ASH 2024 Sessions for CML Advocates Network

Prepared by Patvocates and the iCMLf

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Up-Front Therapy for Chronic Myeloid Leukaemia

Key Message: The key message of this article is that asciminib is transforming upfront therapy for chronic myeloid leukaemia (CML) by offering superior efficacy and safety compared with traditional TKIs, enabling deeper molecular responses and increasing the likelihood of treatment-free remission (TFR). Advances in genetic profiling and biomarker research are further refining personalised treatment strategies, while addressing challenges such as resistance, side effects, and global access.

At the Friday Satellite Symposium preceding the 66th ASH Annual Meeting, Prof. Andreas Hochhaus (Jena University Hospital, Germany) shared key insights into upfront therapy for CML. His presentation reviewed the progress in treatment strategies over the years, focusing on tyrosine kinase inhibitors (TKIs) and how they have reshaped survival outcomes, quality of life, and treatment goals in 2024 (see Figure) [1].

The primary treatment goal for CML has evolved over time. Initially, therapy aimed for complete cytogenetic remission and progression-free survival. Today, achieving deep molecular response (DMR) is prioritised, enabling treatment-free remission (TFR) and improving quality of life. Balancing efficacy with reduced long-term side effects has become essential in defining therapy success.

Prof. Hochhaus reviewed how the survival of CML patients has dramatically improved with TKI therapy. Data from the TIGER study revealed an 8-year overall survival rate of 95%, comparable to the general population [2]. This progress stems from advancements in imatinib (introduced in 2001) to newer second-generation TKIs (e.g., nilotinib, dasatinib, bosutinib) and, most recently, asciminib, approved for first-line use in 2024.

The ASC4FIRST trial provided evidence that asciminib outperforms standard TKIs [3]. By 96 weeks, 74.1% of patients achieved a major molecular response (MMR) with asciminib, compared to 52% with other TKIs. It also resulted in higher rates of deep molecular response (MR4, MR4.5), which are crucial milestones in achieving TFR.

Despite the success of TKIs, treatment resistance remains a challenge, and the role of genetic profiling has increased. For example, *ASXL1* mutations, detected in 8% of CML patients, are linked to poorer responses across all TKIs. Patients with *ASXL1* mutations also had significantly lower 12-month MMR rates and a 29% risk of developing kinase domain mutations, leading to resistance. The FASCINATION study demonstrated that combining asciminib with ATP-competitive TKIs (e.g., nilotinib, dasatinib) significantly improved outcomes for patients with high-risk chromosomal aberrations.

Prof. Hochhaus pointed out that Treatment-Free Remission (TFR) is an increasing aspiration for patients. Studies like ENESTnd demonstrated that second-generation TKIs enable more

patients to attempt TFR compared to first-generation options [4]. The ability to discontinue treatment while maintaining remission has become a major consideration in selecting upfront therapy.

However, TFR success is influenced by several factors, including longer TKI duration before discontinuation, stable deep molecular response (DMR), and biological markers such as cytokine profiles and B-cell subpopulations.

While TKIs have improved survival rates, Prof. Hochhaus underlined the need to address cardiovascular risks associated with nilotinib and other TKIs, as well as global access disparities, where resource-limited settings prioritise survival over DMR/TFR.

Closing his presentation, Prof. Hochhaus reiterated that asciminib is redefining upfront therapy for CML, offering a safer and more effective alternative to traditional TKIs. He also repeated the value of tailoring treatment to individual patient needs, early genetic profiling to anticipate resistance, continuous monitoring to maximise treatment success and TFR potential.

1. Hochhaus A, et al. What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Chronic Myeloid Leukemia. A CME Friday Satellite Symposium Preceding the 66th ASH Annual Meeting. Dec 6, 2024. San Diego, CA.
2. Hochhaus A, et al. Presented at the European Hematology Association, 2023.
3. Hochhaus A, et al. NEJM. 2024;391:885-98.
4. Kantarjian HM, et al. Leukemia. 2021;35:440-53.

First line options 2024

	Initial label	Concerns	Therapeutic window	New dose recommendations
Imatinib	400 mg QD	Muscle cramps, edema, renal failure	+	400 – 600 mg QD
Nilotinib	300 mg BID	Cardiovascular events, hyperglycemia	(+)	300 mg BID
Dasatinib	100 mg QD	Pleural effusions	+++	100 mg 5 days/week 50 mg QD
Bosutinib	500 mg QD	Gastrointestinal toxicity liver toxicity	+	200-300 mg QD, with gradual dose increase to 400 mg QD
Asciminib	40 mg BID or 80 mg QD	Lipase increase (?)	++	80 mg QD

Figure from Prof. Hochhaus' presentation [1] showing frontline TKIs available and approved for CML. Note that not all medicines are approved or accessible in all parts of the world. Abbreviations: QD, daily; BID, twice daily.

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Managing Tolerability and Practical Issues in CML Therapy

Key Message: Prof. B. Douglas Smith, Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University (USA) addressed the practical

challenges of managing side effects and tolerability in chronic myeloid leukaemia (CML) therapies during the CME Friday Satellite Symposium at the 66th ASH Annual Meeting [1].

Dr Smith's presentation covered the progress of oral anticancer medicines (tablets) in transforming CML management. Tyrosine kinase inhibitors (TKIs), the cornerstone of CML therapy, have extended patient life expectancy significantly. Swedish registry data revealed that life expectancy for patients with CML on TKIs is now within 3 years of the general population, marking a significant milestone [2].

However, as Dr Smith pointed out, these therapies come with challenges. While oral TKIs promise precision and personalisation, side effects are a significant concern. Dr Smith stressed the need for clear communication between clinicians and patients to set realistic expectations and ensure consistent treatment adherence.

He then zoomed into managing adverse events specific to different TKIs (see Figure). For instance, nilotinib is associated with cardiovascular risks, while dasatinib may cause pleural effusions. Asciminib, a newer agent, offers an improved safety profile, but clinicians must remain vigilant for rare events such as elevated lipase levels, which can indicate liver problems. Early and regular monitoring of blood counts, liver function, and electrolytes is critical to mitigate these risks and maintain patient quality of life.

Findings from a 16-year observational study presented at ASH 2024 [3] revealed long-term risks associated with TKIs:

- Ponatinib users showed a 4.56% average reduction in cardiac function over time.
- Bosutinib was associated with a threefold increase in new-onset heart failure compared with imatinib.
- Dasatinib and bosutinib carried a higher risk of pleural effusions and fluid retention.
- Imatinib had the lowest cardiovascular risks but higher rates of long-term fatigue and muscle cramps.

Dr Smith concluded by stressing the importance of tailored therapy. The choice of TKI should consider the patient's age, comorbidities, and potential for side effects.*"Each of these TKIs tends to have a slightly unique profile. While there are common side effects across all of them, such as fatigue or liver function abnormalities, tolerability issues can vary significantly. This highlights the importance of understanding these differences to personalise therapy effectively for each patient."– Douglas Smith*

1. Smith BD, et al. What Clinicians Want to Know: Addressing Current Questions and Controversies in the Management of Chronic Myeloid Leukemia. A CME Friday Satellite Symposium Preceding the 66th ASH Annual Meeting. Dec 6, 2024. San Diego, CA.
2. Bower H, et al. J Clin Oncol. 2016 Aug 20;34(24):2851-7
3. Zureigat H, et al. Cardiovascular Profile of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukaemia: A 16-Year Observational Study, Poster 1777. ASH 7-10 Dec 2024, San Diego, CA, USA.

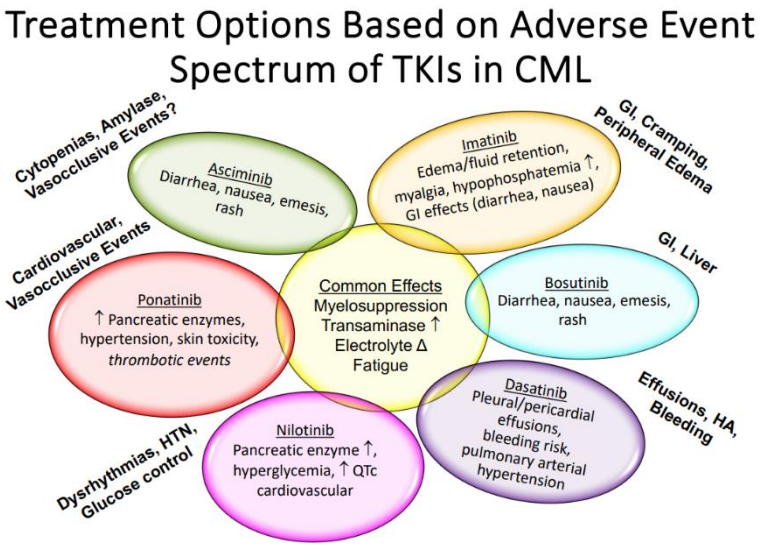


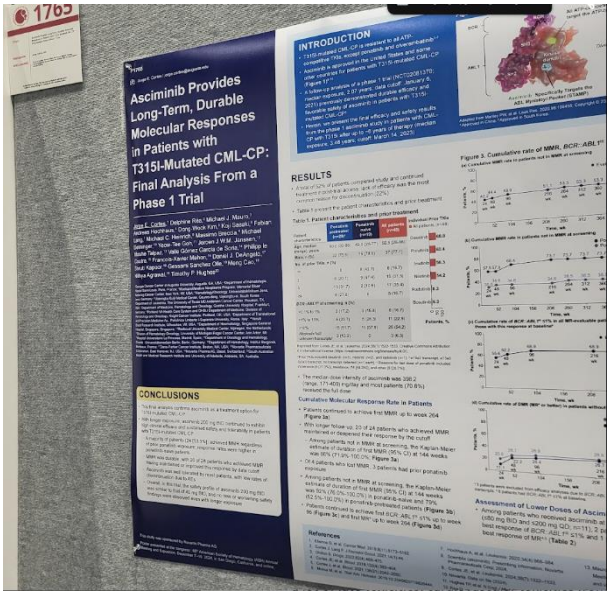
Figure from Prof. Smith's presentation with an overview of common side effects with each TKI in CML. Abbreviations: GI, gastrointestinal; HA, headache; HTN, hypertension; QTc, elongation of the QT interval in an echocardiogram, delta symbol refers to change in lab values; up arrows indicate increases in values.

