CML Advocates Network conference report

- Eglys González, PhD.
- Scientific Project Manager
- eglys@cmladvocates.net

EHA 2023 Hybrid Congress

The 28th Congress of the EHA was held in Frankfurt, Germany, from June 8-11, 2023, and continued virtually on June 14-15, 2023.

Representatives from the CML Advocates Network attended the Congress and participated in several activities and sessions. Our co-founder Jan Geissler gave a presentation on the **patients' perspective on designing novel clinical trials**; and chaired **Session I of the Patient Joint Symposium**. Zack Pemberton-Whiteley, a member of our Steering Committee was part of the Panel discussion on **patient-generated evidence in access**; and chaired Session II of the **Patient Joint Symposium**. Our CML-CAB member Lisa Machado was invited to the Novartis-sponsored satellite symposium titled: **CML is not solved: Transforming treatment expectations and patient outcomes**. Other CML-CAB member Felice Bombaci was invited to talk about the **meaning of PROs for patients with HMs** in the Quality-of-Life session. Other patient advocates and staff members were also there, like Denis Costello, Bahija Gouimi, Gerald Clements, Giora Sharf, Jana Pelouchová, Pat García-González, Felipe Tapia, Toni Montserrat, Özgün Tansöker, Cornelia Borowczak, Nicole Schröter, Lidija Pecova, Nikola Nikolov, Marija Stefkova, Ivana Angelovska, and Eglys González.

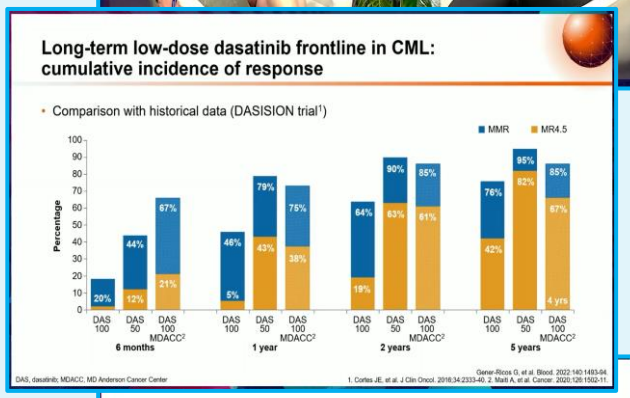
Following we present the conference scientific report with key CML highlights of interest to the patient advocacy community.

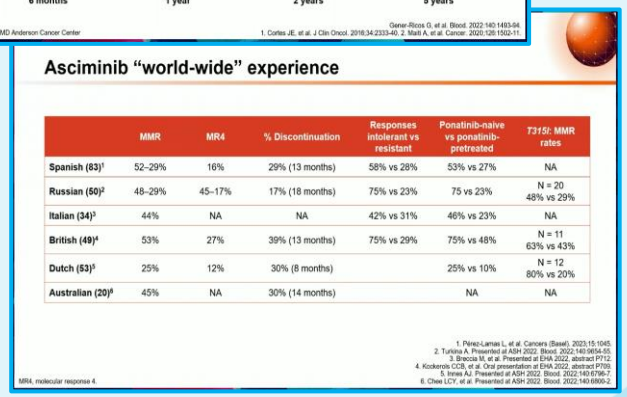
Satellite symposium on CML
CML is not solved: Transforming treatment expectations and patient outcomes

EUROPEAN HEMATOLOGY ASSOCIATION

Dr Timothy Hughes, Lisa Machado, Dr Susanne Saussele and Dr Valentín García Gutiérrez.

- In the panel with Lisa Machado and Dr Saussele they discussed about the **different definitions of CML cure** from each perspective, patients and clinicians. Mentioning the expectations, experiences and needs from patients, for what they agreed that the relation **Patient/Clinician is a partnership**. Dr. Saussele expressed that they **struggle with the time available** to dedicate to each patient and emphasized the importance on not making any decisions in the first appointment with a patient.
- Dr Hughes showed some advances on asciminib studies, where its use in front-line combines early and deep response with favorable tolerability. Other studies have indicated that low-dose dasatinib gives great results in reaching MMR, though further evaluation in a bigger population is required.
- Dr García pointed out the question “Do we need novel agents?”, to which he expressed that **we do need new treatments options and treatment combinations** to make more improvements in CML therapies. He showed some advances on analysing RWD on the use of asciminib in different countries, which showed to be consistent with results from clinical trials.

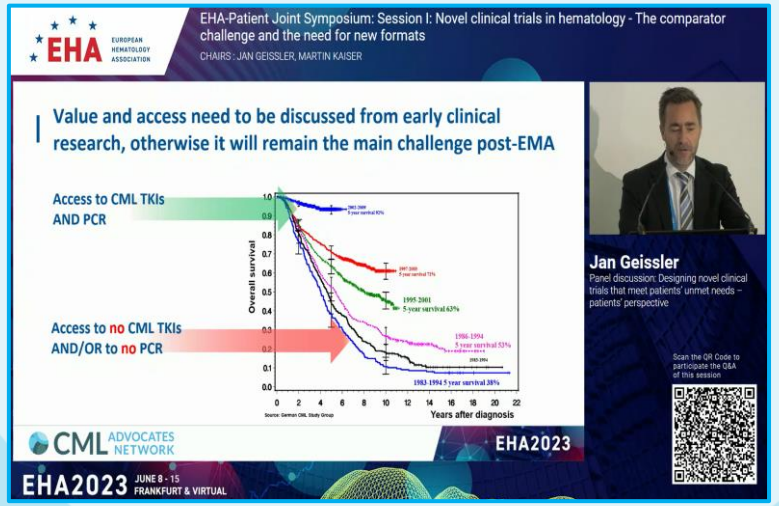




EHA-Patient Joint Symposium: Session I: Novel clinical trials in hematology - The comparator challenge and the need for new formats

Panel discussion: Designing novel clinical trials that meet patients' unmet needs – patients' perspective. Jan Geissler

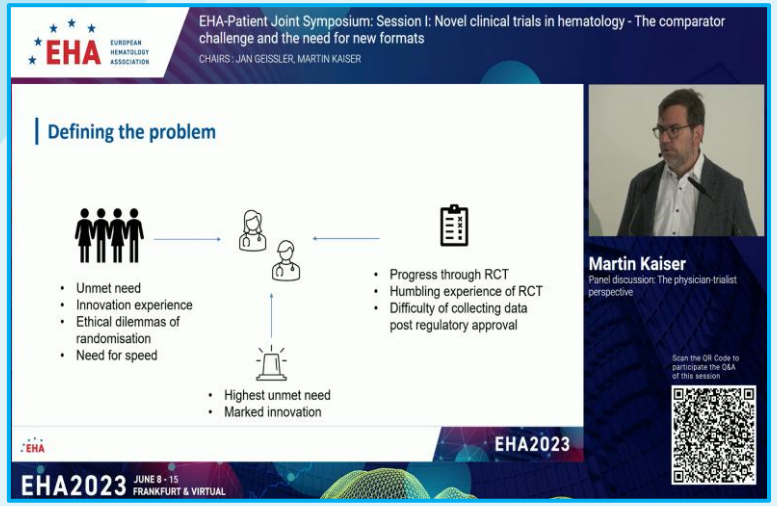
- Jan gave the example of CML, which due to innovation its survival rates greatly improved to almost 95% in CTs. This is ideal but also exceptional, and it only happened because of innovation and researchers that believed more could be done and gave a chance to TKIs. There is still need of innovation in this and other diseases. Courage from researchers and regulators to incentive new and innovative trials are required.
- Patient preference data is essential to understand the patient perspectives. As well PROs are key to understand the patient reality, and we encourage for QoL data to be collected, correctly collected and shared, in order to make improvements. New attitude and incentives are needed in data sharing, as it is the patient's data, and it was given to be shared and used. Also, value and access need to be discussed from early phases, because with no access we go back to low rates of survival, disregard of the innovative therapies available.
- Trials need to cover what is relevant for the patients and not only what the regulator think is relevant, or the academia think is interesting or what industry finds profitable. When talking about innovative trial designs, patient rights and interests come first. We need to highlight patient involvement in Research & Development, where patients can give meaningful contributions.



EHA-Patient Joint Symposium: Session I: Novel clinical trials in hematology - The comparator challenge and the need for new formats

Panel discussion: The physician-trialist perspective. Martin Kaiser

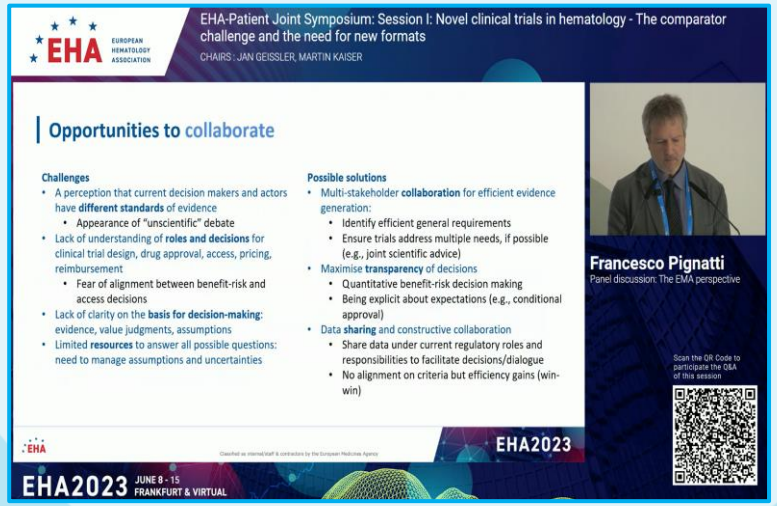
- As a physician Martin showed their definition of the problem and wishes to cover the unmet needs for the patients. Physicians have the privilege of seeing innovation from the first sight, but more responsibility comes with it. If there were **trials that already had outlines that explained how the trial will lead to HTA evaluation and access**, it would be even better, progress have been made, but there is still much to be done.
- Many relevant data has come from randomized clinical trials. If we don't generate evidence, we don't learn for the future, as well as if we don't collect the data in the real world. Unfortunately, the data from RW is not as good as that from CTs.
- He described a new experience in a randomize trial where the comparison arm was retrospective data from patients already treated with the standard of care treatment. This helped to make the trail more attractive, and results were quite interesting.
- Improving the long-term planning, sustainability, and trust would be useful in improving innovation. There is a need for more joint thinking, as in reducing uncertainty for innovators, avoid legal challenges and funding, how to be more inclusive on patient population by including socially deprived areas, generating trusted environment for data and analyses, enable career incentives for young trialists to enter the field, and overall, how to **achieve a win-win for all**.



EHA-Patient Joint Symposium: Session I: Novel clinical trials in hematology - The comparator challenge and the need for new formats

Panel discussion: The EMA perspective. Francesco Pignatti

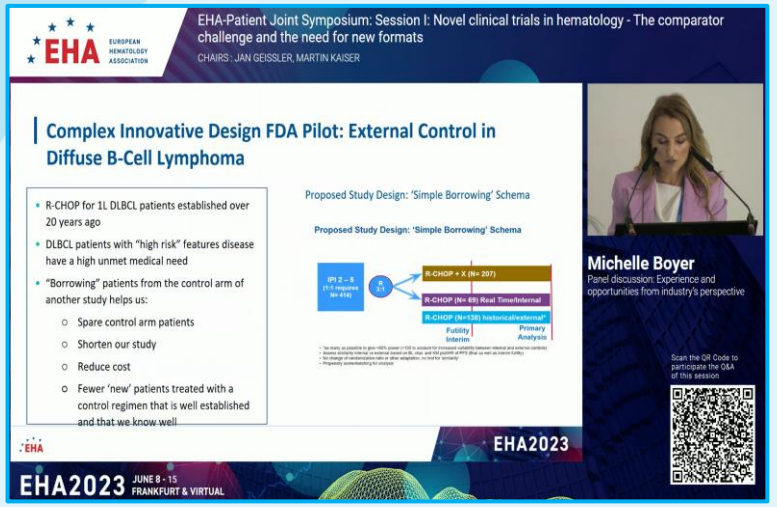
- Francesco mentioned to feel that as regulator they don't match much in originality and extent of contribution as other stakeholders have in clinical trials and advancing in the field. There seems to be a perception of marked differences between what they as stakeholder wants to see in clinical trials, compared to other stakeholders, which does not look good, and it might not be true. The reality is that we all want to answer different questions to optimize the process. All individuals have different preferences, and all should be considered.
- Where do this lead us to? Rather than continuing to think in separate compartments, we need to look at what are the common denominators among all these questions. There are limitations on how many questions one can answer with the data collected, but **collaboration among all organizations** is required, so we can answer to all these questions more efficiently to generate evidence. Additionally, the **transparency of decisions** is relevant for a quantitative benefit. And of course, there is **data sharing**, as there is really no reason for lack of data sharing in a constructive collaboration.

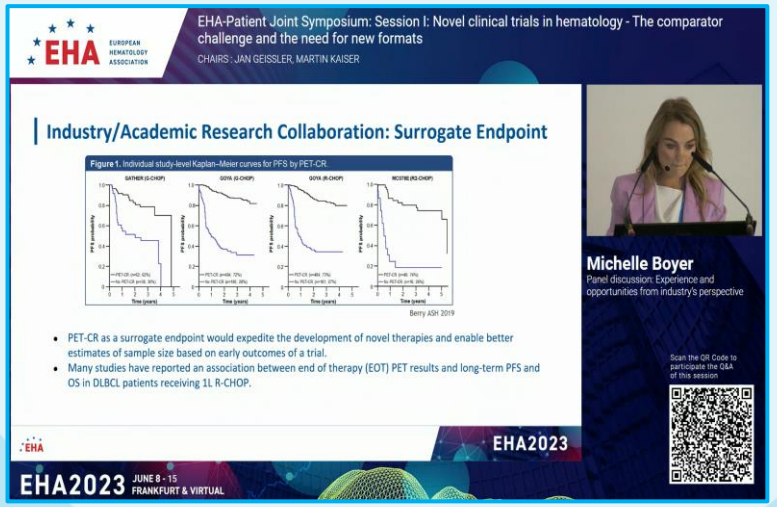


EHA-Patient Joint Symposium: Session I: Novel clinical trials in hematology - The comparator challenge and the need for new formats

Panel discussion: Experience and opportunities from industry's perspective. Michelle Boyer

- Michelle shared the experience from the industry in novel trial designs, as it is a very complicated field. More efforts are being done in making patient-centric trials focusing in delivering innovative therapies faster. We have experienced that the patients are more educated than ever and want to be part of their journey.
- How can we bring treatments faster to patients? There are very complex innovative design pilots, in which data from other trials has been used as control arm. This model is being used for education purposes and teaching forums.
- On real-world evidence and how it can be better used to improve clinical trials and speed access to drugs. They have been evaluating how to use the real-world evidence trial to support data in trial submissions to present more robust proposals. This was not acceptable, but advances were indeed achieved.
- On data sharing, she mentioned that sharing the data with the scientific community is indeed something they want to do, and there are programs ongoing on how to share the data. Additionally, an example on using surrogate endpoints to speed access was given.

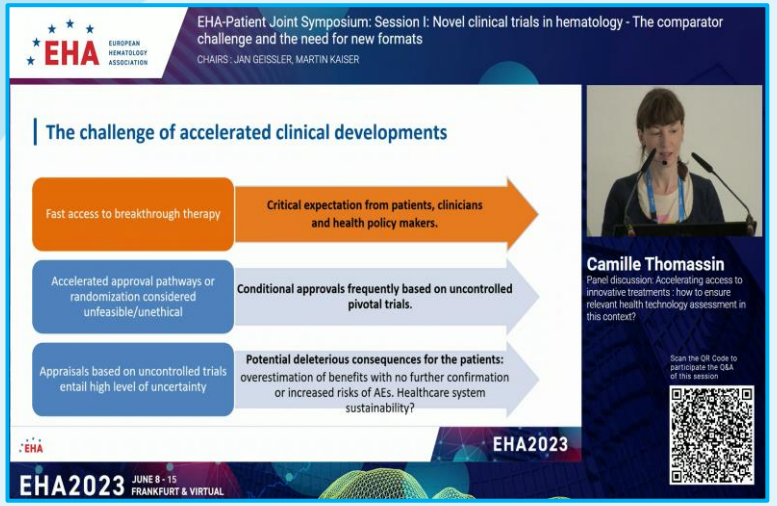


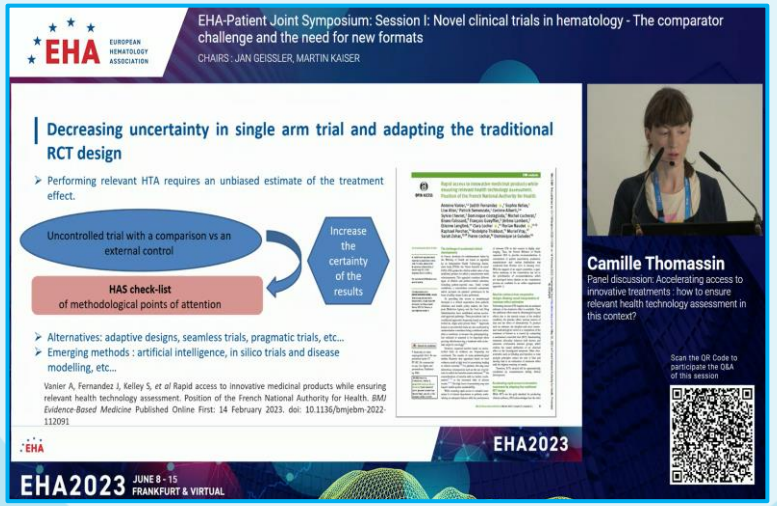


EHA-Patient Joint Symposium: Session I: Novel clinical trials in hematology - The comparator challenge and the need for new formats

Panel discussion: Accelerating access to innovative treatments : how to ensure relevant health technology assessment in this context? Camille Thomassin

- Camille provided the perspective from the HTA bodies on their expectations and how they can accelerate clinical developments, also concerning about deleterious consequences for the patients.
- A group of reflection was made with methodologists and clinicians in order to decrease uncertainty on trials outside the regular randomized trials, like in single arm trials. They have also considered in discussions the uncontrolled trials with external arms, as this approach could be optimized with a good anticipation by the industry to increase the certainty of the results. They have published a check list of the methodology topics that need to be considered for this type of design, as it is very challenging to perform.
- In the context of rare diseases, it is possible to conduct randomized trials, as it remain the gold standard and should be considered first. Other alternatives can of course be explored under exceptional conditions.
- It is important to anticipate the set-up of registries. The registries allow to have comparative data; hence they encourage to perform such registries.

