CML HORIZONS
HYBRID MEETING 2023

CML ADVOCACY - LEARN, SHARE, GROW
21TH INTERNATIONAL CONFERENCE FOR ORGANISATIONS REPRESENTING PATIENTS WITH CML

CML ADVOCATES NETWORK

Berlin, Germany
03-05 Nov 2023

What is the future of CML treatment in LMICs?

Issues and possible solutions

India as an example

Dr. Hari Menon. MD DM
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Bangalore

Oncology treatment in LMIC

- The field of oncology research and treatment is going through exciting time, with innovative therapies seeing success in improving survival.
- However in parallel the cancer divide is larger than ever, with 95% of the world resources for cancer being available to a small proportion of the world's population.
- The treatment of Chronic Myeloid leukemia is seen as a a great example of the success of targeted and personalized therapies
- The access strategies identified in treatment of CML as a disease has shown a way to improve access to patients who would otherwise not have been treated effectively.
- The increasing availability of generic formulations have also significantly contributed to narrowing this divide.

India (resource limited countries): Perspectives & Problems

- 1.43 billion people (estimated 2022)
- 15% of the world's population
- Most populous country – overtaken China this year!
- Population increasing at the rate of 1.2 % (earlier 1.7%) annually!
- Rapidly aging population – presently 40% younger than 15 yrs
- Senior citizens expected to increase by 274%
  - India will have 20% of the world's senior citizens by 2040.
- Loosely structured social system of medicine
- Less than 30% have access to medical insurance

CML – Annual Incidence

CML is the most common adult leukemia in India and possibly, in the other LMICs.

Source	Country	Area	Annual Incidence ($100{,}000^{-1}$)	Type
SEER database[44]	United States	Northern America	1.75	ASR
Tumor registry[43]	Germany	Europe	0.79	CR
Tumor registry[42]	Scotland	Europe	0.64	CR
Tumor registry[41]	Australia	South Australia	1.5	ASR
Tumor registries[39]	China	Asia	0.4-0.6	CR
Government registry[39]	Singapore	Asia	0.7	CR
Government registries[39]	South Korea	Asia	0.8	CR
University hospitals[39]	Thailand	Asia	0.50	CR
Population-based registry[36]	India	India (Mumbai)	0.80*	ASR

Abbreviations: ASR, age standardized rate; CR, crude incidence rate.

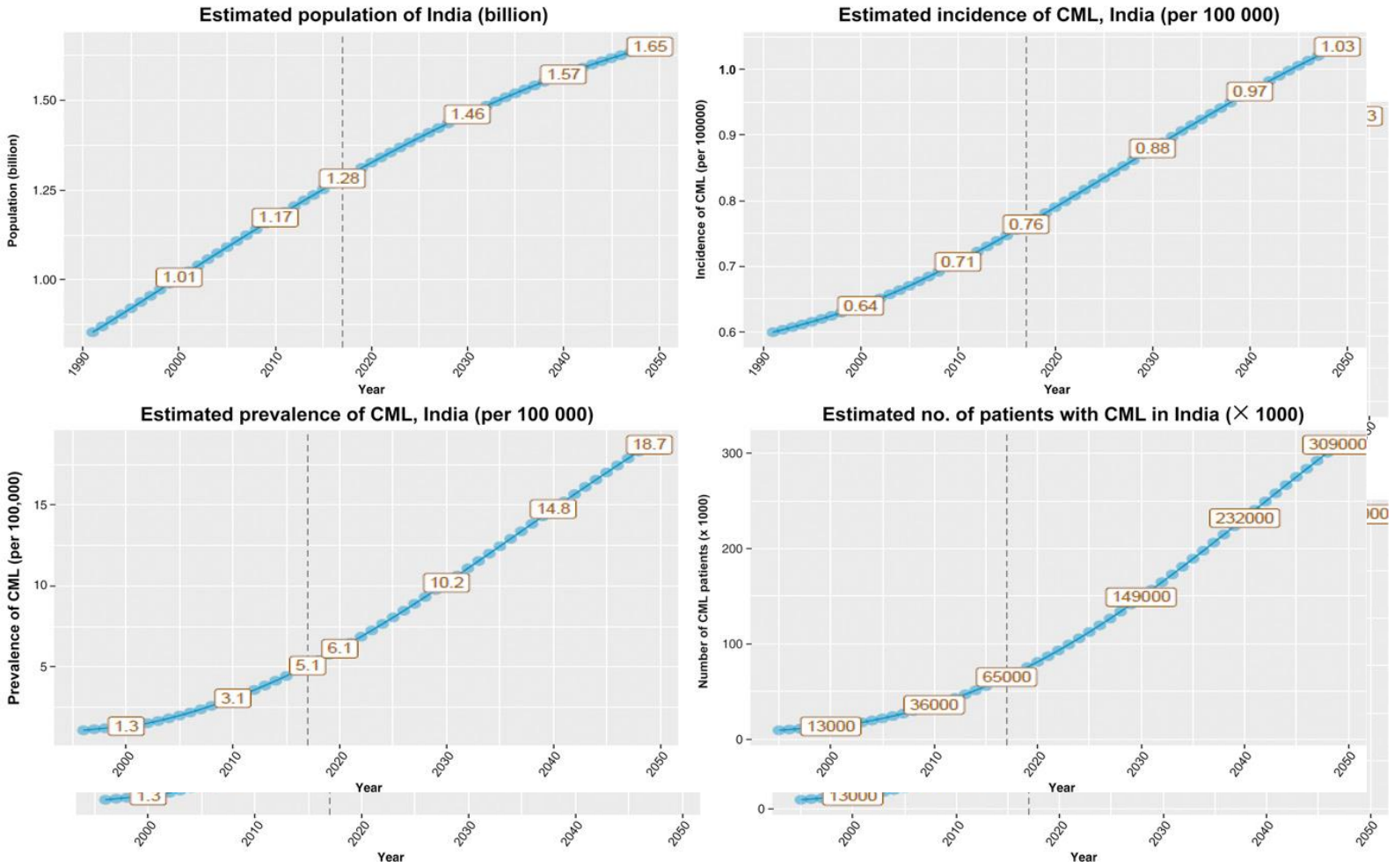
*Age group, 30 to 54 years.

CML incidence - various Indian cancer registries

0.8 to 2.2 per 100 000 population for men

0.6 to 1.6 per 100 000 population for women.

The burden of CML in India / projections



Concerns :

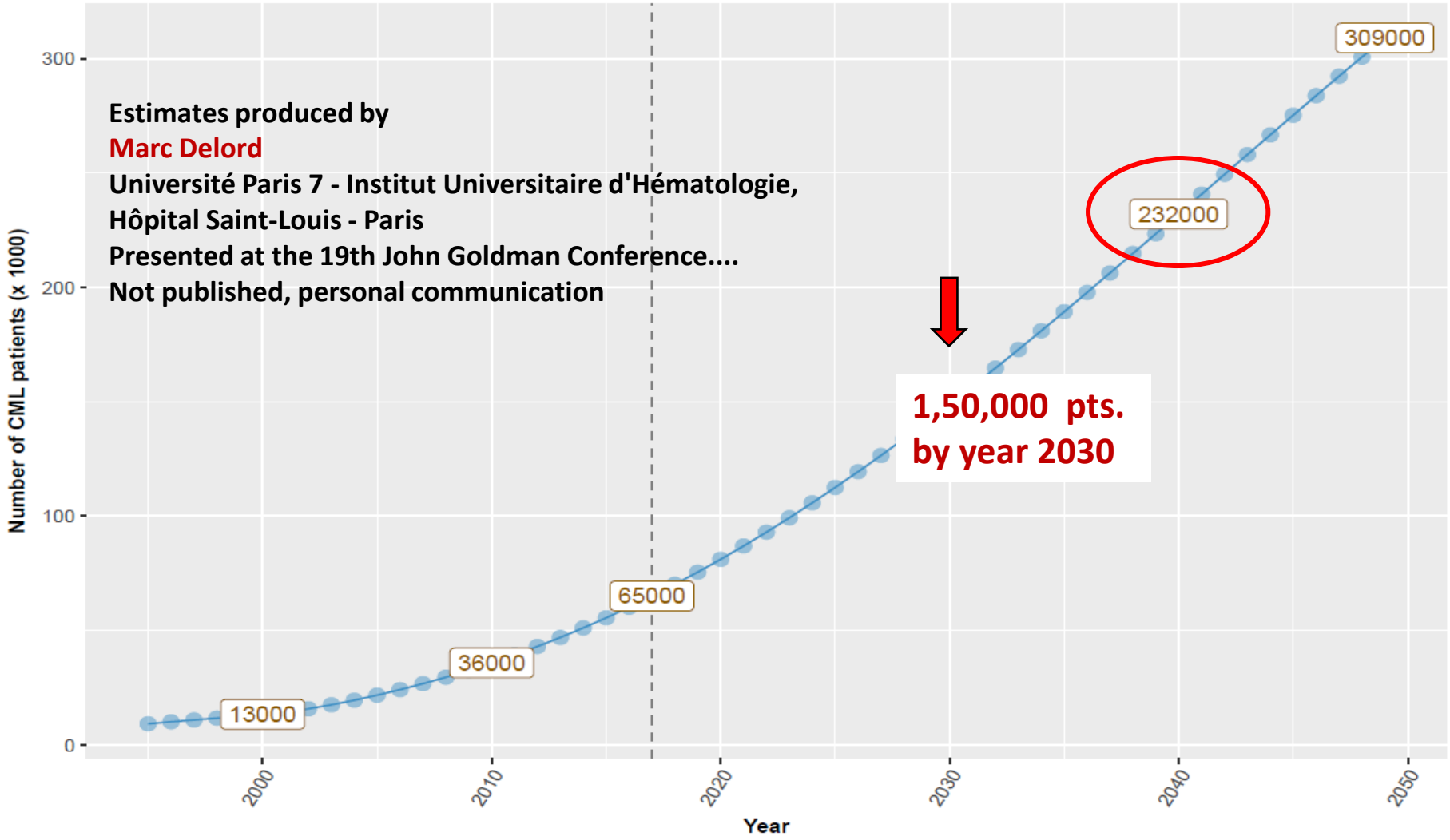
The disease is seen in a younger population, (median age at onset being between 30 to 40yrs).

