CML Community Advisory Board (CML-CAB)

Minutes of the meeting between the CML-CAB and representatives from Novartis held at the Leonardo Hotel, Frankfurt, Germany, from 08:00-15:30 on 26th February 2017

PUBLIC COMMUNITY VERSION, FOR DISTRIBUTION TO MEMBERS OF CML ADVOCATES NETWORK

Participants

CML-CAB Members
Jan Geissler, Germany (Co-chair)
Giora Sharf, Israel (Co-chair)
Jana Pelouchova, Czech Republic
Mercedes Arteaga, (representing Latin America)
Gail Sperling, USA (representing North America)
Bahija Gouimi, Morocco (representing Africa and Middle East)
Rita Christensen, Denmark (representing Western Europe)
Jelena Cugurovic, Serbia (representing Eastern Europe)
Rod Padua, Philippines (representing East Asia and Pacific)
Felice Bombaci, Italy (Western Europe)
Parameswaran Puthen, India (East Asia / Pacific)
Ferdinand Micho, Kenya (Africa)
Silvia Castillo De Armas, Guatemala (Latin America)
Sarunas Narbutas, Lithuania (Eastern Europe)
Lidija Pecova (Programme Manager)
Celia Marin (Programme Manager)

NOVARTIS
Alexey Salamakha, Associate Director, Patient Advocacy and Access
Geoff Cook, Global Head Reputation & Issues Management
Ting Chen, Associate Director, Global Marketing (Dx), CML
Rafik Fellague-Chebra, Senior Global Medical Director
Prashanth Gopalakrishna, Global Clinical Program Leader
Patricia Brandt, Director, Global Value Access

Meeting moderator
Kathy Redmond

Minutes prepared by:
Marion Alzer

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Summary Notes from the Meeting
The CML Community Advisory Board (CML-CAB) meeting was opened by co-chair Jan Geissler. CML Advocates Network had established the CML-CAB to ensure that patient interest is reflected in R&D and to provide pharmaceutical companies with insights into issues that impact on patients' lives. The attending patient advocates estimated to have an outreach to about 60,000 patients in the CML community. Advocates emphasized that they see the Novartis Patient Declaration as the basis for their mutual relationship with the company. This CML-CAB meeting followed a first meeting in May 2016. A brief overview was presented on the follow-up process and pending action items from the earlier meeting. Topics discussed during the current meeting included clinical development program updates, patient-reported outcomes (PRO), CML today and tomorrow, treatment-free remission (TFR) communication & educational materials review, CML TFR project, and next steps. One minute in silence was dedicated to the memory of patients who were missing because the treatment they needed had not been available to them.
Presentation and Discussion: Clinical Development Program Updates
Treatment-free remission clinical update Novartis discussed the concept of TFR which had been validated in several studies including the ENEST trial program. The program includes two ongoing global pivotal trials: ENESTFreedom and ENESTop. ENESTFreedom is a trial to investigate TFR in CP CML patients who achieved durable DMR after ≥3 years frontline nilotinib. ENESTop assesses TFR in CP CML patients who received second line nilotinib ≥2 years after switch from imatinib. Other regional trials (ENESTGoal in US and ENESTPath in Europe) are investigating the duration on TKI before stopping. $MR^{4.5}$ and MR^{4} have been used as milestones for stopping treatment. Molecular monitoring is not standardized in all parts of the world. Data available from ENESTFreedom and ENESTop suggest that TFR is safe for eligible patients in 1st and 2nd line treatment with nilotinib. No new safety signals were observed. It was concluded that achieving $MR^{4.5}$ after switching from imatinib to nilotinib achieves good results with sustained TFR and that a higher proportion of patients achieves TFR compared to patients continuing on imatinib.

