

CML Advocates Network conference report

The graphic features a dark blue background with a grid of white plus signs. A stylized map of Europe is shown in the upper center, with a network of white dots and lines connecting various points. Below the map, there are several overlapping, semi-transparent spheres in shades of red, orange, and blue. A prominent, wavy, wireframe mesh in shades of green and yellow runs horizontally across the middle of the image. The text 'EHA 2023' is displayed in large, white, bold, sans-serif font, centered over the wireframe mesh. Below it, the dates and location 'JUNE 8 - 15 / FRANKFURT & VIRTUAL' are written in a smaller, white, sans-serif font. In the bottom right corner, there is a list of contact information for Eglys González, PhD., including her title and email address. The overall aesthetic is modern and technological.

JUNE 8 - 15 / FRANKFURT & VIRTUAL

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



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.

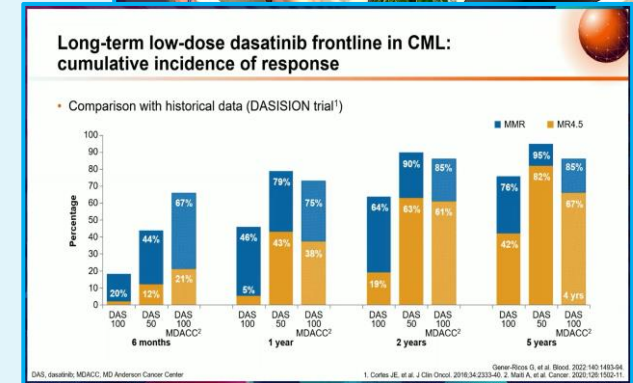
Following we present the conference scientific report with key CML highlights of interest to the patient advocacy community.

Satellite symposium on CML

CML is not solved: Transforming treatment expectations and patient outcomes

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.



Asciminib “world-wide” experience

	MMR	MR4	% Discontinuation	Responses intolerant vs resistant	Ponatinib-naïve vs ponatinib-treated	T3151: MMR rates
Spanish (83) ¹	52-29%	16%	29% (13 months)	58% vs 28%	53% vs 27%	NA
Russian (50) ²	48-29%	45-17%	17% (18 months)	75% vs 23%	75 vs 23%	N = 20 48% vs 29%
Italian (34) ³	44%	NA	NA	42% vs 31%	46% vs 23%	NA
British (49) ⁴	53%	27%	39% (13 months)	75% vs 29%	75% vs 48%	N = 11 63% vs 43%
Dutch (83) ⁵	25%	12%	30% (8 months)		25% vs 10%	N = 12 80% vs 20%
Australian (20) ⁶	45%	NA	30% (14 months)		NA	NA

MMR, molecular response. 1. Pérez-Lamote L, et al. Cancer (Basel). 2023;15:1051. 2. Tarantini A. Presented at ASH 2022. Blood. 2022;140:965A-63. 3. Bracco M, et al. Presented at EHA 2022. abstract P112. 4. Kozlovskiy CB, et al. Oral presentation at EHA 2022. abstract P102. 5. Stone A. Presented at ASH 2022. Blood. 2022;140:736-7. 6. Chen LY, et al. Presented at ASH 2022. Blood. 2022;140:686A-2.

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.



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CHAIRS: JAN GEISSLER, MARTIN KAISER

New attitude and new incentives to data sharing needed: This is patients' data, not owned by those who collected it

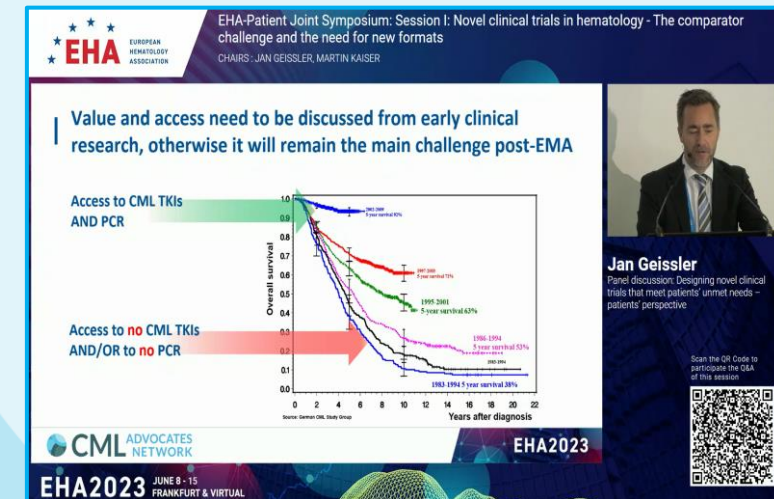
Is this what patients wanted researchers to do when they invested their life into studies?

- Year(s) for negotiating data sharing agreements
- More months until valid data sets are provided
- Academic rivalry, commercial-competitive fears
- GDPR often used as a cheap excuse

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

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Value and access need to be discussed from early clinical research, otherwise it will remain the main challenge post-EMA

Access to CML TKIs AND PCR

Access to no CML TKIs AND/OR to no PCR

Overall survival

Years after diagnosis

Source: Eastern CML Study Group

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

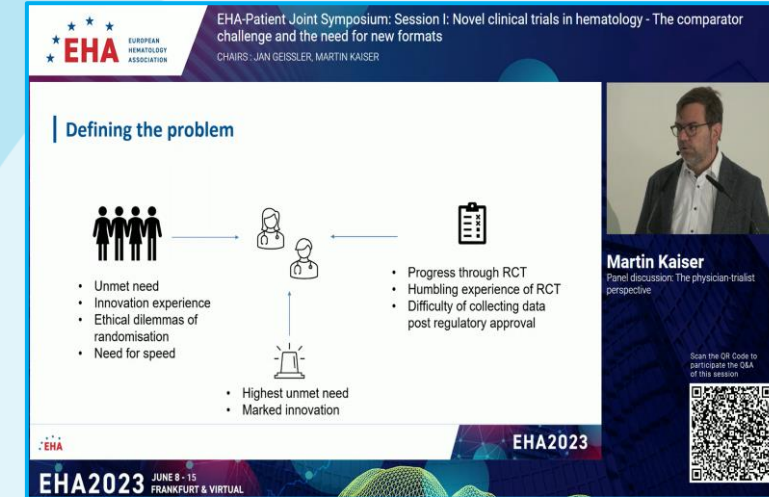
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Panel discussion: The physician-trialist perspective. Martin Kaiser

- 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**.



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Defining the problem

- Unmet need
- Innovation experience
- Ethical dilemmas of randomisation
- Need for speed

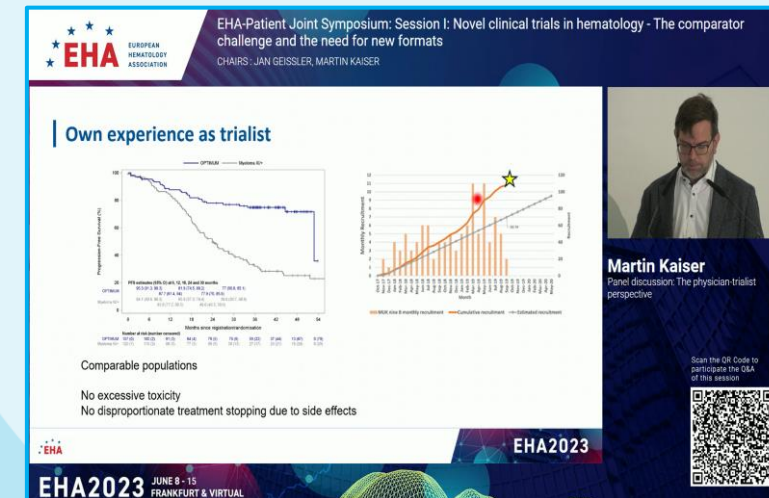
- Progress through RCT
- Humbling experience of RCT
- Difficulty of collecting data post regulatory approval

Highest unmet need
Marked innovation

Martin Kaiser
Panel discussion: The physician-trialist perspective

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Own experience as trialist

Comparable populations

- No excessive toxicity
- No disproportionate treatment stopping due to side effects

Martin Kaiser
Panel discussion: The physician-trialist perspective

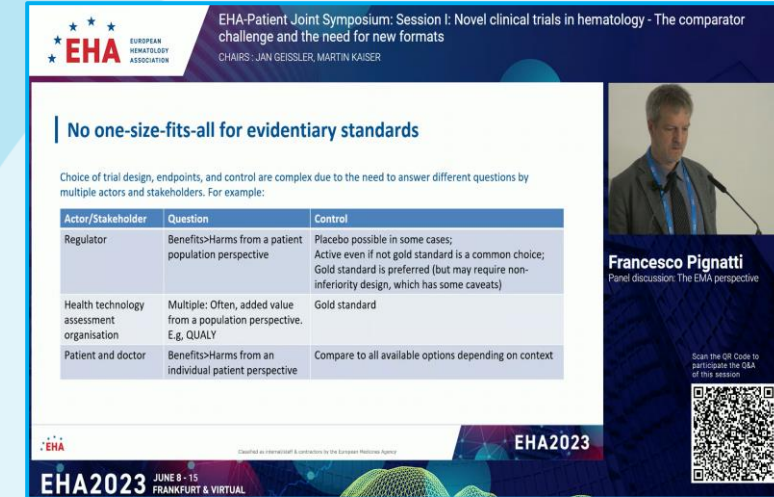
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Panel discussion: The EMA perspective. Francesco Pignatti

- 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.



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No one-size-fits-all for evidentiary standards

Choice of trial design, endpoints, and control are complex due to the need to answer different questions by multiple actors and stakeholders. For example:

Actor/Stakeholder	Question	Control
Regulator	Benefits-Harms from a patient population perspective	Placebo possible in some cases; Active even if not gold standard is a common choice; Gold standard is preferred (but may require non-inferiority design, which has some caveats)
Health technology assessment organisation	Multiple: Often, added value from a population perspective. E.g. QUALY	Gold standard
Patient and doctor	Benefits-Harms from an individual patient perspective	Compare to all available options depending on context

Francesco Pignatti
Panel discussion: The EMA perspective

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Opportunities to collaborate

Challenges

- A perception that current decision makers and actors have **different standards** of evidence
 - Appearance of "unscientific" debate
- Lack of understanding of **roles and decisions** for clinical trial design, drug approval, access, pricing, reimbursement
 - Fear of alignment between benefit-risk and access decisions
- Lack of clarity on the **basis for decision-making**: evidence, value judgments, assumptions
- Limited **resources** to answer all possible questions: need to manage assumptions and uncertainties

Possible solutions

- Multi-stakeholder **collaboration** for efficient evidence generation:
 - Identify efficient general requirements
 - Ensure trials address multiple needs, if possible (e.g., joint scientific advice)
- Maximise **transparency** of decisions
 - Quantitative benefit-risk decision making
 - Being explicit about expectations (e.g., conditional approval)
- **Data sharing** and constructive collaboration
 - Share data under current regulatory roles and responsibilities to facilitate decisions/dialogue
 - No alignment on criteria but efficiency gains (win-win)

Francesco Pignatti
Panel discussion: The EMA perspective

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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.