Asciminib Provides Long-Term, Durable Molecular Responses in Patients with T315I-Mutated CML-CP

Key Message: This small phase 1 study showed that asciminib can be a promising treatment option for patients with T315I-mutated CML-CP, including those who have previously been treated with ponatinib. It showed lasting disease control, manageable side effects, and a novel mechanism of action for patients with limited options.

What is this study about?

This phase 1 study was presented by Prof. Jorge E. Cortes (Georgia Cancer Center, Augusta, GA, USA), who investigated the safety and effectiveness of asciminib, a targeted therapy for patients with chronic-phase chronic myeloid leukaemia (CML-CP) who have the T315I mutation in their CML-causing BCR::ABL1 fusion protein [1]. This mutation makes CML resistant to most tyrosine kinase inhibitors (TKIs) except ponatinib, which has potential safety concerns. The study provides final data on the outcomes of patients treated with asciminib monotherapy.



Why is this important?

Patients with T315I-mutated CML-CP have very limited treatment options. Asciminib works differently from other TKIs by targeting the ABL myristoyl pocket (STAMP), offering a novel approach. Understanding its long-term safety and efficacy is critical for patients with this challenging condition.

What did the researchers do?

The researchers analysed data from 48 patients with T315I-mutated CML-CP who were treated with asciminib at a dose of 200 mg twice daily. Patients were monitored for up to 6 years to assess their molecular response, treatment duration, and side effects.

What were the key findings?

1. Among the 45 patients whose data were complete, 42.2% achieved a major molecular response (MMR) by week 24, and this rate improved over time.
2. Nearly 69% of patients achieved or maintained a BCR::ABL1 level of ≤1%, with 31.1% and 26.7% reaching deeper responses (MR4 and MR4.5, respectively).
3. MMR was lasting, with an 86% probability of maintaining it for 144 weeks.
4. The safety profile of asciminib remained consistent over time, with no new serious concerns reported. The most common grade ≥3 side effects were increased lipase (20.8%) and thrombocytopenia (14.6%).
5. Two new arterial occlusive events occurred in patients who already had cardiovascular risk factors, but no other significant new safety signals emerged during the extended follow-up.

1. Cortes JE, et al. Asciminib Provides Long-Term, Durable Molecular Responses in Patients with T315I-Mutated CML-CP: Final Analysis from a Phase 1 Trial. Poster 1765. ASH 7-10 Dec 2024, San Diego, CA, USA.

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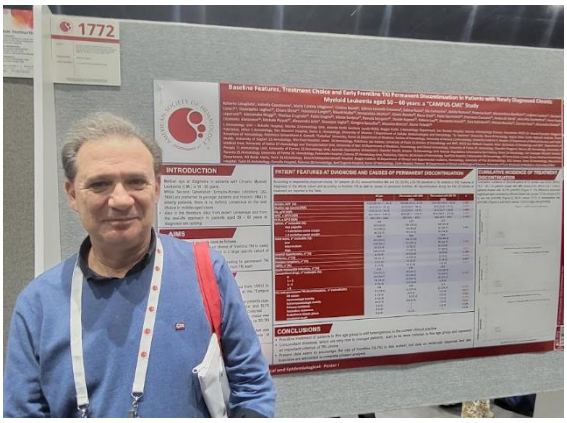
Second-Generation TKIs Better for Middle-Aged CML Patients?



Key Message: Dr. Roberto Latagliata's (Ospedale Belcolle, Rome, Italy, see photo) study analysed treatment choices and early outcomes in middle-aged patients (50–60 years) with newly diagnosed chronic myeloid leukaemia (CML), comparing imatinib (IMA) and second-generation TKIs (2G-TKIs). Findings suggest that 2G-TKIs may be a better option for this specific group of people due to lower likelihood of stopping the treatment together with better management of higher-risk disease [1].

What is this study about?

This study analyses the characteristics, treatment choices, and early outcomes in patients aged 50–60 with newly diagnosed chronic myeloid leukaemia (CML). It examines the reasons for discontinuing tyrosine kinase inhibitors (TKIs) in the first year of treatment in a real-world clinical setting.

Why is this important?

While second-generation TKIs (2G-TKIs) are often preferred in younger patients and imatinib (IMA) is commonly used in elderly patients, there is no clear consensus on the best

treatment for middle-aged patients. Understanding how frontline TKI choices can improve disease outcomes early on can guide more personalised treatment decisions.

What did the researchers do?
The researchers reviewed data from 424 patients aged 50–60 who were newly diagnosed with CML between 2012 and 2019 as part of the Italian "Campus CML" project. They compared patient characteristics, TKI choices, and early discontinuation rates within the first 12 months of treatment.

What were the key findings?

1. 45% of patients received imatinib, and 55% received a second-generation TKI (dasatinib or nilotinib). Patients treated with 2G-TKI had higher white blood cell counts and higher Sokal risk scores, while those treated with IMA were more likely to have more than one health issue (comorbidities).
2. 18.6% of patients discontinued their initial TKI within the first year due to various reasons, including toxicity (haematologic: 2.8%; non-haematologic: 4.8%), resistance (primary: 9.5%; secondary: 0.3%), disease progression (0.6%), or unrelated death (0.6%).
3. Patients taking imatinib were more likely to stop**:** 27.6% of patients treated with imatinib discontinued treatment compared with 10.3% of those on 2G-TKI, with significant differences across all Sokal risk groups. After 12 months, 25.8% of imatinib -treated patients had discontinued compared with 9.5% of 2G-TKI-treated patients.

What does this mean for patients?
These findings suggest that **second-generation TKIs may be a better option for middle-aged patients** with newly diagnosed CML due to lower discontinuation rates and the ability to manage higher-risk disease more effectively. However, comorbidities and other individual factors must also be considered when selecting the best treatment. Further research is needed to understand long-term outcomes, including molecular responses and late toxicities. Patients should discuss these findings with their healthcare team to make informed decisions about their treatment.

Quote from Dr. Latagliata: "We decided to focus on this middle-aged population to understand how Italian physicians approach treatment decisions for this group of patients.

Our analysis showed that treatment is split roughly evenly: about half of the patients are treated with imatinib, while the other half receive a second-generation TKI. In the first 12 months of treatment, second-generation TKIs appear to offer some advantages, particularly a lower rate of treatment discontinuation. However, the 2 groups are not entirely comparable, as patients with comorbidities were more frequently treated with imatinib.

In this age group, comorbidities become a more significant consideration. This is the first decade of life where comorbidities start to play an important role, which is both a challenge and a sign of progress; it reflects that patients are living longer.

These findings are preliminary because we need longer follow-up to fully understand the long-term outcomes of second-generation TKIs. While they have advantages in the short term, late toxicities are a concern, including cardiovascular issues with second-generation

TKIs, or pleural effusion with dasatinib. Prolonged observation is essential to draw firm conclusions about the optimal treatment for this age group."

1. Latagliata R, et al. Baseline Features, Treatment Choice and Early Frontline TKI Permanent Discontinuation in Patients with Newly Diagnosed Chronic Myeloid Leukemia Aged 50 – 60 Years: A "Campus CML" Study. Poster 1772. ASH 7-10 Dec 2024, San Diego, CA, USA.

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Early Pregnancy TKI Exposure in Women with CML Shows Reassuring Outcomes for Mothers and Babies

Key Message: This study found that brief exposure (about 4 weeks) to tyrosine kinase inhibitors (TKIs) did not result in birth abnormalities or worse health in the infant. While some mothers experienced a temporary loss of molecular response, they regained it after resuming treatment postpartum, suggesting that early discontinuation of TKIs may be a safe approach for pregnant women.

What is this study about?

This study examines the effects of brief exposure to tyrosine kinase inhibitors (TKIs) during early pregnancy in women with chronic myeloid leukaemia (CML) and assesses the health outcomes of their infants. Dr Yingling Zu (Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China) also recently published the results from their abstract at ASH [1,2].

Why is this important?

TKIs are the standard treatment for CML but are known to potentially cause birth defects. Women who become pregnant unexpectedly while on TKI therapy face difficult decisions about continuing or stopping treatment. Understanding the risks associated with short-term TKI exposure during pregnancy is crucial for informed decision-making.

What did the researchers do?

Researchers retrospectively analysed 59 pregnancies in 51 women with CML who stopped TKI treatment immediately after discovering they were pregnant. They evaluated the duration of TKI exposure, pregnancy outcomes, and the health of the infants over time.

What were the key findings?

1. All 59 pregnancies resulted in live births without any birth abnormalities.
2. The median duration of TKI exposure during pregnancy was 4 weeks, with most exposures occurring within the first 8 weeks.
3. All newborns had normal birth weights, except for one premature infant with a low birth weight below the 10th percentile.
4. At the time of reporting, all children were in good health.
5. Some mothers experienced a loss of major molecular response (MMR) or complete haematologic response after stopping TKI therapy but regained these responses after resuming treatment post-delivery.

What does this mean for patients?

For women with CML who become pregnant unexpectedly, this study suggests that stopping TKI treatment early in pregnancy may not adversely affect the baby's health. However, it's important to consult healthcare providers to carefully weigh the benefits and risks of continuing or pausing TKI therapy during pregnancy.

1. Zu Y., et al. Tyrosine Kinase Inhibitors Short Exposure in Pregnant Female Patients with Chronic Myeloid Leukemia. Poster 1775. ASH 7-10 Dec 2024, San Diego, CA, USA.
2. Zu Y, et al. Outcome after short exposure to tyrosine kinase inhibitors in pregnant female patients with chronic myeloid leukemia. J Hematol Oncol. 2024 Sep 11;17(1):82.