Questions by CML-CAB and Discussion with:

- What was the incidence of cardiovascular events?
  Novartis explained that, from a statistical point of view, there was no difference in cardiovascular events between consolidation and TFR phase. Results from ENESTPath are not yet available.
- Did patients reach the same level of response after reinitiation of TKI treatment?
  Based on a recent analysis update, Novartis is confident that all patients who continued treatment responded.
- Will nilotinib be provided for patients who discontinue trials in countries where nilotinib is not available?
  Novartis suggested that investigators file a request with local Novartis affiliate. Compassionate use can be considered when access is a problem.
- What was the duration of musculoskeletal pain?
  Novartis referred to statistics presented at EHA: mean duration was between 2-3 months. 1 SAE reported where a patient was hospitalized with musculoskeletal paint. Most patients responded to regular painkillers. 15% of patients had musculoskeletal pain described earlier.
- Are data available on stopping treatment after 1st line imatinib?
  Novartis asserted that data presented were not intended to suggest that patients should not stop taking imatinib. Instead, data are part of available data on TFR which show same rate of TFR after 3.6 years on nilotinib than after 8 years on imatinib.
- What are the future plans for stop studies?
  Novartis explained that their TFR program involved more than 1,000 patients including 600 in ENESTPath of which results are yet to come. Novartis is also supporting ISTs around the world.
- Will there be a label change for nilotinib?
  Novartis has ongoing discussions with FDA and EMA with regard to introducing specific TFR data as a treatment milestone in product label of nilotinib. When companies update a label, health authorities expect strong and concrete evidence that can inform patients in the most appropriate and safe manner.
- Will TFR trials be available in India?
  Novartis pointed to TFR data from EUROSKI Should there be a data gap to fill locally, then Novartis can be asked to support an IST.

Feedback by CML-CAB and Discussion with Novartis:

CML-CAB identified a number of issues of concern to the community in the context of TFR.

- Access to nilotinib
- Willingness to take increased risk associated with nilotinib
- Managing food effects/fasting with nilotinib
- Transition from imatinib to nilotinib
- Access to PCR – quality/frequency/complexity
- Anxiety linked with turnover time for PCR results
- Accessibility to TFR trials in specific countries
- Accessibility to TFR to younger population
- Continued provision of nilotinib for patients who discontinue trials in countries where nilotinib is not available
- Fears about stopping
- Relapse on TFR
- Number of patients who do not regain response
- Lack of up-to-date information to physicians in specific countries
- Physicians making decision to stop in absence of guidelines
- Patients discontinuing treatment themselves
- Need for informed decision making – patient may be pushed to stop
- Inappropriate marketing – bad practice
- Strength of data from ENEST program

Follow-up Action:

- CML community and Novartis to discuss these issues further after results from CML community TFR survey are available

ABL001

Novartis provided insights into a novel TKI under investigation in CML. ABL001 targets a different part of the cancer cell than other TKIs. It was developed to gain disease control in CML, including for patients with resistance to current TKIs. ABL001 has the potential to be combined with existing treatments for greater control of the disease. Early studies have confirmed significant and durable response in CML CP patients with failure of prior TKI. Further studies are being designed to establish safety and efficacy in situations with high medical need. If successful, ABL as a single agent and as a combination with an existing TKI may represent an option for early line patients.

Feedback from CML-CAB and Discussion with Novartis:

CM-CAB shared their perceptions and expectations on the development of ABL001, specifically:

- Choice and dose of comparator
- Mutation testing
- Side effect profile
- Food effect and fasting

Novartis are investing in food effect studies, including high-fat studies in response to regulatory requirements. Food-effect studies follow a standardized process defined by authorities. Advocates requested conduct of studies beyond FDA requirements. They want to be involved in the Advisory Board Committee for the study design to contribute the patient perspective.

Advocates reminded Novartis of their patient declaration and feel it needs to be taken more serious in terms of working with the CML community. They would like to see a plan how the CML community can be more regularly and systematically involved across the whole R&D life cycle rather than be engaged only in incidental projects.

Follow-up Actions:

- Novartis to provide FDA standard requirements on food-effect studies to CML-CAB
- CML-CAB to identify gaps of information/ priorities in food-effect studies and then continue dialog more specifically from there
- Novartis to consider involving advocates in the steering committee for the ABL001 study
- Novartis to come back to the community on how advocates can be better and more involved

Hypothetical Treatment Scenario

Novartis was interested in treatment preferences in the following hypothetical scenario:
A patient was diagnosed with CML 2 years ago and has been on an approved drug since. Tolerability and safety are not of major concern. Access to treatment and monitoring is available. The patient has not reached optimal response but wishes to achieve at least MR^4 and may then consider TFR. Three treatment options are available. Tolerability and safety are assumed to be of no concern in any of them.