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Complex Innovative Design FDA Pilot: External Control in Diffuse B-Cell Lymphoma

- R-CHOP for 1L DLBCL patients established over 20 years ago
- DLBCL patients with "high risk" features have a high unmet medical need
- "Borrowing" patients from the control arm of another study helps us:
 - Spare control arm patients
 - Shorten our study
 - Reduce cost
 - Fewer "new" patients treated with a control regimen that is well established and that we know well

Proposed Study Design: "Simple Borrowing" Schema

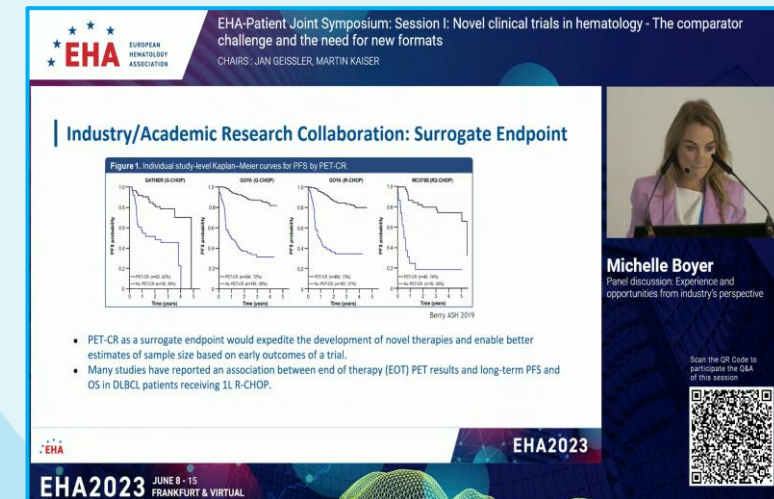


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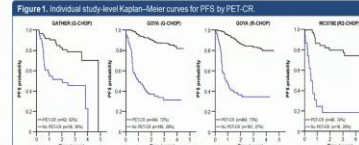
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Industry/Academic Research Collaboration: Surrogate Endpoint

Figure 1. Individual study-level Kaplan-Meier curves for PFS by PET-CR



Berry ASH 2019

- PET-CR as a surrogate endpoint would expedite the development of novel therapies and enable better estimates of sample size based on early outcomes of a trial.
- Many studies have reported an association between end of therapy (EOT) PET results and long-term PFS and OS in DLBCL patients receiving 1L R-CHOP.

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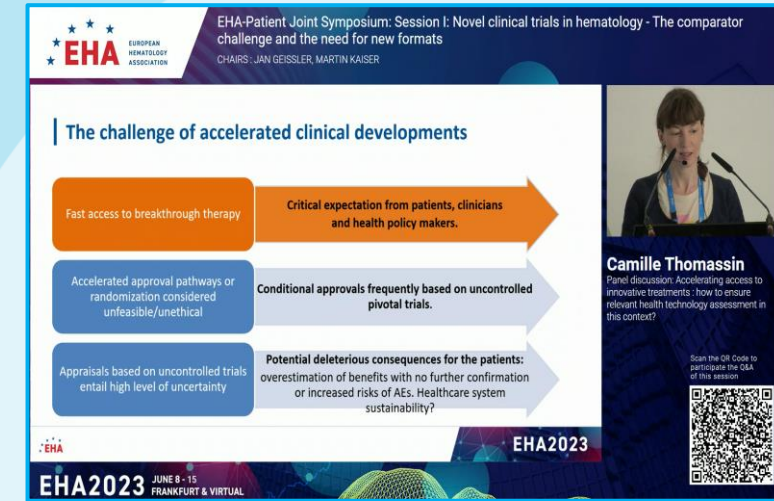


Michelle Boyer
Panel discussion: Experience and opportunities from industry's perspective

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.



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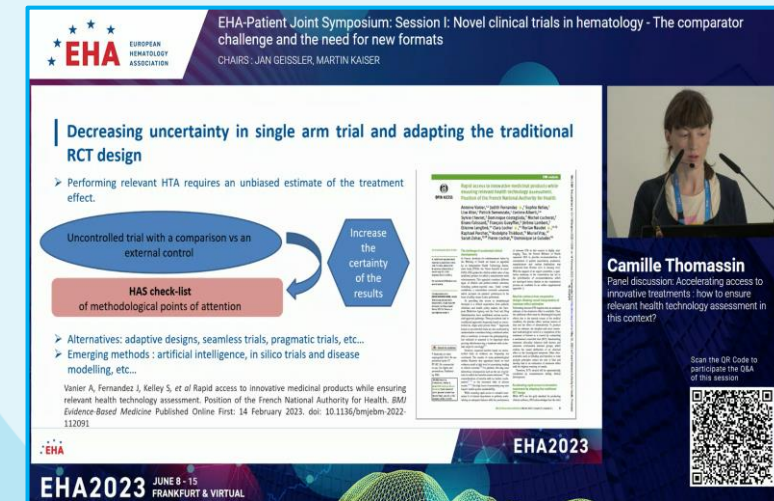
The challenge of accelerated clinical developments

- Fast access to breakthrough therapy → Critical expectation from patients, clinicians and health policy makers.
- Accelerated approval pathways or randomization considered unfeasible/unethical → Conditional approvals frequently based on uncontrolled pivotal trials.
- Appraisals based on uncontrolled trials entail high level of uncertainty → Potential deleterious consequences for the patients: overestimation of benefits with no further confirmation or increased risks of AEs. Healthcare system sustainability?

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

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Decreasing uncertainty in single arm trial and adapting the traditional RCT design

- Performing relevant HTA requires an unbiased estimate of the treatment effect.
- Uncontrolled trial with a comparison vs an external control → Increase the certainty of the results → HAS check-list of methodological points of attention
- Alternatives: adaptive designs, seamless trials, pragmatic trials, etc...
- Emerging methods: artificial intelligence, in silico trials and disease modelling, etc...

Vanier A, Fernandez J, Kelley S, et al. Rapid access to innovative medicinal products while ensuring relevant health technology assessment. Position of the French National Authority for Health. *BMC Evidence-Based Medicine* Published Online First: 14 February 2023. doi: 10.1186/s12916-023-11209-1

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

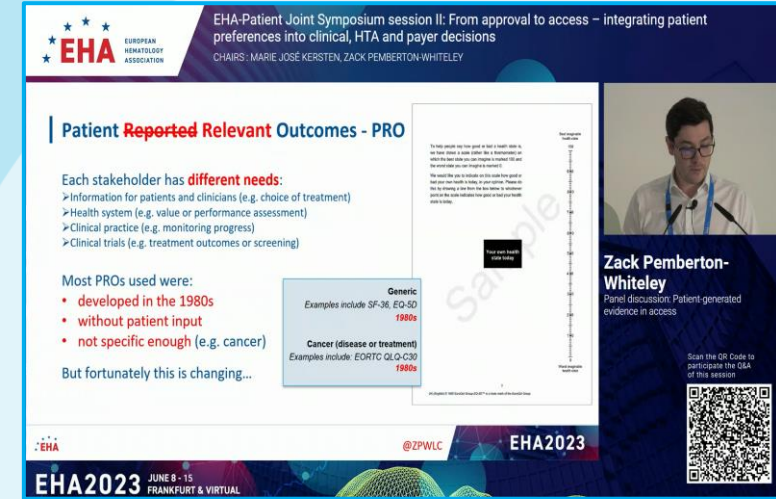
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EHA-Patient Joint Symposium session II: From approval to access – integrating patient preferences into clinical, HTA and payer decisions

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.



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Patient Reported Relevant Outcomes - PRO

Each stakeholder has **different needs**:

- Information for patients and clinicians (e.g. choice of treatment)
- Health system (e.g. value or performance assessment)
- Clinical practice (e.g. monitoring progress)
- Clinical trials (e.g. treatment outcomes or screening)

Most PROs used were:

- developed in the 1980s
- without patient input
- not specific enough (e.g. cancer)

But fortunately this is changing...

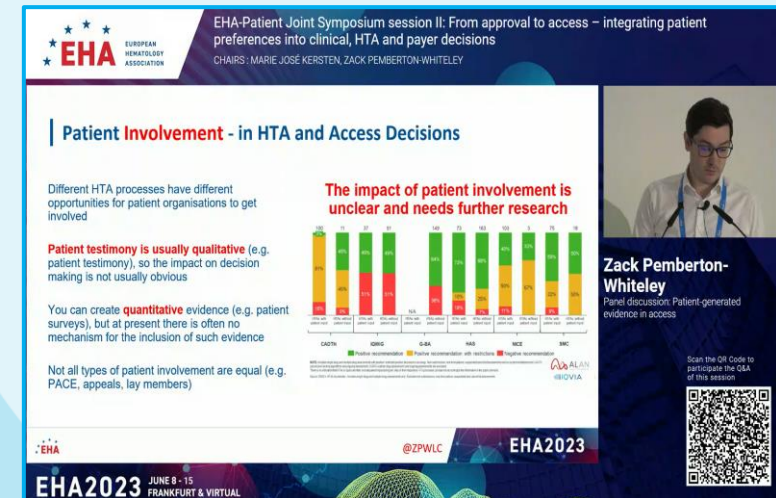
Generic
Examples include SF-36, EQ-5D
1980s

Cancer (disease or treatment)
Examples include EORTC QLQ-C30
1980s

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

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Patient Involvement - in HTA and Access Decisions

Different HTA processes have different opportunities for patient organisations to get involved

The impact of patient involvement is unclear and needs further research

Patient testimony is usually qualitative (e.g. patient testimony), so the impact on decision making is not usually obvious

You can create quantitative evidence (e.g. patient surveys), but at present there is often no mechanism for the inclusion of such evidence

Not all types of patient involvement are equal (e.g. PACE, appeals, lay members)

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

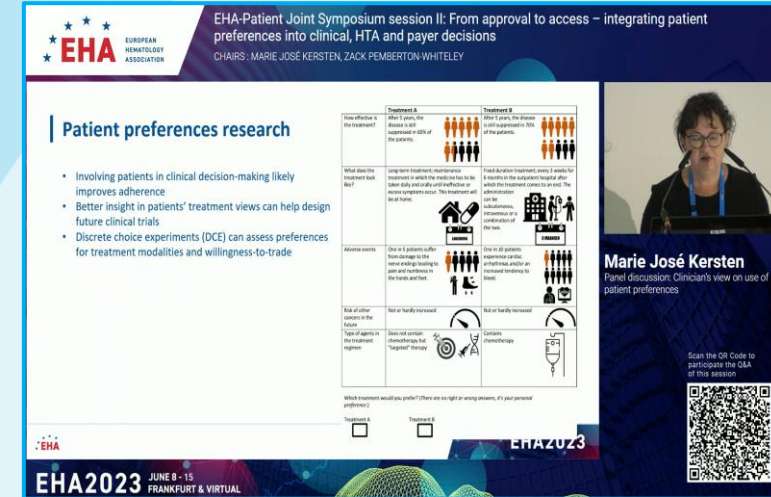
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Panel discussion: Clinician's view on use of patient preferences. Marie José Kersten

- 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.



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Patient preferences research

- Involving patients in clinical decision-making likely improves adherence
- Better insight in patients' treatment views can help design future clinical trials
- Discrete choice experiments (DCE) can assess preferences for treatment modalities and willingness-to-trade

How effective the treatment is	Treatment A	Treatment B
What does the treatment look like?	Long-term treatment, involves a lot of hospital visits, and may have side effects. The treatment is not very convenient.	Short-term treatment, involves a lot of hospital visits, and may have side effects. The treatment is not very convenient.
Access issues	This is a common effect. It is not possible to have the treatment at the same time as other treatments. It is not possible to have the treatment at the same time as other treatments.	This is a common effect. It is not possible to have the treatment at the same time as other treatments. It is not possible to have the treatment at the same time as other treatments.
Risk of other cancer in the future	Not or hardly increased	Not or hardly increased
Type of agent in the treatment regimen	Chemotherapy	Targeted therapy

Which treatment would you prefer? (There are no right or wrong answers, it's your personal preference)

Treatment A Treatment B

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WP2 Patient survey on CAR T-cell therapy launch!

