CML AdvocatesNetwork

First report from the American Society of Hematology Congress 2019

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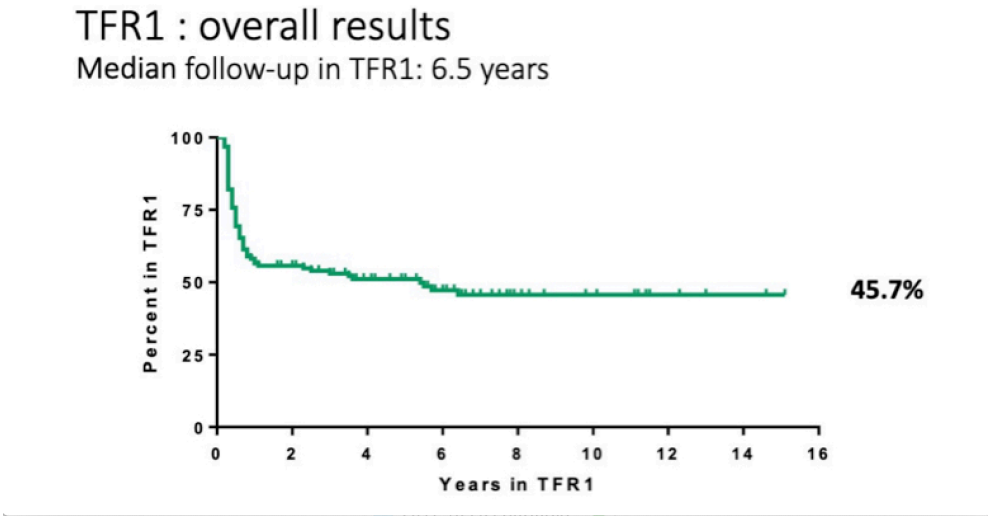
Update on stopping treatment (Therapy-Free Remission)

Achieving therapy-free remission (TFR) continues to be amongst the most discussed topics in CML at the moment. At this year's ASH congress, the first plenary oral session on CML was dedicated to the topic of TFR and there were many posters as well.

Overall, there are no big news in the area of TFR, but research continues intensively. Across all the different studies, about half of all patients that are stopping therapy after years of deep molecular response to TKI (below MR4 / BCR-ABL below 0.01) need to restart treatment. The main open questions remain to predict the individual patients' likelihood of a successful stop, the need for life-long PCR monitoring to catch potential late recurrences of CML, and whether a second attempt to withdraw therapy is feasible and safe.

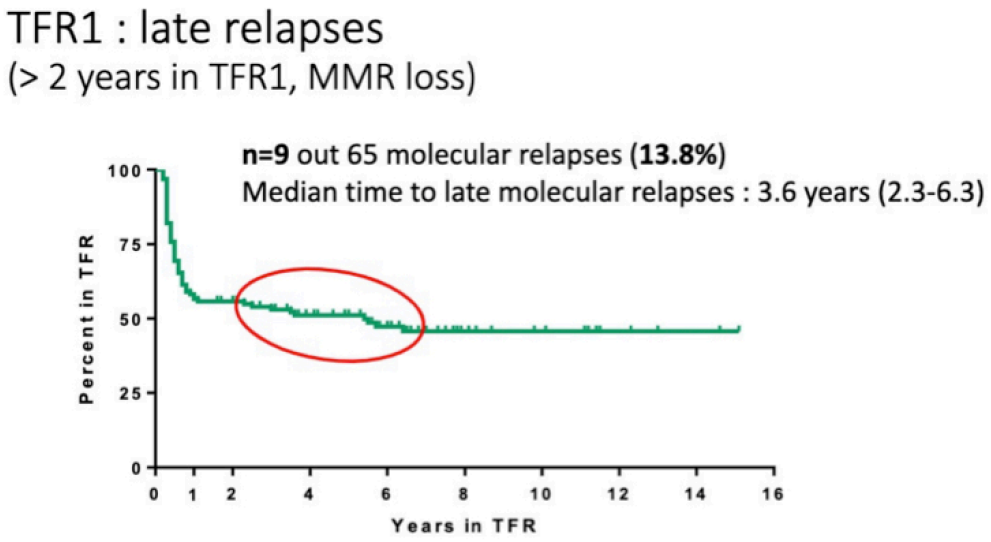
Long term follow-up of patients in TFR

In terms of long-term follow-up on stopping treatment, Prof Philippe Rousselot from the Centre Hospitalier de Versailles in France presented observational data from 114 patients over a period of 15 years on Long Term Follow-up, Late Molecular Relapses and Second stopping Attempts.



