MEETING MINUTES
11th CML Community Advisory Board (CML-CAB) / 21st CAB CML-session
Academic CML-CAB – 12 October 2020, 16:00-20:00 CET
Title: Mechanisms to cure CML – beyond TFR

Executive Summary

CML Community Advisory Board (CML-CAB) is a working group of the CML Advocates Network operating since 2016. It is a global panel of 18 leading patient advocates from all world regions ("CML-CAB members") who all speak from the unique perspective of a CML patient or relative. CML-CAB members work together to address issues of strategic importance to the community and advocate for the best possible research and equal access to the most innovative treatment & care for CML patients around the world. CML-CAB monitors pharmaceutical developments and research in CML through active and targeted interaction, long-term cooperation and continued dialogue with pharmaceutical partners, regulators, medical experts, and the scientific CML-community.

To this first ever ACADEMIC CML-CAB meeting on "Mechanisms to cure CML – beyond TFR" (TFR = treatment free remission), CML-CAB had invited 8 researchers, all of them working on novel areas of CML research. 16 CML-CAB members covering 223 patient years attended this meeting, the main objectives of which were to

- Build a dialogue with academic researchers
- Reach consensus on what the key issues are in CML (status quo)
- Establish a vision of where we want to be and how a cure could look like (beyond TFR)
- Look at different approaches to cure and learn which of these are most promising to cure CML
- Identify what we as a community can contribute to achieve the vision of a cure for CML, and define a "roadmap to cure"

Moderator Eric Low started the meeting with a strong opening statement: The CML patient community recognises that - while significant advances in the treatment of CML have been made - more needs to be done. The CML-community has set the achievement of a cure for CML as being their number one strategic priority. While the community recognizes that this will be a complex undertaking, Eric Low reminded participants that the success will depend upon achieving alignment of the CML community and system stakeholders. In a passionate statement he added that "as NASA required a set of plans to put a man on the moon, we too need a plan to achieve a cure in CML", and that the CML community´s aim is to put this road map in place.

This overall set-the-scene introduction was followed by a quick introduction to CML-CAB in general given by Denis Costello (Executive Director of the CML Advocates Network), and a session entitled „Status quo and vision: Where are we and where do we want to be? An attempt to consensus" given by Jan Geissler (CML-CAB chair). In an urgent appeal, Jan Geissler insisted that CML (which today has become a chronic disease for most patients thanks to 5 TKIs currently available) is often considered a "lucky cancer", a "done deal", or a "ticked box". He reminded participants that – however – in many countries still today there are severe access issues (both to therapy and PCR), and that the side effects burden of a life-long therapy, the toxicity and non-adherence should not be underestimated. Furthermore, TKI-treatment is a real burden especially on younger patients (since it seriously hinders family planning) as well as a

financial burden on healthcare systems due to increasing prevalence. With regards to TFR, he warned attendees that TFR requires a stable deep molecular response which is only possible after many years of deep remission (every +1 year DMR -3% relapse rate). Furthermore, TFR success is only likely for at best 25-35% of patients, the reasons for this being: 1.) requirements to stop treatment aren´t met, 2.) no or limited access to PCR testing, and/or 3.) 50% relapse rate even with best TKI. Moreover, life-long PCR monitoring (if available at all) is a constant reminder of the disease. He questioned loudly: Will healthcare systems cover this after years of TFR? What about late relapses? Participants were reminded that TFR does not eradicate disease. Last but not least, the stigma of cancer adheres to patients, treatment discontinuation causes fear, anxiety and depression, and there remains a risk of undetected (late) relapses that may lead to progression and death. On behalf of the CML- community, Jan Geissler therefore called for:

- **Recognition that cure is an unmet need** in CML, not a done deal with TFR
- **Joint definition of the problem** the community/CML-CAB trying to solve:
  - All CML patients (which is not given with TFR)
  - can live a normal, long life (which is usually given with TFR)
  - with equivalent quality of life of a normal person (there is uncertainty if this is given with TFR)
  - in absence of any CML disease (which is not given with TFR)
  - without need of any CML therapy (which is given with TFR)
  - without need of continuous monitoring (which is not given with TFR)
- **Commitment and collaboration between all stakeholders, first and foremost patient community and CML researchers** to finding a real cure for CML
- More **funding** for research on a cure for CML
- Building a joint, patient-centric **"Research Network for CML cure"** that helps coordinate, drive and fund research in that space

What followed on the agenda were short presentations by each of the 8 researchers who in a short and concise way presented their individual approach to cure as well as enablers and barriers in finding a cure for CML. Each presentation was followed by a short Q&A per speaker and topic. The following topics were presented:

1. **Mathematical modelling and simulation strategies to understand mechanisms of cancer development and treatment** (Prof Dr Ingo Roeder, Director Institute for Medical Informatics and Biometry IMB (TU Dresden, Germany)
2. **Molecular monitoring of the BCR-ABL1 gene and beyond - Approach to cure, enablers & barriers** (Prof Susan Branford, Associate Professor, School of Medicine and School of Molecular and Biomedical Science of Adelaide University, Australia)
3. **Cancer Immunotherapy - Approach to cure, enablers & barriers** (Prof Satu Mustjoki, Department of Clinical Chemistry, University of Helsinki, Helsinki, Finland)
4. **Vaccine strategies - Approach to cure, enablers & barriers** (Prof Monica Bocchia (Università degli Studi di Siena | UNISI · Department of Medicine, Surgery and Neuroscience, Italy)
5. **CAR-T cell therapy - Approach to cure, enablers & barriers** (Dr Anne-Louise Latif, Honorary Clinical Senior Lecturer School of Medicine, Dentistry & Nursing, Affiliate Institute of Cancer Sciences (Paul O´Gorman Leukaemia Research Centre, Glasgow / Scotland)

