CML Community Advisory Board (CML-CAB)

Minutes of the meeting between the CML-CAB members and representatives from Novartis held at the Novartis Campus, Basel, Switzerland, from 8:00-16:40 on 28th November 2018.

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

Participants
CML-CAB Members Jan Geissler, Germany (CML-CAB chair) Giora Sharf, Israel (CML-CAB co-chair) Jana Pelouchova, Czech Republic Pat Garcia-Gonzalez, USA, The Max Foundation (representing Latin America) Mercedes Arteaga, Argentina (representing Latin 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 Silvia Castillo De Armas, Guatemala (Latin America) Sarunas Narbutas, Lithuania (Eastern Europe) Lisa Machado, Canada (North America) Yair Bar David, Israel Cornelia Borowczak, Germany Zack Pemberton-Whiteley, United Kingdom & Western Europe Yong Yoke Choon, Malaysia Jelena Cugurovic, Serbia (via phone) Lidija Pecova (LePAF, Programme Manager) Celia Marin (LePAF, Programme Manager) **Novartis** Mohit Rawat, Executive Director, Global Commercial Lead, CML Stephan Hois, Clinical Development Medical Director, ABL001 program Paul Robinson, Trial Operation Management Development Unit Head Alexey Salamakha, Director, Global Hematology Patient Advocacy Louise Huneault, Hematology Patient Advocacy, Oncology Region Europe Paola Aimone, Global Program Clinical Head, Oncology Global Drug Development Gonzalo Linares, Communications & Advocacy Director, Global Drug Development (via phone) Lynnette van Heerden, Communications & Advocacy Manager, Global Drug Development Laura McKeaveney, Global Head of Patient Advocacy, Group Patient Advocacy Alex Allepuz, Associate Director, Clinical Development, ABL001 Program Vasant (Vas) Narasimhan, Chief Executive Officer of Novartis (from 15:00 to 16:30 **Meeting moderated by:** Kathy Redmond, Moderator/Facilitator **Minutes prepared by:** Marion Alzer, Medical Writer

Summary Notes from the Meeting
CAB meetings provide an opportunity to foster mutual understanding and build a meaningful relationship between pharmaceutical companies and the patient community to overcome the challenges and needs associated with CML. CML Advocates Network is one of the largest disease-specific networks in the world and includes 119 patient organizations in 89 countries on 6 continents. The CMLCAB members represent 233 years of patient life with CML, have an outreach to 115,000 CML patients and to another 110,000 other cancer patients worldwide. The main objectives of the meeting were to build on discussions from previous meetings and to take tangible actions forward for Novartis, the patient community and both in collaboration. The meeting was held under confidentiality terms from all parties to allow for an open and frank discussion. Topics discussed during the current meeting included the clinical development and value proposition of asciminib (ABL001), a multi-stakeholder approach to managing healthcare systems in CML, preliminary results of the TFR patient survey, and a meeting with the CEO of Novartis. Key discussion points and findings as well as action items are summarized below.

Welcome, Objectives, Housekeeping / Ground Rules
The 6th CML Community Advisory Board (CML-CAB) meeting with Novartis was opened by Jan Geissler. CAB members were welcomed by Novartis at their premises. Ground rules were set out for the meeting, and a round of brief introductions followed. Recap of topics discussed at CML-CAB in May 2018: • Research: site selection and recruitment for asciminib phase-III study, bone marrow biopsies in precision medicine, understanding patient reported outcomes (PROs), setting up CAB trial working group, continuing search for cure • Access: optimize goals for access to treatment and diagnostics and take action, share data on access issues • Treatment-free remission (TFR): more cross-talk between region Europe and global team, educate physicians and patients according to needs, use different communication channels, continue supporting monitoring • Collaboration: continue level of support to patient organizations

Clinical Development Updates – Presentation and Discussion

Current asciminib development programme:

- CML CP in 3rd line (3L): potential treatment option for CML-CP patients resistant/intolerant to available therapies
- CML CP with T315I mutation: potential treatment option for patients resistant/intolerant to ponatinib
- CML CP in 1st line (1L): potential add-on treatment to imatinib to enable more patients to achieve TFR eligibility and potentially remain off treatment; add-on treatment to other tyrosine kinase inhibitors (TKIs) for potentially improved efficacy and quality of life (QoL) with safety/tolerability comparable to single-agent therapy
- Ph+ ALL/Ph+ leukemias: potential new (combination) treatment option

