Future Directions in CML

GET weekend meeting 2019

Timothy Hughes, SAHMRI, Adelaide

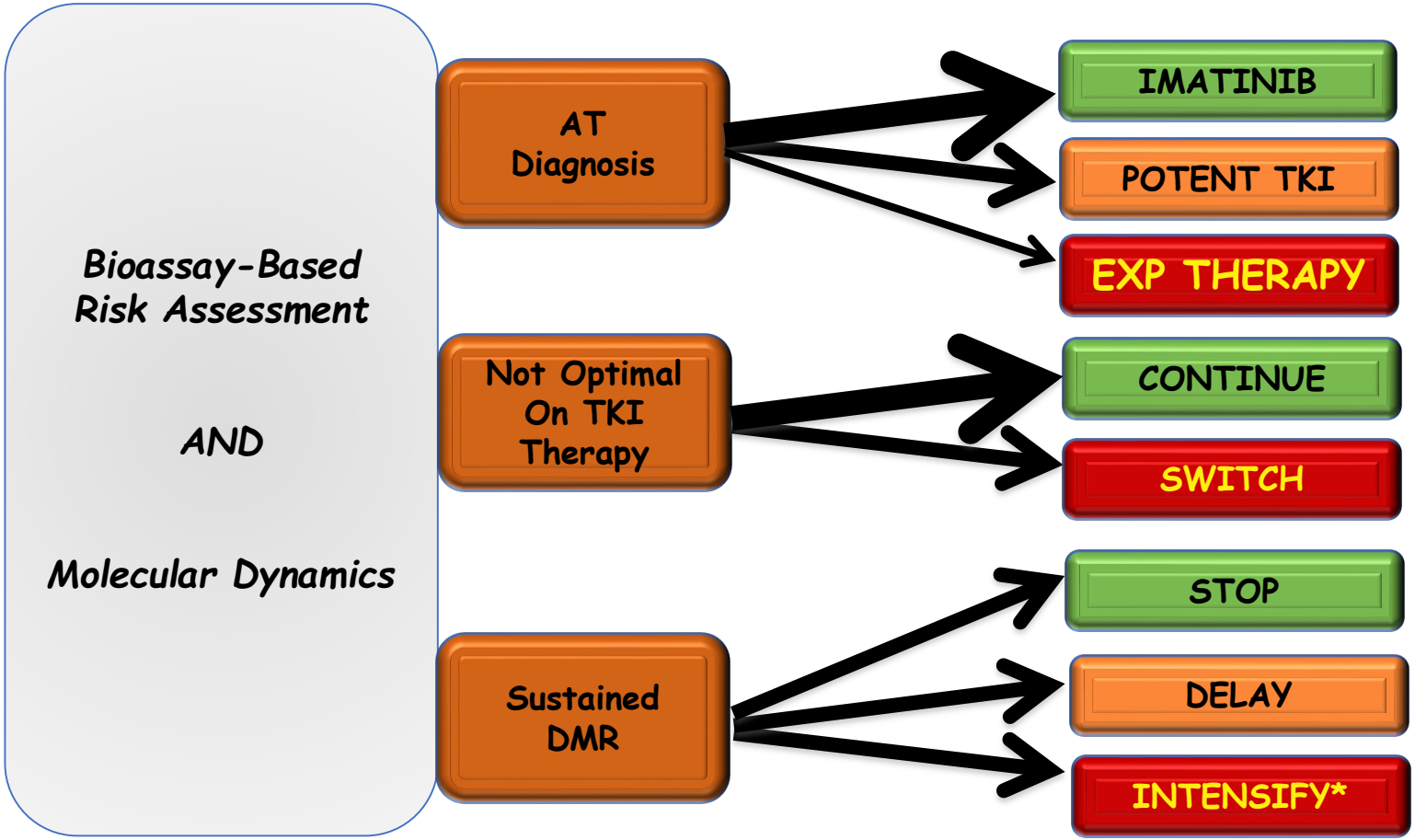
CML - can we do any better?

- 10-20% of CML patients still have poor outcomes
  - 5% CML-related deaths
  - 5% proceed to an allograft
  - 5-10% develop kinase domain mutations
  - Low rate of salvage after second gen TKI failure

CML - can we do any better?

- Long term TKI therapy still needed for most patients
  - Poor quality of life for many
  - Organ damage for some
  - TFR achieved by 20-40% but equal numbers fail TFR attempts

Future of CML Management:
Bioassay and Molecular Dynamics Driven

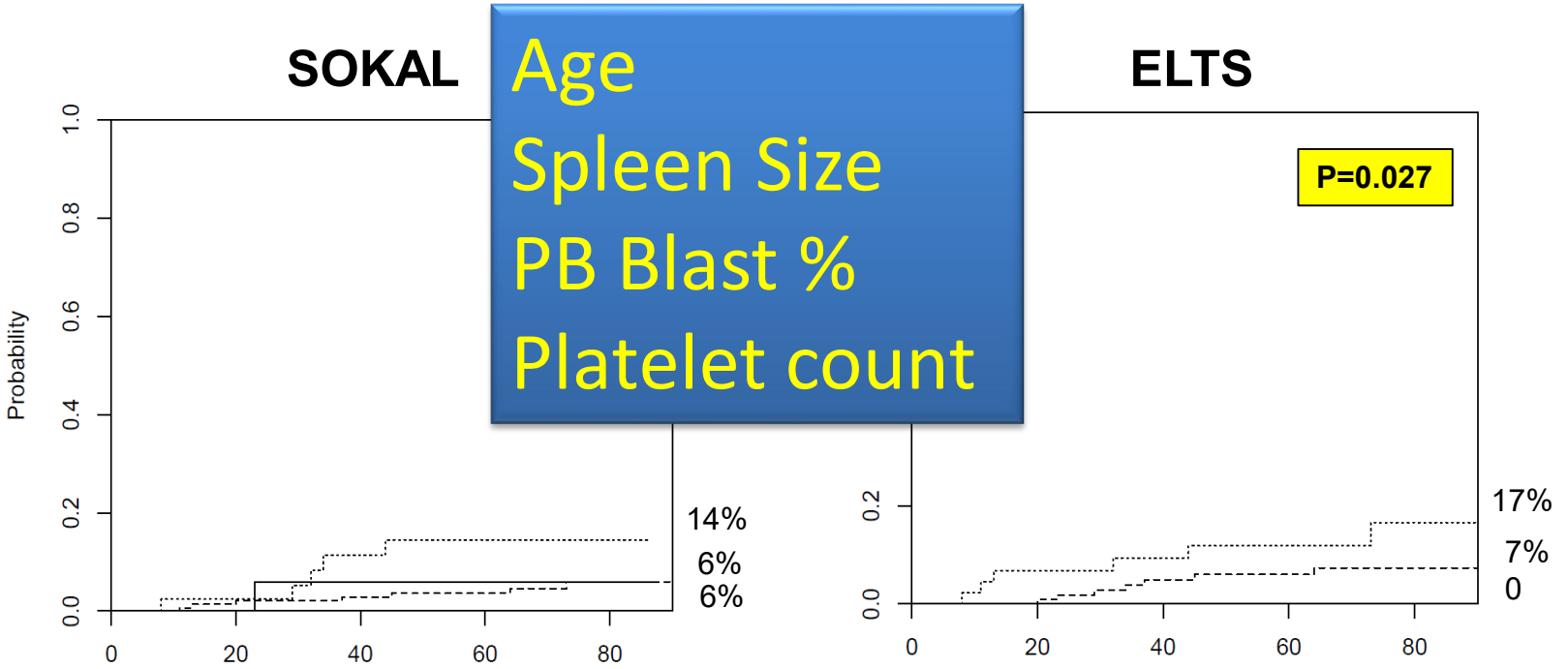


The use of EUTOS Long-Term Survival score instead of Sokal score is strongly advised in elderly CML patients

Fausto Castagnetti, Gabriele Gugliotta, Massimo Breccia, Fabio Stagno, Giorgina Specchia, Luciano Levato, Bruno Martino, Mariella D'Adda, Elisabetta Abruzzese, Patrizia Pregno, Mario Tiribelli, Alessandra Iurlo, Tamara Intermesoli, Francesco Cavazzini, Anna Rita Scortechini, Carmen Fava, Massimiliano Bonifacio, Marzia Salvucci, Monica Bocchia, Emilio Usala, Antonella Gozzini, Micaela Bergamaschi, Simona Soverini, Robin Foà, Giovanni Martinelli, Michele Cavo, Giuseppe Saglio, Fabrizio Pane, Michele Baccarani, Gianantonio Rosti

Elderly patients (≥ 65 yrs)
Leukemia-related survival by risk

N = 202



SPIRIT 2

STI571 Prospective International Randomised Trial

An NCRI randomised study comparing dasatinib with imatinib in patients with newly diagnosed CML

Final 5 year analysis

Stephen O'Brien, Leanne Cork, Valeria Bandiera, Ruth Bescoby, Letizia Foroni, Lynn Alaily, Wendy Osborne, Helen Bell-Gorrod, Nicholas Latimer, Jane Apperley, Corinne Hedgley, Richard Szydlo, Jennifer Byrne, Chris Pocock, Bernard Ramsahoye, Thomas Zwingers, James Wason, Mhairi Copland, Richard Clark.

NCRI National Cancer Research Institute

Newcastle University

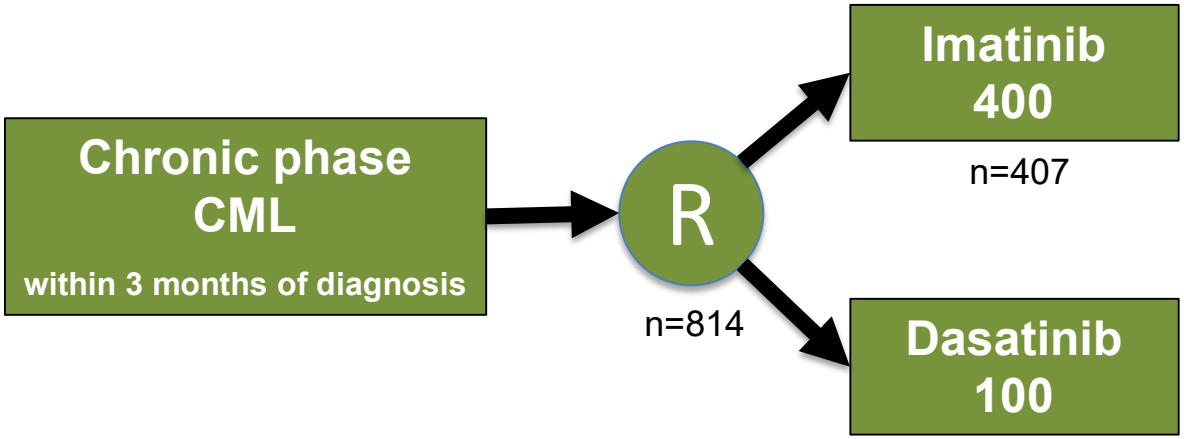
The Newcastle Hospitals NHS Foundation Trust