- A survey for European adult patients (≥ 18 years) who received CAR T-cell therapy for a hematologic malignancy.
- This survey will help to understand patients' experience with CAR T-cell therapy, evaluate the impact of this treatment on quality of life and identify unmet needs.

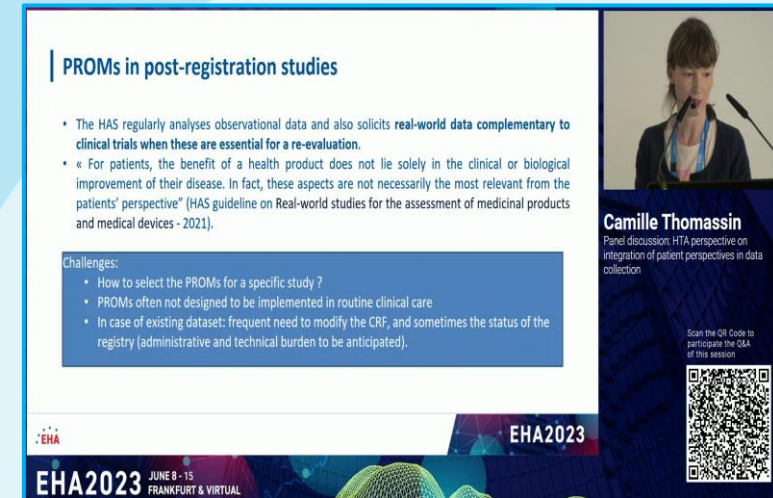
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EHA-Patient Joint Symposium session II: From approval to access – integrating patient preferences into clinical, HTA and payer decisions

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.



PROMs in post-registration studies


- The HAS regularly analyses observational data and also solicits **real-world data complementary to clinical trials when these are essential for a re-evaluation.**
- « For patients, the benefit of a health product does not lie solely in the clinical or biological improvement of their disease. In fact, these aspects are not necessarily the most relevant from the patients' perspective" (HAS guideline on Real-world studies for the assessment of medicinal products and medical devices - 2021).

Challenges:

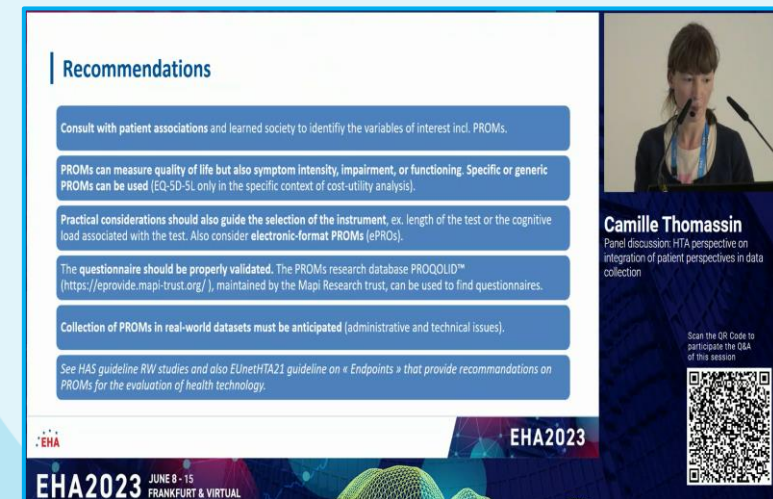
- How to select the PROMs for a specific study ?
- PROMs often not designed to be implemented in routine clinical care
- In case of existing dataset: frequent need to modify the CRF, and sometimes the status of the registry (administrative and technical burden to be anticipated).

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

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Recommendations

Consult with patient associations and learned society to identify the variables of interest incl. PROMs.

PROMs can measure quality of life but also symptom intensity, impairment, or functioning. Specific or generic PROMs can be used (EQ-5D-5L only in the specific context of cost-utility analysis).

Practical considerations should also guide the selection of the instrument, ex. length of the test or the cognitive load associated with the test. Also consider **electronic-format PROMs (ePROs)**.


The questionnaire should be properly validated. The PROMs research database PROQOLID™ (<https://eprovide.mapi-trust.org/>), maintained by the Mapi Research trust, can be used to find questionnaires.

Collection of PROMs in real-world datasets must be anticipated (administrative and technical issues).

See HAS guideline RW studies and also EUnetHTA21 guideline on « Endpoints » that provide recommendations on PROMs for the evaluation of health technology.

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

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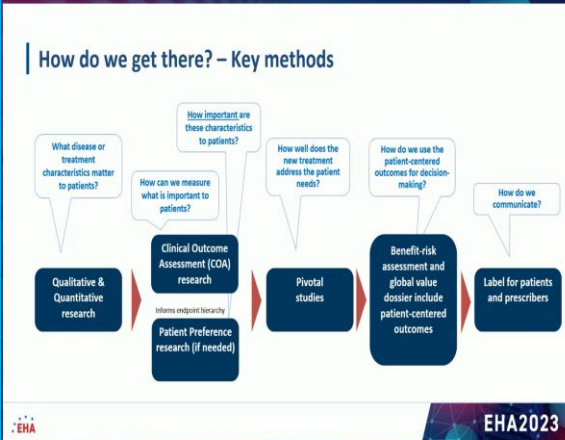


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EHA-Patient Joint Symposium session II: From approval to access – integrating patient preferences into clinical, HTA and payer decisions

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.



How do we get there? – Key methods

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?


Qualitative & Quantitative research → Clinical Outcome Assessment (COA) research → Pivotal studies → Benefit-risk assessment and global value dossier include patient-centered outcomes → Label for patients and prescribers

How important are these characteristics to patients? → Patient Preference research (if needed)

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

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Are there & are we aligned on standards?

Qualitative & Quantitative research: FDA's Patient-Focused Drug Development (PFDD) Guidances 1 & 2

Clinical Outcome Assessment (COA):

- FDA's Patient-Focused Drug Development (PFDD) Guidances 3 & 4
- EU netHTA-21-D4.4-practical-guideline-on-Endpoints-v1.0.pdf

Patient Preference Studies:

- IMI PREFER Recommendations incl Qualification Opinion from EMA: Recommendations - PREFER (imi-prefer.eu)
- qualification-opinion-imi-prefer_en.pdf (europa.eu)
- ISPOR Guidances
- FDA CDRH/CBER Guidance on Patient Preference Information
- NICE health technology evaluations: the manual

prefer. PATIENT PREFERENCES

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

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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 **C**ell regulatory **N**etwork **I**nferece & **C**lustering) to identify LSC GRNs (Gene Regulatory Network), identifying the Canonical Erythroid-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.

ERP are intrinsically IM sensitive vs myeloid progenitors suggesting a novel hypothesis...

CFU-Es are intrinsically TKI-S
CFU-GMs are relatively TKI-R

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Two NK cell gradients

'Hyperfunctional' adaptive

TKI resistance in CML

Adaptive NK

KLRC1 high NK

'HSPC-tolerant' KLRC1 (NKG2A) high

Monoclonal

CML cell

Inert NK cell

NK cell activation receptor

HLA

CONCLUSIONS I: Pre-Rx treatment factors + events acquired on-treatment ultimately determine overall response

Pre-treatment (deterministic?) + **On-treatment (stochastic?)**

TKI response heterogeneity in CML

Opens the door to pre-Rx prognostication & earlier management decisions

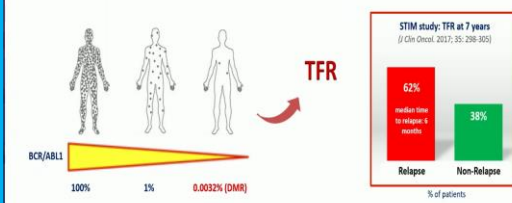
Education Session

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.

TFR: a new and significant goal of CML management



STIM study: TFR at 7 years
(J Clin Oncol 2017; 35: 298-305)

62% Relapse
38% Non-Relapse

% of patients

Discontinuation should be considered for patients in stable DMR after careful discussion in the shared decision-making process

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Massimo Breccia
How to improve eligibility and success of treatment free remission in CML?

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Prognostic features associated to successful TFR

Factor category	Factor	Prognostic value
Patient	Age, sex	Inconsistent results
Disease	Prognostic scores at diagnosis Type of transcript	Inconsistent results e14a2 higher probability
Treatment history and response to therapy	Depth of molecular response Halving time	Inconsistent results Higher TFR rate
	Type of TKI	Possible
	History of suboptimal response or resistance	Yes, decreased TFR probabilities
Immunological indicators	IFN pre-treatment	Yes (in EURO-SKI trial, excluded as prognostic due to possible bias)
	TKI treatment duration	Yes, imatinib better results after at least 5-6 years
Immunological indicators	Deep molecular response duration	Yes, imatinib better results if at least 3 years in MR ⁴
	Increased NK cell count Increased level of CD86	Several positive reports Only in the EURO-SKI

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Massimo Breccia
How to improve eligibility and success of treatment free remission in CML?

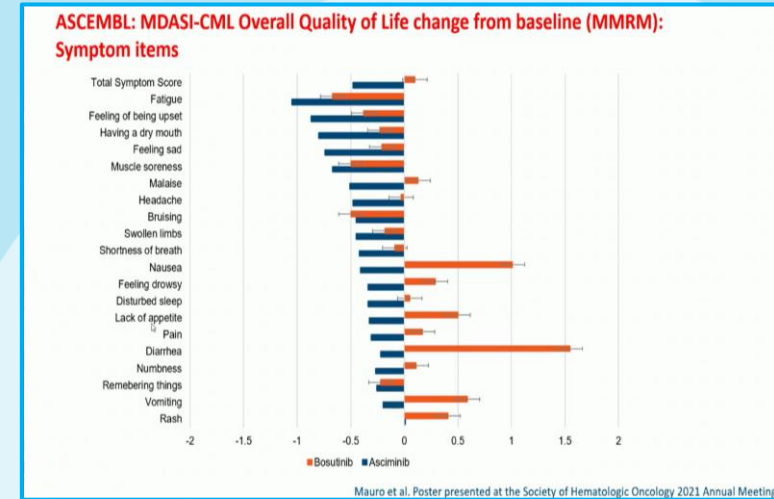
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Education Session

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.




Rough guide to 3L+ therapies

	Rotation of 2G-TKI	Ponatinib	Asciminib	Allo-SCT
Intolerance to ≥ 2 previous TKI	+		+++	
Resistance with BCR::ABL1 mutations	+	+	++	
T3151 mutation		++	(+, US only)	++
Resistance without BCR::ABL1 mutations	+	++	++	+
High risk ACAs		+		+++
Recurrent cytopenias	+		++	+++



Andreas Hochhaus
Late line treatment in chronic phase CML.