Of the 112 patients, 54%, 26% and 20% belonged to low, intermediate and high-risk categories respectively. Median duration of TKIs before the first TFR attempt ("TFR1") was 7.4 years. 31% of patients were previously treated with interferon, 62 (54%) received imatinib only and 52 (46%) were on 2nd generation TKIs at the time of discontinuation. Median follow-up in the first attempt of TFR was 5.4 years. TFR1 rates were 57.6% at 1 year, 53.8% at 3 years, 51.6% at 5 years and 44.5% after 7 years. The longest duration of ongoing TFR is 14.9 years.

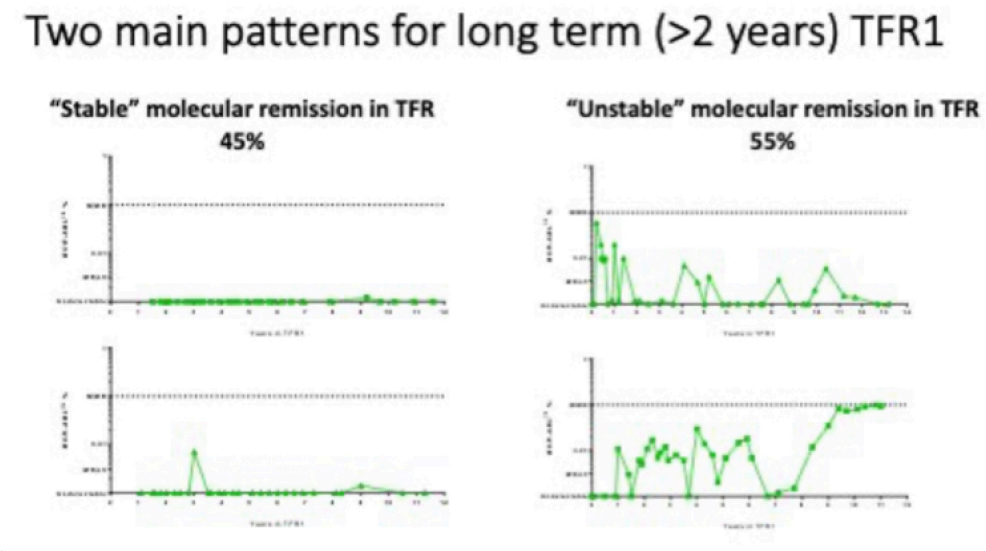
The duration of TKIs and the duration of MR4.5 were associated with a higher TFR rate; a trend was observed for previous exposure to interferon. Patients on second-generation TKIs (first or second line) had similar TFR rates as compared to patients on imatinib.



Fifty-seven patients relapsed, including 8 patients (14%) experiencing late molecular relapses. Of those, 4 patients relapsed after 5 years. The latest molecular relapse was observed after 6.4 years. In late relapsing patients, MR4.5 was lost after 10 months in median and MR4 after 22 months with a long-lasting period of fluctuations of the BCR-ABL1 ratio in-between MR4 and MR3.

Out of the 57 patients who restarted a TKI after TFR failure, 31 patients (54%) experienced a second stopping attempt ("TFR2"). Median duration of TKIs between TFR1 and TFR2 was 2.9 years, and total exposure to TKIs before TFR2 was 9 years. Fifteen patients (48%) were on imatinib before TFR2 whereas 16 where on 2G-TKI (52%). Median follow-up in TFR2 was 3.4 years. TFR2 rates were 53.9% at 1 year, 45.6% at 3 years and 39.9% after 5 years.