NHS

ASH, December 2018

www.spirit-cml.org

SPIRIT 2 study design



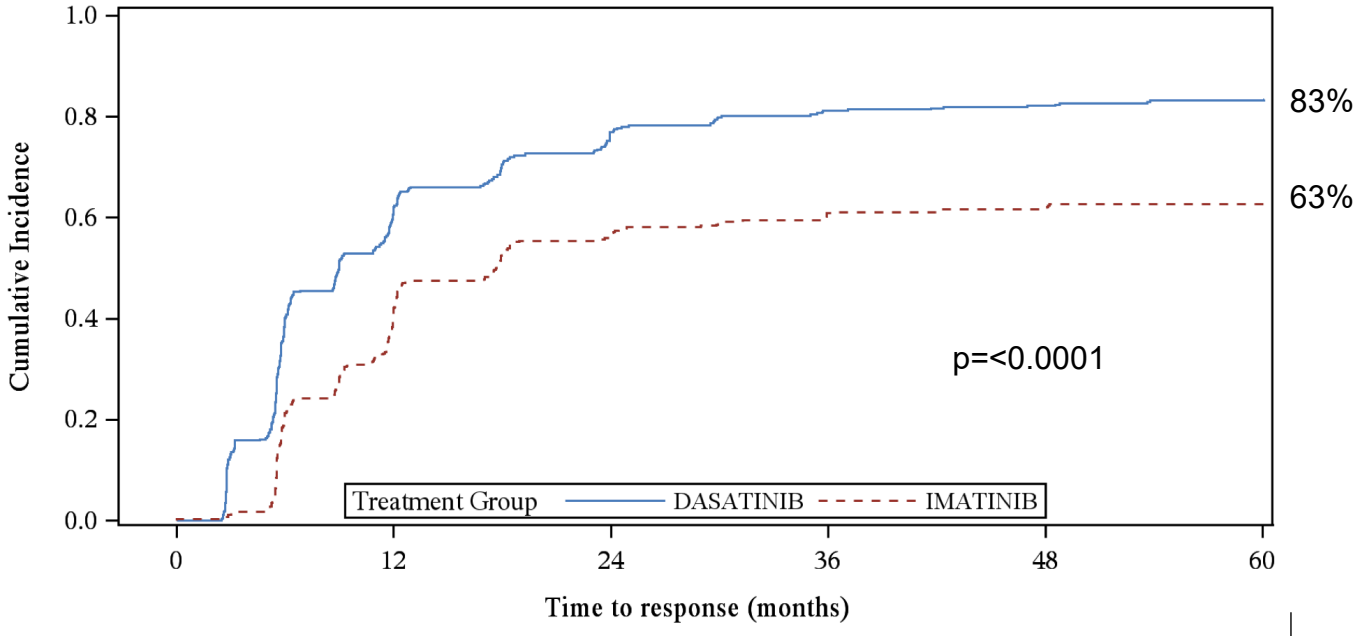
Primary endpoint

- 5 year event-free survival (EFS)

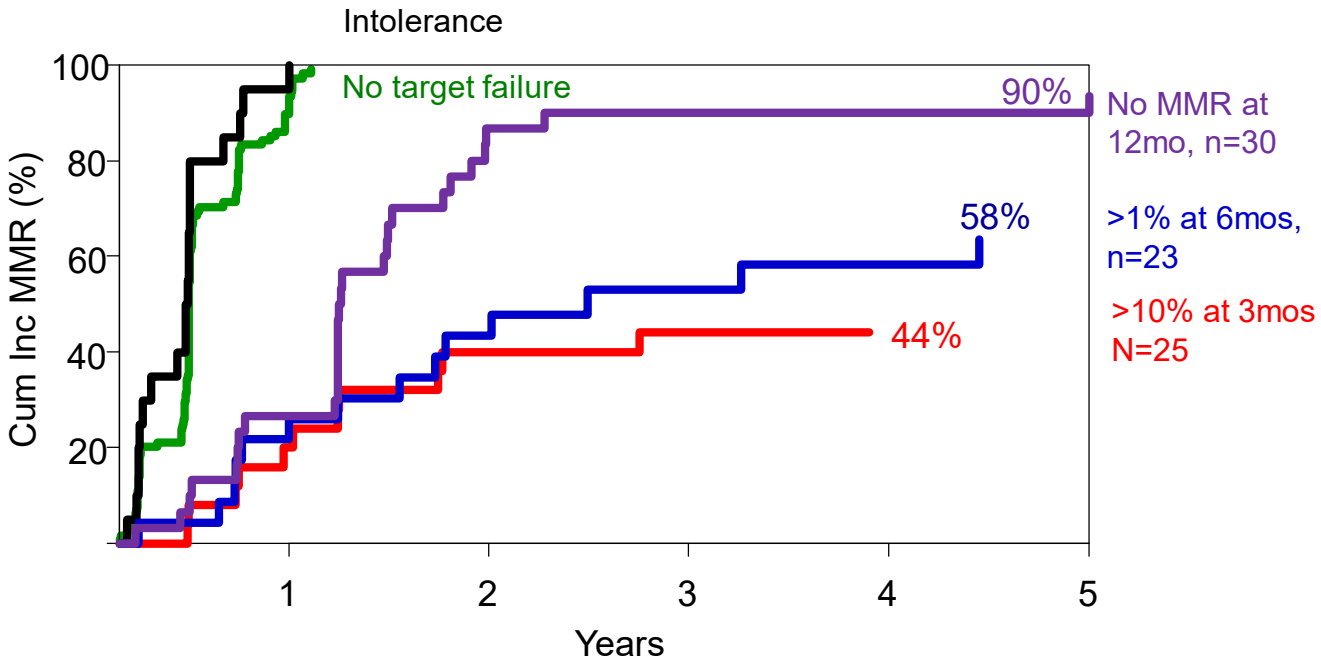
Secondary endpoints

- Complete cytogenetic response (CCR); major molecular response (MMR, MR^3, BCR-ABL1/ABL1 ratio<0.1%); toxicity; treatment failure rate (TFR); complete haematologic response (CHR); quality of life; overall survival (OS)

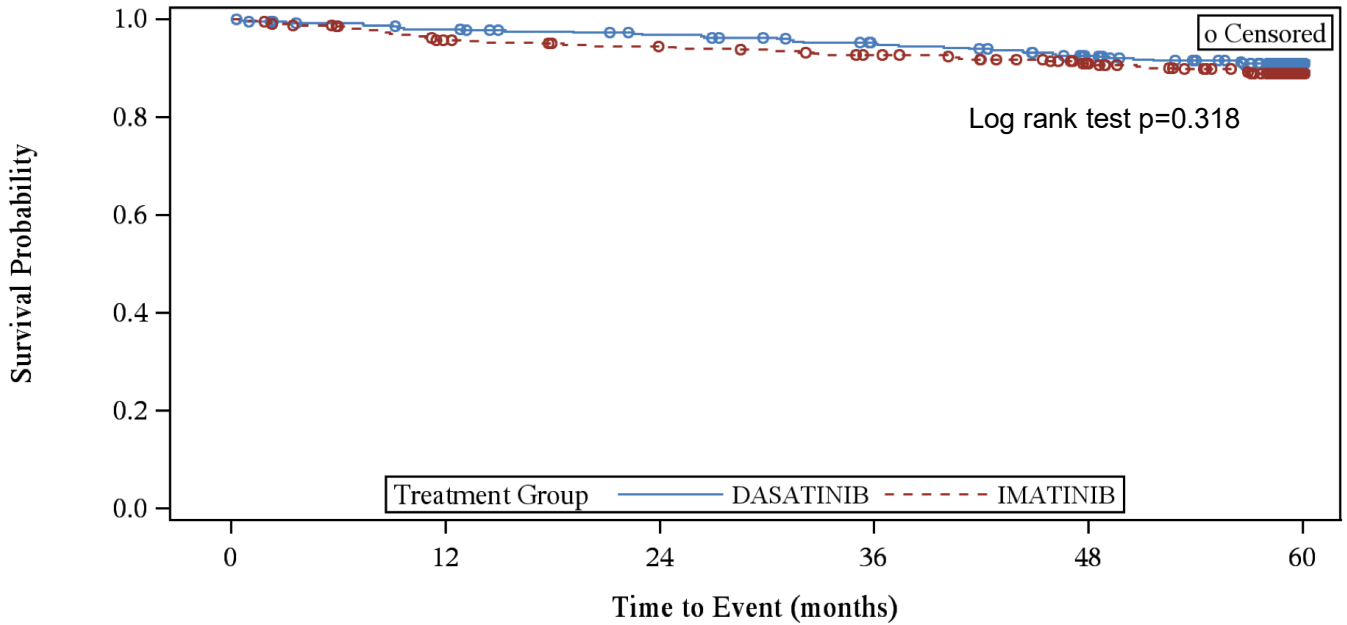
Major molecular response (MMR), MR3 (BCR-ABL/ABL ratio <0.1%)



MMR achievement stratified by TIDEL-II targets

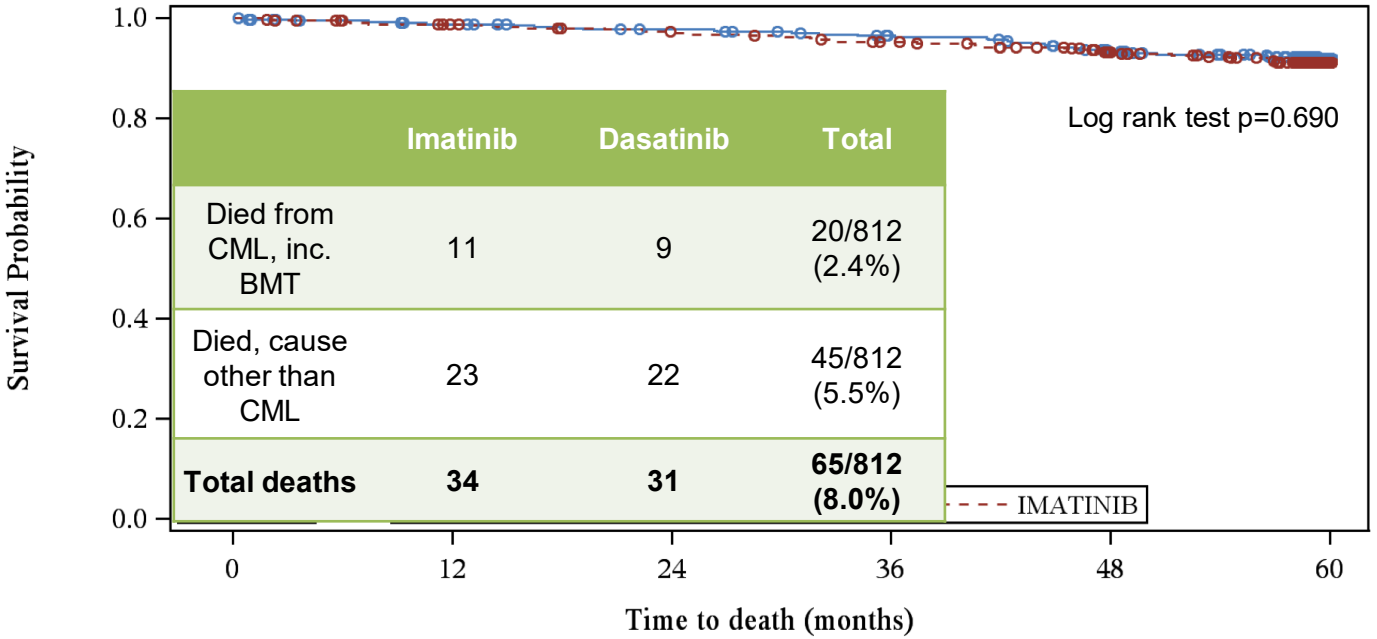


Event-free survival (primary endpoint) Intention to treat analysis, KM



DASATINIB	406	392	381	368	350	152
IMATINIB	406	380	371	360	338	150

Overall survival
Intention to treat analysis, KM



	Imatinib	Dasatinib	Total
Died from CML, inc. BMT	11	9	20/812 (2.4%)
Died, cause other than CML	23	22	45/812 (5.5%)
Total deaths	**34**	**31**	**65/812 (8.0%)**

SPIRIT 2
STI571 Prospective International Randomised Trial

Comparison of Deaths on SPIRIT & DASISION

	DASISION	
	IMATINIB	DASATINIB
Pt Number	259	260
Total Deaths	10%	10%
CML related	6.5%	3.5%
Non CML	3.5%	6.5%

Comparison of Deaths on SPIRIT & DASISION

	DASISION		SPIRIT 2	
	IMATINIB	DASATINIB	IMATINIB	DASATINIB
Pt Number	259	260	407	407
Total Deaths	10%	10%	8.3%	7.6%
CML related	6.5%	3.5%	2.7%	2.2%
Non CML	3.5%	6.5%	5.6%	5.4%

Combination of Nilotinib and Pegylated Interferon Alfa-2b Results in High Molecular Response Rates in Chronic Phase CML:

Interim Results of the ALLG CML 11 Pinnacle Study

David T Yeung, Andrew P Grigg, Naranie Shanmuganathan, Ilona Cunningham, Jake Shortt, Philip Rowling, John Reynolds, Rachel Cushion, Rosemary Anne Harrup, David M Ross, David Kipp, Anthony K Mills, Christopher K Arthur, Anthony P Schwarer, Kathryn Jackson, Nicholas Viiala, Robert Weinkove, Agnes S M Yong, Deborah L White, Susan Branford, Timothy P. Hughes

on behalf of the ALLG

Study design – Single arm phase IIb

Newly diagnosed CML-CP
Age ≥18
No active vascular disease
Adequate organ function

AE management:
1. Switch to Imatinib for Grade III/IV AE
2. Maintain TKI dose intensity in preference to Peg-IFN

24 mos

3 mos

Peg-IFNα 2b (MSD) 30-50mcg/wk

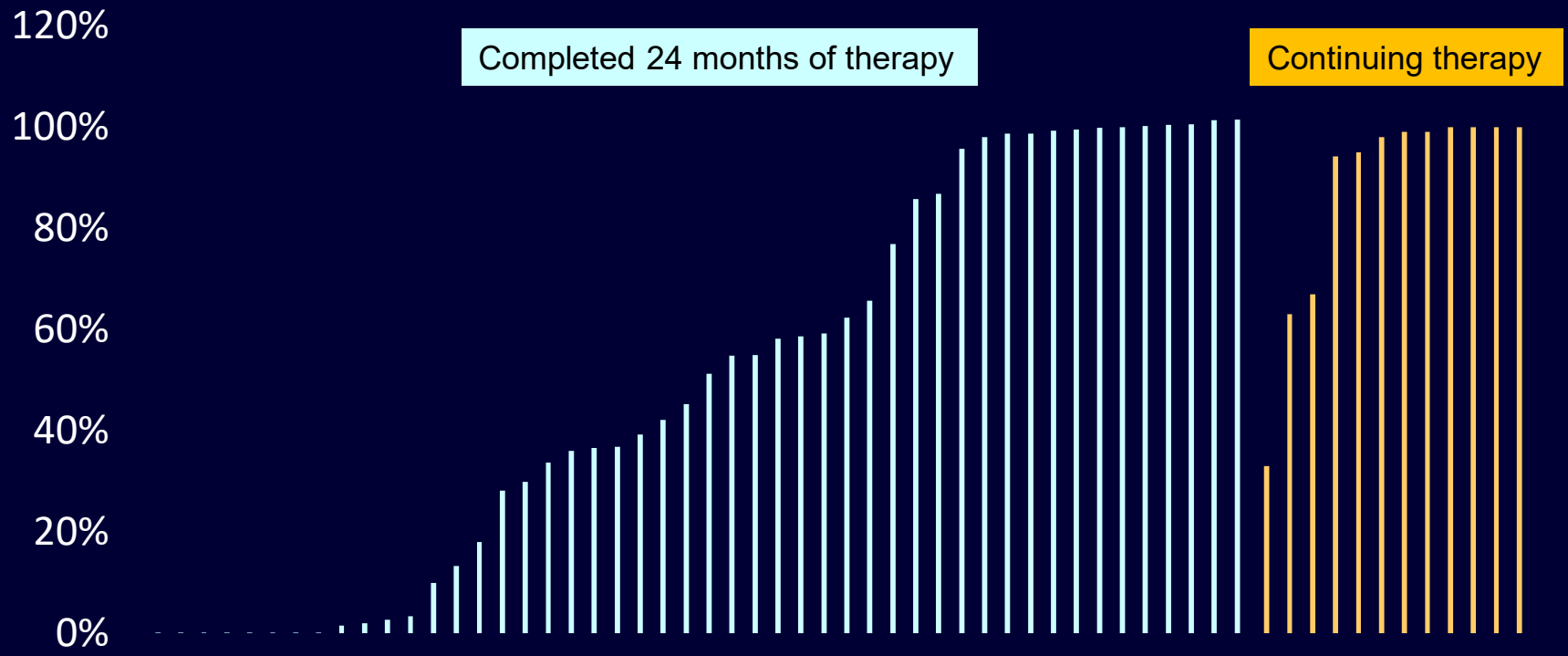
Nilotinib 300mg BID*

60mos

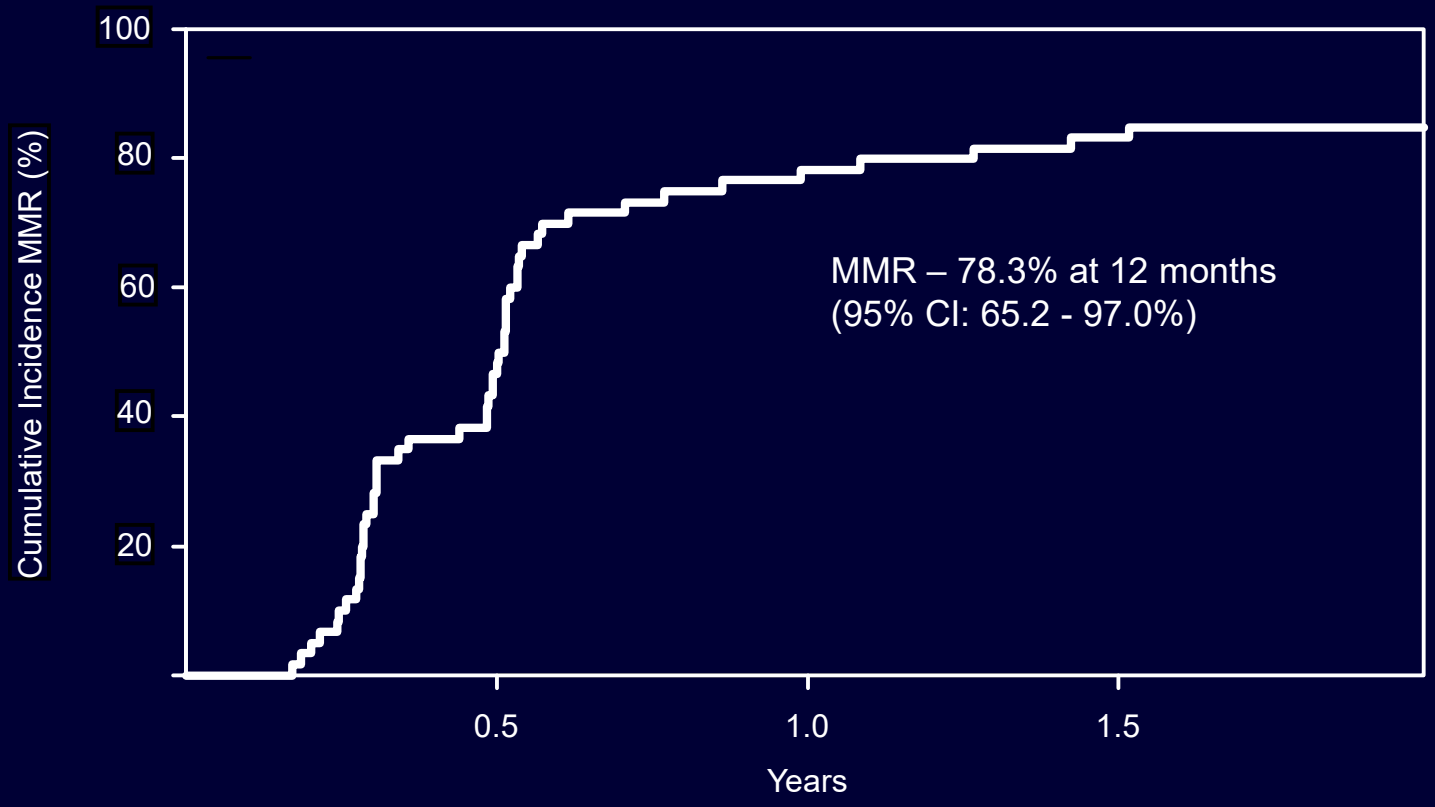
Co-primary end points:
MMR at 12 months
MR 4.5 at 24 months

*Dose escalation permitted for failure to achieve 2013 optimal ELN response

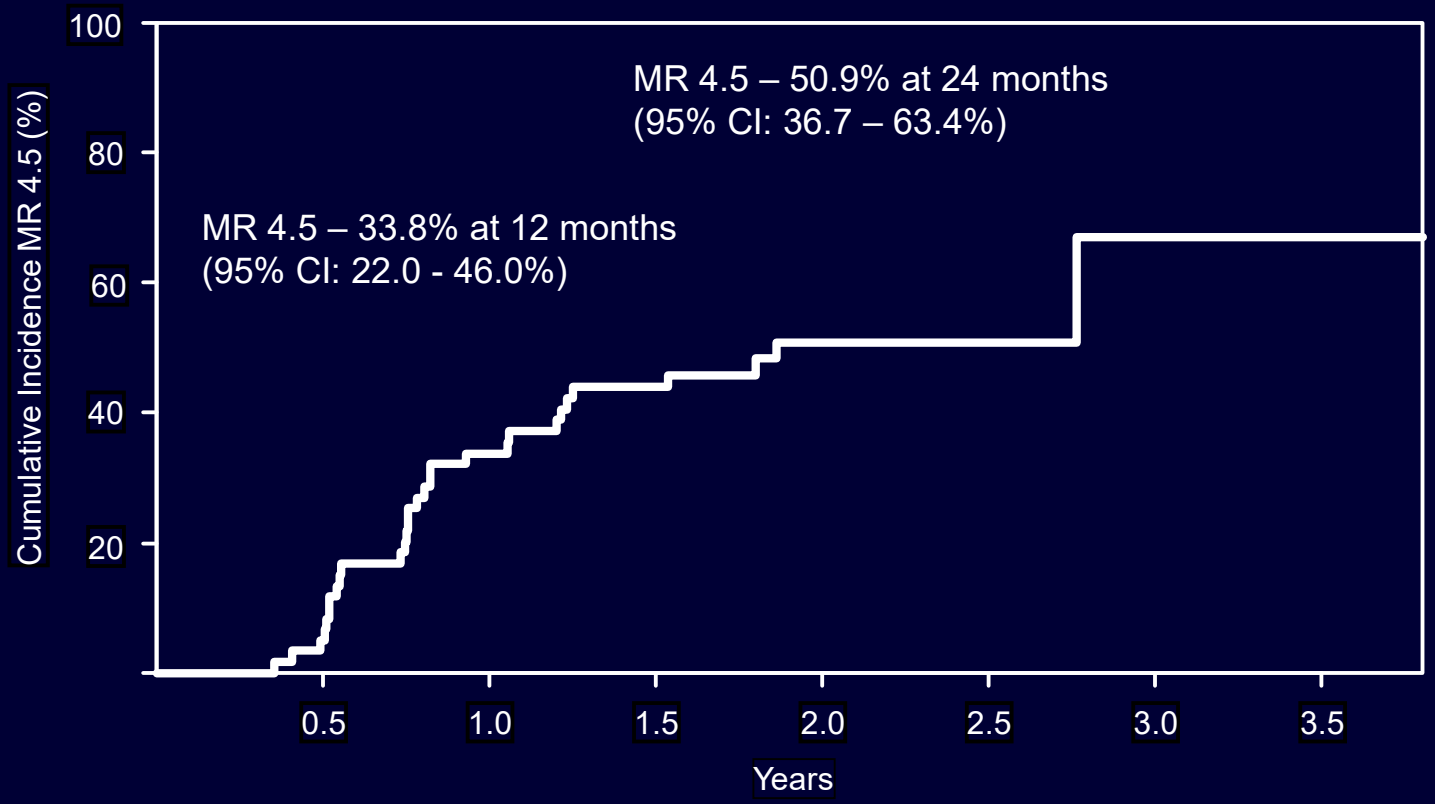
Peg-IFN-α dose assignments



Cumulative incidence: MMR



Cumulative incidence: MR 4.5



Molecular response rate summary

Study	Treatment	12mo MMR	24mo MR4.5
ENESTnd[1]	NIL 300mg BID	55%	25%
ENEST1st[2]		69%	39%
ENESTxtnd[3]		71`%	Not reported
Current	NIL + Peg-IFN	78%	51%

1. Hochhaus et al. Leukemia 2016. 30(5):1044-54
2. Hochhaus et al. Leukemia 2016. 30(1):57-64
3. Hughes et al. Br J Haematol. 2017.179(2):219-228.