More than half of the patients present with intermediate and high Sokal

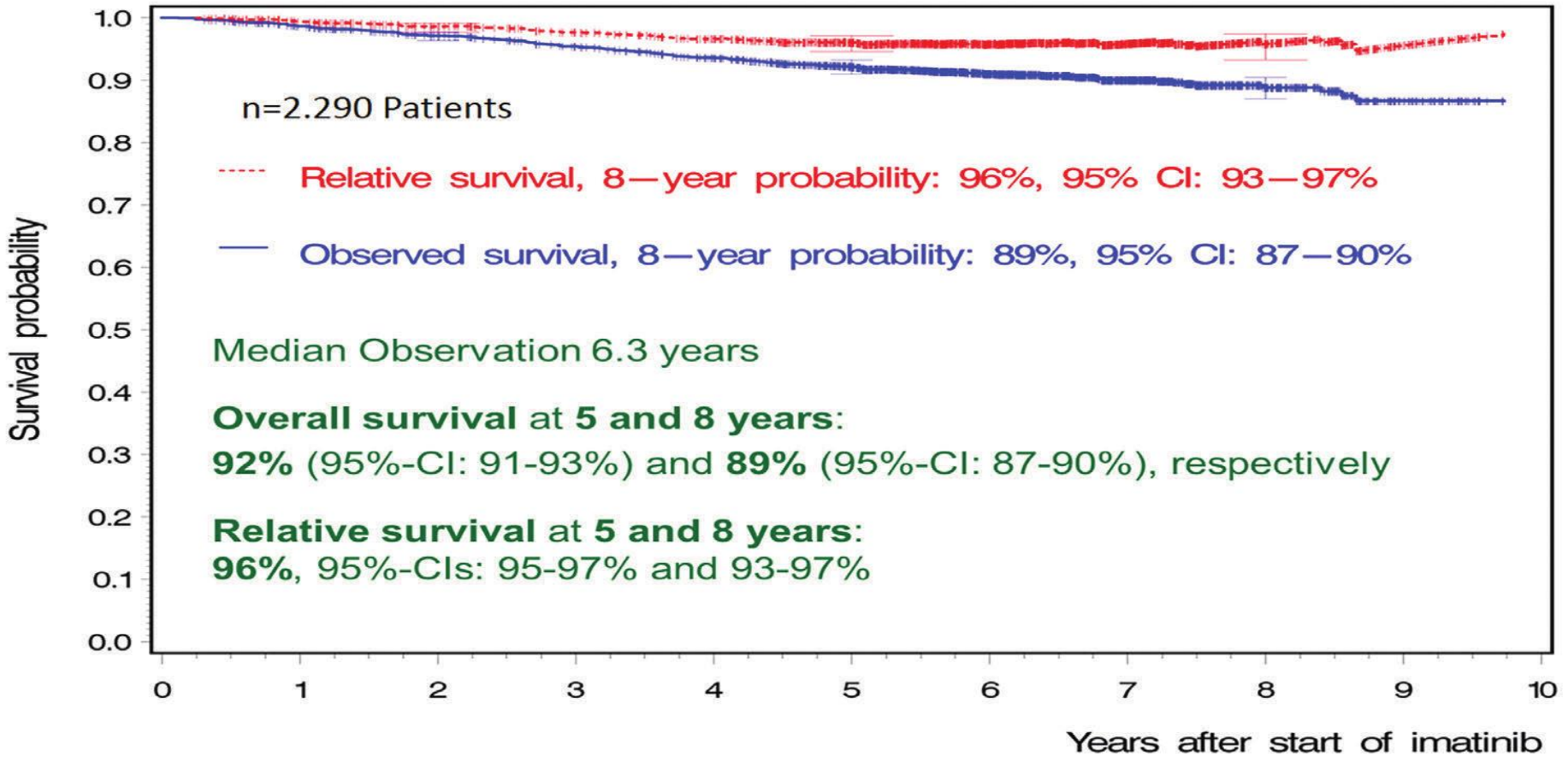
High and European Treatment and Outcomes Score (EUTOS) score.

Ref: Marc Delord, Universite´Paris, Institut Universitaired' He´matologie, Ho^pitalSaint-Louis,Paris,France. Malhotra et al -Haematology 2019