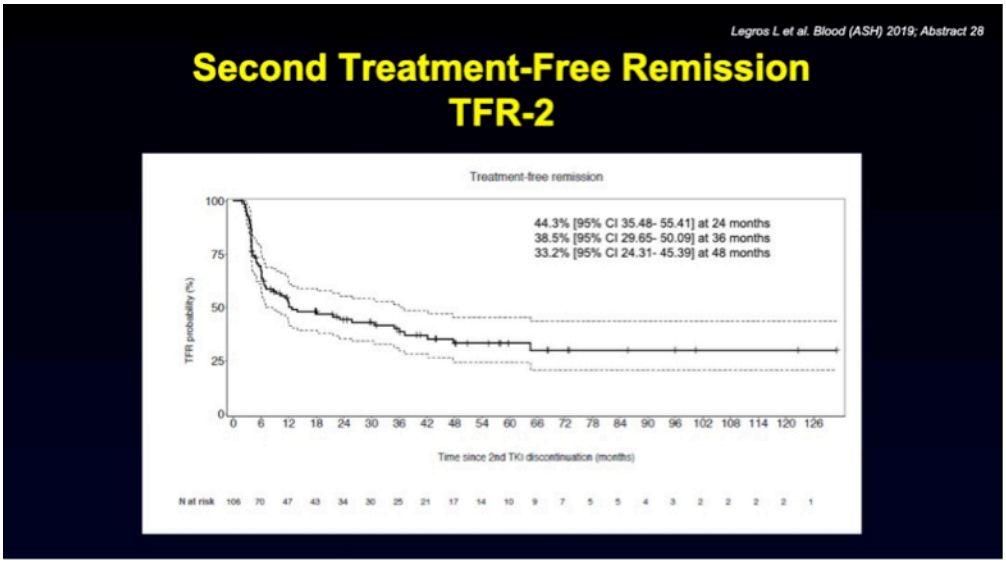
The longest TFR2 is 9 years. No factor was associated with better TFR2 duration, e.g. a switch to 2nd generation TKIs did not provide any advantage. Seventeen patients relapsed including 3 patients (17%) experiencing late molecular relapses. Anecdotally, 5 patients went to a third TFR attempt and 1 is in TFR3 for 5.2 years.



There was an observed difference of "stable" versus "unstable" molecular remission in TFR1. Of those who stayed below MR4 in all PCR assessments after stopping therapy ("stable molecular remission"), 96.5% of all patients stayed in TFR in the long run, while of those whose PCR went above MR4 but stayed below MMR, the criterium for restarting treatment, only 67.3% remained in TFR.

Based on a 15 years' experience we were able to report on long term follow-up in TFR1 and in TFR2. Among patients experiencing molecular relapses, the researchers observed 14% and 17% late relapses after more than 2 years after TFR1 and TFR2 respectively. Other than in earlier reports from the STIM stop studies, there seems to be no true plateau on TFR in the long run. This suggests that a long-term molecular follow-up is mandatory for CML patients in TFR.

Second stop attempt: Successful in about 31% of patients



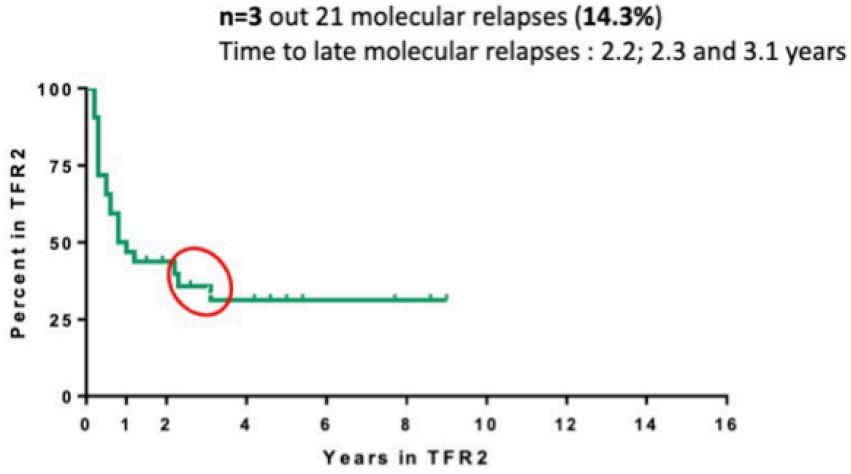
Laurence Legros from Villejuif, France, presented the data of the RE-STIM study, a French observational multi-centre study that is collecting all cases of TFR2 attempts, regardless the type, the duration of TKI, the duration of MR4.5 and the reason of discontinuation of treatment.

