CML Community Advisory Board (CML-CAB)

Minutes of the meeting between the CML-CAB and representatives from Novartis held at the Marriott Hotel, Frankfurt, Germany, from 14:05-18:10 on 29th May 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, Argentina (representing Latin America) Pat Garcia-Gonzalez (representing Latin America) Gail Sperling, USA (representing North America) Bahija Gouimi, Morocco (representing Africa and Middle East) Rita Christensen, Denmark (representing Western Europe) Rod Padua, Philippines (representing East Asia and Pacific) Felice Bombaci, Italy (Western Europe) Yair Bar David (representing Israel) Ferdinand Micho, Kenya (Africa) Silvia Castillo De Armas, Guatemala (Latin America) Sarunas Narbutas, Lithuania (Eastern Europe) Lisa Machado, Canada (representing North America) Cornelia Borowczak, Germany 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 – until 15:30 via teleconference Louise Huneault, Patient Relations Head, Novartis Oncology, Region Europe Bengtaake Wahlberg, Head Patient Advocacy & Communications, Novartis Oncology, Emerging and Growing Markets Meeting moderated by: Kathy Redmond, Facilitator Minutes prepared by: Marion Alzer, Medical Writer

Summary Notes from the Meeting
The CML Community Advisory Board (CML-CAB) meeting was opened by co-chair Jan Geissler. This CML-CAB meeting was held to continue the dialog from the meeting in February 2017. A brief overview was presented on the action items completed and pending since the last meeting. Topics discussed during the current meeting included clinical development program updates, a working session on patient support and education, and community issues.
Action items accomplished since the last meeting: • meeting minutes provided • meeting survey results and feedback from CML-CAB on CML Today and Tomorrow survey results provided • participation in EMA's scientific advisory group meeting discussed • additional information shared by Novartis on FDA and EMA standards on food effect studies • key topics for this CML-CAB meeting agreed Items still pending and not on today's agenda: • collaboration on questions for the CML-CAB treatment-free remission (TFR) survey – CML-CAB to provide questionnaire to Novartis • assessment of quality of life (QoL) in CML trials • work on patient reported outcome (PRO) measures for TFR • continued discussion on benefit-risk of ABL001 • attendance of representatives from Novartis Legal and Compliance at next CML-CAB

Presentation and Discussion: Clinical Development Program Updates
ABL001 update Novartis provided an update on the progress of ABL001 activities since the meeting in February. ABL001 has been developed to gain disease control in CML including instances where patients are resistant to current treatments with tyrosine kinase inhibitors (TKI). The compound has a different location of action than previous TKIs; its structure allows it to be used as a single agent but also in combination with existing compounds. Novartis is planning to investigate ABL001 as a single agent in a global phase III study in 3rd line. Comparing ABL001 with Bosutinib.

Novartis shared further details on the Phase III study:
Key points:

- Study design: randomized, multicenter, open-label
- Study population: 222 CP CML patients after failure or intolerance to ≥2 prior TKIs
- Study medication (randomized 2:1): ABL001 40 mg twice a day (BID) (n=148) or bosutinib at approved dose (n=74)
- Anticipated study start: August/September 2017
- Primary endpoint: MMR at 24 weeks
- Key secondary endpoint: MMR at 96 weeks
- Other objectives: evaluation of safety and tolerability; biomarker evaluations

Key eligibility criteria:

- Male or female CML-CP patients ≥18 years
- Prior treatment with ≥2 TKIs (i.e. imatinib, nilotinib, dasatinib, radotinib, ponatinib)
- Failure or intolerance to last previous TKI with BCR-ABL ratio ≥1% IS as per central lab screening
- No known T315I or V229L mutation at any time before study entry
- No previous or planned allogeneic hematopoietic stem cell transplantation
- No acute pancreatitis within 1 year of study entry or history of chronic pancreatitis

Protocol assessments:

- Efficacy assessments: molecular response, cytogenetic response, hematologic response (bone marrow biopsy and aspirate, peripheral blood samples)
- Safety assessments: physical exam, vital signs, lab evaluations, cardiac and lung assessments
- PK parameters (peripheral blood samples)
- Biomarkers (bone marrow biopsy and aspirate, peripheral blood samples)

Bosutinib was chosen over ponatinib as the comparator as it is the standard of care on a global scale. Open-label design will allow for transparent dose modifications of comparator according to bosutinib label. These may be necessary to address any toxicity issues that may emerge from treatment. A dedicated data monitoring committee including a cardiologist is in place to review the safety and tolerability of both ABL001 and bosutinib.