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Following the Heart Risks of Tyrosine Kinase Inhibitors (TKIs) in CML over 16-Years

Key Message: The cardiovascular risks of TKIs in CML patients, finding that ponatinib carries the highest risk of major adverse cardiovascular events (MACE), including heart failure and stroke, while bosutinib and dasatinib also increase risks compared with imatinib. These findings point to the need for careful patient selection, regular heart monitoring, and personalised risk assessment, particularly for those with pre-existing cardiovascular conditions.

What is this study about?
This research looks at the heart-related risks for chronic myelogenous leukemia (CML) patients taking tyrosine kinase inhibitors (TKIs). While TKIs have dramatically improved outcomes for people with CML, some of these medications can affect the heart, potentially leading to serious complications, sometimes years later. This study focused on understanding these risks and identifying which TKIs are associated with the highest heart-related side effects.

Why is this important?
For patients with CML, treatment with TKIs is often long-term or lifelong. If these medications cause heart problems, they might need to be stopped or switched, which can impact how well the leukaemia is controlled. Knowing which TKIs have higher risks can help patients and doctors make informed decisions about treatment and take steps to monitor and protect heart health.

What did the researchers do?
The study included 343 adult patients treated for CML at the Cleveland Clinic between 2007 and 2022. Researchers collected information on patients' demographics, pre-existing health conditions (like diabetes, high blood pressure, or high cholesterol), and heart-related events during treatment. They also analysed heart function over time using echocardiograms, which measure things like the heart's pumping ability (LVEF).

What were the key findings?

1. Heart risks varied between drugs. Ponatinib had the highest risk of major adverse cardiovascular events (MACE), such as heart attacks, heart failure, and strokes. Bosutinib and dasatinib also showed increased risks compared with the first-generation imatinib, which had the lowest cardiovascular risks overall.
2. Patients on bosutinib were nearly 3 times more likely to develop new heart failure compared with those on imatinib.

3. Ponatinib was the only drug associated with a significant reduction in the heart's pumping ability (measured by LVEF), with an average decrease of 4.56%.
4. Dasatinib and bosutinib were linked to a higher likelihood of fluid buildup around the lungs (pleural effusion).

What does this mean for patients?

- Ponatinib should be used cautiously and may be best reserved for patients with limited treatment options, as it carries the highest risk for serious heart problems.
- Patients with pre-existing heart conditions, such as high blood pressure, diabetes, or smoking history, should discuss these risks with their doctor before starting treatment.
- Regular monitoring of heart function is essential for patients on TKIs, particularly ponatinib, dasatinib, and bosutinib.

Quote from Dr Zureigat: "In this study with CML patients, we were really interested in observing the cardiotoxicity profile of tyrosine kinase inhibitors. Those are the major drugs used in CML, and they've really caused a paradigm shift in outcomes. Given that they're the main sort of drug of use, we really also want to make sure that we're not causing too much cardiotoxicity.

What our study shows is that ponatinib specifically had the highest risk of cardiotoxic side effects. Also, it also was the only one that was associated with a reduction in cardiac function as assessed on echocardiography.

What this means for patients is that this has to be a conversation with their provider, especially taking into account what underlying cardiovascular risk factors they may already have. I think that's the major important takeaway message. It has to be like an individualised sort of conversation. Especially because patients are living longer now, right?"

1. Zureigat H et al, Cardiovascular Profile of Tyrosine Kinase Inhibitors in Chronic Myelogenous Leukemia: A 16-Year Observational Study. Poster 1777. ASH 7-10 Dec 2024, San Diego, CA, USA.

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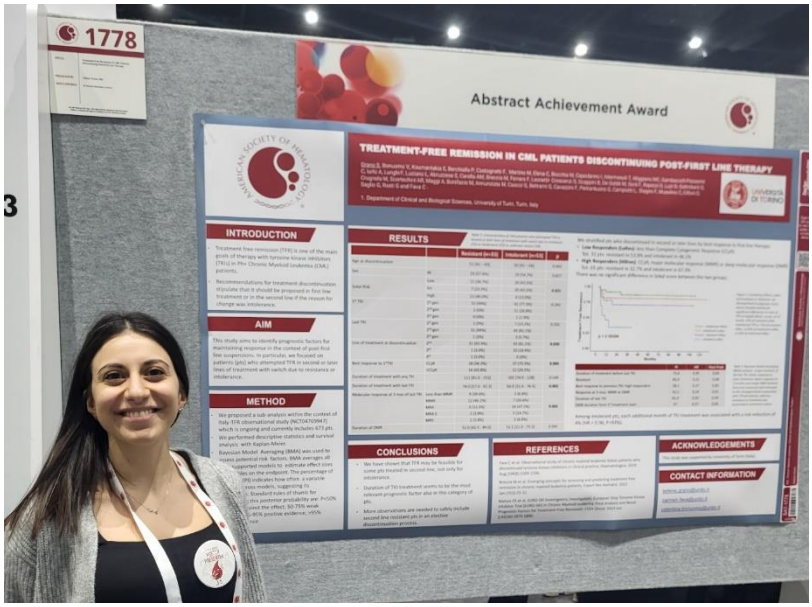
Understanding Treatment-Free Remission (TFR) in CML

Key Message: Dr Selene Grano (University of Torino, Turin, Italy) won an Abstract Achievement Award for her poster [1]. Dr Grano's research on chronic myeloid leukaemia (CML) patients found that stopping tyrosine kinase inhibitor (TKI) treatment could be an option even for those whose CML resisted initial therapy, though success depends on prior treatment response and time spent on medication. This suggests that treatment-free remission (TFR) may be an option for a broader range of CML patients beyond those who are merely intolerant to TKIs.



What was the study about?

This research [1] looked at whether patients with chronic myeloid leukaemia (CML) who stopped taking tyrosine kinase inhibitors (TKIs) could maintain their remission. While current guidelines suggest stopping treatment in second line is usually an option for patients who switch due to side effects (intolerance), this study also included patients who had switched because their CML resisted the first treatment.

What did the researchers aim to find?

The goal was to understand which factors predict whether a patient can stay in remission after stopping their medication, particularly in those who switched treatment due to resistance or intolerance. The study was part of the ongoing Italy-TFR observational project, involving 673 patients.

Who participated in the study?

Data was collected from 144 CML patients who had stopped treatment after switching therapies in a larger group of patients in a study [2]. The reasons for switching were: Resistance (33 patients), Intolerance (53 patients), or unknown reasons (58 patients).

What were the key findings?

The results showed differences in outcomes depending on how patients responded to their first TKI treatment and why they switched to a second or later line of therapy:

2. Patients were categorised as "Low Responders" or "High Responders" based on how well they responded to their first TKI treatment. They were also categorised as “intolerant” if they had to stop their first treatment because of side effects.

1. After stopping treatment, the likelihood of staying in remission after 24 months was:
    - 35% for resistant Low Responders
    - 71% for resistant High Responders
    - 82% for intolerant Low Responders
    - 92% for intolerant High Responders

Key factors influencing outcomes:

1. Patients who stayed on their second treatment longer had better chances of maintaining remission.
2. Patients with a strong response to treatment after 3 months were more likely to stay in remission.
3. Those who achieved deep remission earlier in their treatment journey were also more likely to maintain remission.
4. Resistance to treatment increased the chances of needing to restart therapy.

Important insights:

- For patients who switched treatments because of intolerance, every extra month on TKI therapy reduced their risk of needing to restart treatment by 4%.
- For resistant patients, this benefit wasn’t always observed, showing that resistance presents a unique challenge.

What does this mean for patients?

This study shows that stopping treatment may be an option for some patients even if they switched therapies because their CML became resistant, not just because the side effects became intolerabla. However, the success of stopping treatment depends on factors like how well the CML responded to earlier treatments and how long patients stayed on their medication.

Quote from Dr Grano: “More patients will attempt TFR, not only intolerant patients but also some resistant patients.”

1. Grano, S et al. Treatment-Free Remission in CML Patients Discontinuing Post-First Line Therapy. Poster 1778. ASH 7-10 Dec 2024, San Diego, CA, USA.
2. Mahon FX, et al. European Stop Tyrosine Kinase Inhibitor Trial (EURO-SKI) in Chronic Myeloid Leukemia: Final Analysis and Novel Prognostic Factors for Treatment-Free Remission. J Clin Oncol. 2024 Jun 1;42(16):1875-1880.

prepared by Patvocates: patvocates.net/

Asciminib Offers Superior Outcomes for CML Patients in Phase 3 ASC4FIRST Study.

Key Message: A clinical trial, presented by Prof. Jorge Cortes (Georgia Cancer Center, Augusta, GA, USA, in photo) has shown that asciminib offers significant advantages over standard-of-care (SOC) tyrosine kinase inhibitors (TKIs) for patients newly diagnosed with chronic myeloid leukaemia (CML) in the chronic phase (CP) [1].

What is asciminib?

Asciminib is a newer type of TKI that targets a specific site (the myristoyl pocket) on the BCR::ABL1 protein, which is involved in the growth of cancer cells in CML. This mechanism makes it distinct from other TKIs like imatinib and second-generation TKIs.

Key Results from the ASC4FIRST Trial

1. At 96 weeks, asciminib helped 74.1% of patients achieve a major molecular response (MMR), compared with only 52.0% of patients receiving standard TKIs.
2. Patients on asciminib also showed higher rates of achieving deeper responses (called MR4 and MR4.5), critical milestones indicating better disease control. For example, 48.8% of asciminib patients achieved MR4 compared with 27.5% of those on standard TKIs.
3. Patients taking asciminib were more likely to stay on treatment, with fewer stopping due to side effects or lack of efficacy. Only 5% of asciminib patients discontinued due to side effects, compared to 13.1% on imatinib and 12.7% on second-generation TKIs.
4. Patients taking asciminib experienced fewer severe side effects, and the risk of treatment discontinuation was notably lower than second-generation TKIs.

