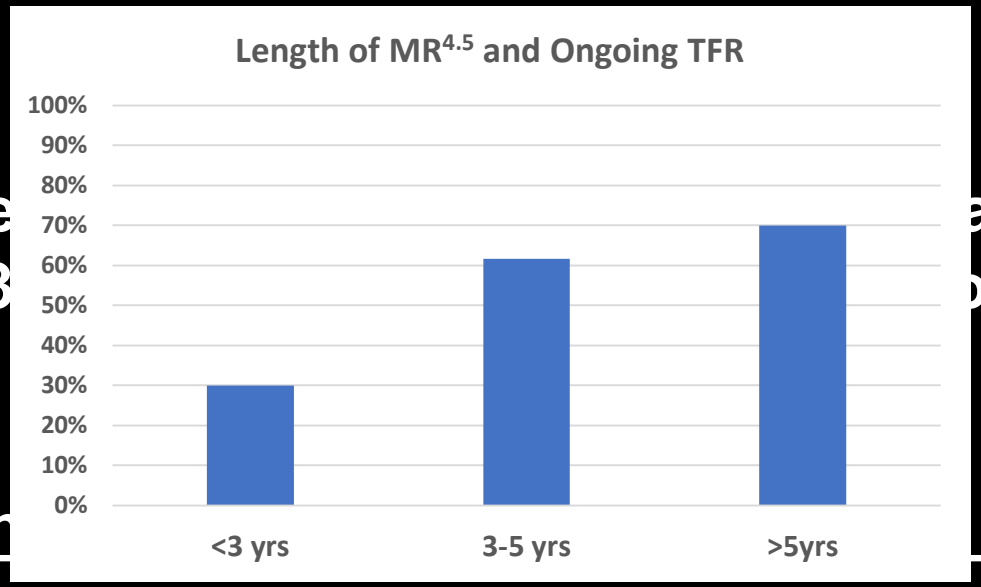


Prognostic Factors - Time on TKI

STIM1	<4.5 yrs – 22%	>4.5 yrs – 50%
EURO-SKI	<5.8 yrs – 34%	>5.8 yrs – 57%
TRAD	<8.7 yrs – 34.6%	>8.7 yrs – 80.5%



Prognostic Factors
Time in Deep Molecular Response (DMR)



"The chance … at 6 mths
increased by 13… of DMR prior

Canadian … 6 mths

Duration of MR4	<7.8 yrs	7.8 – 10.6 yrs	>10.6 yrs
Ongoing TFR at 6mths	41%	70.4%	94.4%

Case Study - 45 yr old male (DM, HT) - low risk Sokal score

Commenced imatinib 400 mg per day

- **at 3 mths - bcr-abl 0.665%** *some periorbital oedema*
- **at 6 mths - bcr-abl 0.182%** *minor dyspepsia for 1-2 hrs each day*
- **at 12 mths- bcr-abl 0.202%** *feels a little "hungover" most days*

- **imatinib level - 2432 ug/L**
  - compliance >90%
  - no drugs interfering with OCT1

eg prazosin, procainamide, ranitidine, metformin, quinidine, amiodarone

- no drugs inducing CYP3A4

eg dexamethasone, phenytoin, carbamazepine, St John's wort

- **at 18 mths - bcr-abl 0.198%**

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Haouala A, et al. Blood (2011) 117:e75-e87

Case Study

Options

1. **continue imatinib at 400 mg per day**
2. **increase imatinib to 600-800 mg per day**
3. **change to nilotinib 300 mg BD**
4. **change to dasatinib 100 mg per day**
5. **change or add to something else:**
   eg bosutinib, ponatinib, interferon, omactaxine
6. **add autophagy inhibitor** *eg hydroxychloroquine, clarithromycin*

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Should Anything Else be Done?