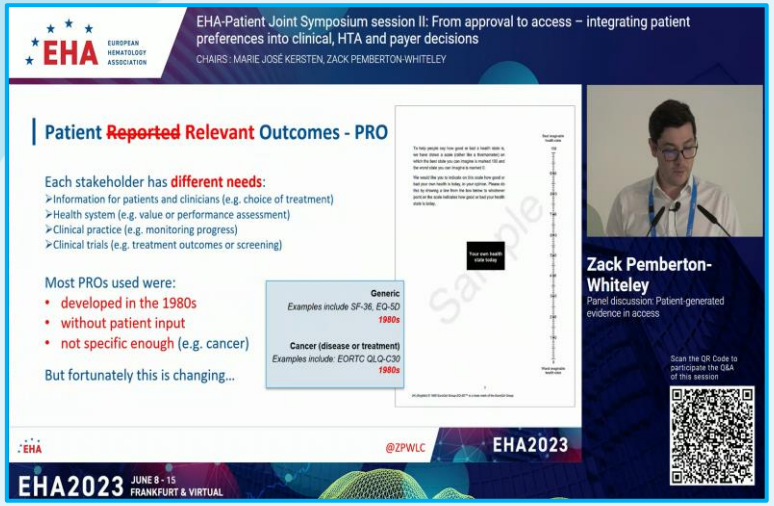


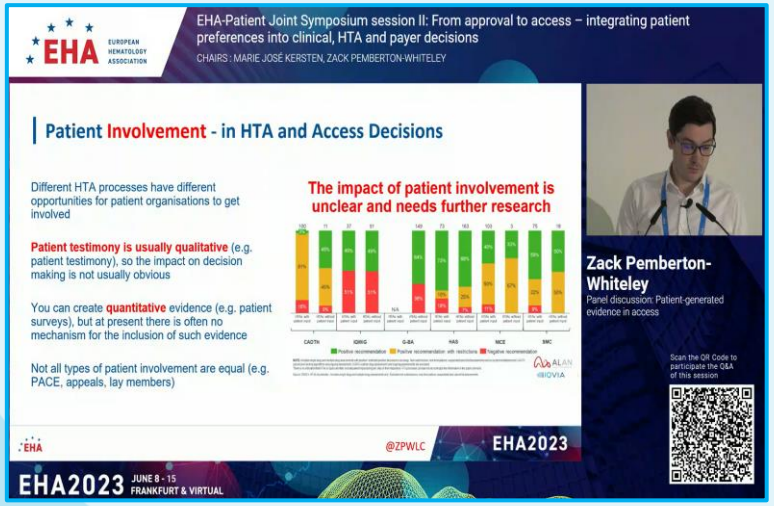


EHA-Patient Joint Symposium session II: From approval to access – integrating patient preferences into clinical, HTA and payer decisions

Panel discussion: Patient-generated evidence in access. Zack Pemberton-Whiteley

- Zack explained why there is a need to hear from patients in access decisions, considering the different perspectives from each stakeholder. A third party can see things from their own perspective and not from the patient's side, hence involving patients is relevant, and to do it in a systematic way we need patient evidence. Evidence Based Advocacy is using evidence in a well-educated and professional manner, like evidence generated by the patient community (e.g., surveys).
- A way to see patient evidence and experience is with PROs, which is also about what is relevant for the patients. Are we really recording things that are relevant for the patients? Many routinely PROs being used are old, developed without the patient input and not disease-specific. A relevant project in this topic is the EuroAct, which is mapping the use of PROs and QoL instruments over the last 5 years.
- Patient preferences studies can be used to look at the factors that inform treatment decision making. There is always a trade-off between survival and QoL, as in reality we do not get an excellent treatment that extends survival with perfect QoL. Is relevant to know to what extend are the patients willing to trade-off.
- Patients need to be involved in R&D, as well as in HTA and access decisions, though for the latter it is still not clear where this involvement makes the most impact.

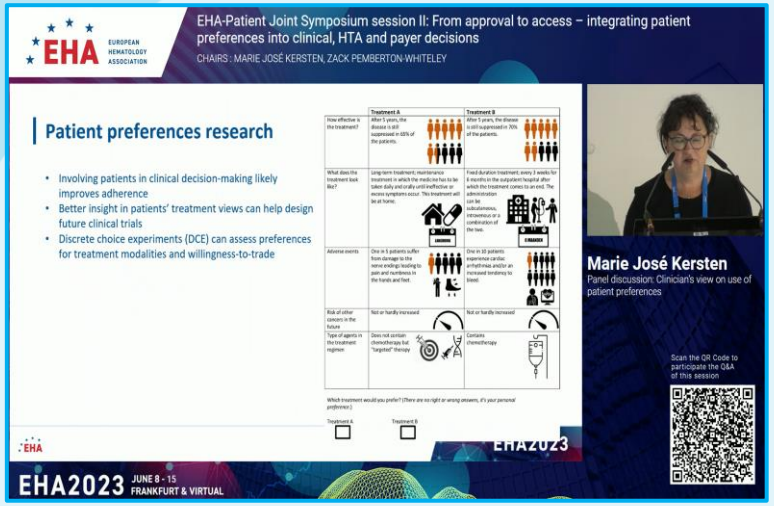


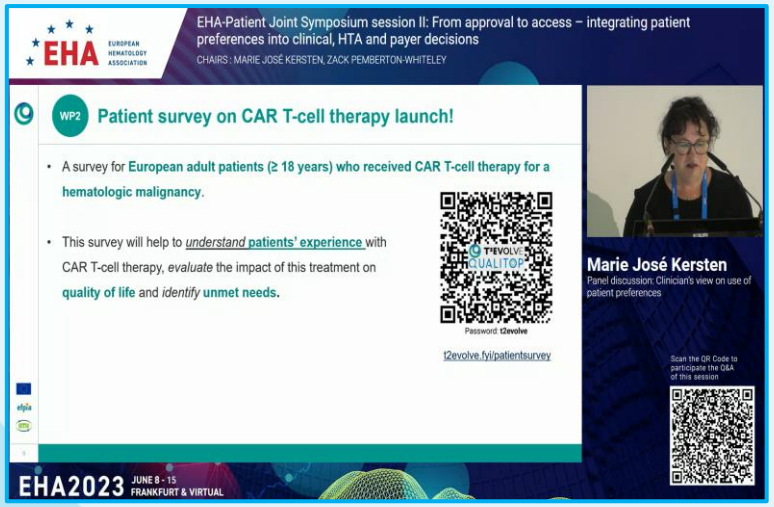


EHA-Patient Joint Symposium session II: From approval to access – integrating patient preferences into clinical, HTA and payer decisions

Panel discussion: Clinician's view on use of patient preferences. Marie José Kersten

- When looking to the outcomes of cancer treatments, there is also an interest in searching for treatment related mortality, toxicity and QoL. Hence, the relevance of PROMs. There is a lack of concordance between the symptoms recognized by physician and those self-reported by patients, as physicians often underestimate the severity of symptoms and toxicities, defined as manageable. The tools are PROMs, PREMs and patient preferences research.
- Involving patients in clinical decision-making will most likely improve adherence. And a better insight in patients treatment views can help better develop clinical trials.
- A lot is still to be done as PROMs are still not specific enough for certain diseases. Additionally, improvement in monitoring and symptom management will help improve QoL and adherence to therapies.
- As part of the T2EVOLVE project a survey on CAR-T cell therapy developed with the collaboration of patient organizations has been launched, to look at the symptoms and toxicities, the impact of the patient's experience, evaluate the impact of the treatment in QoL and identify unmet needs.

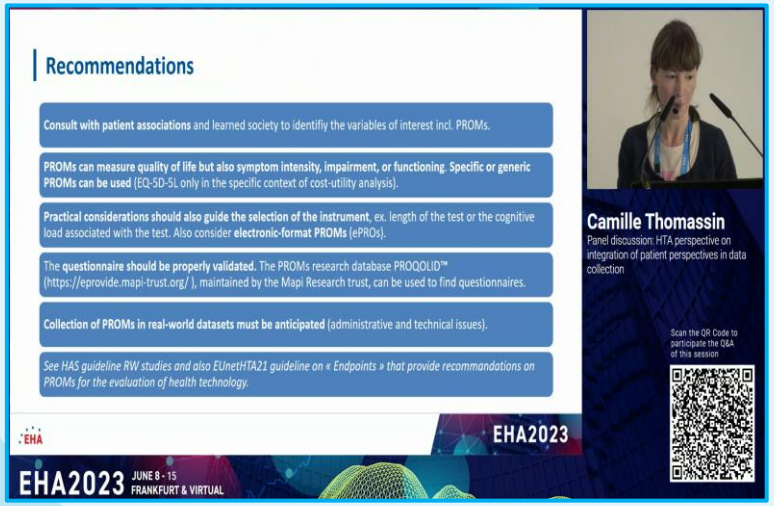




EHA-Patient Joint Symposium session II: From approval to access – integrating patient preferences into clinical, HTA and payer decisions

Panel discussion: HTA perspective on integration of patient perspectives in data collection. Camille Thomassin

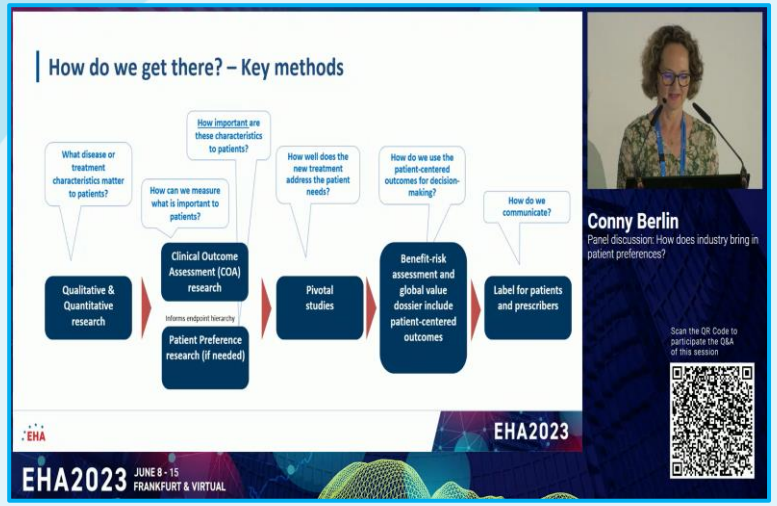
- Camille presented the panorama on how the Haute Autorité De Santé (HAS) regularly analyses observational data. When including PROMs in post registration studies, they are facing challenges on how to select the PROMs for a specific study, also considering that these tools are often not design to be implemented in routine clinical care, and related administrative and technical burden need to be anticipated.
- They have some recommendations, like consulting patient associations to identify variables of interest. PROMs can measure QoL but also symptom intensity, impairment or functioning. The questionnaires must be properly validated. Electronic format PROMs could be used to optimize collection of data considering the length and cognitive load associated. Collection of PROMs in real-world datasets must be anticipated considering administrative and technical issues. They suggest to consult the HAS guideline on Real-world studies and the EUnetHTA21 joint action for recommendations on PROMs for evaluation of health technology.
- On early-access authorisations in France, they have set-up a plan to collect variables in routine care, including the use of PROMs to have information on QoL and safety.

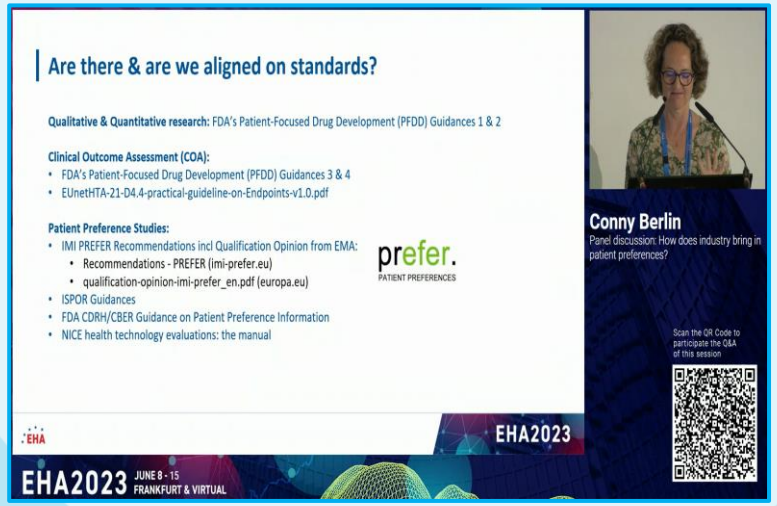


EHA-Patient Joint Symposium session II: From approval to access – integrating patient preferences into clinical, HTA and payer decisions

Panel discussion: How does industry bring in patient preferences? Conny Berlin

- Conny expressed that when thinking about patient-focused drug development, Novartis wants to achieve new medicines that are effective and safe on endpoints which matter to patients, and that are convenient for patients. Within this goal, they produced questions that can help them guide conversations with their clinical team to know how to get to patient-relevant endpoints: • What disease or treatment characteristics matter to patients? • How can we measure what is important to patients? • How important are these characteristics to patients? • How well does the new treatment address the patient needs? • How do we use the patient-centered outcomes for decision-making? • How do we communicate this to patients?.
- This generated key messages on achieving qualitative and quantitative research, looking at clinical outcome assessment (COA) research, and patient preference research to learn what is most important for patients. Out of this, they expect to have pivotal studies leading to assessing benefit-risk and global value dossier that include patient-centered outcomes that will go to the decisions makers and HTA bodies. Communication to the patients in form of labels with relevant information, also directed to prescribers. All these as part of a patient experience data strategy.
- On COA and patient preference studies regulatory organizations have developed related guidelines. However, it does not mean it is fully used for decision-making.

