The most important European meeting of hematologists, the 27th Annual Congress of the European Hematology Association (EHA), was held this year in Vienna from June 9 to 17 as a hybrid event due to the COVID-19 pandemic.

Every **year, the latest research data on various blood diseases were presented by leading experts in their field. Representatives of the various patient organizations also had the opportunity to attend, and this report summarizes the most important news on chronic myeloid leukemia from a patient advocate's perspective.**

Treatment and follow-up in CML

Prof. Delphine Rea, France, presented an update after 96 weeks of treatment (cut-off date 10/06/2021) on the current data from the phase III ASCEMBL clinical trial on the efficacy and safety of asciminib, the first STAMP (Specifically Target the ABL myristoyl Pocket) inhibitor, compared with bosutinib. This study included patients with CML in the chronic phase who were pre-treated with at least two or more tyrosine kinase inhibitors (TKIs). The rate of deep molecular response (MMR) at 24 weeks in the primary analysis was 25.5% with asciminib versus 13.2% with bosutinib. Fewer grade ≥ 3 adverse events (AEs) leading to treatment discontinuation had occurred while taking asciminib.

After more than 2 years of follow-up, asciminib continued to show both clinically and statistically significant superior efficacy and better tolerability compared with bosutinib. The response was durable, and MMR was more than twice as high with asciminib as with bosutinib. The difference in MMR rates between the two groups increased from 12.2% at week 24 to 21.7% at week 96. A higher proportion of asciminib-treated patients in a later line of therapy achieved response with BCR-ABL1 levels ≤1%, which was associated with improved long-term survival. These results would support the use of asciminib as a new CML therapy.

Therapy-free remission (TFR) is one of the most important goals of CML treatment, but to date, the best therapy to achieve this goal has not been defined. Sustained deep molecular remission (DMR) is a prerequisite for stopping therapy, and it is hypothesized that for patients who start treatment with imatinib and do not achieve early molecular remission (EMR) on that therapy, switching to a second-generation TKI may improve the likelihood of achieving DMR. An international prospective study investigating this assumption aims to validate it. It compares therapy with nilotinib (NIL) vs. imatinib (IMA) with an early switch to NIL to achieve sustained treatment-free remission. It was presented by Prof. Fabrizio Pane, Italy. He said that this is the first and only prospective study to date comparing not only DMR rates but, more importantly, TFR rates as a function of treatment: first-line treatment with a second-generation TKI versus first-line IMA, followed by a switch to nilotinib in the event of suboptimal response.

From November 2016 to January 2021, 457 patients with newly diagnosed CML in the chronic phase were enrolled in this study, of whom 448 (228 and 220 randomized to the NIL and IMA arms, respectively) were evaluable. The median age was 54.2 years. The median follow-up time for the entire patient cohort was 30.4 months. Sixty-five (25.4%) of the 220

patients in the IMA arm would not have met ELN criteria for an optimal response within the first 12 months of treatment and had been switched to NIL therapy according to the protocol. The last analysis in February 2022 included data from 304 patients. Of these, 35 had not responded optimally to therapy. The analysis after 24 months of follow-up would have shown that 76 (23.6%) of the 322 patients were able to achieve MR4.5. It was achieved significantly more often by patients in the NIL arm (48 versus 28). The analysis had shown that the early switch in IMA patients to NIL was effective in achieving a DMR. A subsequent analysis will clarify whether the higher DMR rates in the NIL arm may lead to a higher TFR rate.

The meta-analysis of a Dutch study group also addressed the issue of TFR and which patients might be suitable for it. Digital PCR could be used to identify CML patients in the chronic phase who are suitable for early discontinuation. Digital PCR is a new technique that enables highly accurate BCR-ABL1 quantification, even in CML patients with low residual disease, he said. This is critical for patient selection, he said. However, it is unclear how the prognostic value is related to temporal variables, such as the duration of treatment before the TFR attempt, he said. The current guideline from the Netherlands would recommend aiming for a TKI treatment duration of more than 6 years to increase the TFR success rate. Data from this meta-analysis, presented by Camille Kockerols, The Netherlands, could have shown that the depth of molecular response, as measured by digital PCR, had predictive value for successful TFR regardless of treatment and DMR duration. Digital PCR could help identify patients suitable for an "early" discontinuation attempt of the TKI. In the future, combining digital PCR with other predictive factors could help further improve the prediction of successful TFR.