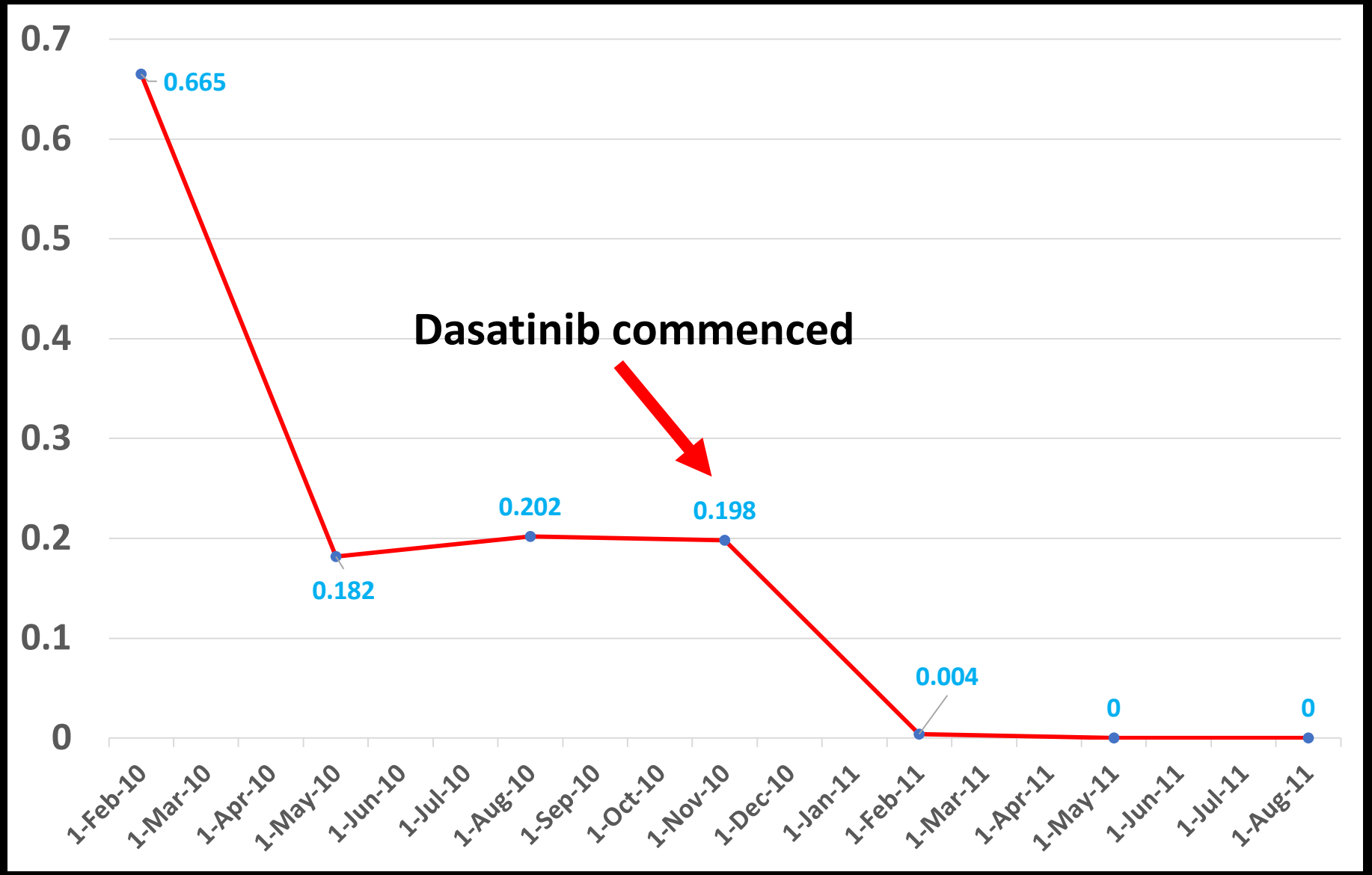
No

- Better the devil that you know
- Patient almost to MMR – probably will get there soon
- Little proven clinical benefit of MMR over 0.1-1%
- Only minor side-effects to imatinib
- Increasing imatinib dose may worsen side-effects
- Other TKIs have potentially serious side-effects
- Longer experience with imatinib c/w newer TKIs

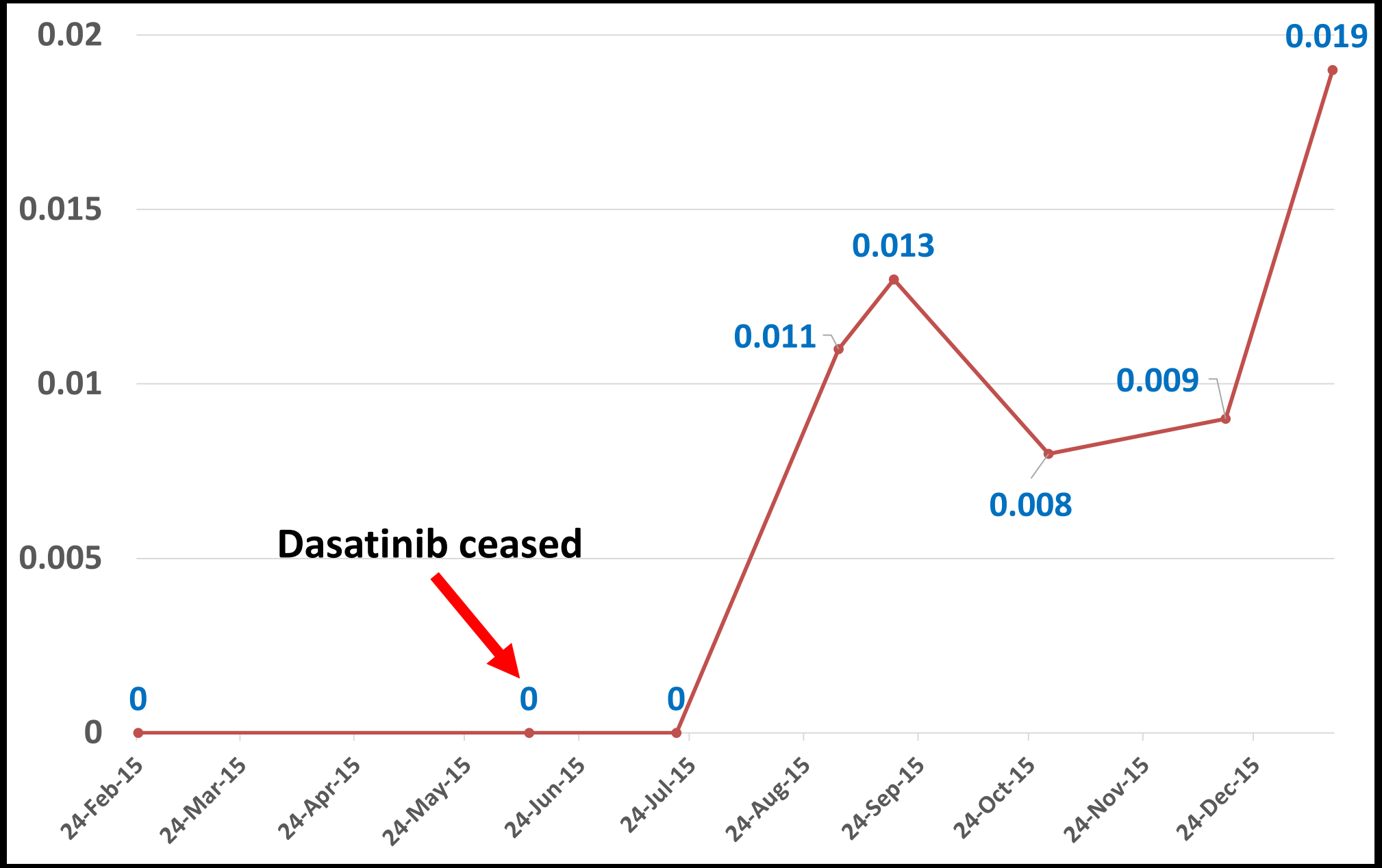
Yes

- The “nuisance” side-effects much less common with the newer TKIs
- The more time that goes by, the less likely that MMR will be obtained
- The higher the bcr-abl level, the greater the risk of acquiring a mutation
- Obtaining CMR ($MR^{4.5}$) should be the goal