Phase III study ASCEMBL (CABL001A2301) in CML-CP 3L

- Ongoing registration study with asciminib monotherapy
- Comparator: bosutinib, no cross-over design (since initially not accepted by authorities)
- Objectives: efficacy (MMR at 24 and 96 weeks), safety and tolerability
- Inclusion criteria: patients with CML-CP in 3rd line who have not responded or are resistant to at least two previous TKIs; BCR-ABL1^{IS} ≥ 1% at screening; acceptable laboratory values at screening, electrolytes within normal limits, and adequate end-organ function
- Exclusion criteria: presence of T315I or V299L mutation as bosutinib is not effective in these mutations; history of acute pancreatitis within 1 year of study entry, history of chronic pancreatitis, or history of acute or chronic liver disease
- Study treatment: ABL001 (asciminib) 40 mg twice daily or 500 mg bosutinib once daily
- Treatment duration: 96 weeks, thereafter survival follow up

CML-CAB members saw a need to include QoL assessments. Novartis explained that a phase III study needs to show primarily efficacy and safety for regulatory purposes. QoL will be assessed after drug has been approved.

Due to lower than anticipated recruitment problems and following feedback from investigators and patient community, the following inclusion/exclusion criteria and study design aspects were changed:

- Pancreatic enzymes at screening
- Blood counts and bone marrow assessments
- Concomitant medication
- Decrease of entry threshold of 1% BCR-ABL for patients with intolerance to previous treatment
- Switch from bosutinib to asciminib in patients with bosutinib failure as per ELN guidelines; intolerance alone not sufficient to justify a switch as intolerance is a more subjective criterion than failure and might not be accepted by regulatory authorities

There has been no direct comparison of asciminib monotherapy vs. asciminib plus imatinib since monotherapy is targeted at patients resistant/intolerant to available therapies whereas add-on to imatinib is targeted at patients who have already responded to imatinib.

Clinical Development Updates – Presentation and Discussion, continued

Phase II study ASC4MORE: asciminib in combination with imatinib in early CML-CP (CABL001E2201)

Study is ongoing in Czech Republic, France Spain, UK and US. Sites in further countries to be opened soon. No other key update available.

Phase I study (CABL001X2101)

- Ongoing first-in-human study with asciminib monotherapy in CML/ALL and combinations of asciminib + nilotinib or imatinib or dasatinib in CML
- Objectives: safety, preliminary efficacy, dose-finding
- Patient population: patients with CML or ALL who have not responded or are resistant to one or two TKIs

Rationale for dose expansion in T315I cohort of CABL001X2101

- Among patients who develop resistance mutation to TKIs, 10-27% carry T315I mutation
- T315I mutation drives development of resistance to TKIs and indicates poor prognosis
- Ponatinib is only approved TKI effective in T315I mutation, but tolerability is poor
- No really effective rescue therapies available other than bone marrow transplant (BMT), important unmet need

Study status and preliminary findings

- Study in T315I cohort (200 mg twice daily) ongoing in the US and in Europe
- Efficacy in clinical cohort expansion was similar: patients with T315I mutation treated at 200 mg twice daily (=5 times the dose used in patients without the mutation) showed better molecular responses
- Safety profile was similar as for 40 mg twice daily (no cardiovascular events observed; increased risk of QT prolongation as with all TKIs)

CML-CAB members were aware of a large number patients with the T315I mutation in countries outside the US and Europe. They proposed that Novartis explored the possibility of bringing these patients to the participating trial sites. Novartis agreed to look into this option on an operational level in consideration of ethical and regulatory requirements.

Clinical Development Updates – Presentation and Discussion, continued

Asciminib: dosing regimens and conditions of administration

The initial asciminib dose of 40 mg twice daily fasting had been determined in a phase I study and then been implemented in the ongoing phase III study. Following concerns from CML-CAB members during previous meetings, Novartis looked into optimizing conditions of asciminib intake. The preferred scenario would be once daily administration with food. To achieve this, Novartis is taking a stepwise approach: from administration under fasting conditions twice daily to with food twice daily, then with food twice daily to with food once daily. Any proposed modification in dose, regimen or conditions of administration needs to ensure that efficacy, safety and benefit/risk assessment remain unchanged. Therefore, data needs to be generated in food-drug interaction studies in healthy volunteers and, subject to authority requirements, possibly also in patients. There is evidence suggesting that asciminib as a single agent is best given with a light low-fat meal. Novartis hoped to have results on administration with food available in time for the launch as a 3L therapy.