Whether a second discontinuation attempt with dasatinib can be successful was investigated in the TRAD (Treatment-free Remission Accomplished with Dasatinib) trial. It was designed to determine whether patients benefit from a switch to a second-generation TKI upon resumption of therapy after relapse. The study enrolled patients previously treated with imatinib who relapsed after discontinuation. The final results of this Canadian study were presented by PhD. Dr Dennis Kim.

He said the final results of the study showed that resumption of treatment with dasatinib after TFR1 failure with prior imatinib treatment was effective. In most cases, at least MR4 was achieved again very quickly. However, 12 months of therapy with dasatinib did not result in a significant improvement in TFR2 rates. It was suggested that the time of taking dasatinib should be extended before a second discontinuation attempt.

A group of researchers In Quebec, Canada, also presented the results of their studies. They had been investigating the question of whether CML therapies are switched due to intolerance or whether there are other reasons for this. In their opinion, real-world studies could provide information on treatment patterns, efficacy, and side effects, and they would help identify the unmet medical needs of patients. This study aimed to determine the frequency of TKI switching, the reason for switching, and the duration of the treatment without switching as a function of treatment and specific TKI using real-world data from a registry in Quebec. The registry was initiated in 2009. It was shown that TKI switching was

common and mainly due to intolerance in all lines of therapy. Patients requiring 3 or more lines of therapy would be at a survival disadvantage. The results would suggest that one of the most important demands for CML treatments is the availability of better-tolerated drugs.

Novartis Symposium – The impact of CML on humans after 2 TKIs

The symposium, organized by Novartis, addressed open questions and unresolved issues in the treatment of CML and aimed to show what known data mean for patients in later lines of therapy and clinical practice. The leader of the symposium, Prof. Andreas Hochhaus, Germany, asked the rhetorical question of whether everything has been achieved in the treatment of CML or whether there is a need for further clinical research and new treatment methods. He stated his point of view very clearly: Of course, there is still a need to improve the response to therapy, and the quality of life, to achieve the conditions for a safe therapy stop, for a sustained therapy-free remission and the prevention of a worsening of the disease. Although four TKIs are available in the various European countries for first-line therapy and five for a later line of therapy, which is necessary for various reasons, long-term toxicities are known, which can be a problem, especially for those patients who do not achieve a therapy-free remission due to an insufficient response and have to take the TKI for 5 years or longer. Toxicities are particularly because TKIs inhibit not only the BCR-ABL kinase but also many others. To avoid complications, pre-existing and concomitant diseases should be considered when choosing a TKI. Currently, great expectations would be placed on the new agent asciminib, which has already been approved in the United States. Because asciminib is a STAMP inhibitor (Specifically Targeting the ABL-Myrestol Pocket) that targets a different site of the BCR-ABL protein than the previously approved TKIs, a faster and deeper therapeutic response and fewer side effects are expected.

Despite a variety of treatment options, allogeneic stem cell transplantation (SCT) would still be necessary for 3% of CML patients. Determining the optimal timing for this intervention is a problem that remains to be solved. Although transplants are known to be more successful when performed in the chronic phase, they are mostly performed in the advanced stages of the disease. Prognostic markers are needed to identify patients in the chronic phase who will require transplantation in the future. However, these markers still need to be identified, which is another task that remains to be solved. It is already known that additional BCR-ABL-dependent and -independent chromosomal alterations can complicate or even prevent an optimal response to treatment with TKIs, he said. Next generation sequencing (NGS), an improved DNA sequencing technology, is hoped to provide new insights.
Another research focus, he said, is treatment-free remission (TFR). Evaluations of studies on TFR show that 50% of all patients who interrupt TKI therapy suffer a relapse. The reason for this seems to be the activity of the residual disease. The question, therefore, arises whether maintenance therapy can prevent relapses. The first results of various studies on the efficacy of interferon-α as an additional drug to the TKI would be expected at a later date in 2022 and 2023.

Prof. Massimo Breccia, Italy, focused on data describing the efficacy and safety of later lines of current and new CML therapies. All TKIs would cause side effects, and 20% of patients

would have to discontinue their therapy due to adverse side effects, which is associated with a lower probability of response and poorer overall survival. Sequential treatment would lead to the emergence of new mutations, with the frequency of the T315I mutation reported to be 3-15%. Currently, the only available options for patients with T315I mutation outside the United States are ponatinib or allogeneic SCT, he said. Asciminib, which has been approved by the FDA for patients previously treated with two or more TKIs, acts with unique allosteric inhibitory mechanisms and is a promising therapeutic approach. Recent data suggest that asciminib is an effective and safe option for intensively pretreated CML patients without treatment alternatives. Several trials with asciminib are ongoing, he said. Future results would help determine the right time to initiate therapeutic intervention and identify the patient population for which asciminib treatment could be considered.