TFR Attempt


0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.665
0.182
0.202
0.198
0.004
0
0
Dasatinib commenced
1-Feb-10
1-Mar-10
1-Apr-10
1-May-10
1-Jun-10
1-Jul-10
1-Aug-10
1-Sep-10
1-Oct-10
1-Nov-10
1-Dec-10
1-Jan-11
1-Feb-11
1-Mar-11
1-Apr-11
1-May-11
1-Jun-11
1-Jul-11
1-Aug-11

TFR Attempt


0.02
0.015
0.01
0.005
0
0.019
0.013
0.011
0.009
0.008
0
0
0
Dasatinib ceased
24-Feb-15
24-Mar-15
24-Apr-15
24-May-15
24-Jun-15
24-Jul-15
24-Aug-15
24-Sep-15
24-Oct-15
24-Nov-15
24-Dec-15

Case Study

Options

1. continue TFR
2. change back to imatinib
3. change to nilotinib 300 mg BD
4. Restart dasatinib 100 mg per day
5. do mutation analysis first

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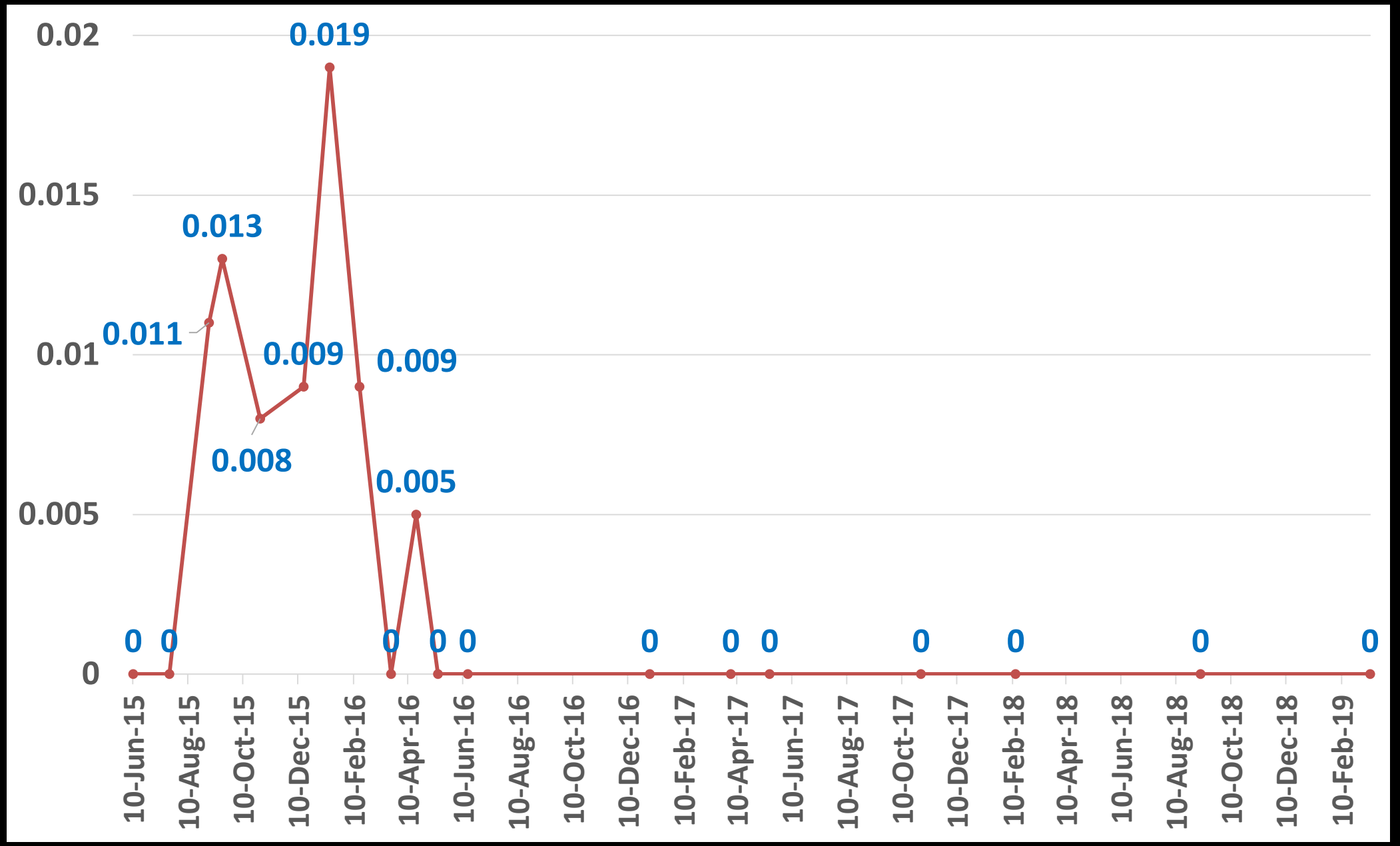
Successful TFR Attempt



Study outline

Loss of $MR^{4.5}$ does not necessarily lead to loss of MMR (so far)

