Newsletter

iCMLf International Chronic Myeloid Leukemia Foundation

June 2018
Edition 17

About the iCMLf
The International CML Foundation (iCMLf) is a Foundation established by a group of leading hematologists with a strong interest in CML. The mission of the iCMLf is to improve the outcomes for patients with CML globally. The Foundation is registered as a charitable organisation in England and Wales but its charter is global. Its aims are to foster and coordinate global clinical and research collaborations and to improve clinical practice and disease monitoring in CML, especially in emerging economic regions. Scientific advisors and national representatives spanning over 30 countries provide guidance and advice to further the aims of the iCMLf.

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Please support the iCMLf! Your donations and unrestricted grants enable us to support the opportunity for all CML patients to have the best possible outcome no matter where they live.

Dear Colleagues,

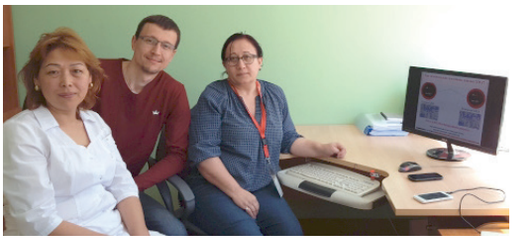
"CML is not a common disease, but it is an important disease. It's deadly, but nowadays it can be managed very well and nobody should die of CML and that's our goal in our professional life time and for this foundation that nobody should die of this disease."
Jorge Cortes, iCMLf Director and cofounder

This is the underlying principal of the work of the iCMLf. We focus on the training and educating physicians on how to use therapeutic strategies and how to improve the outcome for patients all over the world. In the last six months we have added eight presentations from CML experts to our online education program. Topics include; managing toxicities, adherence, the immunology of CML and biomarkers and response prediction.

We make the most of expert speakers and presentations at the major international haematology meetings to provide the educational content on the iCMLf website and keep our global audience up to date. We also share knowledge through the key publications of the month and articles, such as the one on page 4 by Professor Cortes, that gives an overview of the five year PACE trial.

Until now we have not had a formal step-by-step program on the key aspects of CML management. However, this changes today and we are very pleased to bring you the iCMLf Knowledge Centre. The iCMLf Knowledge Centre is an interactive eLearning tool with distinct content for both clinicians and molecular biologists/ pathologists managing CML patients. The four modules cover; CML treatment goals, monitoring in CML, practical considerations of testing and patient cases focusing on the aforementioned subjects. All the content has been produced in collaboration with international CML experts and we are exceptionally grateful for their time and effort over many months to make this a relevant, useful program. The Knowledge Centre would not have been possible with out the support of Novartis Oncology and we sincerely thank the people involved there too. You can read more on the iCMLf Knowledge centre on page 6 of this newsletter.

The iCMLf Forum for physicians from emerging regions and the iCMLf clinical preceptorships are both critical parts of our mandate to assist physicians who treat CML patients in low and middle-income countries. You can read our 2018 updates on these programs on page 3.



Drs Baktigul and Krauchanka with Dr Lomaia during their preceptorship in St Petersburg

Another part of the iCMLf's work is to increase access to high quality CML diagnostics. The iCMLf Diagnosis and Testing Program provides a multifaceted approach to build sustainable local capacity for CML diagnosis and testing in the emerging economic regions. To date, nearly 4,000 tests have been offered as a direct result of this iCMLf program and countless others a result of the staff training and equipment purchased with iCMLf grants. Many thousands of patients receive improved care as a direct result of the projects supported by this iCMLf funding. Applications for the 2018 program are now being sought. You can find out more on page 8. The iCMLf Diagnosis and Testing program is life changing for the people and communities we reach.

"The impact of the grant was immense, in 2016, we had a total of 59 patients, in 2017 the patients numbers shot up to 181, over 300% increase."
Dr Boniface K Githaiga, Nairobi, Kenya

Thank you for being part of the iCMLf community. For more information on how you can help the Foundation, or how we can work together, please email us at *info@cml-foundation.org*

Your iCMLf team

News from the iCMLf

2018 PRIZES

We are delighted to present the 2018 iCMLf prize winners.

Rowley Prize

Professor Nick Cross (UK)

This award acknowledges outstanding contributions to the understanding of the biology of CML and is awarded to Nick Cross in recognition of his scientific achievements to better understand the molecular pathogenesis of CML and the development, validation and standardisation of genetic tests.