Prof. Dragana Milojkovic, UK, provided an overview of optimizing CML treatment in the future. Additional chromosomal alterations at diagnosis have been identified as prognostic markers on treatment response and achievement of early molecular remission. Identification of somatic mutations such as ASXL 1 would also predict treatment outcomes. Whether transcript type has an impact on treatment outcome continues to be debated, he said.

The randomized, controlled phase III ASC4FIRST trial is designed to show whether starting CML therapy with asciminib after diagnosis confers an advantage for patients over imatinib, dasatinib, nilotinib, and bosutinib. The primary endpoint of this study was the achievement of deep molecular response (MMR) at 48 weeks. Secondary endpoints would include MMR rates at 96 weeks, timing of treatment discontinuation due to adverse events, quality of life data, pharmacokinetics, progression-free survival, and overall survival.

First-line therapies, as well as later lines of therapy, would be further investigated concerning alternative potent TKIs as well as combination therapies with interferon. In this regard, Prof. Milojkovic mentioned French, Spanish and German studies (TIPI, ResToP, PonaZero, TIGER, BosuPeg), which are listed in the European and international study registers (www.clinicaltrialregister.eu, www.clinicaltrials.gov). The results of these studies are eagerly awaited.

For personalized CML management, optimization of TKI dosing would need to be further explored. The results of various studies are expected soon (DESTINY, DasaHIT, OPTIC). They should help to define optimal dosages.

A significant field of research is both therapeutic approaches targeting leukemic stem cells and the use of checkpoint inhibitors. The combination of venetoclax, a BCL2 inhibitor, with a TKI was cited as an example of a new treatment strategy. BCL-2 has been identified as an important survival factor for CML stem/progenitor cells. Combined inhibition of BCL-2 and the BCR-ABL tyrosine kinase had the potential to significantly improve the depth of response. The combination of PD-1/checkpoint inhibitors and TKIs are also being investigated, he said. Other clinical trials for third-line and later-line CML are investigating the inhibition of therapies directed against BCR-ABL1. These include the ATP-competitive TKI PF-114, which also inhibits the T315I mutation, and the JAK/STAT inhibitor ruxolitinib.

In summary, Prof. Milojkovic emphasized that quality of life and treatment-free remission remain important treatment goals.

Safe pregnancy and healthy babies with CML

Very important and understudied issues are family planning and pregnancy, said Prof. Elisabetta Abruzzese, Italy. While many research questions have been answered in recent years, several problems remain unresolved in this area, she said:

1) Male patients can father children whilst in therapy, but is this also true for ponatinib and newer drugs?

All TKIs are teratogenic and embryotoxic and can lead to miscarriages at high doses. In animal studies, however, they were not genotoxic or mutagenic, he said. The prevalence of congenital defects in birth registries is 2.78%. About 450 pregnancies have been reported in partners of men on therapy, he said. Most of these took imatinib (327), nilotinib (50), dasatinib (45), bosutinib (17), or ponatinib (2). Observed events in neonates do not appear to be related to therapy, as they occur with similar frequency as in the general population.

2) Female patients should not take TKIs during pregnancy. But when should be stopped if the patient becomes pregnant under TKI therapy?

As soon as a positive pregnancy test is available, therapy with TKIs should be stopped. This usually occurs in the 4th-5th week of pregnancy. In this early phase of pregnancy, no negative effects are to be expected from taking the tablets, because the fetus has not yet fully implanted itself in the uterus. The placenta is not yet fully formed and therefore does not come into contact with the drug.

3) If TKIs have to be used during pregnancy, which one should be used when and for how long?