Prevalence of CML in India

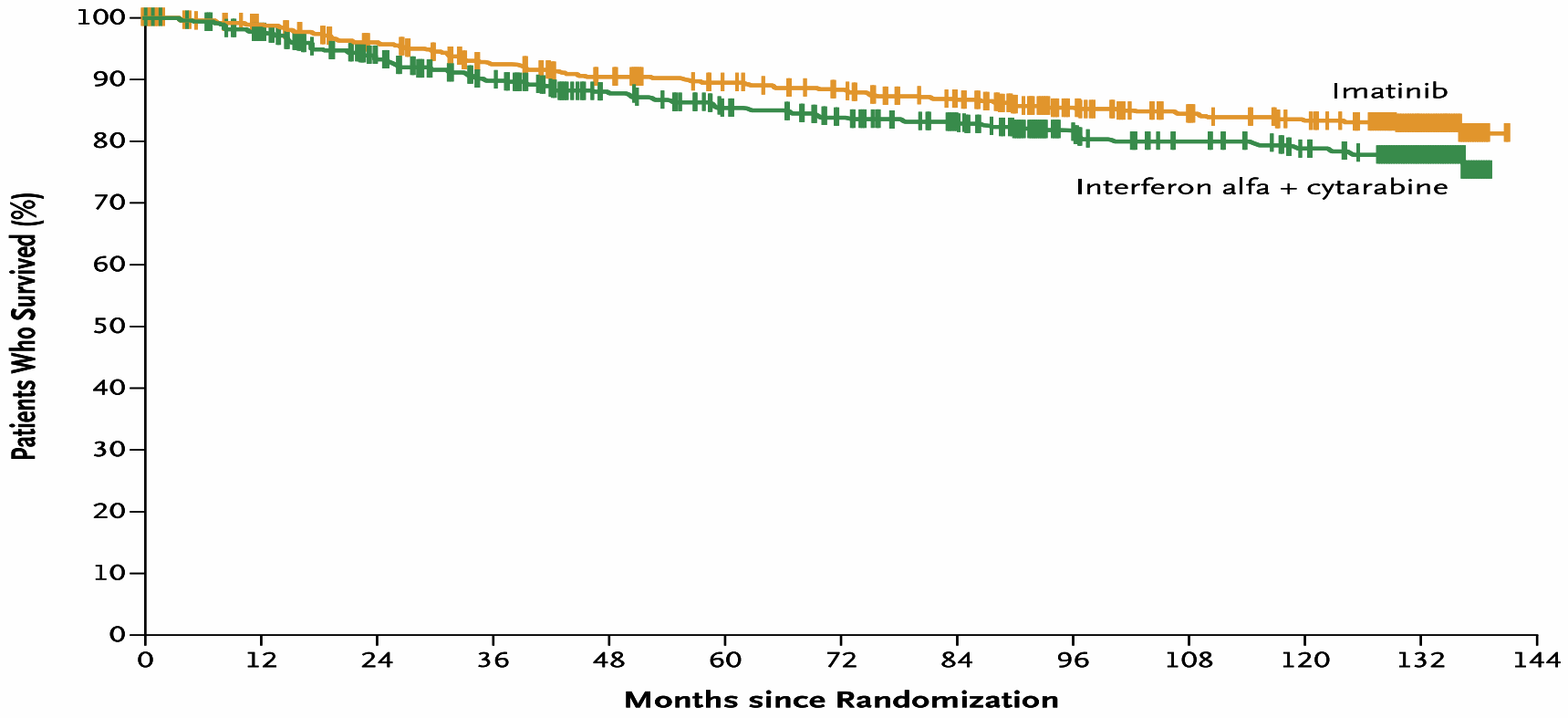


Survival with CML -the German CML Study Group



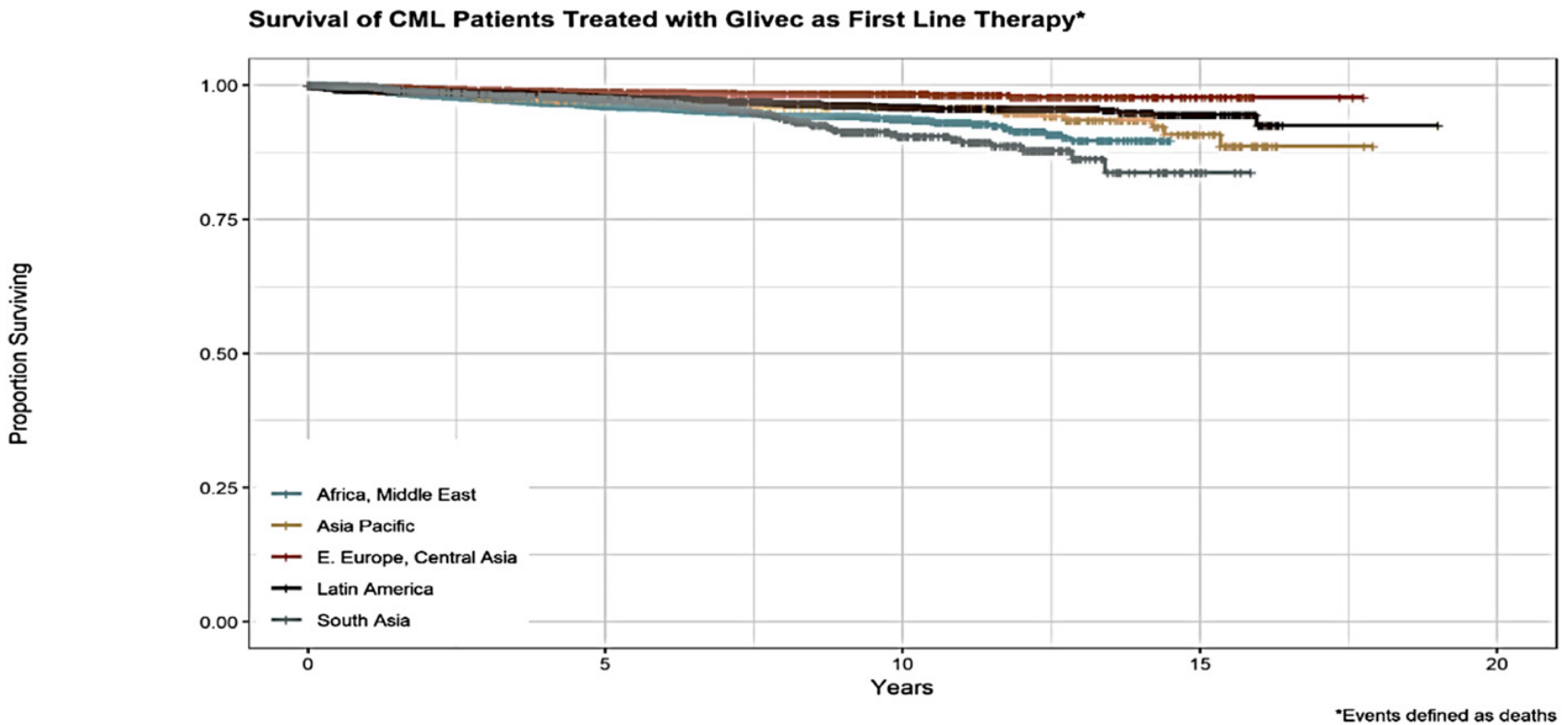
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 MARCH 9, 2017 VOL. 376 NO. 10

	No. of Patients	No. of Deaths	No. of Patients with Censored Data	10-Yr Survival % (95% CI)
Imatinib	553	89	464	83.3 (80.1–86.6)
Interferon alfa + cytarabine	553	105	448	78.8 (75.0–82.5)



No. at Risk								
Imatinib	553	542	492	461	430	368	250	0
Interferon alfa + cytarabine	553	512	441	388	358	299	199	0
No. of Deaths								
Imatinib	0	6	41	57	71	82	88	89
Interferon alfa + cytarabine	0	12	52	73	83	96	104	105

Overall survival (OS) of CML patients supported by MAS.



OS : lower in Africa, the Middle East, and South Asia compared with Eastern European and Central Asian countries.

Indian J Hematol Blood Transfus (Jan-Mar 2019) 35(1):37–42
https://doi.org/10.1007/s12288-018-1009-y

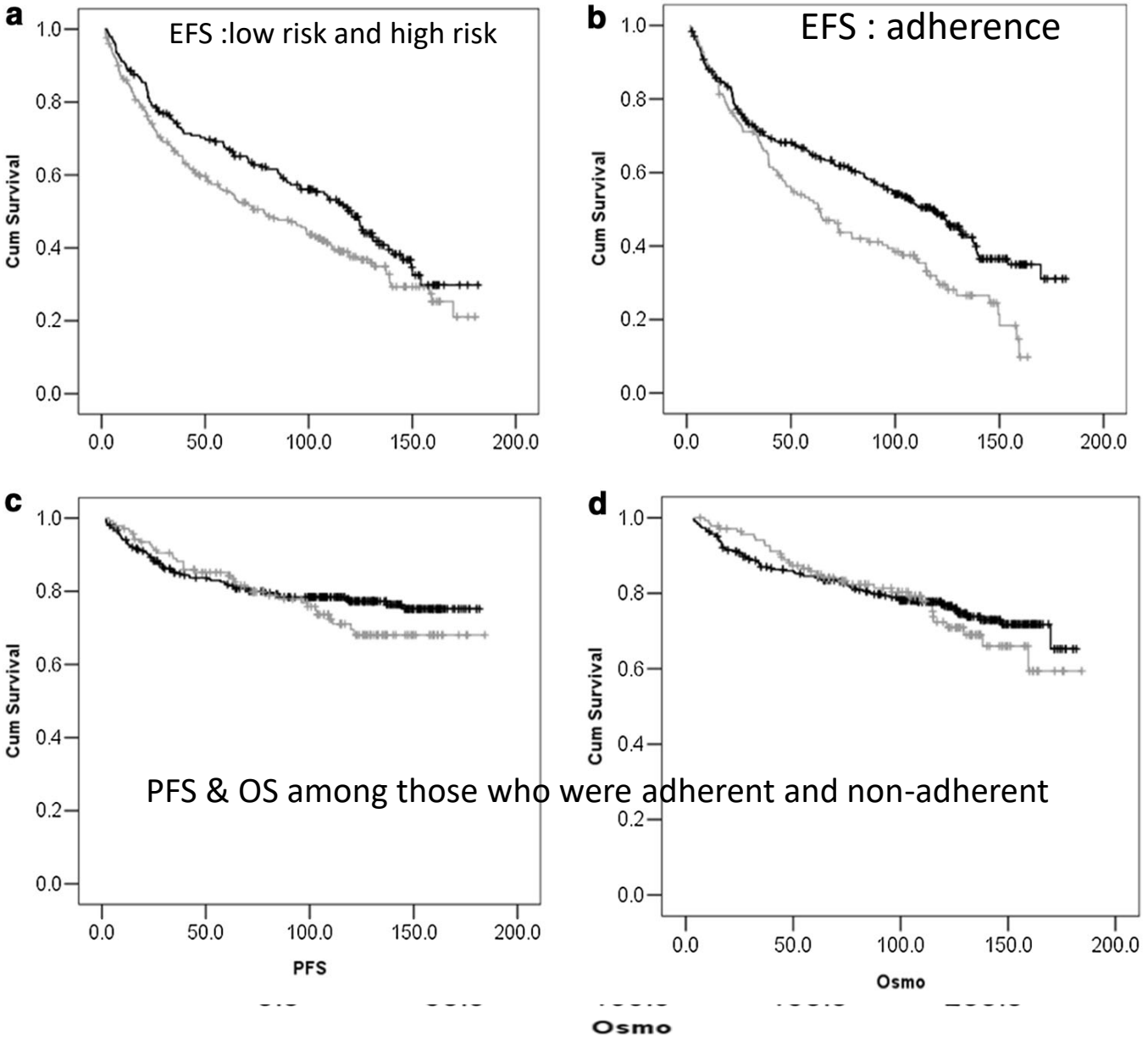
ORIGINAL ARTICLE

Chronic Myeloid Leukemia: Long-Term Outcome Data in the Imatinib Era

Prasanth Ganesan[1] · Trivadi S. Ganesan[1] · Venkatraman Radhakrishnan[1] ·

Table 1 Patient characteristics at baseline (n = 443)

Characteristics (n = 443)	N (%)
Age, years	
Range	18–70
Median	36
Age category	
≤ 35 years	211
> 35 years	232
Time from diagnosis	
≤ 3 months	329 (74)
> 3–≤ 6 months	43 (10)
> 6 months–≤ 12 months	26 (6)
> 12 months	45 (10)
Male:female	301:142
Use of non-TKI medications[a]	162 (37)
Sokal risk category	
Low	97 (22)
Intermediate	206 (47)
High	140 (32)
Hasford risk category	
Low	192 (43)
Intermediate	191 (43)
High	60 (14)
EUTOS risk category	
Low	379 (86)
High	64 (14)



The issues with management of CML in LMIC - How to improve?
Knowing the challenges….

- Understanding the basics of the disease
- Relatively younger population of CML patient
- Higher proportion of intermediate and high risk groups. (need for higher dose of IM or using 2nd gen TKIs)
- Non- compliance/Adherence to continued therapy. (Patient education)
- Access to medications especially 2nd line therapy. *(Not available in most LMIC)*
- Challenges faced with effective follow up (*long travel*)
- Challenges with monitoring to guide therapy in a dynamic way. *(Laboratory back up and Cost)*
- Problem of younger populations, child bearing , cultural issues.
- Exploring treatment free remission strategies with a framework *(reproducibility and authentic results as per IS)*

How do you improve outcomes with existing standard treatment option?

