The best arguments for using second-generation TKI in first line in CML

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HOSPITAL DA LUZ

IA

- 23 year-old man
- Referred due to leucocytosis and thrombocytosis on routine FBC
- PMH: none significant
- Not on medication

- O/E normal
  - No palpable spleen

- FBC:
  - Hb 10.8 g/dL
  - WBC 130x10^9/L
  - Plt 998x10^9/L

MB	0%
Myelocytes	22%
MT	11%
PMN	55%
Baso	5%
Eos	1%

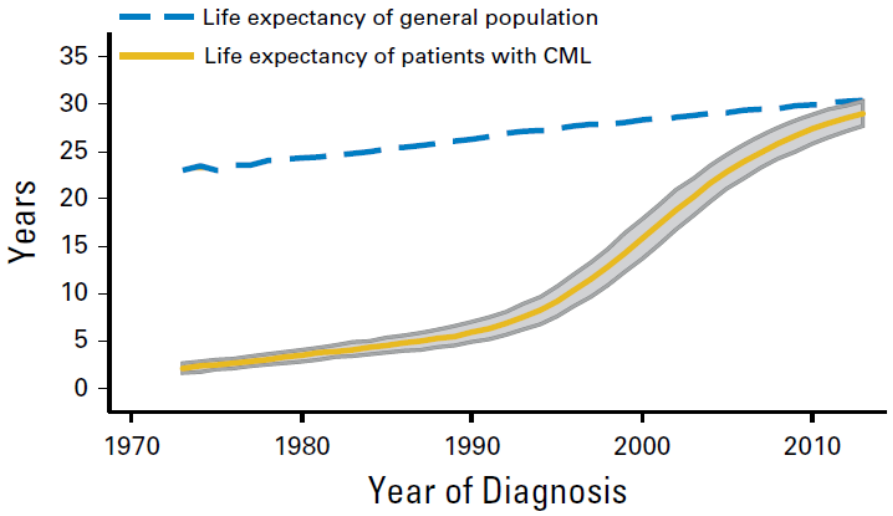
- Biochemistry: LDH 504 IU/L
- BM: chronic phase CML

- Cytogenetics: 46.XX,t(9;22)(q34;q11)[30]
- PCR: BCR-ABL b3a2

Personal data

IA

- Starts nilotinib 300 mg BID
- 3 months: CHR and CCyR
- PCR BCR-ABL 0.2%
- 12 months
  - PCR BCR-ABL 0.08%
- 18 months
  - PCR BCR-ABL 0.0005%



Bower et al, JCO 2016

Personal data

Evolution of aims in treatment of CML

1900-1980

Cytoreduction/RT

38% 5 yr survival[1]

→ **Control WBC**
Prevent leucostasis

1980-2000

IFN/BMT

65% 5 yr survival[2]

→ **Cytogenetic remission**
Prevent progression

2000-2019

TKI

93% 5 yr survival[3]

→ **Molecular remission**
Normal survival
Minimize toxicity

1. Sokal et al, 1976
2. R. Hehlmann, German CML Study Group
3. Druker et al, NEJM 2006

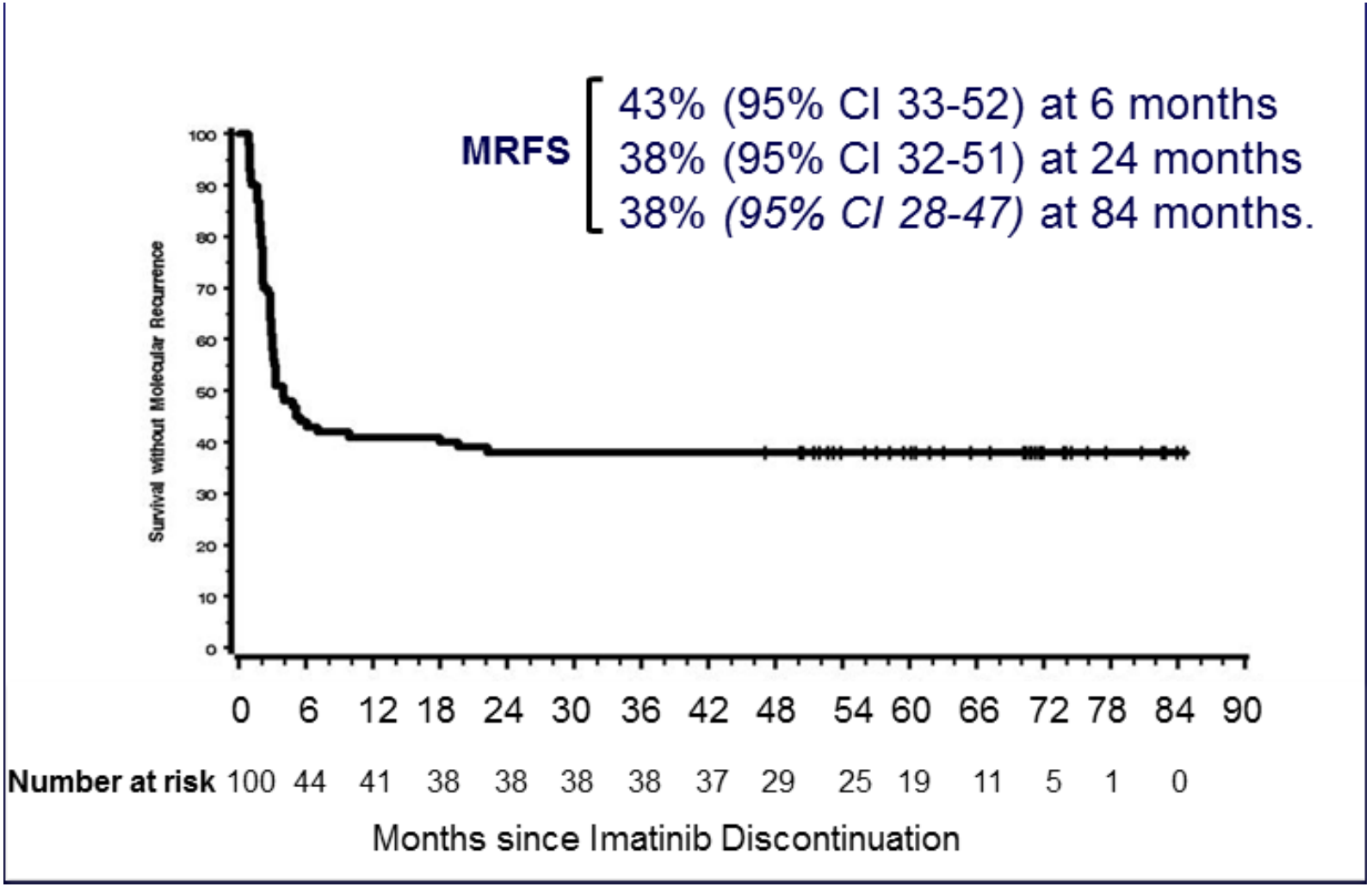
Aims of CML therapy in 2019

- Prevent progression
- Ensure normal survival

- **SAFE operational CURE for all**
  - **Undetectable disease in the absence of treatment**
  - *BMT offers cure for <25% with 10% TRM and high morbidity*

Afreen and Safran, J Carcinogene Mutagene 2013, S14

STIM study – operational cure?



Molecular relapse occurred in 61 pts with 58 relapses occurring during the first 7 months 3 late relapses at month 19, 20 and 22, respectively

Etienne, Blood 2015 126:345

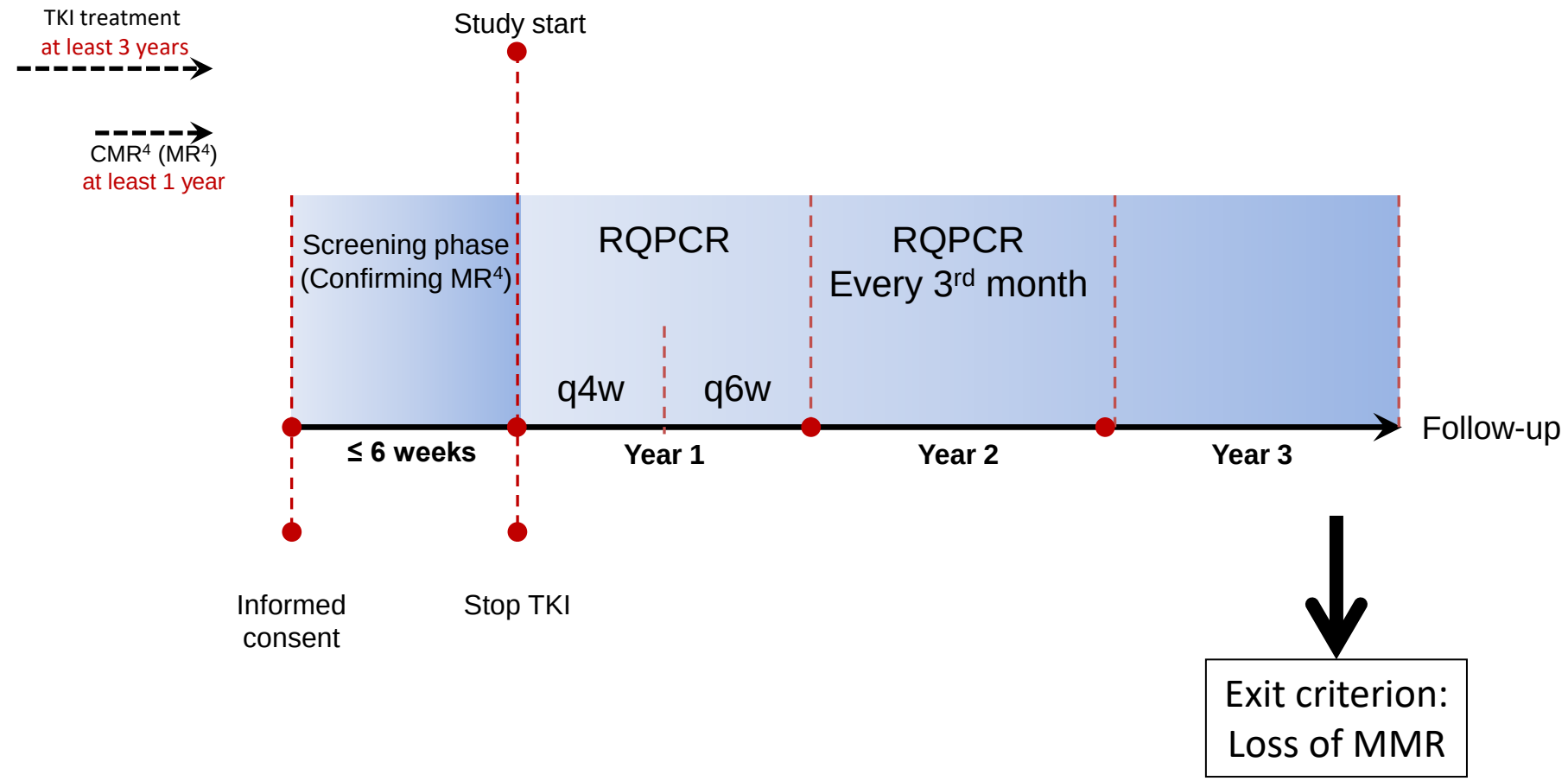
IA

- Month 36 treatment
- Enrolled in EUROSKI study
- $MR^{4.5}$ maintained at 3 years TFR
- No side effects

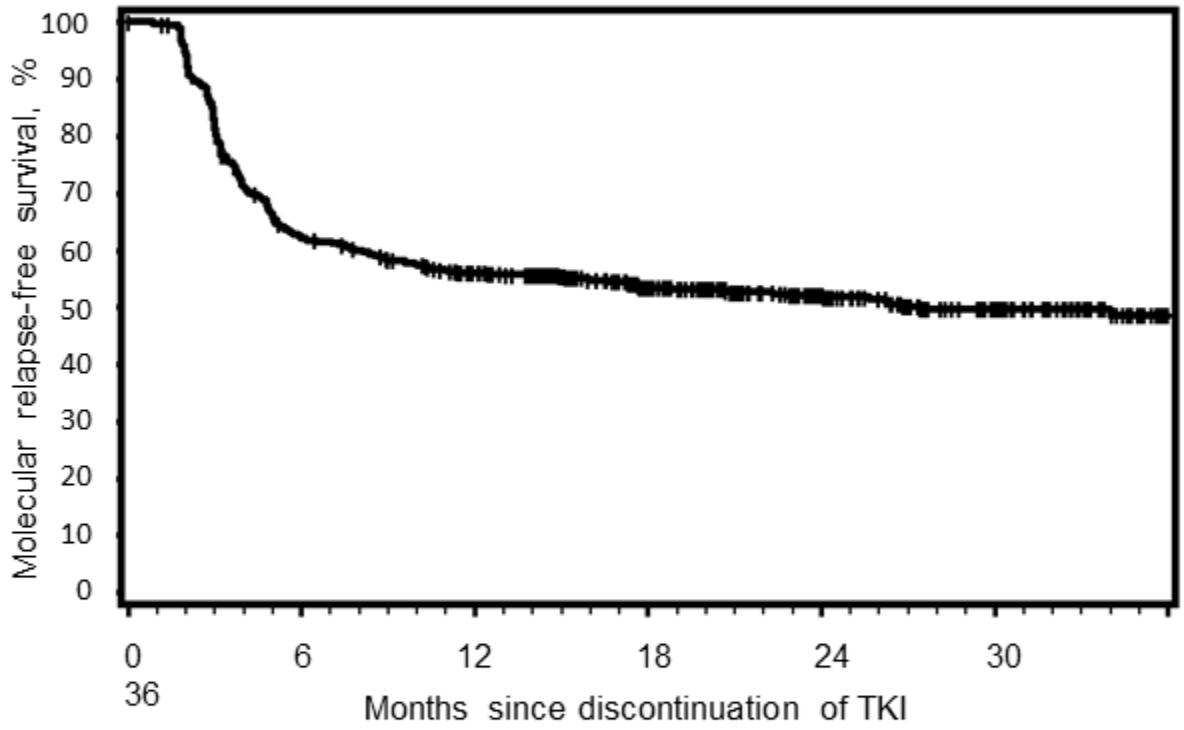
Personal Data

EUROpe Stop TKI
EURO-SKI

Inclusion criteria



Molecular relapse-free survival (n=750)