Case Study

Commenced imatinib 600 mg per day

- **at 3 mths - bcr-abl 2.3%**
- **at 6 mths - bcr-abl 0.28%**
- **at 12 mths- bcr-abl 0.04%**

- **joined ENESTop study 16.12.13**

  - persistently undetectable bcr-abl at local lab

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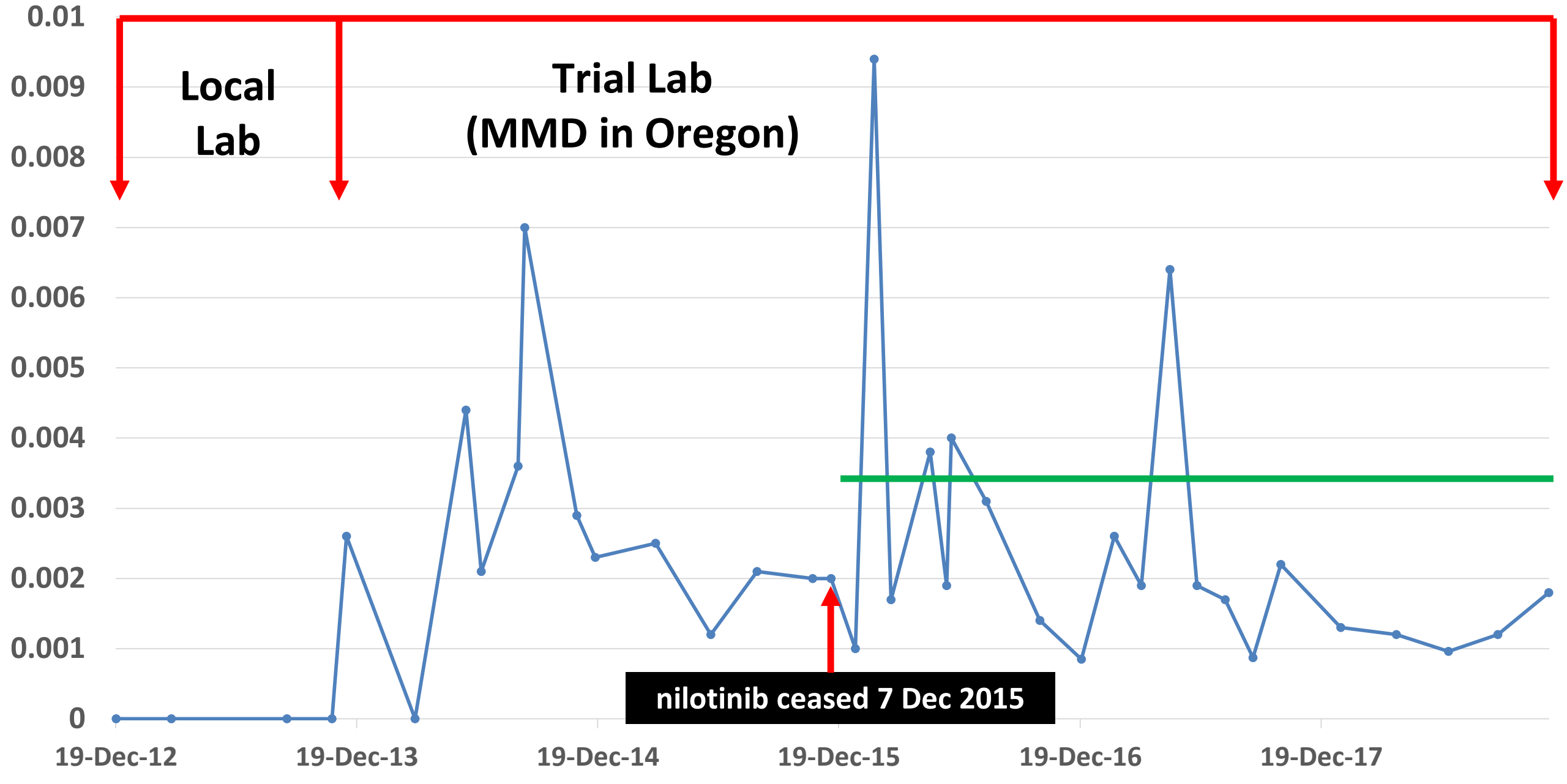
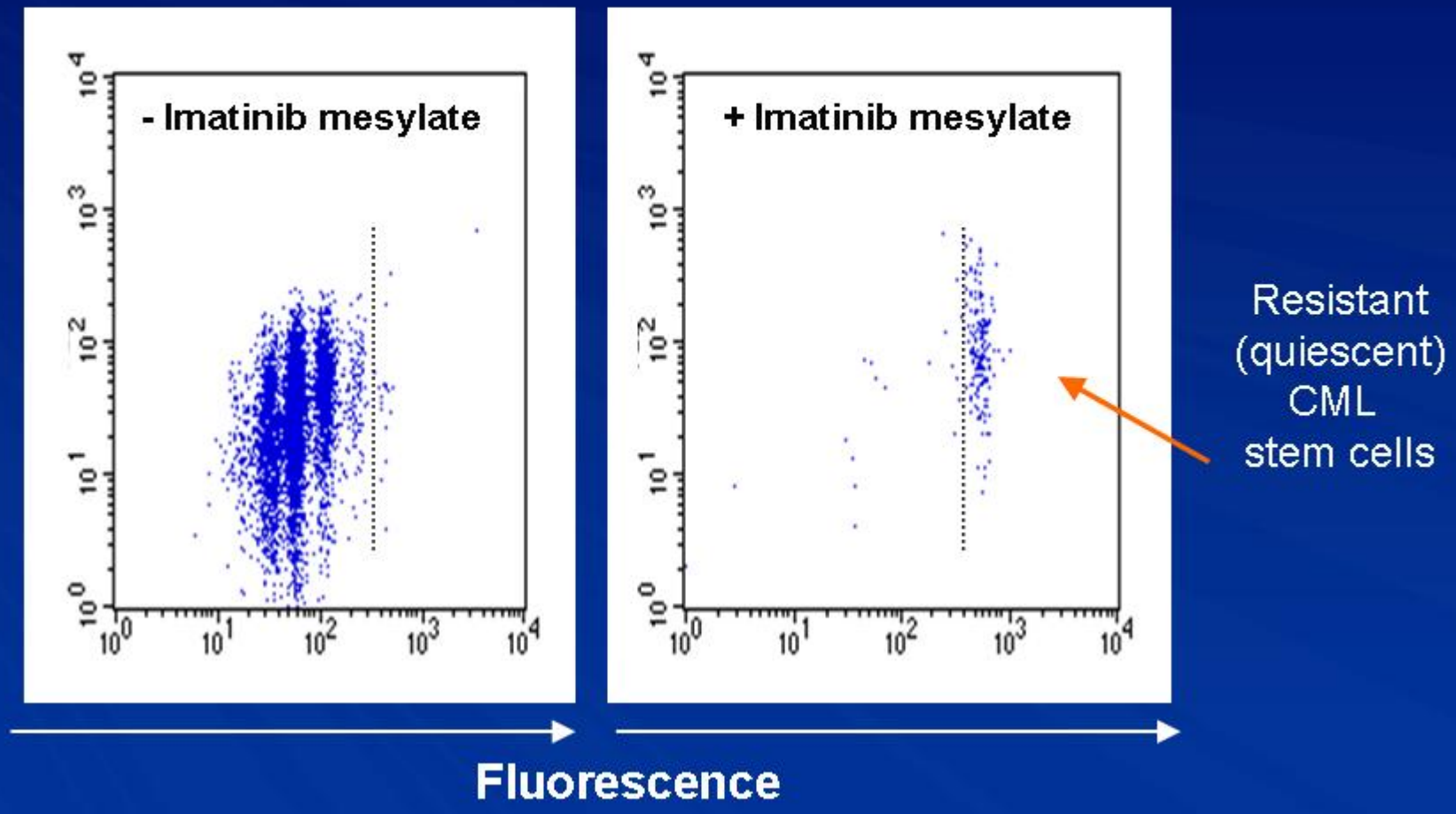
ONCOLOGY