- Educating patient – The nature / need for therapy/ rationale of Rx/ Adherence
- Identifying patient requiring more/ different
- Envisaging end points for patients –
    - Young vs. old
    - Exploring TFR vs. Continued therapy
    - Access
    - Financial health.

Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Social and Financial Barriers to Optimum TKI Treatment in Patients with Chronic Myeloid Leukemia- A Knowledge-Attitudes-Practices Study from India

Naveen Gupta[1], Manoranjan Mahapatra[2], Tulika Seth[2], Seema Tyagi[2], Sudha Sazawal[2] and Renu Saxena[2].

Question	Response
1. At what time do you take imatinib?	Fixed routine – 377 (94.25%) • Morning- 58 (14.5%) • Afternoon- 44 (11%) • Night- 263 (65.75%) • Split dose- 12 (3%) Variable timing- 23 (5.75%)
2. Do you get reminded by family members to take the tablet?	Y- 108 (27%) N- 292 (73%)
3. Are you taking oral medicines for other diseases?	Y- 51 (12.75%) N- 87.25%)
4. Do you feel it is an inconvenience taking tablets daily?	Yes- 118 (29.5%) No- 282 (70.5%)

Drug taking practices.

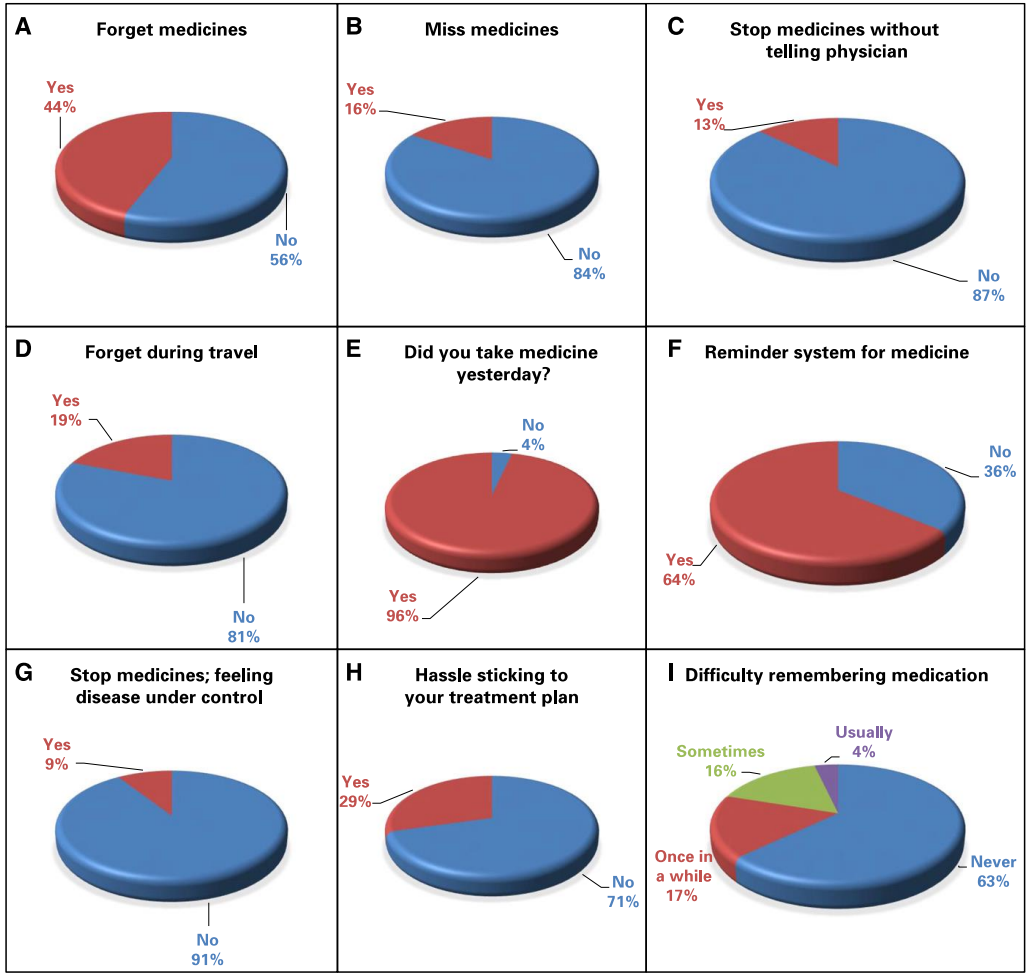
Knowledge about disease and treatment.

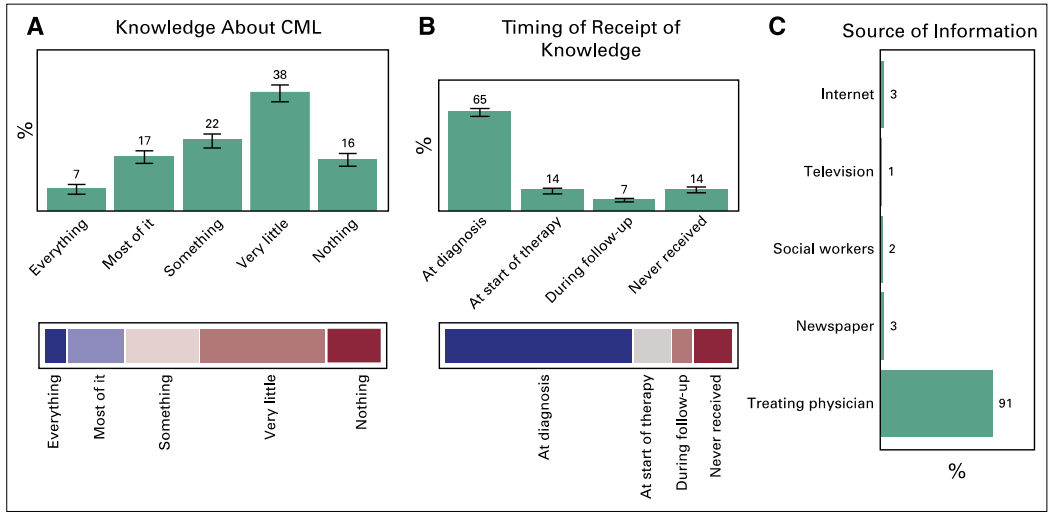
Question	Response
1. Do you feel you have been explained about the disease? • Yes • No	 358 (89.5%) 42 (10.5%)
2. What is the nature of your disease? # • Blood cancer • Disease of the spleen • Blood infection • Others • Don't know	 346 (86.5%) 10 (2.5%) 23 (5.75%) 4 (1%) 32 (8%)
3. Do you know the name of your disease? • Yes (CML) • No	 186 (46.5%) 214 (53.5%)
4. What is the treatment of the disease? # • Oral tablets • Bone marrow transplant • Blood transfusions • Don't know	 344 (86%) 2 (0.5%) 0 56 (14%)
5. Do you know the name of the tablet given for this disease? • Yes • No	 216 (54%) 184 (46%)
6. Till what duration are you supposed to take these tablets? • Lifelong • Till resolution of symptoms • Till doctor advises • Fixed duration • Don't know	 265 (66.25%) 9 (2.25%) 35 (8.75%) 17 (4.25%) 74 (18.5%)
7. Are you aware of the risks of stopping treatment? • Yes • No	 233 (58.75%) 167 (41.75%)