The study will be conducted and sponsored solely by Novartis; bosutinib will be purchased from Pfizer. Study sites identified in Latin America, North America, Europe and Asia-Pacific.

Feedback/Questions/Comments by CML-CAB and Discussion with Novartis:

- Does the study include a cross-over design?
  Novartis: The initial study design included cross-over of study medications, but this was rejected by all regions and had to be removed.
- Has ABL001 been investigated as a single agent in resistant and intolerant CML patients?
  Novartis: ABL001 has been investigated as a single agent at a dose of 40mg in a phase I study in about 50 CML patients. There was clear evidence that ABL001 provided clinical benefit in a diverse population of heavily pretreated patients and patients resistant or intolerant to previous TKIs. The current study will carefully test the treatment concept in a larger group of patients.
- Have you taken into account that many patients on bosutinib drop out early because of gastrointestinal side effects?
  Novartis: A higher drop out rate has been taken into account in the statistical considerations for the bosutinib arm.
- Does the dosage really need to be twice daily in a registration study? If successful, this will go into the label. Once daily (QD) dosing would be better for compliance reasons.
  Novartis: Investigations are based on information currently available for BID use. QD dosing is being explored in another study. Results should be available in next 12 months and could then be included in label. Not enough data available to proceed with QD use at this point.
- How frequently will bone marrow biopsies be taken? Can patients decline or defer assessments?
  Novartis: According to the protocol, every 6 months up to 2 years, thereafter at the discretion of the investigator. This is to ensure that there are no efficacy issues and to look for biomarkers that will help understand the disease. Patients can decline or defer assessments.
- What might be the incentive of a patient who failed 2 TKIs to join a trial with a new unknown drug when other options are available.
  Novartis: ABL001 has a new mechanism of action and could avoid drop-out because of toxicity issues. The study is trying to find out whether the new drug can benefit patients in a far better way than current treatments.
- Where in the trial design does Novartis plan to involve patients? The patient perspective should be represented in the steering committee.
  Novartis: Patients have been involved in an advisory board discussing the trial design.
- Is the decision not to involve patients in the steering committee a company decision or driven by investigators? A data safety monitoring board might be a point where patient input can be valuable, e.g. where difficult decisions need to be made, such as treatment reinitiation or transplantation.
  Novartis: The company made the decision taking into account input from investigators and patients in other indications. They did not consider that patient time and input would be required to fulfil the purpose of the steering committee. Novartis confirmed that they do want to involve patient representatives where it is appropriate.
- Who is the leader of the Steering Committee?
  Novartis: There will not be a principal investigator, but equal representation from all regions.

Questions by Novartis and Feedback from CML-CAB:

- What are your concerns about the study?
  CML-CAB: Recruitment might be a challenge because the targeted study population is small. Recruitment will also depend on the question of access. Patients who have failed 2 prior TKIs and have access to 3rd line treatment would try another TKI before using an investigational product. Patients with no access to 3rd line treatment might be inclined to join. Some patients might prefer the new drug to avoid potentially severe side effects with ponatinib. There is a clear need for more data on efficacy and safety.
  Novartis: The objective of the study is to generate more data to hopefully answer these questions. Currently, enough data are available on the safety and tolerability to move from phase II to phase III.

Follow-up Actions:

- Novartis to share list of countries participating in the phase III study with CML-CAB
- Novartis to consider involving a patient advisor on relevant safety issues for the study

Food effect studies

Novartis presented results of food effect studies performed between 2005 and 2014 with different formulations of nilotinib.