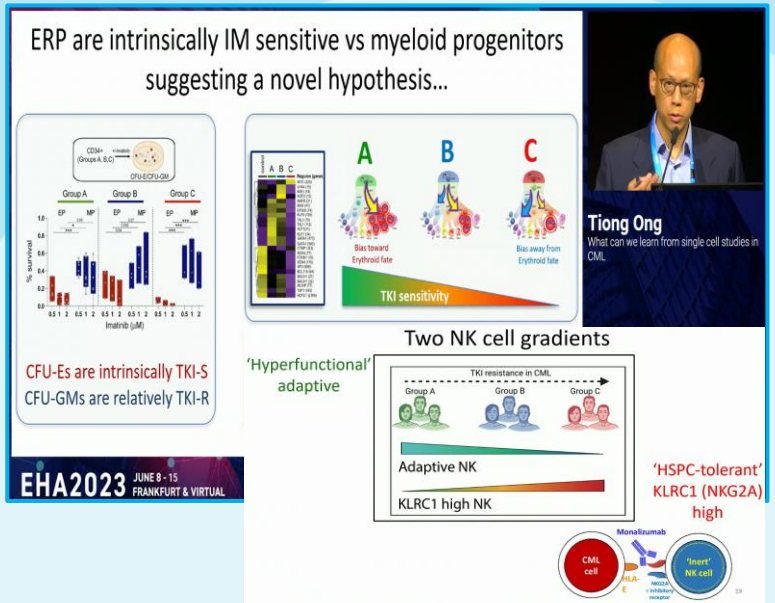


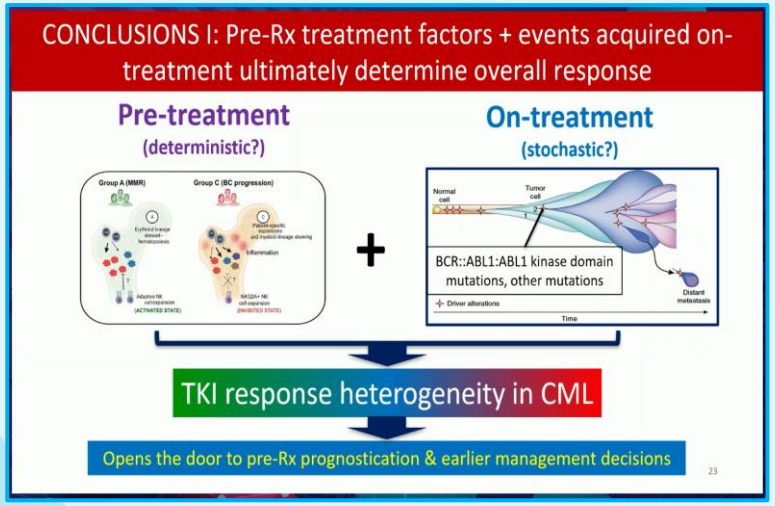


Education Session
Chronic myeloid leukemia (CML)

What can we learn from single cell studies in CML. Dr. Tiong Ong

- Each patient present a unique constellation of prognostic factors, which is challenging for prognostication, but also creates opportunities to improve CML management. Resistant factors may exist prior to treatment initiation, which drives to ask if this would have any relevance in predicting the response.
- Single cell multi-omics was used to identify pre-treatment factors in three groups: patients in failure (A), warning (B) and optimal (C) response. The use of Machine Learning allowed to identify three cell types with high predictive power, with an accuracy of about 90%.
- The use of the algorithm SCENIC (**S**ingle **CE**ll regulatory **N**etwork **I**nference & **C**lustering) to identify LSC GRNs (Gene Regulatory Network), identifying the Canonical Erithroyd-like network of genes, allowed to conclude that LSC lineage fate decision at diagnosis contribute to TKI response heterogeneity.
- Also, the NATMI tool allowed to identify two NK cell gradients, one which could be interfered to inert the cell and allowing it to be activated for response.
- Dr. Ong concludes that this opens a door to allow begining treatment thinking about pre-treatment prognostication and earlier management decisions.

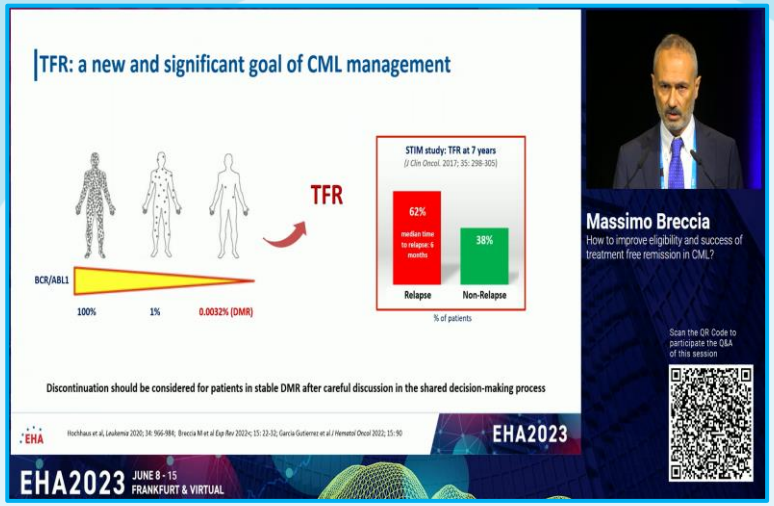


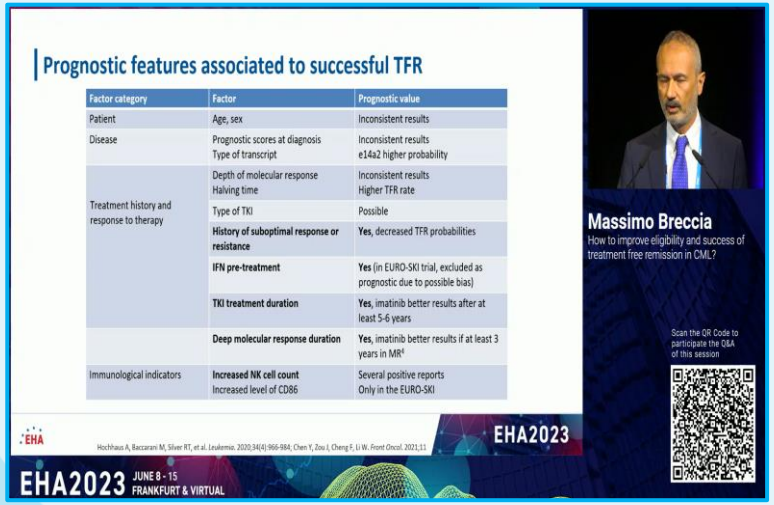


Education Session
Chronic myeloid leukemia (CML)

How to improve eligibility and success of TFR in CML?. Dr. Massimo Breccia

- Discontinuation has become a new and significant goal in CML management. Most studies have indicated that only around 40% were able to maintain molecular response. While some prognostic models have been identified.
- The response of patients 3 months after initiating treatment can help identify candidates for TFR. But how can we define optimal candidates? A meta-analysis was performed, identifying 4 sub-groups using a digital drop PCR. This indicated that patients treated for more than 6 years and low D-PCR at the time of discontinuation had only 33% of probability of relapse at 24 months.
- Dr. Breccia suggested some options on how to improve eligibility to TFR. 1) Early switch to more potent TKIs is an option and many trials have aim to achieve this – SUSTRENIM, DASCERN. 2) First-line combination treatments have shown some improvement in clinical trials like PETALS, TIGER, ASCEND, FASCINATION. 3) Pro-active switch of treatment to increase DMR can make improvements, as in trials like ENESTop, ENESTPath, ASC4MORE, DESTINY. 4) Dose optimization as de-escalation trials like DANTE, READIT.
- He mentioned future approaches by targeting LSC via BCL2 or p53, as other actionable targets and surface markers, currently still under study.

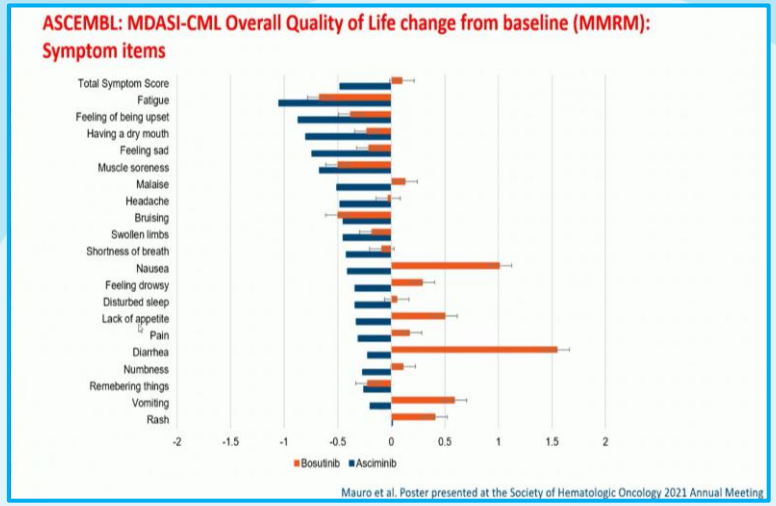


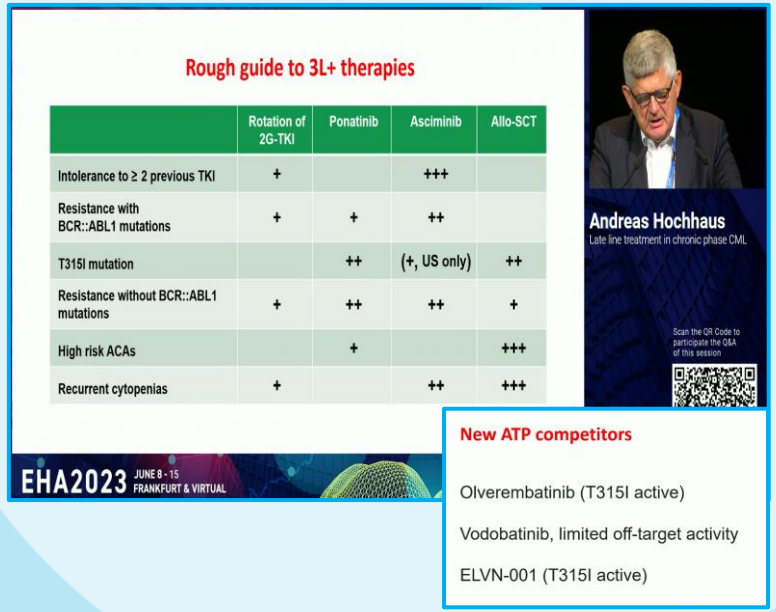


Education Session
Chronic myeloid leukemia (CML)

Late line treatment in chronic phase CML. Dr. Andreas Hochhaus

- Dr. Hochhaus mentioned that they need to think also about those patients who do not respond optimally to initial treatments and need alternative options, which are the majority. Indicating also the relevance of switching treatment soon before reactivation of the BCR::ABL1 which leads to failure.
- When revising predicting responses to second line TKIs, it has been identified that patients with recurrent neutropenia during several lines of therapies combined with high-risk score and lack of cytogenetic response should be directed to transplantation still in 2023. **Find good timing for transplantation!** Transplantation has shown to be more effective in chronic phases.
- Updated data on the ASCEMBL study were presented, indicating higher MMR rates, but also more than 50% failed treatment. And QoL data was also measured seeing improvement with asciminib.
- He gave his personal opinion on a guide for 3L therapies based on his experience and not trials. All (6) therapies should be available worldwide allowing to choose the best options for the patients considering the biology of the drugs and comorbidities of the patients. Improvement of late line therapies! New components under current study were also mentioned.



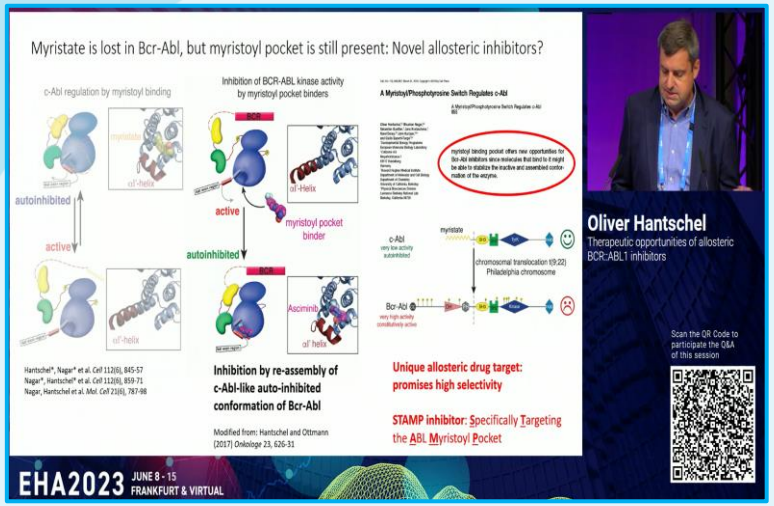


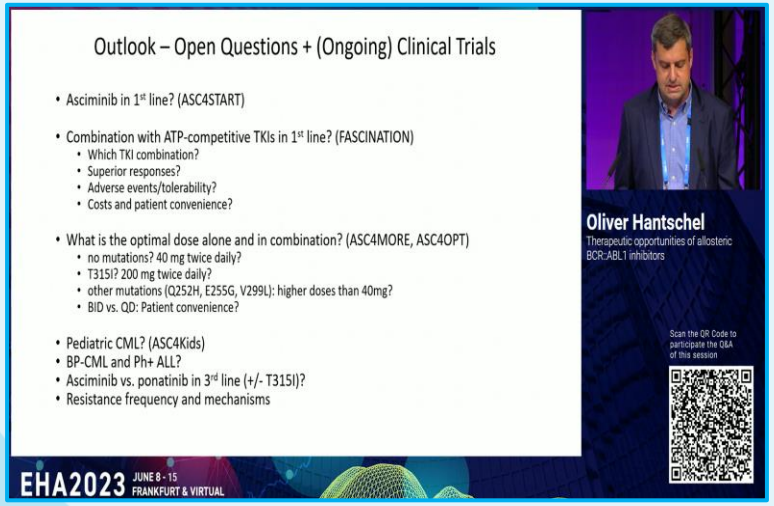
Specialized Working Group Session
ELN-EHA SWG for CML - CML: Modelling the future

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Therapeutic opportunities of allosteric BCR::ABL1 inhibitors. Dr. Oliver Hantschel

- Dr. Hantschel mentioned his group studies on determining that the myristoylation is required for autoinhibition of the ABL kinase. Indicating that although Myristate is lost in Bcr-Abl, the myristoyl pocket is still present and could be the target for new inhibitors. This research resulted in the development of the so-called STAMP inhibitor, asciminib.
- Asciminib has a high selectivity since no other tyrosine kinases have homologous myristate binding pocket, with significant and clinically meaningful superiority in efficacy. These led to FDA and EMA approval in 2021 and 2022 respectively, with a dose of 40mg twice a day.
- Current efforts are being made in evaluating asciminib resistance, understanding the molecular mechanism and predicting response. Also, combinations are being evaluated, as in the FASCINATION trial. Some mutations have been identified to be related to resistance (A337V, P242E, E117K, F359V)

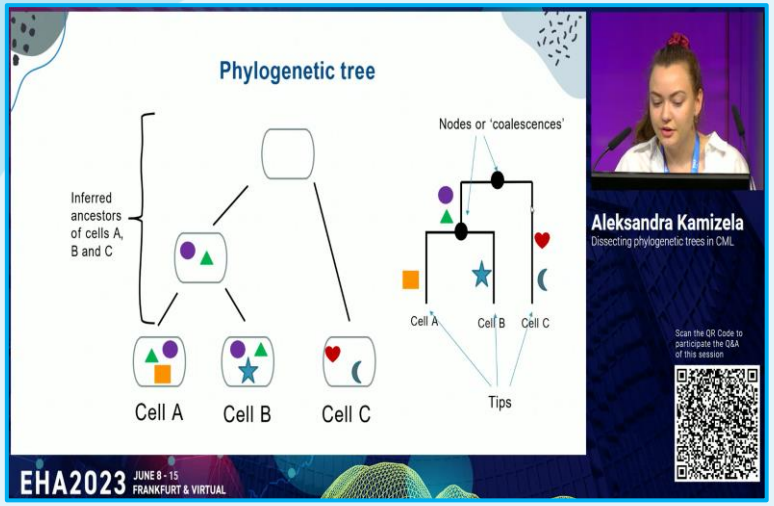


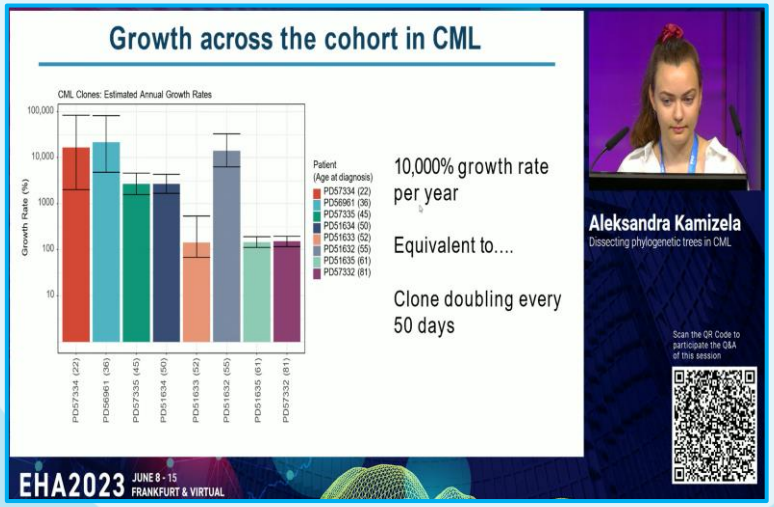


Specialized Working Group Session
ELN-EHA SWG for CML - CML: Modelling the future

Dissecting phylogenetic trees in CML. Aleksandra Kamizela, Postgraduate Student.

- Aleksandra spoke about Phylogenetic trees in cancer, which is possible to perform in cancer cells, since all cells are constantly acquiring somatic mutations throughout life independently of cell division. It is a tool that allows to go back in time and define an ancestor that the cells share, also allowing to get back into the ancestor that had no mutation yet. Additionally, slow and fast expansions can be identified, which means long and short distances among the ancestors, respectively, allowing to estimate the branching into time units and objectively detect the time a specific event.
- This was applied in clonal hematopoiesis across a wide range of ages, learning some basics on hematopoiesis and also in some neoplasms and solid tumors. They searched the timing BCR::ABL driven clonal expansion in CML, finding that for some patients, the clonal expansion started just 5 years before diagnosis, which is considered fast. Hence, they looked if the cells were dividing quicker, finding that indeed BCR::ABL cells seem to have a quicker division.
- The clonal expansion occurs in 3-13 years before diagnosis, much faster than clonal hematopoiesis and other cancers. The growth rate is about 10.000% a year, making BCR::ABL the strongest single driver mutation reported to date.

