CML Community Advisory Board (CML-CAB)

Minutes of the meeting between the CML-CAB and representatives from Takeda Oncology and Incyte held at the Leonardo Hotel, Frankfurt, Germany, from 14:00-18:30 on February 25, 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)

TAKEDA (formerly ARIAD)
Ruth du Moulin - VP Medical Affairs Operations
Sergio Santillana - VP clinical research and development, acting CMO
Deyaa Refaat Adib - Senior Medical Director Clinical Research Team

TAKEDA ONCOLOGY
Fatima Scipione - Senior Director, Patient Advocacy

INCYTE
Julie Bekaert - Medical Director Hematology Europe

Meeting moderator
Kathy Redmond

Minutes prepared by:
Marion Alzer

LEUKEMIA PATIENT ADVOCATES FOUNDATION

CML AdvocatesNetwork
Community Advisory Board

Summary Notes from the Meeting
The 2nd CML-CAB meeting was opened by co-chair Jan Geissler. CML Advocates Network established the CML Community Advisory Board (CML-CAB) with the objective of providing interested companies with advice and input on issues that impact on patients' lives. Topics discussed during the meeting included the ponatinib development pipeline, an update on current and future CML trials, access to ponatinib as well as ways of improving the collaboration between Incyte/Takeda and CML patient advocates.
Presentation and Discussion: Clinical Development
Takeda provided insights into the history and structure of Takeda Oncology. Following the recent acquisition of ARIAD Pharmaceuticals, Inc., the company has expanded its oncology portfolio and extended its reach to patients with hematological diseases and solid tumors. The focus is on rare cancers with high unmet needs. Before the acquisition, Incyte was ARIAD's partner for marketing ponatinib. This relationship is now owned by Takeda. In the last 25 years, ARIAD, now part of Takeda Oncology, developed compounds for hematological malignancies and lung cancer. This includes ponatinib which is approved under the product name Iclusig for CML and Ph+ ALL. The company is currently sponsoring 4 CML trials: PACE – a global pivotal phase 2 trial, currently being closed out OPTIC – a global dose-finding trial, currently enrolling OPTIC 2L – a global 2nd line trial with ponatinib vs. nilotinib, currently enrolling OMNI – a patient registry, due to open in March 2017 Ponatinib is the only drug available that is highly sensitive to the T315I mutation in CML. Ponatinib was shown to have high efficacy but also be associated with a risk of developing arterial occlusive events (AOE). This toxicity was first described with ponatinib. Both efficacy and risk of developing AOEs appear to be highly dose-related. AOEs have also been observed with other 2nd generation TKIs. The challenge is to test lower doses to optimize the benefit for patients. Ponatinib was initially approved in the US, Europe and Japan via fast track. In November 2016, the FDA granted full approval in the US based on 4-year follow-up data from the PACE trial. The product is not approved for use in 1st line treatment. Although ponatinib is now fully approved, Takeda still has the obligation to complete the OPTIC trial requested by the FDA in 2013.

Takeda presented updates on current and future CML trials and invited CML advocates to give input and feedback.

Update on OPTIC

The phase 2 OPTIC trial is conducted to characterize the efficacy and safety of 3 starting doses of ponatinib (15 mg, 30 mg and 45 mg once daily). The trials is a post-approval requirement by the FDA and was planned to include 450 adult CP-CML patients resistant to at least 2 TKIs. The primary endpoint is MCyR at 12 months. A dose reduction to 15 mg once daily is mandatory when patients have achieved MCyR or MR 2 at 3, 6, 9, or 12 months.

The trial started in September 2015. Enrollment is poor. One of the reasons for this is that the primary endpoint MCyR and some eligibility criteria no longer reflect current practice or the ELN treatment recommendations (2013). The sponsor plans to accelerate enrollment with initiatives on a local, regional and global level, by taking the trial into new countries and aligning the protocol with current clinical practice.