- Early trials in 2006 revealed food to substantially increase nilotinib systemic drug exposure (up to 80% when taken with a high-fat diet and up to 30% with a low-fat diet), resulting in food intake restrictions in current label
- Effect of yogurt/apple sauce on nilotinib tested in reference to pediatric use, resulting in current recommendations for use in children
- Various studies undertaken between 2006 and 2014 to overcome food effects through different formulations (including capsules, tablets, slow and fast release) but failed; investigations halted in 2014
- Inherent properties of nilotinib effected by food; variations in formulations were unable to overcome this effect

Feedback/Questions/Comments by CML-CAB and Discussion with Novartis:

- In clinical practice, physicians do allow patients to eat an apple when taking nilotinib although this is not covered by the label. CML community would like to better understand the data on food effects from initial studies in 2005 and 2009 (A2106 and (A2127). What were the threshold values of drug exposure?
  Novartis: Threshold values were between 10% and 15%. Lower values were not acceptable because of the narrow window between risk of cardiotoxicity and lack of efficacy.
  Taking nilotinib with apple sauce is in the label as apple sauce does not change Cmax. The company is not allowed to interpret the wording in the label. Physicians might handle this differently.

Questions by Novartis and Feedback from CML-CAB:

- Has CML community had any interactions with authorities to make wording in the label more flexible to reflect their needs?
  CML-CAB: The community will be in a position to discuss this with regulators only if they can provide evidence. Therefore, it would be useful if Novartis could share their data from the food effect studies. The community would try to understand the data with the help of an expert. It would also be useful to have joint discussions together with authorities and manufacturer.
  Once the community understands the data from the previous studies, they could identify patient needs to be investigated.
  Once daily dosing is a very important topic for the community, also with regard to the development of ABL001.
  Novartis: In-house experts who have looked at the data could become involved with the CML community and discuss together how to move forward. As for ABL001, the new compound is a different product to nilotinib. Food decreases absorption instead of increasing it. Novartis is aware that it is a big disadvantage not to have QD for nilotinib and hope to have this for ABL001.

Follow-up Action:

- Novartis to provide dossiers of food effect and formulation studies for nilotinib and ABL001
- Novartis to provide information of food effects for ABL001 as they become available
- CML-CAB to specify patient needs to be investigated in food effect study
- CML-CAB to analyze the dossiers with help of qualified independent medical experts
- CML-CAB/Novartis to discuss the analysis once conducted and findings are summarized

Collaborative efforts for advocate engagement

Novartis presented the company's progress to drive patient engagement (PE) in drug development. They recognize that PE provides benefits to their programs and trials along the entire drug discovery and development process. The company has made it a formal requirement for their clinical development to outline PE in their work. The new PE initiative was developed over several years in consideration of the patient perspective. Novartis hopes to work with the patient community on a strategic level and intends to use patient experts wisely, when it is the most valuable to community and to Novartis. The new initiative is related to the Novartis Patient Declaration but was not driven by it. It is seen as a recipe to develop a new drug. Novartis would like to test the PE program with the CML-CAB in a pilot project on ABL001. They are convinced that systemic implementation of PE will help get drugs to patients faster and better. The theory behind the program will now have to be tried in practice.

Feedback/Questions/Comments by CML-CAB and Discussion with Novartis:

- At which points in the process would the patient voice be captured best?
  Novartis: The CML-CAB meeting is such a point where Novartis are explaining the big picture first and then ask the community where it would make sense to hear the patient voice and engage with experts. This will then have to be put into practice.

Follow-up Action:

- CML-CAB to propose suitable candidates for the Novartis patient engagement program.