Ongoing Successfull TFR



CML Stem Cells Are Resistant to Imatinib



Graham et al. *Blood*. 2002.

Ph+ and JAK2+ Circulating Endothelial Cells in Patients with MPD or CML

Piaggio G et al. Blood 2009;114:3127-3130

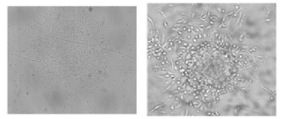
A

	ECFC				
	CML	PMF	PV	ET	CTRL
Median frequency (range) per 10^7 MNCs	0 (0-0.6)	0.25 (0-8.1)	0 (0-4)	0 (0-6)	0.14(0-8)
Sample with at least one colony	8/19 (42%)	17/28 (61%)	10/25 (40%)	3/7 (43%)	14/27 (52%)

B

	CFU-EC				
	CML	PMF	PV	ET	CTRL
Median frequency (range) per 10^7 MNCs	0 (0-12)	6.0 (0-97)	3.0 (0-14)	4.0 (0-19)	3.75 (1-27)
Sample with at least one colony	8/19 (42%)	20/28 (71%)	20/25 (80%)	4/7 (57%)	27/27 (100%)

C



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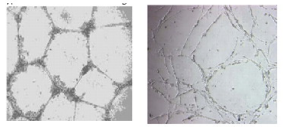
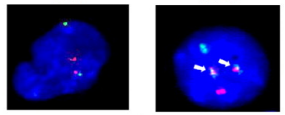


E



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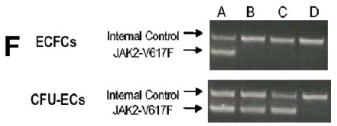
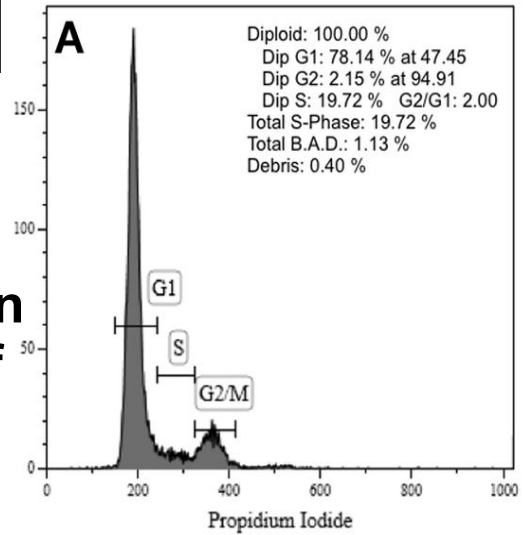
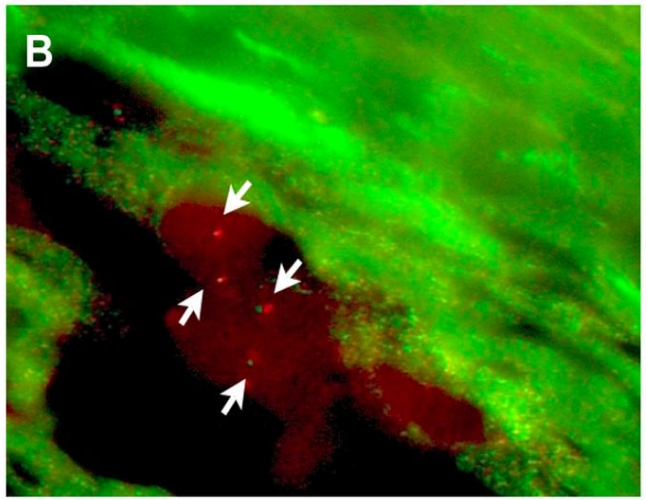