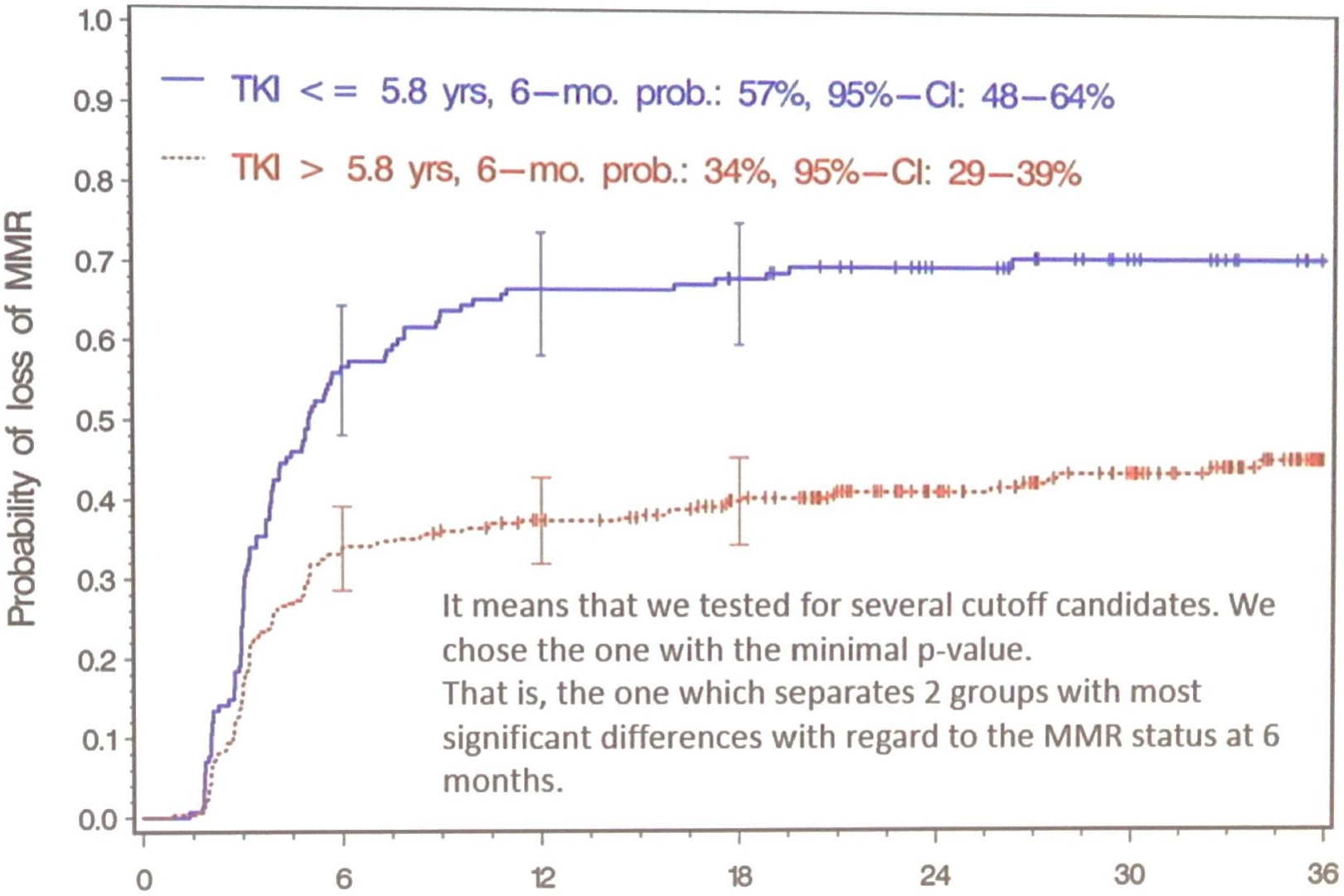


Month	MolRFS %	95%-CI
6	62	59-67
12	56	52-59
24	52	48-56
36	49	44-53

Events:
Molecular relapse n= 348
Death in remission n=5

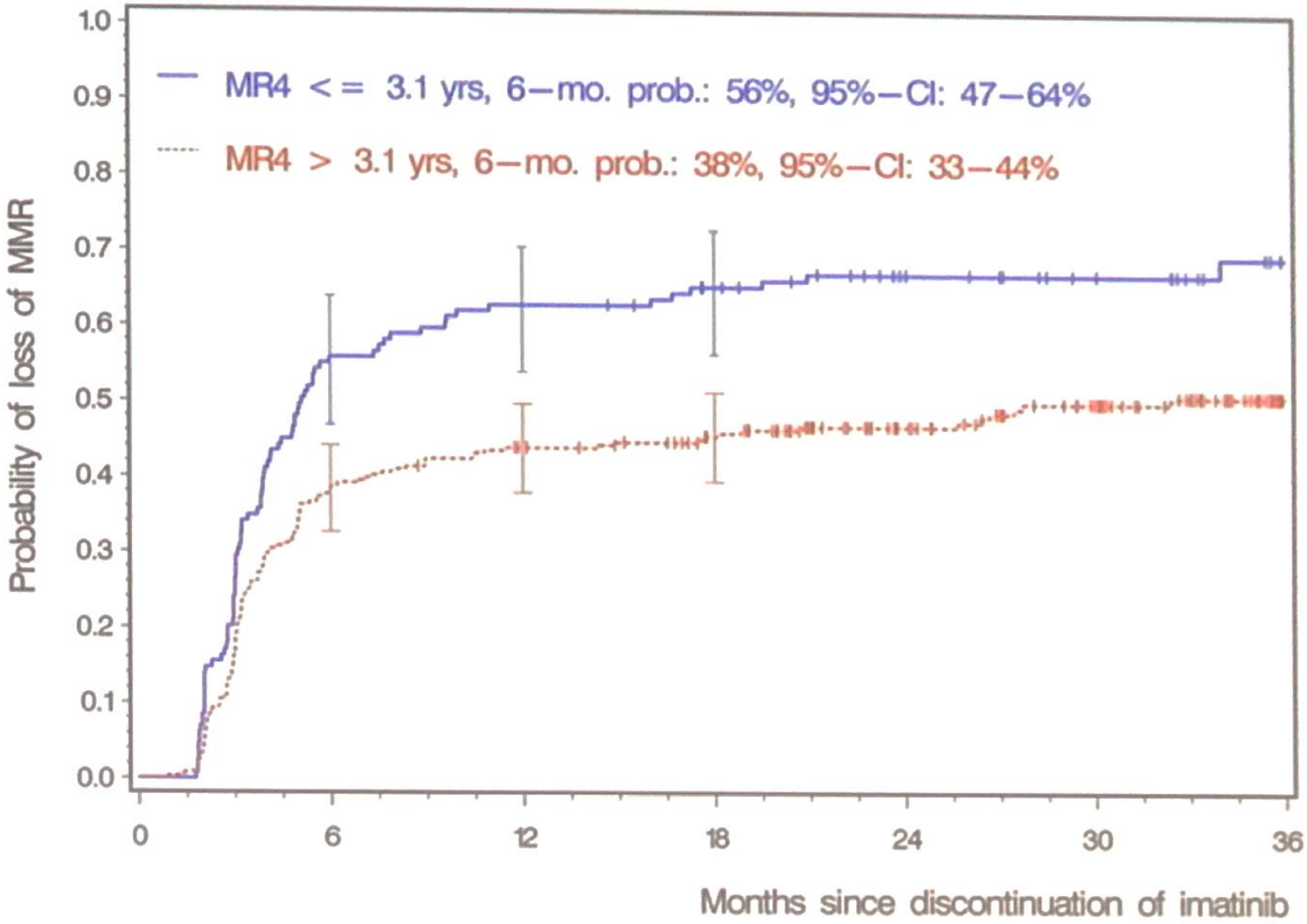
For patients who resumed treatment, median time to restart was 4.1 months

Treatment duration cut-off for loss of MMR @ 6 months



313 Saussele et al ASH 2017

MR^4 duration cut-off for loss of MMR @ 6 months



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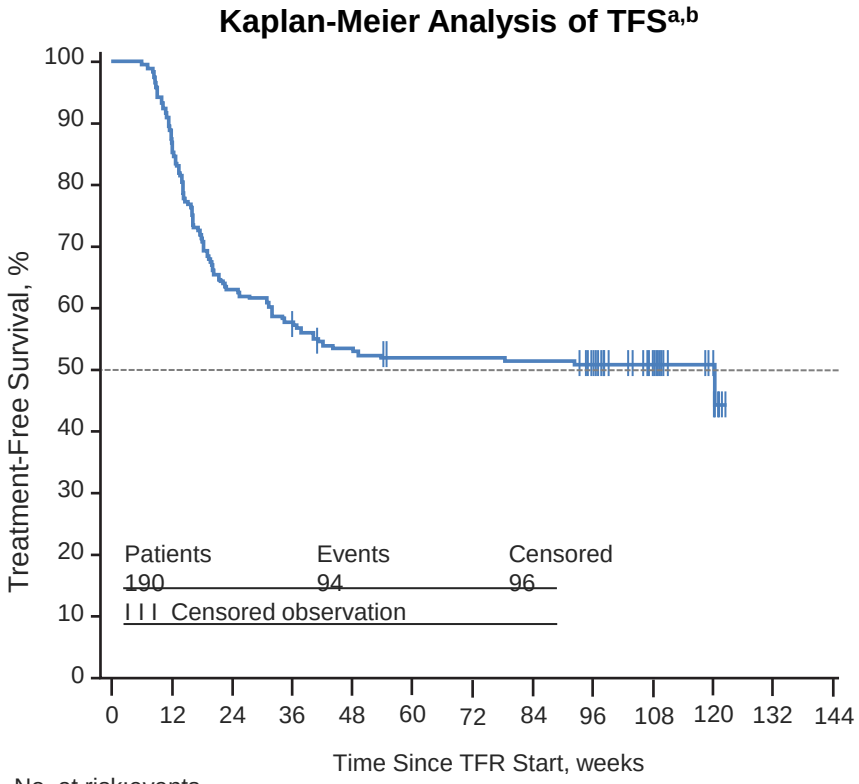
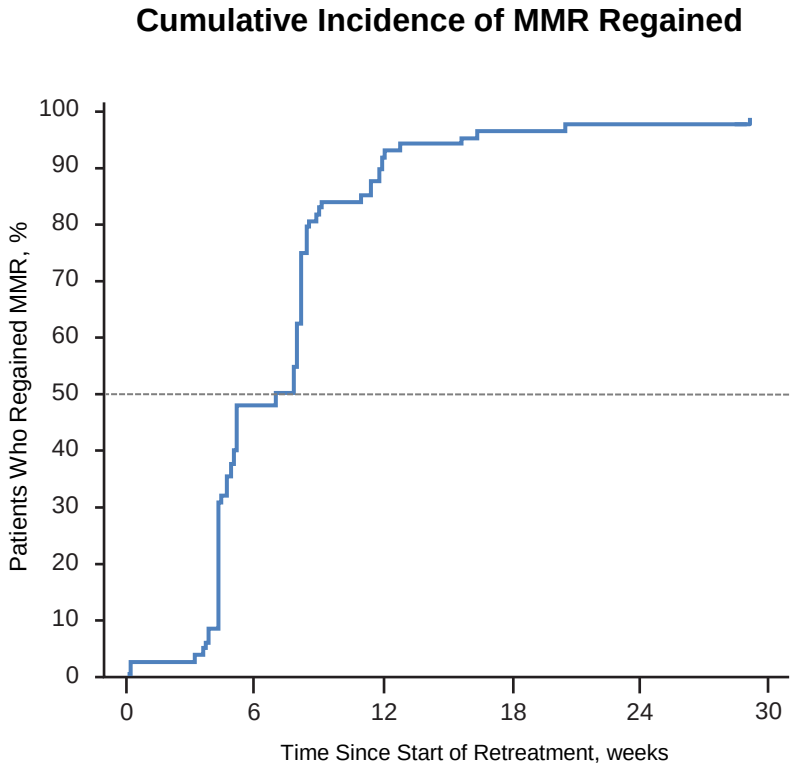
ENESTfreedom TFR at 96 Weeks

- **3 year treatment**
- **1 year DMR**

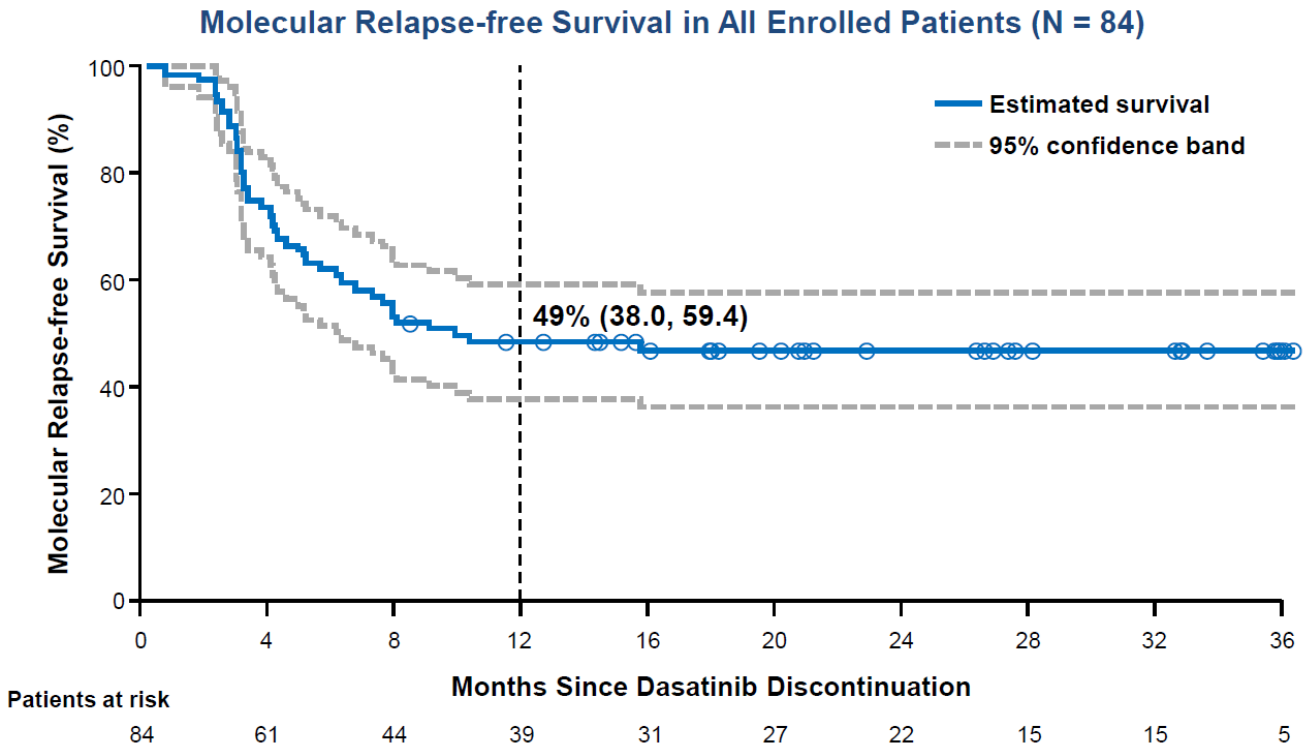




[a] Defined as the time from the start of TFR until the earliest of any of the following: loss of MMR, reinitiation of nilotinib for any reason, progression to AP/BC, or death due to any cause.
[b] By the data cutoff date, 1 patient lost MMR at week 120, at which time only 8 patients were considered to be at risk, resulting in the artificial drop seen at the end of the curve.