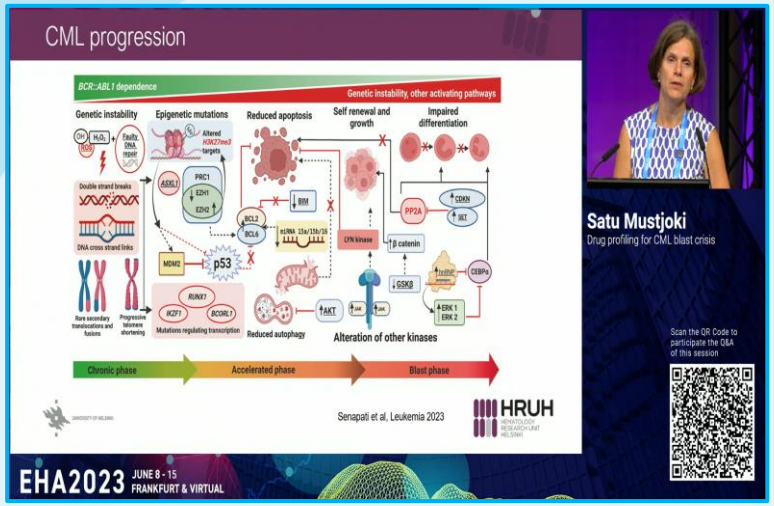


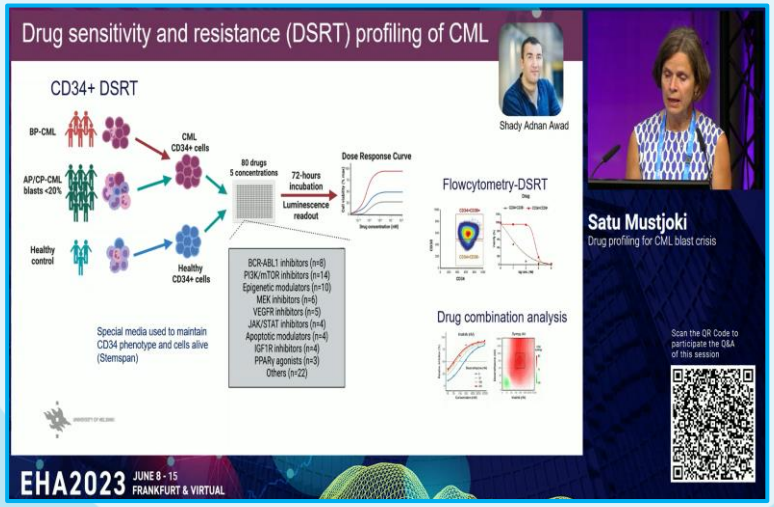


Specialized Working Group Session
ELN-EHA SWG for CML - CML: Modelling the future

Drug profiling for CML blast crisis. Dr. Satu Mustjoki.

- Dr. Mustjoki started by showing a review on the processes happening in CML progression. And considering the mutation profiles, a treatment algorithm was proposed. However, a poor overall survival is seen with the current treatments. Blast phase CML needs improvement in therapy options, either with novel drugs, combinations with TKIs or also immunotherapies.
- Within her research group a CML profiling in drug sensitivity and resistance is being made, finding some new drug vulnerabilities in the CML cells such as tivozanib, RG7112, mepacrine, azd1775 and navitoclax. As well CRISPR KO screening has been made to identify resistance mechanisms, such as reduction of KCTD5-mediated ubiquitination of the Bcr-Abl protein.
- She explained that the identified pathways of ubiquitination, apoptosis and autophagy represent potential targets for TKI-drugs combinations.

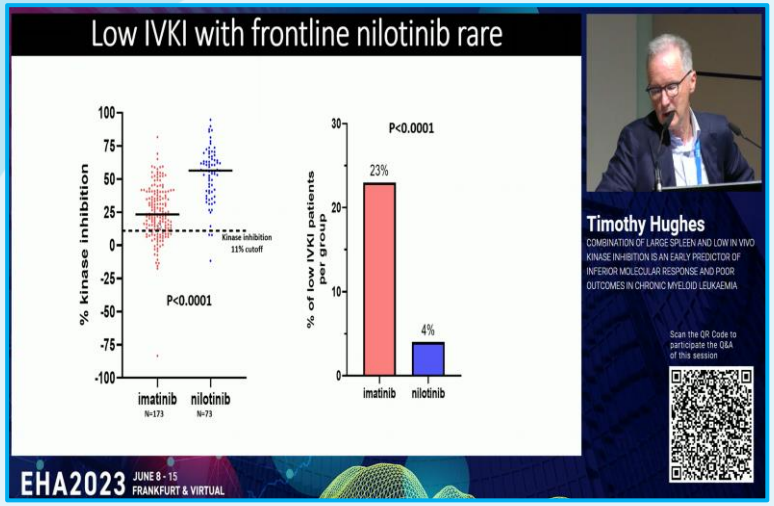


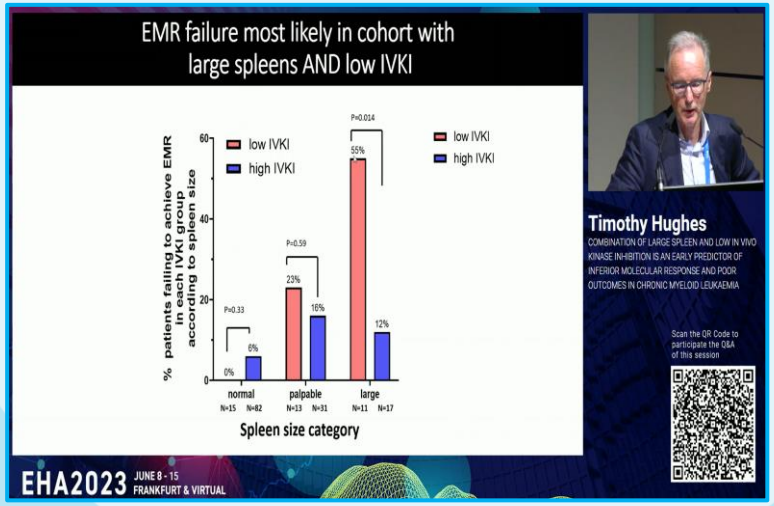


Oral Session
CML biology and translational research

Combination of large spleen and low in vivo kinase inhibition is an early predictor of inferior molecular response and poor outcomes in chronic myeloid leukaemia. Dr. Timothy Hughes.

- Dr. Hughes started by asking whether the level of kinase inhibition of a TKI can be measured and if it is clinically relevant in CP-CML. Therefore, over the last 14 years they have measured it in patients included in the Australasian Leukaemia & Lymphoma Group (ALLG), identifying a cutoff of 11% and an average of inhibition of 24% for imatinib and over 50% for nilotinib.
- A difference in the inhibition is observed among patients failing or achieving Early Molecular Response (EMR) but is not very high. However, a characteristic that was noticeable was the spleen size, as it is enlarged with low kinase inhibition, and this enlargement is also related to EMR failure and blast crisis.
- This gives a unique opportunity to optimize the TKI dose or consider switching TKIs well-before time dependent molecular targets are assessable. However, with the limitation that sampling patients from day 0 to day 7 is not realistic. He suggested a kit-based assay should be developed.

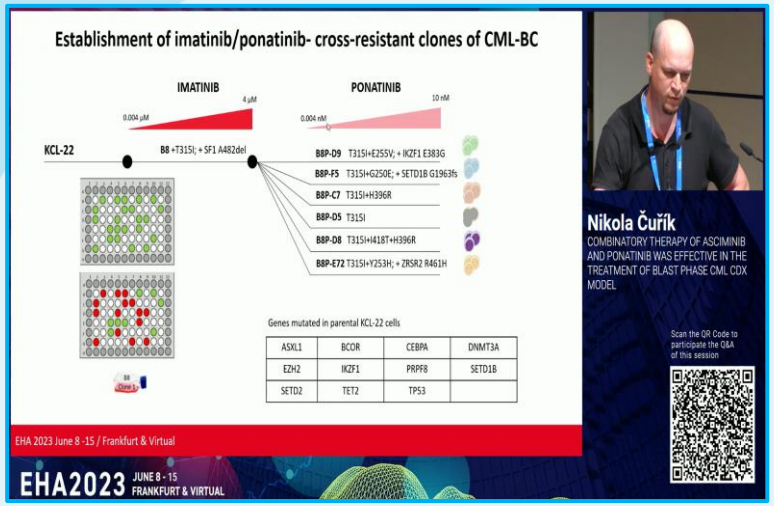


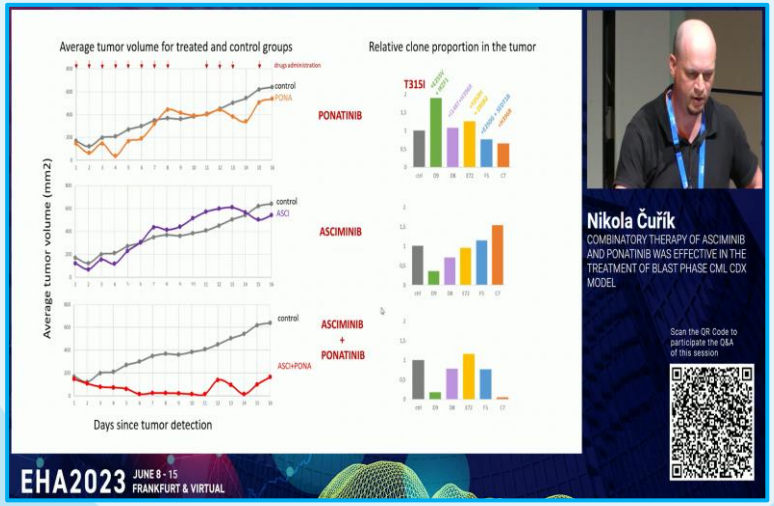


Oral Session
CML biology and translational research

Combinatory therapy of asciminib and ponatinib was effective in the treatment of blast phase CML CDX model. Nikola Čuřík.

- Nikola spoke about the current need for new therapeutic options for patients with BC-CML. He mentioned that besides asciminib and ponatinib, they have used venetoclax in their research studies.
- In their work they have selected imatinib/ponatinib cross-resistant clones, whit a different profile of mutations, and used them for induction of disease in experimental mice to model an aggressive disease and evaluate therapy with asciminib, ponatinib, venetoclax and their combinations. As results they observed a slight improvement when using venetoclax alone or in combination with ponatinib. While ponatinib combined with asciminib resulted in an effectively suppression of tumor growth.

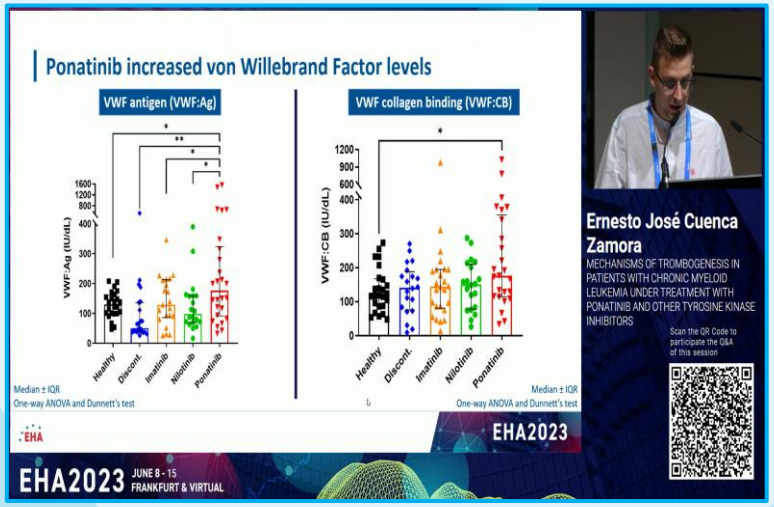




Oral Session
CML biology and translational research

Mechanisms of trombogenesis in patients with chronic myeloid leukemia under treatment with ponatinib and other tyrosine kinase inhibitors. Ernesto José Cuenca Zamora.

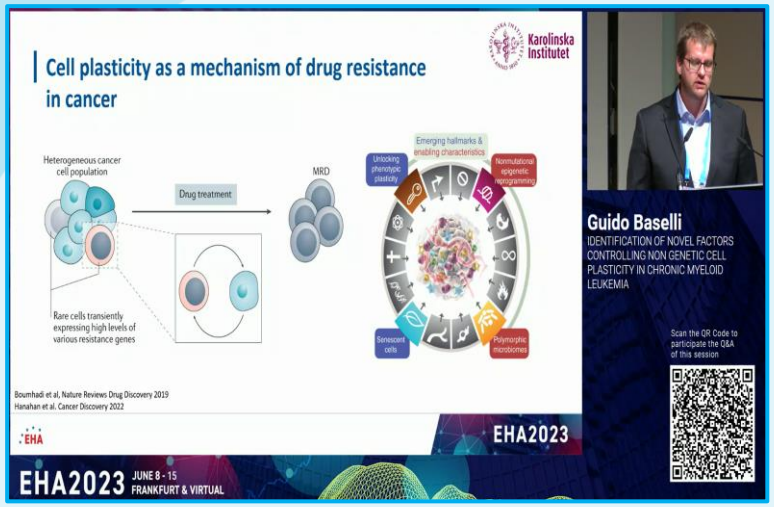
- Considering the known and published data on the mechanism of thrombogenesis generated by nilotinib and ponatinib, Ernesto addressed the hypothesis that ponatinib induces thrombogenesis by a different mechanism to the other TKIs, promoting a thromboinflammatory effect. And to prove the hypothesis he measured relevant thromboinflammatory markers in blood samples from CP-CML patients treated with imatinib (300-400 mg/day), nilotinib (300-400 mg/12h) and ponatinib (30-45 mg/day). Controls included healthy patients as well as patients in TFR.
- The results indicated that patients under TKI therapy have increased levels of cell free DNA, and ponatinib particularly increases levels of citH3-DNA. Also, referring to platelets he demonstrated that they are hyporeactive in CML patients, suggesting unneeded antiplatelet treatment. And finally, ponatinib increases levels of Tissue Factors and particularly the Von Willebrand factor (VWF), a protein involved in platelet adhesion, being then identified as biomarkers and possible drug targets.

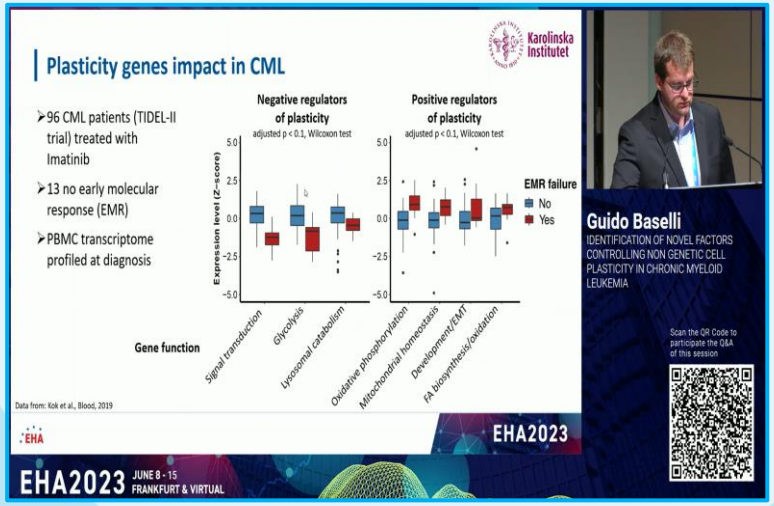


Oral Session
CML biology and translational research

Identification of novel factors controlling non genetic cell plasticity in chronic myeloid leukemia. Guido Baselli.

- Epigenetic factors are well known drivers of drug resistance in tumors, and due to gene fluctuations cancer cells can acquire drug resistance phenotypes. This phenotypic plasticity is defined as a hallmark of cancer. In CML. the cell lines express the CD24 marker in a reversible and regulated process, therefore, in his study he aimed to identify genetic regulators of this plasticity and any drug sensitivity association, by CRISPR-KO in K562 cells.
- Findings indicated expected switches from stable $CD24^{+}$ and $CD24^{-}$ stable lines and changing cell lines. The cells were screened, and plasticity associated genes were identified, finding 32 being depleted and 17 enriched in the KO events. Further, the expression level of the genes were associated with drug sensitivity in CML (imatinib resistance), in which 13 out of 96 patients were not able to achieve EMR. Some negative regulators of plasticity were related to mechanisms like glycolysis and lysosomal catabolism.
- As further aims he mentioned to validate the KO models and discovering mechanistic insights of the models.