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New ATP competitors

- Olverembatinib (T3151 active)
- Vodobatinib, limited off-target activity
- ELVN-001 (T3151 active)

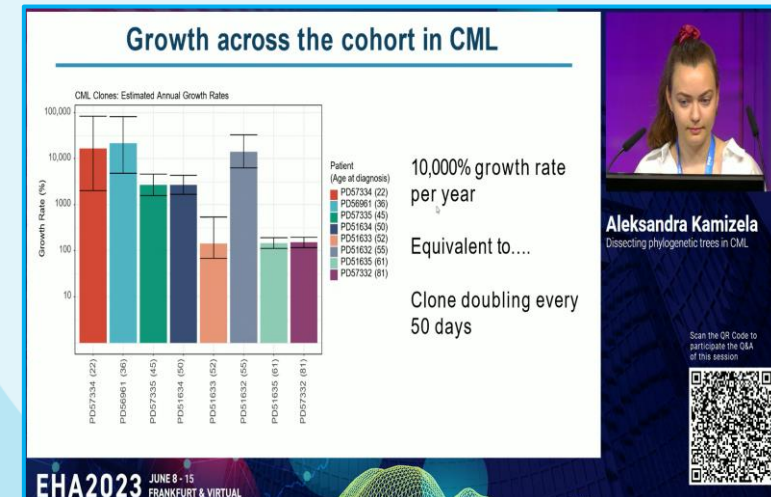
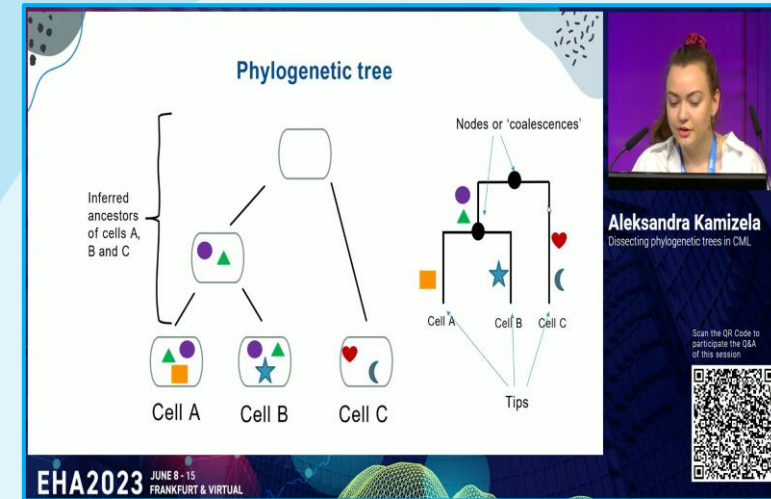
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Specialized Working Group Session

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.

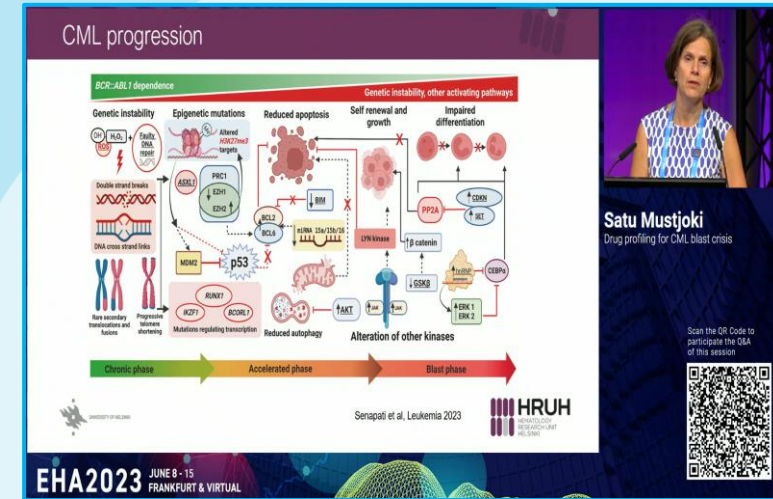


Specialized Working Group Session

ELN-EHA SWG for CML - CML: Modelling the future

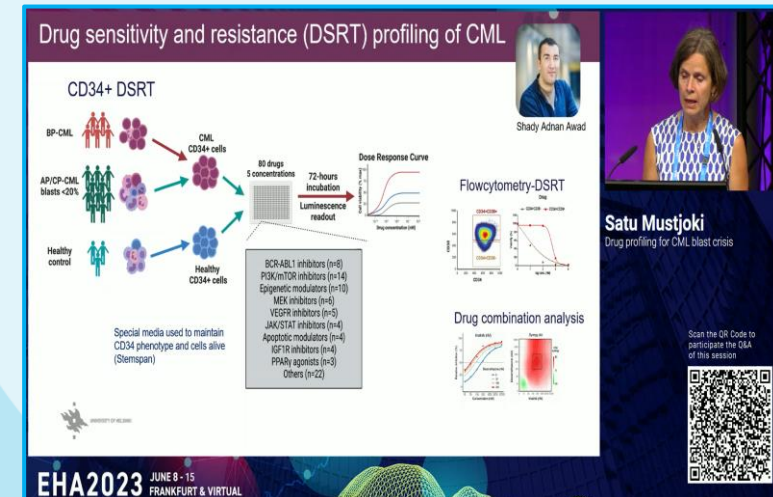
Drug profiling for CML blast crisis. Dr. Satu Mustjoki.

- 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.




Satu Mustjoki
Drug profiling for CML blast crisis

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Satu Mustjoki
Drug profiling for CML blast crisis

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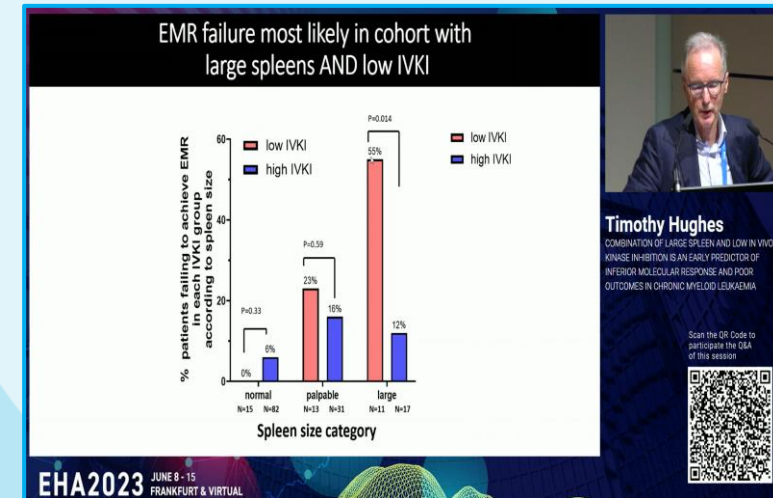
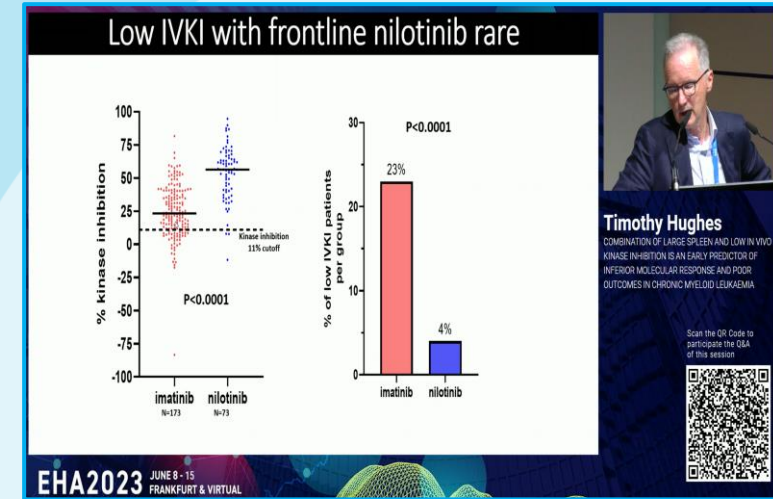
Oral Session

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.

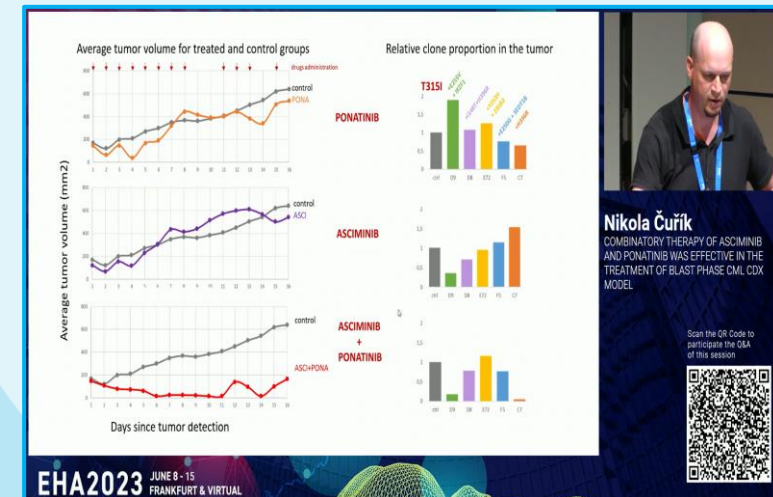
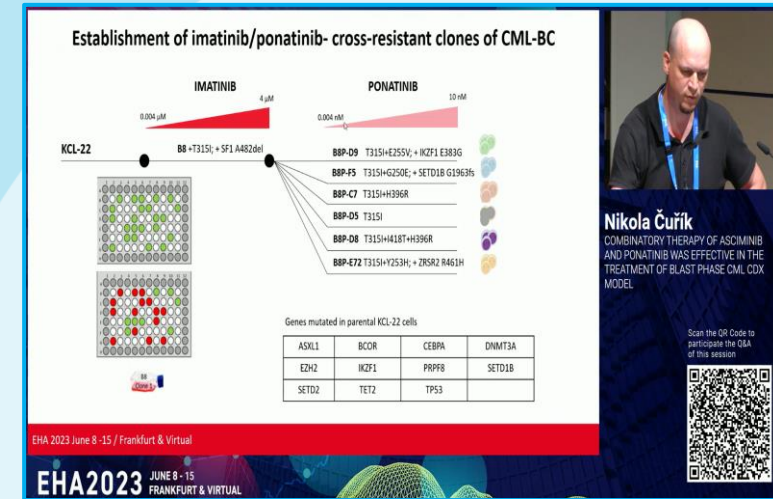
- Dr. Hughes started by asking whether the level of kinase inhibition of a TKI can be measured and if it is clinically relevant in CP-CML. Therefore, over the last 14 years they have measured it in patients included in the Australasian Leukaemia & Lymphoma Group (ALLG), identifying a cutoff of 11% and 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.

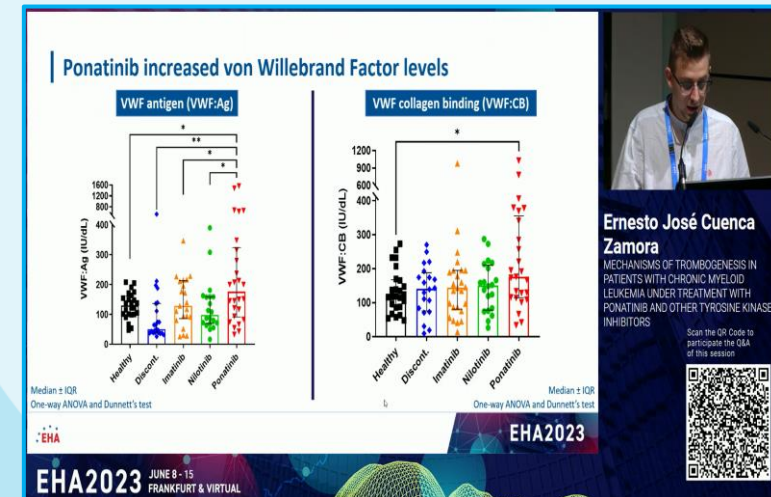
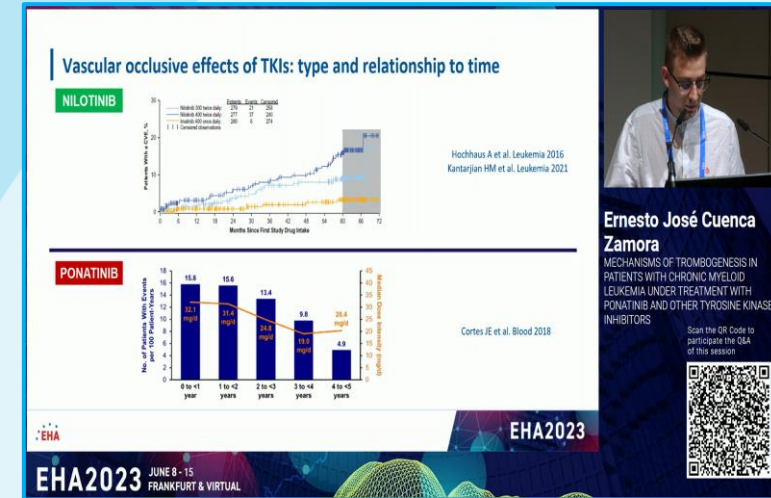
- Nikola spoke about the current need for new therapeutic options for patients with BC-CML. He mentioned that besides asciminib and ponatinib, they have used venetoclax in their research studies.
- In their work they have selected imatinib/ponatinib cross-resistant clones, with a different profile of 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 thrombogenesis 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.