DasFree TFR at 96 Weeks

- **2 year treatment**
- **1 year DMR**



	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

No predictors of molecular relapse identified

This product is not registered in Malaysia

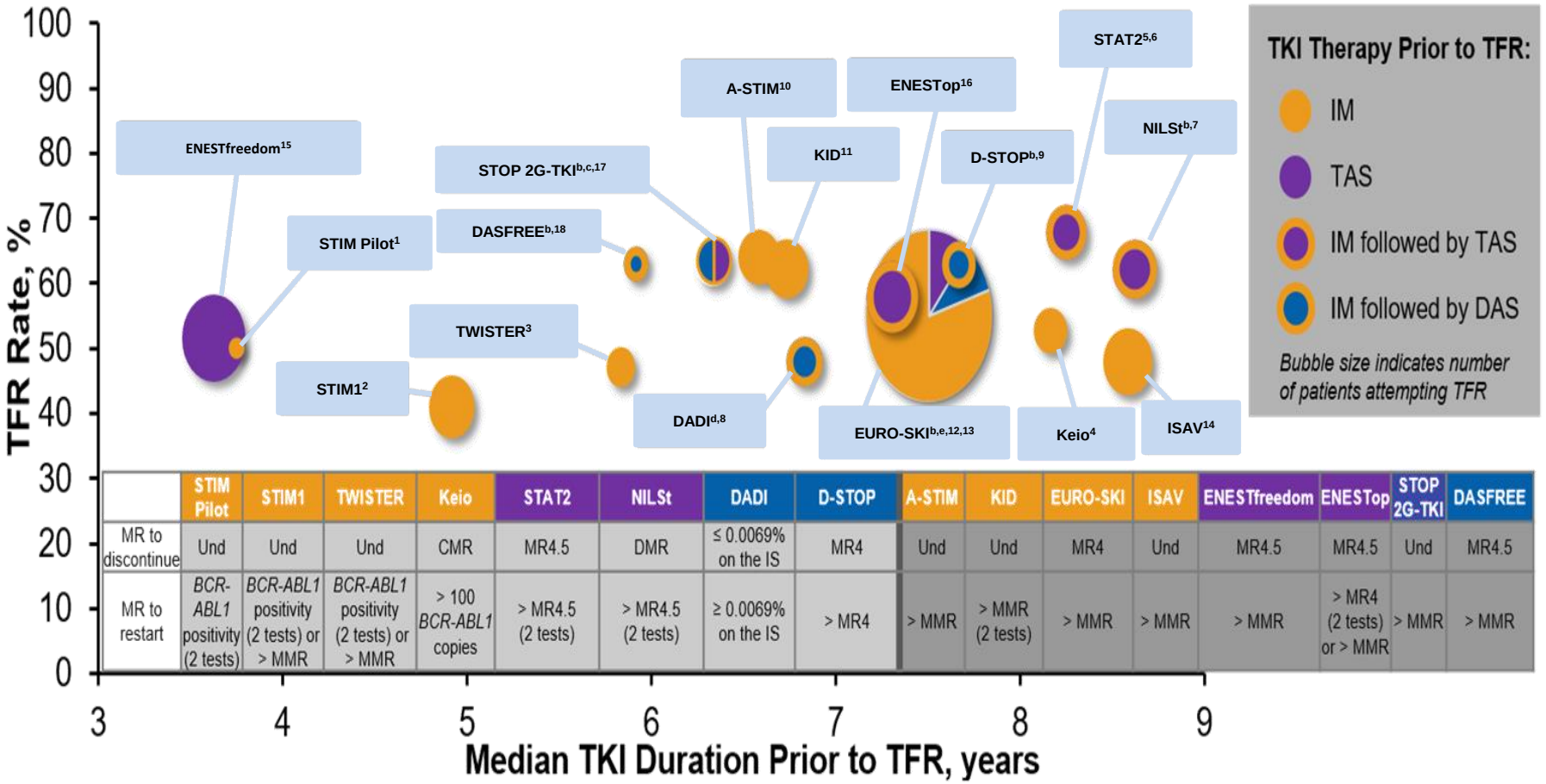
314 Shah et al ASH 2017

Lessons learnt from TFR studies so far

- Safe with adequate monitoring
  - Most relapses in first 12 months
  - No progressions on study
  - >80% regain MR^4 after restart

- Restarting after loss of MMR safe
- 1st line TKI not associated with loss of response after TFR

- *>5.8 yr treatment and response duration better*
- *Responses deeper than MR^4 no better*



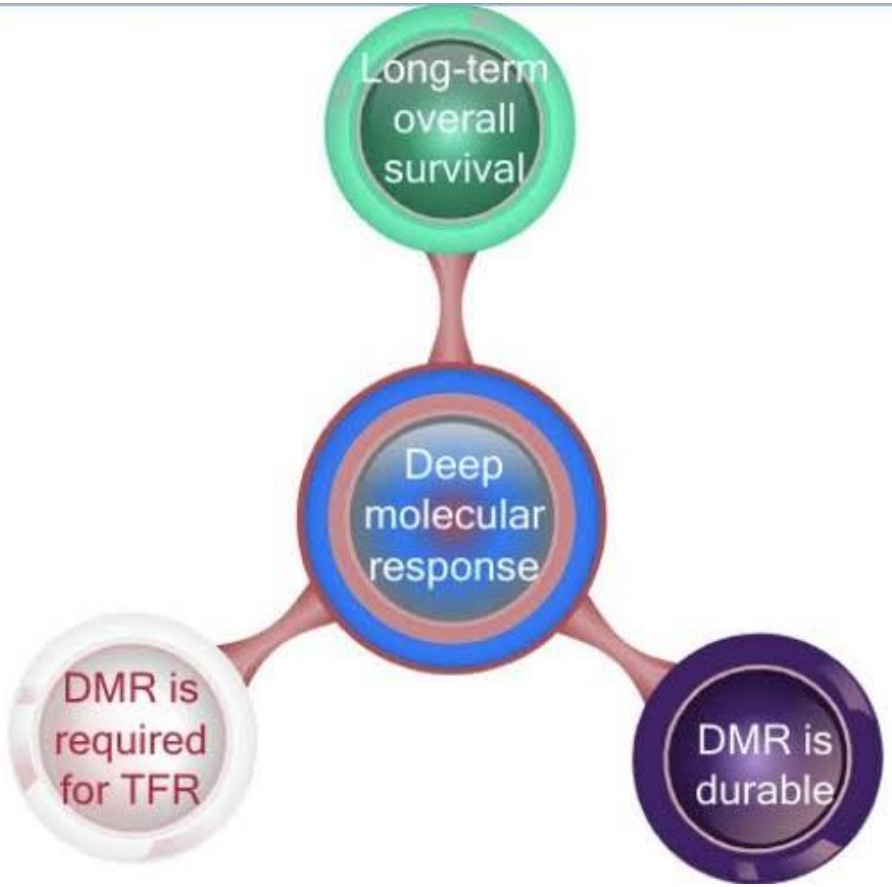
	STIM Pilot	STIM1	TWISTER	Keio	STAT2	NILSt	DADI	D-STOP	A-STIM	KID	EURO-SKI	ISAV	ENESTfreedom	ENESTop	STOP 2G-TKI	DASFREE
MR to discontinue	Und	Und	Und	CMR	MR4.5	DMR	≤ 0.0069% on the IS	MR4	Und	Und	MR4	Und	MR4.5	MR4.5	Und	MR4.5
MR to restart	*BCR-ABL1* positivity (2 tests)	*BCR-ABL1* positivity (2 tests) or > MMR	*BCR-ABL1* positivity (2 tests) or > MMR	> 100 *BCR-ABL1* copies	> MR4.5 (2 tests)	> MR4.5 (2 tests)	≥ 0.0069% on the IS	> MR4	> MMR	> MMR (2 tests)	> MMR	> MMR	> MMR	> MR4 (2 tests) or > MMR	> MMR	> MMR

Differing trial criteria and definitions may impact reported TFR rates across studies

Und, undetectable. [a] TFR rate is based on a median follow-up of 18 months for the STIM Pilot study and a minimum follow-up of 12 months for ISAV. For other studies, TFR rates at 1 year (A-STIM, DADI, DASFREE, D-STOP, ENESTfreedom, ENESTop, EURO-SKI, KID, NILSt, STAT2, STOP 2G-TKI) or 2 years (Keio, STIM1, TWISTER) are shown. [b] Pts discontinuing frontline or second-/later-line 2G-TKI therapy were eligible. [c] Proportion of pts discontinuing NIL or DAS, regardless of prior treatments. [d] Prior combined duration of DAS and IM only (6 pts also received NIL or BOS). [e] Estimated proportion of pts discontinuing each TKI. [f] DMR defined as MR4.5, < 5 copies/assay by TMA, and negativity by nested PCR. [g] Occasional *BCR-ABL1* positivity allowed. [h] Treatment reinitiated if quantitative PCR value exceeded 100 copies using the TMA method. [i] Two consecutive positive tests with ≥ 1 showing loss of MMR.

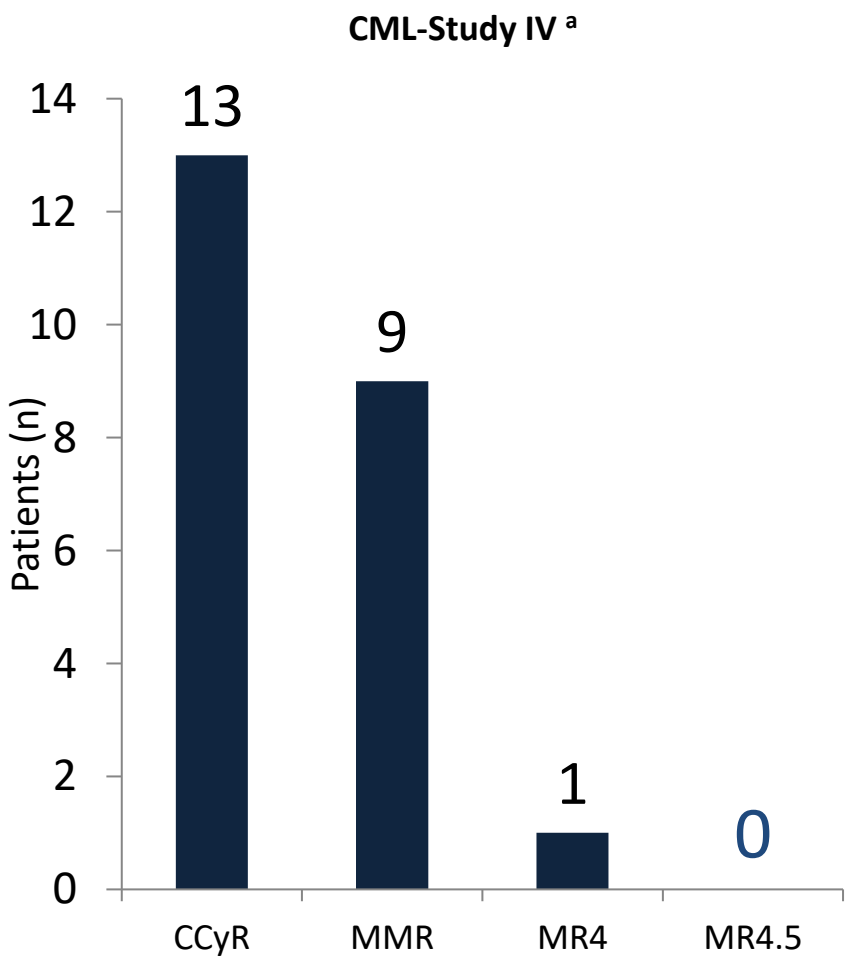
1. Rousselot P, et al. *Blood*. 2007;109:58-60. 2. Etienne G, et al. *Blood*. 2015;126 [abstract 345]. 3. Ross DM, et al. *Blood*. 2013;122:515-522. 4. Matsuki E, et al. *Blood*. 2016 [abstract 1887]. 5. Takahashi N, et al. *Haematologica*. 2016 [abstract P229]. 6. Takahashi N, et al. *Blood*. 2016 [abstract 1889]. 7. Kadowaki N, et al. *Blood*. 2016 [abstract 790]. 8. Imagawa J, et al. *Lancet Haematol*. 2015;2:e528-e535. 9. Kumagai T, et al. *Blood*. 2016 [abstract 791]. 10. Rousselot P, et al. *J Clin Oncol*. 2014;32:424-430. 11. Lee SE, et al. *Haematologica*. 2016;101:717-723. 12. Richter J, et al. *Haematologica*. 2016 [abstract S145]. 13. Mahon FX, et al. *Blood*. 2016 [abstract 787]. 14. Mori S, et al. *Am J Hematol*. 2015;90:910-914. 15. Saglio G, et al. *Haematologica*. 2016. [abstract LB618]. 16. Hughes TP, et al. *Haematologica*. 2016. [abstract LB237]. 17. Rea D, et al. *Blood*. 2016 Dec 8 [Epub ahead of print]. 18. Shah NP, et al. *Blood*. 2016 [abstract 1895].

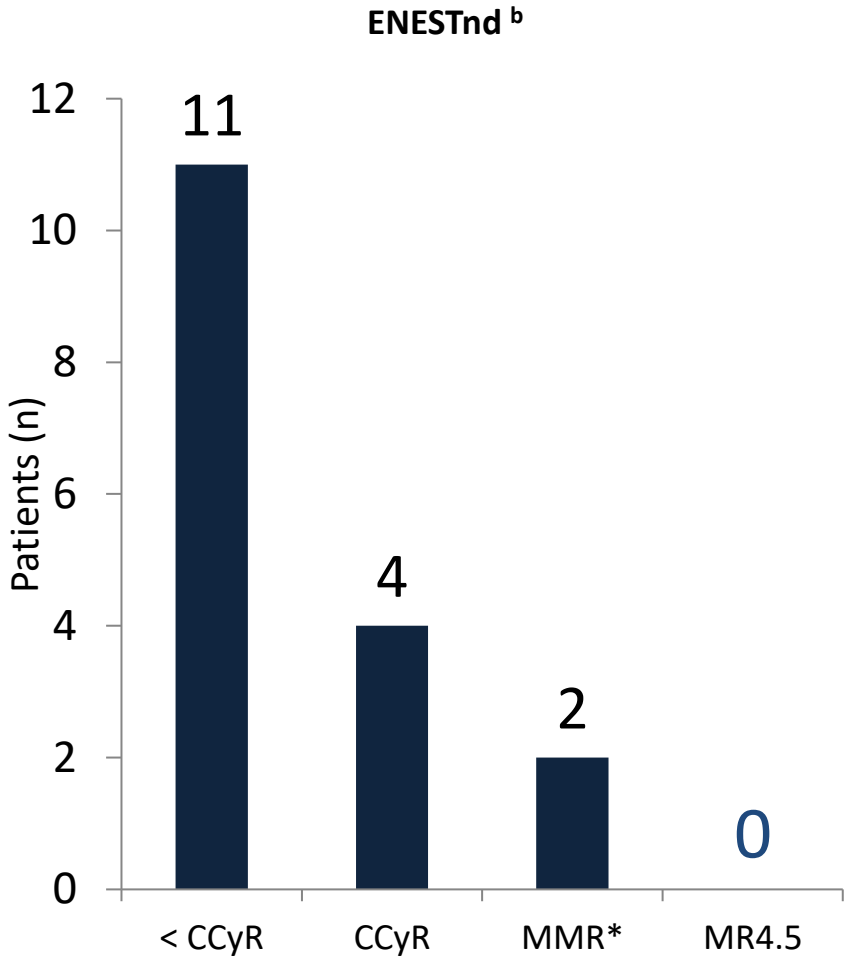
Main goal for CML is DMR



J Apperley, ASH 2018

The Deeper Molecular Response Prevent CML Progression Events



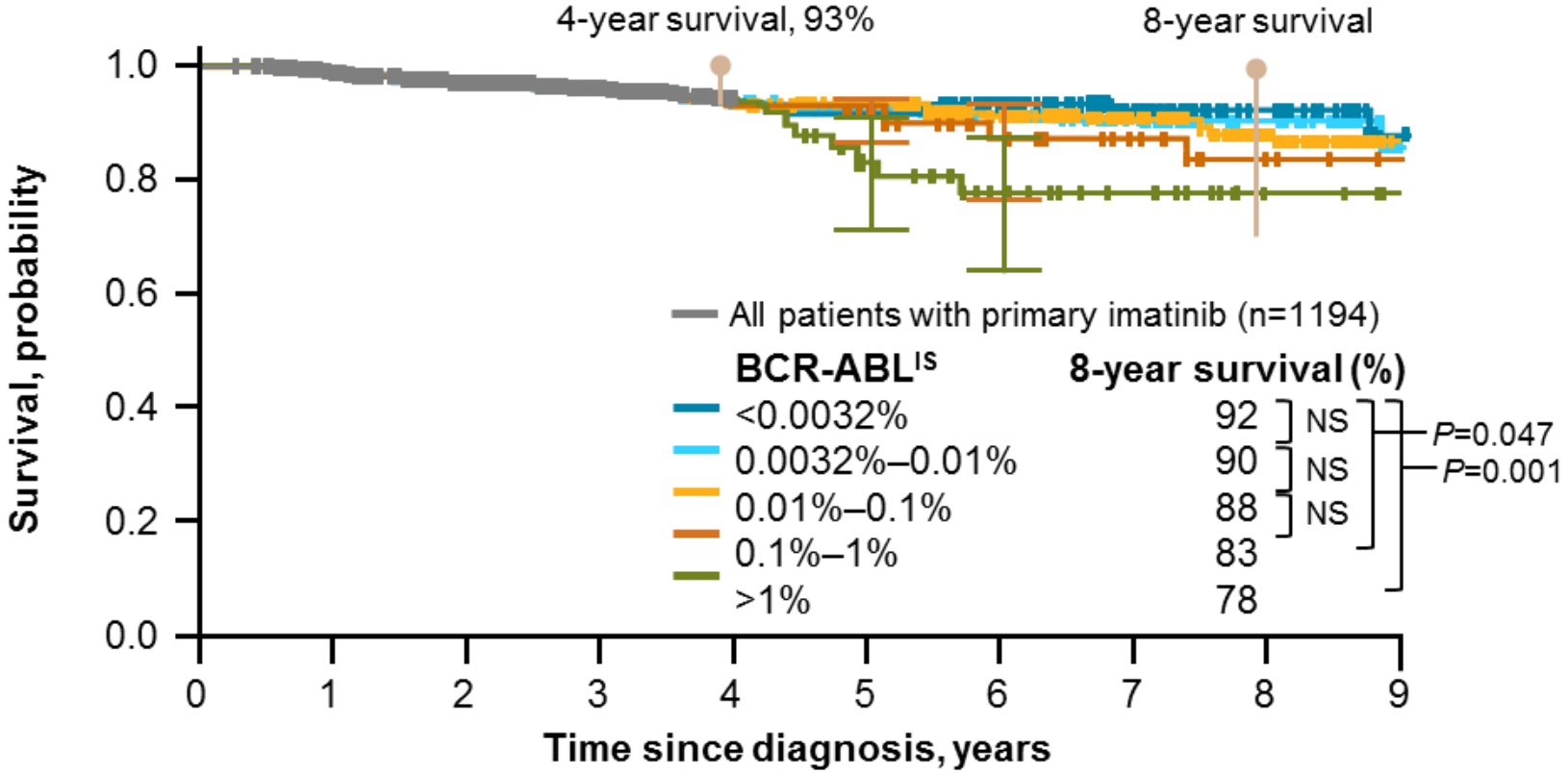


*includes one patient with $MR^{4.0}$

a. Hehlmann R, et al. *J Clin Oncol 2014; 32(5): 415-423.;* b. Kantarjian HM, *et al. Blood*. 2012;120(21):[abstract 1676]