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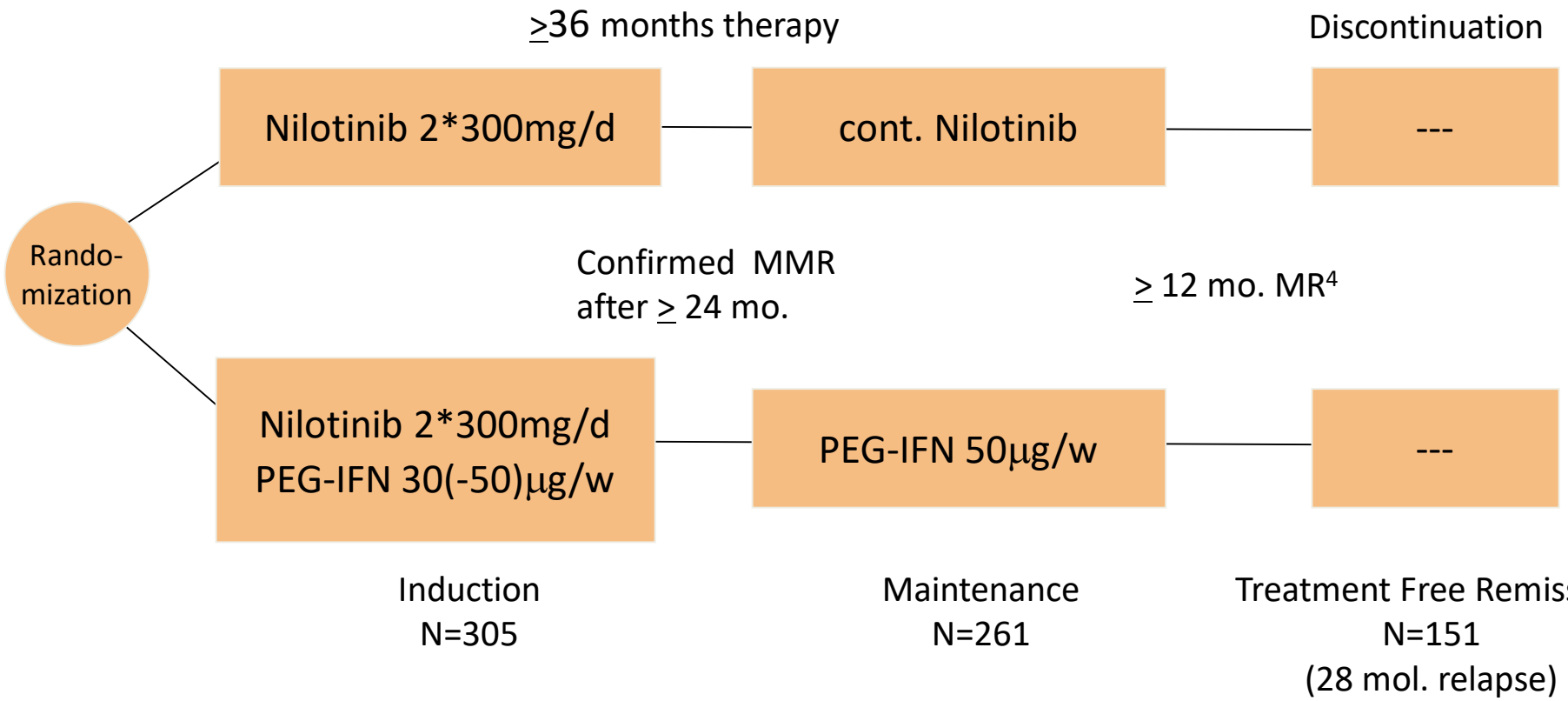
Nilotinib vs Nilotinib plus Pegylated Interferon-α2b Induction and Nilotinib or Pegylated Interferon-α2b Maintenance Therapy for Newly Diagnosed BCR-ABL+ CML Patients in Chronic Phase: Interim Analysis of the TIGER (CML V)-Study.

Andreas Hochhaus, Jena,

for the German CML Study Group

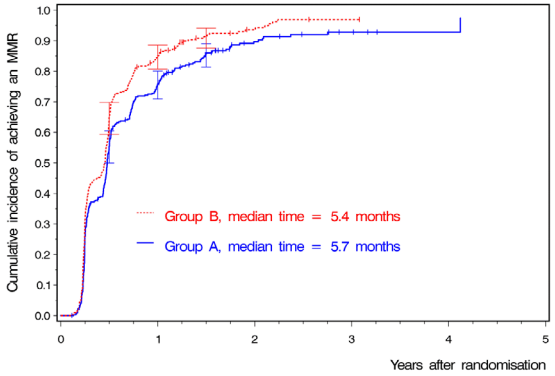
TIGER STUDY

N=717 (Median follow up 34.1 mo.)



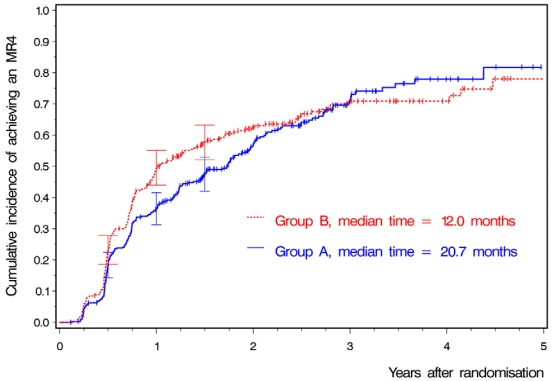
Cumulative incidence of molecular response

MMR



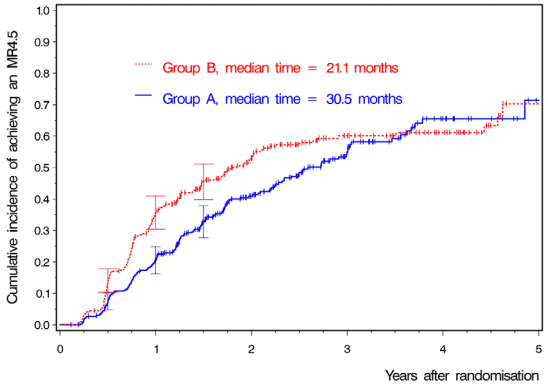
By 18 mo:
Group B: 0.91 [0.88, 0.95]
Group A: 0.86 [0.81, 0.89]

MR^4



By 18 mo:
Group B: 0.57 [0.52, 0.63]
Group A: 0.48 [0.42, 0.53]

MR$^{4.5}$



By 18 mo:
Group B: 0.46 [0.40, 0.51]
Group A: 0.33 [0.28, 0.38]

5 EUTOS IS standardized central labs; typical transcripts only

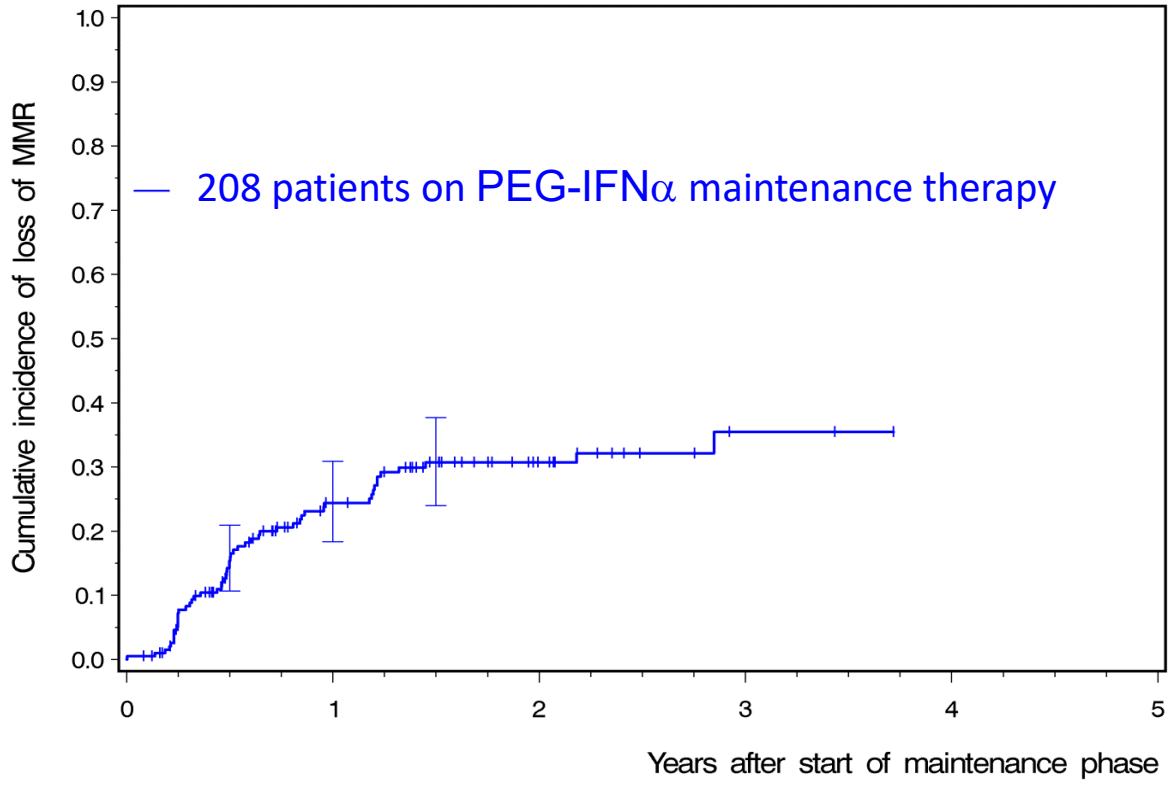
Loss of molecular response (BCR-ABL1 levels >1%) on PEG-Interferon α maintenance therapy, n=208