Goldman Prize

Professor Jorge Cortes (USA)

This prize recognises outstanding contributions to the clinical management of CML and is awarded to Jorge Cortes for his globally recognised expertise and life-long commitment to the management of patients with CML.

iCMLf Prize

Professor Hemant Malhotra (India)

The iCMLf prize recognises outstanding contributions to improving the treatment of CML in the emerging economic regions. Hemant Malhotra receives the prize for his remarkable achievements to improve the treatment of patients with CML in India and neighbouring countries

NEW PEOPLE AT THE iCMLf

The trustees and advisors of the Foundation are all key CML experts. These people are critical to the strength of the iCMLf giving most generously of their time and expertise. In 2018 we welcome two new Directors, four new Advisors and a new ERSAP coordinator to the iCMLf.

Board of Directors

Michael Mauro directs the Myeloproliferative Neoplasms (MPN) Program at the Memorial Sloan-Kettering Cancer Center in New York.

Giuseppe Saglio is Professor of Internal Medicine and Haematology at the University of Turin, Italy.

Scientific Advisors

- Professor Mhairi Copland (UK)
- Dr Carolina Pavlovsky (Argentina)
- Dr Delphine Réa (France)
- Professor Susanne Saußele (Germany)

ERSAP Program Coordinator

Please welcome Arlene Harris-Buchan as the new ERSAP Program Coordinator.

We take this opportunity to thank all our Directors, Scientific Advisors and National representatives for their commitment to the iCMLf. It's only through your tireless support that we are able to make a difference to the lives of so many patients with CML worldwide.

Program update

PRECEPTORSHIPS

21 *preceptors from*
12 *countries at* **10** *CML centres of excellence*

ONLINE EXPERT PRESENTATIONS

Take a look at the eight new CML *presentations on line* this year. These cover; factors infulencing adherence, imatinib treatment of children and adolescents, the burden of CML in China and India. Presentaions on; treatment free remission, the immunology of CML, managing toxicities and biomarkers and response predication, are also available.


Deborah White


Agnes Yong


Marc Delord


Naranie Shanmuganathan


Meinolf Suttorp


Timothy Hughes


David Ross


Jana Pelouchová

FORUM FOR PHYSICIANS FROM EMERGING REGIONS

Despite wind and snow in Atlanta the iCMLf Forum for Physicians from Emerging Regions went ahead with over 50 attendees.

Topics were:

- **Perspectives on Molecular Monitoring for CML** with perspectives from Associate Professor Susan Branford (Australia) and Dr Elza Lomaia (Russia)
- **Perspectives on Treatment Free Remission** with perspectives from Professor Susanne Saußele (Germany) and Dr Katia Pagnano (Brazil)

The webstreams for all the presentations and discussions are available on the iCMLf website

Thanks to our partners, The Max Foundation, a new highlight of the Forum was a 'Meet the Expert' round table discussion specifically for physicians from the emerging regions. This was a unique opportunity for these physicians from Honduras, Argentina, Brazil, Venezuela, Ghana, Ethiopia, Russia and China to have in depth conversations with CML experts.

Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: F

Jorge E Cortes, et al.

The following article gives an outline of the paper analysing the five year results of the Ponatinib PACE trial. Blood published this paper in March 2018 and the full paper, including references, can be found online at *http://www.bloodjournal.org/content/early/2018/03/21/blood-2016-09-739086*

Key Points

- Ponatinib continued to provide deep, durable responses in heavily pretreated patients with chronic-phase chronic myeloid leukemia.
- Tolerability was acceptable in this heavily pretreated population with five years of follow up.

Paper Overview

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) with potent activity against native BCR-ABL1 and clinically relevant resistant mutants, including the BCR-ABL1^{T315I} gatekeeper mutant, which confers a high degree of resistance to all other currently available TKIs.

The pivotal phase 2 PACE trial evaluated the efficacy and safety of ponatinib at a starting dose of 45 mg once daily in 449 CML or Ph+ ALL patients with resistance or intolerance to dasatinib or nilotinib, or with the BCR-ABL1^{T315I} mutation. Overall, 93% of patients had previously received ≥2 approved TKIs and 56% had received ≥3 approved TKIs. The primary results of the PACE trial demonstrated substantial responses to ponatinib in this heavily pretreated patient population with a median follow-up of 15 months.

Parallel to the high response rates to ponatinib an accumulation of arterial occlusive events (AOEs) was observed.