CML-CAB members wanted to know why it has taken the company so long to address the food-effect issue after the topic was first raised in 2016.

Extension of the footprint for phase III trial (A2301A230)

Following previous feedback from CML-CAB members, Novartis opened trial sites also in Chile, Colombia, Hong Kong, Jordan and Serbia. Other countries were considered for participation but were not added due to investigator barriers (e.g. Nordic), regulatory barriers (e.g. India), infrastructure barriers (Africa) or Novartis internal barriers.

CML-CAB members suggested to bring patients from non-EU Eastern European countries who do not have access to the trial in their own country to Serbia. Local doctors in the region have been contacted and have agreed to share patients. This innovative approach could be considered in other regions.

Novartis emphasized their commitment to running trials in countries where the drug will be available post-trial. In Africa, however, capabilities/infrastructure are not in place everywhere to conduct clinical trials. The company is running trials in indications where relevant experience/infrastructure are available. CML-CAB members asked Novartis to work on capacity building and healthcare strengthening with at least some sites in Africa with the goal that more clinical trials will be possible in the future.

Access via compassionate-use programs can be a solution in some countries, depending on the regulatory framework in place. Novartis to map barriers so that appropriate action, e.g. advocacy involvement, can be taken (specifically in Africa, India and Malaysia).

Clinical Development Updates – Presentation and Discussion, continued

Patient engagement (PE) in asciminib program

Novartis emphasized that hearing the patient voice is a guiding principle for the company. In the asciminib program, patients have been engaged:

- In the study design: patient expert in advisory boards; invitation of patient experts in study SC (CABL001E2201)
- During the study conduct: patient thank you letters (CABL001E2201, CABL001A2301); plain language summaries for patients at end of trial; patient interviews (PRO development, CABL001E2201); PROs

CML-CAB members criticized that patients had been involved much too late in the phase III trial. Novartis acknowledged this. Because of the lessons learned, they had involved patients earlier in the phase II study. Cross-over design in phase II is a result from patient interaction.

Novartis commented that sometimes resistance to patient engagement comes from outside. Participants agreed that involving patients at investigator meetings can be an excellent opportunity to demonstrate the value that patients can bring to a clinical trial. Patient engagement should become an integral part of investigator meetings.

Patient-Reported Outcome as measured in asciminib program

PROs are needed to capture the patient perspective in a trial, and are also often required by authorities. For asciminib, PRO tools were chosen based on literature searches, previous experience, and interviews with patient advocates and investigators, and include:

- In phase III study CABL001A2301: MDASI-CML (symptom-specific inventory), EQ 5D 5L (quality of life, QoL), PGIC (patient global impression of change), WPAI (work productivity and activity impairment), and
- In phase II add-on study CABL001E2201: EORTD QLQ C30 + CML24 (quality of life), TSQM (treatment satisfaction), FACIT GP5 (treatment side effects). In addition to questionnaires, qualitative telephone interviews are conducted through a trained agency in currently 4 English speaking countries + 2 other countries/languages. Face-to-face interviews by physicians or nurses are not possible due to operational limitations.

CML-CAB members pointed out not only the type of instrument used, but also the timepoint when QoL assessments are being made are essential. QoL assessments should be done regularly at short intervals or timepoints of therapeutic changes to capture changes in QoL. CML-CAB stressed that QoL and toxicity over time may be the key differentiator of this drug to other available TKIs, not efficacy. CML-CAB mentioned that MDASI provides less meaningful insights than EORTC-QLQ 30 – CML24 in terms of CML-specific symptoms and side effects.
Novartis to check assessment points for QoL in phase II add-on study protocol.

Pilot program in phase II study CABL001E2201 "Sharing Individual Trial Results with Patients"

In addition to publishing patient summaries which reflect overall study results, the company will share individual trial results with trial participants who consent to this. If pilot is successful, then model might be implemented in other oncology studies.

Clinical Development Updates – Presentation and Discussion, continued

Communications & advocacy support for asciminib program

Novartis has drafted a communications and advocacy support plan specifically for the asciminib program. The aim is to achieve greater awareness and understanding of the potential value of asciminib and the clinical development program with the two ongoing phase II and phase III trials, and to increase referral. CML-CAB members confirmed their interest in a working group outside of the formal CAB meetings to address recruitment issues and access to the clinical trials and to map potential barriers.