Probability of mol. relapse

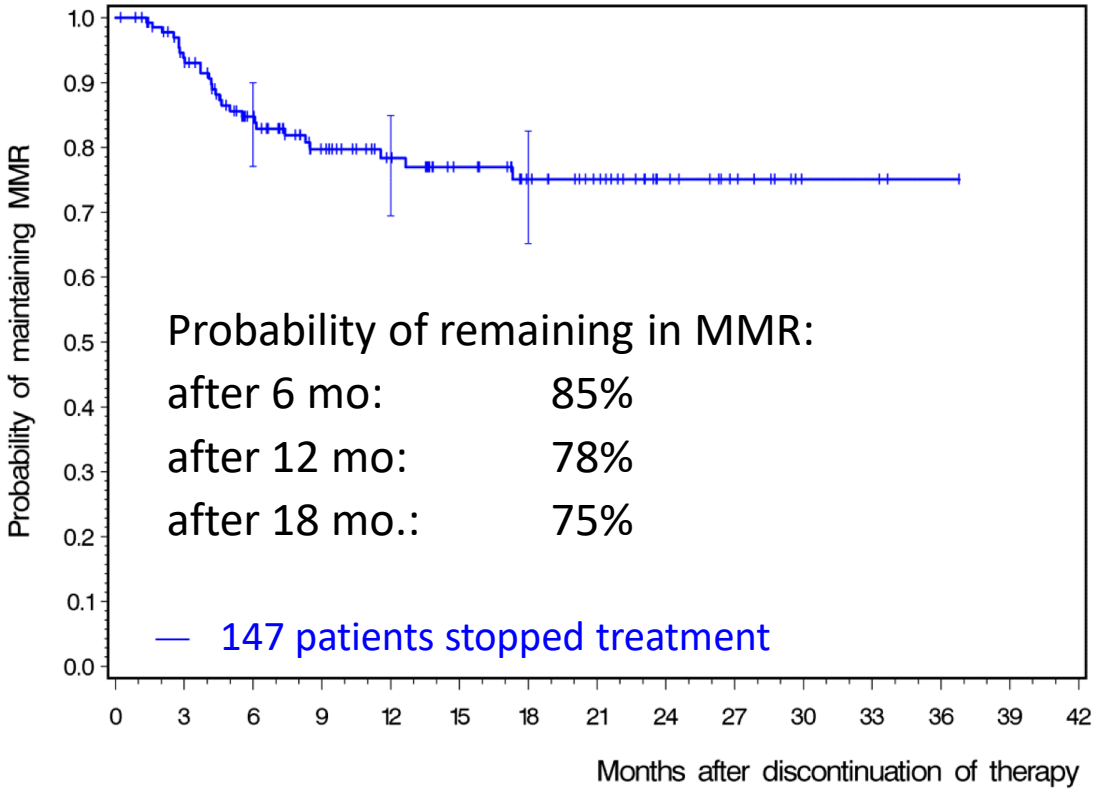
after 6 mo.: 15%

after 12 mo.: 24%

after 18 mo.: 31%



Treatment free remission, n=147



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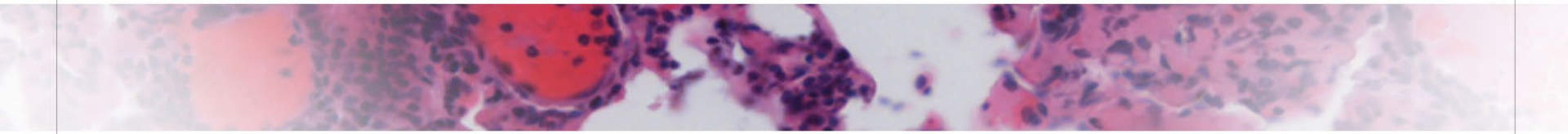
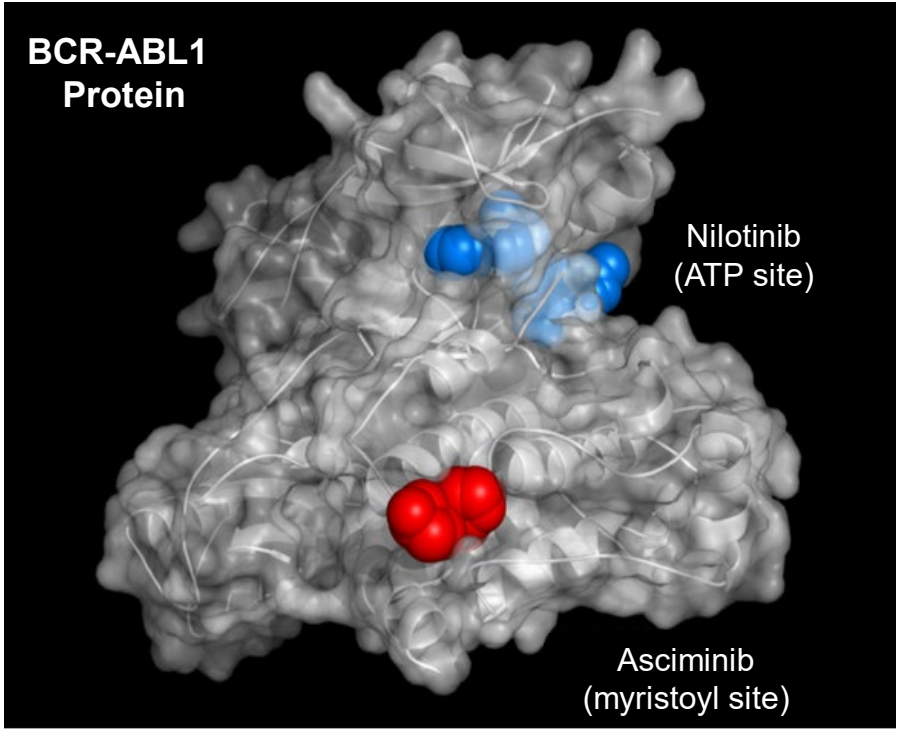


Asciminib, a Specific Allosteric BCR-ABL1 Inhibitor, in Patients with Chronic Myeloid Leukemia Carrying the T315I Mutation in a Phase 1 Trial

Delphine Rea, MD, PhD

Asciminib Is a Potent, Specific Inhibitor of BCR-ABL1 With a Distinct Allosteric Mechanism of Action

- Potent BCR-ABL1 inhibition
- High specificity
- Less susceptible to mutations that confer resistance to TKIs
- Potential to combine with TKIs



ATP, adenosine triphosphate; TKI, tyrosine kinase inhibitor.

Clinical development of asciminib

Phase 1 first-in-human study (NCT02081378)[1]

- Patients with Ph+ leukemias
- Failure of ≥ 2 ATP binding-site TKIs
- Multiple asciminib doses/regimens

Randomized phase 3 study (NCT03106779)[2]

- Patients with CML-CP and failure of ≥ 2 ATP binding-site TKIs

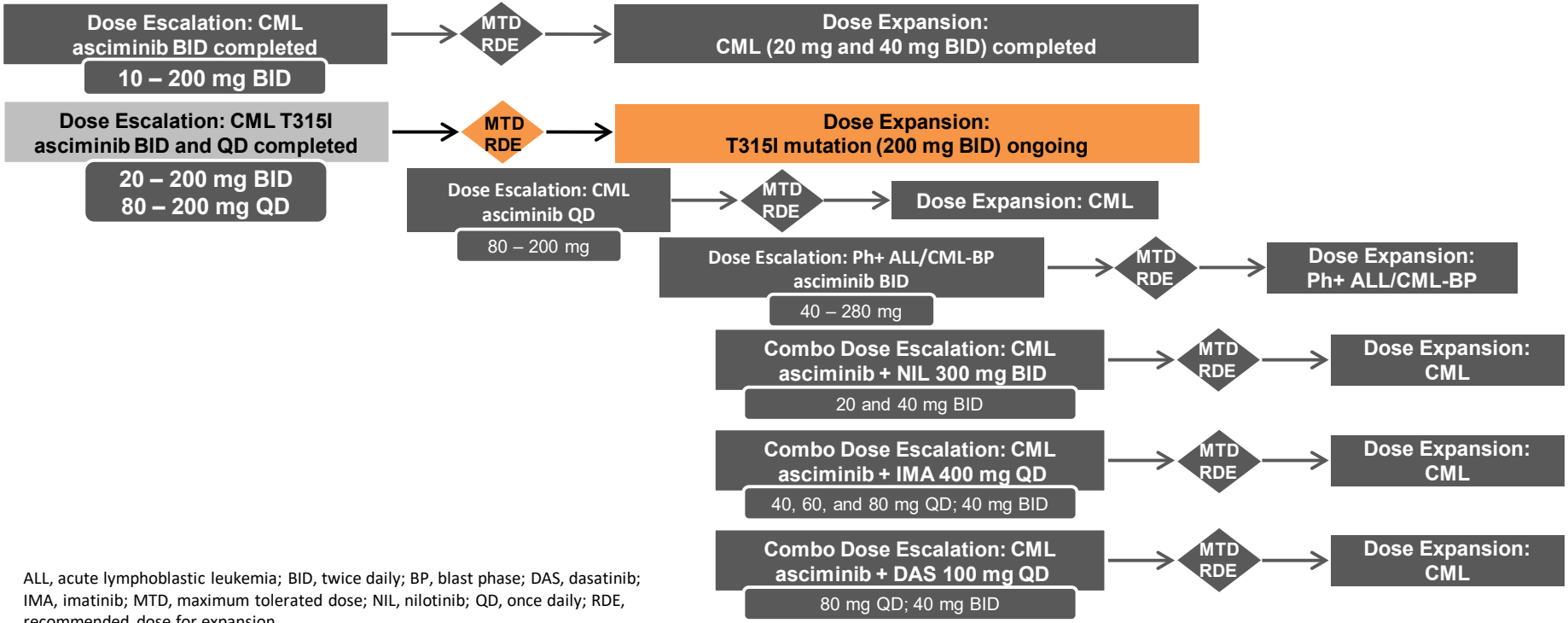
Randomized phase 2 study (NCT03578367)[3]

- Patients with CML-CP and no DMR after ≥ 2 y of 1L imatinib

1L, frontline; CP, chronic phase; DMR, deep molecular response; Ph+, Philadelphia chromosome–positive.

1. Hughes TP, et al. *Blood*. 2016;128: abstract 625. 2. Mauro MJ, et al. *J Clin Oncol*. 2018;36: abstract TPS7081. 3. Saglio G, et al. Presented at the 20th Annual John Goldman Conference on Chronic Myeloid Leukemia: Biology and Therapy; September 13-16, 2018; Miami, Florida.

First-in-human phase 1 study design



ALL, acute lymphoblastic leukemia; BID, twice daily; BP, blast phase; DAS, dasatinib; IMA, imatinib; MTD, maximum tolerated dose; NIL, nilotinib; QD, once daily; RDE, recommended dose for expansion.

Baseline disease characteristics

Demographics and Prior Therapy	N = 32
Age, median, years (range)	54.0 (29-77)
Male, n (%)	25 (78.1)
ECOG performance status, n (%)	
0	26 (81.3)
1	6 (18.8)
Number of prior TKIs, n (%)	
1	3 (9.4)
2	11 (34.4)
3	11 (34.4)
≥ 4	7 (21.9)
Prior ponatinib treatment, n (%)	19 (59.4)
Ponatinib resistant[a]	12 (37.5)
Ponatinib intolerant[b]	7 (21.9)

} 56%

Disease Characteristics	N = 32
Disease phase, n (%)	
CML-CP	30 (93.8)
CML-AP	2 (6.3)
CHR at screening, n (%)	
No	15 (46.9)
Yes	17 (53.1)
CCyR at screening, n (%)	
No	22 (68.8)
Yes	7 (21.9)
Incomplete[c]	3 (9.4)
MMR at screening, n (%)	
No	30 (93.8)
Yes	1 (3.1)
Not assessable[d]	1 (3.1)

AP, accelerated phase; CCyR, complete cytogenetic response; CHR, complete hematologic response; MMR, major molecular response (*BCR-ABL1* ≤ 0.1% on the International Scale [IS]).
[a] Patients who discontinued due to disease progression, completed prescribed regimen, or showed lack of efficacy at their last ponatinib regimen. [b] Patients who discontinued due to toxicity or adverse events (AEs) at their last ponatinib regimen. [c] Insufficient number of metaphases available to evaluate for CCyR. [d] One patient had atypical *BCR-ABL1* transcript.

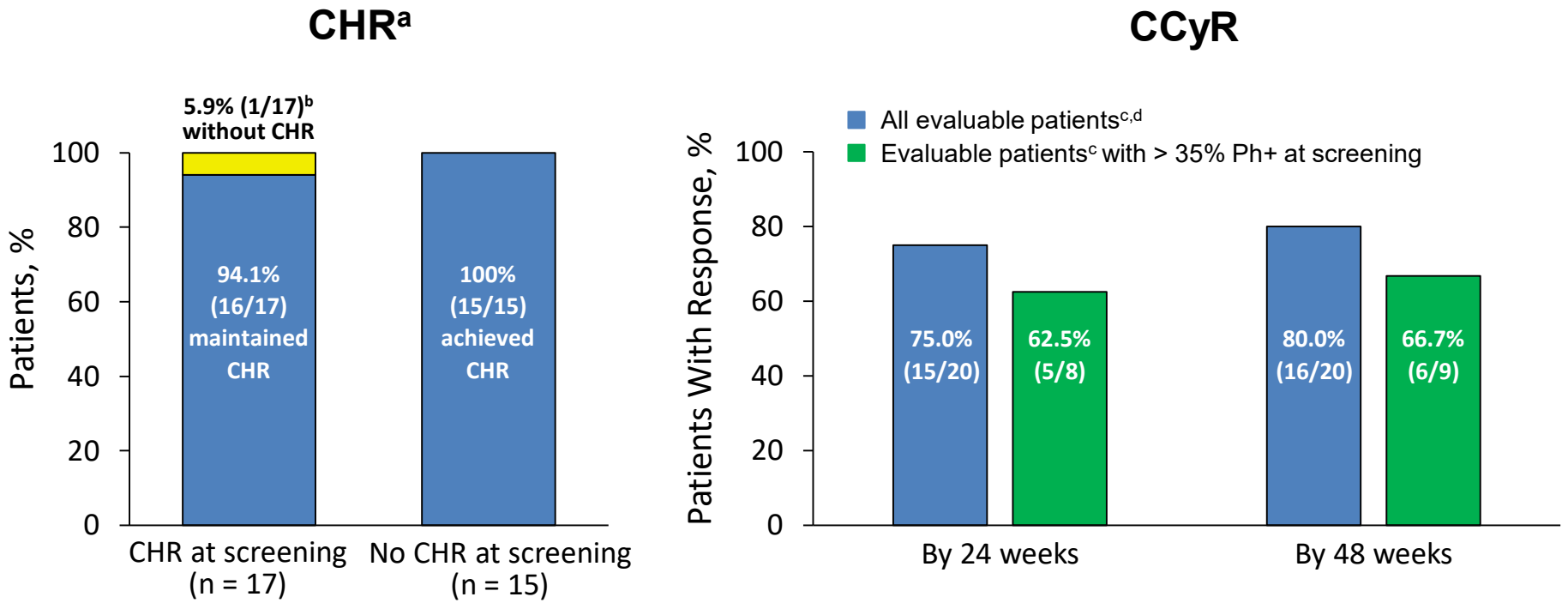
Patient disposition

Patients, n (%)	200 mg BID (N = 32)
Treatment ongoing	29 (90.6)
Treatment ended	3 (9.4)
Lack of response[a]	2 (6.3)
Adverse event	1 (3.1)