Why Does This Matter for Patients?

For patients with newly diagnosed CML, asciminib offers:

- Higher chances of achieving and maintaining disease control.
- A better safety profile, making it easier to stay on treatment without interruption.
- Improved quality of life due to fewer severe side effects.

These advantages could mean longer, healthier lives for patients and fewer challenges associated with long-term treatment.

Approval and Future Use

In October 2024, the U.S. Food and Drug Administration granted accelerated approval for asciminib based on earlier data from this trial. With its proven effectiveness and tolerability,

asciminib is now a strong contender as the standard first-line treatment for patients newly diagnosed with CML-CP. It is not yet approved in Europe.

1. Cortes JE, et al. Asciminib (ASC) Demonstrates Favorable Safety and Tolerability Compared with Each Investigator-Selected Tyrosine Kinase Inhibitor (IS TKI) in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) in the Pivotal Phase 3 ASC4FIRST Study. Oral Presentation 475. ASH 7-10 Dec 2024, San Diego, CA, USA.

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High Response Rates and Manageable Side Effects with Asciminib

Key Message: The ASCEND trial reported an 87% cumulative incidence of major molecular response at 24 months and deep molecular responses (MR4 and MR4.5) of 73% and 55%, respectively, at 3 years. *"Deep molecular responses continued to improve even after three years, showcasing the long-term potential of asciminib."*– David Yeung

What is this study about?
Dr David T Yeung (Central Adelaide Local Health Network, Australia) presented updated results from the ASCEND trial looking at the safety and effectiveness of asciminib, a myristoyl pocket inhibitor, for patients with newly diagnosed chronic-phase chronic myeloid leukaemia (CP-CML). He focused on 24-month outcomes, response rates, and management of patients who did not respond well to treatment or developed mutations.

Why is this important?
Asciminib offers a new approach to treating CP-CML with promising molecular response rates. Understanding how it performs over time, especially in patients with suboptimal responses or resistance, can help optimise treatment strategies and improve outcomes for newly diagnosed patients.

What did the researchers do?
Researchers treated 101 patients with asciminib, starting with 40 mg twice daily for the first 12 months and switching to 80 mg once daily afterward. Patients who did not meet treatment milestones (early molecular response [EMR] or major molecular response [MMR]) could have their dose increased or add other therapies like dasatinib or nilotinib. They monitored molecular responses and tracked treatment failures, adverse events, and genetic mutations.

What were the key findings?

1. High response rates were observed. 93% of patients achieved EMR by 3 months, and 79% achieved MMR by 12 months. By 24 months, 82% were in MMR, 58% achieved MR4, and 32% achieved MR4.5.

2. Common side effects included high blood pressure (22%) and increased lipase levels (Note: this does not always cause clinical problems; 21%). Only one patient progressed to advanced disease, and no deaths were reported.
3. Patients whose disease did not improve or who developed resistance were managed with dose increases or combination therapy, with some still achieving good responses. Dose escalation for patients failing to meet molecular milestones led to a median BCR::ABL1 log reduction of 0.4, improving outcomes in warning and failure categories.
4. in BCR::ABL1 genetic mutations (e.g., T315I and A337T) were identified in a small number of patients, but most responded well to adjustments like switching to dasatinib or ponatinib. Mutations, particularly at residues 337 and 244, were the most common resistance mechanisms, but responses were salvageable with subsequent therapies like dasatinib.
5. Some patients without MMR at 12 months eventually achieved it with continued therapy, showing the potential benefit of persistence.

What does this mean for patients?
Asciminib shows promise as a frontline treatment for CP-CML, achieving high response rates and manageable side effects. While most patients achieve significant therapy milestones, continued monitoring and tailored approaches (e.g., dose adjustments or adding other therapies) may help overcome resistance or suboptimal responses.

1. Yeung DT, et al. Update of the Ascend-CML Study of Frontline Asciminib: High Rate of Optimal Response and Resistance Due to Mutations Is Rare. Oral Presentation 476. ASH 7-10 Dec 2024, San Diego, CA, USA.

prepared by Patvocates: patvocates.net/ and iCMLF: cml-foundation.org/

TGRX-678 Is a Promising New Option for Resistant CML

Key Message: TGRX-678 shows promise as a treatment for patients with resistant or intolerant CML, including those with the challenging T315I mutation or who have failed other advanced therapies. Its effectiveness and manageable side effects suggest it could become an important option in the treatment landscape. However, ongoing clinical trials will further clarify its role and long-term benefits. ***"The absence of significant new mutations with TGRX-678 is a critical finding in resistant CML therapy."– Qian Jiang***

What is this study about?
This study evaluates TGRX-678, a new inhibitor targeting the ABL myristoyl pocket (STAMP), in patients with chronic-phase (CP) or accelerated-phase (AP) chronic myeloid leukaemia (CML) who are resistant or intolerant to multiple prior treatments. Prof. Qian Jiang (Peking University Institute of Hematology, China) showed updated data on the safety, effectiveness, and pharmacokinetics of TGRX-678.

Why is this important?
Patients with treatment-resistant CML, particularly those with the T315I mutation, often have limited options. TGRX-678 represents a novel therapeutic approach that could offer effective treatment with manageable side effects, even for those who have failed other advanced therapies like second- or third-generation TKIs or other STAMP inhibitors.

What did the researchers do? 158 patients with CML-CP or CML-AP who were resistant or intolerant to prior TKIs received TGRX-678 at various doses (10–80 mg twice daily or 40–240 mg once daily) in phase Ia and at 80 or 240 mg once daily in phase Ib. The study monitored safety, molecular responses (e.g., complete haematologic response [CHR], major cytogenetic response [MCyR], and major molecular response [MMR]), and drug pharmacokinetics.

What were the key findings?

1. They saw high response rates. In CML-CP patients, 82% achieved CHR within 3 cycles, and at 18 months, the cumulative incidences of MCyR, CCyR, and MMR were 52%, 40%, and 26%, respectively. For patients with the T315I mutation, 80% achieved CHR, and MMR was achieved by 50% at 18 months.
2. 83% of accelerated-phase CML-AP patients achieved major haematologic response (MaHR), and 79% achieved CHR within 3 cycles. The 18-month cumulative incidences of MCyR, CCyR, and MMR were 35%, 30%, and 14%, respectively.
3. The most common severe side effects were blood-related, including thrombocytopenia (46%) and neutropenia (44%). No new safety signals were identified, and only one death occurred, which was unrelated to the treatment.
4. TGRX-678 showed dose-proportional drug exposure and a long half-life (>120 hours), indicating substantial drug accumulation and potentially longer-lasting effects.

1. Jiang Q, et al. Safety and Efficacy of Tgrx-678, a Potent BCR::ABL1 allosteric Inhibitor, in Patients with Tyrosine Kinase Inhibitor Resistant and/or Intolerant Chronic Myeloid Leukemia: Updated Results of Phase 1 Study Tgrx-678 -1001. Oral Presentation 477. ASH 7-10 Dec 2024, San Diego, CA, USA.

prepared by Patvocates: patvocates.net/ and iCMLF: cml-foundation.org/

Asciminib as a Second-Line Treatment for CML-CP

Key Message: The study reported an MMR rate of 43% by 12 months, with deep molecular responses (MR4) in 25% of patients at 6 months: *" The second-line efficacy of asciminib reinforces its potential across multiple treatment lines."*
– Jorge Cortes

What is this study about?
The ASC2ESCALATE study is evaluating the safety and effectiveness of asciminib in patients with chronic-phase chronic myeloid leukaemia (CML-CP) who have already been treated with one tyrosine kinase inhibitor (TKI). It also explores dose escalation for patients who do not achieve specific treatment milestones. Although the first author of this study is Dr Ehab Attalah, Prof. Jorge Cortes (Georgia Cancer Center, Medical College of Georgia, Augusta University, Augusta, GA, USA) presented the interim results, joking that Dr. Attalah preferred to do his rounds in the ward.

Why is this important?
Patients with CML-CP who switch from their first TKI often face worse outcomes with each successive treatment. Asciminib offers a novel mechanism of action, targeting the BCR::ABL1 myristoyl pocket, providing a promising new option for patients who progress despite or cannot tolerate their first TKI.

What did the researchers do? 71 patients with CML-CP who had previously been treated with one TKI participated. Patients started asciminib at 80 mg once daily, with the option to increase the dose to 200 mg daily or twice daily if molecular milestones were not met at specific time points. Safety and molecular response rates were tracked for up to 24 weeks.

What were the key findings?

1. The researchers reported high molecular response rates. By 24 weeks, 85% of patients achieved a BCR::ABL1 level ≤1%. 43% of patients achieved a major molecular response (MMR), while 35% reached MR4 (deep molecular response), and 10% achieved MR4.5 (near-undetectable disease levels).
2. Patients who switched due to intolerance or resistance to their first TKI showed strong responses, with even those starting with high transcript levels (>10%) achieving good outcomes.

3. Most side effects were mild (grade 1 or 2), including nausea (21%), vomiting (17%), and hypertension (17%). Severe side effects (grade ≥3) were infrequent, with hypertension being the most common (11%). Only one patient discontinued treatment due to adverse events.

4. Only 2 patients required dose increases due to suboptimal response, highlighting the drug's potency even at standard dosing.

What does this mean for patients?
Asciminib demonstrates strong effectiveness as a second-line treatment for CML-CP, with high rates of molecular response and manageable side effects. Its ability to deliver deep responses, even in patients with resistance or intolerance to previous therapies, makes it a promising option. Patients should discuss with their healthcare teams whether asciminib might be a suitable treatment for their condition. Further data from this ongoing trial will provide additional insights into its long-term benefits.