There are 300 documented pregnancies with imatinib. These included fetal abnormalities such as cranial synostoses (premature ossification of the cranial sutures), exomphalos (covered umbilical cord herniation of the newborn), hemivertebrae (hemifacial vertebrae), Polydactyly (excess number of fingers or toes), hydrocephalus (accumulation of cerebrospinal fluid in the skull), myelomeningocele (congenital malformation of the spinal cord), cerebral hypoplasia (malformation of the cerebellum), and vascular and organ defects described. Imatinib was reported to have minor placental toxicity. Sixty patients became pregnant during therapy with nilotinib. Omphalocele (umbilical cord rupture) and intrauterine death of twins were described. Nilotinib was reported to have low or no placental toxicity. When dasatinib was taken in the first or advanced (2nd or 3rd) trimester, serious problems such as intrauterine death, omphalocele, and organ or skeletal malformations were seen in 40 of 80 documented pregnancies. Dasatinib was placenta-permeable and therefore could cause complications at any time. Sixteen pregnancies with bosutinib were uneventful, and the drug was stopped at 5 weeks of gestation in each case. Of two pregnancies on ponatinib, one ended in miscarriage at 9 weeks gestation, and the

second was unremarkable (Assi R et al 2021, Madabhavi I et al J Glob Oncol. 2019, Alizadeh H Leuk Res 2015, Pye SM Blood 2008, Cortes JE AmJHem 2015).

The best therapeutic option in pregnancy is still interferon-α (IFN-α), Abruzzese said. It cannot be detected in the blood of the fetus and is therefore safe. However, its use is limited because a response to therapy is very slow and because it must be injected subcutaneously every day. Nowadays, a polyethylene glycol molecule is added to INF-α during its production. This is said to improve its half-life and reduce the risk of allergy. The resulting pegylated IFN-α (PegIFN-α) is available in three commercial forms: PegIFNα-2a (Pegasys), PegIFNα-2b (PegIntron), and ROPegIFNα-2b (Besremi). PegIFN is classified as a Category C therapeutic in pregnancy because there are no well-controlled, large-scale studies in pregnant women, Abruzzese added, but the potential benefits may justify its use in pregnant women despite potential risks.

The need for therapy during pregnancy could be predicted by tumour burden at the beginning of pregnancy and the length of time on a TKI and assessed on an individual basis:

- Imatinib was teratogenic mainly during periods of organogenesis. The pregnancies of 51 patients treated beyond the 2nd trimester were without adverse events, Abruzzese said. The European Leukemia Network (ELN) documented the pregnancies of 33 patients and demonstrated low placental toxicity of imatinib.
- Nilotinib occasionally (1:3) passed the placenta. The ELN reported 7 patients treated with a reduced dose (400 mg/d) after 21 weeks gestation.
- Dasatinib crosses the placenta and should not be used at any time during pregnancy. The ELN reported one case of intrauterine death at 27 weeks; Cortes et al reported 5 cases with serious adverse events and death.
- IFN is said to be safe throughout pregnancy and can be used to maintain remission when transcript levels begin to increase.

Inferring from the courses of documented pregnancies, it is now possible to make recommendations for CML patients:
- Therapy with IFN is possible at any stage of pregnancy.
- The TKIs imatinib and nilotinib can be used, if necessary, after the complete formation of the placenta.
- No treatments until 13-15 weeks of pregnancy unless necessary considering tumour burden and kinetics of transcript increase

The management of pregnancy is not just a question of drugs, as Prof. Abruzzese emphasized in her presentation. There are always different aspects to consider, she said:

(a) disease-related:
- Disease stage (chronic vs. advanced phase).
- CML status (time of diagnosis, remission, depth of remission)
- Pregnancy status (weeks of gestation and course of pregnancy).
- timing and duration of TKI exposure for embryo/fetus
- Which TKI was/is being taken?

b) Patient-related:
- physical and psychological aspects (patient's age, sociocultural and religious environment, motivation)

c) Pregnancy-related:
- Pregnant patient diagnosed with CML
- CML patient who wishes to have a child
- CML patient who became pregnant unplanned

4) Is breastfeeding possible?
If the mother is in complete cytogenetic remission or MR3 after delivery without TKI treatment, she could breastfeed her baby. Breastfeeding is also possible during therapy with interferon.

Better understanding the development of CML - a topic of the ELN-EHA CML Scientific Working Group:

Prof. Katerina Machova Polakova, Prague, reported on the findings of the European Treatment Outcome Study (EUTOS) in 2018-2021. The goal of EUTOS 2018, she said, is to make progress toward a cure for chronic myeloid leukemia. This includes:
The implementation of molecular quality standards and the standardization of BCR-ABL1 diagnosis:

- Recommendation for the measurement of major types of transcripts according to international standards (IS) had been defined.
- recommendations for the measurement of atypical transcript types according to IS would not exist, these PCR measurements would represent an individual molecular response
- the improvement of diagnostics through the introduction of new molecular methods and technologies
- Application of Next Generation Sequencing (NGS)-based mutation analysis in clinical trials would have shown, for example, for the gene ASXL1, that patients with this mutation are significantly less likely to achieve MMR at 12, 18 and 24 months.
- NGS is recommended for mutation analysis both for patients with unstable MMR and after the loss of deep molecular remission (DMR).
- the investigation of molecular predictive factors associated with molecular relapse after TKI discontinuation
- the results of DMR measurements by ddPCR mRNA and ddPCR DNA seem to allow predictive statements before TKI stop/discontinuation (Machova Polakova et al. Leukemia 2020)
- A deeper understanding of the maintenance of TFR due to immunological mechanisms.
- NK cells are a particular distinguishing feature of the CML immune system compared to other cancers
- plasmacytoid dendritic cells (pDC) are of importance in maintaining TFR

If you want to learn more about EUTOS, you can find all the information you need on the website https://www.uniklinikum-jena.de/eutos/.

Prof. Shady Awwad, Finland, explained the importance of non-BCR ABL1 molecular biomarkers for CML prognosis. He said that reality has shown that CML is not a cancer caused solely by a single oncogene in every case. There are BCR-ABL-independent mechanisms that are causative of resistance or toxicities that prevent successful TFR, he said. Meanwhile, several BCR-ABL1-independent genes have been identified that are associated with a worse prognosis. In therapy, there are various challenges to overcome at different time points, which would be easier to solve with reliable biomarkers in the interest of patients. For example, predictive molecular biomarkers could support the recommendation to stop therapy at the optimal response. In case of resistance or progression, the decision for or against allogeneic stem cell transplantation could be made quicker. If the disease stage is more advanced and the patient is already in an accelerated phase or blast crisis, biomarkers could be used to decide whether switching to a second or third-generation TKI is promising or whether the patient should be prepared for allogeneic stem cell transplantation.

PD Dr Mirle Schemionek-Reinders, Germany, highlighted another exciting aspect of CML pathogenesis. In her presentation, she spoke about the importance of persistent leukemic stem cells (LSCs) being clinically relevant, for example, for successful TFR. She said that prognostically relevant leukemic stem cell markers have been described in various publications (Mustjoki et al, Leukemia 2013, Thielen et al, Clin. Cancer Res. 2016). They would allow monitoring of the persistence of LSCs, characterizing them, and treating them using targeted therapies. Possible therapeutic strategies to treat persistent LSCs could target LSC antigens, block their cellular survival mechanisms, inhibit survival-related signals from the bone marrow microenvironment, and involve the immune system.
The last speaker in this session was Assoc. Prof. Tiong Ong, Singapore, on progression mechanisms of accelerated (AP) and blast phase (BP) CML. Disease progression is characterized by considerable genetic and epigenetic diversity, he said. Identifying commonalities could lead to biomarkers and treatment approaches applicable to the majority of patients with BP, he said. Progression into BP is characterized by a common or "core" transcriptome that governs biological behaviour. The results of his research suggest that in the future, patients in the chronic phase could be identified in whom progression is imminent. Future work is needed to identify those cellular factors that mediate heterogeneity of response to therapy in the chronic phase, he said.

New insights into CML biology

Petra Nygren, Finland, presented the results of her research group's investigation of the potential of anticancer drugs to enhance natural killer (NK) cell activity in CML. Immunotherapies with natural killer cells are promising new cancer therapies, she said, and complete remission has been achieved in patients with relapsed/refractory myeloid leukemias. The importance of NK cells in patients with chronic myeloid leukemia (CML) has been highlighted in several studies. A targeted NK cell response against remaining tumour cells could help patients achieve and maintain a therapy-free remission (Ilander et al 2017).

Accordingly, in CML patients a higher proportion of mature NK cells experience longer relapse-free survival after treatment discontinuation. In addition, complex interactions between TKIs and NK cell function have been discovered in CML. For example, dasatinib and imatinib are thought to enhance NK cell cytotoxicity by regulating activating and inhibitory receptors.

NK cell responses are generally short-lived, he said, and attempts have been made to improve their function against malignant cells using cytokines, bi- and trispecific antibodies, and small molecule inhibitors. However, large-scale drug screening to evaluate the combinatorial effects of NK cells and anticancer drugs has not yet been performed. This study aimed to evaluate the potential of small molecule anticancer drugs for synergistic effects with NK cell immunotherapy in CML and to determine which drugs can enhance or inhibit NK cell cytotoxicity in CML cells. Of the drugs studied, the SMAC mimetics (a new class of agents designed to drive cancer cells to suicide) birinapant and LCL-161 were the most potent enhancers of NK cell cytotoxicity. However, several of the drugs studied can also inhibit the NK cell response. Their use should be considered with caution when planning new CML treatments. The results of the study would have shown in vitro that new classes of drugs have both activating and inhibitory effects on NK cell cytotoxicity against CML cells. Defining the interactions between NK cells, drugs, and CML cells could provide a framework for future combination immunotherapies to improve treatment-free remission.