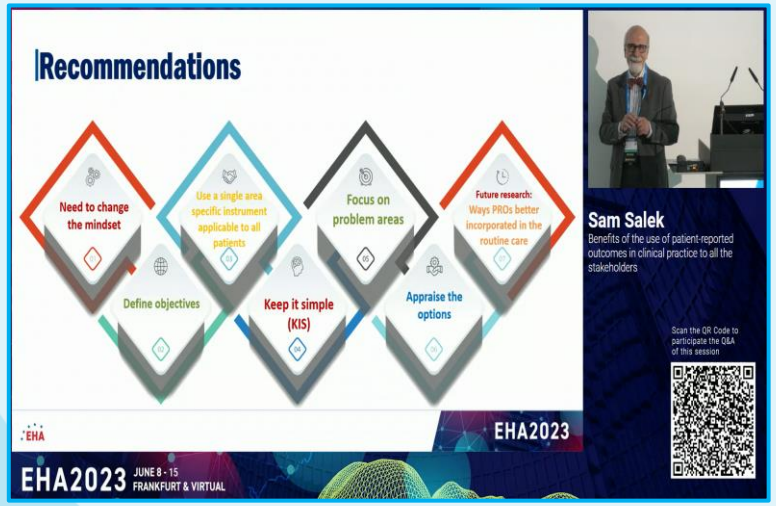




Quality of life and symptoms: Frontiers in the use of patient-reported outcomes in clinical practice and clinical research

Benefits of the use of patient-reported outcomes in clinical practice to all the stakeholders. Sam Salek.

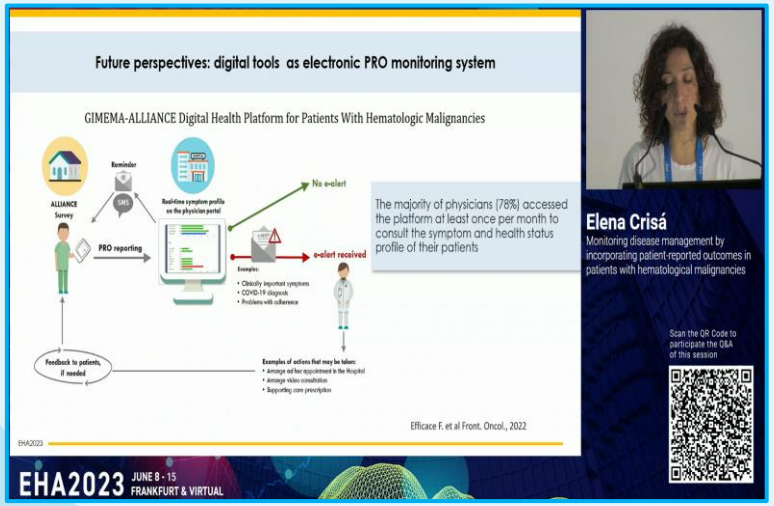
- Sam opened the conversation describing all stakeholders: clinicians are anyone involved in delivering care, researchers are those generating the evidence, policy makers also include the payers, and the patients are the simplest ones, those we all want to focus upon.
- Initially when the PROs were not developed, the first measure used was the health status measure with about 140 items, developed either for surveys or CTs. Now the PROs are wanted to be used in the day-to-day care to monitor the patients, as its use will benefit them by capturing all patient-relevant symptoms, and missing those symptoms can have significant consequences. However, there are challenges in integrating PROs into the routine care, mostly administrative, technical and workflow issues. Nevertheless, if those issues are anticipated then the benefits are noteworthy, as patient data will be immediately transferred to electronic medical records, PROs can support decision making and clinicians can focus on symptoms that are most problematic for patients.
- Our mind set needs to be changed and we should apply all we are preaching.



Quality of life and symptoms: Frontiers in the use of patient-reported outcomes in clinical practice and clinical research

Monitoring disease management by incorporating patient-reported outcomes in patients with hematological malignancies. Elena Crisá.

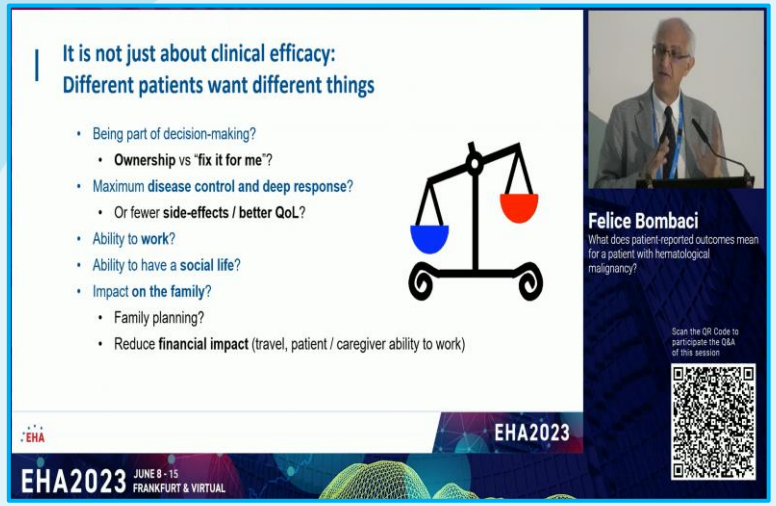
- Patients with cancer typically experience disease- and treatment-related symptoms that affect their health-related quality of life; hence it is critical to capture the patient experience with validated tools like PROMs. It is also important to align clinicians' and patients' goals for a better outcome.
- A disease like MDS is associated with significant symptom burden that reduces health-related QoL. In this area, a survey was implemented to explore the impact of MDS and treatment on patients and caregivers, patients' preferences and their unmet needs. This resulted in learning about many aspects that have been affecting patients and caregivers, which can now help improve the general management of patients. Confirming the relevance of patient preference studies.
- As future perspectives in including PROs in routine care, a digital tool has been developed as an electronic PRO monitoring system, the GIMEMA-ALLIANCE Digital Health Platform for patients with hematological malignancies, which can be easily accessed by physicians to consult the symptoms and health status profiles of their patients.



Quality of life and symptoms: Frontiers in the use of patient-reported outcomes in clinical practice and clinical research

What does patient-reported outcomes mean for a patient with hematological malignancy?. Felice Bombaci.

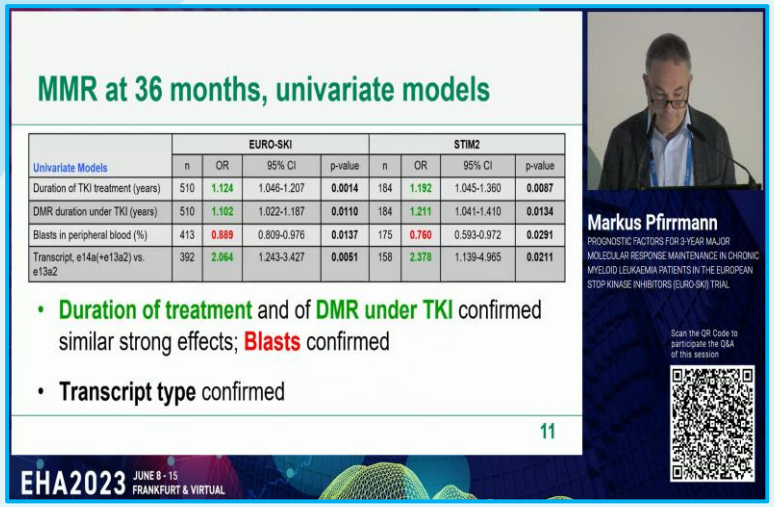
- Being a patient himself, Felice shared his personal experience when diagnosed with CML and receiving INF treatment in a clinical trial, in which he noticed that not much attention was being paid to his life environment but just on the disease, the overall status and toxicity. Most typically, physicians tend to underestimate symptoms severity and overestimate the overall health status of the patients. The disease should not be looked at as an issue independent from the patient's own life environment and projects, and the social, professional and family impact. Felice emphasized that the main goal of a treatment should not be just about preserving the life of a patient but preserving their projects and future.
- It is important to follow the patients experience not only in clinical trials but in the regular clinical visits by using PROs. The use of the right PRO for each situation is also relevant, as there are generic and specific PROs that can be used in each case. More tools should be developed and done in an interactive way by actively involving the patients in the development process.

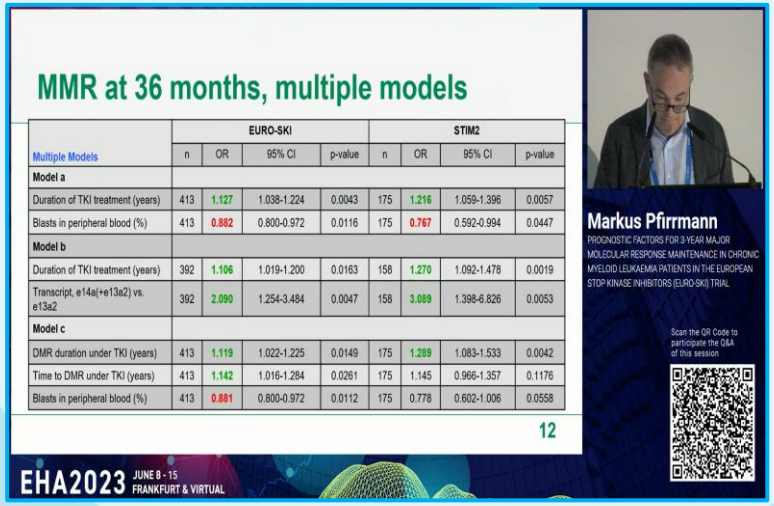


Oral Session
Evolution of clinical management in CML

Prognostic factors for 3-year major molecular response maintenance in chronic myeloid leukaemia patients in the european stop kinase inhibitors (EURO-SKI) trial. Markus Pfirrmann.

- In the **Euro**pean **S**top **K**inase **I**nhibitor (EURO-SKI) trial previous results have indicated that the most discriminating cutoff was 6 years before stopping, and 3 years for DMR. Now they evaluated the prognostic factors for remaining in molecular relapse-free survival after 3 years of TKI-stop.
- The candidate prognostic factors were median age at diagnosis 52, and at TKI-stop 60. Median duration of treatment before TKI-stop was 7.5 years, MR^4 before TKI-stop was 4.7 years, and to achieve DMR while receiving TKI was 1.9 years. Regarding transcript types, there were some additions to the e14a2.
- In the STIM2 trial with the validation sample, MMR maintenances at 3 years was 45%, whereas for the EURO-SKI trial was 41%. For the univariate modelling - MMR at 36 months, the **duration of TKI treatment**, **DMR duration under TKI**, **Blasts % in peripheral blood**, and **transcript type** were significant in the EURO-SKI trial. Also, in addition to the previous factors, multiple modelling were found, with 3 significant models.
- Validation was successful despite the smaller size in the STIM2 trial.

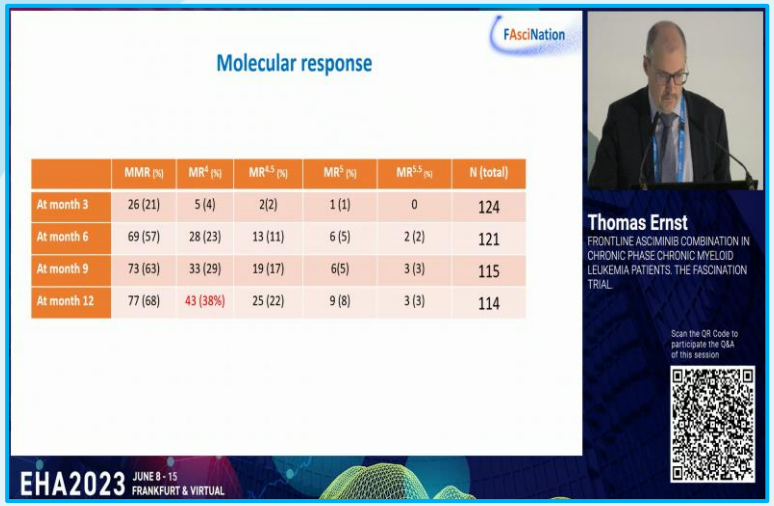




Oral Session
Evolution of clinical management in CML

Frontline asciminib combination in chronic phase chronic myeloid leukemia patients. The FAsciNation trial. Dr. Thomas Ernst.

- Dr Ernst presented results of the pre-planned interim analysis of the primary endpoint, the MR^4 rates at month 12, time achieved in January 2023.
- In the first year 38% of the patients presented adverse events of grade 3 & 4, with no significant difference between the cohorts of combinations; and the most common effects were blood disorders, followed by skin, gastrointestinal, cardiac, and metabolism disorders.
- In the first 3 months, before starting the asciminib therapy, 19 patients drop out mostly due to toxicities. And then within the first 12 months a total of 21 patients discontinued the combination therapy mostly due to toxicities (skin, gastrointestinal) and treatment failure/progression (3), with one developing Blast crisis and receiving transplantation.
- Regarding the molecular response, **38% achieved MR^4 at 12 months**, with no statistical differences among the four cohorts of combination. Concluding that **the combination increases DMR rates but with moderate tolerability**. Longer follow up is planned to investigate asciminib maintenance treatment after DMR and TFR.



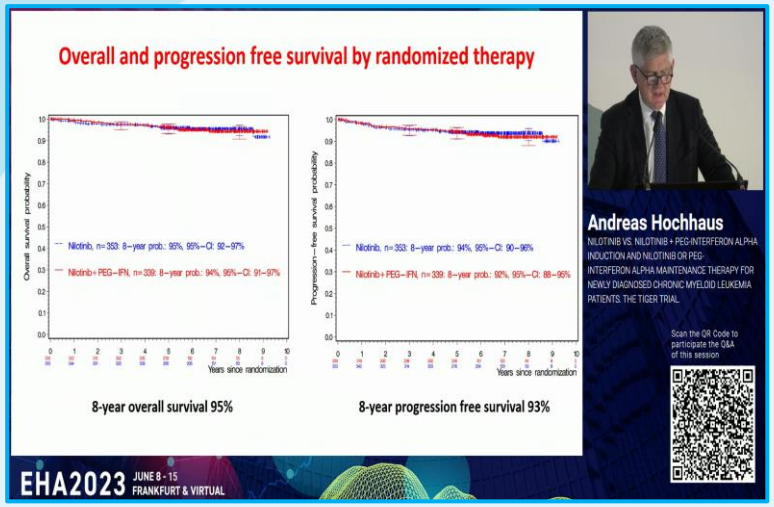
	MMR (%)	MR^4 (%)	$MR^{4.5}$ (%)	MR^5 (%)	$MR^{5.5}$ (%)	N (total)
At month 3	26 (21)	5 (4)	2(2)	1 (1)	0	124
At month 6	69 (57)	28 (23)	13 (11)	6 (5)	2 (2)	121
At month 9	73 (63)	33 (29)	19 (17)	6(5)	3 (3)	115
At month 12	77 (68)	43 (38%)	25 (22)	9 (8)	3 (3)	114

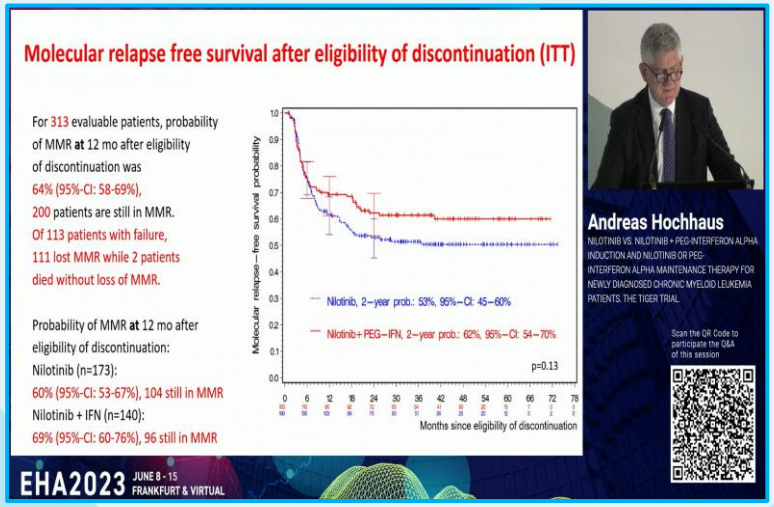
Cohort	Cohort	Number of recruited patients	Number of patients eligible for molecular response at month 12	Number of patients with MR^4 at month 12 (%)
1	Nilotinib 300 mg BID + Asciminib 20 mg BID	30	28	9 (32.1)
2	Nilotinib 300 mg BID + Asciminib 40 mg QD	32	31	13 (41.9)
3	Dasatinib 100 mg QD + Asciminib 80 mg QD	32	27	9 (33.3)
4	Imatinib 400 mg QD + Asciminib 60 mg QD	31	28	12 (42.9)
	Total	125	114	43 (37.7)

Oral Session
Evolution of clinical management in CML

Nilotinib vs. Nilotinib + peg-interferon α induction and nilotinib or peg-interferon α maintenance therapy for newly diagnosed chronic myeloid leukemia patients. The TIGER trial. Dr. Andreas Hochhaus.