CML advocates proposed to connect the company with local patient groups to help increase recruitment. They suggested initiating the trial in countries where ponatinib is not commercially available or where the drug is not reimbursed. They also shared their views on the chosen primary endpoint and on the mandated dose reductions. Takeda admitted that it would have been better to integrate the patient perspective earlier.

Update on OPTIC-2L

OPTIC-2L is a global 2nd line phase 3 trial comparing ponatinib and nilotinib in 600 CP-CML patients resistant to imatinib. The rationale behind the trial is that many CP CML patients show resistance to imatinib (20-25%) or intolerance (15-20%) to 1st line TKIs. The unmet need in 2nd line treatment remains high, especially in patients with mutations. Like ponatinib, nilotinib-treated patients have experienced peripheral vascular events. Ponatinib is efficacious and has a significant arterial occlusion signal. Both of these findings are population-related. Therefore, the drug needs to be tested in different populations.

The primary endpoint of the trial is MMR by 12 months. Patients will be randomized into three treatment arms and will receive either ponatinib 30 mg once daily, ponatinib 15 mg once daily or nilotinib 400 mg twice daily. The ponatinib dose will be reduced upon achievement of MCyR or MMR 12 months.

Patient enrollment in OPTIC-2L is very poor. Acceleration strategies include acceleration of site activation, launching medical outreach programs and tackling trial design challenges. More sites will be opened in countries where ponatinib is not approved or available or reimbursed.

Advocates advised that doctors tend to perceive ponatinib as risky but efficacious. Good treatment options like nilotinib and dasatinib are available to patients resistant to imatinib. Therefore it might be easier to recruit patients who have failed 2nd generation TKIs. They also suggested including a patient in the data safety monitoring committee of the trial. Advocates offered to collaborate on a local/regional level, e.g. the Philippines or Latin America, where they can help understand and address logistical hurdles.

Update on the OMNI registry study

The OMNI is a FDA-mandated post-marketing requirement based on the PACE trial to characterize the safety profile of ponatinib in routine clinical practice in the US. It is a prospective, observational, non-interventional registry in adult patients with CP-CML, AP-CML, BP-CML, or Ph+ ALL who are being treated with ponatinib with or without anticoagulant and/or antiplatelet agents. Patients can request to be enrolled within 30 days of starting ponatinib. Data will be collected for 12 to 30 months to capture late occurring events. Primary objectives are assessing the incidence of vascular occlusive events (VOEs), risk factors for development of VOEs and outcomes of VOEs. Launch of the registry is expected in Q1 2017.

There are no eligibility criteria other than exclusion of previous use of ponatinib. The FDA requires real-world data of patients receiving ponatinib as per labeling. Initially the study ran as phase 4 trial but failed. Takeda now intends to provide the safety data required by the FDA via the registry study.

Patient advocates shared that a patient organization is using a mobile app to enroll patients in a colorectal cancer registry in Canada. This may prove to be a good way of capturing patient data without needing an expensive infrastructure. Takeda expressed their interest in "cross-talking" with patient representatives about using different tools.

Update on investigator-sponsored trials (IST) in CML

Takeda is supporting several ISTs on ponatinib. Most of these trials are conducted outside the US where lower doses than 15 mg can be investigated. This is not possible in the US because of lack of FDA approval.

Takeda agreed to share the profiles of the ISTs so this information can be included in the clinical trials registry of CML Advocates Network. This will raise awareness in the community on all the support Takeda is providing.

Access to Ponatinib

Summary of Takeda presentation

Incyte and Takeda will continue to manage different alliance partners for commercial access of ponatinib (Iclusig) in different regions of the world. Both companies collaborate with the MAX Foundation Donation Program in low and middle income countries. Takeda has extended a small compassionate use program to 100 "slots". If a patient drops out of the program, their "slot" can be filled by a new patient. In some countries, the MAX Foundation can be utilized through distribution partners. Another program is in set up to provide access in further countries through the MAX Foundation.