6. **CRISPR gene-editing technology - Approach to cure, enablers & barriers** (Prof Francois-Xavier Mahon, Professor and Senior House Physician (University of Bordeaux, France)
7. **Stem Cells and molecular pathways - Approach to cure, enablers & barriers** (Prof Ravi Bhatia, Director of the University of Alabama Division of Hematology-Oncology and Deputy Director of the O'Neal Comprehensive Cancer Centre at the University of Alabama in Birmingham, USA)
8. **Clinical trial data: Hedgehog signaling, CHOICES, TASTER - Approach to cure, enablers & barriers** (Prof Mhairi Copland, Professor of Translational Haematology (Paul O´Gorman Leukaemia Research Centre, Glasgow / Scotland)

The following main enablers were mentioned:

- Willingness of patients to participate in research and being research subjects, donating blood or marrow samples and participating in clinical trials.
- Related to the above: availability of samples for validation of research findings, bio banking
- Collaboration across institutions to pool efforts, share technologies and expertise, and enhance progress

The following main barriers were identified:

- Funding to support research expenses and personnel since research costs with modern new techniques are high
- Patient consent for genomic testing and cost of testing if genomics is to be introduced to aid patient management
- Appropriate legislation / ethics and compliance governance for genomic testing, data collection and sharing: sometimes collaboration with other teams is very difficult due to restrictions in data and sample sharing
- Translation of findings in clinical care: many biomarkers and novel findings but how to take them to the next level

Following the individual presentations, there was a 45 minutes discussion round that enabled the sharing of different perspectives and offered all participants the chance to ask questions. While Prof Satu Mustjoki openly professed the sentence "The status quo in treatment is unacceptable", criticizing the attitude of many clinicians and researchers ("Treatment is so good. So why to study any longer on immunity in CML or other factors?"), she encouraged CML-CAB members to insist on fighting for a real cure. Dr Anne-Louise Latif joined here in encouraging CML-CAB to "keep campaigning that a permanent cure is needed", as well as to push for CAR-T research on expendable antigens to cure chronic phase CML as well as blast crises as well as to continue to engage with clinicians and scientists and keep their work relevant. Jan Geissler expressed his wish to "connect the dots between the work of all" researchers to make sure the data come together. Prof Sue Branford highlighted that she sees the role of patient advocates in providing a bridge between similar on-going projects that already have solutions such as the International CML Genomics Alliance and the European driven "HARMONY Alliance".

As a next step, the moderator encouraged participants to determine whether there will be only one cure or even different cures for different patient populations and geographical locations. In view of allocating scarce resources, he posed the question if cure is the most important aim or if the aim should be to improve current therapies (as a potentially more achievable scenario) so to get more and more patients into TFR and get dormant leukemic stem cells into a stage where there is very little risk for relapse. He asked participants not to forget that a lot of the innovative therapeutic approaches are very complex, will

be very long-term and require high investments until being applicable to patients. With regards to the question what the hypothesis for cure is and how research projects fit together, the moderator asked if pulling data together will give us the chance of finding a cure (or cures) for CML patients. Besides the challenge of aligning and unifying all stakeholders involved in the ecosystem, Eric sees funding as one of the main challenges since historical big research funders are not investing to the same degree as they did in the past (partly because of COVID-19) - the landscape is changing dramatically. Last but not least, he posed the question what a realistic time frame is to achieve a cure (or cures) for CML, reminding participants that after clinical trials there is still a long way to go before the results of trials can be made available to all patients by bringing them to bed-side. After thanking all participants for their fantastic contributions, he closed with the following observation: "The CML community seems to be small enough that things can be done, but not too big that things never get done", while praising the great degree of readiness and preparedness and encouraging the community to write a blueprint from bench to bedside and back again.

Jan Geissler thanked the research community for their engagement and for not resting until we have made that important step towards a cure, stressing again that the patient community is very determined to move that way. He closed his speech of thanks with the following words: "I´d really love to see CAB moving forward with all of you on this!"

Pat Garcia-Gonzalez, CML-CAB co-chair, formally closed the meeting with an anecdote from a 16-year-old Cambodian patient who was diagnosed with CML when she was only 3 years old and had – by coincidence – sent an audio file just that same morning of the Academic CML-CAB thanking her parents, the doctors but also all of the researchers working on CML, and expressing the wish to grow up and be a doctor herself one day to help other patients affected by CML.

This anecdote shows the importance of the work each and every one is doing – let´s help her and others patients live a normal, long life, with the QoL of a normal person in absence of any residual disease and without the need of any CML therapy and continuous monitoring.

Meeting moderated by:
Eric Low

Minutes prepared by:
Denis Costello (Executive Director CML Advocates Network) and Nicole Schröter (CML-CAB officer)