CML patients who had to restart therapy after a first attempt had to achieve a sustained MR4.5 (PCR below 0.0032%) on any TKI to be eligible. Loss of MMR was the trigger for therapy re-introduction.

At the time of analysis (1st June 2019), 106 patients (median age: 55 years, range: 25-81 years) were included with 41 months (2-131) of follow-up after 2nd discontinuation. 33.2% of patients were still in second treatment-free remission at 48 months, all others had to restart therapy.

In TFR2, 13% of all recurrences of CML occurred very late: 3 patients had a molecular relapse after 2.2, 2.3 and 3.1 years.

TFR2 : late relapses
(> 2 years in TFR2, MMR loss)



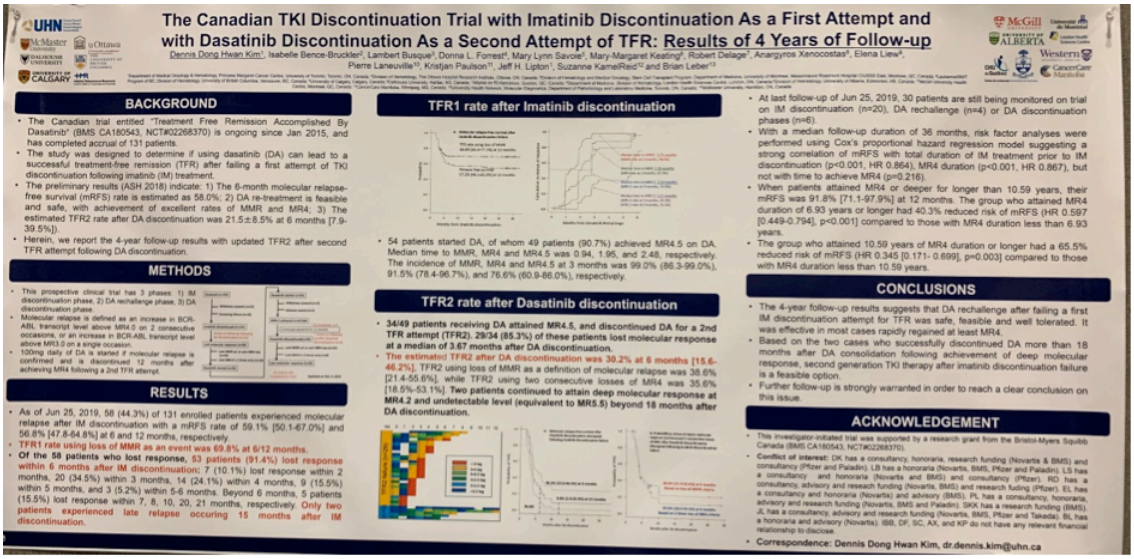
Overall, second stop attempts in MR4.5 are successful in the long run about one third of patients. The speed of molecular relapse after the first TKI discontinuation and the TKI-free duration after the first stop remain major factors significantly associated with the success rate of a second stop.

The observations confirm that TKIs could safely and successfully be discontinued a second time in CML patients after the first attempt failed of performed under a close and extended molecular and medical monitoring. The authors do not recommend a 2nd stop attempt outside of a prospective trial.

A TFR2 success rate of around 30% seems also to be supported by data of the Canadian TKI Discontinuation trial presented by Dr. Dennis Dong on a poster at ASH.

In that trial, patients on imatinib discontinued therapy, and in case of loss of major molecular response, patients restarted with dasatinib (100mg/day) and discontinued again 12 months after re-achieving MR4.

In this study, 59.8% of patients needed to restart therapy after the second stop attempt within the first 6 months.



In the presentation of Philippe Rousselot, the factors associated with successful second stops were the duration of MR4 as well as the duration of TFR in the first stopping attempt. However, in his analysis, duration of TKI therapy before the first stop attempt, and between the first and second attempt, total TKI duration, the type of TKI and prior Interferon therapy did not have an influence on the success of the second attempt.