Feedback/questions/comments by the CML-CAB and discussion with Takeda:

- Are there any plans to expand into countries that are neither low nor middle income countries but where no distributor is established? Advocates offered their help with mapping access challenges and finding solutions all over the world.
  Takeda has compassionate use programs for other therapeutic areas. The company will provide information on compassionate use in CML and on access programs in countries outside the scope of the Max Foundation and where there is no commercial distribution partner.
- Is Takeda committed to provide access to drugs after a clinical trial until the drug becomes commercially available?
  Takeda confirmed their commitment to providing access to drugs after a clinical trial until the drug becomes commercially available. This had always been company policy. The mechanisms may change due to the acquisition, but the commitment stays the same. Takeda has a named patient program (NPP) and an access-to-medicines commitment which will include ponatinib.
- In Kenya public health insurance companies are willing to enter into some kind of partnership with pharmaceutical companies. An advocate asked Takeda to consider this option and its impact on patients who are already in a compassionate use program.

Collaboration
Collaboration Takeda explained that the mission of their Global Patient Advocacy is to ensure that the patient voice is heard in Takeda programs and products. The company has realized that it is important to involve patient representatives early on. They have therefore created a global patient leadership counsel in Multiple Myeloma to identify opportunities for collaboration and better use the patient perspective in the research & development process. Patient representatives are involved in steering committees during trial protocol design. A similar structure could be applied for CML. Takeda suggested to connect at EHA to discuss how to exchange ideas and involve the patient community. Global Patient Advocacy also manages grant requests with a focus on Multiple Myeloma, Lymphoma, CML and Non-small Lung Cancer (NSCLC). Grant requests from specific countries will be directed to that particular country. Grant requests covering a wider geographical region will at least be considered. During the meeting, the following opportunities and wishes were identified for improving collaboration between Takeda Oncology, Incyte and CML patient advocates **Opportunities** • Engage with community early on trial design • Raise awareness about trials via patient groups • Find patients to participate in trials via patient groups • Address concerns about ponatinib • Work with community to address barriers to setting up trials • Include patient advocate at meeting with investigators • Meet at EHA to discuss access initiatives and share details • Map access challenges and find solutions

Wish list

- Find a structured process to involve patient representatives into all trials (commercial and ISTs)
- Involve patients early and often
- Maintain relations between Takeda/Incyte and community
- Transform how Takeda/Incyte engage with patients
- Alignment between Incyte and Takeda
- Meet again at CML Horizons 2017 and subsequent CAB on May 29-30, 2017
- Maintain funding for CML Horizons
- Provide clarity about grant giving process
- Clearer lines of communication, preferably direct and not through agencies
- Draw on community expertise – this is effective and cheaper
- Do not duplicate efforts
- Find a way to work in markets that Takeda Oncology/Incyte have not entered
- Greater geographical presence
- More trials in different world regions
- Map access challenges
- Connect local CML patient organizations with Takeda Oncology/Incyte locally
- Share information about CML pipeline
- Global patient registry beyond vascular occlusive events
- More focus on quality of life
- Become a true partner
- Patients to express their interest in QoL studies and support the importance of such studies
- CML breakfast at EHA to connect patient advocates with Takeda

Outlook – how to keep the dialogue going, how to ensure follow-up:
CML Horizons and the next CML-CAB meeting in May, and EHA are opportunities coming up where CML advocates and Takeda/Incyte can meet.

The CML community emphasized their commitment to help companies overcome local or other hurdles. All parties stressed their interest in delivering on the wish list and exploring further opportunities to collaborate for the benefit of the patients.

Follow-up Actions:

- Advocates to share a list of the currently 113 CML member organizations
- Advocates to map access challenges
- Takeda to check their availability for CAB meeting on May 29-30, 2017
- Takeda to provide information about grant giving process
- Takeda to provide information on compassionate use in CML and on access programs in countries outside the scope of the Max Foundation and where there is no commercial distribution partner
- Takeda to share details of the ISTs to be included in the clinical trials registry of CML Advocates Network

Jan Geissler closed the meeting at 18:30.