Presentation and Discussion: Working Session on Patient Support and Education
Status updates Novartis still awaiting response from EMA regarding inclusion of TFR in nilotinib label. Meanwhile company is preparing educational materials on TFR for physicians and patients. Specific feedback given by CML-CAB in February being integrated into materials on global and regional level. A framework for a regional program in Europe has been developed and needs to be filled with content including input from patients.
Overview of Novartis programs and initiatives Novartis presented their global "All Patients Matter" patient support program (PSP). The program provides support on a number of topics relevant to CML and is divided into two parts: • Tasigna/Glivec program supporting CML patients taking branded nilotinib • CML monitoring program supporting any CML patients Stakeholders in the program include PSP launch teach/marketers, sales reps, HCPs/clinical educators and, most importantly, patients and caregivers. Novartis also showed real world examples of adapting global PSP content for delivery on a regional/national level. The wide range of channels used included digital tools, call centers, pharmacist counselling, financial assistance workshops, group meetings etc.
Group exercise: identifying topics for patient support and education Prior to the meeting, Novartis had requested CML-CAB members to identify emotional, logistical and educational gaps experienced throughout their patient journey. Patients had specified anxiety, fear and coping as major themes in their CML experience and identified gaps and unmet needs at diagnosis, on first-line treatment, on switching treatment and around considering TFR. In a group exercise on unmet patient needs, Novartis asked the CAB to prioritize topics that should be included in CML patient support/education. CAB members also added relevant topics they found missing.

Group 1 assessed topics related to:

- **Diagnosis and initiating treatment:**
  Most important topics: understanding CML; information about available therapies; potential side effects; relevance of other conditions present at diagnosis; tips for adherence.
  The group disagreed on whether TFR should be mentioned at diagnosis.
  Missing topics: How to contact patient organizations; fertility and pregnancy, ability to work; how to talk to your family/children/employer/insurance.
- **Monitoring:**
  Most important topics: importance of monitoring; frequency and importance of monitoring tests; how monitoring tests are performed and understanding test results; importance of adherence to monitoring.
  Missing topics: International Standard (IS); App for tracking; NCCN and ELN guidelines.
- **Productive office visits:**
  Most important topics: guidance for asking difficult questions/discussing uncomfortable topics; productive patient-physician communication; prioritizing information at visits; tips for asking for information or support from the doctor.
  Missing topics: App to set time of visit; discuss side effects and adherence.

Group 2 assessed topics related to:

- **Staying motivated and building a routine:**
  Most important topics: understanding where you are against treatment goals; understanding why it is important to maintain response and regular monitoring; tips for staying adherent/building a routing.
  Missing topics: risks of non-adherence.
- **Switching TKI therapy and understanding TFR:**
  Most important topics: information on molecular response and treatment goals; discussing reasons for switch with your physician; what to expect after TKI switch.
  Missing topics: understanding the different situation of intolerance and resistance; co-morbidities
- **Expectations for stopping treatment:**
  Most important topics: what is TFR, and why consider TFR; eligibility criteria for TFR; what happens if I lose response after stopping treatment; expectations for monitoring.
  Missing topics: importance of regular monitoring; monitoring schedules; importance of high-quality sensitive standardized PCR.

Group 3 assessed topics related to:

- **Managing emotions**
  Most important topics: managing emotions; finding support groups; managing monitoring fatigue; managing potential side effects after stopping treatment.
  Missing topics: psychological aspects related to TFR; family planning.
- **Financial and works concerns**
  Most important topics: understanding options for access to monitoring.
  The group disagreed on: managing cost of care, finances; finding financial support.
  Missing topics: social benefits available at national level.

- **Logistical concerns**
  Most important topics: managing other conditions and working with a multi-specialist team.
  Missing topics: telemedicine consultations.

Discussion: Community issues

Community issues

During the brainstorming session about increasing the impact of CML Horizons it was suggested that perhaps CML Horizons could be held every other year rather than annually as it has been for the last 15 years. This course of action would be a huge setback to the growth of the community as CML Horizons is essential for the CML community to come together to share, learn and grow. This enables them to reach out to regions and give help and support to local groups. Although budget was a concern the Novartis team also witnessed first-hand the benefit and success of Horizons and we believe that by working together and having the transparency between all parties once the grant has been awarded the CML Steering Committee can make their own strategic decisions on how the funds are allocated for Horizons. Novartis emphasized that the company cannot and does not engage in group's strategic planning and decision-making process.

For Novartis, transparency is a key aspect of every collaboration. A few years ago, Novartis supported 7 or 8 indications; they are now faced with the challenge of supporting over 20 indications. They therefore believed it is necessary to address the issue of budget allocation openly and ask whether the community had considered changing meeting intervals of CML Horizons to reduce costs. Novartis needs to consider whether they can support these meetings at levels it has in past years, given additional requests for funding from regions and countries as well as the need to support groups in other therapeutic areas. .