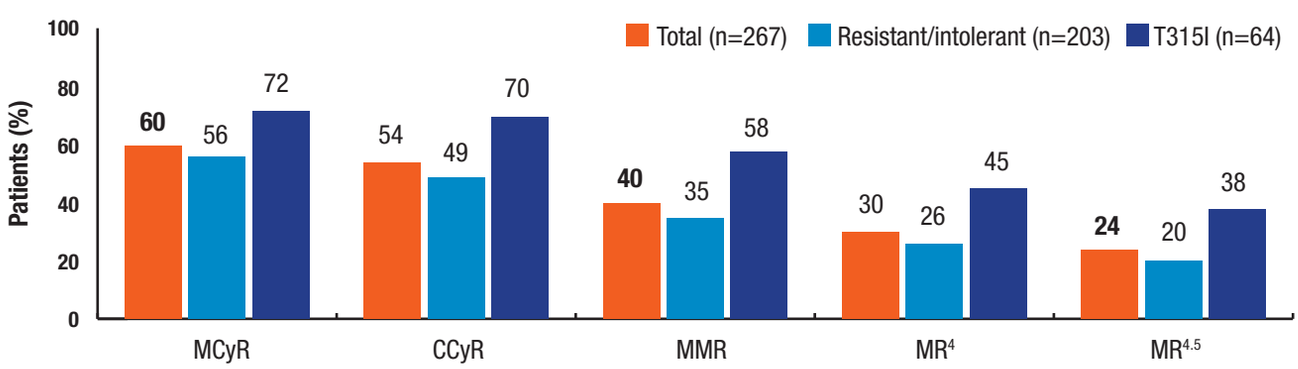
Dose reductions to 30 mg or 15 mg once daily were applied to manage adverse events (AEs), per protocol, or implemented proactively following recommendations from the sponsor in October 2013. Unless benefit-risk analysis justified treatment with a higher dose, the following dose reductions were recommended: 15 mg once daily for CP-CML patients with MCyR, and 30 mg once daily for CP-CML patients without MCyR, AP-CML patients, and BP CML patients. Treatment was continued until disease progression (per protocol), intolerance, or the patient/investigator decision to stop treatment.

This paper focuses on CP-CML patients (n=270) with 56.8 month median follow-up.

Key Efficacy Points

- **82%** of responders estimated to remain in MCyR at five years.
- **59%** of responders estimated to remain in MMR at five years.
- PFS and OS at five years were **53%** and **73%**, respectively.

Figure 1. Efficacy of ponatinib in patients with CP-CML, overall and among patients resistant or intolerant to previous treatment with dasatinib or nilotinib or with the BCR-ABL1^{T315I} mutation. Response at any time.



≥90% of CP-CML patients who had achieved MCyR or MMR maintained response 40 months after elective dose reductions.

Key Safety Points

- In CP-CML patients, the most common treatment-emergent adverse events were rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), dry skin (42%), and constipation (41%).
- The cumulative incidence of arterial occlusive events in CP-CML patients increased over time to 31%, while the exposure-adjusted incidence of new arterial occlusive events (AOEs) did not increase over time.
- When considering risk factors for the development of serious AOEs, patients without any of the known risk factors for such events had a lower relative risk of developing serious AOEs patients with one risk factor had an intermediate relative risk and patients with ≥2 risk factors had the highest relative risk.

Conclusions

After five years of follow-up of the PACE trial, ponatinib provided clinical benefit for patients with heavily pretreated CML or Ph+ ALL. Considering the extent of prior exposure to multiple TKIs in this patient population, these results compare favorably with those of second-generation TKIs in both the second-line setting and later lines. Responses in CP CML patients in PACE have deepened over time, with 24% of CP-CML patients having achieved $MR^{4.5}$ at any time. Maintenance of response, including deep response, was high among CP CML patients irrespective of dose reductions.

For patients with advanced disease, initial responses were rapid, and durability of response was similar to that observed with second-generation TKI therapy for advanced disease after imatinib therapy.

The types of AEs reported with ponatinib in this five year follow-up were generally similar to those reported previously.

The continued follow-up of patients in the PACE trial has elucidated the vascular occlusive event profile in this population. While the cumulative incidence of AOEs continued to increase over time, the exposure-adjusted incidence of newly occurring AOEs did not increase with longer duration of ponatinib treatment. Patients receiving ponatinib should be monitored for high blood pressure, evidence of arterial occlusive or thromboembolic events, and reduced cardiac function. These conditions should be managed as clinically indicated, and ponatinib dosing should be reduced, interrupted, or discontinued as needed.

'These final PACE results demonstrate ponatinib provides durable and clinically meaningful responses, irrespective of dose reductions, in this population of heavily pretreated CP-CML patients.'

While the mechanistic basis for ponatinib-associated AOEs is unknown, this vascular toxicity appears to be dose-related and modified by pre-existing cardiovascular disease and other risk factors. In contrast to AOEs, venous thromboembolic events (VTEs) do not appear to be dose-related, and the frequency of VTEs in this study was within the range observed in the general cancer population.

The final results of the PACE study support ponatinib as an effective treatment for patients with CML who have received prior therapies. The decision to initiate ponatinib therapy should be guided by carefully weighing the risk: benefit ratio for each patient, particularly in those who may be at increased risk of AOEs. Appropriate dose reduction/interruption, and active monitoring and management of pre-existing conditions, are important to mitigate risk in patients receiving ponatinib treatment.