1. Attalah EL, et al. Efficacy and Safety of Asciminib in Chronic Myeloid Leukemia in Chronic Phase (CML-CP): Interim Results from the Phase 2 ASC2ESCALATE Trial in the Cohort of Patients (Pts) after 1 Prior Tyrosine Kinase Inhibitor (TKI). Oral Presentation 479. ASH 7-10 Dec 2024, San Diego, CA, USA.

prepared by Patvocates: patvocates.net/ and iCMLF: cml-foundation.org/

Olverembatinib as Second-Line Therapy in CP-CML

Key Message: Olverembatinib emerges as a viable option for second-line therapy, particularly for patients with resistant mutations and limited options. *"The efficacy in TKI-resistant cases demonstrates its robust potential as a second-line agent." – Li Weiming*

What is this study about?
Dr Li Weiming (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology in Wuhan, China) presented their single-arm, multicentre, open-label ChiCTR2200061655 study, which evaluated olverembatinib as a second-line treatment for patients with chronic-phase chronic myeloid leukaemia (CP-CML) who were resistant or intolerant to first-line tyrosine kinase inhibitors (TKIs) [1]. The study is exploring olverembatinib's safety, efficacy, and response rates over time.

Why is this important?
Patients with CP-CML who do not respond to first-line TKI therapy often have limited options and may face poorer outcomes. Olverembatinib, a third-generation BCR-ABL1 inhibitor, offers a potential treatment alternative for this challenging group of patients.

What did the researchers do? 43 patients with CP-CML who had either progressed despite, or could not tolerate, first-line TKI therapy enrolled. Patients received 40 mg of olverembatinib orally every other day in 28-day cycles, with response and safety evaluations every 3 cycles. Assessed cytogenetic and molecular response rates, and tracked adverse events over a median follow-up of 16 months.

What were the key findings?

1. Second-line olverembatinib looks promising. Among efficacy-evaluable patients, 74.1% achieved complete cytogenetic response (CCyR) and 40.6% achieved major molecular response (MMR). Response rates improved over time, with CCyR and MMR rates reaching 77.7% and 43.9%, respectively, by 18 cycles.
2. Patients previously treated with second-generation TKIs achieved CCyR and MMR rates of 78.9% and 43.5%, respectively. Patients previously treated with imatinib achieved CCyR and MMR rates of 50% and 33.3%, respectively.
3. 14% of patients experienced treatment-related serious adverse events, including decreased platelet counts (7%). No deaths related to treatment were reported, and the safety profile was consistent with prior studies. Grade 3 and 4 haematologic toxicities (e.g., thrombocytopenia) were manageable, and no arterial occlusive events were reported.
4. Patients with no mutations achieved CCyR and MMR rates of 65% and 34.8%, respectively. However, those with mutations other than T315I achieved higher response rates, with 85.7% achieving CCyR and 55.6% achieving MMR. There were no patients with the T315I mutation.
5. Durable responses were seen. 95% progression-free survival (PFS) at two years in chronic-phase patients, with no new mutations detected during treatment.

What does this mean for patients?
Olverembatinib offers a promising second-line treatment option for CP-CML patients who cannot continue with first-line TKI therapy due to resistance or intolerance. Its ability to deliver high response rates, especially in patients with BCR-ABL1 mutations, and its manageable safety profile make it a viable alternative.

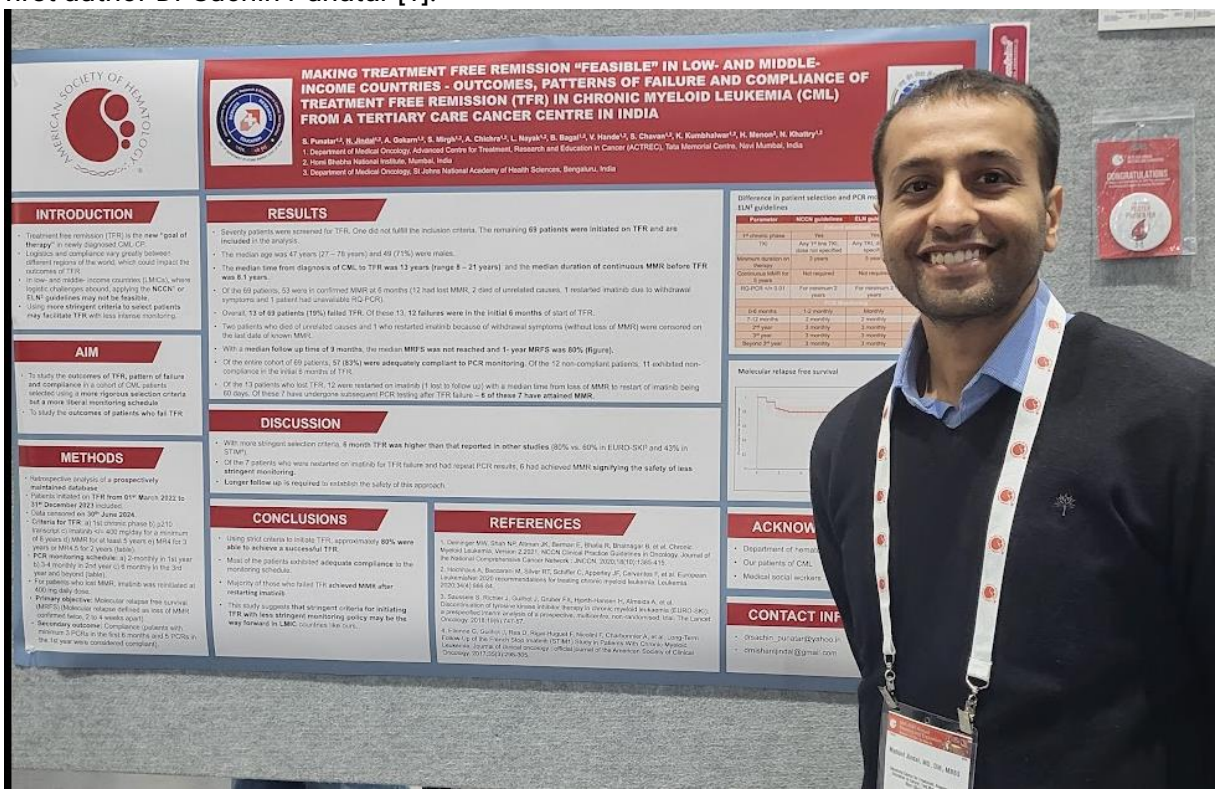
1. Weiming L, et al. Olverembatinib As Second-Line (2L) Therapy in Patients (pts) with Chronic Phase-Chronic Myeloid Leukemia (CP-CML). Oral Presentation 480. ASH 7-10 Dec 2024, San Diego, CA, USA.

prepared by Patvocates: patvocates.net/ and iCMLF: cml-foundation.org/

Making Treatment-Free Remission in CML "Feasible" in Low- and Middle-Income Countries

Key Message: For patients in LMICs, where frequent monitoring can be challenging due to logistical, financial, and geographic barriers, this study suggests a pathway to achieve TFR with less frequent monitoring, making it logistically more feasible. By carefully selecting patients who are more likely to succeed in TFR, this approach balances patient safety with accessibility.

This poster was presented by Dr Nishant Jindal (in photo) on behalf of his colleague and first author Dr Suchin Punatar [1].



What is this study about?

A healthcare institute in India explored a new approach to treatment-free remission (TFR) for patients with chronic myeloid leukaemia (CML), focusing on making TFR more accessible and manageable for patients, especially in low- and middle-income countries (LMICs). TFR is when patients with CML, who have achieved deep and sustained responses to therapy, can stop their medication (such as imatinib) while still keeping the disease under control. Achieving TFR can improve the quality of life by reducing side effects and the financial burden of ongoing treatment. This initiative aimed to reduce the burden of frequent and costly monitoring while ensuring the optimum outcomes.

What did the researchers do?

The researchers selected patients using more rigorous criteria to ensure a higher likelihood of success. Patients were chosen if they: had been on imatinib at a dose ≤400mg per day for >8 years, maintained a major molecular response (MMR) for >5 years, and achieved deep molecular responses (MR4) for 3 years or MR4.5 for 2 years.

Unlike standard guidelines, which recommend monthly monitoring after stopping treatment for at least 6 months, this study adopted a less intense monitoring schedule. Patients were monitored every 2 months in the first year, every 3-4 months in the second year, and every 6 months thereafter.

What were the key results?

1. Out of 69 patients enrolled, 80% successfully maintained TFR at 1 year after stopping treatment. This success rate is higher than the average seen in other studies, likely due to the rigorous patient selection process.
2. Most patients who experienced a relapse did so within the first 6 months. Importantly, patients who remained in remission at the 6-month mark had a very low risk of relapse afterwards (<2%).
3. After restarting treatment, nearly all patients who relapsed regained control of their disease and achieved remission again.

Quote from Dr Jindal: "I practice in India, where patients often travel long distances from across the country, making frequent visits for monthly PCR monitoring challenging. The test is also expensive and takes about 15 days for results. To address this, we explored whether we could monitor a select group of more rigorously selected patients less frequently.

“We identified patients who had been on TKIs (tyrosine kinase inhibitors) for over 8 years, compared to the usual recommendations of 3–5 years, and applied more stringent patient selection criteria. These patients had maintained MMR for more than 5 years and deep molecular response for at least 3 years: a very select group. Our results showed an impressive TFR success rate of around 80%, compared with 50% in other studies, likely due to our careful patient selection.

“By reducing monitoring frequency, we could ease the burden on patients. Instead of monthly visits, we scheduled follow-ups every 2 months, extending to every 3-4 months over time. This approach is particularly helpful in resource-limited settings like ours, where many patients lack health insurance. We're now expanding this strategy to more patients in our clinic and hope to see similar success on a larger scale."

1. Punatar S, et al. Making Treatment Free Remission “Feasible” in Low- and Middle- Income Countries - Outcomes, Patterns of Failure and Compliance of Treatment Free Remission (TFR) in Chronic Myeloid Leukemia (CML) from a Tertiary Care Cancer Centre in India. Poster 3161. ASH 7-10 Dec 2024, San Diego, CA, USA.