- The **T**KI plus **I**nterferon in **Ger**many (TIGER) study has shown a median observation time in TFR of 39 and 40 months with the monotherapy and combination, respectively. The overall and progression free survival after 8 years reached 95 and 93% for both arms, respectively; close to the normal survival in normal population.
- At 18 months after randomization 84% of patients achieved MMR in total. While the cumulative incidence of DMR was improved with the combination arm. For the IFN monotherapy in maintenance, about 50% patients started TFR phase, and in a 39-month observation 86% had a 2-year probability of maintaining MMR. The molecular relapse free survival after eligibility of discontinuation at 12 months was of 64% probability, with differences among the two arms, but non-statistically significant.
- In total 54% and 60% of patients presented grade 3-5 adverse events with the monotherapy and combination, respectively; being vascular events and fatigue the most common.
- This allowed to conclude that the combination can be associated with higher rates of molecular response but also impaired tolerability. And the IFN maintenance may abbreviate the TKI treatment time but will not improve chances of long-term TFR.

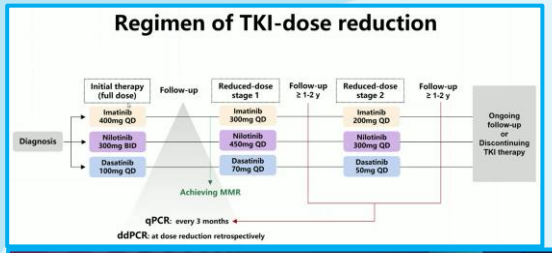


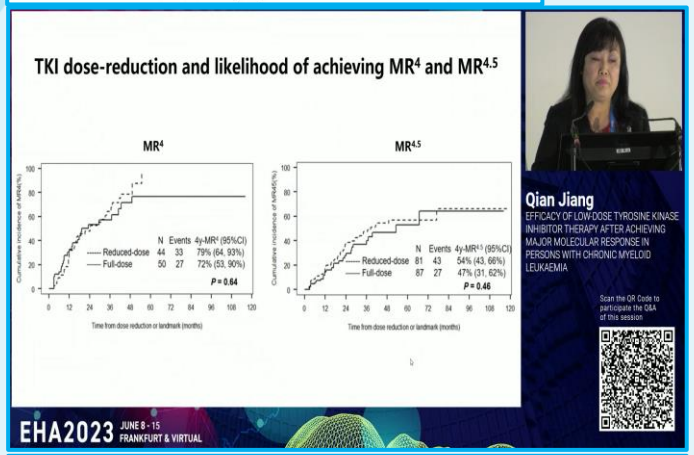


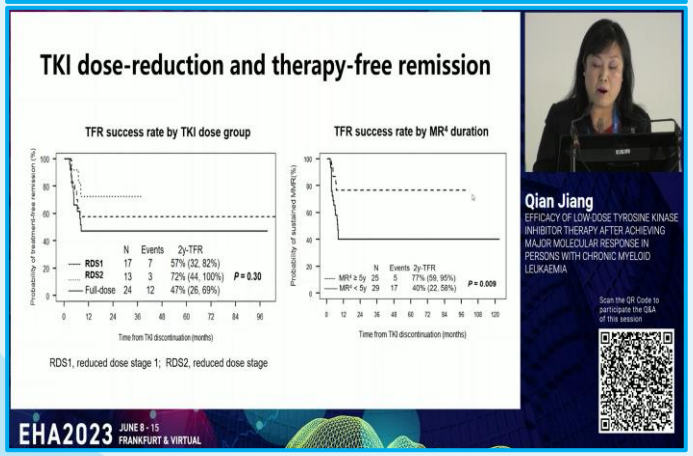
Oral Session
Evolution of clinical management in CML

Efficacy of low-dose tyrosine kinase inhibitor therapy after achieving major molecular response in persons with chronic myeloid leukaemia. Dr. Qian Jiang.

- During long-term TKI therapy, concerns on quality of life of patients are raised, also on the increase of the financial burden of patients and society. To solve this, besides TKI discontinuation there is also TKI dose reduction. Dr. Jiang presented this study that mainly evaluated the consequences of reducing TKI-dose after achieving MMR.
- Among all, 35% met requirements for TKI discontinuation at the time of dose reduction. TKI dose-reduction did not impacted the likelihood of achieving MR^4 and $MR^{4.5}$, or its maintenance, as well as did not impair the success of TFR. As in other studies, patients with longer MR^4 achievements of ≥ 5 years had a higher TFR success probability. Observing a sustained response of MMR of 95% at 5 years.
- Co-variate were evaluated, and some were related to loss of molecular response. Patients older than 60 years had the highest risk, and clinical co-variates like high WBC counts and low haemoglobin were also relevant.
- TKI-dose reduction had an improvement in the adverse events reported.



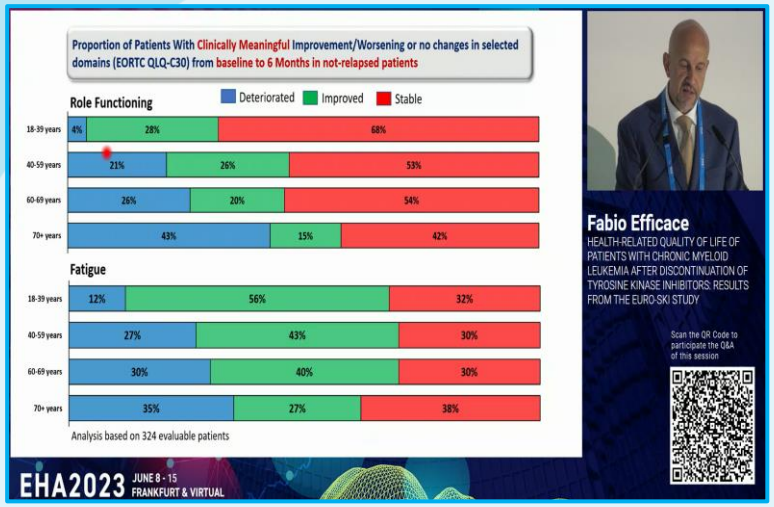


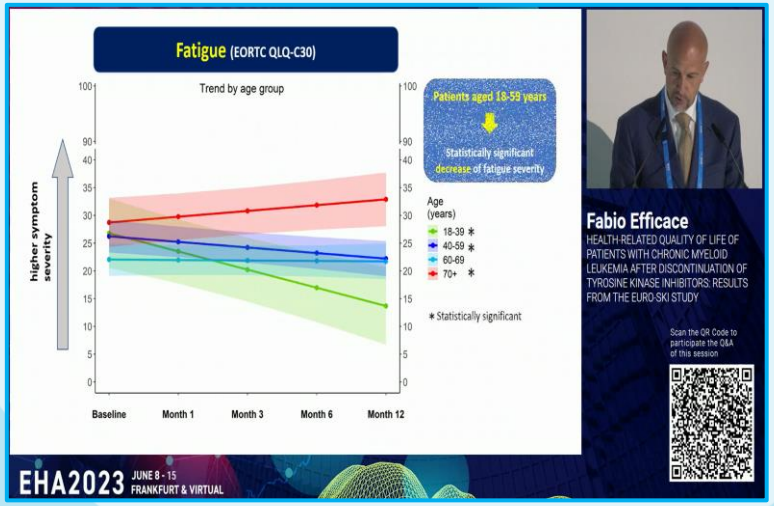


Oral Session
Evolution of clinical management in CML

Health-related quality of life of patients with chronic myeloid leukemia after discontinuation of tyrosine kinase inhibitors: results from the EURO-SKI study. Dr. Fabio Efficace.

- Access to QoL data from the EURO-SKI trial has helped learn about effects on patients when stopping TKI, and HRQoL improvements. **Are there indeed patients that can benefit more in TKI-stop?**
- Younger patients (18-49 years old) reported substantial impairments compared to older patients. The MR^4 duration media was 5 years and median age at TKI-stop was 58. And relapse did not differentiate among age groups.
- With only descriptive data, **at the time of TKI-stop** the study showed quite good physical functioning of patients and symptoms, similar to the general population. Now, **after TKI-stop** some changes in QoL were observed. **Fatigue** decreased only for those aged 18-59, **diarrhea** and **vomiting** improved in general disregard of age, while patients aged >40 showed increased **pain**. And cognitive functioning improved only in patients aged 18-39. Any non-TKI-related factor shall be evaluated to be affecting these results.
- A better understanding of the functional limitations and persistent symptoms after TKI-stop are required to offer more efficient supportive care.



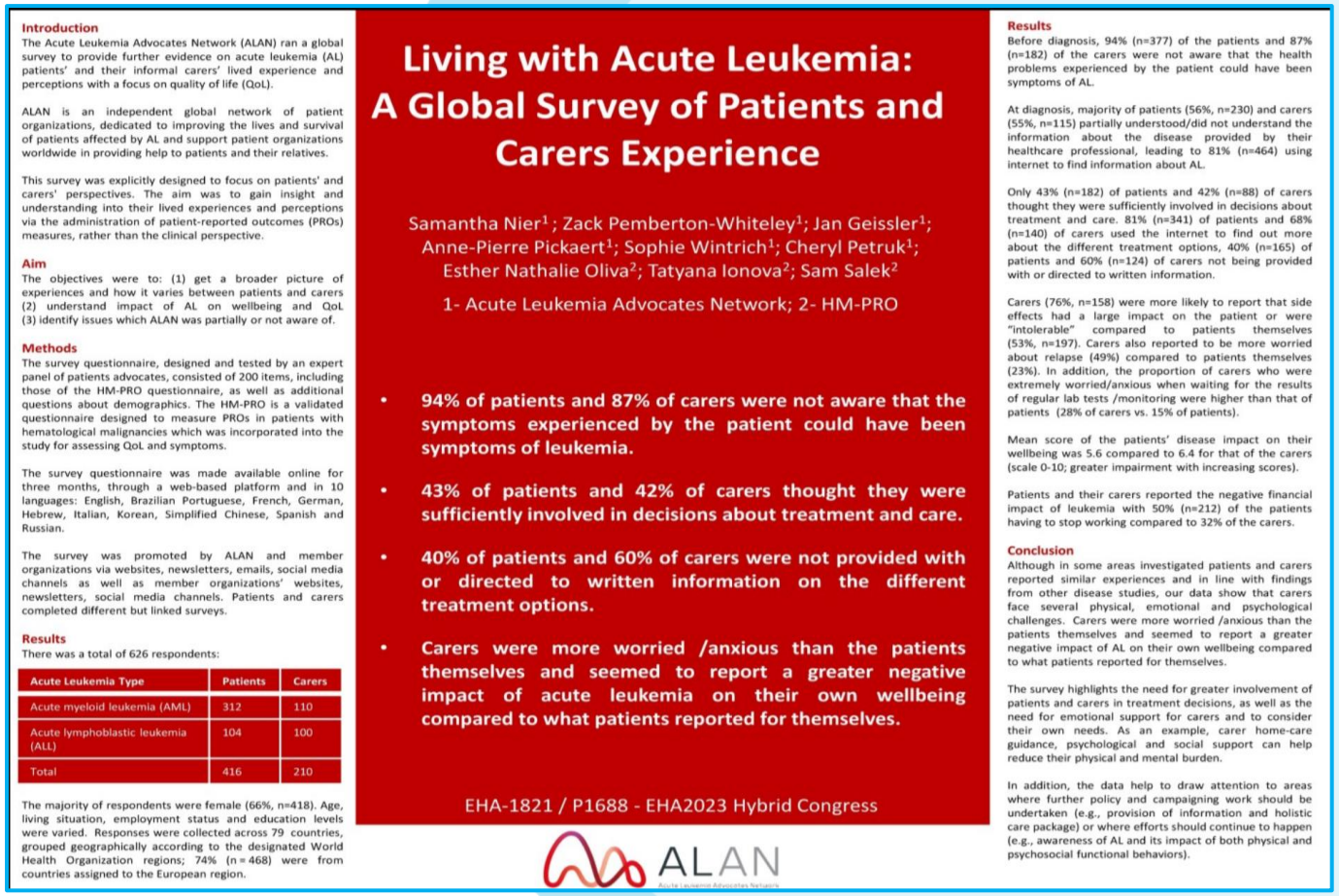


Poster Presentations

P1688. Living with acute leukemia: A global survey of patients and carers experience

Zack Pemberton-Whiteley. Acute Leukemia Advocates Network - ALAN

- The survey aimed to provide evidence on the experience and perception of Acute Leukemia (AL) patients and their informal carers, focusing on Quality of Life. In total 79 countries participated.
- 94% of patients and 87% of carers were not aware that the experienced health problems by the patient could have been symptoms of AL. Half of them expressed have partially/not understand the information given by the health care provider about the disease at diagnosis.
- 43% of patients and 42% of carers thought they were sufficiently involved in decisions about treatment and care.
- Carers tended to report higher impact of side effects, be more worried about relapse and anxious for test results than patients themselves. This highlights the need for greater involvement and emotional support for both populations.



Introduction

The Acute Leukemia Advocates Network (ALAN) ran a global survey to provide further evidence on acute leukemia (AL) patients' and their informal carers' lived experience and perceptions with a focus on quality of life (QoL).

ALAN is an independent global network of patient organizations, dedicated to improving the lives and survival of patients affected by AL and support patient organizations worldwide in providing help to patients and their relatives.

This survey was explicitly designed to focus on patients' and carers' perspectives. The aim was to gain insight and understanding into their lived experiences and perceptions via the administration of patient-reported outcomes (PROs) measures, rather than the clinical perspective.

Aim

The objectives were to: (1) get a broader picture of experiences and how it varies between patients and carers (2) understand impact of AL on wellbeing and QoL (3) identify issues which ALAN was partially or not aware of.

Methods

The survey questionnaire, designed and tested by an expert panel of patients advocates, consisted of 200 items, including those of the HM-PRO questionnaire, as well as additional questions about demographics. The HM-PRO is a validated questionnaire designed to measure PROs in patients with hematological malignancies which was incorporated into the study for assessing QoL and symptoms.

The survey questionnaire was made available online for three months, through a web-based platform and in 10 languages: English, Brazilian Portuguese, French, German, Hebrew, Italian, Korean, Simplified Chinese, Spanish and Russian.

The survey was promoted by ALAN and member organizations via websites, newsletters, emails, social media channels as well as member organizations' websites, newsletters, social media channels. Patients and carers completed different but linked surveys.

Results

There was a total of 626 respondents:

Acute Leukemia Type	Patients	Carers
Acute myeloid leukemia (AML)	312	110
Acute lymphoblastic leukemia (ALL)	104	100
Total	416	210

The majority of respondents were female (66%, n=418). Age, living situation, employment status and education levels were varied. Responses were collected across 79 countries, grouped geographically according to the designated World Health Organization regions; 74% (n = 468) were from countries assigned to the European region.

Living with Acute Leukemia: A Global Survey of Patients and Carers Experience

Samantha Nier[1]; Zack Pemberton-Whiteley[1]; Jan Geissler[1]; Anne-Pierre Pickaert[1]; Sophie Wintrich[1]; Cheryl Petruk[1]; Esther Nathalie Oliva[2]; Tatyana Ionova[2]; Sam Salek[2]

1- Acute Leukemia Advocates Network; 2- HM-PRO

- **94% of patients and 87% of carers were not aware that the symptoms experienced by the patient could have been symptoms of leukemia.**
- **43% of patients and 42% of carers thought they were sufficiently involved in decisions about treatment and care.**
- **40% of patients and 60% of carers were not provided with or directed to written information on the different treatment options.**
- **Carers were more worried /anxious than the patients themselves and seemed to report a greater negative impact of acute leukemia on their own wellbeing compared to what patients reported for themselves.**

EHA-1821 / P1688 - EHA2023 Hybrid Congress

ALAN

Results

Before diagnosis, 94% (n=377) of the patients and 87% (n=182) of the carers were not aware that the health problems experienced by the patient could have been symptoms of AL.

At diagnosis, majority of patients (56%, n=230) and carers (55%, n=115) partially understood/did not understand the information about the disease provided by their healthcare professional, leading to 81% (n=464) using internet to find information about AL.

Only 43% (n=182) of patients and 42% (n=88) of carers thought they were sufficiently involved in decisions about treatment and care. 81% (n=341) of patients and 68% (n=140) of carers used the internet to find out more about the different treatment options, 40% (n=165) of patients and 60% (n=124) of carers not being provided with or directed to written information.

Carers (76%, n=158) were more likely to report that side effects had a large impact on the patient or were "intolerable" compared to patients themselves (53%, n=197). Carers also reported to be more worried about relapse (49%) compared to patients themselves (23%). In addition, the proportion of carers who were extremely worried/anxious when waiting for the results of regular lab tests /monitoring were higher than that of patients (28% of carers vs. 15% of patients).