- Analysis is based on a data cutoff date of July 15, 2018
- Median duration of exposure: 27.6 weeks (range, 1.0-85.6 weeks)

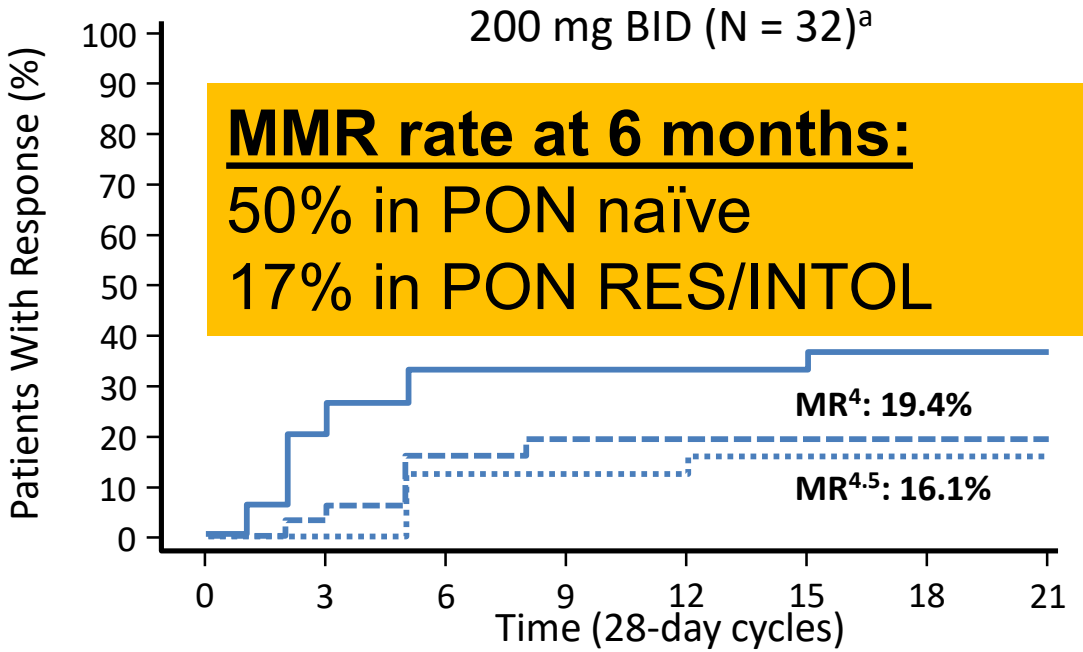
[a] One patient had *BCR-ABL1*^{IS} > 10% and thrombocytosis at screening, and discontinued after continued *BCR-ABL1*^{IS} > 10% and grade 1 thrombocytosis. The other patient had CML-CP at study entry and persistent thrombocytosis with no progression to AP on study.

Hematologic and cytogenetic responses



[a] Maintenance or achievement of CHR by the data cutoff, based on clinical review of laboratory parameters. [b] One patient with persistent thrombocytosis was in CHR at screening (platelets 395K) and not in CHR during follow-up due to thrombocytosis (platelets 539K). [c] Evaluable patients had a cytogenetic evaluation within the specified time window or achieved a CCyR or discontinued treatment before that time window. [d] Maintenance or achievement of CCyR.

Cumulative molecular response rates



MMR % (N = 30): 0.0	26.7	33.3	33.3	33.3	36.7	36.7	36.7
MR^4 % (N = 31): 0.0	6.5	16.1	19.4	19.4	19.4	19.4	19.4
$MR^{4.5}$ % (N = 31): 0.0	0.0	12.9	12.9	16.1	16.1	16.1	16.1

MR^4, *BCR-ABL1*^{IS} ≤ 0.01%; $MR^{4.5}$, *BCR-ABL1*^{IS} ≤ 0.0032%. [a] One patient with atypical *BCR-ABL1* transcript and no molecular data was excluded from analyses of cumulative molecular responses; 1 patient with MMR at screening was excluded from analysis of cumulative MMR. [b] Among patients who achieved MMR.

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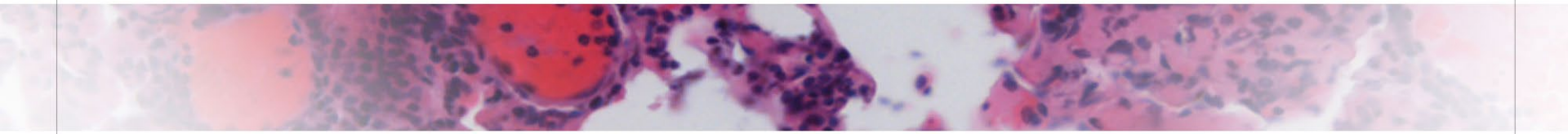

Phase-1 Study of PF-114 Mesylate in CML Failing Prior Tyrosine Kinase-Inhibitor Therapy

NCT02885766

60th ASH Annual Meeting
December 1-4, 2017
San Diego, CA

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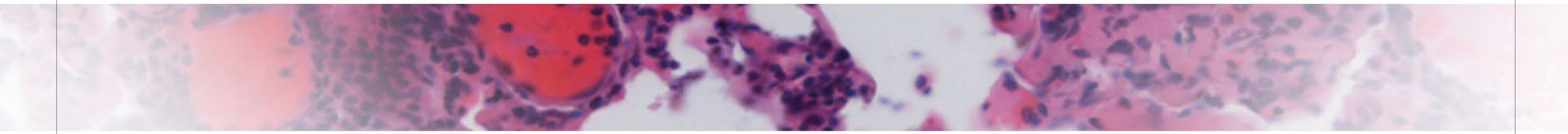


Safety and Efficacy of HQP1351, a 3rd Generation Oral BCR-ABL Inhibitor in Patients with Tyrosine Kinase Inhibitor-Resistant Chronic Myeloid Leukemia: Preliminary Results of Phase I Study

Qian Jiang, M.D.[1], Xiaojun Huang, M.D., Ph.D.[1], Zi Chen, M.D., Ph.D. [2], Lichuang Men[2], Wei Liu, M.D., Ph.D. [2], Xuemei Sun, M.D.[2], Jiao Ji, M.D., Ph.D. [2], Hengbang Wang, M.D., Ph.D. [2], Ting Zhao, M.D.[1], Yue Hou[1], Po Hu[2], Lei Zou[2], Hua Yan[2], Yingjie Huang, M.D.[2,3], Dajun Yang, M.D., Ph.D. [2,3] and Yifan Zhai, M.D., Ph.D. [2,3]

[1]Peking University People's Hospital, Peking University Institute of Hematology, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing, China. [2] HealthQuest Pharma Inc. Room F314, GIBI, No.3 Lanyue Road, Guangzhou, China.[3]Ascentage Pharma Group Inc. 9400 Key West Avenue, Suite 280, Rockville, MD 20850.

The evaluation of residual disease by digital PCR and TKI duration are critical predictive factors for molecular recurrence after stopping Imatinib : Results of the STIM2 study

Eudract #: NCT01343173

Franck E Nicolini, Stéphanie Dulucq, Joëlle Guilhot, Gabriel Etienne, François-Xavier Mahon and the Fi-LMC group

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Bergonié UNICANCER NOUVELLE-AQUITAINE

CHU Hôpitaux de Bordeaux

CHU de Poitiers

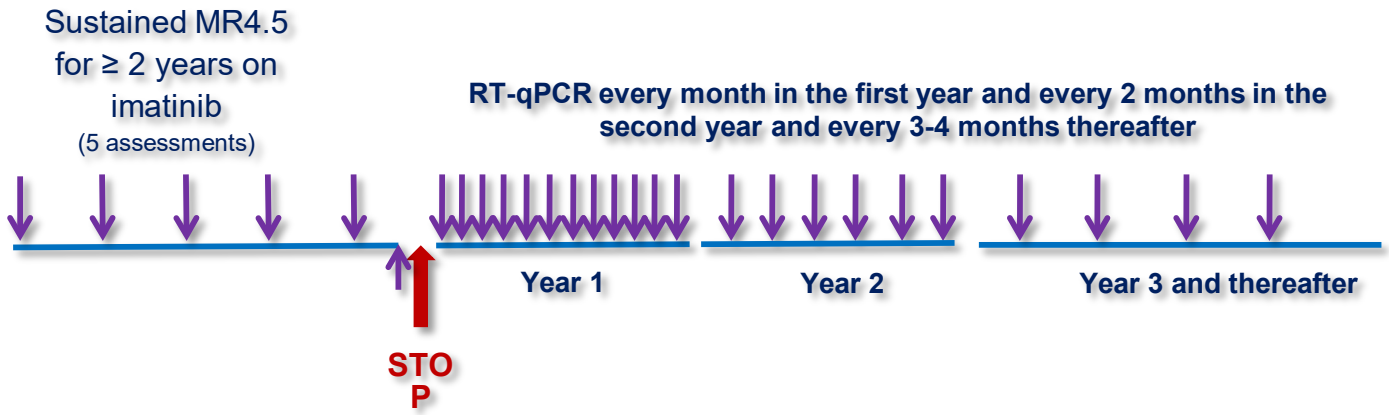
Inserm Institut national de la santé et de la recherche médicale

fiLMC FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

~~STIM 1~~ STIM 2 study design

n=200

≥ 3 years on Imatinib **front-line**



Molecular recurrence: Positivity of *BCR–ABL 1* transcript confirmed by *a* second consecutive analysis indicating at least one log increase, or loss of MMR on one point.