Variation in Adherence Measures to Imatinib Therapy

Uday Yanamandra
Pankaj Malhotra

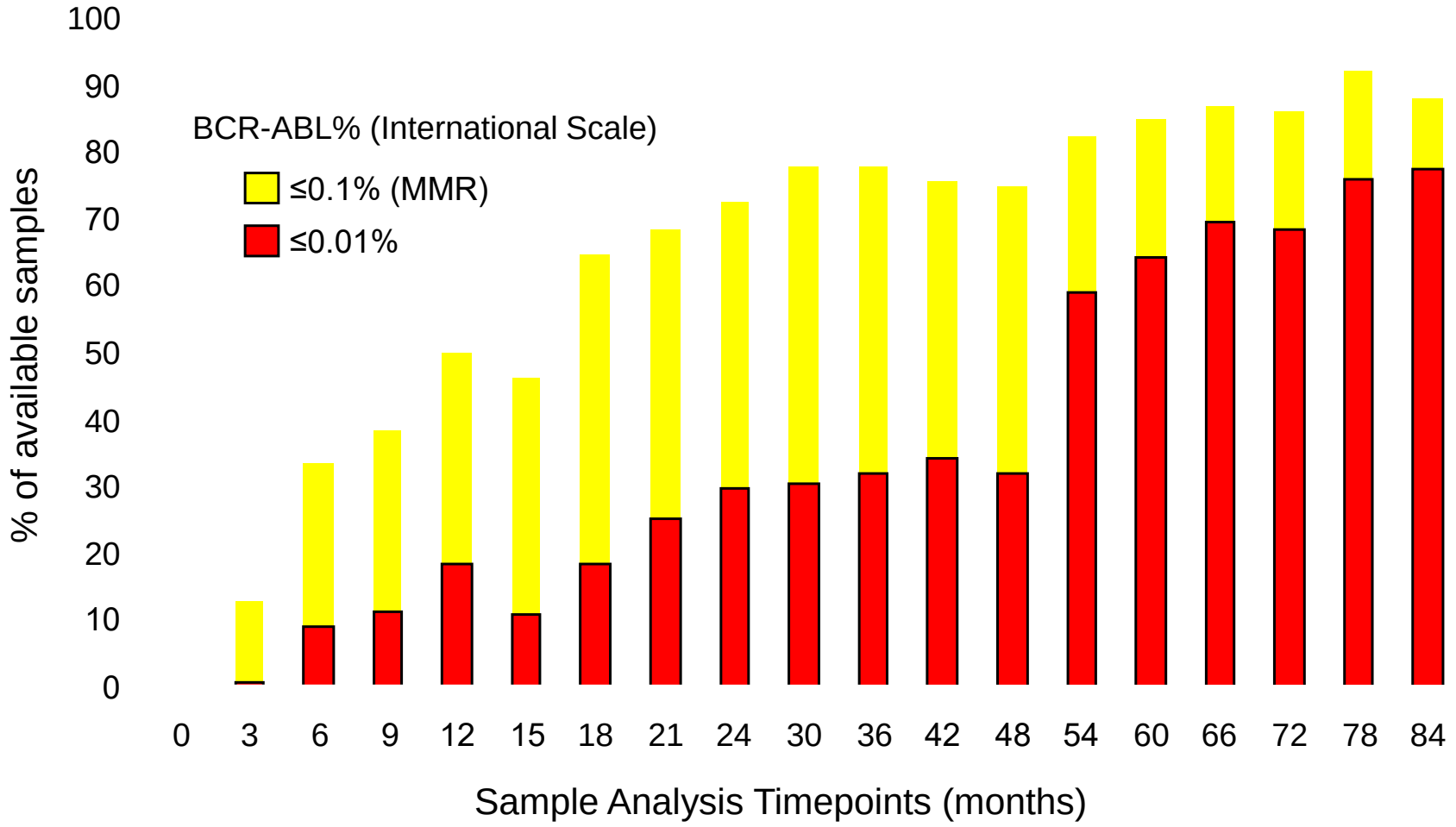
jgo.org **JGO – Journal of Global Oncology**





Deepening Response – an ongoing process with TKI

- Major molecular response (MMR) and the depth of molecular response increase over time



IRIS 7 year update

- The problem of higher risk scores at presentation.
- The problems of relatively younger patients at diagnosis.

- Consistently 2/3rd of the patients presenting are in the intermediate to high risk Sokal score. Although the proportion comes to hals when applying the EUTOS score.

Question :

- More appropriate to use higher dose of Imatinib –
  The CML IV data.
- Consider using 2nd generation TKI –
  The ENeST-ND and Dassision Data
- Switching over to a 2nd generation TKI if early response is not optimal - TIDEL

VOLUME 32 · NUMBER 5 · FEBRUARY 10 2014
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Deep Molecular Response Is Reached by the Majority of Patients Treated With Imatinib, Predicts Survival, and Is Achieved More Quickly by Optimized High-Dose Imatinib: Results From the Randomized CML-Study IV

Rüdiger Hehlmann, Martin C. Müller, Michael Lauseker, Benjamin Hanfstein, Alice Fabarius,

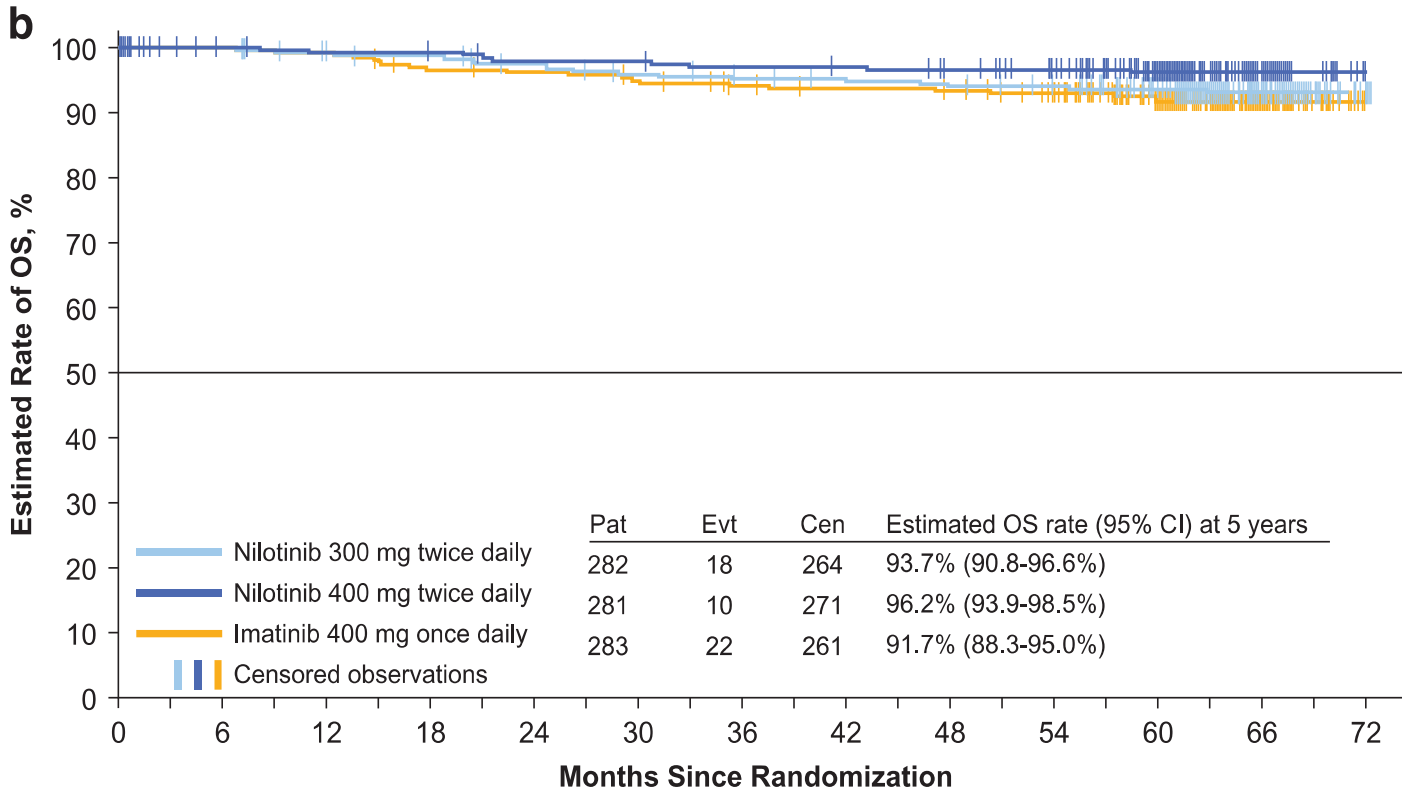
- The cumulative incidence of $MR_{4.5}$ after 9 years was 70% (median, 4.9 years);
- $MR_{4.5}$ was reached more quickly with optimized high-dose imatinib than with IM 400 mg/day.
- High-dose IM and early major molecular remission predicted $MR_{4.5}$.
- No patient with confirmed $MR_{4.5}$ has experienced progression.