Follow-up actions:

- Novartis to explore option of bringing patients with the T315I mutation from outside the US and Europe to sites recruiting for study CABL001X2101
- Novartis to map barriers to implementing phase III trial A2301A230 so that appropriate action, e.g. advocacy involvement, can be taken (specifically in Africa, India and Malaysia)
- Novartis to check assessment points for QoL in phase II add-on study protocol
- Novartis and CML-CAB to set up communications & advocacy support working group for asciminib

Multi-stakeholder approach to managing healthcare systems in CML Presentation and Discussion

CML-CAB discussed opportunities to engage with Novartis and other stakeholders around key access issues in their respective regions. The goal was to work on these issues together to improve the situation for the patients concerned.

CML Path to Care/barriers to expanding access in low- and middle-income countries

Following up on an action item from the last meeting, advocates had collected data on countries with access issues to TKIs. The following situations were identified:

- 21 known countries without access to any TKIs: Angola, Belize, Burundi, Cape Verde, Chad, Comoros, Eritrea, Guinea, Guinea-Bissau, Guyana, Lao PDR, Lesotho, Mauritania, Mozambique, Myanmar, Pacific Islands, South Sudan, Swaziland, The Gambia, Vanuatu, Yemen
- 7 countries with no access to Tasigna: Bangladesh, Botswana, Cote d'Ivoire, Ghana, Nigeria, Venezuela
- 7 countries with current access program, yet unaffordable to many patients: China, India, Kenya, Pakistan, Philippines, Sri Lanka, Vietnam
- 16 countries with access scheme but large sections of population are left out: Azerbaijan Dominican Republic, El Salvador, Ethiopia, Guatemala, Kazakhstan, Macedonia, Mauritius, Mexico, Mongolia, Morocco, Namibia, Paraguay, South Africa, Sudan, Zimbabwe

Novartis was asked to verify the findings. CML-CAB is aware of 39 countries where Novartis is willing to donate Tasigna.

Multi-stakeholder approach to managing healthcare systems in CML
Presentation and Discussion, continued

The overall access strategy to Tasigna is not clear, especially in countries where Novartis is not or no longer present. CML-CAB members asked Novartis to explain their global access strategy for Tasigna, how decisions are made, and how company and CML-CAB members can work together to address the challenges.

Market Access Challenges in Countries with HTA processes
In many Eastern & Central European countries including former Soviet Union states, HTA processes are in place, but differ from those in Western Europe. Generally speaking, patients in Eastern and Central Europe have access to treatment, diagnosis and possibly monitoring on condition that funding is available. The cost of testing can be a big barrier to access as it is not always covered by public health systems. If available, PCR tests, concentration tests, genetic profiling and mutational tests often have to be paid out of pocket. In many instances, analyses are carried out in a third country. Patients who cannot afford to pay for testing are placed at a higher risk of treatment failure if not monitored regularly. Once CML progresses and enters acceleration phase, the only option is a bone marrow transplant.

HTA in Eastern & Central Europe does not take into account the costs of testing (e.g. companion diagnostics) but only compares the cost of one TKI with that of the other TKIs. Tasigna has been approved widely as 2L therapy, but not as 1L option due to the availability of less expensive generic therapies.

The following access challenges for Tasigna were identified:

- Affordability issues:
  - Governments cover use of Tasigna only for a few months or for a few patients
  - Not all patients covered by social security
  - Patients cannot afford co-payment for donated products
- Policy issues:
  - No HTA processes in place
  - CML not a health priority
- Strategy issues:
  - Inconsistent global access programs (Novartis)
  - Local pricing strategy (Novartis)
  - Competitor strategy in particular markets
- Testing issues:
  - Availability, frequency and cost of PCR/concentration testing
  - Availability and cost of mutation testing
- Other issues:
  - Lack of physicians and/or physician knowledge, e.g. how to use drugs or what to do with PCR results
  - Temporary tenders, drugs not available after end of tendered period
  - Novartis not/no longer present in country
  - Geopolitical issues
  - Stigmatization

Multi-stakeholder approach to managing healthcare systems in CML
Presentation and Discussion, continued

Participants broke out into three groups to brainstorm solutions on how to address the needs. The following questions were discussed:

1. How can the Novartis access principles be applied to address challenges faced in accessing Tasigna?
2. What are tangible actions that can be taken by Novartis, the CML Community and Novartis working in collaboration with patient community and other stakeholders?