G

Patient	QRT-PCR (p210%)§		D-FISH	
	ECFC	CFU-EC	ECFC	CFU-EC
n.° 2	0,000	17.4	Neg*	75% pos**
n.° 4	0,000	19.2	Neg*	75% pos**
n.° 8	0,000	18.9	Neg*	80% pos**
n.° 11	0,000	11.5	Neg*	70% pos**
n.° 12	0,000	7.7	Neg*	70% pos**
n.° 18	0,000	36.2	Neg*	100% pos**
n.° 19	0,000	74.5	Neg*	100% pos**





JAK2+ Endothelial Cells in Splenic Blood Vessels of Patients with MF

Rosti V et al. Blood 2013;121:360-368

Case Study

- 46 yr old female – home duties
- FBE done re URTI and weight loss - Dx of CML April 2008
- Hb 110 g/L WCC 142.5x10^9/L Plat 432x10^9/L
- Sokal 0.92 - intermediate risk
- Hasford 693; Eutos 74 - both low risk
- ELTS 1.536 - low risk
- no comorbidities

Case Study

- Commenced imatinib 400 mg per day 15 May 2008

  - bcr-abl at 3 mths - 0.25%
  - bcr-abl at 6 mths - 0.041% (MMR)
  - bcr-abl at 12 mths - 0.019% (MMR)

- Joined ENESTcmr Study with bcr-abl 0.007%

  - commenced nilotinib 25 June 2010

  - bcr-abl at 12 mths on study - 0.003% ($MR^{4.5}$)
  - bcr-abl at 24 mths on study - 0.000% ($MR^{4.5}$)

Case Study

- +36 mths on ENESTcmr Study - persistently undetectable bcr-abl

- Joined ENESTop Study 2.9.13 and nilotinib was ceased 8.9.14

  - quickly developed headache, arthralgias, joint swelling, fluid retention and wt gain
  - quiet troublesome