The CAB also expressed unease that Novartis may be introducing regional, sub-regional or local groups. Like the East Africa Network or Arabic Network are being established, leading to division of the global network. Novartis will need to look at ways to split funding between all these networks. There was concern that this development was driven by Novartis and not by the community with reports of regional initiatives in Kenya and local initiatives in Italy and elsewhere that were driven by Novartis and excluded CML Life Africa, the Max Foundation and the existing patient organizations. CML Advocate Network has requested if possible to be informed when new groups are formed so they can invite them into their global network and support them. The CML-CAB is wondering if this is a new plan by Novartis and if so, would like to understand the objectives behind it.

Novartis emphasized that it is natural for networks to develop and it is up to the community to decide which network they want to belong to. This is not a company decision. In response to the concerns raised, the Novartis team indicated the company does not drive establishment of patient organizations and does not introduce regional, sub-regional or local groups. The Arabic Network is an independent group that have reached out to Novartis MEA and requested support to establish their organization. East Africa Network was discussed among patients attending a CML educational meeting supported by Novartis, not organized or driven by Novartis. They agreed to to speak with the countries about this.

Novartis explained that the pressures on the company are much greater today than they were a few years ago, not only due to the loss of revenues of imatinib. Costs of research are going up and companies have to figure out how to continue the dynamic process of providing access to innovation. They need to use their economic resources more efficiently.

Follow-up Action:

- Novartis agreed to speak to the Novartis colleagues in Africa to learn more about the meeting of English speaking groups in East Africa. This outreach confirmed that Novartis supported the meeting but was not involved in any decisions made by the community during the meeting.

Wish lists

Amended wish list for improving the collaboration between Novartis and CML patient advocates
(initial wishes from February 2017 in italics):

CML community wish list:

- *Use engagement with CML community as a model*
- *Engage patients across entire medicines life cycle*
- *Patient engagement early and often/regular interactions*
- *Bring representatives from Legal and Compliance to next CML-CAB*
- *Maintain commitment to CML community and continue to be true partners*
- *Food effect study on ABL001*
- *Provide update on nilotinib TFR label*
- *More presence and support in different world regions*
- *Focus on physician education about TFR*
- Continue to focus on access
- GIPAP transition completed successfully
- More proactive approach to engagement
- Support CML Horizons / Rising Sun
- Keep global perspective
- More strategic discussions linked with implementation

Novartis wish list:

- *For CML-CAB to share their strategic plans of continuing to support the CML community and advancing the dialogue with industry partners to provide a clear understanding of the goals of the community and the opportunities to work together to address patient unmet needs*
- *Discuss together how to develop right PRO measures for assessing TFR in a systematic way*
- *Better assessment of QoL in CML trials*
- *Secure feedback on patient materials*
- *More efficient meetings*
- *Better advance planning*
- *Complete action items*
- Translate education and resources for physicians
- Co-creation of Patient Support Programs with Patient Advocacy Groups
- Change materials as new knowledge emerges
- Understand what Patient Advocacy Groups are doing to generate participation
- Eliminate duplication and integrate community evidence into Novartis materials
- Keep global perspective
- More presentations from CML-CAB
- Divide and conquer subcommittees

Closing remarks:

Novartis appreciated the honest discussion that will help move things forward. For them it was very valuable to hear different opinions and also receive input from representatives from different geographical regions. In the future, Novartis would like to have more efficient meetings with a more focused agenda and an equal share of presentations between CML-CAB and Novartis.

The CML-CAB thanked all participants for the openly sharing their opinions. They thanked Novartis for showing how their patient declaration translates into real life and for inviting the CML-CAB to collaborate as pioneers in the PSP pilot project on ABL001. The CML-CAB acknowledged that the wish list emerging from the meetings is growing and it will be challenging to find better tools to efficiently work on implementing these in real life.

Jan Geissler closed the meeting at 18:10.