Actions were identified and prioritized:

- Multi-stakeholder actions:
  - Cover PCR testing as part of managed care agreements
  - Co-create approach to physician education where Tasigna not marketed
  - Find ways to make CML management sustainable
  - Explore innovative models of creating a sustainable PCR testing model
  - Healthcare system strengthening
  - Educate tier 2/3 physicians
  - Multi-stakeholder alliance on side effect management (e.g. cardiovascular events)
  - Increase in physician awareness about burdens of side effects
  - Work together to improve faulty healthcare systems
  - Tackle corruption
- Novartis actions:
  - Address inconsistencies in application of global strategy
  - Understand root causes
  - Share information on how decisions are made
  - Update and resubmit HTA submissions
  - Consistent support of national CML patient advocacy groups (PAGs)
  - Information in national languages for paediatric indication
  - Work together with generic manufacturers to ensure availability
  - Monitor impact of dasatinib generic introduction
  - Help community understand transition to social business model
- Patient community actions:
  - Cascade information to countries (subtitled/translated)

The highest priority was assigned to covering PCR testing as part of managed care agreements, co-creating an approach to physician education where Tasigna is not marketed, cascading information to countries, and finding a way to make CML management sustainable/exploring innovative models of creating a sustainable PCR testing model.

It became apparent that a multi-stakeholder approach is needed to find solutions to the complex issues of access and that following reflection, the topic may need to be revisited at the next CML-CAB meeting.

Follow-up action:

- Novartis to verify list of countries with access issues and come back to CML-CAB members
- Novartis to investigate innovative ways in making PCR more available and "part of the sustainability package for healthcare systems"
- Novartis and CML-CAB members to co-create approach to physician education

Value Proposition of Asciminib – Presentation and Discussion
. Outcomes of the QoL-assessments via PROs were not yet known. Big challenges are anticipated in convincing regulators, HTA bodies and governments that there is still high unmet need in CML. This is where the voice of PAGs and health care providers (HCPs) can be very helpful. Participants agreed that the ultimate treatment goal is cure. T CML-CAB was encouraged to raise their voice and talk with experts to drive the update of the ELN guidlines forward. CML-CAB members appreciated the development of asciminib as an important drug because it provides value for many patients in specific situations where other TKIs are not effective, too toxic or simply not available. However, patient advocates were concerned that approval by HTA bodies might be jeopardized by focusing mainly on proving better efficacy and this may lead to failure of achieving reimbursement after achieving marketing authorization, hence jeopardizing patient access. For HTA approval it is imperative that QoL and toxicity are measured with appropriate instruments. The company committed to involve patients much earlier on in the development of other drug candidates and admitted that involvement has been too late on asciminib.
Follow-up actions: • CML-CAB members to put value proposition for asciminib on agenda of next meeting • Novartis to investigate better and more meaningful ways to generate data on QoL and toxicity, and come back to CML-CAB members how this will be done • Novartis to review internal approach to affordability models

TFR patient survey: preliminary results analysis
Presentation and Discussion

CML-CAB members presented preliminary key findings from their global survey on TFR for patients with CML. The objectives of the project had been:

- To provide patients and HCPs with relevant information in three TFR phases: when considering stopping treatment, when having stopped treatment and when having failed therapy-free remission
- To avoid patient confusion by using consistent terminology
- To inform HCPs about patients concerns, considerations and needs in connection with TFR

The survey had been conducted online in 11 languages from March 2018 to August 2018. Patients had been recruited with the support of PAGs via online forums and other methods. A total of 1,016 responses had been received covering 68 countries. No or very few responses had been counted from Africa, South America and Asia, presumably due to lack of access to required PCR tests and lack of education on TFR for HCPs in those regions. Of the respondents, 45% were male and 55% female. 24% were in the age group 18-40 years whereas 76% were older than 40 years. 70% of participants had been living with CML for more than 5 years. Of the respondents who stopped, 50% had been on imatinib before stopping, 30% on nilotinib, 16% on dasatinib, 3% on interferon, and 1% on bosutinib. At the time of the survey, 48% of respondents were considering stopping, 52% had already stopped; of the respondents who had already stopped, 24% had had to restart treatment.