Achievement of MR4.5 by 4 years has been associated with improved overall survival

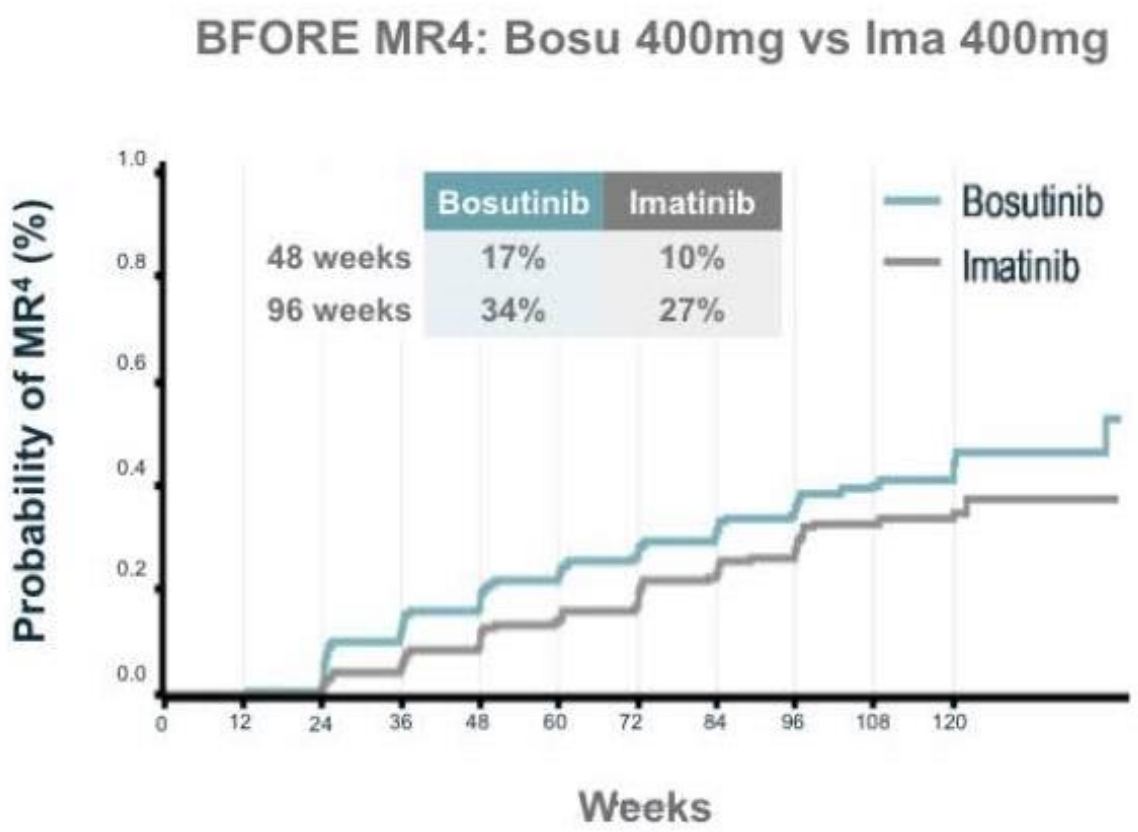
CML-Study IV: Prognostic impact of confirmed deep molecular response (MR4.5) at 4 years vs lower response levels



Achievement of MR4.5 at 4 years was associated with improved 8-year survival vs. CCyR without MMR* (*P*=0.047), BCR-ABL^{IS} >1% (*P*=0.001), and no MR4.5 (*P*=0.047)

CCyR, complete cytogenetic remission; NS, not significant.* BCR-ABL^{IS} 0.1%–1%, corresponding to CCyR without MMR.
Hehlmann R, *et al. J Clin Oncol* 2014;32:415–423.

Bosutinib 1st line

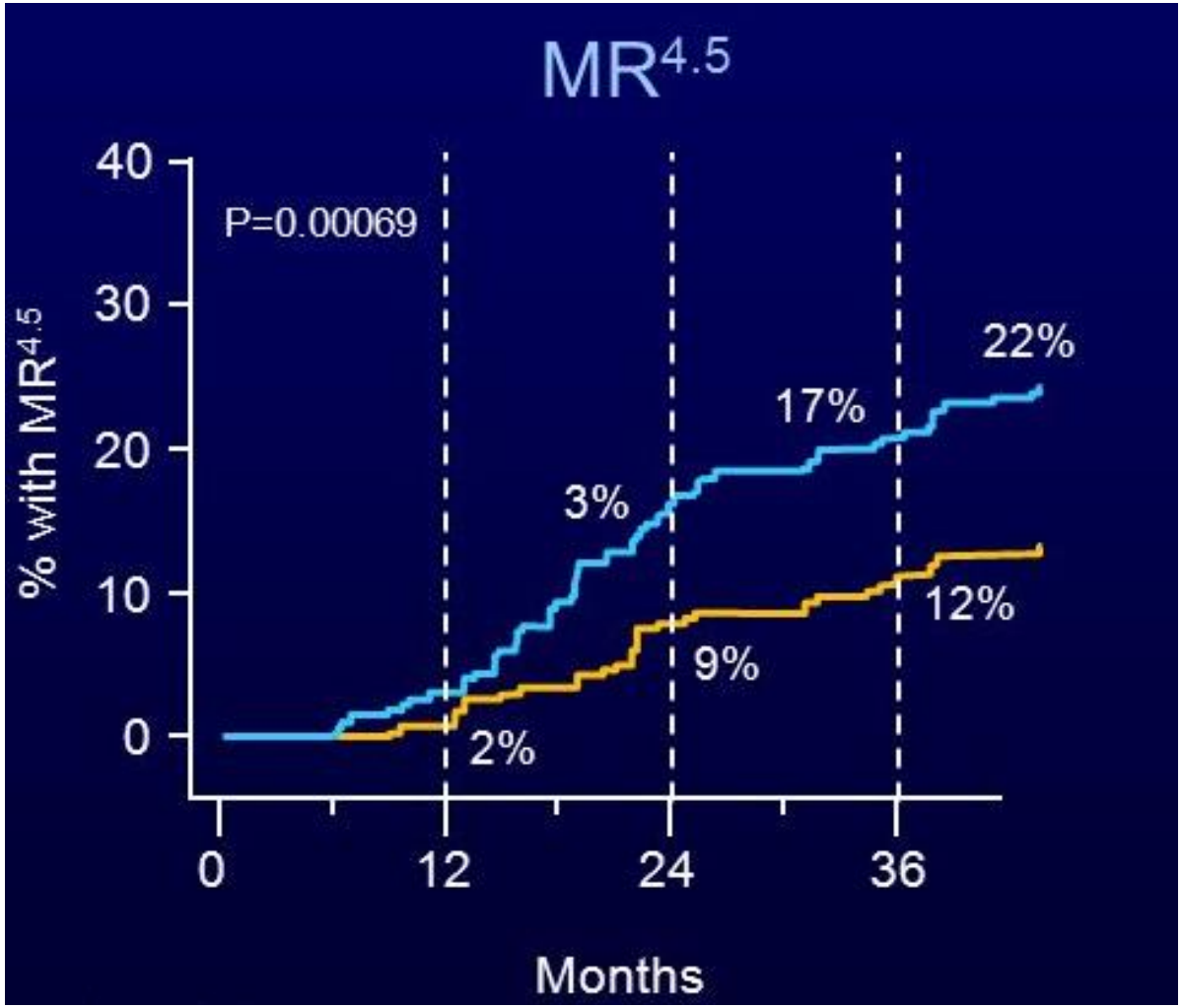


Cortes et al, ASCO meeting, 2018

J Apperley, ASH 2018

This product is not registered in Malaysia

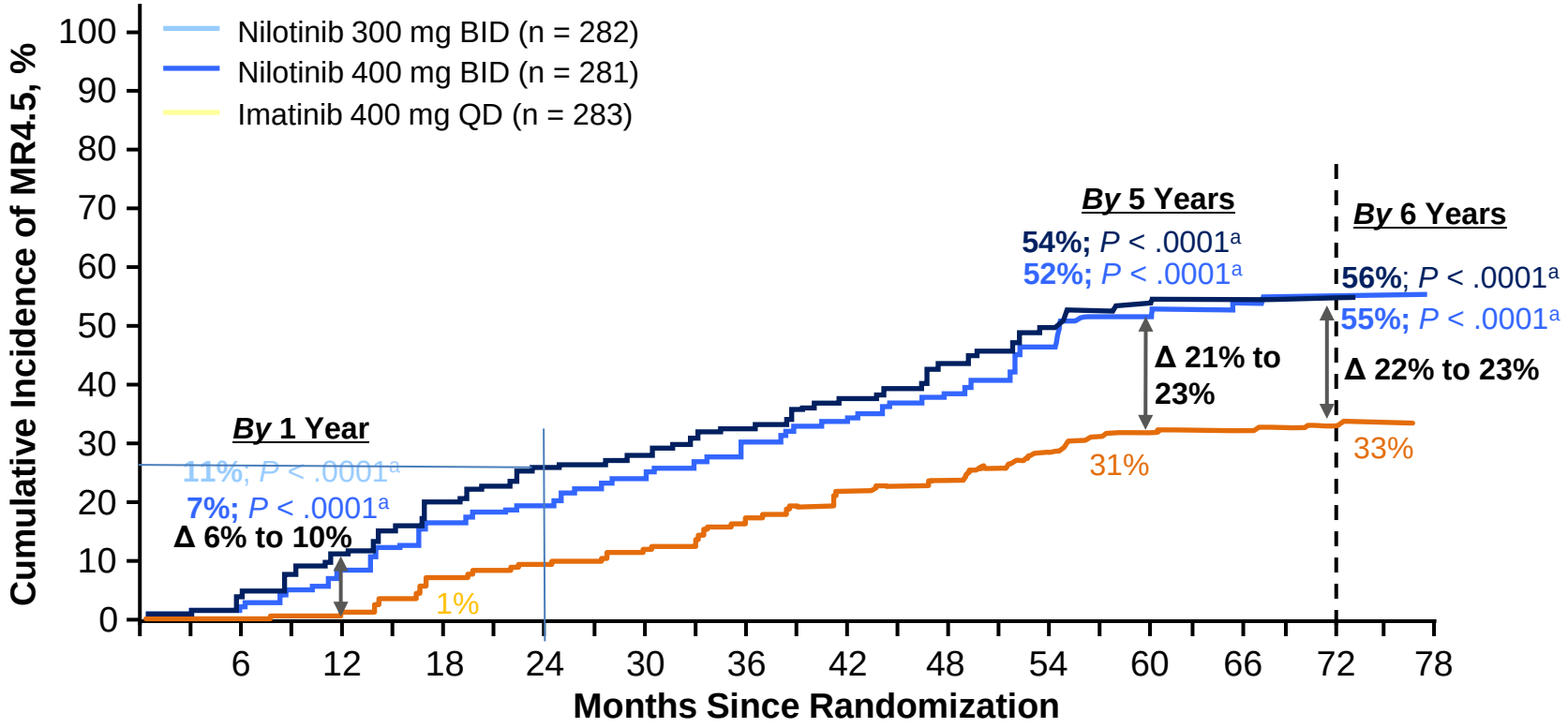
Dasatinib 1st line



Hocchaus JCO 2012

This product is not registered in Malaysia

Cumulative Incidence of MR4.5 in ENESTnd

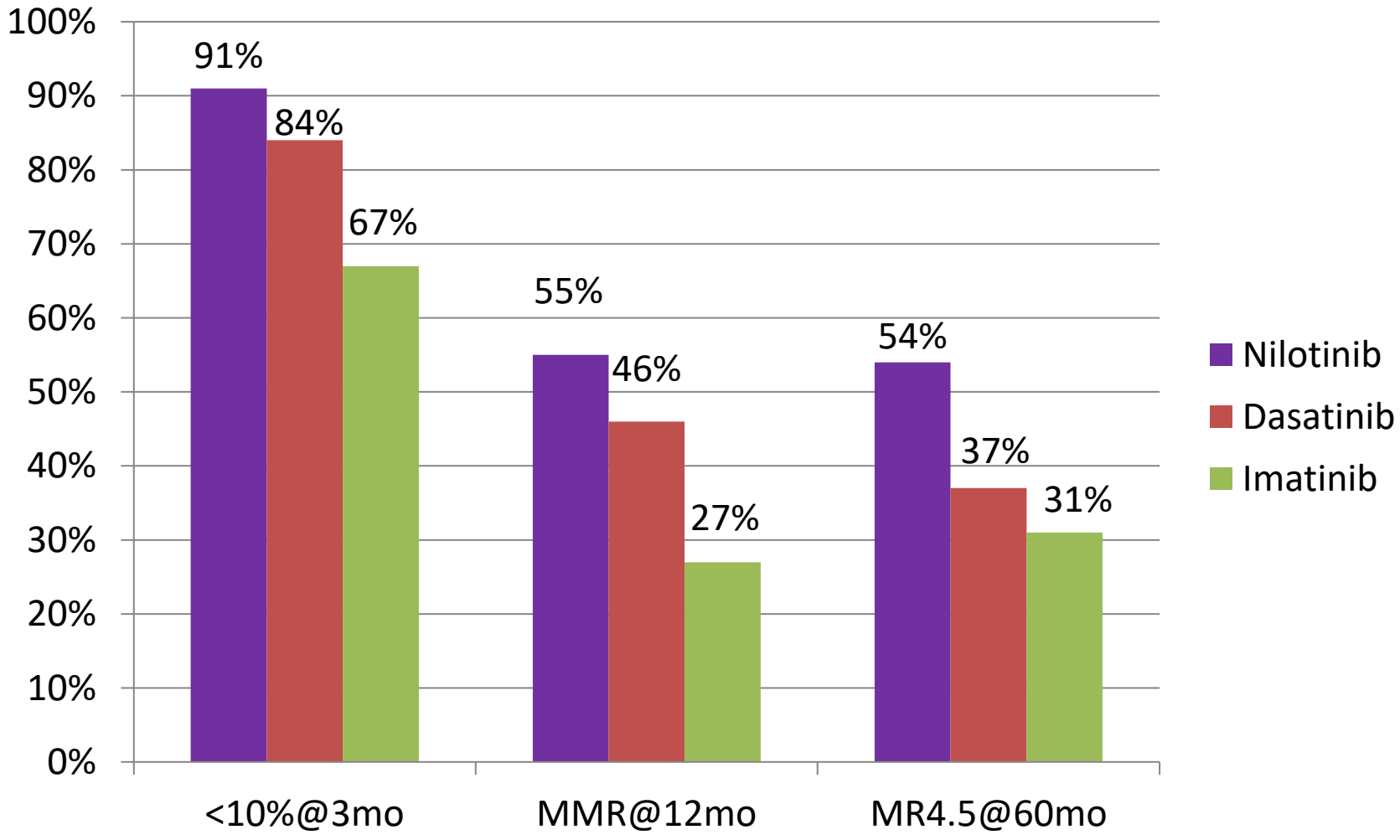


Treatment Arm	Kaplan-Meier Estimated Median Time to First MR4.5, months	Hazard Ratio vs Imatinib (95% Confidence Interval)	*P* value[a]
Nilotinib 300 mg BID	45.5	2.0387 (1.5807-2.6295)	< .0001
Nilotinib 400 mg BID	49.8	1.7770 (1.3780-2.2915)	< .0001
Imatinib 400 mg QD	61.1	–	–

[a] *P* values are nominal, were provided for descriptive purposes only, and were not adjusted for multiple comparisons.