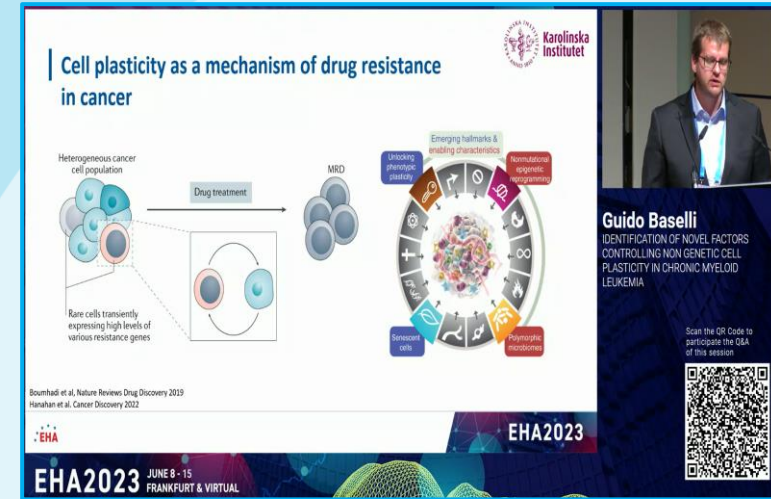


Oral Session

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.



Cell plasticity as a mechanism of drug resistance in cancer

Heterogeneous cancer cell population → Drug treatment → MRD

Rare cells transiently expressing high levels of various resistance genes

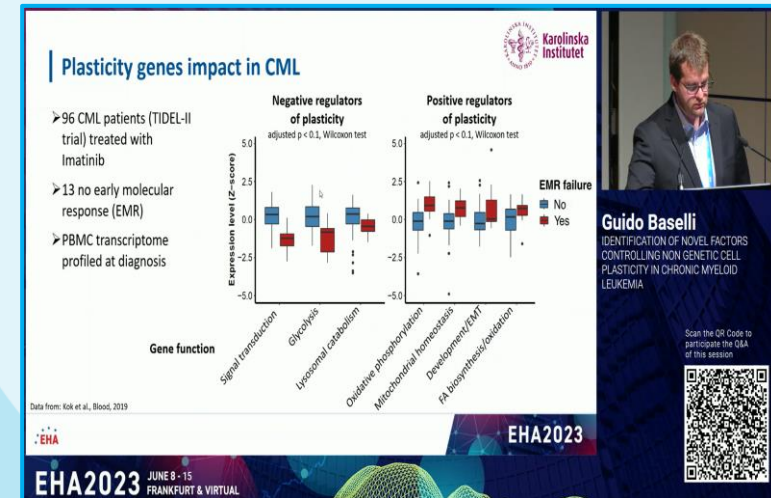
Emerging hallmarks & enabling characteristics

- Uniquing phenotypic plasticity
- Normative response programs
- Phenotypic heterogeneity
- Resistant cells

Guido Baselli
IDENTIFICATION OF NOVEL FACTORS CONTROLLING NON GENETIC CELL PLASTICITY IN CHRONIC MYELOID LEUKEMIA

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Plasticity genes impact in CML

Expression level (z-score)

Gene function

- Signal transduction
- Glycolysis
- Lysosomal catabolism
- Oxidative phosphorylation
- Mitochondrial homeostasis
- Developmental EMT
- FA biosynthesis/catabolism

EMR failure: No (blue), Yes (red)

► 96 CML patients (TIDEL-II trial) treated with Imatinib

► 13 no early molecular response (EMR)

► PBMC transcriptome profiled at diagnosis

Guido Baselli
IDENTIFICATION OF NOVEL FACTORS CONTROLLING NON GENETIC CELL PLASTICITY IN CHRONIC MYELOID LEUKEMIA

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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.



Challenges with integrating PROs into routine care


- **Administrative**
 - routine recording of treatment side effects not well documented
 - easily accessible within medical records
- **Technical**
 - understanding the clinical severity of particular symptoms
 - appropriate care options when outside the hospital environment
- **Workflow issues**
 - online patient reporting during and beyond cancer treatment
 - remotely report symptoms and side effects

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

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Recommendations

- Need to change the mindset
- Define objectives
- Use a single area specific instrument applicable to all patients
- Keep it simple (KIS)
- Focus on problem areas
- Appraise the options
- Future research: Ways PROs better incorporated in the routine care

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

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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.



Patients reported outcomes (PRO) measures allow patients to directly report the severity and frequency of their symptoms

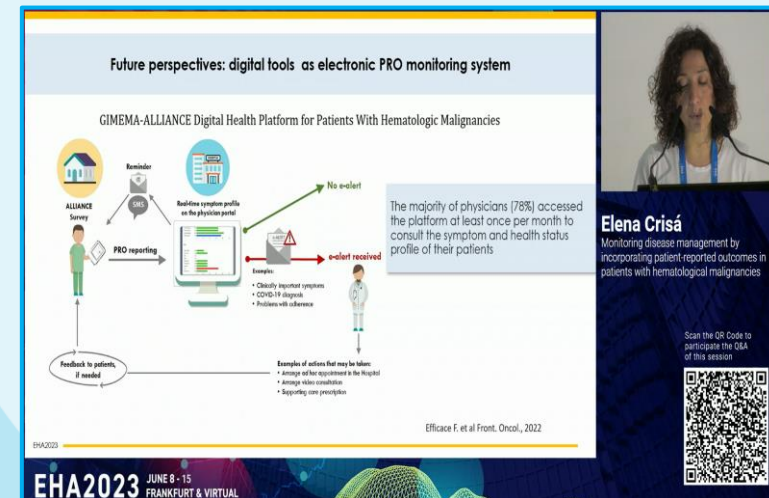

PRO instruments, such as questionnaires or surveys, capture various domains

- cognitive function
- physical functioning
- emotional well-being
- social interactions

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

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Future perspectives: digital tools as electronic PRO monitoring system

GIMEMA-ALLIANCE Digital Health Platform for Patients With Hematologic Malignancies

The majority of physicians (78%) accessed the platform at least once per month to consult the symptom and health status profile of their patients


Examples of actions that may be taken:

- Arrange off-hour appointment in the Hospital
- Arrange video consultation
- Supporting care prescription

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

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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.


It is not just about clinical efficacy: Different patients want different things

- Being part of decision-making?
 - Ownership vs "fix it for me"?
- Maximum disease control and deep response?
 - Or fewer side-effects / better QoL?
- Ability to work?
- Ability to have a social life?
- Impact on the family?
 - Family planning?
 - Reduce financial impact (travel, patient / caregiver ability to work)



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

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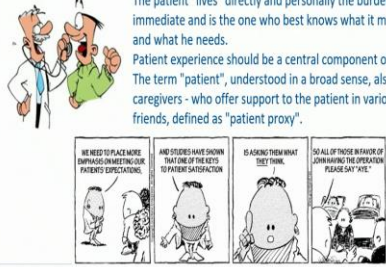
PRO = "patient experience"

The outcome is generally understood as the impact of a health problem, of a specific health intervention, of a specific health service of the person, in its various components (physical, mental, social).

The patient "lives" directly and personally the burden of the cures in the immediate and is the one who best knows what it means living with a disease and what he needs.


Patient experience should be a central component of any "care service"

The term "patient", understood in a broad sense, also includes the figures - caregivers - who offer support to the patient in various forms, such as family and friends, defined as "patient proxy".



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

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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 **European Stop Kinase Inhibitor (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, MR⁴ 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.


MMR at 36 months, univariate models

Univariate Models	EURO-SKI				STIM2			
	n	OR	95% CI	p-value	n	OR	95% CI	p-value
Duration of TKI treatment (years)	510	1.124	1.046-1.207	0.0014	184	1.192	1.045-1.360	0.0087
DMR duration under TKI (years)	510	1.102	1.022-1.187	0.0110	184	1.211	1.041-1.410	0.0134
Blasts in peripheral blood (%)	413	0.889	0.809-0.976	0.0137	175	0.760	0.593-0.972	0.0291
Transcript: e14a(+e13a2) vs. e13a2	392	2.064	1.243-3.427	0.0051	158	2.378	1.139-4.965	0.0211

- **Duration of treatment** and of **DMR under TKI** confirmed similar strong effects; **Blasts** confirmed
- **Transcript type** confirmed


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Markus Pfirrmann
PROGNOSTIC FACTORS FOR 3-YEAR MAJOR MOLECULAR RESPONSE MAINTENANCE IN CHRONIC MYELOID LEUKAEMIA PATIENTS IN THE EUROPEAN STOP KINASE INHIBITORS (EURO-SKI) TRIAL

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MMR at 36 months, multiple models

Multiple Models	EURO-SKI				STIM2			
	n	OR	95% CI	p-value	n	OR	95% CI	p-value
Model a								
Duration of TKI treatment (years)	413	1.127	1.038-1.224	0.0043	175	1.216	1.059-1.396	0.0057
Blasts in peripheral blood (%)	413	0.882	0.800-0.972	0.0116	175	0.767	0.592-0.994	0.0447
Model b								
Duration of TKI treatment (years)	392	1.106	1.019-1.200	0.0163	158	1.270	1.092-1.478	0.0019
Transcript: e14a(+e13a2) vs. e13a2	392	2.090	1.254-3.484	0.0047	158	3.089	1.398-6.826	0.0053
Model c								
DMR duration under TKI (years)	413	1.119	1.022-1.225	0.0149	175	1.289	1.083-1.533	0.0042
Time to DMR under TKI (years)	413	1.142	1.016-1.284	0.0261	175	1.145	0.966-1.357	0.1176
Blasts in peripheral blood (%)	413	0.881	0.800-0.972	0.0112	175	0.778	0.602-1.006	0.0558

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Markus Pfirrmann
PROGNOSTIC FACTORS FOR 3-YEAR MAJOR MOLECULAR RESPONSE MAINTENANCE IN CHRONIC MYELOID LEUKAEMIA PATIENTS IN THE EUROPEAN STOP KINASE INHIBITORS (EURO-SKI) TRIAL

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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 MR⁴ 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 MR⁴ 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.