Key findings during specific TFR phases are summarized below:

Phase I – Considerations around stopping treatment

- First source of information on possibility of stopping treatment:
  HCP = 49%; PAG = 21%; internet = 12%; social media/Facebook = 8%; other = 10%
  Source depended largely on geographic location: 43% of respondents from Middle East & Africa and 45% from Central Eastern Europe & West Asia first heard about TFR from a PAG.
- Topics discussed with doctors during decision phase:
  Risks of stopping = 60%, requirements for stopping = 50%; benefits of stopping = 48%; timing of stopping = 34%; drug withdrawal symptoms = 21%; none = 14%; other = 5%
- Topics of continued concern following discussion with doctor:
  Recurrence = 55%; restarting treatment after unsuccessful stopping = 37%; molecular response criteria = 27%; medication after restarting treatment = 22%; frequency of PCR tests = 19%, no concerns = 19%; other 6%
- Reasons for considering stopping were mainly:
  Eliminating or fearing side effects and being CML-free without medication/not needing medication every day; no differences between genders observed
- Side effects affecting everyday life before stopping, rated by respondents as grade 3 or higher (scale ranging from 1-5):
  Fatigue (3.35) and muscle soreness or cramping (3.27)

TFR patient survey: preliminary results analysis
Presentation and Discussion, continued

- Doctor support by CML Advocate Group regions:
  Most respondents reported that their doctor supported their decision to try stopping treatment. Big differences were seen between regions: respondents from Western Europe and North America (85% and 78%, respectively) versus Asia & Pacific and Central Eastern Europe & West Asia and (57% and 35%, respectively).
- Information patients would like to have received:
  Results from clinical trials on TFR (52%), information along the entire TFR journey (49%); information on risks and opportunities of stopping (44%); withdrawal symptoms after stopping (40%); side effects on restarting treatment (36%); PCR monitoring (32%); psychological effects (22%); other (5%)

Phase II – Stopping phase (probation period)

- Topics discussed with doctor during stopping phase:
  Frequency of PCR testing = 92%; response levels/restarting treatment = 76%; waiting time for PCR test results = 70%
- Management of physical withdrawal symptoms:
  40% reported no support from their doctor in managing withdrawal symptoms; only 24% felt their doctors supported them completely in managing withdrawal symptoms
- Emotional impact:
  Not fearful/anxious: 44% (thereof 55% male, 37% female); fearful/anxious before and/or after PCR test = 31% (thereof 22% male, 37% female); fearful/anxious at other times = 25%
- Reported benefits of stopping treatment:
  Relief from need to remember to take regular medication = 82%; positive impact on emotional well-being = 63%; positive impact on family and social relationships = 56%; positive impact on work/education = 49%; positive impact on finances = 27%

Phase IIIA – Restarting treatment

- Length of time until recurrence of CML:
  87% of relapses occurred within 12 months from stopping
- Feelings upon recurrence of CML:
  Relapsed patients felt disappointed = 72%; scared = 35%; depressed = 35%
- Psychological and/or emotional support when restarting treatment:
  Patients considered this not necessary = 48%; support received = 26%; no support received but would have liked support = 25%
- Feelings on considering stopping treatment again in the future:
  70% were open to considering stopping a second time

TFR patient survey: preliminary results analysis
Presentation and Discussion, continued

Phase IIIB – Long-term TFR

- Major concerns about being in long-term remission:
  Late recurrence of CML = 58%; misunderstanding of people that patient is now cured = 29%
- Changes respondents would make to stopping experience:
  Quicker communication of PCR results = 42%; better understanding of current expert's knowledge of stopping treatment = 41%; contact with other patients in same phase on TFR journey = 29%
- Monitoring in long-term remission:
  Any degree of concern about fluctuations/changes in PCR results: 49% male vs. 71% female.
- Psychological support in the long-term:
  Males in long-term remission were much more likely than females to feel no need for psychological/emotional support (71% vs. 46%). Females in long-term remission were more likely than men to say they received psychological/emotional support (34% vs. 13%)

Final advice

In conclusion, psychological concerns are an important issue along the entire TFR journey. To help manage these concerns, respondents would advise other patients who consider stopping treatment to always be well informed about their PCR results and treatment options, look for the best doctor with experience in stopping treatment, talk with other patients on the same journey, receive information from PAGs about stopping treatment, look for simple and useful information about each step of stopping treatment, and get emotional/psychological support.