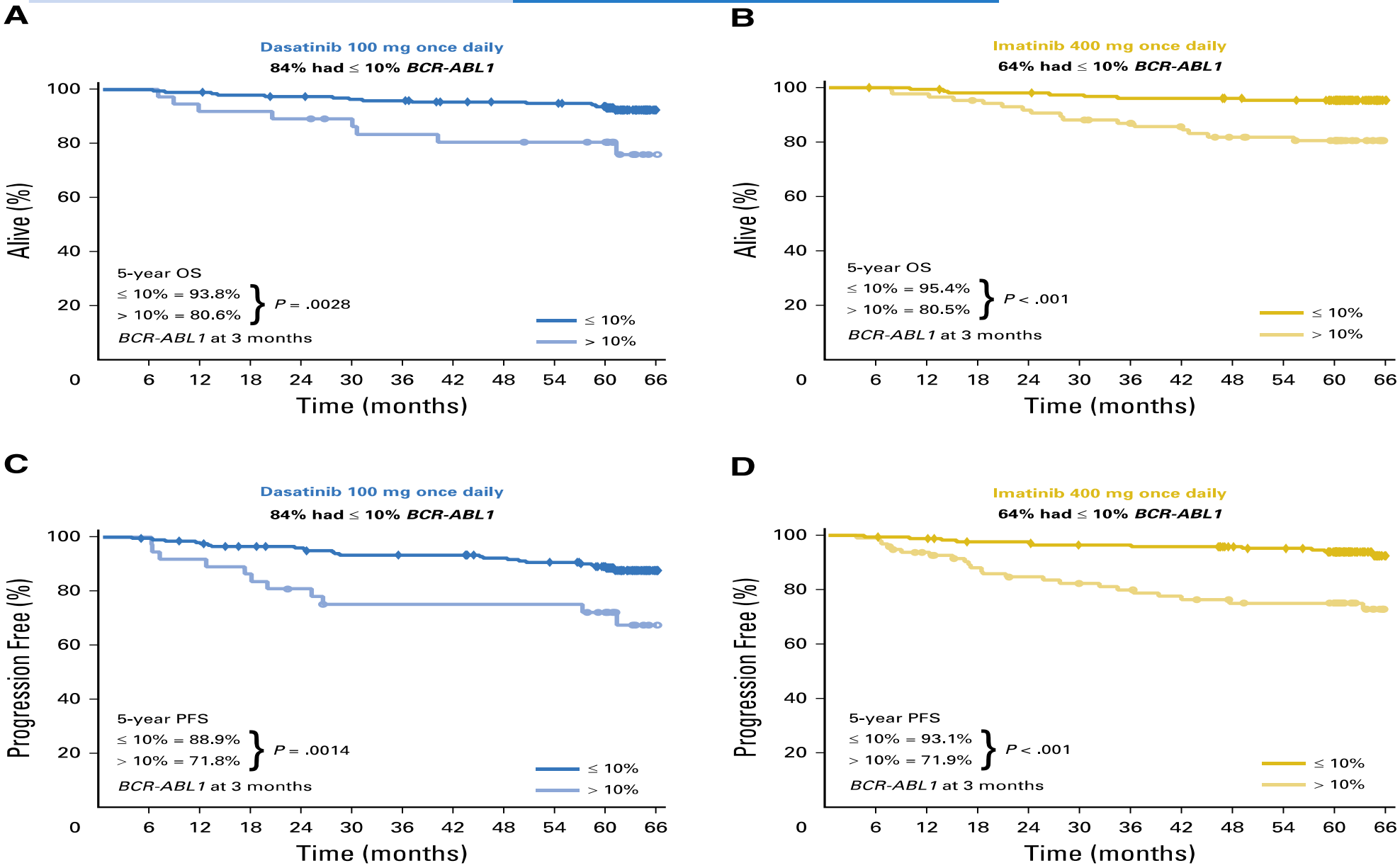
Leukemia (2016) **30,** 1044–1054

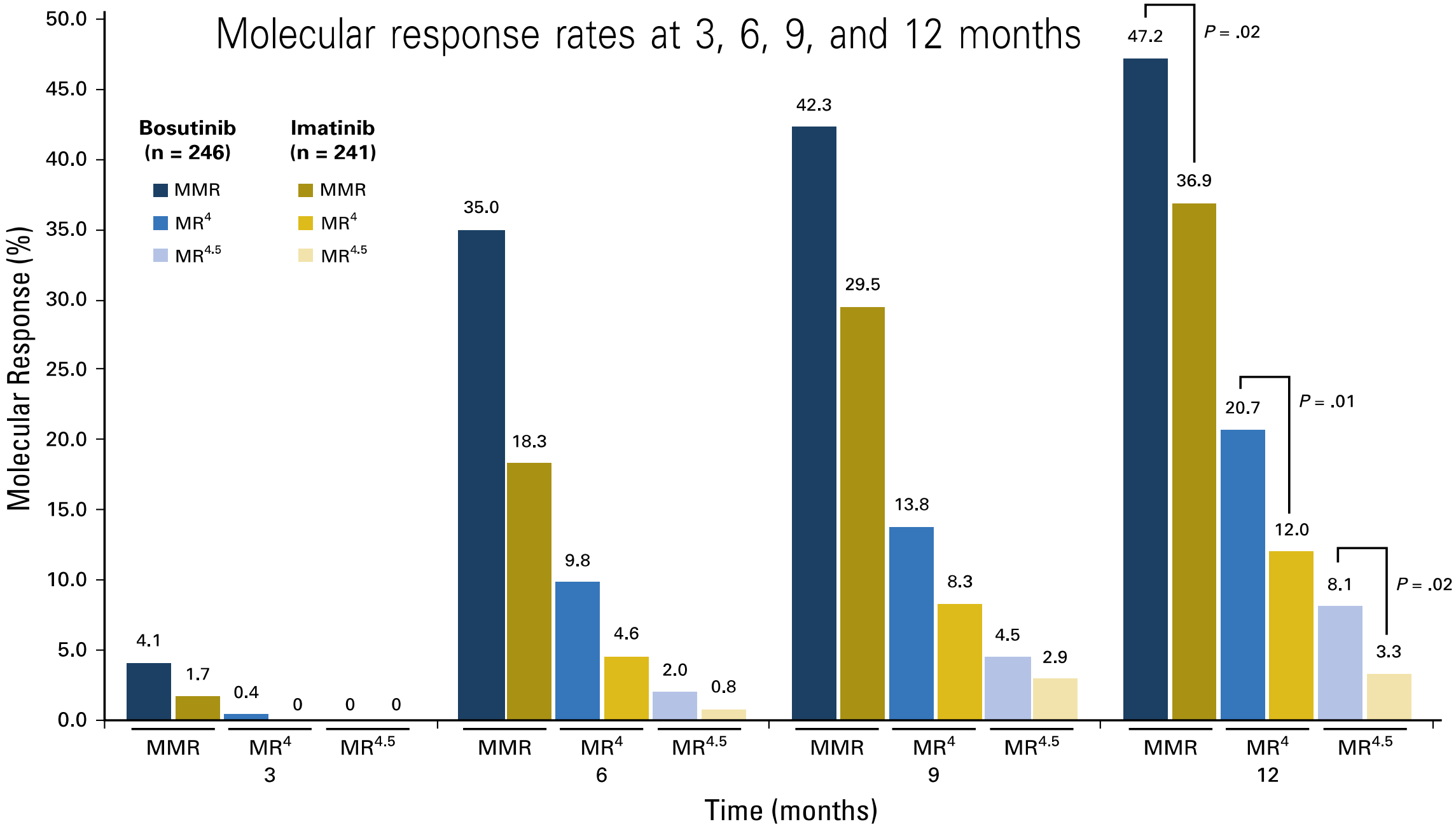
ORIGINAL ARTICLE

Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial

A Hochhaus[1,16], G Saglio[2,16], TP Hughes[3], RA Larson[4], D-W Kim[5], S Issaragrisil[6], PD le Coutre[7], G Etienne[8], PE Dorlhiac-Llacer[9], RE Clark[10], IW Flinn[11], H Nakamae[12], B Donohue[13], W Deng[13], D Dalal[13], HD Menssen[14] and HM Kantarjian[15]




A
Dasatinib 100 mg once daily
84% had ≤ 10% BCR-ABL1
Alive (%)
100
80
60
40
20
0
5-year OS
≤ 10% = 93.8%
> 10% = 80.6%
P = .0028
BCR-ABL1 at 3 months
≤ 10%
> 10%
6 12 18 24 30 36 42 48 54 60 66
Time (months)
B
Imatinib 400 mg once daily
64% had ≤ 10% BCR-ABL1
Alive (%)
100
80
60
40
20
0
5-year OS
≤ 10% = 95.4%
> 10% = 80.5%
P < .001
BCR-ABL1 at 3 months
≤ 10%
> 10%
6 12 18 24 30 36 42 48 54 60 66
Time (months)
C
Dasatinib 100 mg once daily
84% had ≤ 10% BCR-ABL1
Progression Free (%)
100
80
60
40
20
0
5-year PFS
≤ 10% = 88.9%
> 10% = 71.8%
P = .0014
BCR-ABL1 at 3 months
≤ 10%
> 10%
6 12 18 24 30 36 42 48 54 60 66
Time (months)
D
Imatinib 400 mg once daily
64% had ≤ 10% BCR-ABL1
Progression Free (%)
100
80
60
40
20
0
5-year PFS
≤ 10% = 93.1%
> 10% = 71.9%
P < .001
BCR-ABL1 at 3 months
≤ 10%
> 10%
6 12 18 24 30 36 42 48 54 60 66
Time (months)


Molecular response rates at 3, 6, 9, and 12 months
Bosutinib (n = 246)
Imatinib (n = 241)
MMR
MR4
MR4.5
Molecular Response (%)
50.0
45.0
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
4.1
1.7
0.4
0
0
0
35.0
18.3
9.8
4.6
2.0
0.8
42.3
29.5
13.8
8.3
4.5
2.9
47.2
36.9
20.7
12.0
8.1
3.3
P = .02
P = .01
P = .02
MMR
MR4
MR4.5
3
6
9
12
Time (months)

Switching therapy. When do you make that decision?