Posters

The EHA featured 34 posters looking at a wide variety of CML topics including disease biology, translational research, and clinical aspects. A few selected contributions are summarized below.

P691 - Dose reduction before TFR.

Many studies have reported that approximately 50% of patients can achieve sustained TFR, while the other 50% usually experience molecular disease relapse within two years of stopping therapy. It is speculated that the immune system (IS) plays an important role in controlling the rate of residual disease and may influence individual relapse behaviour. The recently published DESTINY trial (Clark et al., Lancet Haematol, 2019; NCT 01804985) had shown that TKI dose reduction before discontinuation may proactively increase the proportion of patients who remain in sustained TFR. However, there has been no systematic review evaluating how dose reduction regimens can further improve the success of TKI discontinuation trials. Subanalyses have shown that some patients require complete CML eradication to maintain a TFR, while other patients can control residual disease even after treatment discontinuation. Since prospective stratification of patients was difficult to achieve, the aim was to investigate whether further optimized dose reduction before treatment discontinuation could further improve TFR. Using computer simulations, it had been shown that TKI dose reduction before treatment discontinuation appeared to be as efficient an approach as in which patients remained on TFR with treatment at the full dose for the same duration. The model simulations would confirm clinical findings describing that the total duration of TKI treatment is an important determinant of TFR success while

suggesting that lower-dose TKI treatment is sufficient for many patients. The model results of this study presented at the EHA would suggest that a gradual dose reduction before TKI discontinuation (e.g., 12 months after MR4 at 100% TKI, 12 more months at 50%, and 12 more months at 25%) does not limit the overall success rate of TFR, while it significantly reduces the total amount of TKI administered and thereby the side effects and overall cost of treatment.

P692 Immune factors for the maintenance of TFR after discontinuation of imatinib.

The study presented in this poster aimed to determine immune factors responsible for the elimination or control of residual CML cells. They may be critical for achieving long-term relapse-free survival (RFS) and TFR after imatinib discontinuation. Peripheral blood mononuclear cells from 63 CML patients were analyzed by flow cytometry at two-time points: upon discontinuation of imatinib and 3 months after discontinuation. Key components of the immune system that have a potential impact on the maintenance of a patient's remission were assessed. The BCR-ABL1 transcript was analyzed by two molecular biology methods: standard real-time quantitative polymerase chain reaction (RQ-PCR) and digital droplet PCR (ddPCR). The detected changes in immune cells had been able to show the importance of immunocompetent cells in maintaining the TFR of the patients. Characterization of the immune system, which likely plays the most important role in achieving long-term RFS and maintaining TFR, may help define the group of patients who can safely discontinue imatinib.

P696 Subtherapeutic TKI doses to maintain response in the treatment of CML patients with intolerance.

There are few documented cases of patients receiving subtherapeutic doses, i.e., doses lower than those indicated in the TKI package insert. Subtherapeutic doses are used in clinical practice when the patient does not wish to discontinue treatment, when a discontinuation attempt has failed, as a maintenance strategy, or in patients with intolerance, among others. Although use in practice is likely, there would be little information on outcomes. The authors of this poster have examined the feasibility of using subtherapeutic doses in CML patients, as well as the rationale for dose reduction and its impact on molecular response. Subtherapeutic doses were defined as 20 mg dasatinib, 100 mg or 200 mg imatinib, 150 mg nilotinib, and 100 mg bosutinib. Data from 13 CML patients were examined. The median follow-up time since the start of dose reduction was 60.5 months and 40.7 months after the last dose reduction. None of the patients experienced TKI resistance or progression during the follow-up period. 3 patients reduced dose as a practical alternative for fear of discontinuation; 2 patients discontinued treatment and remained at the minimum dose to maintain MMR after relapse; the remainder of patients reduced dose due to intolerance. All patients had MMR at the last follow-up and 92.3% had deep MMR (≥MR4). The results would indicate that TKI doses could be optimized to subtherapeutic levels on an individual basis and an MMR could be maintained. Limitations included the small number of patients studied, but none of them experienced TKI resistance or progression over an average 5-year period. In intolerant patients, side effects resolved and quality of life improved after reduction to the subtherapeutic dose. This approach could also

be a good option for "maintenance therapy" for patients who relapse after a discontinuation attempt or for patients who do not want to discontinue. The use of subtherapeutic doses instead of complete discontinuation of TKIs would also lead to economic savings. In addition, it would be interesting to investigate whether long-term use of subtherapeutic doses can prevent the development of serious off-target TKI toxicities, such as vascular events. Studies with larger cohorts of patients would be needed to assess the feasibility of this clinical practice.