Molecular response



	MMR (%)	MR ² (%)	MR ^{3.5} (%)	MR ³ (%)	MR ⁴ (%)	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

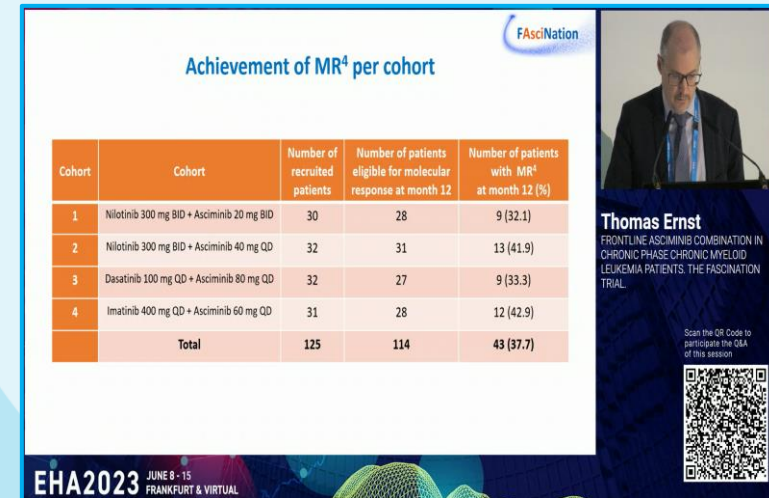
Thomas Ernst
FRONTLINE ASCIMINIB COMBINATION IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA PATIENTS. THE FASCINATION TRIAL.

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Achievement of MR⁴ per cohort



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)

Thomas Ernst
FRONTLINE ASCIMINIB COMBINATION IN CHRONIC PHASE CHRONIC MYELOID LEUKEMIA PATIENTS. THE FASCINATION TRIAL.

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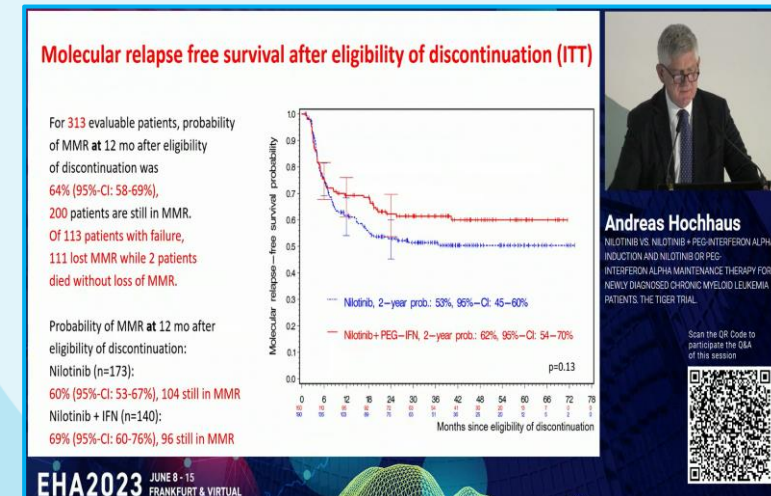
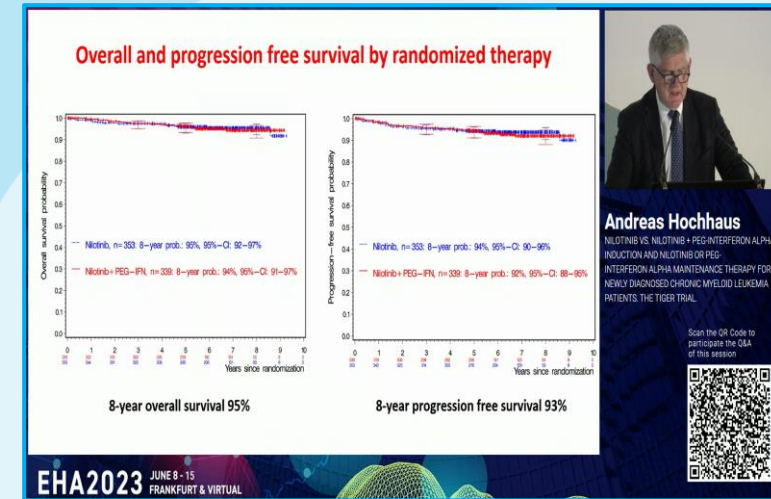
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Oral Session

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 TKI plus Interferon in **Germany** (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.

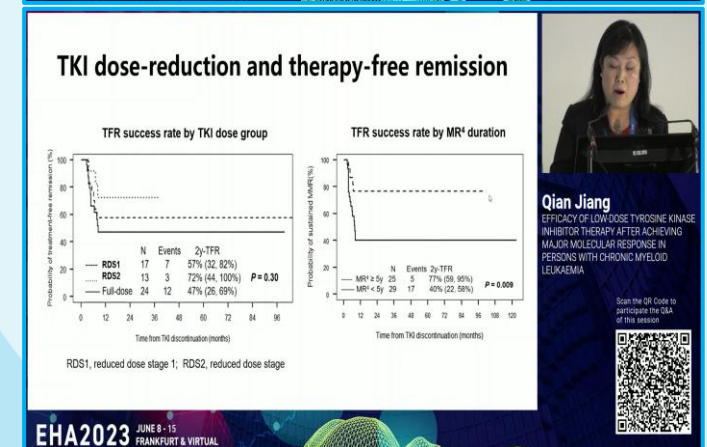
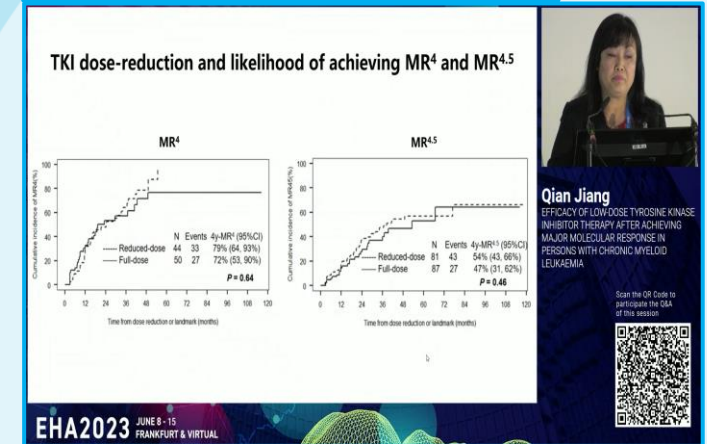
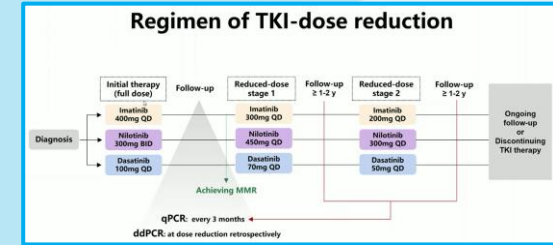


Oral Session

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 MR⁴ and MR^{4.5}, or its maintenance, as well as did not impair the success of TFR. As in other studies, patients with longer MR⁴ 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-variables like high WBC counts and low haemoglobin were also relevant.
- TKI-dose reduction had an improvement in the adverse events reported.

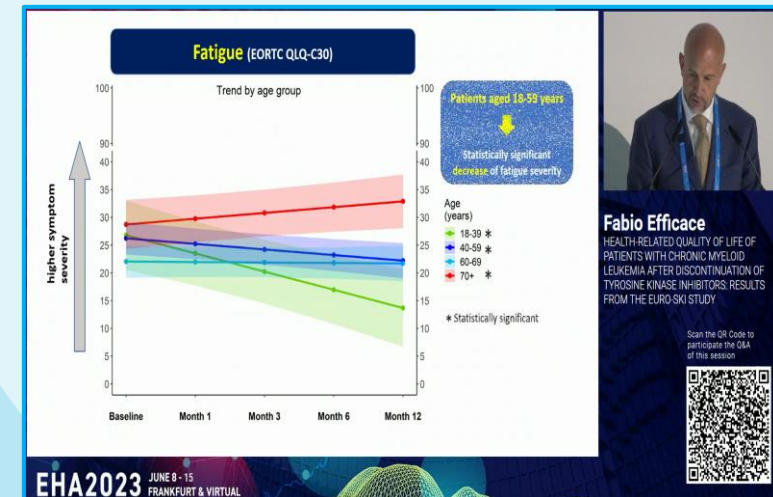
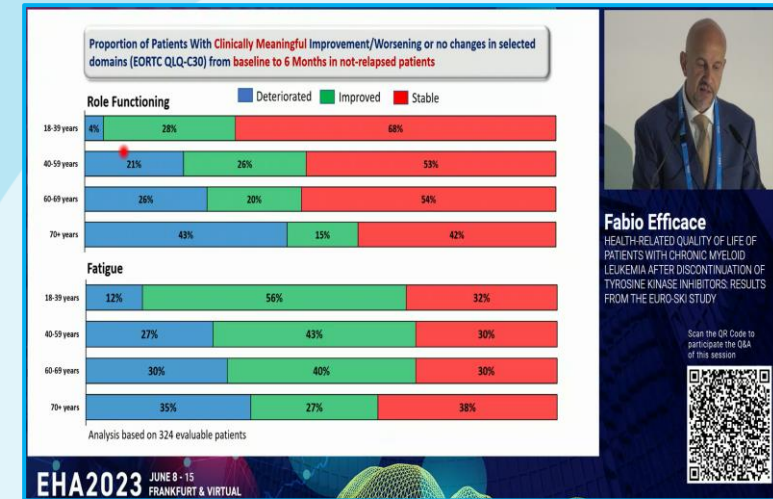


Oral Session

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 MR⁴ 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.



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 Nier¹; Zack Pemberton-Whiteley¹; Jan Geissler¹;
Anne-Pierre Pickaert¹; Sophie Wintrich¹; Cheryl Petruk¹;
Esther Nathalie Oliva²; Tatyana Ionova²; Sam Salek²

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.

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).

EHA-1821 / P1688 - EHA2023 Hybrid Congress

ALAN
Acute Leukemia Advocates Network

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
- $\leq 1\%$ 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. 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.

Background

- Patients with imatinib-resistant chronic myeloid leukaemia (CP-CML), harboring the BCR-ABL1 T315I mutation respond inadequately to first- and second-generation BCR-ABL1 tyrosine kinase inhibitors (TKIs), leading to poor clinical outcomes.
- Ponatinib is the only BCR-ABL1 inhibitor TKI currently approved to potently inhibit all known and emerging resistance-mutation variants of BCR-ABL1, including T315I.
- OPTIC (ponatinib vs. imatinib) in CP-CML, NCT01632222 is a phase 2 trial evaluating the efficacy and safety of ponatinib using a novel, response-based dose-adjustment strategy in patients with CP-CML, whose disease is resistant to ≥ 2 TKIs or who harbor T315I.
- Here we present a post hoc analysis of patient response by T315I mutation status from the OPTIC trial 3-year data cut.

Methods

Figure 1: OPTIC study design: An ongoing, multicenter, randomized phase 2 trial

Results

Figure 2: 51% BCR-ABL1 response rate at 3 months by mutation status*

Figure 3: 51% BCR-ABL1 response rate at 36 months by mutation status*

Figure 4: PFS for patients with no mutations, T315I mutation, and mutation other than T315I by dose cohort

Figure 5: OS for patients with no mutations, T315I mutation, and mutation other than T315I by dose cohort

Figure 6: Most common grade ≥ 3 TEAEs

Table 1: Demographics and baseline disease characteristics

Characteristic	Subcategory	45mg (n=101)	30mg (n=101)	15mg (n=101)
Age, median (range)		61 (21-81)	61 (21-81)	61 (21-81)
ECOG PS score 0 or 1, n (%)		81 (80)	81 (80)	81 (80)
Time since diagnosis, median (range)		5.2 (0-16)	5.1 (0-16)	5.1 (0-16)
Patients with CV risk factors, n (%)		38 (37)	38 (37)	38 (37)
	Arterial hypertension	28 (28)	27 (26)	27 (26)
	Diabetes mellitus	2 (2)	2 (2)	2 (2)
	Hypertension	14 (14)	14 (14)	14 (14)
	Other	1 (1)	1 (1)	1 (1)
Patients with ≥ 2 CV risk factors, n (%)		1 (1)	1 (1)	1 (1)
Median prior TKI for resistance, n (%)		33	34 (33)	34 (33)
BCR-ABL1 mutation, n (%)		84 (83)	84 (83)	84 (83)
	No mutation	17 (17)	17 (17)	17 (17)
	T315I mutation	11 (11)	11 (11)	11 (11)
	Other mutation	56 (56)	56 (56)	56 (56)
	Other or none	61 (61)	60 (59)	60 (59)
Best response to last prior TKI, n (%)		43 (43)	43 (43)	43 (43)
	$\leq 1\%$ BCR-ABL1*	2 (2)	7 (7)	7 (7)

*Complete remission (CR) or partial remission (PR) according to International Working Group (IWG) criteria.