Hughes TP, et al. *Haematologica*. 2015;100 [abstract P228].

Speed and depth of response
Indirect comparison



Adapted from: Larson RA, et al. Blood. 2014:[abstract 4541] and Cortes J, et al. Blood. 2014;124 [abstract 152].

TFR candidates whole CML population

- Imatinib 1st line
  - Only about 33% will reach MR^4
    - **2/3 CML patients who receive Imatinib 1st line will NOT be candidates for TFR**
- Nilotinib 1st line
  - ~56% reach MR^4
    - **>1/2 CML patients who receive Nilotinib 1st line will be candidates for TFR**

Saglio G, et al. N Engl J Med. 2010;
Kantarjian,et al, Blood 2012.

WHO BENEFITS FROM 2G TKI FIRST LINE?

PL

- 20 yr old statistics student
- PMH: femoral osteomyelytis following rugby injury
- Nov 2012: WBC $25x10^9/L$
  - BM reported as reactive local hospital
  - No cytogenetics collected
- Jan 2013: WBC 124
- BM: CML; b2a2 by PCR
- Starts Imatinib 400mg daily

Personal Data

PL

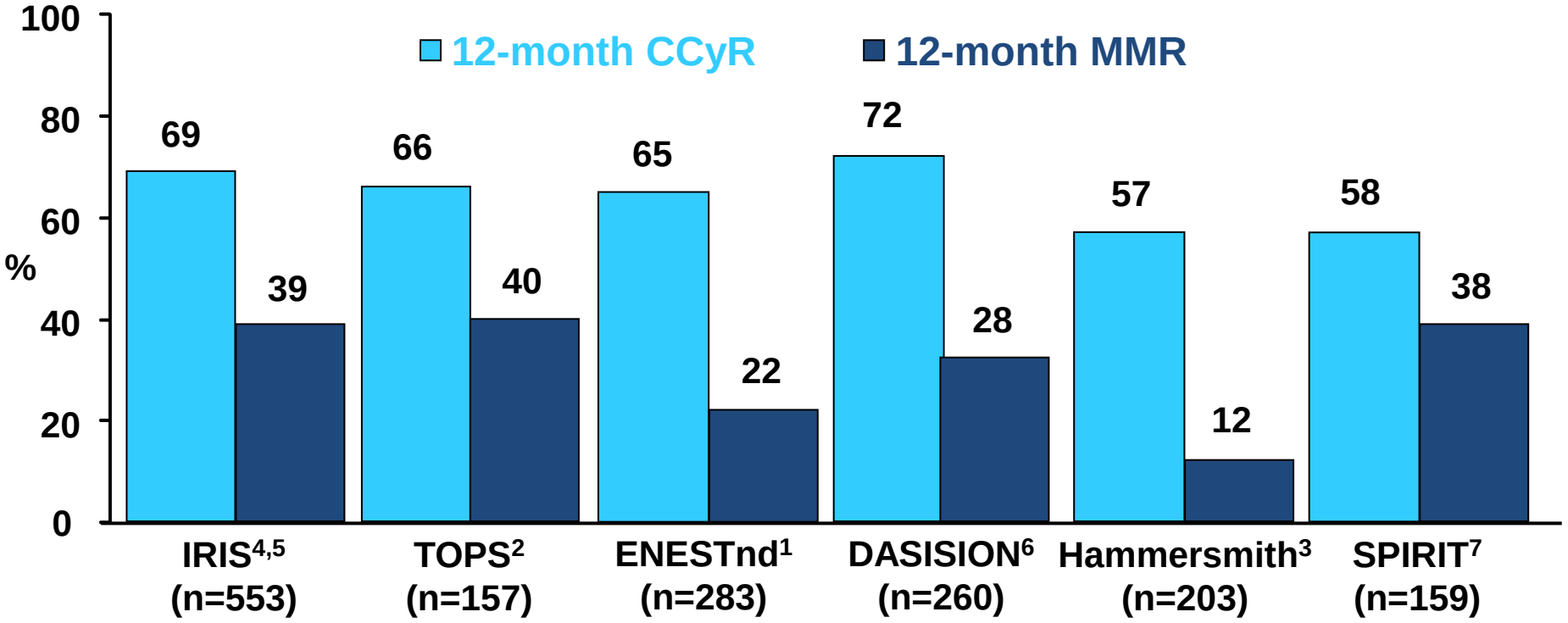
month	3	6	12
Cytogenetics (%Ph)	0%	0%	
qPCR (%BCR-ABL)	1,6%	2,2%	0,47%

Compliance?

Personal Data

Many patients on imatinib fail to achieve CCyR or MMR by 12 months

- With first-line imatinib 400 mg/day treatment of newly diagnosed CML-CP
  - 55–63% fail to achieve a CCyR by 6 months[1–3]
  - 28–43% fail to achieve a CCyR by 12 months[1–7]
  - 60–88% fail to achieve a MMR by 12 months[1–3,5–7]



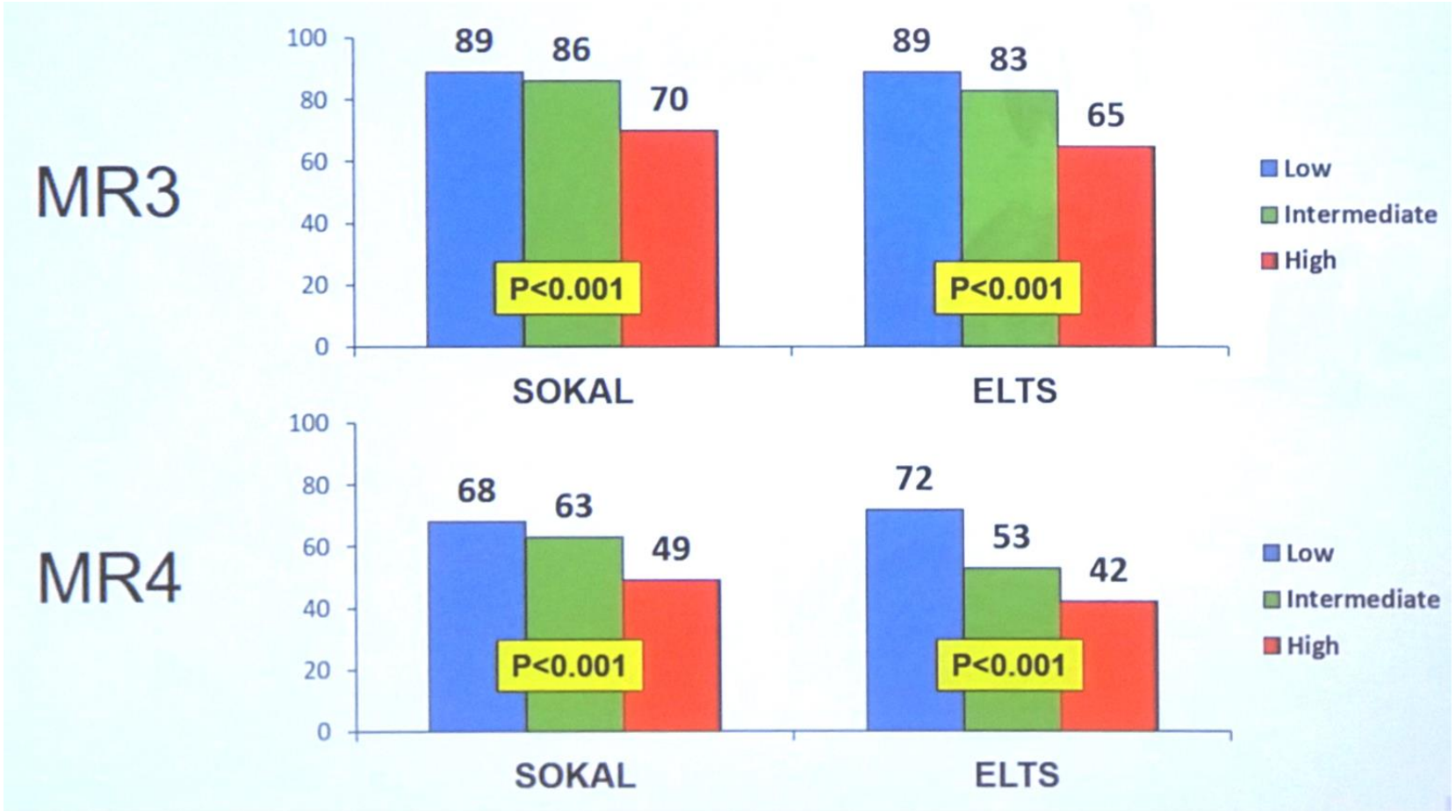
1. Saglio G, et al. N Engl J Med 2010;362:2251–9
2. Cortes JE, et al. J Clin Oncol 2010;28:424–30
3. de Lavallade H, et al. J Clin Oncol 2008;26:3358–63
4. Druker BJ, et al. N Engl J Med 2006;355:2408–17
5. Hughes T, et al. N Engl J Med 2003;349:1423–32
6. Kantarjian H, et al. N Engl J Med 2010;362:2260–70
7. Preudhomme C, et al. N Engl J Med 2010; In press

Age

Younger patients:

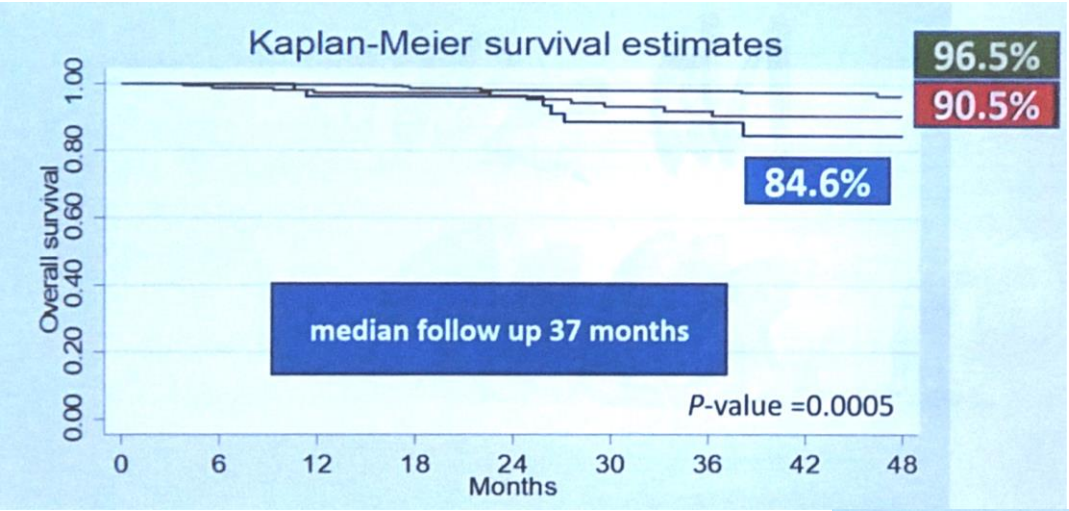
- Same response rates
- Higher WBC
- Larger spleens
- Longer time with CML
- Life plans - parenting