P701: COVID-19 in CML patients in TFR: disease severity and its impact on TFR status.

In patients with hematologic malignancies, severe SARS-CoV-2 infections associated with high mortality are observed more frequently compared to the general population. In CML, patients with the uncontrolled disease have a higher risk of death. The impact of SARS-CoV-2 infection on CML patients in TFR has not been studied to date. In particular, because control of residual disease by the immune system may be important for TFR, there would be a concern that infection could lead to loss of TFR.

From March 2020 to December 2021, the CANDID study, organized by the international CML Foundation iCMLf, collected data on COVID-19-positive CML patients worldwide. Details of this registry were presented at ASH 2021. For the subanalysis on patients in TFR presented in this poster, additional information was collected, including molecular remission status (BCR-ABL1 ratios) before, during, and after SARS-CoV-2 infection for at least 6 months. As of December 2021, 1050 COVID-19-positive CML patients were registered. Ninety-five patients were in TFR at the time of SARS-CoV-2 infection, of whom 89 (93.68%) recovered and 6 died (6.32%). The median age of the TFR patients was 57 years, and men were 51 (53.68%). The median time from CML diagnosis to report date was 13 years (range 3.7-27.0 years). The median duration of TFR was 2.83 years (range, 0.5 months-10.1 years), including 19 patients with a TFR duration of less than one year. Of the 89 recovered TFR patients, 74 patients had 6 months of follow-up (83%), and an additional 6 patients with a shorter follow-up of 3 to 5 months after COVID-19 diagnosis were still in TFR. Of the 74 patients with a 6-month follow-up, 69 remained in TFR (93%) and 5 lost it. PCR results before, during, and after infection could be recorded in 71 patients.

As a result of this subanalysis, it could be said that CML patients in TFR have similarly severe disease course and survival rates as CML patients on TKI therapy. There would be no evidence of increased risk of TFR loss after SARS-CoV-2 infection.

P703 Association between bariatric surgery and treatment response in CML patients with TKI therapy.

Bariatric surgery is widely used in patients with morbid obesity, with great success in reducing associated metabolic disease. However, it can alter the pharmacokinetics of oral medications, which include TKIs. The impact of bariatric surgery on CML treatment outcomes is largely unknown. A retrospective analysis was conducted to investigate the clinical impact of bariatric surgery, such as gastric bypass, gastric sleeve, or gastric banding, on the outcomes of CML patients treated with TKIs. Twenty-eight patients with CML and a

history of bariatric surgery (22 had surgery before CML diagnosis) and 56 patients in a matched control group were identified and analyzed. Of the bariatric surgery patients, 61% required more than one TKI during the course of their disease due to intolerance or resistance, compared with 25% in the control group. BCR-ABL1 bisection time was higher in the bariatric surgery group compared with the control group (26 days vs. 13 days), suggesting slower response dynamics. The median time to complete cytogenetic response (CCyR) and deep molecular response (MMR) was twice as long in bariatric surgery patients: 6 months versus 3 months. Bariatric surgery is associated with a slower response to TKIs and higher rates of treatment failure. There would be an unmet need to develop treatment strategies for these patients. Studies are also needed to measure drug levels in these patients to determine which TKI has better bioavailability, which in turn could lead to better outcomes.

P704 Asciminib induces a durable sustained molecular response in CML patients with a T315I mutation: updated efficacy and safety data from phase I study.

In patients with CML, the T315I mutation is associated with poor clinical outcomes and resistance to previously approved TKIs. Until recently, ponatinib (PON) was the only TKI available for these patients, but its use had been limited by associated cardiovascular side effects. In the primary analysis of the Phase I X2101 trial, asciminib demonstrated efficacy and a favourable safety profile in heavily pretreated patients with CML with a T315I mutation. These results supported FDA approval of asciminib.