Objective

To assess the results from the OPTIC trial at the 3-year data cutoff date by mutation status

Results

- By 36 months, median PFS in the overall population was 72.5, 67.1, and 69.7 months in the 45-mg, 30-mg, and 15-mg cohorts, respectively.
- Median PFS was not reached in any dosing cohort for patients with no BCR-ABL1 mutation (Figure 4).
- In patients with the T315I mutation, median PFS was not reached in the 45-mg cohort and was 23.4 months and 65.6 months in the 30-mg and 15-mg cohorts, respectively.
- Median PFS was not reached in any dosing cohort for patients with a mutation other than T315I.

Key takeaways

At the 3-year data cutoff, 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.

Table 2: Dose re-escalation after loss of response*

Characteristic	T315I					
	45 mg (n=101)	30 mg (n=101)	15 mg (n=101)	45 mg (n=101)	30 mg (n=101)	15 mg (n=101)
Attained $\leq 1\%$ BCR-ABL1* at any time, n (%)	38 (38)	27 (27)	16 (16)	8 (8)	9 (9)	6 (6)
Lost $\leq 1\%$ BCR-ABL1* at any time, n (%)	4 (4)	5 (5)	3 (3)	2 (2)	0	0
Dose re-escalated after loss of response, n (%)	3 (3)	3 (3)	2 (2)	2 (2)	0	0
Re-gained $\leq 1\%$ BCR-ABL1*						
Yes, n (%)	2 (2)	2 (2)	0 (0)	1 (1)	1 (1)	0
No, n (%)	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)	0

*Patients who lost response, most re-achieved $\leq 1\%$ BCR-ABL1 after dose re-escalation.

References Cortes J, et al. *N Engl J Med*. 2016;374:1079-1090. **Acknowledgements** This study was supported by Novartis. **Disclosures** Cortes J, et al. *N Engl J Med*. 2016;374:1079-1090. **Presented at the European Hematology Association 2023 Congress, June 8-11, Frankfurt, Germany**

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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.

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

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INTRODUCTION

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the presence of the BCR-ABL oncoprotein, which has deregulated tyrosine kinase activity. Despite a high response rate to tyrosine kinase inhibitors, such as imatinib (IMA), some patients develop resistance to treatment. Several mechanisms are involved in IMA resistance and alternative signaling pathways are activated by the BCR-ABL oncoprotein, including the PI3K/AKT/mTOR pathway, increasing cell survival and resistance to apoptosis. Thus, the identification of new therapeutic targets that enable new alternatives to the treatment of CML-resistant patients is extremely important.

RESULTS

Buparlisib Monotherapy

Buparlisib Daily Administration

Buparlisib combination with Imatinib

Figure 1. Buparlisib (BKM-120) dose response curves in chronic myeloid leukemia cell lines sensitive (K-562) and resistant (K-562 RC and K-562 RD) to imatinib. Buparlisib induced metabolic activity in a time- and dose-dependent manner, with IC50 after 72h of 1.13 μM in K-562 cells, 1.2 μM in K-562 RC cells, and 1.0 μM in K-562 RD (Figure 1A). Fractionated daily administration of Buparlisib (Figure 1B) shows to be better than single administration, only in the imatinib-resistant cell lines (K-562 RC and K-562 RD). *** p<0.01 comparing to the control; S p<0.05, SS p<0.01, SSS p<0.001 comparing to CH; EEE p<0.001 comparing to the single dose.

Table 1. Cytostatic effect of Buparlisib (BKM-120) in chronic myeloid leukemia cell lines sensitive (K-562) and resistant (K-562 RC and K-562 RD) to imatinib.

	Sub-G ₀	G ₀ /G ₁	S	G ₂ /M
Control	1.0 ± 0.0	35.7 ± 0.9	55.7 ± 0.3	6.0 ± 1.2
K-562 1 μM BKM-120	3.7 ± 0.7	34.7 ± 0.7	35.7 ± 8.9***	29.7 ± 2.9***
K-562 3 μM BKM-120	8.0 ± 1.5**	31.0 ± 1.0**	8.7 ± 0.9***	80.3 ± 1.8***
Control	0.7 ± 0.3	58.3 ± 0.3	30.3 ± 0.3	10.0 ± 0.0
K-562 RC 1 μM BKM-120	1.0 ± 0.6	55.8 ± 2.3	30.7 ± 0.9	18.0 ± 1.5*
K-562 RC 3 μM BKM-120	19.3 ± 1.1***	46.3 ± 2.2**	27.0 ± 1.2	30.7 ± 2.1***
Control	1.0 ± 0.0	59.3 ± 1.8	38.3 ± 0.3	10.0 ± 0.6
K-562 RD 1 μM BKM-120	0.7 ± 0.7	54.3 ± 2.2	29.0 ± 0.6**	16.0 ± 1.6**
K-562 RD 3 μM BKM-120	29.0 ± 3.8***	28.7 ± 0.9***	36.3 ± 1.5	54.3 ± 0.3***

Buparlisib (BKM-120) induced a cytostatic effect by cell cycle arrest in G₀/G₁ phase. Cell cycle evaluation was performed by FC using propidium iodide/DAPI. Results represent the mean ± SEM of at least 3 independent experiments and are expressed as percentage of cells in each population. * p<0.05; ** p<0.01 and *** p<0.001 comparing to the control.

OBJECTIVES

This work aimed to evaluate the therapeutic potential of **Buparlisib (BKM-120)**, a PI3K inhibitor, in *in vitro* models of **CML sensitive and resistant to Imatinib**.

METHODS

The study was carried out in an IMA-sensitive CML cell line, K-562 cells, and two IMA-resistant cell lines, the K-562 RC and K-562 RD cells. Cell lines were incubated in the absence and presence of Buparlisib in a single dose and in a daily fractionated administration. Additionally, the combined effect of the PI3K inhibitor, buparlisib, with Imatinib was also evaluated in the three models. The metabolic activity was evaluated by the resazurin assay. Cell death was evaluated by flow cytometry (FC) using annexin V and 7-AAD staining and by cell morphology using light microscopy (Giemsa staining). The cell cycle was analyzed by FC using propidium iodide (PI)/RNase. The results were statistically analyzed and were considered significant when p<0.05.

CONCLUSION

Our results suggest that Buparlisib (BKM-120) could be a new therapeutic strategy in the treatment of CML, with the most promising results in the case of resistance to imatinib.

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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 were 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.

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

INTRODUCTION

Primary care for patients (patients) with chronic myeloid leukemia (CML) in Germany is mainly provided by decentralized oncology practices. In contrast, clinical trials for new substances are usually carried out in specialized centers and university clinics, resulting in a lack of data on current treatment practice outside these centers.

OBJECTIVE(S)

The aim of this study was to assess clinical routine treatment practice in patients with CML in real-world setting of private oncology practices in Germany.

METHOD(S)

Patients with a confirmed diagnosis of CML in 2013 or later were eligible for inclusion. European Leukemia Net (ELN) recommendations for CML 2013 definitions were used for diagnosis and response assessment. Anonymized and aggregated data per site was used.

RESULT(S)

A total of 819 patients (mean age 58.5 years, range 15-91) were reviewed (figure 1,2, 3). CML specific risk scores at diagnosis were available for 343 (41.8%, EUTOS score in 86.0% of these) patients (table 1). 61.9% (n=503) patients had data available on spleen size and the calculated European long-term survival scores (ELTS) were low, intermediate, high in 53.0, 32.2 and 14.9% of patients, respectively. At diagnosis, 84.2% (n=690) and 9.4% (n=77) patients were in chronic or accelerated phase, 0.7% (n=6) had a blast crisis and data was missing in 5.6% (n=46) patients. Molecular Monitoring was provided EUTOS certified laboratories for 87.7% (n=718). A typical BCR::ABL1 transcript was detected in 86.6% (n=709). Cytogenetics at diagnosis were obtained in 71.2% (n=588) of patients. Mean time from initial diagnosis to treatment was 1.2 months (m, range 0-92m). Molecular response was assessed after 2.8, 6.0, 9.4 and 12.9 m (mean) after start of treatment. 11.1% (69/623) of patients with available qPCR data did not achieve early molecular response (BCR::ABL1 IS $\leq 10\%$ at 3 months, figure 4). At 18 m, 83.7% (328/392) of patients with available PCR data had at least a major molecular response. Treatment had been changed to 2L in 41.5% (n=340) of patients (288: 2nd TKI, 2: HSCT, 50: off treatment) after a mean of 21.0 m (figure 1, 8). 56 patients had a mutation analysis of the ABL1-kinase domain at the time of treatment change (figure 5). The most common reasons for 2L treatment were side effects (43.4%), followed by insufficient response (31.4%), suboptimal response or failure according to ELN 2013, figure 6). Of the 288 patients switching to 2L treatment, 106 went on to 3L treatment (after a mean of 17.6 m, range 0-97 m) and 17 patients did not receive further treatment 2 patients entered a clinical trial (figure 1). Molecular response assessments in 2L were done after 2.3, 5.3, 8.3, and 11.7 m (mean). 31.1% (n=33/106) of all patients switched to 4L treatment and 92.8% (n=39/42) of patients still on 3L treatment achieved BCR::ABL1 IS $\leq 1\%$ at 12 m (figure 7). 6 patients discontinued 3L and treatment was switched (HSCT:4, TKI: 2) after a mean time of 14.5 m (range 0.3-80.5 m, figure 8). Reasons for change were side effects in 42.4%, insufficient response in 33.3%, and other reasons in 24.2% of patients. 8 patients were referred to a specialized center.

Table 1: Patient Characteristics

Number of patients	819
Sex, n (%)	female 388 (48.6) / male 421 (51.4)
Age at diagnosis, range	58.5 (15-91)
Spleen palpation done at dx, n (%)	yes 503 (61.4) / not done 316 (38.6)
Risk score at dx calculated at treatment center, n (%)	none or missing 476 (58.2) / EUTOS low (0-10) / ELTS 29 (3.5) / other 3 (0.3)
Calculated scores by investigator, n (%)	EUTOS: low 422 (50.3) / high 48 (5.9%) / missing 350 (43.8) / ELTS: low 242 (29.6) / intermediate 147 (17.9) / high 48 (5.9) / missing 362 (44.2)
ELN2013 disease phase, n (%)	chronic phase 690 (84.2), accelerated phase 77 (9.4), blast crisis 6 (0.7), missing 46 (5.6)
Cytogenetics at dx, n (%)	yes 588 (71.8) / no 238 (29.2) / missing 13 (1.6)
HSCT/previously post-treatment, n (%)	yes 276 (33.8) / no 529 (64.6) / missing 15 (1.8)

Figure 3: Patients by center and treatment line

Figure 6: Reasons for switching treatment by line

Figure 4: Overview of patient distribution

Figure 5: ABL1-Kinase domain mutation analysis

Figure 7: Molecular response to 3rd line & later treatment

Figure 8: Mean time to treatment change

Figure 2: Total number of CML patients treated and number of documented patients in the participating centers

CONCLUSIONS

Patients with CML in Germany are mainly treated in private practices. CML specific risk scores are calculated at diagnosis in only about 60% of patients, whereas cytogenetic analysis at initial diagnosis and molecular monitoring in a EUTOS certified lab were performed in most patients. About 1/3 of all patients received hydroxyurea pre-treatment before initiation of 1st line therapy. Regardless of good molecular responses, 35.2% of patients received a 2L treatment, mainly due to adverse events. In contrast to ELN recommendations, cytogenetic or mutational analysis was performed only in a minority of patients with treatment failure.