- At 3 months when there is inadequate response.
- Wait until 6 months.
- The critical need to evaluate compliance

ENESTcmr: Switch to Nilotinib in CP CML w/Residual Disease on Long-term Imatinib

Stratified by duration of previous imatinib (≤ 36 vs > 36 mos), duration of previous interferon (none vs ≤ 12 vs > 12 mos)

Ph+ CP CML previously treated with imatinib 400 or 600 mg/day for ≥ 2 yrs; patients with confirmed CCyR and persistently detectable BCR-ABL transcripts
(N = 207)

Switch to Nilotinib 400 mg BID
(n = 104)

Continue on Imatinib 400-600 mg QD*
(n = 103)

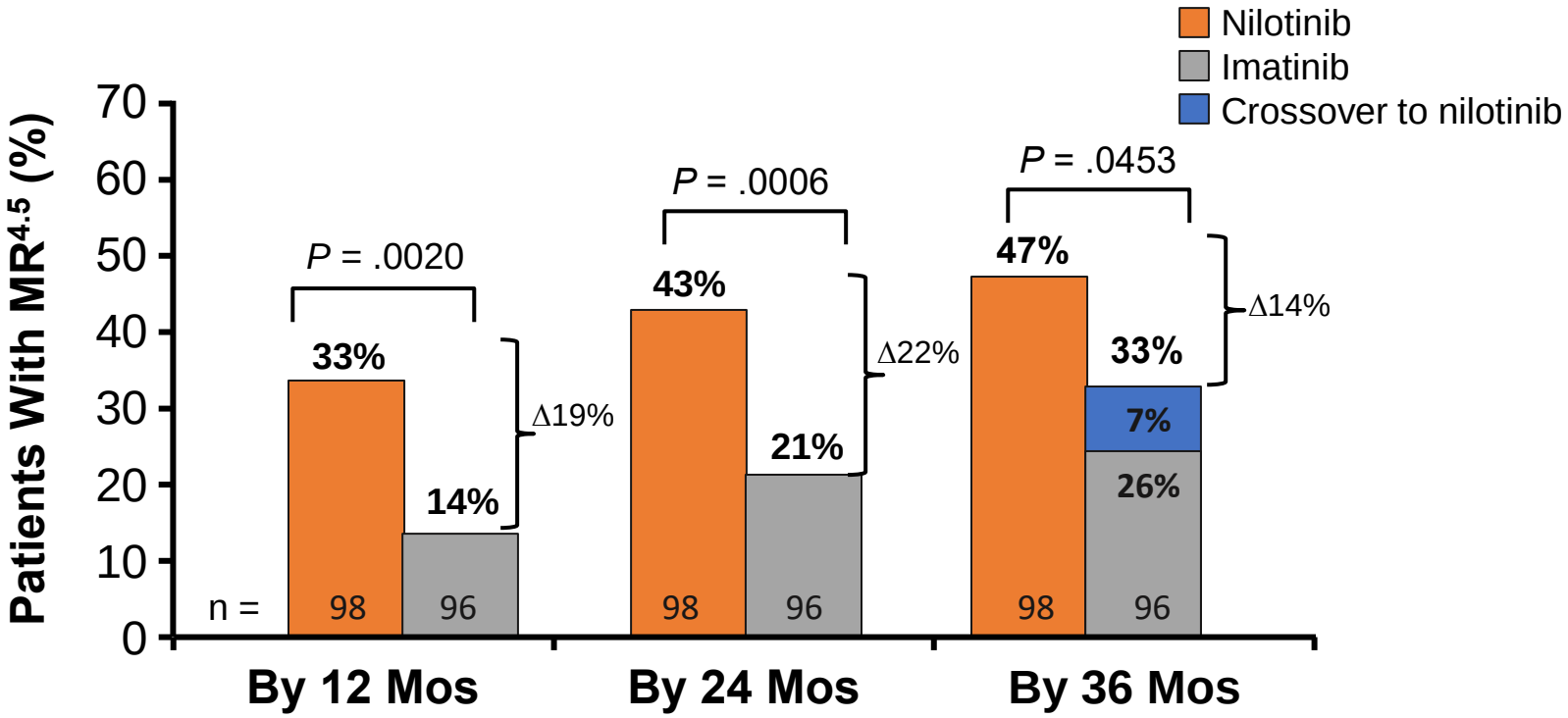
→ *4 yrs*

Leber B, et al. ASH 2013. Abstract 94.

Switch to Nilotinib in CP CML on Long-term Imatinib: Efficacy

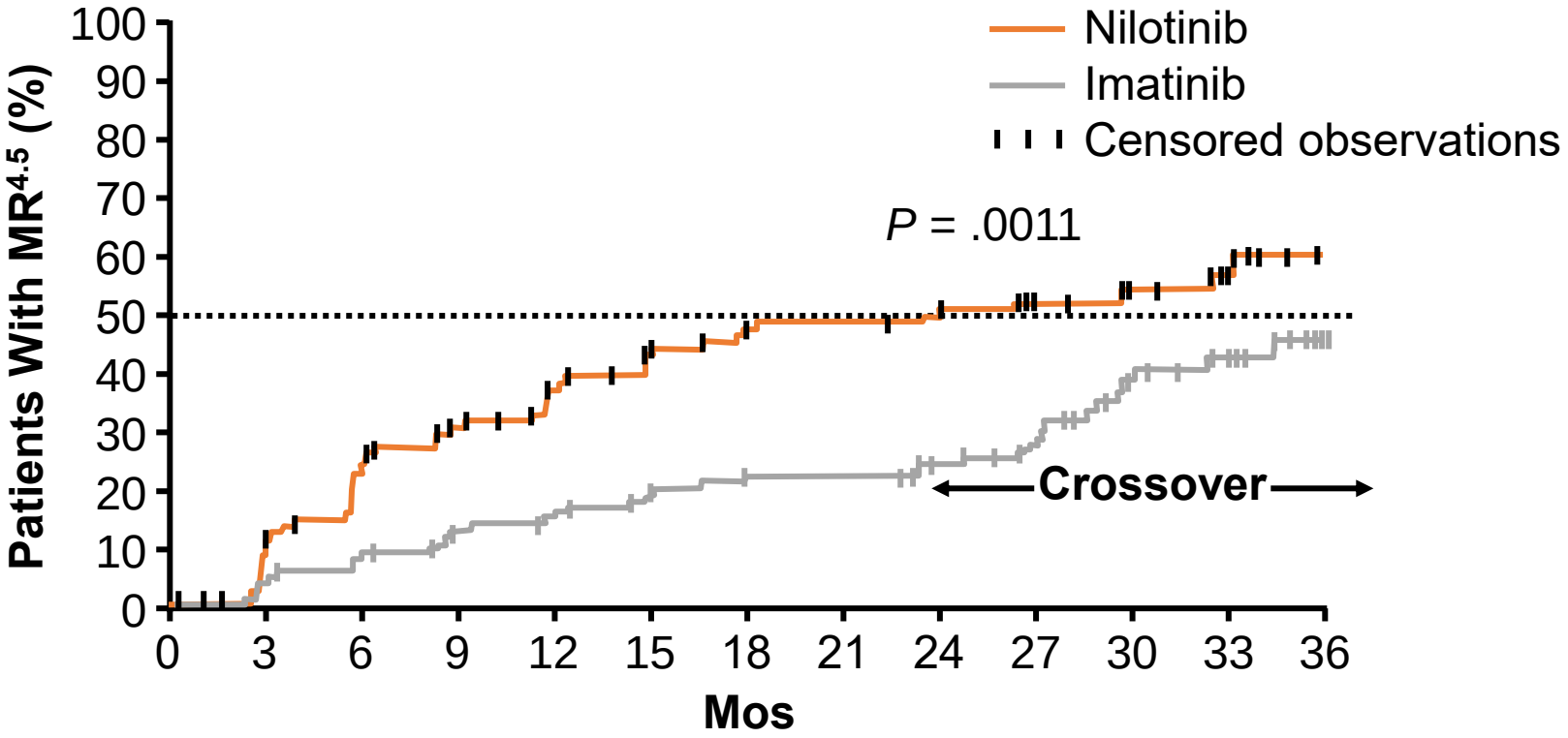
Cumulative Incidence of $MR^{4.5}$ in Pts Without $MR^{4.5}$ at Baseline

- *Subgroup analysis - limited to responses up to crossover*
- *$MR^{4.5}$ achieved in 47% with Nilotinib vs 24% with Imatinib (P = .0003)*



Leber B, et al. ASH 2013. Abstract 94.

Switch to Nilotinib in CP CML on Long-term Imatinib: Time to First $MR^{4.5}$



- Median time to $MR^{4.5}$ accelerated by > 1 yr with nilotinib
  - 24 mos with Nilotinib vs not reached with Imatinib