To read the full paper go to at *http://www.bloodjournal.org/content/early/2018/03/21/blood-2016-09-739086*

iCMLf Knowledge Centre – new interactive eLearning tool for CML

The iCMLf is pleased to offer a unique training tool to the CML community. The iCMLf Knowledge Centre is an interactive, eLearning program providing educational content on CML for different user groups. This new resource complements the other iCMLf educational programs we offer. All these initiatives strive to improve clinical practice and disease monitoring for CML through education initiatives worldwide.

Key features:

- Interactive eLearning tool
- Two distinct learning paths for clinicians and molecular biologists/pathologists
- Four learning modules with educational content on CML
- Relevant topics on CML patient management and monitoring
- Certified content produced in collaboration with international experts
- Quizzes to check your knowledge
- Certificates on completion of modules

FOUR LEARNING MODULES

The modules cover relevant topics on CML patient management and monitoring combining current knowledge with practical considerations.

Module 1

CML treatment goals
The first module focuses on evolving treatment milestones and on the importance on early molecular response, major molecular response, and deep molecular response. The content covers clinical data and the clinical implications of achieving key molecular responses.

Module 2

Monitoring in CML
The second module features a discussion on molecular vs. cytogenetic monitoring, optimal test frequency, current and future techniques/ trends and optimal test reports.

Module 3

Practical considerations of testing
The third module discusses the importance of standardisation, test accuracy and timing, interpretation of test results, and identifying kinase domain mutations. The laboratory path also covers sample handling, available test platforms and implementation of IS-standardised testing, and recommendations and techniques for standardisation and recalibrate.

Module 4

Patient case studies
The patient case examples focus on concepts presented in previous modules. The laboratory path also includes examples of best practices (eg lab networks, reference labs, registries).

Each slide set is followed by a quiz to check your knowledge. Certificates are available on completion of each module.

COLLABORATION WITH INTERNATIONAL CML EXPERTS






Clinical path:

- Professor Giuseppe Saglio, Italy (Chair)
- Professor Tim Hughes, Australia
- Professor Jerald Radich, USA

Laboratory Path:

- Associate Professor Susan Branford, Australia (Chair)
- Professor Nick Cross, UK
- Professor Martin Müller, Germany

How to begin?

1. You can easily access the iCMLf Knowledge Centre on the iCMLf website: *https://www.cml-foundation.org/index.php/science-education/icmlf-knowledge-center-2*
2. Once you have signed up you can choose the learning path that suits you best
3. Click through the modules and check your knowledge after each slide
4. Download your personal certificate

THANK YOU

We are especially grateful to Novartis Oncology whose support has enabled us to bring this more formal CML education program to you.

We hope that this new interactive online resource will help you enhance your knowledge in CML patient management, understand available options for molecular monitoring, and learn about practical considerations of BCR-ABL1 testing. If you have any questions, or comments on further study modules please email us at *info@cml-foundation.org.* We will forward these to the topic moderators.

Upcoming iCMLf activities

iCMLf Diagnosis and Testing Program: 2018 grants

Apply Now!

The iCMLf Diagnosis and Testing Program offers seeding grants to hematology institutions in emerging economic regions. These iCMLf grants facilitate diagnosis, testing and long-term disease monitoring of CML patients where it is limited, or not currently available.

Building on the success of the previous forty-eight projects awarded iCMLf grants, the Foundation will offer further funding in 2018 for ten new proposals with a funding of up to $10,000.

Expressions of interest are welcome to *arlene@cml-foundation.org*

Applications close on the 30th July 2018.

Read more *www.cml-foundation.org/index.php/emerging-regions/diagnostics-program*

We hope to see you

20th Annual John Goldman Conference on
CHRONIC MYELOID LEUKEMIA: BIOLOGY AND THERAPY

Chairs: J. Cortes, T. P. Hughes, D. S. Krause
Organizers: R. Bhatia, M. Copland, M. Deininger, P. Hari, D. Perrotti, J. Radich, D. Réa

MIAMI, FL, USA | SEPTEMBER 13-16, 2018

Program will include:

- John Goldman Prize
- Janet Rowley Prize
- iCMLf Prize
- Keynote lectures
- Special lectures and oral presentations selected from submitted abstracts
- Workshops for non-clinical scientists
- Clinical and biology manned poster walks
- 2018 Symposium on Ph+/PH- like ALL
- Concurrent 'Meet the Expert' sessions

Thank you to all our supporters!

We appreciate and thank all the 'Friends of the Foundation' who give both of their time, and financially to further the aims of the iCMLf.

We thank our corporate partners for their generous contributions that help us to improve the outcomes for patients with CML globally.

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To donate to the work of the iCMLf go to *cml-foundation.org*