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Asciminib, Once or Twice per Day?

Key message: Both dosing schedules showed good efficacy, with numerically higher responses seen in the twice daily group, which were not statistically significant. Both doses were safe and did not show any new side effects. The availability of a once-daily dosing option may improve quality of life and treatment adherence for some patients. These findings further support asciminib as a standard of care for patients with CML-CP who have not responded optimally to prior treatments.

Prof. Andreas Hochhaus (Comprehensive Cancer Center Central Germany – Campus Jena, Klinik für Innere Medizin II, Jena, Germany, in photo) presented the primary analysis from the ASC4OPT study [1].

What is this study about?
This ASC4OPT study evaluated the safety and effectiveness of two dosing schedules of asciminib, a BCR::ABL1 inhibitor, in patients with chronic-phase chronic myeloid leukaemia (CML-CP) who have already been treated with 2 or more tyrosine kinase inhibitors (TKIs). It compares once-daily (QD) and twice-daily (BID) dosing regimens to determine their impact on patient outcomes and treatment adherence.

Why is this important?
Patients with CML-CP who do not respond optimally to prior TKIs often require alternative treatment options. Asciminib, with its novel mechanism targeting the ABL myristoyl pocket, offers a promising solution. Comparing different dosing schedules can help improve patient quality of life by enhancing convenience and adherence without compromising effectiveness.

What did the researchers do? A total of 169 patients with CML-CP across multiple centres who had previously been treated with at least 2 TKIs were randomised patients to receive

either 40 mg of asciminib twice daily (BID) or 80 mg once daily (QD). They tracked molecular response rates, cytogenetic responses, and adverse events over 48 weeks.

What were the key findings?

1. Major molecular response (MMR) at week 48 was achieved by 38.5% of patients overall, with 42.4% in the BID group and 34.5% in the QD group. The difference was not statistically significant.
2. Complete cytogenetic response (CCyR) rates were 58.8% for BID and 54.8% for QD.
3. Deep molecular responses (MR4 and MR4.5) were more frequent in the BID group (20.0% and 11.8%) than in the QD group (13.1% and 8.3%).
4. Most patients (89.3%) experienced side effects, with 29.8% experiencing severe (grade ≥3) adverse events. The most common side effects included low platelet counts (15.5%), joint pain (13.7%), and low white blood cell counts (11.3%).
5. Of the 30 patients in MMR at the start of the trial, 93.3% maintained their response at week 48, with 100% in the BID group and 87.5% in the QD group.

Quote from Prof. Hochhaus: "For patients, every study is important because our goal is always to improve outcomes for those with CML. In this case, asciminib was originally developed as a twice-daily drug. However, patients expressed concerns about the twice-daily schedule early on, and from what we know about the drug's biology, pharmacokinetics, and dosage, a twice-daily regimen isn't strictly necessary.

The FDA has approved a once-daily schedule as an alternative to twice-daily dosing, but we need more data to fully understand its efficacy and tolerability. That's why we conducted this study, comparing 80 mg once daily with 40 mg twice daily. While this wasn't a non-inferiority study -meaning we weren't trying to show one schedule is better than the other - we wanted to confirm that both dosing regimens are well-tolerated and effective."

1. Hochhaus A, et al. Asciminib Shows High Efficacy and Favorable Tolerability at 80 Mg Once Daily and 40 Mg Twice Daily in Patients with Chronic Phase Chronic Myelogenous Leukemia Previously Treated with 2 or More Tyrosine Kinase Inhibitors: Primary Analysis from the ASC4OPT Study. Poster 4526. ASH 7-10 Dec 2024, San Diego, CA, USA.

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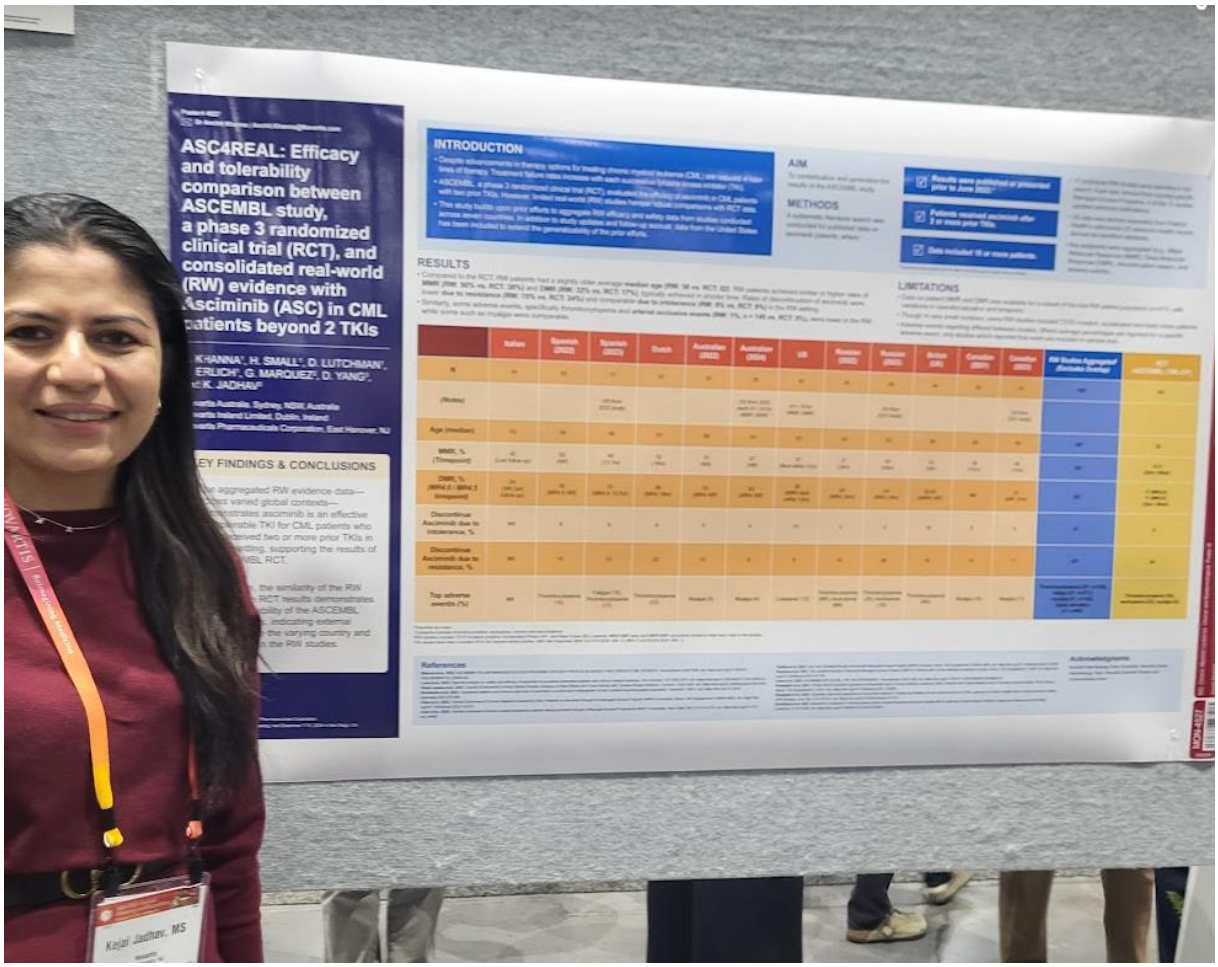
ASC4REAL: Asciminib Real World Use vs Clinical Trial

Key message: This study confirms that asciminib is an effective and tolerable treatment for CML patients who have failed multiple prior TKIs, both in clinical trials and real-world settings. The consistency between RW and RCT outcomes supports asciminib's role as a viable option for patients with limited treatment alternatives. Patients can be reassured that asciminib performs well across diverse populations and contexts, providing an important new option in the management of chronic myeloid leukaemia.

Senior author Dr Kejal Jadhav (Novartis, East Hanover, New Jersey, USA; in photo) presented the poster [1].



What is this study about?
This analysis compares the effectiveness and safety of asciminib, a tyrosine kinase inhibitor (TKI), in clinical trials versus real-world (RW) settings. Asciminib targets the myristoyl pocket of the BCR::ABL1 protein, offering a novel mechanism for treating chronic myeloid leukaemia (CML) patients who have failed at least 2 prior TKIs.

Why is this important?
Patients with CML often face limited treatment options as resistance increases with successive therapies. While clinical trials like the ASCEMBL study provide valuable data on the safety and efficacy of new treatments, real-world evidence (RWE) helps confirm these findings in broader, more diverse patient populations.

What did the researchers do?

Aggregated data from 10 RW studies (421 CML patients) across various countries, including newly added US data and updates from earlier studies. They then compared key outcomes such as molecular response rates, reasons for treatment discontinuation, and adverse events in RW studies to those observed in the ASCEMBL clinical trial (157 patients). They analysed how asciminib performs in real-world contexts, focusing on patients who had already been treated with at least two TKIs.

What were the key findings?

1. RW studies showed similar or better major molecular response (MMR) and deep molecular response (DMR) rates than the ASCEMBL trial, often achieved in shorter

timeframes. In RW studies, 52% of patients achieved MMR and 32% achieved DMR within a median of 13 months, compared to 38% achieving MMR and 17% achieving DMR within 22 months in the RCT.

2. Discontinuation due to intolerance was comparable (9% in RW vs. 8% in RCT). Discontinuation due to resistance was lower in RW studies (12% in RW vs. 24% in RCT).

3. Some serious side effects, such as thrombocytopenia and arterial occlusive events, were less frequent in RW studies, while others, such as myalgia and muscle spasms, were slightly more common.