Discussion/feedback/comments:

- TFR group is exploring several options of how to proceed with the publication and which journal to select. The aim is to publish in a source with open-access. Novartis will consider buying x number of reprints of the publication and disseminate them to reach more HCPs.
- CML-CAB members proposed that Novartis invited members of the TFR group to present the data to HCPs at international symposia of congresses like ASH and EHA as well as at advisory board/medical/scientific meetings. The data also needs to be presented to smaller groups at country level to reach not only key opinion leaders but community-level hematologists and general practitioners who may not be aware of withdrawal symptoms of TFR or the need for psychological support. Specifically, presenting data from a particular country at local/national meetings can have a real impact on local physicians. Attention needs to be paid that survey results presented orally are in line with the planned publication.
- A further step will be to develop educational materials, possibly localized to countries/regions, for HCPS and patients.
- TFR group to consider performing a subgroup analysis of the 14% of patients who in considering phase did not discuss their thoughts with their doctor. Also, possibly, to combine percentages of patients considering stopping and actually stopping who did not discuss stopping with their doctors.
- CML-CAB members proposed that Novartis could have a standing committee composed of company representatives and physicians to address TFR topics.

TFR patient survey: preliminary results analysis Presentation and Discussion, continued
Follow-up actions: • CML-CAB members to put TFR survey again on agenda of future CML-CAB meeting.

Meeting with the CEO of Novartis
Novartis is working on advancing patient engagement across the full medicine life-cycle. Part of this is engaging with the most senior executives of the company. Following a brief introduction of CML Advocates Network and the individual advocates present, CML-CAB and Novartis CEO Vasant (Vas) Narasimhan discussed three central topics: • Patient engagement in research • Access to diagnostics and treatments • Commitment to the CML community **Vision** The CEO shared his vision of a world where deep molecular response can be achieved with front-line therapies or front-line combination therapies like ABL001 in combination with Glivec. ABL001 is being developed in 3L, but there is a strong interest to develop it in 1L. Given the young age of most CML patients in less developed countries, CML-CAB members urged Novartis to not focus on TFR alone but continue searching for a cure. Looking at the advances made with CAR-T-cells and T-cell cancers, it may take another decade to find a cure. CAR-T-cell therapies produce durable responses and deep remissions in 80-90% of children and in about 40% of adults. These types of therapies appear to be well suited for blood cancers, not so well for solid tumors. Novartis is looking at some CAR-T-cell therapies and targets in research at an early stage. **Patient engagement in research** Novartis has made a public commitment to patients to include community input early in drug development and trial design. With regard to the development and value proposition of asciminib, the CML community has been involved very late in the process. According to Novartis, this is not due to lack of intent but to internal and regulatory challenges to meet timelines. The company needs patient input to understand what are the relevant endpoints for a trial to see if a drug actually improves a patient's quality of life. Patient advocates expressed their keen interest in working with Novartis also in diseases other than CML, and in engaging in a more systematic manner. This would create a win-win situation for both parties as it would help avoid mistakes that are difficult to correct at a later stage.

Meeting with the CEO of Novartis, continued

With about 100 new trials launched per year and about 17,000 people working in research & development, Novartis finds it challenging to develop simpler mechanisms for their teams to engage. If they could see that patient input makes a trial more relevant, easier to conduct, and had a better medicine come out, then they would be able to see the value of patient engagement. CML-CAB members believed they can provide quality input based on their different approach to trial design, taking HTA assessment as a starting point to determine backwards what scientific questions a trial needs to ask and what data need to be generated. Discussions between patient experts and company experts could be the key to open some of the doors.

Novartis made the commitment that it would set a target within 5 years of what percentage of Novartis trials will have clear patient engagement involvement upfront before the protocol is finalized.

Access to diagnostics and treatment

The new access principles indicate a fundamental mindset shift for Novartis. The current approach is to think about access during the development of every one of the products and to show how the company enables broad access to a medicine and how health systems will be strengthened to support that approach. In some instances the issue of access is very complex and may need to be addressed with emerging market brands with tiered pricing, managed access programs or, in some instances, donation programs.

CML-CAB members explained how difficult it has been to understand the access strategy for Tasigna and wondered whether Novartis was going to review that. According to Novartis, the access principles will be applied systematically step by step. The aspiration is to have the entire innovative non-generic portfolio covered by the access principles.

Novartis encouraged CML-CAB members to share with them proactive ideas and innovative solutions. Access works differently in every country and needs to be addressed with different tools. Getting continuous proactive feedback would be very helpful. CML-CAB members confirmed their ability to provide meaningful input and work with different stakeholders.

In terms of access to medicines in low and middle-income countries, Novartis is following a multi-level approach. This includes (1) a large-scale drug donation program; (2) building up primary healthcare; (3) providing 30 chronic medicines at 1 USD/dose. However, new innovations were still not coming fast enough, and it can take 5-10 years for a new innovation to get to the market in Africa. It is a long journey because the basic infrastructure is still not in place and in cancer, diagnostics still remain a challenge.