Risk group
ELTS

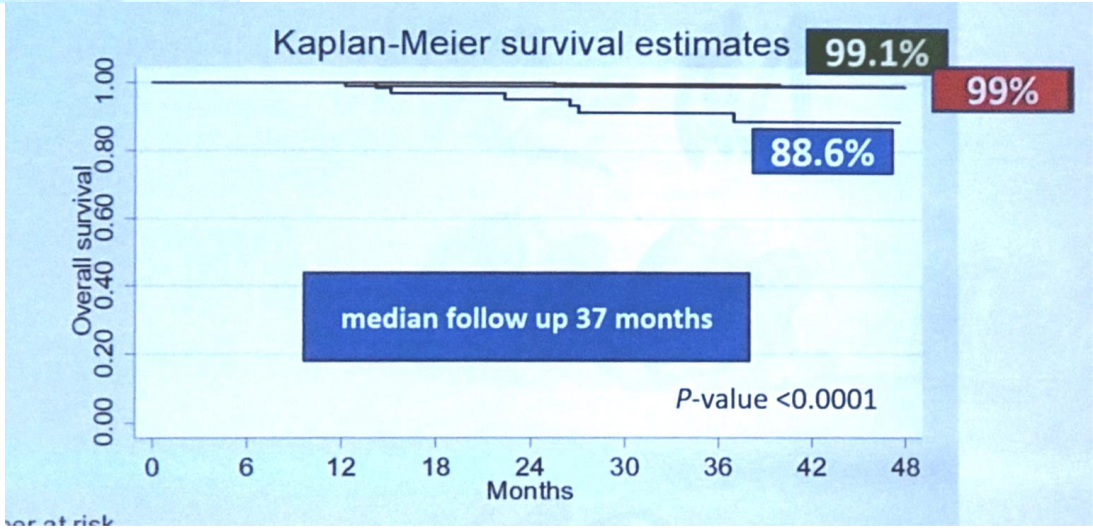


Castagnetti et al, ASH 2018

Risk group
ELTS



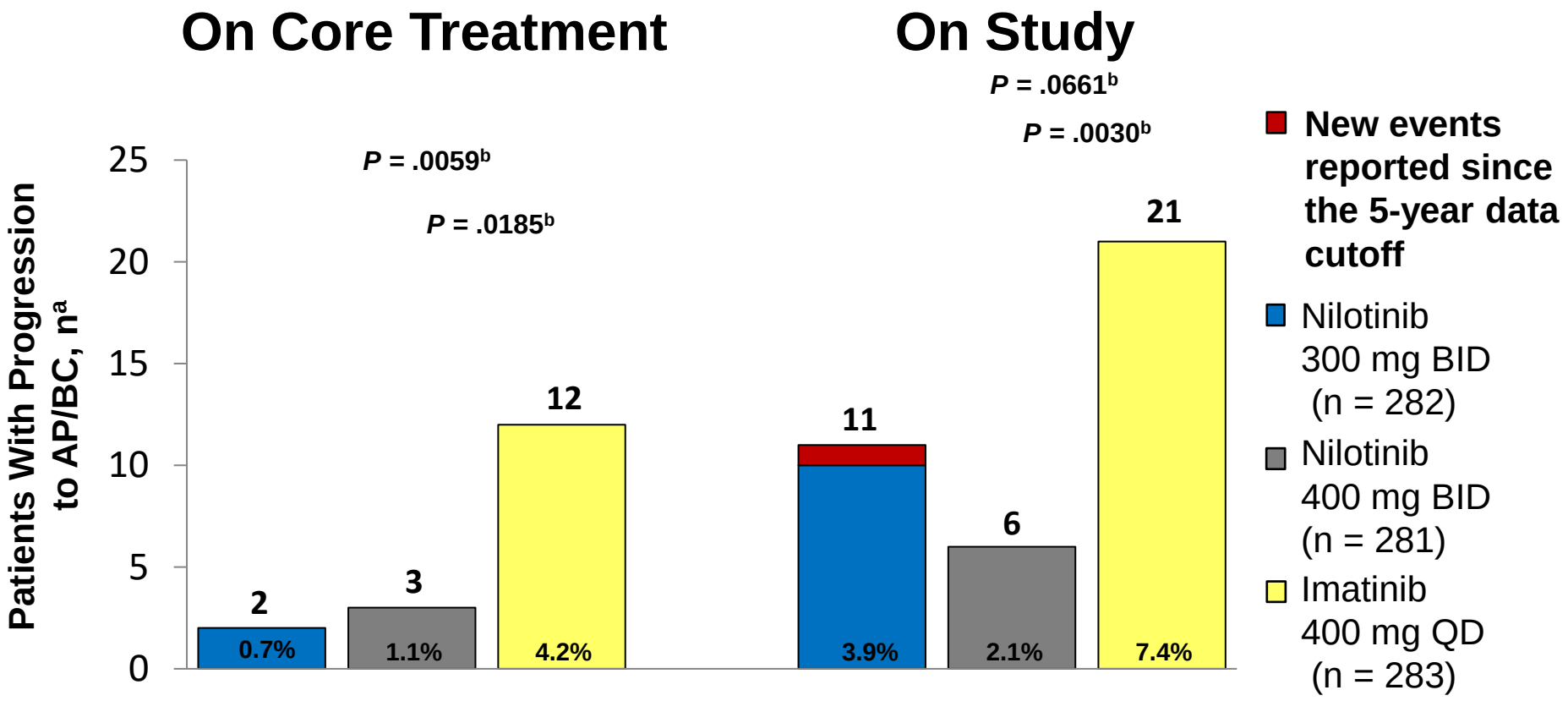
Imatinib



2G TKI

Saglio et al, ASH 2018

ENESTnd: Progression to AP/BC

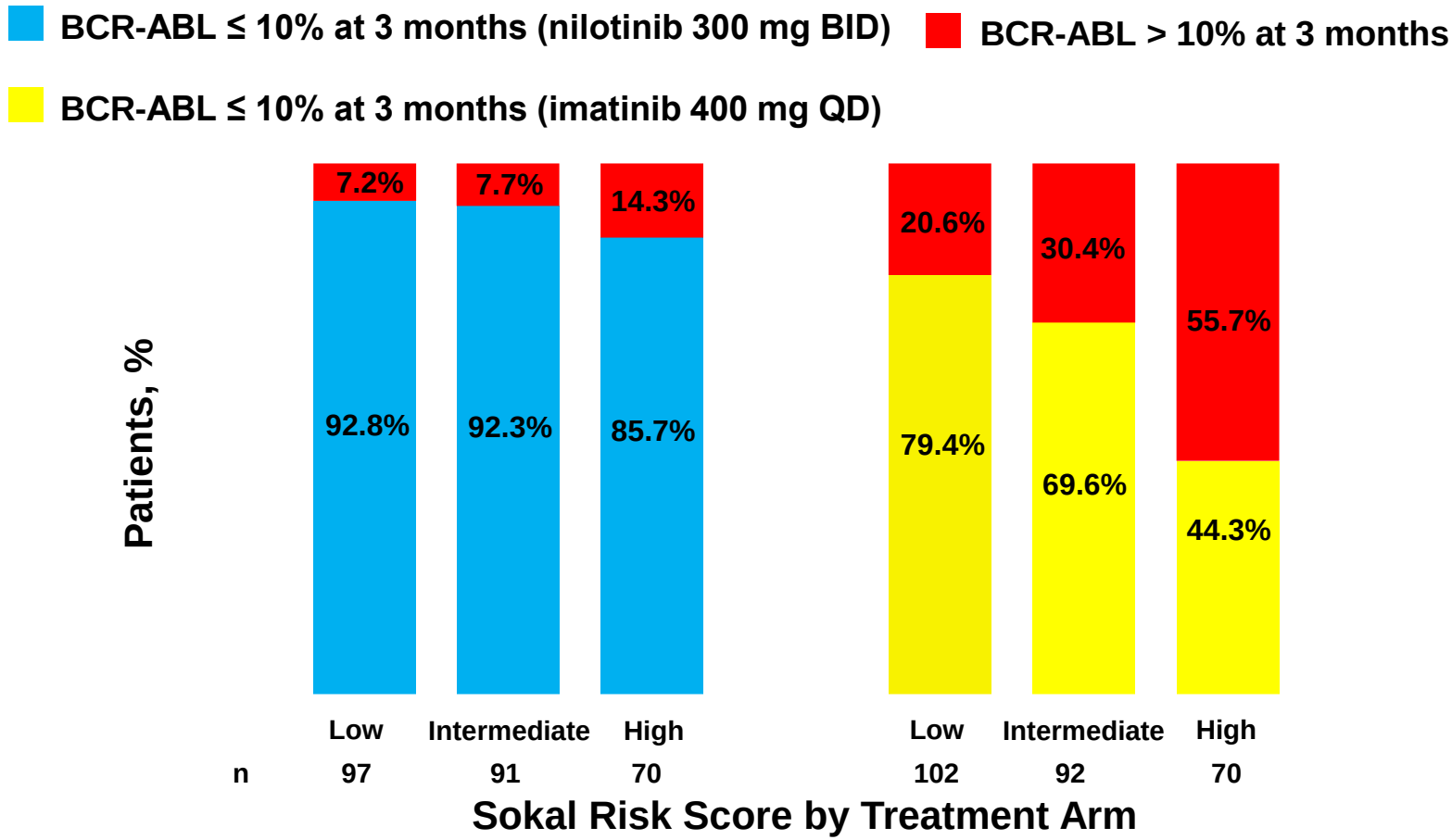


- Since the 5-year data cutoff, 1 new progression to AP/BC on study was reported in the nilotinib 300 mg BID arm (**Figure 4**); this patient had a low Sokal risk score at baseline, achieved *BCR-ABL*^{IS} ≤ 10% at 3 months, and discontinued core treatment due to neutropenia ≈ 5 years before progression to AP/BC was reported

[a]Defined as progression to AP/BC or death due to advanced CML. [b]*P* values are nominal.

Larson RA, et al. Blood. 2014:[abstract 4541].

BCR-ABL levels at 3 months according to Sokal risk score at baseline[a]

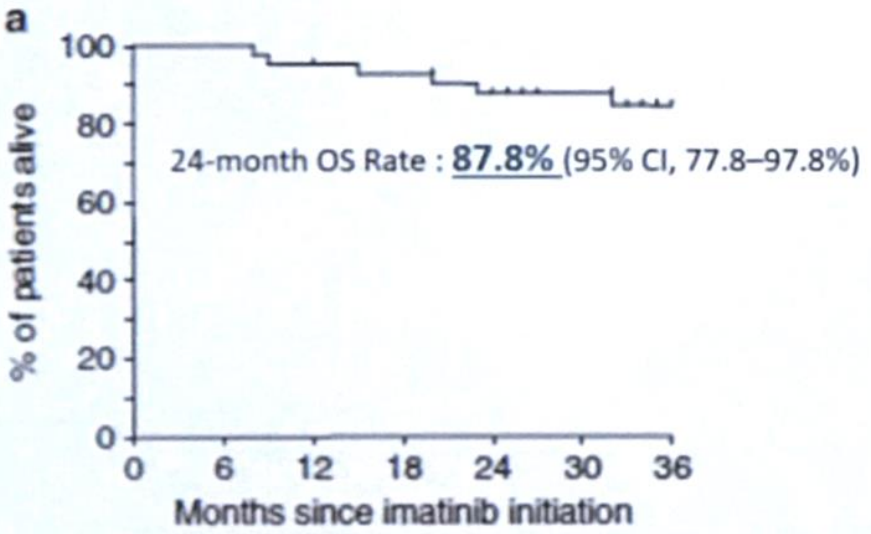


- The majority of patients in the nilotinib arm achieved BCR-ABL ≤ 10% at 3 months, regardless of Sokal score
- At 3 months, fewer patients achieved BCR-ABL ≤ 10% at 3 months in the imatinib arm (vs nilotinib) across all Sokal risk groups, and more than half of imatinib-treated patients with high Sokal risk had BCR-ABL > 10%

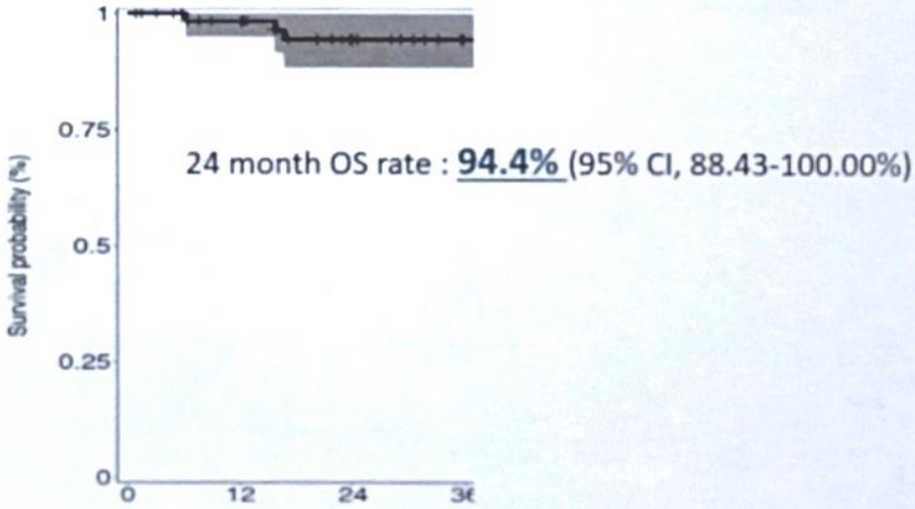
[a]Calculated from total number of patients with evaluable PCR assessments at 3 months.

Saglio G, et al. J Clin Oncol. 2013;31(s) [abstract 7054].

Risk group
accelerated phase patients
N=66



Rea et al., Leukemia 2012



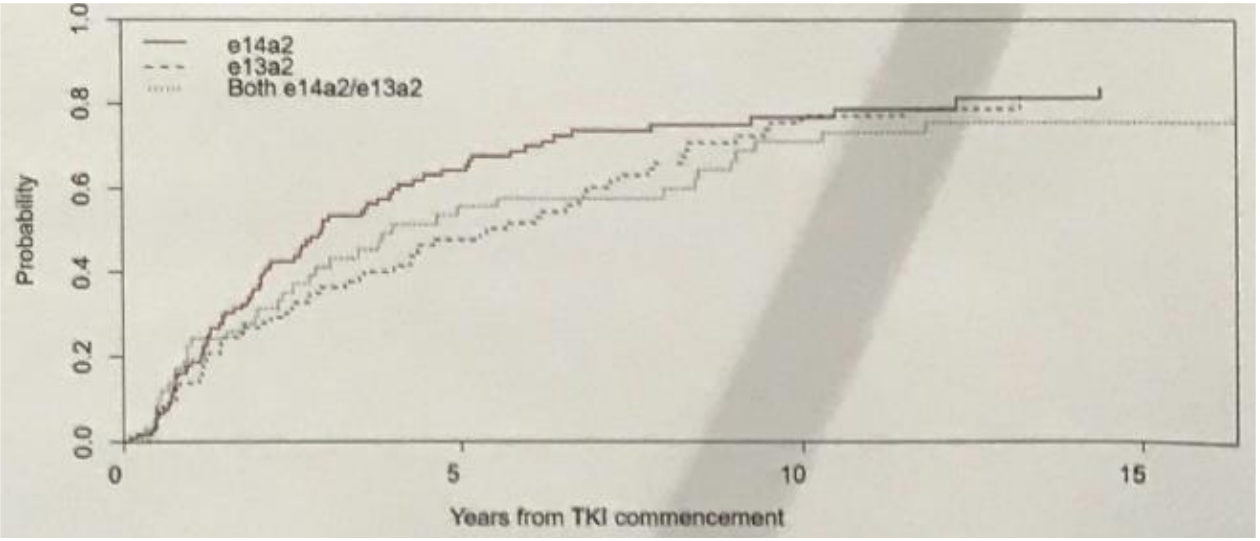
Balsat et al.

Balsat et al, ASH 2018

e14a2 Transcript type and response

Study	No	CCyR	MMR	DMR	EFS	PFS	OS
Lucas 2009	71	Y			N		N
Castagnetti 2012	201	N	N		N	N	N
Hanfstein 2014	1105	N	Y	Y		N	N
Dmytrenko 2015	508		Y	Y	Y	N	N
Lin 2016	166		N				
Jain 2016	481	N	Y	Y	N	Y	N
Marum 2017	523		N	Y	N	N	N
Castagnetti 2017	559	N	Y	Y	Y	Y	Y