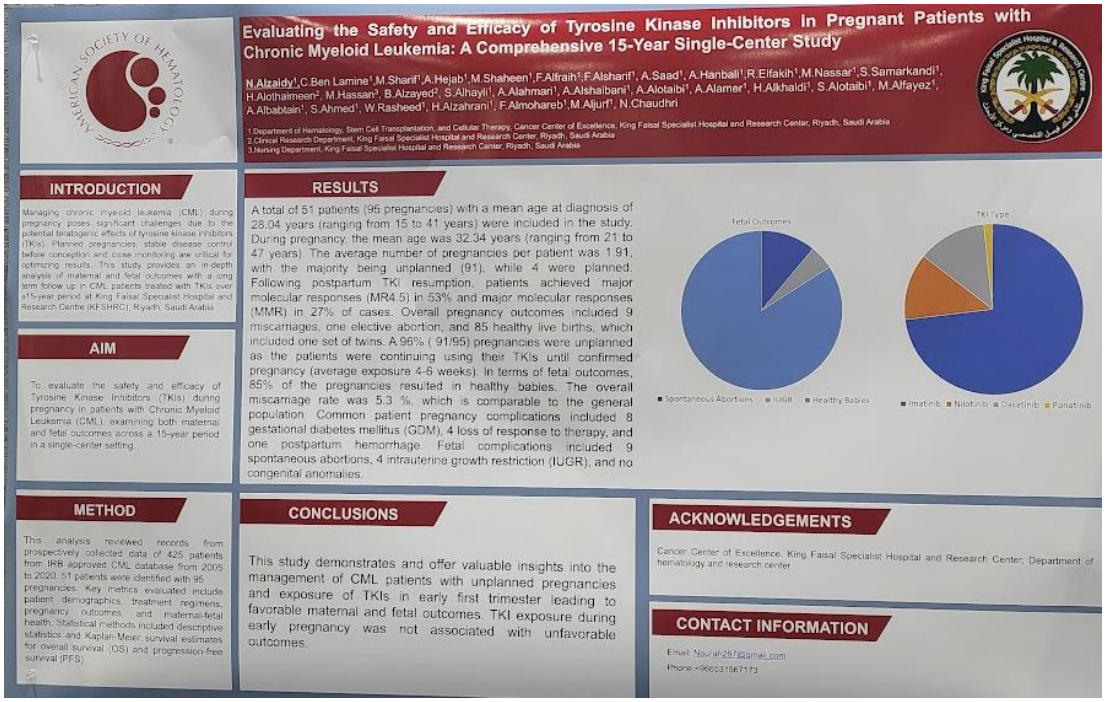
4. RW patients were older on average (59 years) than RCT participants (52 years), demonstrating the generalisability of asciminib's efficacy across a broader age range.

1. Khanna A, et al. ASC4REAL: Efficacy and Tolerability Comparison between Ascembl Study, a Phase 3 Randomized Clinical Trial (RCT), and Consolidated Real-World (RW) Evidence with Asciminib in CML Patients Beyond 2 TKIs. Poster 4527. ASH 7-10 Dec 2024, San Diego, CA, USA.

prepared by Patvocates: patvocates.net/

Reassuring Outcomes with Early TKI Exposure During Pregnancy

Key Message: This study provides reassuring evidence that TKI exposure during early pregnancy does not lead to unfavourable maternal or fetal outcomes. Women with CML can achieve healthy pregnancies with careful monitoring and disease management. Patients planning pregnancies or those with unplanned pregnancies should consult their healthcare providers for personalised guidance to ensure the best outcomes for both mother and baby.



What is this study about?
Dr Nourah Alzaidy (King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia) spoke with us about her study [1]. This study examines the outcomes of managing chronic myeloid leukaemia (CML) during pregnancy, focusing on maternal and fetal health in patients treated with tyrosine kinase inhibitors (TKIs). It provides insights based on 15 years of data from the King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia.

Why is this important?
TKIs, while highly effective for treating CML, pose potential risks during pregnancy due to their teratogenic effects. Understanding the outcomes of TKI exposure during early pregnancy can help guide the management of unplanned pregnancies in women with CML, optimising both maternal and fetal health outcomes.

What did the researchers do? Records of 51 CML pregnant patients with 99 pregnancies from 2005 to 2020 were analysed. Patient demographics, TKI treatment regimens, and pregnancy outcomes, including maternal and fetal health were used for the analysis.

What were the key findings?

1. 82% of pregnancies resulted in healthy live births, including one set of twins. The miscarriage rate was 5.3%, similar to the general population.
2. After resuming TKIs postpartum, 53% of the mothers achieved deep molecular response (MR4.5), and 27% achieved major molecular response (MMR). Common maternal complications included gestational diabetes mellitus (8 cases), loss of therapy response (4 cases), and one instance of postpartum haemorrhage.
3. No congenital anomalies were reported. Fetal complications included 9 spontaneous abortions and 4 cases of intrauterine growth restriction (IUGR).
4. Most pregnancies (96%) were unplanned, with TKI exposure continuing until pregnancy confirmation (average exposure 4–6 weeks). Early TKI exposure was not associated with adverse maternal or fetal outcomes.

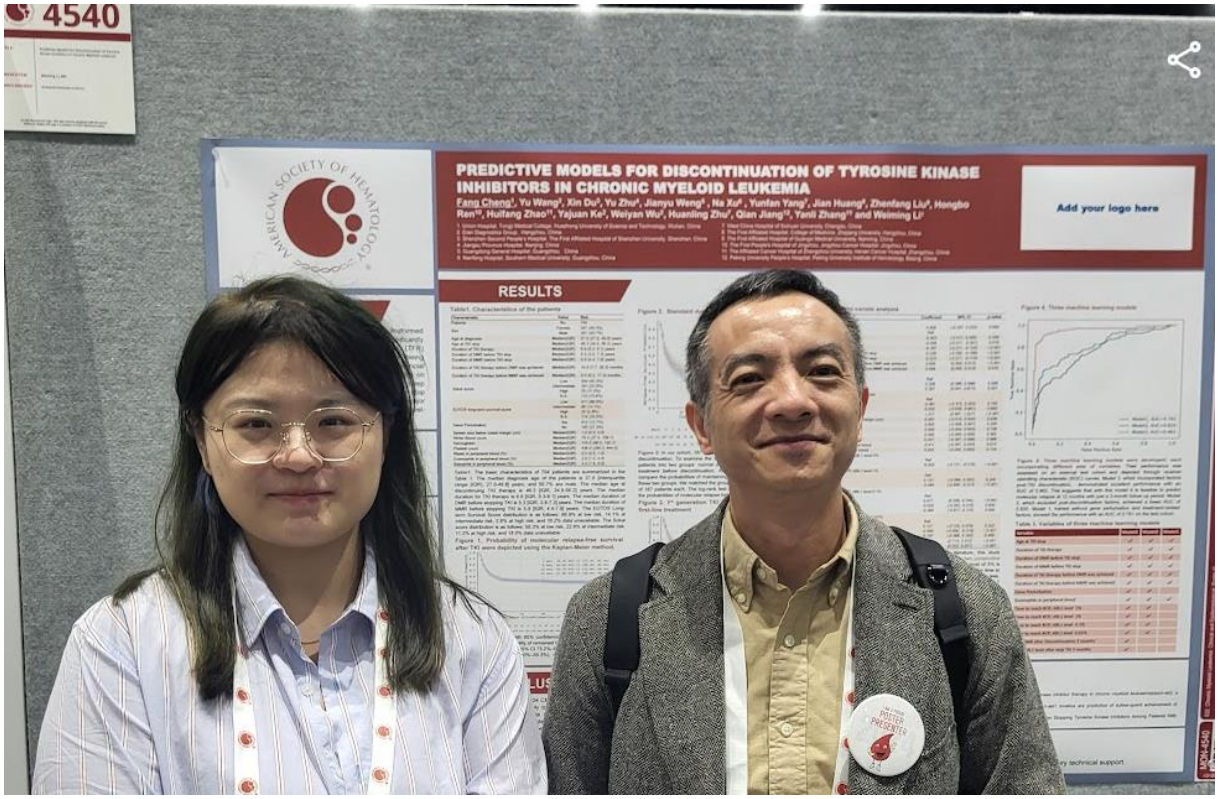
1. Alzaidy N, et al. Evaluating the Safety and Efficacy of Tyrosine Kinase Inhibitors in Pregnant Patients with Chronic Myeloid Leukemia: A Comprehensive 15-Year Single-Center Study. Poster 4536. ASH 7-10 Dec 2024, San Diego, CA, USA.

prepared by Patvocates: patvocates.net/

New Machine Learning Model Might Facilitate Treatment-Free Remission

Key message: This study provides a tool to help patients and doctors make more informed decisions about stopping TKI therapy. By using predictive models, patients with a higher chance of successful TFR can be identified, potentially reducing risks of relapse and unnecessary stress. Future research will aim to validate the model in larger patient groups and refine it further.

Prof. Weiming Li presented the poster together with his colleague Dr Di Wu (both are affiliated with Union Hospital, Wuhan, China, both shown in photo) [1].



What is this study about?
This study focuses on predicting the likelihood of successful treatment-free remission (TFR) in patients with chronic myeloid leukaemia (CML) who stop tyrosine kinase inhibitor (TKI) therapy. Using patient-specific clinical factors, researchers developed a machine learning model to help identify patients who are more likely to maintain remission after discontinuing TKI treatment.

Why is this important?
TKIs have transformed CML treatment, but long-term therapy can cause side effects and financial burdens for patients. Stopping TKIs is an important goal for many patients who have achieved a deep molecular response (DMR), but around half lose their response within 6 months of discontinuation. Predictive tools can help select patients who are more likely to successfully stop therapy, reducing risks and improving quality of life.

What did the researchers do? They reviewed data from 704 CML patients treated across 11 centres in China between 1999 and 2020. Using patient data such as age, treatment duration, blood counts, and risk scores, the team developed a machine learning model to predict whether patients would maintain major molecular response (MMR) for 12 months after stopping TKIs. The model was tested on an independent group of patients for validation.