Meeting with the CEO of Novartis, continued

CML-CAB members have contacts in and information about Africa and offered their help and insights to solve access problems. Within the "CML – Path to Care" program, Novartis and all other TKI companies are delivering medication to countries through the Max Foundation. The program has enabled access to all TKIs in Africa, and preferential pricing has been achieved for diagnostics. But there is still much more to do. CML-CAB members stressed that patients are still dying of CML, physicians are not properly educated on CML, and clinical trials in oncology are not in sight.

Novartis has a large clinical trial network in infectious diseases in Africa. This can build up capacity among local physicians and in local hospitals and, if successful, will open up possibilities for clinical research in malignant hematological diseases and oncology.

The expansion of CAR-T-cell therapies into further indications and larger patient populations is associated with the access principles of affordability and healthcare system strengthening. Both are crucial in making the therapies available to larger patient populations and also in countries where currently this is not a possibility. To achieve progress, Novartis is focusing on (1) reducing the cost of CAR-T-cells, (2) getting ahead of stem cell transplantation, (3) investing in building capacity in middle-income countries to at least ensure there is a single center of excellence that can perform this kind of therapy. Novartis is optimistic that CAR-T-cell therapy will get to middle-income countries, but at the moment does not have a solution for low-income countries.

To ensure that health systems can afford novel therapies in the long-term, infrastructure needs to be in place to collect data and measure long-term payment. This is where Novartis could use help from the patient community to make it clear that these types of technologies are hugely cost-effective. Novartis will keep advocating for a fundamental system change but a much bigger group of voices is needed to drive this change.

Novartis commitment to the patient community

Novartis confirmed their continued commitment to working with the CML and other communities. The company is engaged because of its history in CML and considers patient engagement as part of their identity. The challenge for the company is to allocate funding to where it can create the biggest impact. This can lead to situations at the country level where there might be a decrease in financial support compared to previous years.

Meeting with the CEO of Novartis, continued

CML-CAB observed that continuity and some connections had been lost in Africa and Central America following reorganization of Novartis. In certain countries, primarily Eastern Africa, Novartis decided that the best way to provide access would be through Novartis Social Business which tries to bring an entire Novartis portfolio into the country. This is more effective than each division going into the country separately. Novartis committed to connecting local PAGs with responsible people from Social Business.

Other topics

- Changing the face of the pharmaceutical industry:
  Generally speaking, pharmaceutical companies do not have a good reputation, especially with respect to working with patient organizations. The CEO was optimistic that this perception can be changed by being consistent over time. The improvement in life expectancy over the last 100 may be one of the greatest accomplishments in human history and is largely due to clean water and medicines. The pharmaceutical industry has a great story to tell, but has to improve their behavior. If the company can be consistent in value-based pricing, developing breakthrough medicines and improving access, than they can win back a good reputation.
- Overcoming unnecessary bureaucracies and legal restrictions:
  Collaboration between patient community and Novartis is getting more and more complicated, often because of compliance issues. Novartis is addressing the issue by working on the company culture, including drastic simplification of collaborating with HCPs and PAGs. The company is trying to prepare one easy-to-understand contract for the whole world. This effort of simplification is a co-creation project driven by the patient community and is another example of successful collaboration beyond CML.
- Support from patient communities like CML Advocates Network to help Novartis develop better medicines and get these medicines to patients in need as soon as possible.

CML-CAB members invited the CEO to speak at the opening of CML Horizons.

CML-CAB members gave a brief overview of the environment that they work in: the European Cancer Patient Networks, European disease-specific patient advocacy networks and collaborations with professional societies and multi-stakeholder initiatives. This provides scope to continue the dialogue with the patient community beyond CML. Closing the session, the participants expressed their wish to meet again to discuss a broader range of topics or meet with a broader set of cancer organizations for more feedback.

Follow-up actions:

- Novartis to report back on earlier and more meaningful patient engagement in early development on new therapies with CML community, based on quantifiable measures
- Novartis to report back on steps made towards achieving CML cure
- Novartis to connect local PAGs with responsible Novartis Social Business persons.

Next Steps and Closing Remarks

The next CML-CAB meeting will take place on 16 May 2019 in Lisbon; exact details to be agreed.

Jan Geissler closed the meeting at 16:40.