Mean score of the patients' disease impact on their wellbeing was 5.6 compared to 6.4 for that of the carers (scale 0-10; greater impairment with increasing scores).

Patients and their carers reported the negative financial impact of leukemia with 50% (n=212) of the patients having to stop working compared to 32% of the carers.

Conclusion

Although in some areas investigated patients and carers reported similar experiences and in line with findings from other disease studies, our data show that carers face several physical, emotional and psychological challenges. Carers were more worried /anxious than the patients themselves and seemed to report a greater negative impact of AL on their own wellbeing compared to what patients reported for themselves.

The survey highlights the need for greater involvement of patients and carers in treatment decisions, as well as the need for emotional support for carers and to consider their own needs. As an example, carer home-care guidance, psychological and social support can help reduce their physical and mental burden.

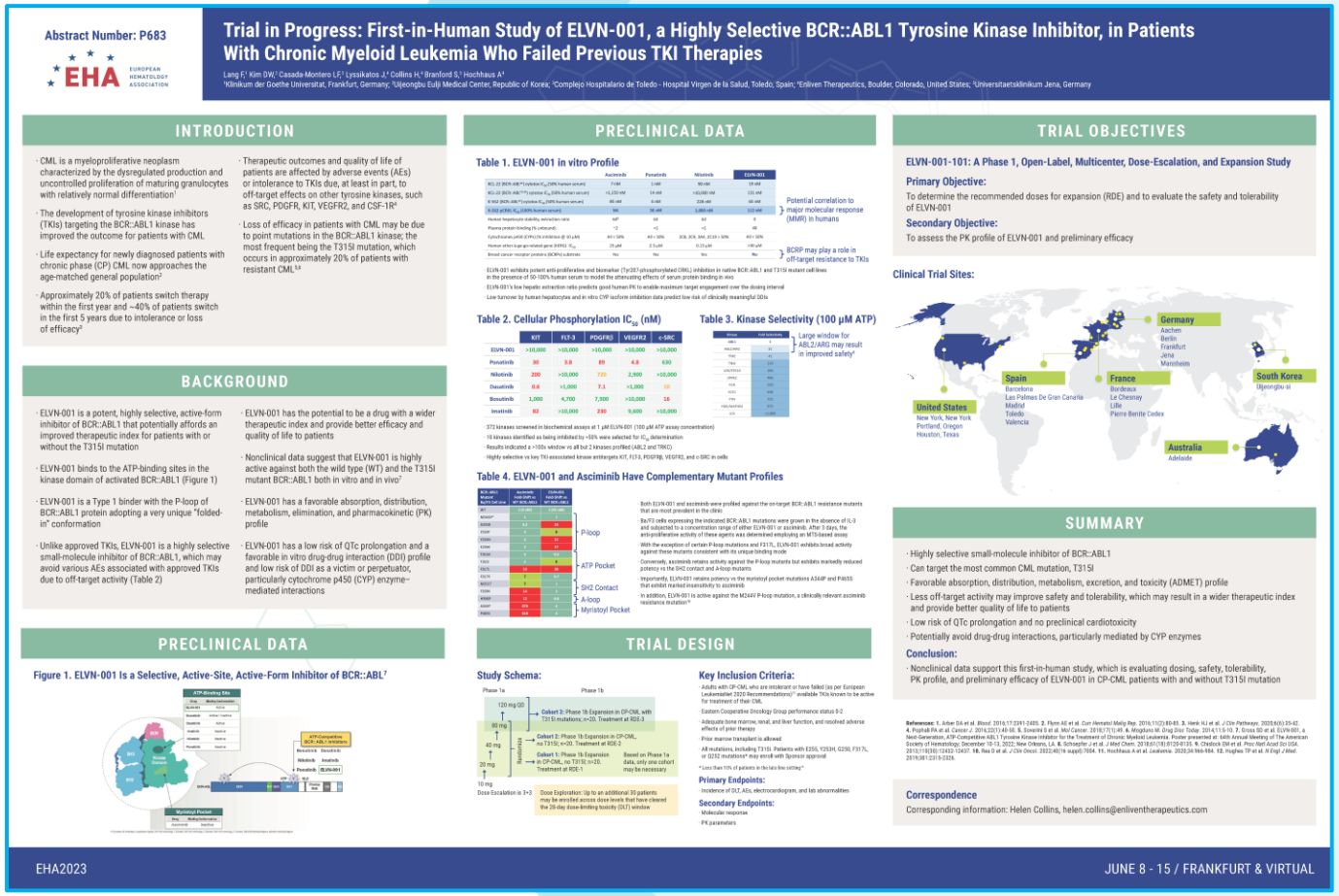
In addition, the data help to draw attention to areas where further policy and campaigning work should be undertaken (e.g., provision of information and holistic care package) or where efforts should continue to happen (e.g., awareness of AL and its impact of both physical and psychosocial functional behaviors).

Poster Presentations

P683. Trials in progress: first-in-human study of elvn-001, a selective BCR::ABL1 tyrosine kinase inhibitor, in patients with chronic myeloid leukemia who failed previous tyrosine kinase inhibitor therapies

Fabian Lang. Klinikum der Goethe Univarsitat – Frankfurt, Germany

- The percentage of patients that need to switch therapy, the affected QoL of patients by AEs or intolerance to TKIs, and those patients with resistant CML, call for new potent and tolerable drugs. ELVN-001, a highly selective small-molecule inhibitor of BCR::ABL1 is being studied in CML patient with or without the T315I mutation, with *in vitro* studies showing potential correlation to MMR.
- ELVN-001 has shown favourable absorption, distribution, metabolism, excretion, and toxicity profile. It has a broad activity against mutants, also myristoyl pocket mutations A344P and P465S, and the M244V P-loop mutation, a clinically relevant asciminib resistance mutation; all consistent with its unique binding mode.
- This first-in-human study is in progress to evaluate dosing, safety, tolerability, pharmacokinetic profile and preliminary efficacy.

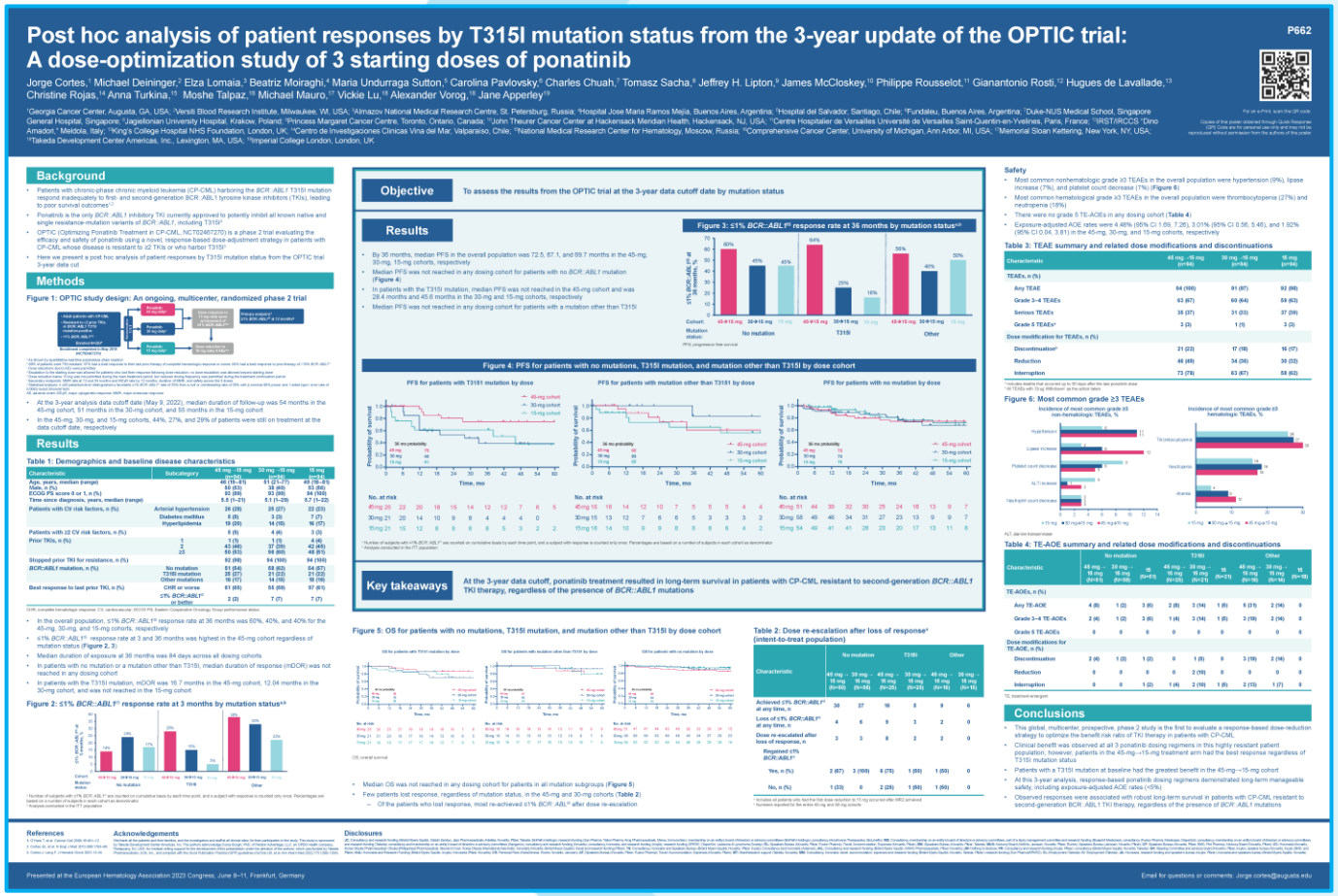


Poster Presentations

P662. Post hoc analysis of patient responses by T315I mutation status from the 3-year update of the OPTIC trial: A dose-optimization study of 3 starting doses of ponatinib

Jorge Cortes. Georgia Cancer Center - Augusta, GA, USA

- The OPTIC study evaluates efficacy and safety of ponatinib using a response-based dose-adjustment strategy in patients with CP-CML resistant to ≥2 TKIs or with the T315I mutation. Here a 3-year cutoff
- ≤1% BCR::ABL1 response rate at 3 and 36 months was highest in the 45-mg cohort regardless of mutations.
- In patients with no mutation or a mutation other than T315I, median duration of response (mDOR) was not reached in any dosing cohort. Median PFS was not reached in any dosing cohort for patients with no BCR::ABL1 mutation or with a mutation other than T315I, also not reached in the 45-mg cohort with the T315I mutation.
- In general, ponatinib treatment resulted in long-term survival in patients with CP-CML resistant to second-generation BCR::ABL1 TKI therapy, regardless of the presence of BCR::ABL1 mutations.

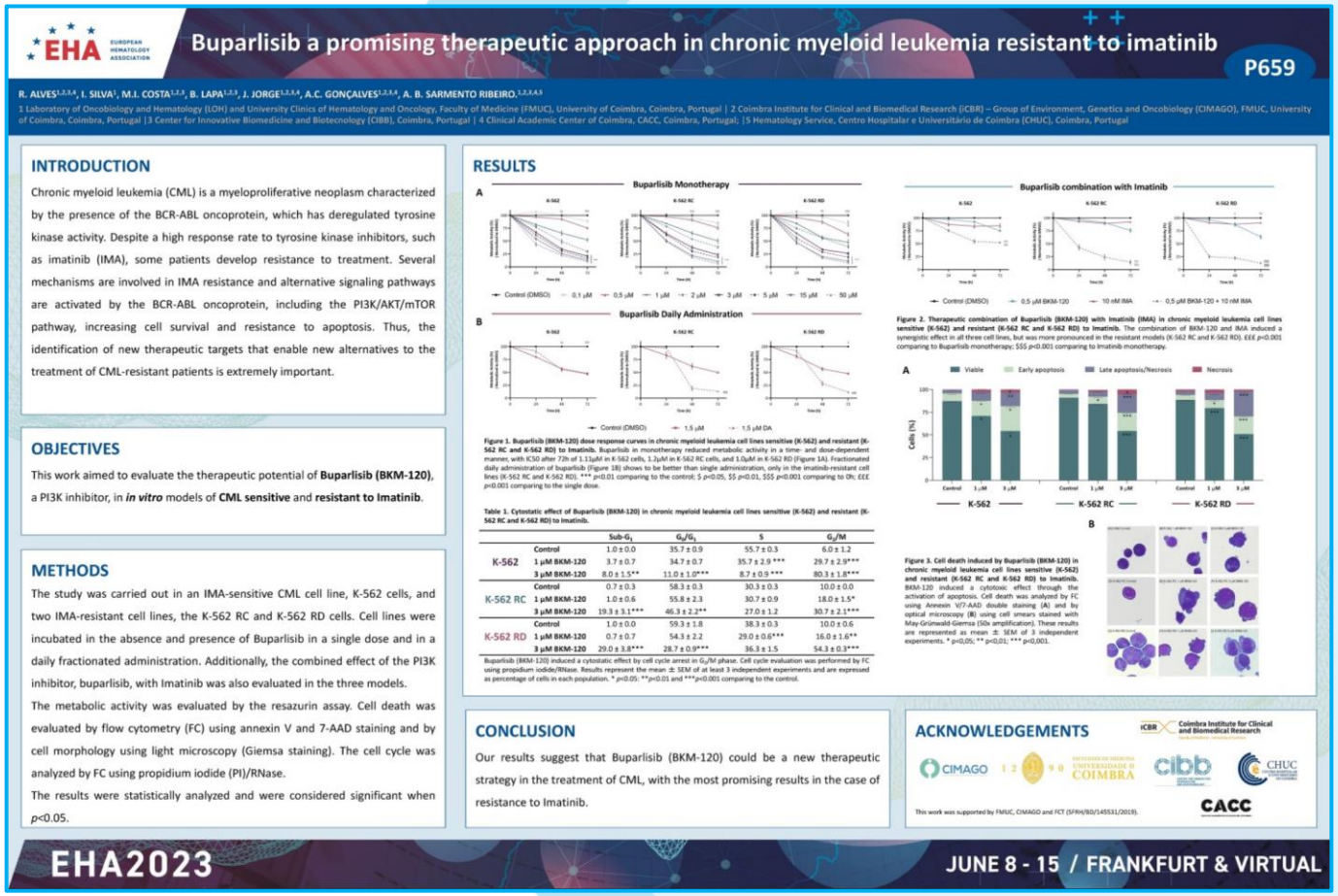


Poster Presentations

P659. Buparlisib a promising therapeutic approach in chronic myeloid leukemia resistant to imatinib

Anabela Ribeiro. University Of Coimbra - Coimbra, Portugal

- In TKI resistance, alternative signalling pathways are activated by the BCR-ABL oncoprotein, including the PI3K/AKT/mTOR pathway, increasing cell survival and resistance to apoptosis. The identification of new alternatives for CML-resistant patients is extremely important. This is an *in vitro* study to evaluate the therapeutic potential of buparlisib (BKM 120), a PI3K inhibitor in imatinib-sensitive and resistant cell lines.
- Buparlisib have shown to reduce metabolic activity in a time- and dose-dependent manner, with more benefits when administered fractionated. The combination with imatinib induced a synergistic effect in all three cell lines, though more pronounced in the resistant models. Buparlisib induced the activation of apoptosis and showed a cytostatic effect.
- Results suggest that buparlisib could be a new therapeutic strategy for further study in imatinib-resistance CML.