Molecular recurrence → **Imatinib** re-challenge

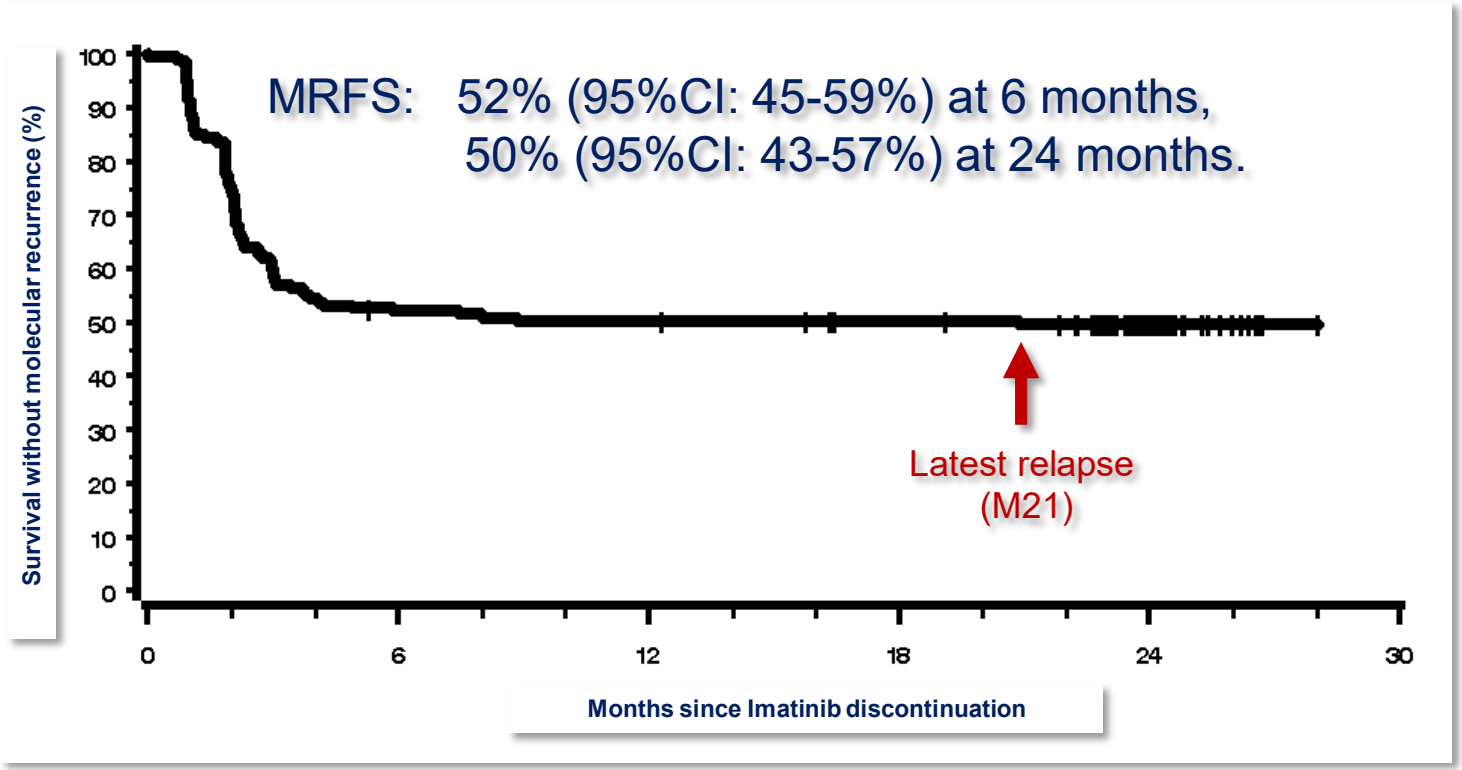
Mahon FX et al. The Lancet Oncology, 2010;11(11): 1029-1035
Etienne G. et al. J Clin Oncol 2016; 35: 298-305

fiolmc
FRANCE INTERGROUPE DE LA LEUCEMIE MYELOIDE CHRONIQUE

STIM 2: General characteristics of the patients

Variables		value
Median age at diagnosis	Years	55.5 (15.3-84.8)
Median age at IM cessation	Years	61.9 (24.2-91.1)
Interval Diagnosis-IM initiation	Months	0.9 (0-58.5)
Interval Diagnosis-IM cessation	Months	80 (39.1-188.3)
Imatinib duration	Months	78.7 (38.5-150.2)
Interval IM initation-1st UMRD	Months	28.2 (2.7-104)
UMRD duration prior to IM cessation	Months	38.9 (24.1-124.6)

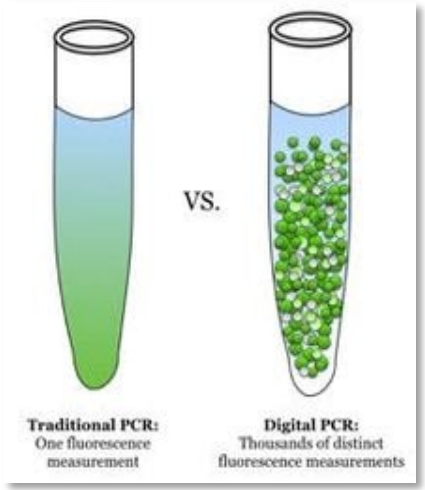
STIM 2: Molecular recurrence–free survival (n=218)



Median follow-up after imatinib cessation: 23.5 (1-64) months.

STIM 2: Is there any room for digital droplet PCR ?

ddPCR can detect 1 positive cell in a mix of 10^7 cells



RESEARCH ARTICLE

AJH

Age and dPCR can predict relapse in CML patients who discontinued imatinib: The ISAV study

Silvia Mori,[1] Elisabetta Vagge,[1†] Philipp le Coutre,[2] Elisabetta Abruzzese,[3] Bruno Martino,[4] Ester Pungolino,[5] Chiara Elena,[6] Ivana Pierri,[7] Sarit Assouline,[8] Anna D'Emilio,[9] Antonella Gozzini,[10] Pilar Giraldo,[11] Fabio Stagno,[12] Alessandra Iurlo,[13] Michela Luciani,[1] Giulia De Riso,[1] Sara Redaelli,[1] Dong-Wook Kim,[14] Alessandra Pirola,[1] Caterina Mezzatesta,[1] Anna Petroccione,[15] Agnese Lodolo D'Oria,[15] Patrizia Crivori,[15] Rocco Piazza,[1] and Carlo Gambacorti-Passerini[1,16*]

ISAV Study

Mori S. et al. A J Hematol 2015; 90: 910-914

Chronic Myeloid Leukemia

ARTICLE

Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: the KID study

Sung-Eun Lee,[1] Soo Young Choi,[1] Hye-Young Song,[1] Soo-Hyun Kim,[1] Mi-Yeon Choi,[1] Joon Seong Park,[2] Hyeoung-Joon Kim,[3] Sung-Hyun Kim,[4] Dae Young Zang,[5] Sukjoong Oh,[6] Hawk Kim,[7] Young Rok Do,[8] Jae-Yong Kwak,[9] Jeong-A Kim,[10] Dae-Young Kim,[11] Yeung-Chul Mun,[12] Won Sik Lee,[13] Myung Hee Chang,[14] Jinny Park,[15] Ji Hyun Kwon,[16] and Dong-Wook Kim[1,17]

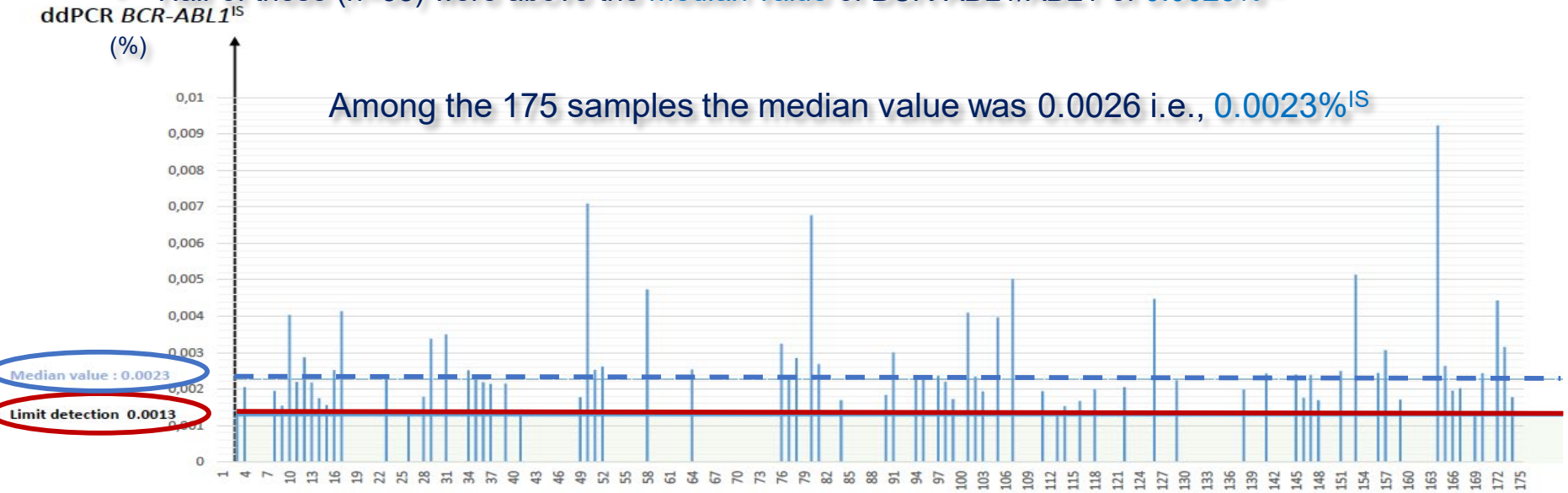
Haematologica 2016
Volume 101(6):717-723

KID Study

Lee A-E. et al Haematologica 2016; 101: 717-723.

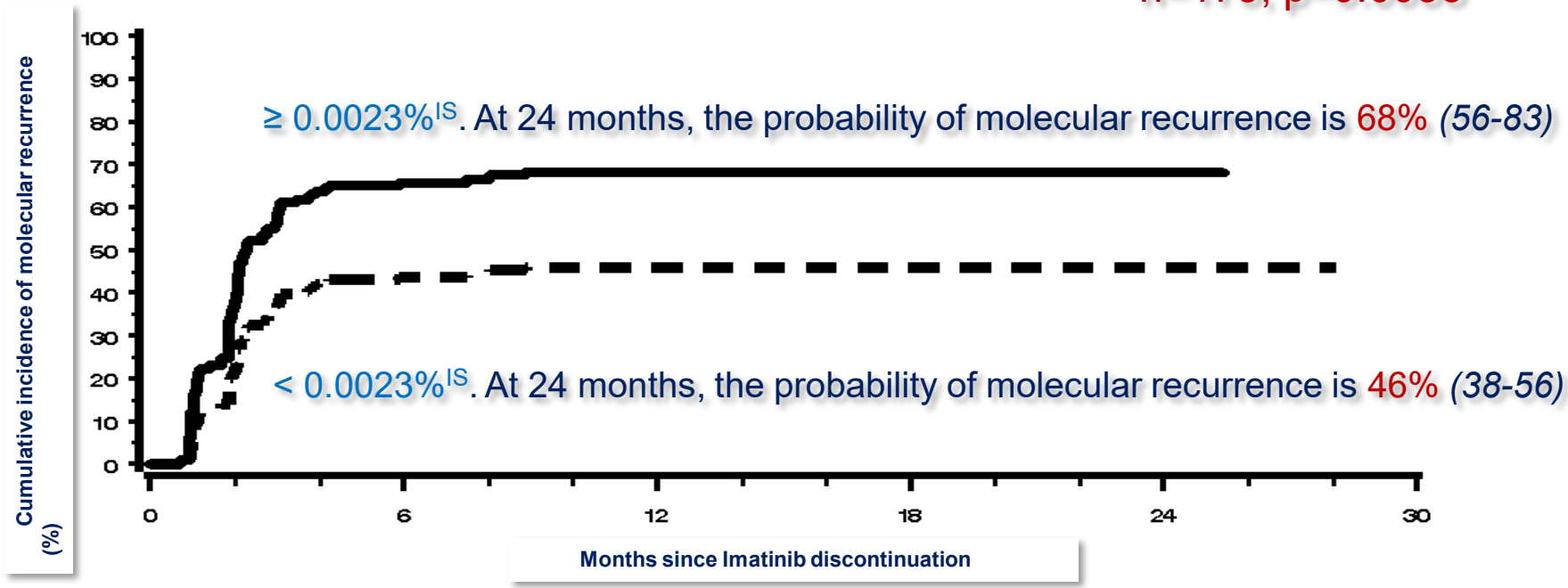
RT-ddPCR BCR-ABL1 values of 175 patients undetectable using RT-qPCR

- The positive threshold value obtained from BCR-ABL 1 “negative” samples was 0.0015% i.e. 0.0013%^{IS}.
- 75 patients’ samples were found to be evaluated by ddPCR above this threshold value of 0.0013%^{IS} and considered “positive ddPCR” (ddPCR+).
- Half of these (n=38) were above the median value of BCR-ABL1/ABL1 of 0.0023%^{IS}