What were the key findings?

1. The machine learning model accurately predicted TKI discontinuation success, achieving a sensitivity of 56.5%, specificity of 90.4%, and overall accuracy of 74.8%.
2. The model outperformed traditional predictors, such as the duration of DMR, which had lower accuracy (64.4% for DMR >3.1 years).

3. The success of TKI discontinuation was influenced by several factors, including fluctuations in specific genes, the duration of DMR and MMR before stopping, platelet and white blood cell counts, and the Sokal risk score.

Quote from Dr Weiming:

"I believe that most patients face challenges from side effects, as well as the financial burden of treatment. That's one of the key reasons we wanted to conduct this study.

As for the conclusions, we believe that for Chinese patients, and potentially for patients around the world, it is possible to aim for treatment-free remission (TFR). If we manage patients well and help them achieve deep molecular responses (DMR), they have a real chance of successfully reaching this goal."

5. Chang F, et al. Predictive Models for Discontinuation of Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia. Poster 4540. ASH 7-10 Dec 2024, San Diego, CA, USA.

prepared by Patvocates: patvocates.net/

Strong Association between Cancer Gene Variants at Diagnosis, Especially *ASXL1*, and Emergence of Kinase Domain Mutation-Driven Resistance in CML Patients Despite Frontline Treatment with More Potent BCR::ABL1 Inhibitors

Speaker: Dr. Naranie Shanmuganathan (Adelaide, Australia)

"ASXL1 variants were associated with inferior outcomes, despite treatment with potent TKIs." – Naranie Shanmuganathan

Key points:

- **Cancer variant prevalence**: 20% of patients treated with potent TKIs had cancer variants at diagnosis, with *ASXL1* being the most frequent (8%).
- **Inferior molecular responses**: Patients with *ASXL1* mutations had significantly lower 12-month MMR rates and higher kinase domain mutation acquisition rates at two years.
- **Resistance patterns**: *ASXL1*-mutated patients faced a 29% risk of developing kinase domain mutations, often driving treatment resistance.
- **Comparison of TKIs**: *ASXL1* mutations showed poorer outcomes across all TKI types, with failure-free survival significantly impacted.
- **Future strategies**: Results suggest the need for combination therapies to improve outcomes in high-risk patients with *ASXL1* mutations.

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Molecular Outcome of Chronic Myeloid Leukemia-Affected Patients Not in Deep Molecular Response: The "Others" from the GIMEMA Labnet Network

Speaker: Prof. Fabio Stagno (Naples, Italy)

"The GIMEMA LabNet-CML network harmonises molecular diagnostics across Italy, ensuring equitable access to testing." – Fabio Stagno

Key points:

- **Stability of response**: 32% of patients maintained a stable MR3/MR2 response at 48 months, while 66% progressed to a deep molecular response.
- **Early fluctuations**: Molecular fluctuations in BCR::ABL1 transcripts were predictive of instability and relapse risk.
- **Uniform diagnostic tools**: The GIMEMA LabNet provided harmonized molecular diagnostic access for over 9,000 patients across Italy.
- **Age-independent outcomes**: No significant differences in molecular responses were observed between age groups.
- **Clinical utility**: Molecular response monitoring using the GIMEMA framework aids in identifying patients at risk of poor outcomes.

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Increased Inflammatory Cytokines in Plasma Are Associated with Sustained Treatment-Free Remission in Chronic Myeloid Leukemia

Speaker: Dr. David Ross (Adelaide, Australia)

"Patients with a 'hot' cytokine profile had significantly better treatment-free remission outcomes." – David Ross

Key points:

- **Cytokine clustering**: Patients were categorised into "hot" (high cytokine levels) and "cold" (low cytokine levels) groups, with 73% of hot patients achieving TFR.
- **Biomarker development**: A six-cytokine panel predicted TFR outcomes across Australian and U.S. cohorts with high consistency.
- **Independence of clinical features**: Cytokine profiles were independent predictors of TFR, unaffected by traditional factors like treatment duration or transcript type.

- **Validation across cohorts**: Both Australian and U.S. cohorts displayed similar cytokine clustering patterns and predictive outcomes.
- **Simplified analysis potential**: Findings suggest that streamlined cytokine testing could improve TFR prediction accuracy.

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Common Lymphoid Progenitors and B Cell Subpopulations in the Bone Marrow Are Predictive of Treatment-Free Remission in Chronic Myeloid Leukemia

Speaker: Dr. Shaun Patterson (UK)

"Memory B-cell expansion and skewed progenitor differentiation may be critical for predicting relapse." – Shaun Patterson

Key points:

- **Progenitor differences**: Reduced common lymphoid progenitors (CLPs) and altered differentiation patterns were observed in relapsing patients.
- **B-cell subtypes**: Increased activated switched memory B-cells were a hallmark of relapsing patients, reflecting immune perturbations.
- **Metabolic insights**: Downregulated mTORC1 signaling in relapsing patients indicated potential metabolic disruptions.
- **Predictive modeling**: A ratio of naïve to memory B-cells emerged as a strong predictive marker for TFR.
- **Therapeutic implications**: Findings highlight immune modulation as a potential strategy for improving TFR outcomes.

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FATE and Role of Peripheral Blood CD26+ Leukemia Stem Cells at Diagnosis in Chronic Myeloid Leukemia Patients: FINAL Results of Prospective Flowers Study

Speaker: Prof. Monica Bocchia (Siena, Italy)

"The CD26+ leukemia stem cell burden at diagnosis is a prognostic indicator of treatment outcomes." – Monica Bocchia

Key points:

- **Stem cell presence**: CD26+ leukemia stem cells were detectable in 100% of patients at diagnosis, with high variability in numbers.
- **Decline with treatment**: CD26+ stem cells rapidly decreased during TKI therapy but persisted at low levels over time.
- **Prognostic value**: High CD26+ cell counts at diagnosis correlated with poorer molecular responses and higher treatment failure rates.
- **TFR persistence**: Persistent CD26+ cells did not prevent successful TFR in some patients, suggesting immune system control mechanisms.
- **Clinical application**: CD26+ cell quantification offers a simple, rapid biomarker for predicting TKI response and outcomes.

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Longitudinal Clonal Tracking Reveals That Early and Sensitive Detection of Blood Cancer-Related Gene Variants in Patients with Chronic Myeloid Leukemia Predicts Treatment Failure

Speaker: Prof. Susan Branford (Australia)

"Early detection of cancer variants may enable proactive intervention to prevent treatment failure." – Susan Branford

Key points:

- **Variant co-occurrence**: 83% of patients with treatment failure had cancer variants, often preceding kinase domain mutations by nine months.
- **Clonal complexity**: Multiple cancer gene variants were detected, with ASXL1 being prevalent in chronic phase and other genes dominating in blast phase.
- **Dynamic evolution**: Clonal tracking revealed convergent evolution, clonal competition, and mutation emergence tied to treatment changes.
- **Predictive insights**: Early cancer variant detection offered a proactive avenue for mutation management and treatment adjustment.
- **Targeted therapies**: Findings highlight the potential for combined therapies targeting both BCR::ABL1 and associated cancer variants for improved outcomes.

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18-months follow-up of the trial of imatinib after ponatinib induction (TIPI) in the front-line

treatment of chronic phase CML setting

Presenter: **Dr Delphine Réa (Paris)**
" A strong induction phase followed by lighter maintenance could redefine frontline CML treatment." – Delphine Réa

Key points:

- **Ponatinib-induction results:** The trial reported MMR in 57% of patients at six months and 72% at 18 months. Deep molecular responses (MR4 and MR4.5) reached 45% and 21%, respectively, at 18 months.
- **Transitioning to imatinib:** After ponatinib induction, molecular responses were maintained or deepened during imatinib maintenance, with only 7% of patients losing MMR.
- **Mutation control:** BCR::ABL1 mutation analysis revealed three mutations, two of which emerged during imatinib maintenance. None were associated with T315I.
- **Cardiovascular safety:** Grade 3 and 4 cardiovascular events occurred in 4.5% of patients during ponatinib induction, but no significant events were reported during imatinib maintenance.
- **Study implications:** This strategy may provide a safer path to treatment-free remission, particularly for patients at risk of mutation-driven resistance.

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Management of relapsed CML, including in patients with T315I mutation

Speaker: **Professor Michael Mauro (New York, USA)**
"Mutational analysis is central—resistance isn't a blanket issue; it's about identifying which drugs will work for which mutations and tailoring treatment accordingly."– Michael Mauro

- **Assessing treatment failure:**
    - Early identification of suboptimal response or resistance involves evaluating adherence, drug interactions, and mutation analysis.
    - Guidelines emphasise prompt mutation profiling and therapy adjustment for patients failing to achieve molecular response milestones (e.g., MMR by six months).

- **Mutational analysis and resistance mechanisms:**
    - Point mutations in the ATP-binding or myristoyl pockets can lead to drug resistance, necessitating tailored treatment strategies.
    - Asciminib shows efficacy in overcoming resistance linked to ATP-binding mutations but may face challenges with newer mutations.

- **Advanced disease management:**
    - Ponatinib: Effective for T315I mutations, as evidenced in the PACE trial, but requires vigilant cardiovascular monitoring due to arterial occlusive risks.
    - Asciminib: Superior to bosutinib in the ASCEMBL trial, with promising results even in heavily pretreated patients, but requires attention to mutation-specific efficacy and safety concerns.
    - Transplant remains a vital option for selected high-risk cases with advanced disease or refractory mutations.

- **Emerging therapies and future directions:**
    - New ATP-competitive agents like olverembatinib and allosteric inhibitors like TERN701 are showing promise in clinical trials for resistant mutations and later-line therapy.
    - Sequencing TKIs based on resistance mechanisms and individual patient profiles is becoming more nuanced, particularly for T315I-positive and multi-resistant cases.

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