- Option 1: continue with treatment A (10% success rate, low risk)
- Option 2: switch to treatment B (25% success rate, higher risk)
- Option 3: add new treatment C to existing treatment A (50% success rate, higher risk)

Advocates pointed out missing aspects that would impact on their decision, such as age, willingness to take risk, work life, family planning, QoL, comorbidities. They suggested taking a more methodological approach and find out how the CML community is clustered in terms of risk and benefit with regard to adding another drug. This will be more useful then looking at individual criteria.

Patients shared different perspectives on their willingness to take the risk of adding the new drug. Given the availability of effective therapies and in the absence of sufficient data on the new drug, many patients would place their priorities on survival and QoL. Others stated that they would be willing to try the new drug if it offered hope for cure.

Results: Option 1 – 2 votes; Option 2 – 2 votes; Option 3 – 10 votes

Follow-up Action:

- Continue discussion on benefit-risk of add-on treatment

Presentation and Discussion: Patient-Reported Outcomes (PRO)

PROs for TFR and ABL001

Novartis presented an evaluation of five cancer-specific PRO measures, including CML-specific EORTC QLQ-CML24 and MDASI-CML. They found that few published studies described symptom or AE differences in CML-CP patients according to disease response. There was no direct evidence that any of the reviewed PRO measures would be sensitive enough to detect a change in patients with CML-CP with MMR or DMR. Key opinion leaders (KOLs) reported that patients with CML-CP were generally asymptomatic and AEs do not tend to vary as a function of disease response.

Novartis also presented the MDASI-CML and EQ-5D-5L questionnaires and EQ VAS which had been used in ENESTop and ENESTFreedom to assess the severity of symptoms and their interference with daily life. Very little change in global change scores was seen between consolidation phase to TFR phase or reinitiation phase.

Questions by Novartis and Feedback from CML-CAB:

Novartis: Are existing measures appropriate and sensitive enough to detect unique symptoms in patients with MMR or DMR? Are the symptoms listed in existing measures still relevant during TFR?

Advocates stated that most patients were not familiar with the presented measures. A new questionnaire could be developed specifically for TFR and tested in patients in TFR. PROs should be captured frequently and in a manner convenient to the patient, e.g. using an app on mobile devices. This would allow data entry independent from hospital staff- Data could be anonymized and go directly into registry. PROs for TFR should include questions on adherence, psychological effects (e.g. anxiety, fear, sleeping disorders) and TFR discontinuation effects (e.g. musculoskeletal pain)..

Follow-up Actions:

- Novartis to explore how to collaborate on this topic and incorporate suggestions from CAB and results of planned CML community TFR survey

Presentation and Discussion: CML Today and Tomorrow

CML Today and Tomorrow

Novartis presented an online survey in 2016 that captured current practices among HCPs to help prepare for success tomorrow. Physicians were involved in designing the questionnaire to explore the perception of managing CML from a doctor's perspective. The survey involved 1,050 physicians in 11 countries across the world. Global findings were announced via Novartis social media channels.

Follow-up Actions:

- Novartis to send the survey questions to CML-CAB by email
- Advocates to share their thoughts on the questions with Novartis

Presentation and Discussion: TFR Communication & Educational Materials Review
TFR Communication and Educational Materials Novartis requested CAB feedback based on their experiences with CML for future materials for patients, caregivers, and doctors. Specifically: • Patients' perception and understanding of Treatment-Free Remission (TFR) • Feedback on proposed educational materials • Education and support needs throughout the CML experience • Communication between patients and doctors Novartis made it clear that it was not the role of the company to determine whether or when a patient should discontinue treatment. This decision is to be made jointly by patient and physician. The CAB broke up in two groups to provide feedback on materials they had received shortly before the meeting from Novartis via email. Novartis also welcomed any feedback that CAB members would send later via email. • **Group 1** looked at how information on TFR can be integrated into the existing **patient brochure**. • **Group 2** assessed whether they felt the **physician-patient discussion guide** was suitable to help enter into and lead a dialog with a patient on which route to take. The CAB commented on comprehensiveness of topics covered, level of detail, clarity of language and terminology, format/type and missing information, and made specific suggestions to improve the materials.
Follow-up Actions: • Novartis to incorporate suggested changes and send revised file for further review to advocates • Advocates to return their comments on the revised version within 2 weeks