Safe, but no real plateau: Need for life-long PCR monitoring further strengthened by study data

All data seems to suggest that continuous and consistent monitoring is important after stopping treatment even in the long run. The studies presented at ASH all seemed to observe a very small number of late recurrences which happened years after treatment – and within those clinical studies, patients restarted treatment quickly and responded to treatment, except one patient in the French STOP-2G-TKI who was found in sudden myeloid blast crisis at the month 6 TKI reintroduction visit, but was subsequently treated successfully with stem cell transplant after chemotherapy plus ponatinib, and is still alive in remission 29 months later.

Overall, at this year's ASH, in different presentations and posters, four single case reports of patients who progressed from TFR to CML blast crisis were reported within different STOP studies. When we asked different experts about potential explanations, they consider them to be spontaneous progressions which would have equally happened to the same patients under continuous therapy.

Similar progressions were observed already during Interferon times after years of complete remission. However, even though this is an extremely rare phenomenon given thousands of CML patients are under close observation in CML stop studies and only four cases of sudden transformation to blast crisis have been observed, this certainly needs to be followed and studied further.

Overall, late recurrences after stopping treatment and also the aforementioned effects clearly tell that continued regular monitoring is required even for those patients how have been in therapy-free remission for some years – even though TFR is a blessing for those patients who can stop successfully, there is no escape from PCR.

Good practice, bad practice: Is close monitoring in TFR taken serious enough?

So is close PCR monitoring in TFR taken serious enough? Dr. Ehab L. Atallah from the Medical College of Wisconsin presented a poster at ASH about this. His team assessed the clinical practice of US physicians managing CML patients with CML discontinuation following the publication of the first NCCN practice guidelines and the ESMO Guidelines which include specific considerations for TKI therapy discontinuation.

From 3-31 July 2019, in total 111 oncologists/hematologists from different US regions completed a survey on their clinical practice with regards to the management of patients with CML in the chronic phase receiving TKI therapy. The hematologists had to have completed their medical subspecialty training and be responsible for treatment decisions and follow-up for at least adult CML patient who received TKI therapy outside of a clinical trial setting since January 2017. The survey collected information on physician practice setting and experience with CML management with a focus on molecular monitoring and TKI therapy discontinuation.

The physicians were from the community- (56.8%) and academic-based practice (43.2%). Most (54.1%) were from large practices (10 physicians or more), with the remainder mostly being in small/intermediate practices of 2-9 physicians (42.3%) with a few in individual practice (3.6%). The practice setting environment was mainly urban (49.5%), followed by suburban (42.3%) and rural (8.1%). The majority of physicians (55.9%) had more than 10 years of practice since completing medical subspecialty training, 32.4% had 5-10 years, and 11.7% had less than 5 years of practice. All physicians reported testing patients for molecular response and having access to molecular results reported on the international scale (IS).

Of the 111 physicians, 86.5% reported having attempted TKI discontinuation after achieving an adequate response for at least 1 patient and 64.0% did so outside of a clinical trial. Among these 71 physicians, the majority would consider TKI therapy discontinuation for medical reasons (62.0% adverse events, 60.6% pregnancy planning), with fewer for economic reasons (31.0% high deductible, 14.1% change in health plan coverage); 35.2% reported they would consider it for all of their patients who achieved an adequate response; reasons for TKI therapy discontinuation after achieving an adequate response were not mutually exclusive. Among these 71 physicians who have attempted TKI discontinuation outside of a clinical trial, only 43 (60.6%) were aware of the updated clinical practice guidelines for TKI therapy discontinuation.

The authors conclude that TKI discontinuation is becoming more common both in the community- and academic-based practices in the US, but unfortunately it appears to be attempted without the use of accurate and sensitive tools to assess the adequate response when determining patient eligibility for TKI therapy discontinuation.

Half of the physicians surveyed did not have access to a reliable qPCR test with a sensitivity to detect at least MR4.5. As TKI discontinuation practice is likely to be increasingly adopted, guidelines also need to be broadly communicated to physicians.