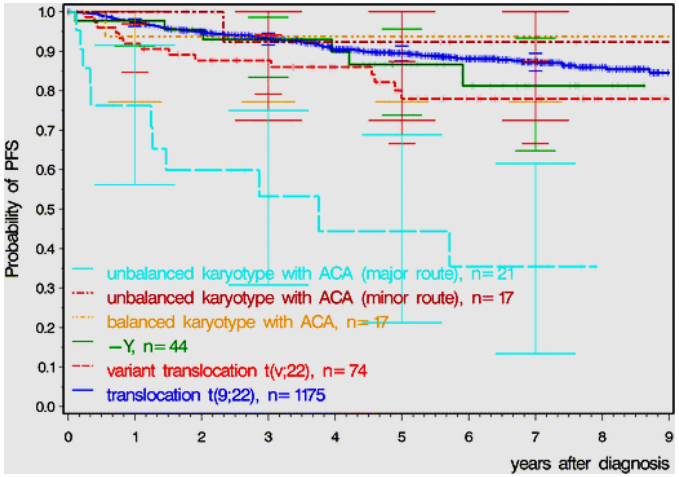
J Apperley, ASH 2018



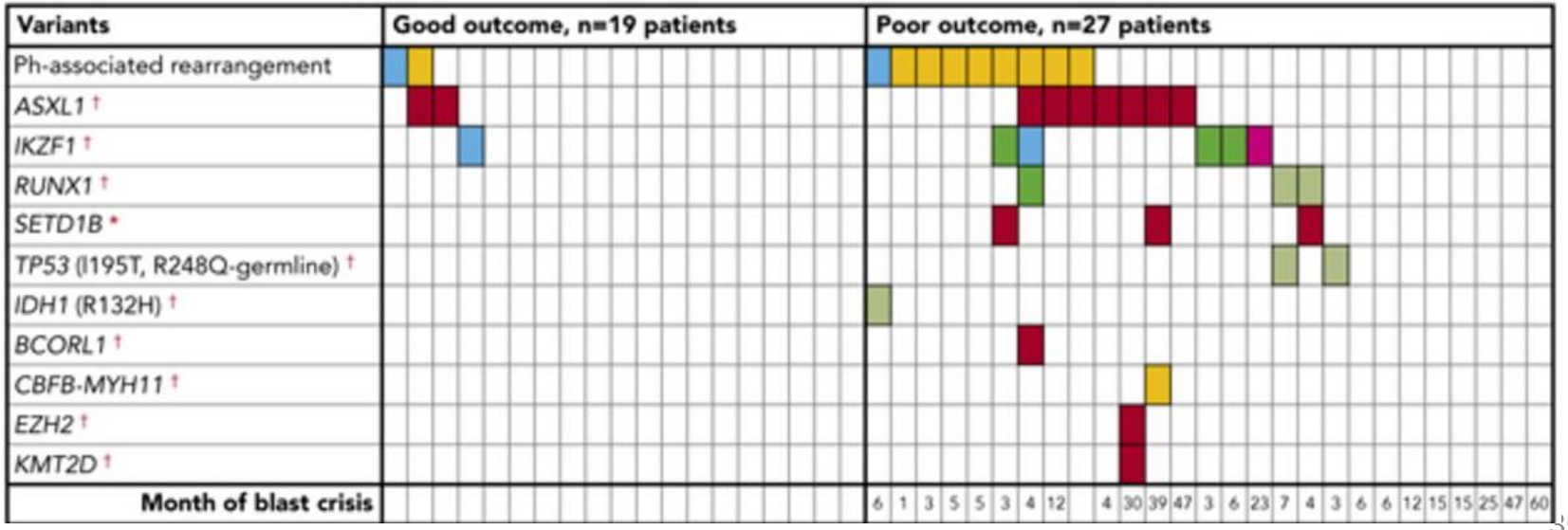
Shanmuganathan, ASH 2018

Additional genetic abnormalities

Cytogenetic

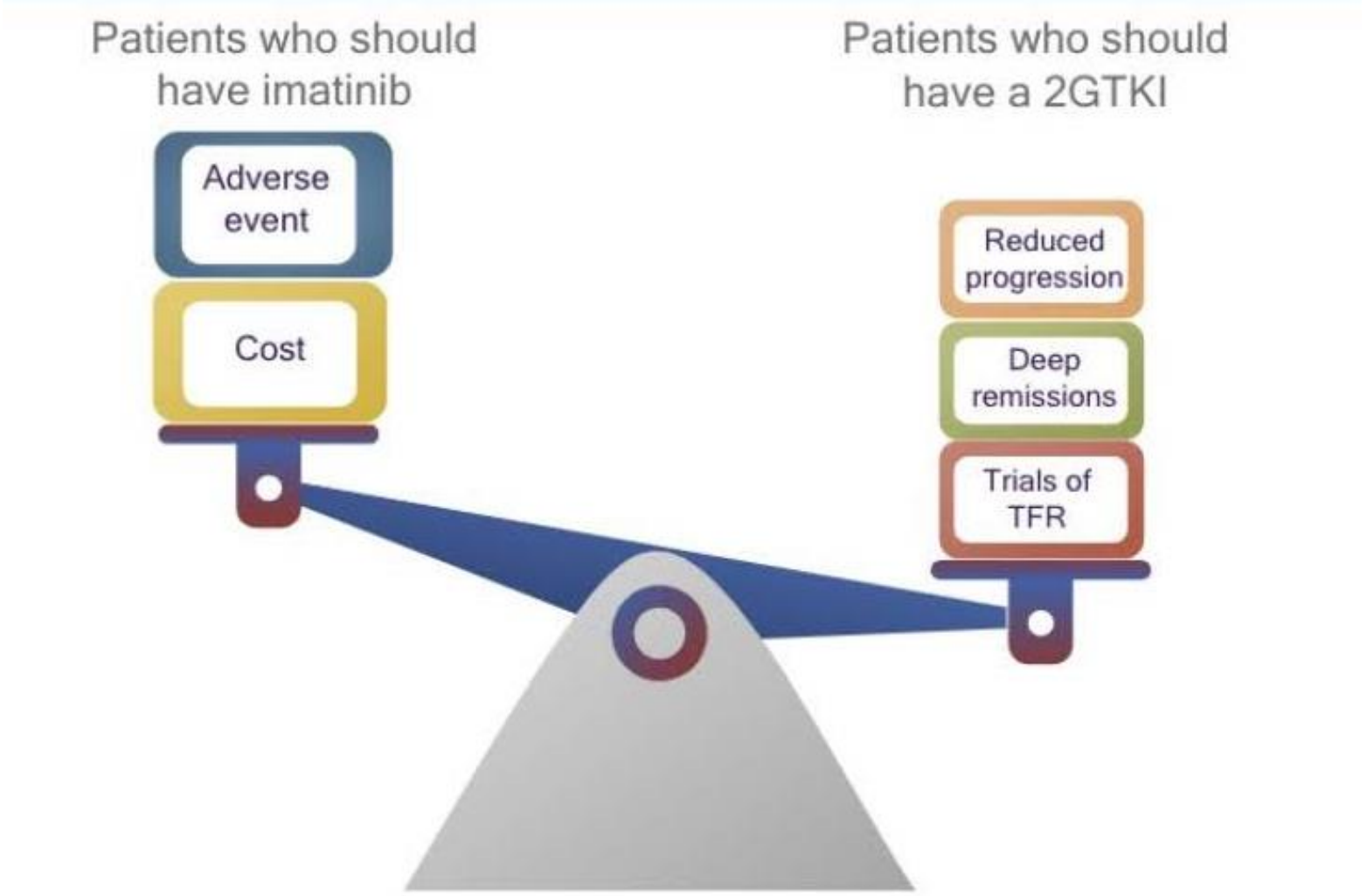


Fabarius et al Ann Hemat 2015



Banford et al Blood 2018

Strike a balance



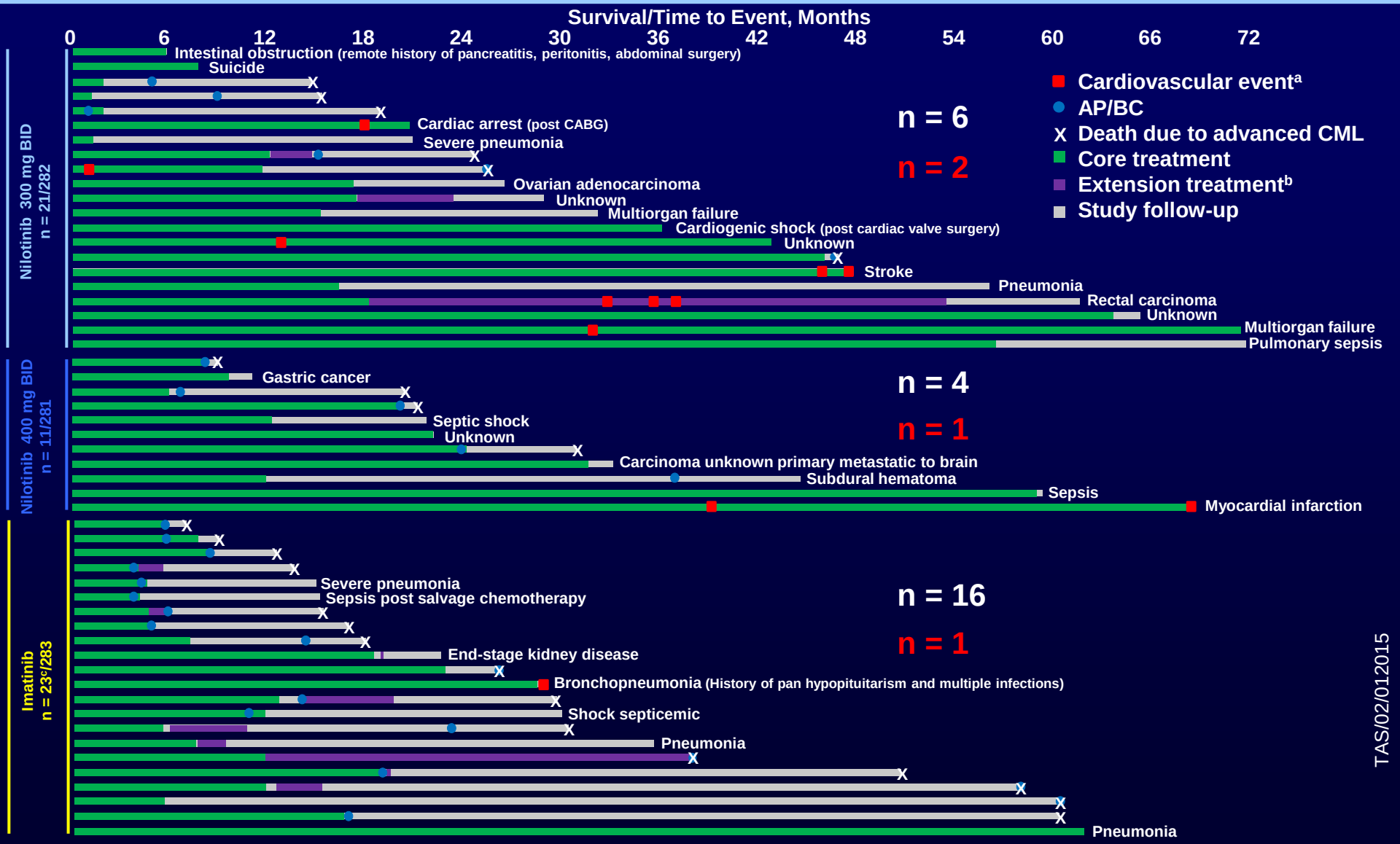
J Apperley, ASH 2018

Toxicity

- Nilotinib 1st line has greater efficacy vs imatinib
- Does treatment-related toxicity outweigh benefit?

Larson RA, et al. *Blood*. 2014:[abstract 4541].

ENESTnd Deaths by Treatment Arm



TAS/02/012015

CABG, coronary artery bypass grafting. [a] Presence/absence of cardiovascular events was collected during treatment (core or extension) only. [b] Patients who discontinued core treatment and entered the ENESTnd extension study were followed for progression, survival, and safety per the extension study protocol. [c] One patient randomized to imatinib who died prior to receiving treatment is not shown.

PL

month	3	6	12
Cytogenetics (%Ph)	0%	0%	
qPCR (%BCR-ABL)	1,6%	2,2%	0,47%

Compliance?

Will we ever be able to offer TFR???

Personal Data

PL

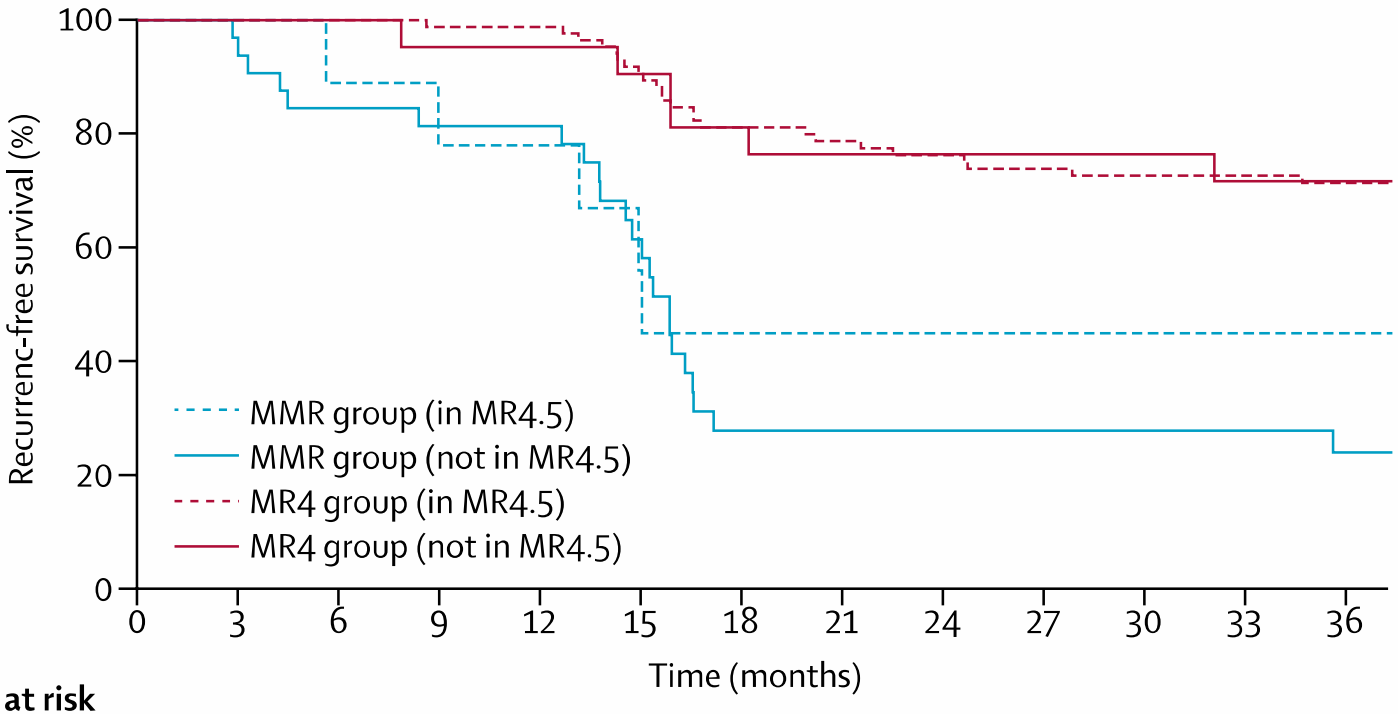
- starts Nilotinib 300mg bid

Month	0	3	6	9	12	15
% BCR-ABL	0,1	0,0128	0,0013	0,0026	0,0081	0,000

- Stopped after month 24
- In $MR^{4.5}$ at month 48

Personal Data

DESTINY: 12 months descalation before stop



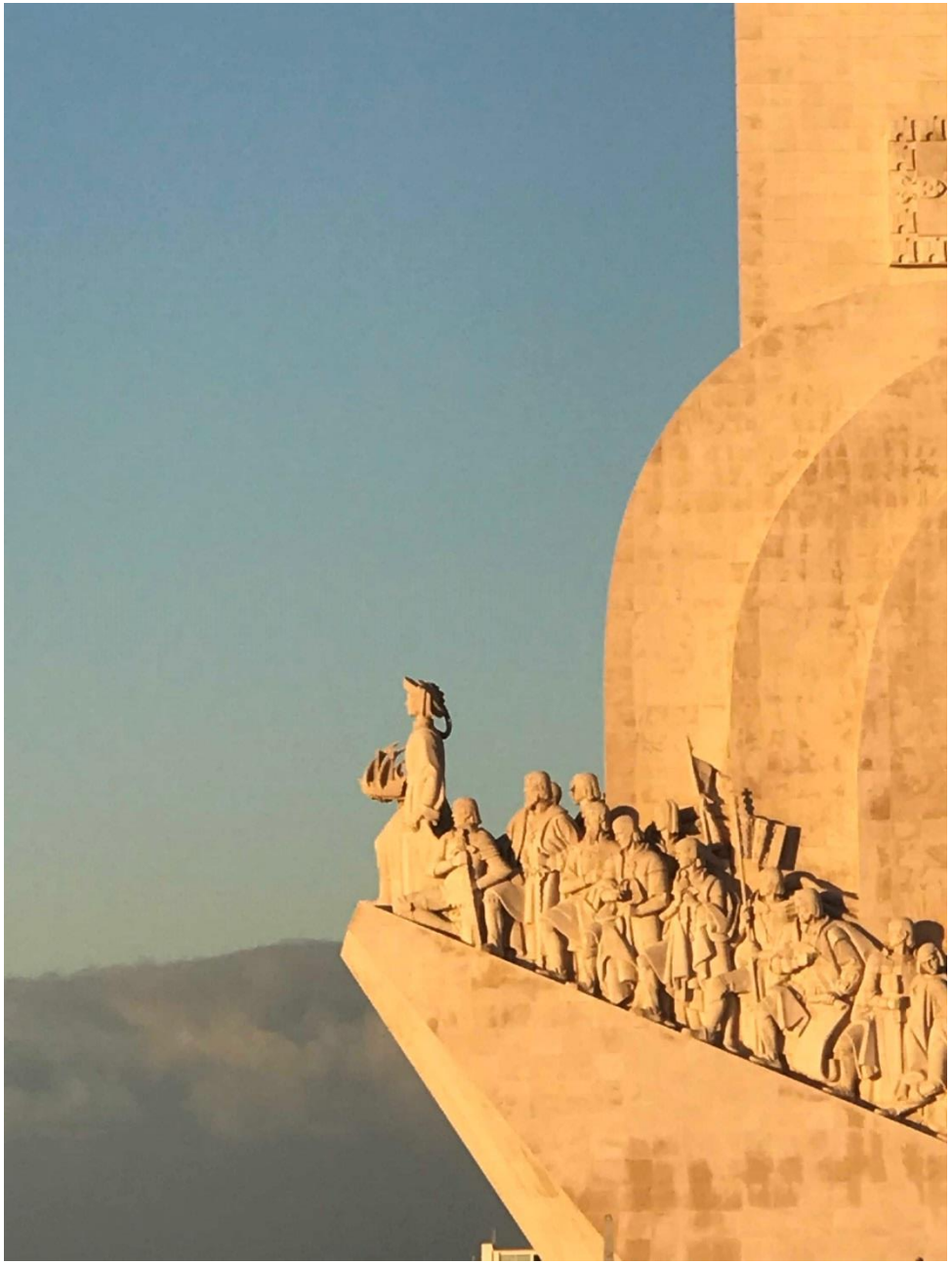
Number at risk

MMR group (in MR4.5)	9	9	8	7	7	5	4	4	4	4	4	4	4
MMR group (not in MR4.5)	32	30	27	26	26	18	7	7	7	7	7	7	6
MR4 group (in MR4.5)	87	87	85	84	84	76	66	64	62	60	59	59	58
MR4 group (not in MR4.5)	21	21	21	20	20	19	17	16	16	16	16	15	15