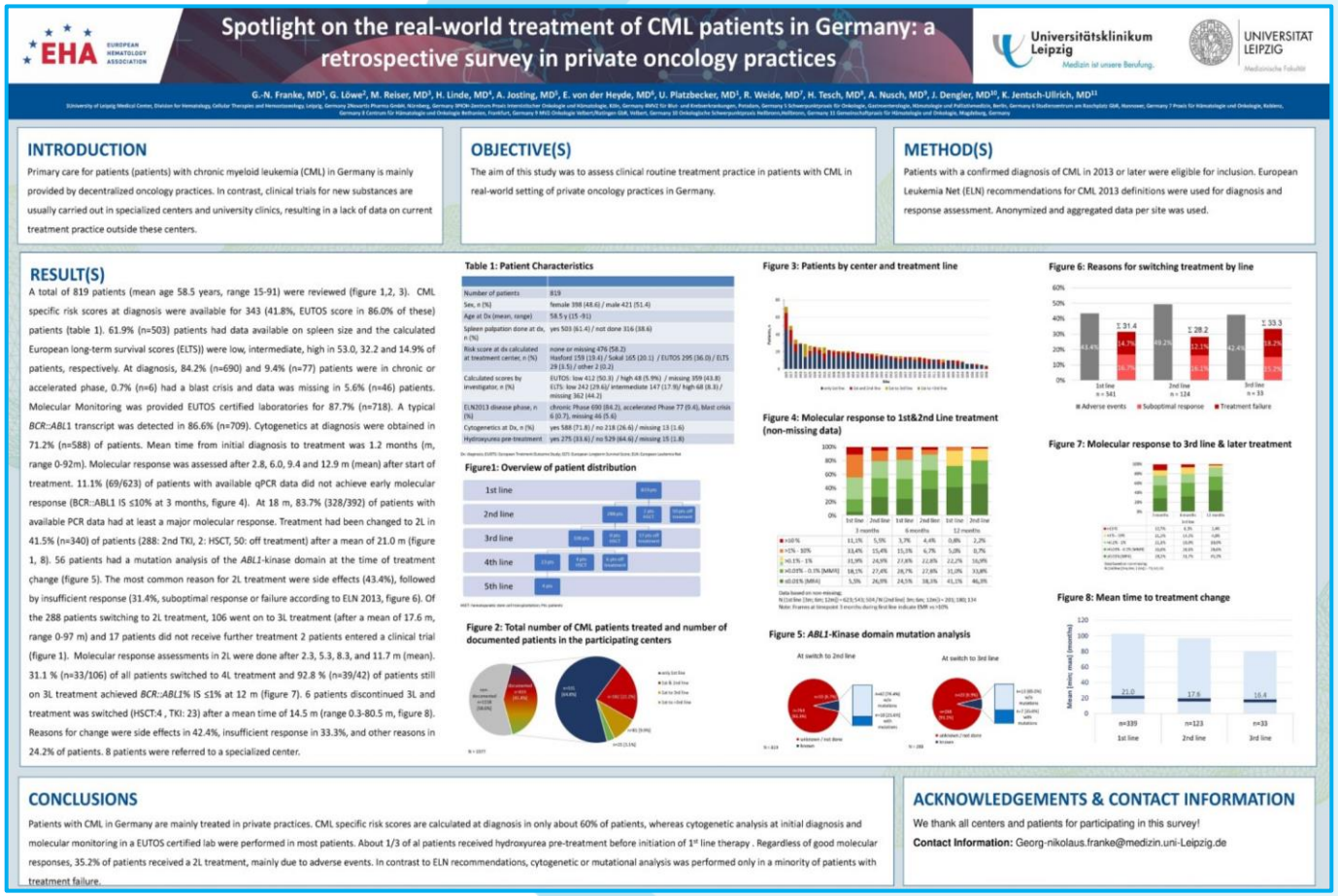


Poster Presentations

P679. Spotlight on the real-world treatment of CML pts in Germany: a retrospective survey in private oncology practices

Georg-Nikolaus Franke. University Of Leipzig Medical Center - Leipzig, Germany

- This study assessed clinical routine treatment practice in 819 CML pts from 43 private oncology practices in Germany. At diagnosis, CML specific risk scores were available for 41.8% pts (mostly EUTOS). 84.2% and 9.4% pts were in chronic or accelerated phase, 0.7% in blast crisis and 5.6% had missing data. A typical BCR::ABL1 transcript was detected in 86.6%, and Cytogenetics were obtained in 71.2% of pts.
- At 18 months, 83.7% (328/392) of pts with available PCR data had achieved MMR. At 21 months, 41.5% pts had changed to 2L treatment, mainly due to side effects, and from those almost half went on to 3L after 17 months. Changes for insufficient response was 33.3%, and other reasons 24.2%.
- Referral to a specialized center (8 pts) or including pts into a clinical trial was rare. Adherence to current treatment guidelines regarding pts with insufficient response should be improved.

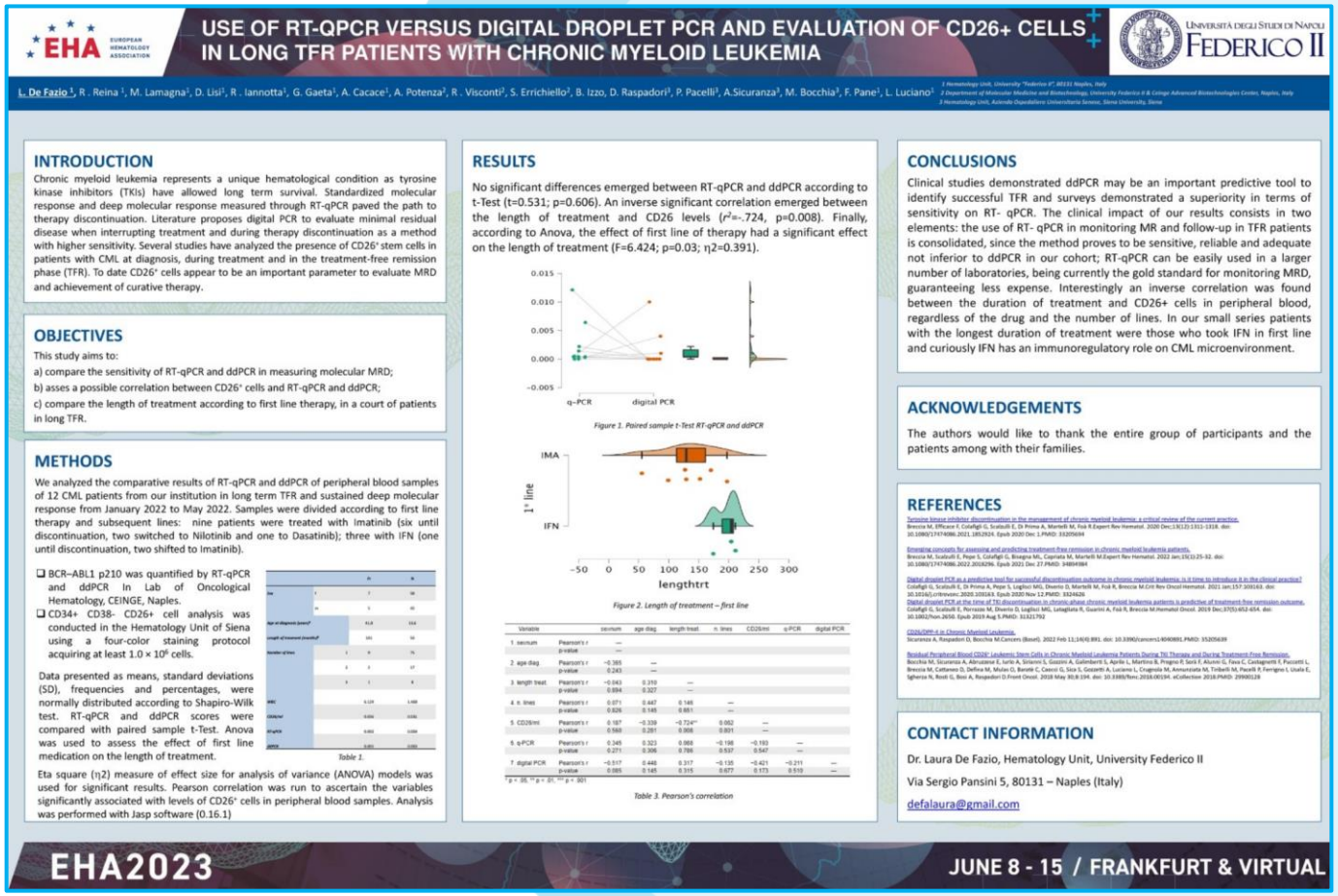


Poster Presentations

P671. Use of RT-qPCR versus digital droplet PCR and evaluation of CD26+ cells in long TFR patients with chronic myeloid leukemia

Laura De Fazio. University “federico Ii” , Hematology Unit - Naples, Italy

- CD26⁺ stem cells have been identified in CML patients at diagnosis, during treatment and in TFR. These cells appear to be an important parameter to evaluate MRD and achievement of curative therapy. A small approach was made in this study with 12 patients in long-term TFR and sustained DMR.
- There were no significant differences between RT-qPCR and dd-PCR, which consolidates the use of RT-qPCR in monitoring MR and follow-up in TFR phase.
- Interestingly an inverse significant correlation was observed between the length of treatment and CD26 levels, regardless of the drug and the number of lines.
- The effect of first line of therapy showed to have a significant effect on the length of treatment. In our small cohort those who took IFN in first line had the longest duration of treatment, curiously IFN has an immunoregulatory role on CML microenvironment.

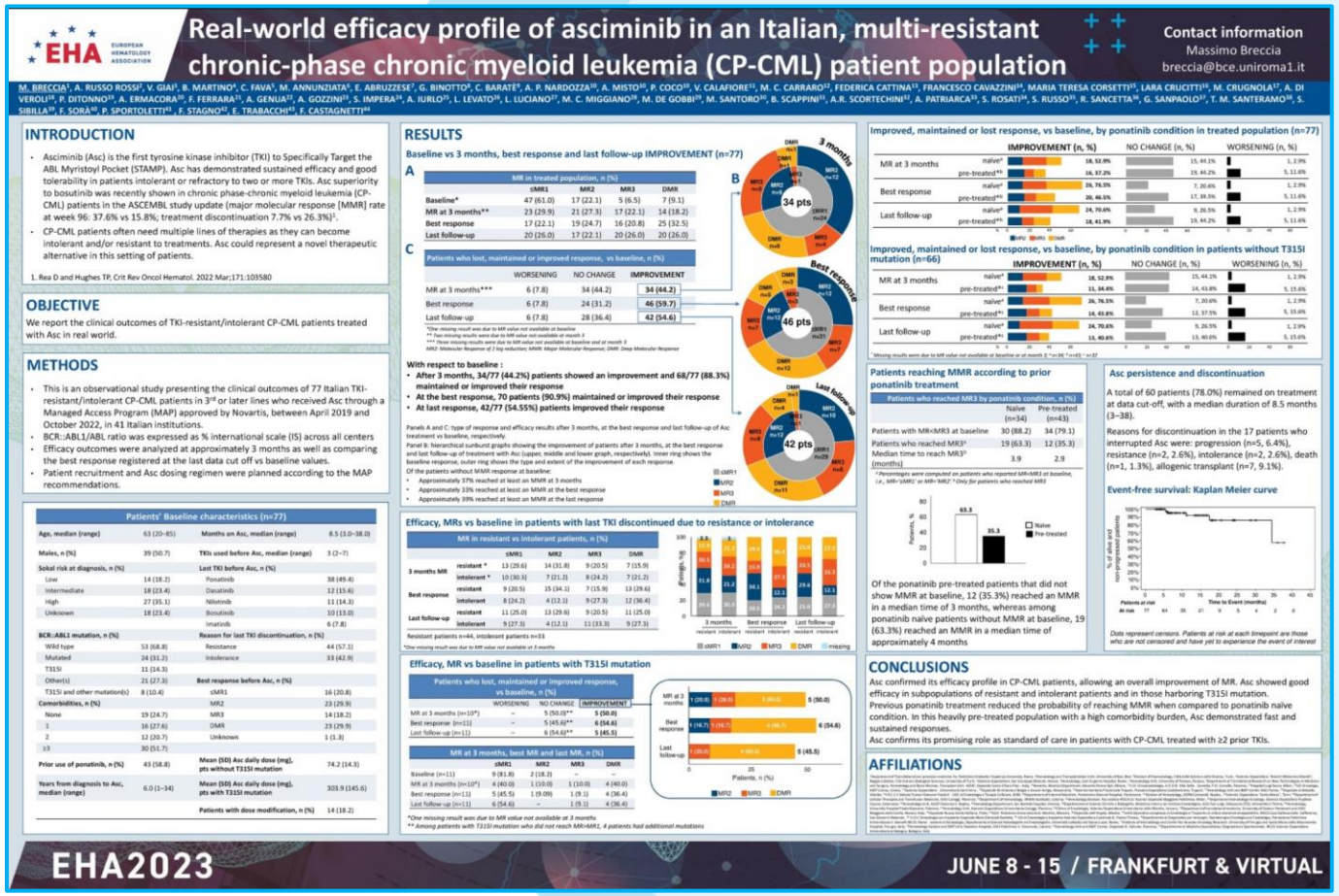


Poster Presentations

P686. Real-world efficacy profile of asciminib in an italian, multi-resistant chronic-phase chronic myeloid leukemia (CP-CML) patient population

Massimo Breccia. Policlinico Umberto I-Sapienza University - Rome, Italy

- 77 TKI-resistant/intolerant CP-CML patients in 3rd line or later, received asciminib (Asc) through a Managed Access Program (MAP) in 41 Italian institutions.
- Median time of Asc treatment was 8.5 months, with median of 3 prior TKIs and ≥3 comorbidities reported in 51.7% patients. Switch to Asc due to resistance in 57.1% and intolerance in 42.9%. Prior exposure to ponatinib was reported in 43 patients (55.8%) and 38 of them received it as last TKI before switching to Asc.
- 88.3% patients maintained or improved their previous response at 3 months, and after that 44.2% patients improved their previous baseline response, with about 33% of patients now achieving MMR. This demonstrated fast and sustained responses for Asc.
- Previous ponatinib treatment determined a reduced probability of reaching MMR when compared to ponatinib naive condition, 35.3% versus 63.3% in a median of 3 and 4 months, respectively.



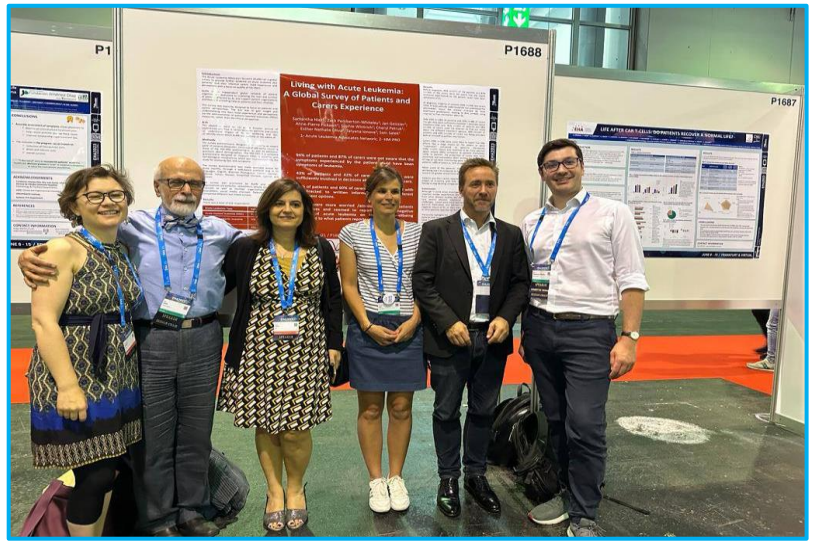
Poster Presentations

P1689. Real-world evidence of using telemedicine to capture electronic PROM improves quality of life assessment, healthcare resources management and overall survival in patients with lymphoma

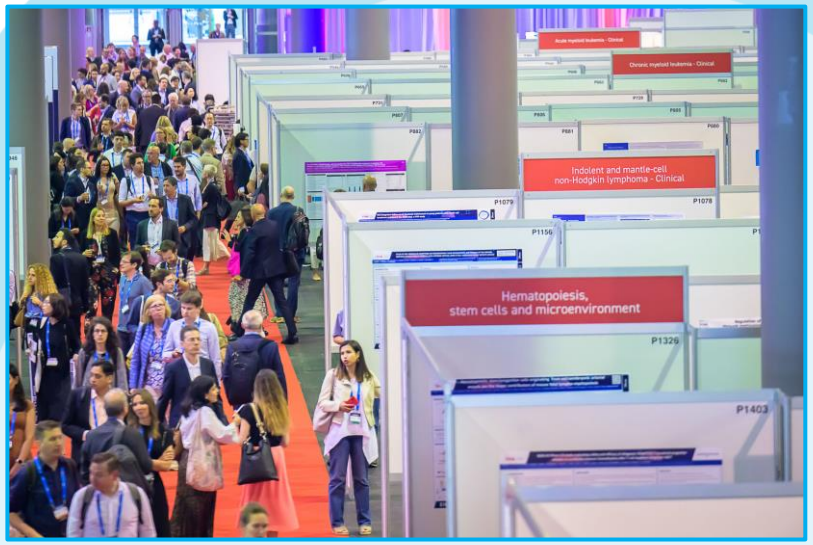
Sergio Ramos. Hospital Universitario Fundación Jiménez Díaz – Madrid, Spain

- For this study, the PRO-CTCAE™ questionnaire was electronically sent through the app at 3 points, after 1st, 3rd and 6th course of therapy.
- Those who adhered to the program had fewer visits to the Emergency Room (33.3% vs. 55.7%) and showed a tendency to require fewer unscheduled hospital admissions (21.5% vs. 32.0%). More patients among those included in the program were able to complete the full initially planned treatment (94.2% vs. 83.6%)
- After a median follow-up of 18.8 months, median overall survival was not reached in either group, but it was significantly longer among patients included in the program (88.2% vs. 79.7%)
- Better understanding of patient-reported symptoms could aid physicians to develop individualized treatment plans, and early feed-back seems to improve self-perception of health.

EHA 2023


P1
P1688
P1687
Living with Acute Leukemia: A Global Survey of Patients and Carers Experience


Patients Advocacy Hub


Indolent and mantle-cell non-Hodgkin lymphoma - Clinical
Hematopoiesis, stem cells and microenvironment
P1329
P1403


EHA2023


EHA2023


GILEAD
Kite
BeiGene
Genmab