STIM 2 results: MRFS according to ddPCR at Imatinib cessation

n=175, p=0.0053

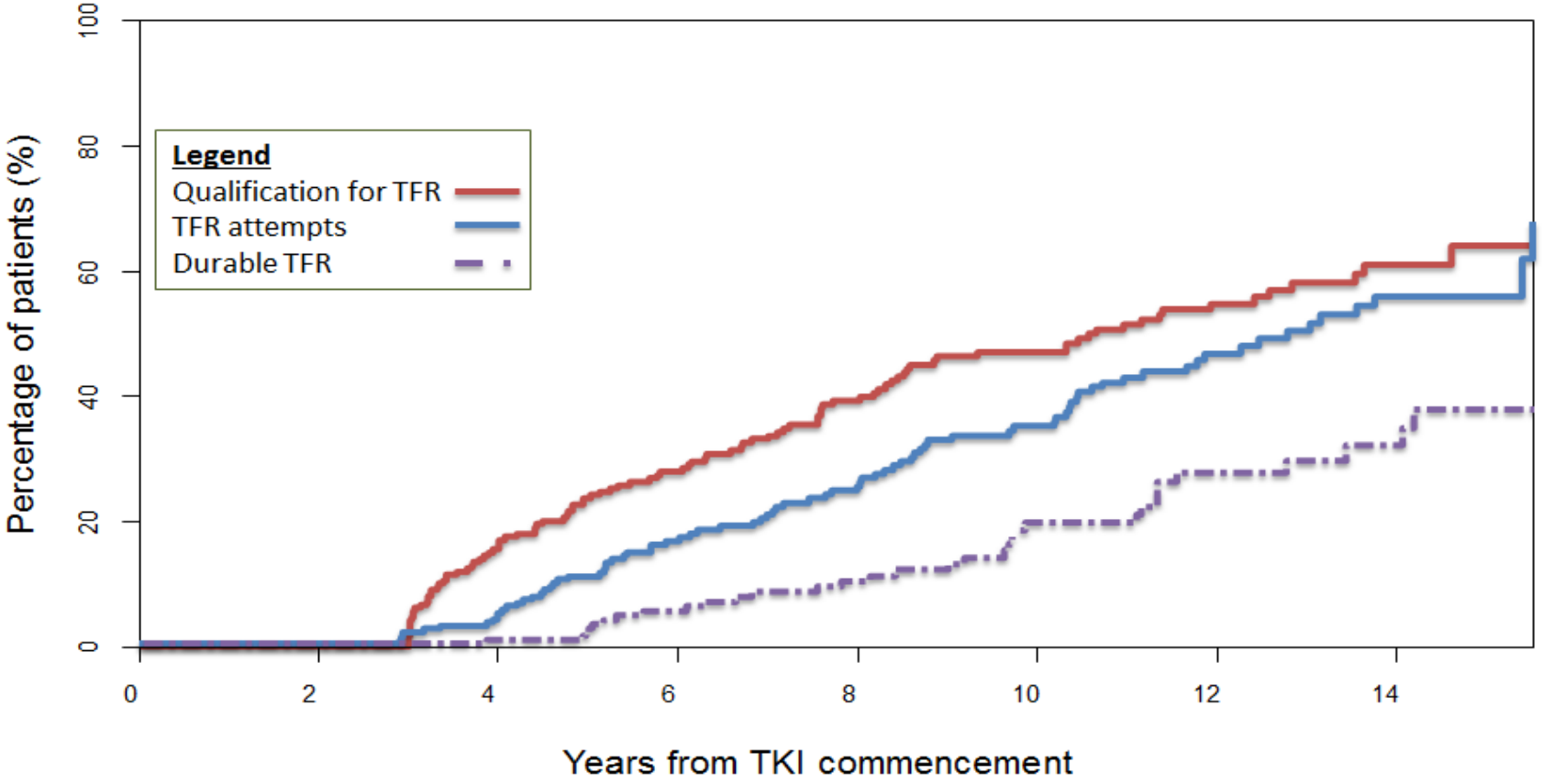


Nicolini FE et al. submitted.

Multivariate analysis

Variables		Hazard ratio (95% CI)	p value
ELTS n=144	Low Other	0.661 (0.39-1.119)	0.661
Imatinib duration n=144	<75 Months ≥75 Months	0.574 (0.359-0.916)	0.0201
ddPCR quantitation n=144	<0.0023%^{IS} ≥0.0023%^{IS}	0.546 (0.337-0.885)	0.0141

Adelaide Cohort: Cumulative Incidence of TFR



15 YRS:

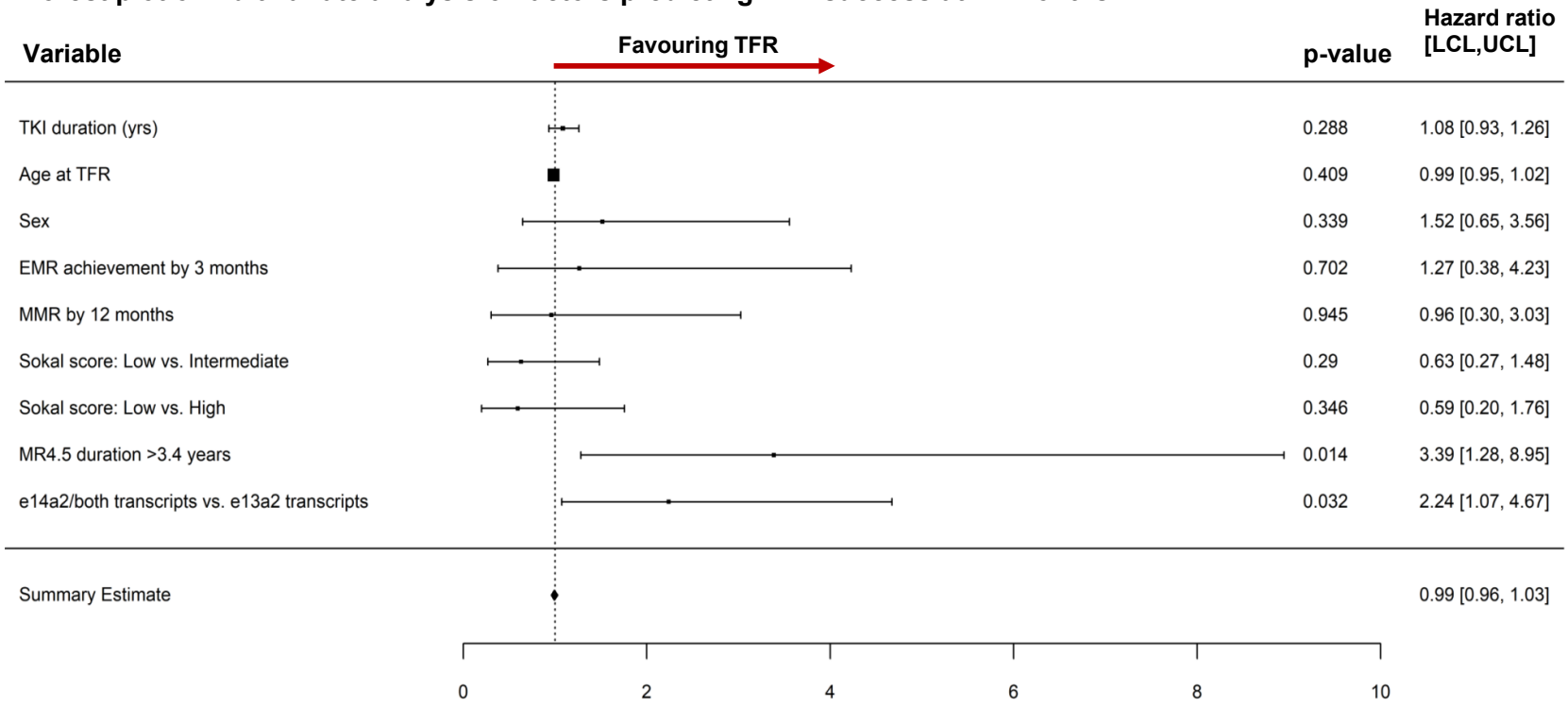
65%

57%

39%

Multivariate Analysis of Factors Predicting TFR

Forest plot of multivariate analysis of factors predicting TFR success at 12 months



Conclusions (1)

- ELTS now the preferred RISK SCORE
- SPIRIT 2 confirms previous studies – no survival advantage for dasatinib BUT better early molecular responses
- PINNACLE shows PEGintron plus nilotinib tolerable and encouraging rate of MR4.5
- TIGER study may point the way to the optimal early TFR approach

Conclusions (2)

- STIM2 provides further support for predictive value of sensitive MRD in TFR studies
- Emerging biomarkers hold promise for rational timing of TFR.
- Asciminib active in T315I mutant CML- especially in PON naïve group
- New TKIs with T315I activity look promising and may be less toxic than ponatinib

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- Jerry Radich

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DEADLINE FOR ABSTRACTS: MAY 8th, 2019

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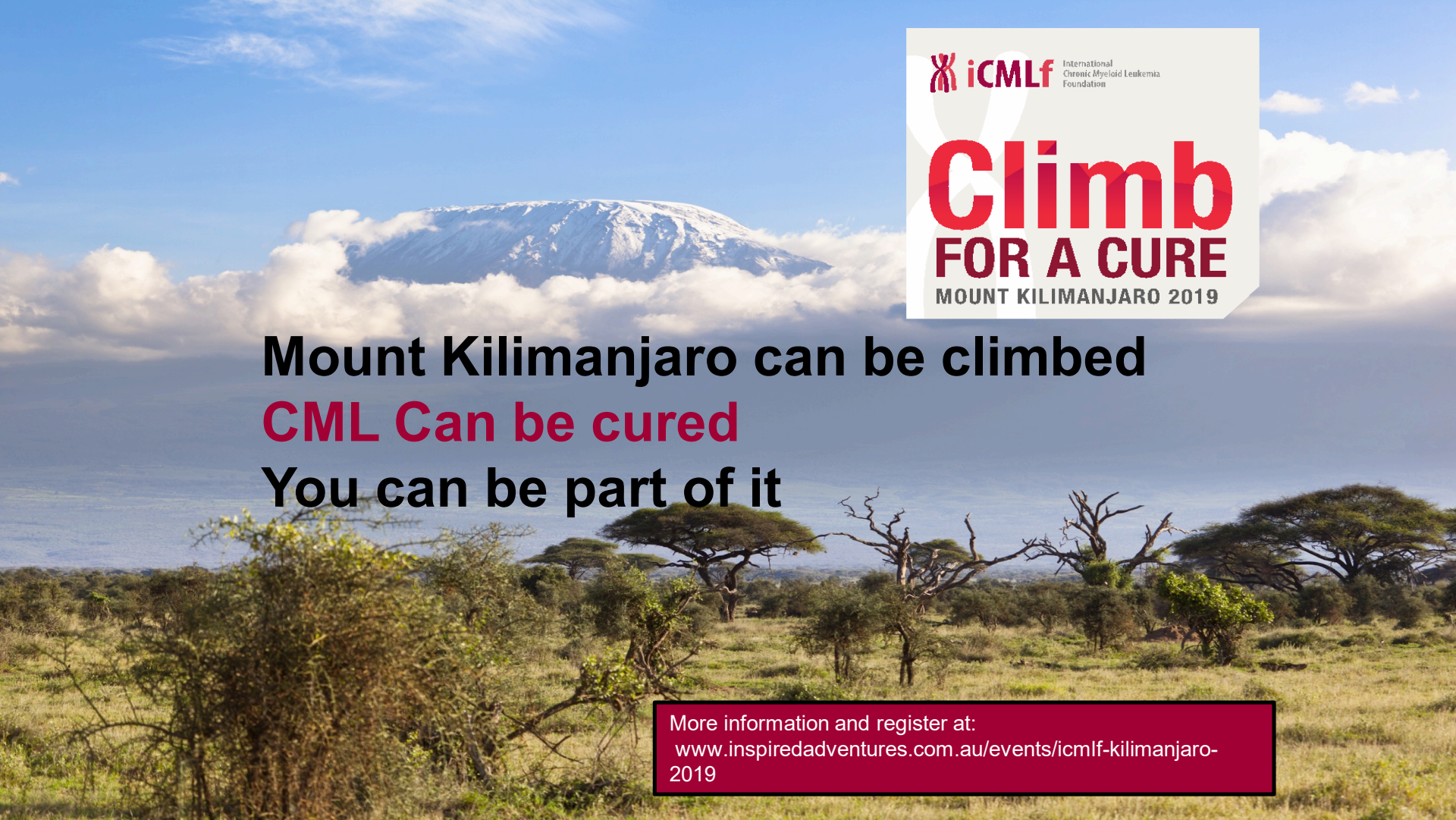
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