Clark et al, Lancet Haematol, 2019

The best arguments for using second-generation TKI in first line in CML

- Normal lifespan of CML patients
  - TFR realistic target
  - 2G TKI increase probability of TFR
- Poor prognostic factos
  - Speed of response essential
  - Reduce progression rates



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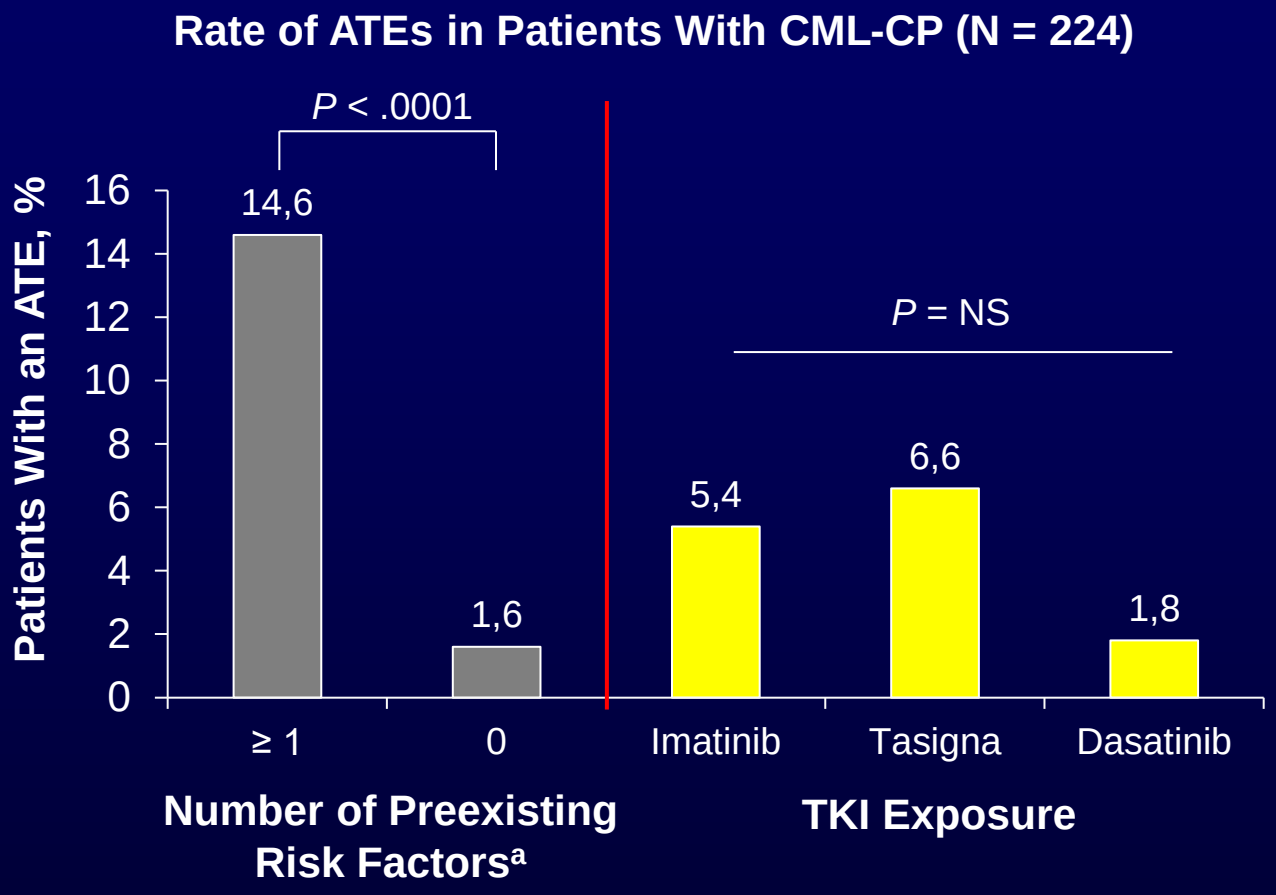
Hekmatjou et al: CVEs by Risk Factors and Treatment

Data from Weill Cornell/New York Presbyterian Hospital



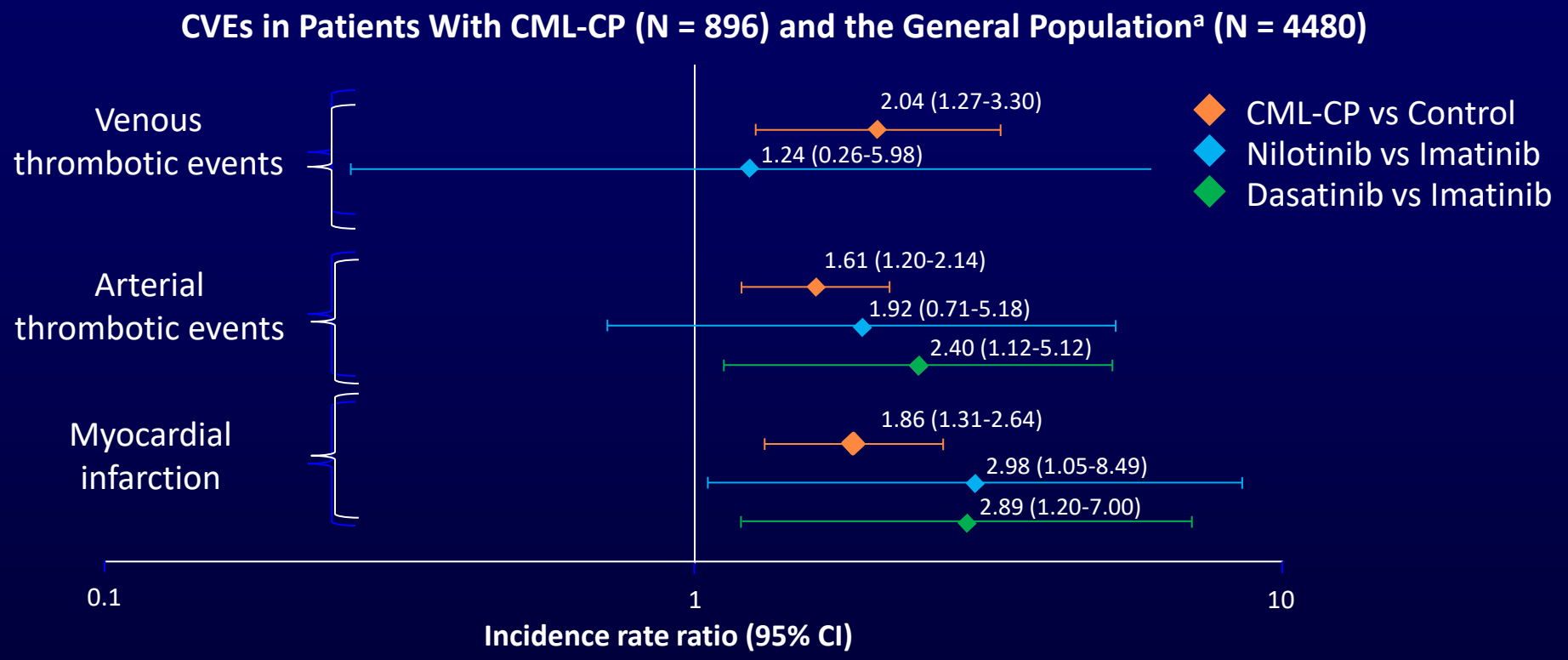
- ATEs were uncommon in patients without prior risk factors and occurred at similar frequencies in patients exposed to Tasigna or imatinib

AT, arterial thrombosis (defined as ischemic heart disease, stroke, and peripheral artery disease); ATE, arterial thrombotic event; NS, not significant.

[a] Includes prior AT, diabetes, hyperlipidemia, hypertension, and smoking.

Hekmatjou H, et al. *Blood.* 2014; 124 [abstract 1811].

Risk of CVEs among patients with CML: data from the Nationwide Swedish CML Register

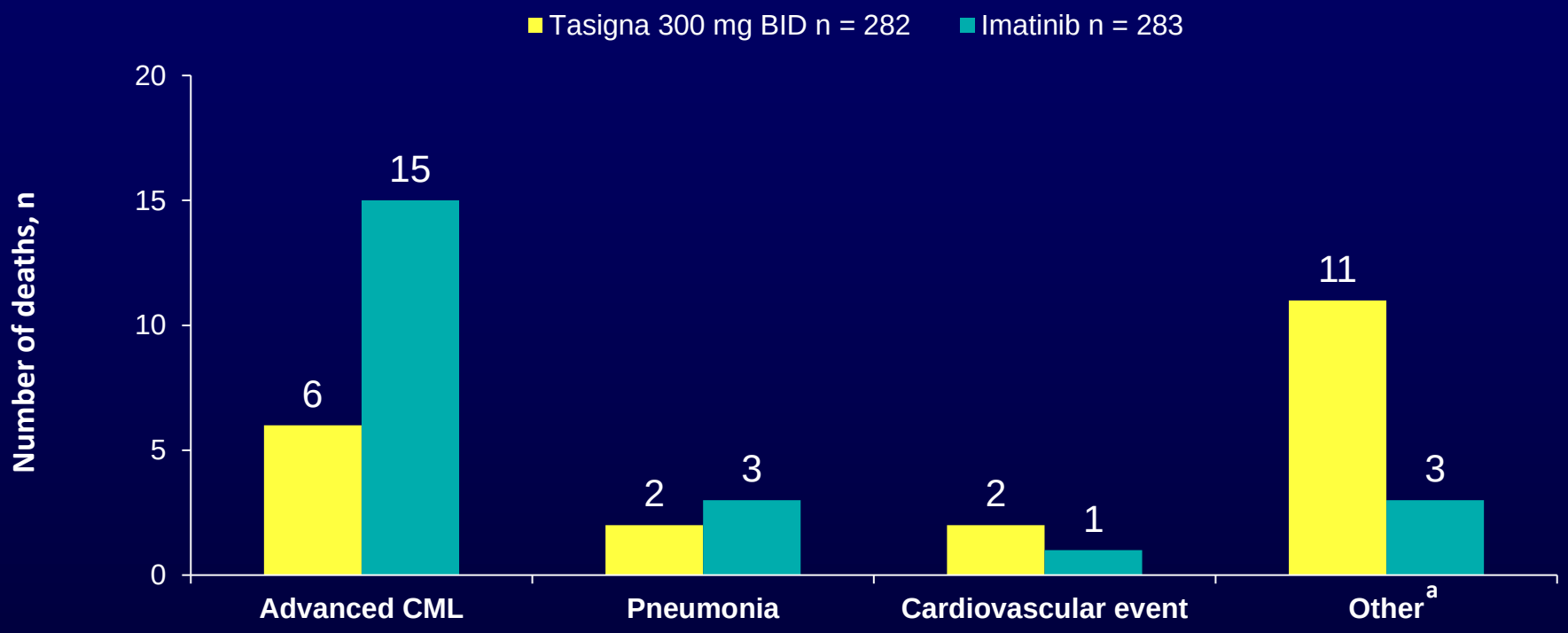


- CVEs were more common among patients with CML vs the general population
- Patients on nilotinib or dasatinib had an increased risk of myocardial infarction vs imatinib-treated patients

[a]An age- and sex-matched control cohort was used.

Dahlén *et al*, Blood 2014;124 [abstract 3134]

Most Common Cause of Death in ENESTnd was Advanced CML and other causes (Tasigna 300 mg BID and imatinib arms)

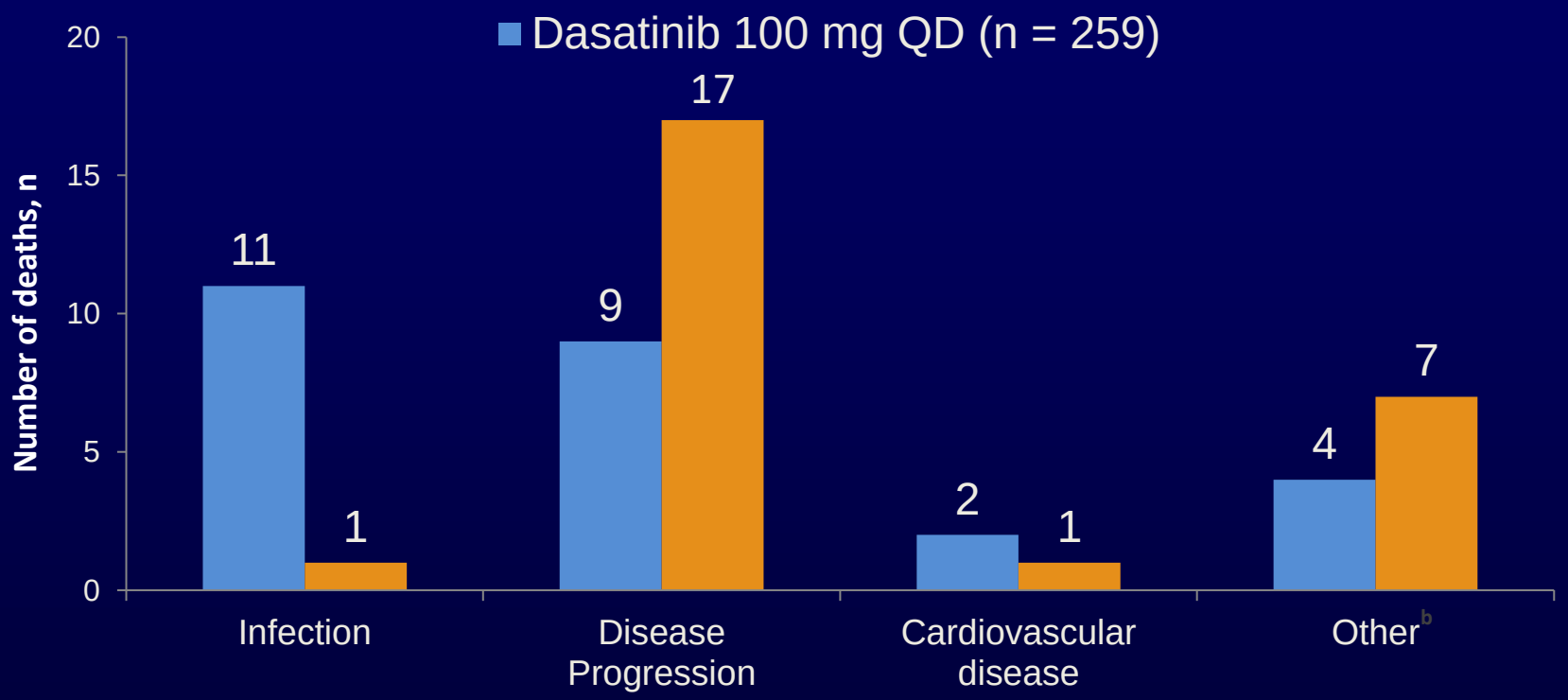


[a] Cardiogenic shock (post cardiac valve surgery), intestinal obstruction, pulmonary sepsis and suicide (1 each, Tasigna); multiorgan failure and other malignancy (2 each, Tasigna); 3 unknown (Tasigna); sepsis (post chemo), kidney disease and shock septicemic (1 each imatinib).

Larson RA, et al. *Blood*. 2014;124(21) [abstract 4541].

Most Common Cause of Death in DASISION was Disease Progression disease progression and infection

(Both treatment arms)[a]



[a] On study treatment and in follow-up after discontinuation of randomized treatment.

[b] Other malignancy, septic shock and cardiac failure, multi-organ failure, and whole body swelling (1 each dasatinib); stem cell transplantation complications and unknown (2 each imatinib); severe chest pain, clinical deterioration and decrease in performance status, and fatal bleeding (1 each imatinib).

Cortes J, et al. *Blood*. 2014;124(21) [abstract 152].

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