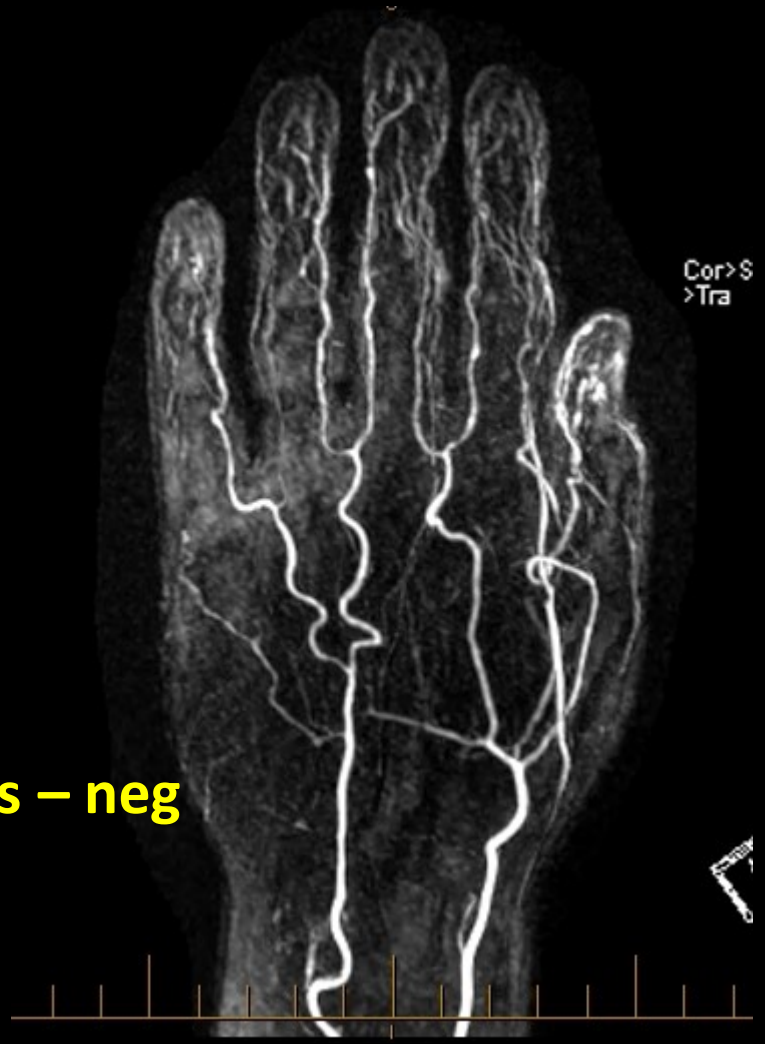
Case Study

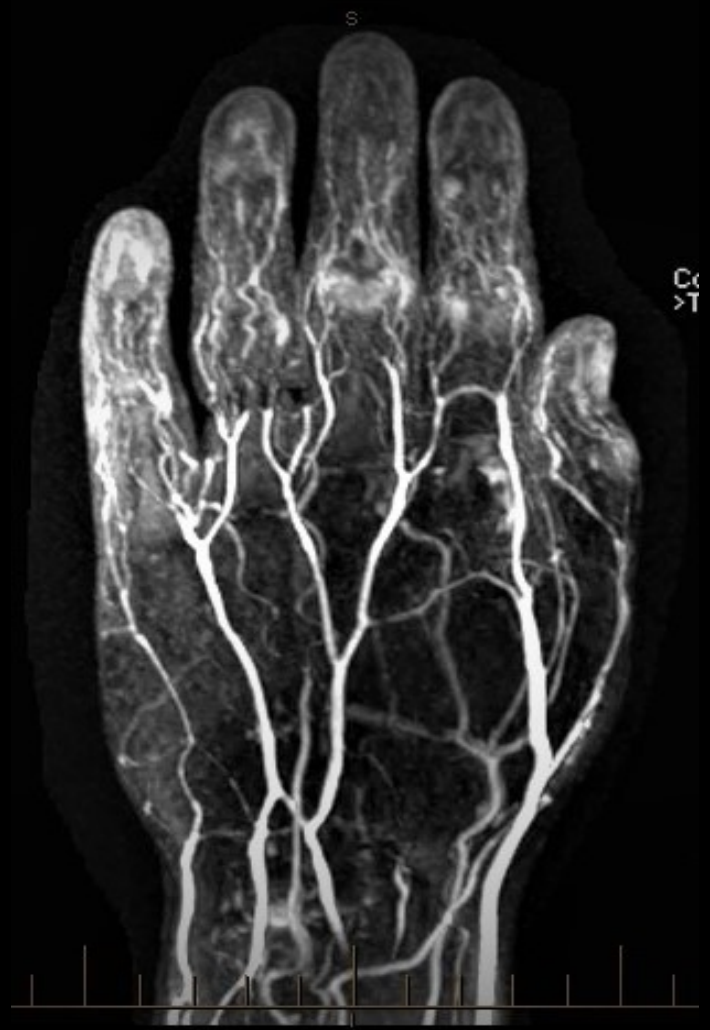
- After 3 mths - fluid retention settled but arthralgias and finger swelling persisted

- prednisolone, NSAIDs, hydroxychloroquine, Rheumatologist, acupuncture, fish oil, turmeric

- prednisolone	– helped considerably but caused moodiness
- hydroxychloroquine	– may have helped a little
- others	– no help

- Small erosions carpal bones
- Synovial enhancement of most small joints





ANA 640
Rh factor 12
ENA - neg
Complements – neg
ESR 16
CRP <2

No PH or FH of autoimmune disorders

Case Study

- Patient depressed tearful – “at the end of her tether”
- Patient requesting to restart TKI

Case Study

- Patient decided to stay off TKI and not to try any further treatments for the arthralgias
- At +16 mths off TKI – arthralgias and swelling confined to L hand
- At 25 mths – all pains and swelling has settled
- Now 4.5 yrs since stopping nilotinib

  - gets occas swelling of fingers but no pain

- bcr-abl - 0.00000% to 0.00088% (no trend)

Adverse Events – Musculoskeletal symptoms

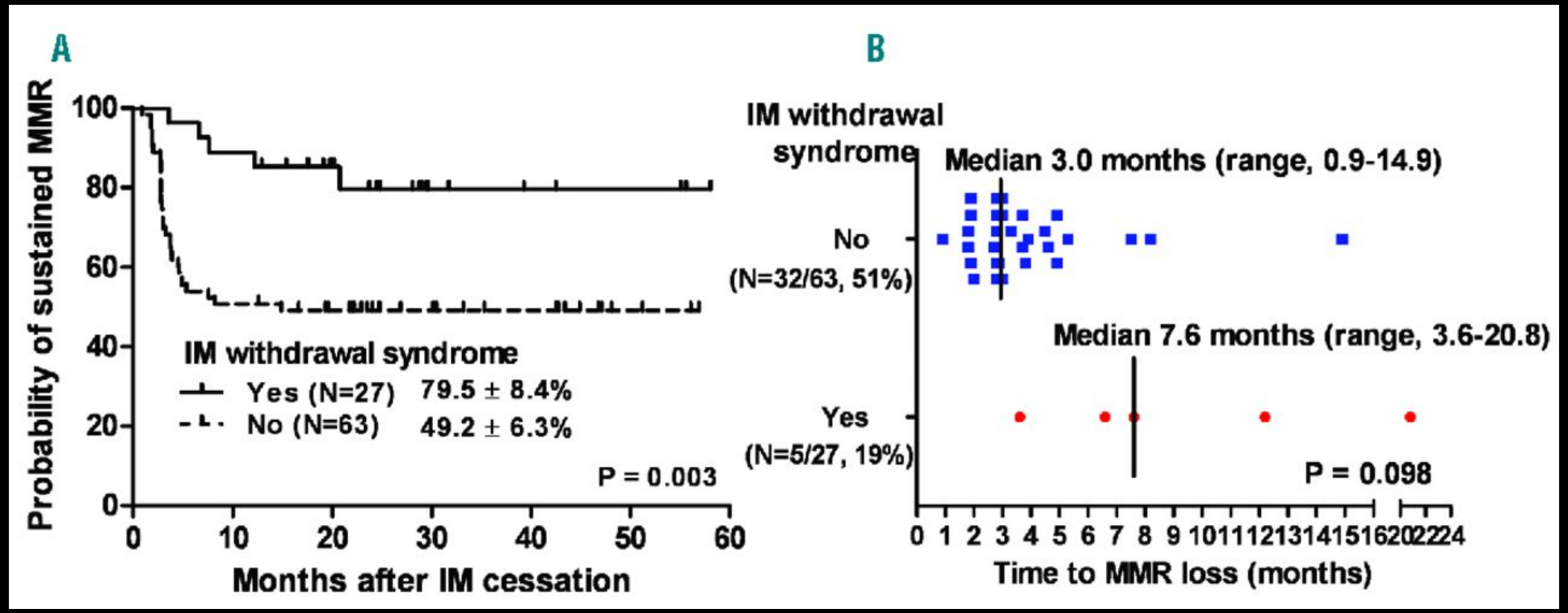
Previously a TKI withdrawal syndrome has been described in a sub cohort of patients in EURO-SKI (Richter et al. JCO 2014). This consists of newly emerging, but mostly transient, pain or discomfort from the musculoskeletal system. This has also been described in other cessation trials (Mori et al. Am. J. Hematol. 2015, Lee et al. Haematologica 2016).