ACKNOWLEDGEMENTS & CONTACT INFORMATION

We thank all centers and patients for participating in this survey!
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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 had the longest duration of treatment, curiously IFN has an immunoregulatory role on CML microenvironment.

USE OF RT-QPCR VERSUS DIGITAL DROPLET PCR AND EVALUATION OF CD26+ CELLS IN LONG TFR PATIENTS WITH CHRONIC MYELOID LEUKEMIA

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INTRODUCTION

Chronic myeloid leukemia represents a unique hematological condition as tyrosine kinase inhibitors (TKIs) have allowed long term survival. Standardized molecular response and deep molecular response measured through RT-qPCR paved the path to therapy discontinuation. Literature proposes digital PCR to evaluate minimal residual disease when interrupting treatment and during therapy discontinuation as a method with higher sensitivity. Several studies have analyzed the presence of CD26+ stem cells in patients with CML at diagnosis, during treatment and in the treatment-free remission phase (TFR). To date CD26+ cells appear to be an important parameter to evaluate MRD and achievement of curative therapy.

OBJECTIVES

This study aims to:

- compare the sensitivity of RT-qPCR and ddPCR in measuring molecular MRD;
- asses a possible correlation between CD26+ cells and RT-qPCR and ddPCR;
- compare the length of treatment according to first line therapy, in a cohort of patients in long TFR.

METHODS

We analyzed the comparative results of RT-qPCR and ddPCR of peripheral blood samples of 12 CML patients from our institution in long term TFR and sustained deep molecular response from January 2022 to May 2022. Samples were divided according to first line therapy and subsequent lines: nine patients were treated with imatinib (six until discontinuation, two switched to Nilotinib and one to Dasatinib); three with IFN (one until discontinuation, two shifted to imatinib).

□ BCR-ABL1 p210 was quantified by RT-qPCR and ddPCR in Lab of Oncological Hematology, CEINGE, Naples.

□ CD34+ CD38- CD26+ cell analysis was conducted in the Hematology Unit of Siena using a four-color staining protocol acquiring at least 1.0 × 10⁶ cells.

Data presented as means, standard deviations (SD), frequencies and percentages, were normally distributed according to Shapiro-Wilk test. RT-qPCR and ddPCR scores were compared with paired sample t-Test. Anova was used to assess the effect of first line medication on the length of treatment.

Eta square (η²) measure of effect size for analysis of variance (ANOVA) models was used for significant results. Pearson correlation was run to ascertain the variables significantly associated with levels of CD26+ cells in peripheral blood samples. Analysis was performed with Jasp software (0.16.1)

RESULTS

No significant differences emerged between RT-qPCR and ddPCR according to t-Test (t=-0.531; p=0.606). An inverse significant correlation emerged between the length of treatment and CD26 levels (r²=-.724, p=0.008). Finally, according to Anova, the effect of first line of therapy had a significant effect on the length of treatment (F=6.424; p=0.03; η²=0.391).

Figure 1. Paired sample t-test RT-qPCR and ddPCR

Figure 2. Length of treatment - first line

Variable	securum	age diag	length treat	n lines	CD26%	q-PCR	digital PCR
1 securum	Patients n = 12	---	---	---	---	---	---
2 age diag	Patients n = 12	---	---	---	---	---	---
3 length treat	Patients n = 12	---	---	---	---	---	---
4 n lines	Patients n = 12	---	---	---	---	---	---
5 CD26%	Patients n = 12	---	---	---	---	---	---
6 q-PCR	Patients n = 12	---	---	---	---	---	---
7 digital PCR	Patients n = 12	---	---	---	---	---	---

Table 3. Pearson's correlation

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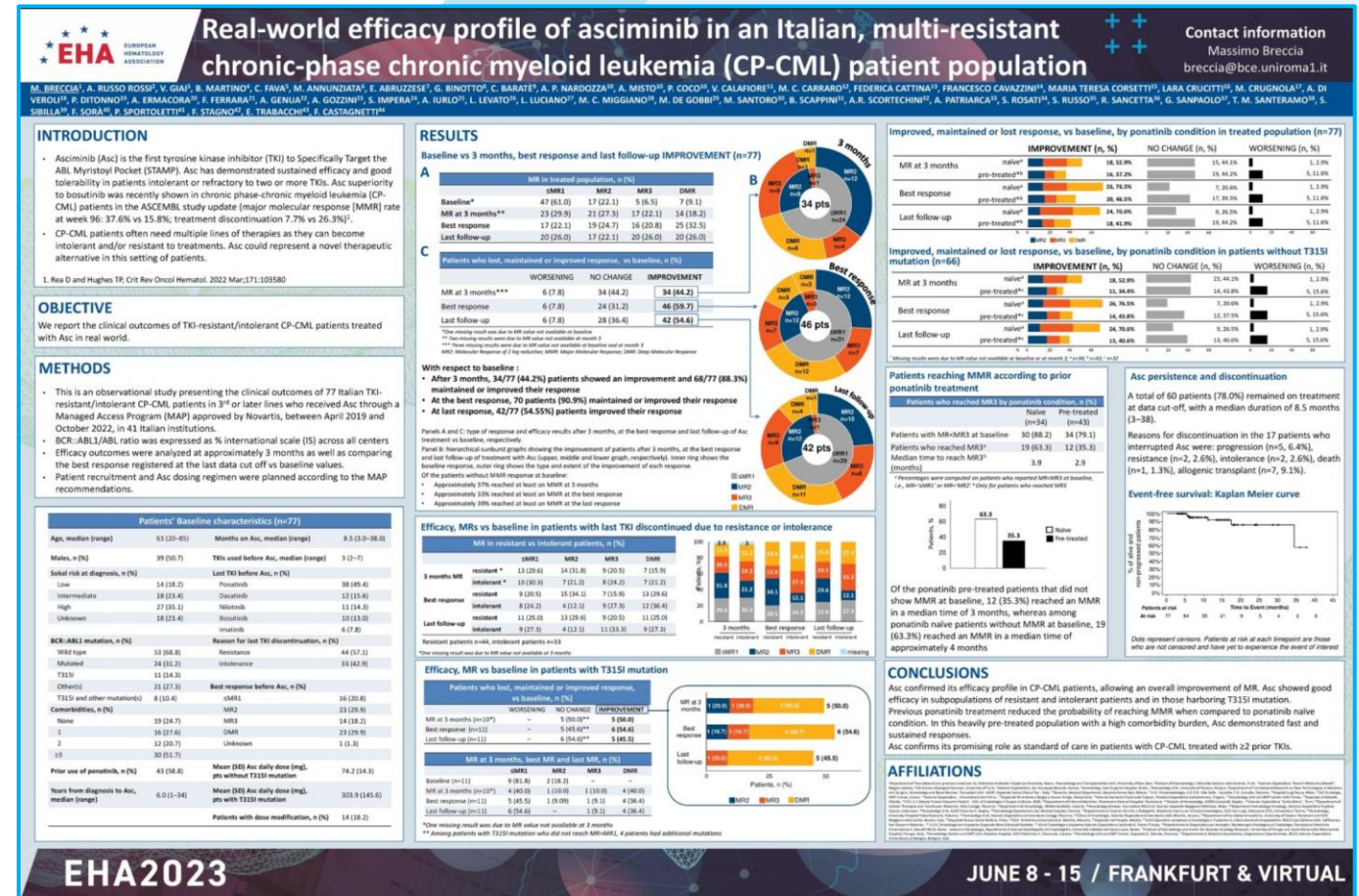
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Poster Presentations

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.

P-1689. Real-World Evidence of Using Telemedicine To Capture e-PROM Improves Quality Of Life Assessment, Healthcare Resources Management And Overall Survival In Patients With Lymphoma Receiving Intravenous Therapy.

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INTRODUCTION

PROMs are reports of health status or quality of life (QoL) directly provided by patients (pts), routinely captured within clinical trials. Integrating PROMs in daily healthcare of pts with cancer has the potential to improve their care delivery and outcomes.

"E-Res Salud" is a value-based healthcare program implemented in a 4 public hospitals network in Madrid which aims to improve process management and patient journey giving voice to pts by collecting individual and aggregated data.

OBJECTIVES

The primary objective was to compare the adverse events (AEs) profile reported by physicians in the electronic medical records (EMR) and those reported by patients through PRO-CTCAE™ questionnaire.

Secondary objectives were to analyse the impact of a PROM program in the reduction of visits to Emergencies and unscheduled hospitalizations as well as in efficacy outcomes such as completion of planned treatment or overall survival (OS).

METHODS

- Any type of lymphoma in need of starting iv. therapy.
- 1st January 2020 -> 30th June 2022.
- Participation in the PROMs program was offered since January 2020. Those patients rejecting inclusion were used as control arm.
- Patients may answer ePRO-CTCAE™ questionnaire of symptoms every month during therapy.
 - Low intensity → automatically sent recommendations (App).
 - High intensity → teleconsultation call by a specialized nurse.
- Association between inclusion in PROMs and:
 - reduction of hospital admissions/visits to Emergencies.
 - impact on survival.

RESULTS

- 244 pts were included in the study. 121 (49.6%) reported outcomes (ePROMs).
- Baseline characteristics were balanced (age, sex, ECOG, diagnosis and previous lines of therapy); in spite of not having been previously randomized.
- 14 categories of AEs (PRO-CTCAE™) were analyzed. Low grade of agreement was met between AEs reported by physicians and patients.
- No differences between AEs reported by physicians and patients were only found in 3 categories: gastrointestinal (63% vs. 68%; p=n.s.), neurological (29% vs. 31%; p=n.s.) and respiratory (12% vs. 7%; p=n.s.).
- Cutaneous, oral and sleep disorders were reported by >50% of patients but only at 26, 22 and 19% (p<0.05) of electronic medical records.

CLINICAL BENEFITS

- Patients in the program had fewer visits to Emergencies (Fig. 1) and showed tendency to require fewer unscheduled hospital admissions (Fig. 2).
- More patients among those in the program were able to complete the planned treatment (Fig. 3).
- Median OS was not reached in either group after a median follow-up (FU) of 18.8 months (IQR 11.3–23.2). However, OS was significantly longer among those pts included in "E-Res" program (88.2% vs. 79.7% after 18 months of FU; HR 2.25; 95%CI 1.23 to 4.13; p=0.007) (Fig. 4).

CONCLUSIONS

- Accurate assessment of symptoms allows physicians to:
 - develop an individualized treatment plan.
 - help cancer patients manage these issues.
 - improve survivorship experience and QoL.
- The inclusion in the program has an impact on:
 - reduction of Emergencies visits.
 - direct and indirect costs.
 - overall survival.

"E-Res Salud" aims to incorporate patients' voice into healthcare decision process in order to establish a consensus to value the intervention possibilities.

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