This poster presented updated efficacy and safety data for this new drug (data cutoff date: January 6, 2021). Monotherapy with asciminib 200 mg twice daily showed a sustained, favourable safety profile in chronic-phase CML patients with a T315I mutation - a patient population with a high unmet medical need. The clinical efficacy of asciminib would be evidenced by the high proportion of patients achieving durable MMR and BCR-ABL1 ≤ 1%. The updated analysis confirmed asciminib as a treatment option for patients with CML-CP with T315I, including those who have failed treatment with PON.

P717 Bosutinib in newly diagnosed CML: gastrointestinal, hepatic, renal, and effusion safety assessment in the BFORE study.

Bosutinib is approved for the treatment of CML patients resistant/intolerant to prior therapies and in newly diagnosed Ph+ CML in the chronic phase (CP). The efficacy and safety of bosutinib (BOS) versus imatinib (IMA) in patients with newly diagnosed CP-CML were evaluated in the phase III BFORE study. This poster evaluated the safety profile of bosutinib after 5 years of follow-up with a focus on gastrointestinal, hepatic, renal, and effusion adverse events (TEAEs).
The safety profile of BOS and IMA in BFORE was different, with more TEAEs occurring with BOS therapy, but no new safety signals were detected after 5 years of follow-up. The occurrence of TEAEs was mainly in year 1, with fewer TEAEs observed in later years. Discontinuations due to serious adverse events (SARs) generally occurred at baseline, with discontinuations due to SARs in the gastrointestinal tract, liver, effusions, and kidneys. The

long-term safety results of the study would justify the use of BOS in first-line treatment as a standard of care in patients with CML in the chronic phase.

PB1903 planned study: multicenter, unblinded phase IB/II study to determine the dose and safety of asciminib in pediatric CML patients in the chronic phase.

Tyrosine kinase inhibitors (TKIs) are the standard of care for adult and pediatric patients with CML in the chronic phase (CML-CP). Five TKIs are approved for adults: Imatinib, dasatinib, nilotinib, bosutinib, and ponatinib; for pediatric patients, only imatinib, dasatinib, and nilotinib are approved. The efficacy and safety profiles of the TKIs are similar in adult and pediatric patients; however, growth retardation has been reported in the pediatric population, with unknown long-term side effects. Therefore, safer and more effective options for pediatric patients are needed. Asciminib is a recently approved drug that inhibits BCR-ABL1 by targeting the ABL myristoyl pocket (STAMP). In the phase III ASCEMBL trial for adults with heavily pretreated CML-CP, asciminib (40 mg twice daily [BID]) showed an improved major molecular response rate (25.5% vs. 13.2%) at week 24 and a better safety profile compared with bosutinib (500 mg once daily). The phase Ib/II study evaluating asciminib in pediatric patients is described here.
The primary objectives of this study are to determine the pharmacokinetic (PK) profile of asciminib in pediatric patients: and to identify a pediatric dosage that results in asciminib uptake comparable to the adult dose (40 mg BID). The study will include CML patients in the chronic phase who have been pretreated with ≥1 TKIs, do not have a T315I mutation, and are between ≥1 and <18 years of age. Adolescent patients aged ≥14 to <18 years and weighing ≥40 kg will be enrolled in a separate study group and will receive the adult dose until pediatric dosing is available.
In the first part of the study (dose-ranging cohort), 4 to 6 patients aged ≥1 to <18 years will receive dosing adjusted for body weight and taken with meals). This study is designed to determine whether the average drug intake in pediatric patients is comparable to adult patients taking asciminib 40 mg 2x daily without food. PK and safety will be assessed during the first 28 days after treatment initiation.
In Part 2, an expanded cohort, the body weight-adjusted dosing determined in Part 1 will be used and the total pediatric formulation will be increased to 30 patients, including those from Part 1 (15 patients aged 1 to <12 years and 15 patients aged 12 to <18 years). Patients receiving the adult dosage may switch to the pediatric formulation in Part 2. However, they will not be counted among the 30 patients included in Part 2. A 2nd preliminary PK and safety analysis will be conducted after all patients in Part 2 have completed 28 days of treatment.
The study duration is 5 years. The primary PK endpoints, safety, and pharmacodynamics will be assessed after all patients have participated in the study for 52 weeks or earlier discontinued. After all, patients have participated in the study for 5 years or have discontinued the study early, a final analysis will be conducted. Patients who drop out of the study early will continue to be followed until the study is completed. Primary endpoints include PK parameters. Secondary endpoints include hematologic and molecular response, safety, acceptability, and palatability of asciminib.

Data from this study will be used to determine pediatric dosing and to develop a strategy for fully translating data from adults to pediatrics.