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Presentation and Discussion: CML Advocates Treatment-free Remission Project
Summary of the presentation: CML Advocates Network presented their CML treatment-free remission project. The objective is to provide patients with information about TFR and inform doctors about patients' needs. The TFR workgroup is composed of expert patient advocates contributing their personal experience with TFR. The project workgroup determined different TFR phases: • Phase 1: consideration, discussion and decision phase • Phase 2: stopping phase: probation period (duration still to be established, maybe 6-12 months) • Phase 3 split into: TFR failure phase vs. stopping phase: long-term TFR The TFR project includes an FAQ section, a glossary, a survey and an information kit. The objective of the survey is to collect data on new aspects of TFR, including patient perceptions, needs and concerns. It comprises about 50 questions addressed specifically to the different identified phases (e.g. patient characteristics, treatments, QoL, adverse/psychological effects, access to/intervals of molecular monitoring and turnaround times for test results, withdrawal symptoms, psychological support, concerns, family perceptions). The survey is currently being tested in a pilot phase. Global launch is planned for March 2017 in all 84 member countries of CML Advocates Networks. First results are hoped to be available at CML Horizons in May 2017. Survey closure is expected in September 2017, followed by data analysis and publication. Follow-up on the survey is currently not planned due to limitations of the survey set-up. An agency with expertise in designing surveys has not been involved for cost reasons.
Feedback from Novartis: • Rephrase the term "failure" to "treatment reinitiation" or "molecular recurrence" and make a concerted effort to use the new term to reflect a change in perception. • Strive for data analysis in August which would enable presentation at ASH. • Involve an expert in designing the questions and analyzing the results. **Feedback from meeting moderator:** • Add survey questions on co-payment and distance to travel for monitoring. The CAB appreciated the constructive feedback for improving the survey and encouraged Novartis to provide any further comments by email.
Follow-up Actions: • Advocates to add "treatment reinitiation" and "molecular recurrence" to their glossary • Advocates to add survey questions on co-payment and distance to travel for monitoring. • Novartis to refer workgroup to expert on designing questionnaires or have survey questions revised in-house.

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Wish lists, Dialogue and Next Steps
Wish list for improving the collaboration between Novartis and CML patient advocates: **CML community wish list:** • Use CML community as a lighthouse of patient involvement • Implement theory of patient involvement/engagement across entire drug life cycle • Patient engagement early and often/regular interactions • Regular progress report and updates • Complete action items • Build on community experience by consulting CML-CAB rather than engaging expensive agencies • Attend next CAB in May and bring representatives from Legal and Compliance • Maintain commitment to community and continue to be true partners • Food effect study on ABL001 • Update on Nilotinib label • More presence and support in different world regions (e.g. Africa) • Focus on physician education about TFR, especially in children and adolescents **Novartis wish list:** • Discuss together how to develop right PRO measures for assessing TFR in a systematic way • Use input and insights from CML community for assessing QoL in clinical trials/earlier lines • Feedback on patient materials • Increase familiarity with selected topics from ICH guidelines • Discuss within Novartis on how to make CAB meeting more efficient and integrate it into work • Better advance planning
Summary of dialogue and next steps: Novartis reassured the CML community of the company's continued commitment. Novartis is the only company developing a 3rd line agent in CML and they are investing into TFR to possibly change the goal of treatment in a profound way. In terms of access, the company is engaged in a GIPAP program with the Max Foundation and supports monitoring in many parts of the world. Novartis acknowledged that the CML community is the lighthouse and sets the bar for advocacy. The company sees the collaboration continuing and evolving but in a different way. The CML CAB appreciated that controversial issues had been discussed openly and that Novartis and the CML community were now in a position to move forward together for the benefit of the patients.
Follow-up Actions: • Novartis to send list of most relevant ICH topics

Jan Geissler closed the meeting at 15:30.