	Patients with AE grade 1-2	%	Patients with AE Grade 3	%	Total	%
Musculoskeletal symptoms*	226	29.7	9	1.2	235	30.9

*Musculoskeletal pain, bone and/or joint pain, arthralgia, muscle pain, myalgia, joint stiffness, lumbalgia, articular pain, muscular pain, neck pain, arthromyalgia, pain both arms, pain legs

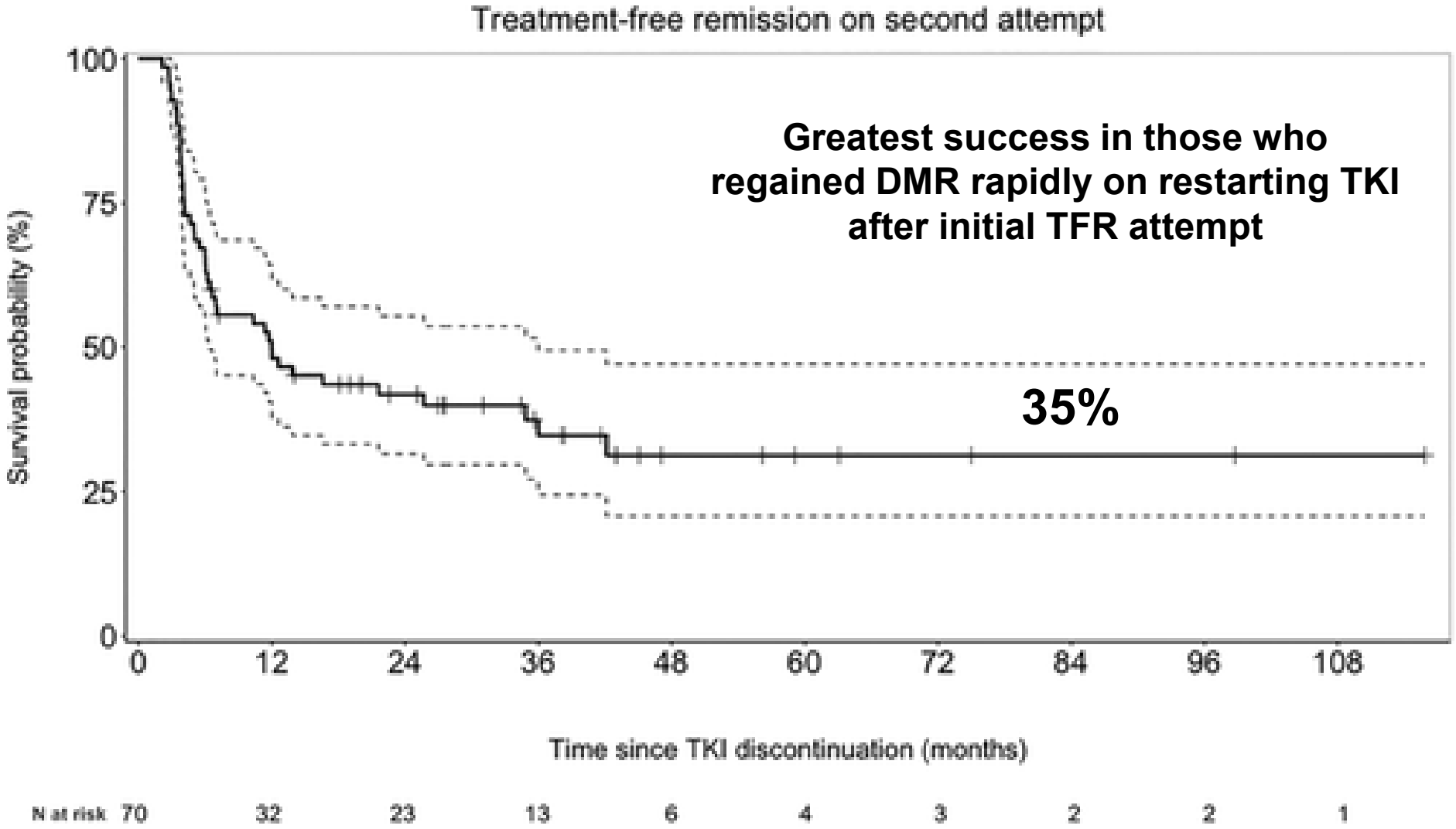
Musculoskeletal Pain in Patients With Chronic Myeloid Leukemia After Discontinuation of Imatinib:

A Tyrosine Kinase Inhibitor Withdrawal Syndrome



Lee SE, et al. Haematologica (2016) 101:717-723

Second tyrosine kinase inhibitor discontinuation attempt



Legros L, et al. Cancer (2017) 123: 4403-4410

My Approach to CML-CP

- Start talking TFR possibility shortly after diagnosis

- TKI for > 4yrs – the longer the better

- DMR (<MR4.5) for at least > 2 yrs - the longer the better
  - if no side-effects aim for 5 yrs
  - if side-effects – maybe earlier

- RT-PCR
  - each month for 6 mths
  - each 2 mths for 6 mths
  - each 3 mths until 5 yrs TFR
  - each 6 mths until 10 yrs TFR
  - each 6-12 mths thereafter

- Restart TKI when MMR is lost


Thank you