Leber B, et al. ASH 2013. Abstract 94

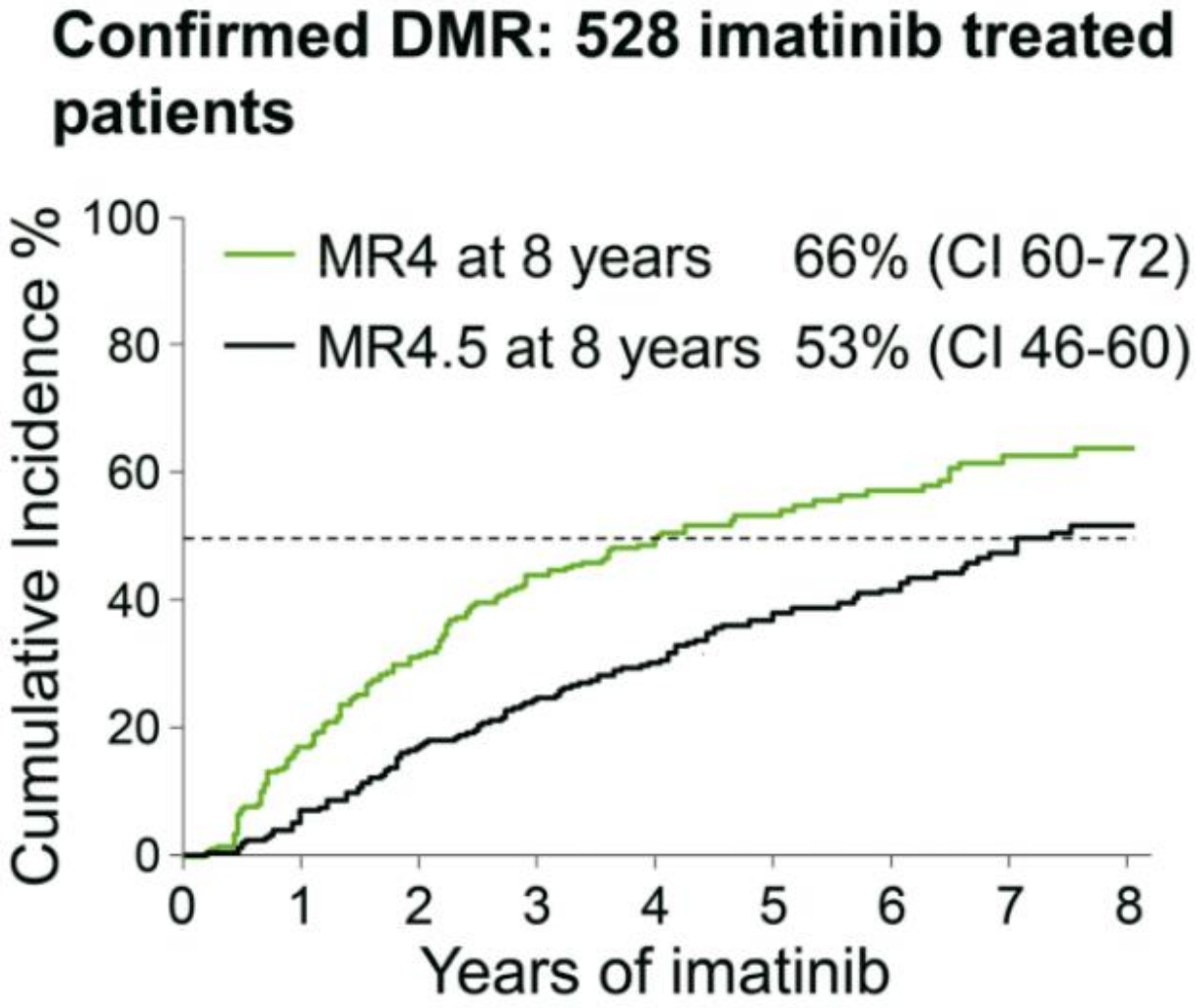
Generic Availability in India – Can make this a possibility

TFR in LMICs!!

Why should TKI cessation be a key endpoint of therapy?

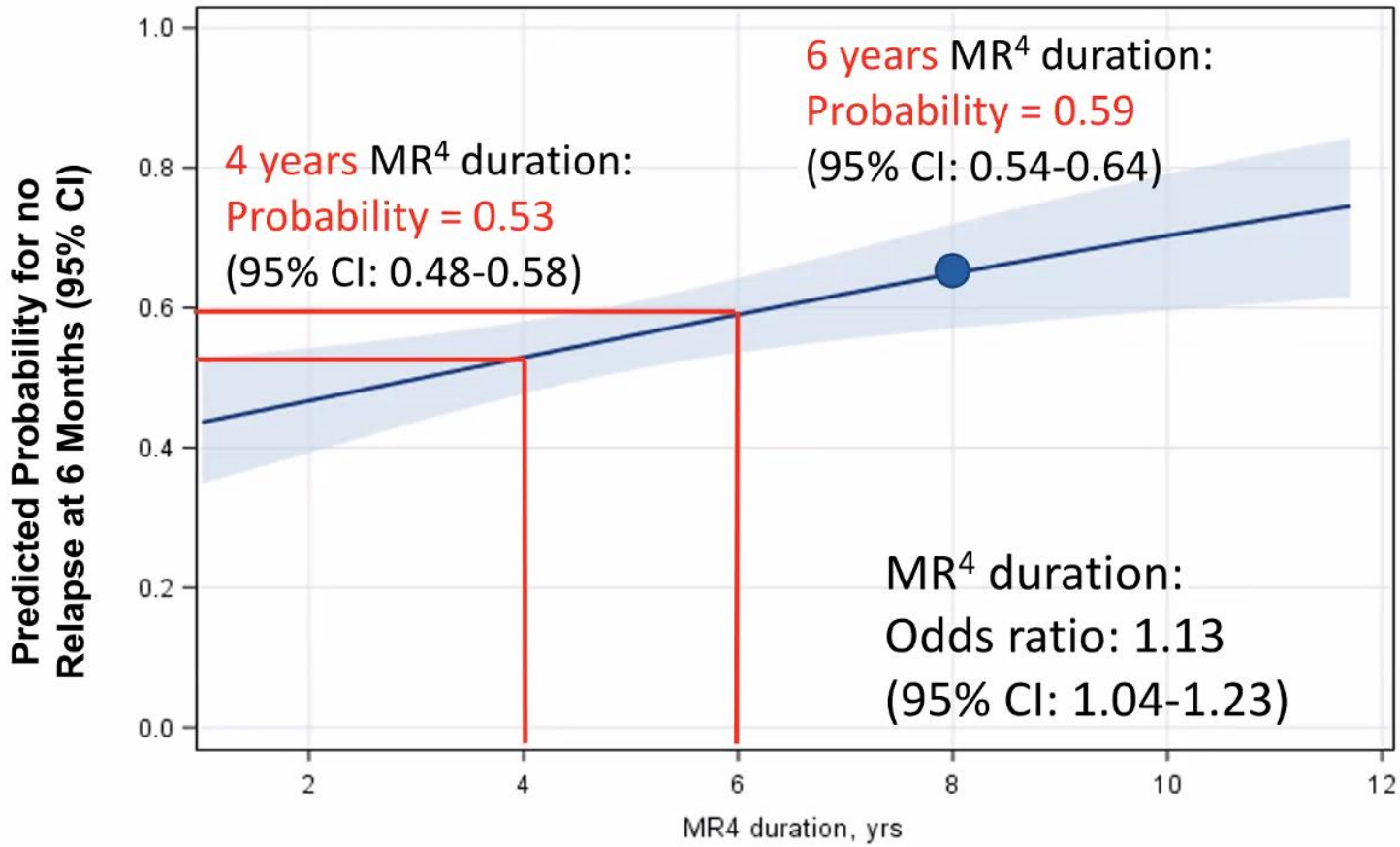
- Potential for organ toxicity with long term TKI therapy – particularly relevant in India (and other LMICs) b/o the large number of young patients!
- Quality of life impact of TKI therapy
- Safe pregnancies
- Cost of life-time TKI therapy
- Emerging evidence that TFR/cure may be possible

Total duration of TKI exposure directly propositional to depth of MR (and TFR possibility)!!



EURO-SKI: MR^4 Duration and TFR Probability

Absolute increase of probability of about 3% per year (n = 405)



CML - TFR in resource-constrained Countries: Some Suggestions-1!

- TFR attempt even more important in LMICs - large number of young patients
- Minimum duration of imatinib: 8 years
- Minimum duration of 2nd Gen. TKI: 5 years

[longer duration of TKI exposure suggested b/o higher disease load at diagnosis, higher incidence of non-compliance with drug & testing and greater chance delayed f/u]

CML - TFR in resource-constrained Countries: Some Suggestions-2!

- Minimum duration of MR 4.0: 5 years; MR 4.5: 3 years
- TKI restart trigger: loss of MMR
- Patients with high Sokal risk & Imatinib resistance/failure to be considered for half-TKI (DESTINY model) for 12 months, then STOP TKI if still in MMR
- Monitoring: BCR-ABL RT-PCR every month for 1st six months, then 2 to 3 monthly for next 12 months, then 3 to 6 monthly for at least 5 years

CML - TFR in resource-constrained Countries: Some Suggestions-3!

- Patients on the GIPAP/other support program to be considered very judiciously for TFR
  - Economic reasons
  - issues with re-starting Gleevec
- Important & challenging to ensure QC in labs where RT-PCR testing to be done
- Ways & means to support RT-PCR testing (significantly more expensive than cost of generic TKI!)
- Clinical trials to look at prognostic factors specific to TFR in LMICs

Can we simplify & improve on bcr/abl testing and sample transportation??

Olga Sala Torra et al. Blood 2014;124:4566

Paper or Plastic: RT–PCR of BCR–ABL from Blood Spots Stored and Shipped on Paper

Olga Sala Torra, Lan Beppu, Susan Branford, Linda Fletcher, Gooley Ted, Amy L Paguirigan, Jordan Smith, Jerald P Radich

Blood 2014 124:4566;

Bcr/abl testing on Dried Blood Spot (DBS)

Dr. Jerry Radich, at the 'HUTCH'

CML DBS Project in Collaboration with Radich Lab

DBS Age	Radich Lab ID	RNA yield (ng/UL)	India BCR-ABL	Radich BCR-ABL
99	1	26.43	4%	3.60%
104	2	2.29	0.20%	0.56%
125	3	9.92	0.03%	0.22%
99	4	14.89	21%	14%
125	5	21.36	12%	7.60%
98	6	18.17	NEG	NEG
103	7	4.12	0.36%	0.23%
99	8	11.9	33%	26%
126	9	14.22	26%	17%
94	10	41.79	96%	40%
126	11	20.82	58%	28%

Summary & Conclusions

- Prevalence of CML expected to increase hugely: need to gear up to tackle these large number of patients.
- The availability of generic versions has allowed for its use for the high risk patients and given the data for better chances of TFR goal – can be exercises for younger patients
- Need to revisit guidelines/consensus statements for Rx of CML patients in LMIC
- Standardization of molecular labs – reaching there - but there is need to make it more viable from the cost perspective – reliable, affordable bcr/abl testing and sequencing.
- If these above systems/ access and reliability of tesating is in place – greater proportion can move towards TFR measures