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Poster# **CO102**

# Estimating the mean time in treatment free remission for patients in early line CML

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## KEY FINDINGS & CONCLUSIONS

- Clinical benefits of TFR can be underestimated due to the large proportion of patients who will experience a molecular recurrence and/or reinitiate TKI treatment in the first 6 months of TFR attempt and reporting of median time may not reflect those who maintain remission beyond the first year due to the presence of a survival plateau
- Given the nature of the analysis conducted, results are expected to become more pronounced with longer study follow-up as the majority of events occur in the first year after stopping treatment
- Hence, mean TFR duration may provide a more accurate real-world evaluation, supporting improved outcome projections for eligible CML patients

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## INTRODUCTION

- Chronic myeloid leukemia (CML) is a rare blood cancer characterized by the abnormal proliferation of myeloid cells in the bone marrow, leading to high levels of immature white blood cells in the blood [1]
- Safely discontinuing tyrosine kinase inhibitor (TKI) treatment, also known as treatment-free remission (TFR), is an increasingly recognized key treatment goal in CML therapy
- For patients entering TFR, 41-51% are expected to have a molecular recurrence within 6 months to 1 year, while those who maintain response beyond the first year often experience longer periods of treatment free remission than the median time suggests [2]
- Therefore, when estimating the time a patient may spend in TFR, the mean may provide a more accurate representation and account for the presence of a survival plateau[3]

## METHODS

- Findings from a targeted hand search and systematic literature review were presented at ISPOR 2024 which identified first-line CML clinical studies reporting TFR outcomes[4]
- Electronic databases (Embase®, MEDLINE®, Cochrane) and grey-literature were searched for English language publications from clinical trials published until 12-October-2023 for evidence on clinical-efficacy, QOL and TFR
- Studies were screened and selected based on suitability of endpoints for analysis and criteria of deep molecular response (DMR) definition of at least MR4.5 to be included
- Studies were excluded if they did not present Kaplan-Meier (KM) time-to-event data
- For this analysis, “Time in TFR” refers to the length of time patients remained off treatment after safe discontinuation, without the need for treatment re-initiation, while KM curves reporting 'survival' denote the probability of remaining free from the defined event (e.g., loss of TFR) and not survival from death
- We reported Mean Survival Time (MST) and Restricted Mean Survival Time (RMST) to quantify average time in TFR across studies: MST summarizes observed durations but can be biased with censoring, while RMST provides a robust, interpretable average up to a specific time of 5 years enabling fair comparison with ENESTfreedom when full follow-up is incomplete

## RESULTS

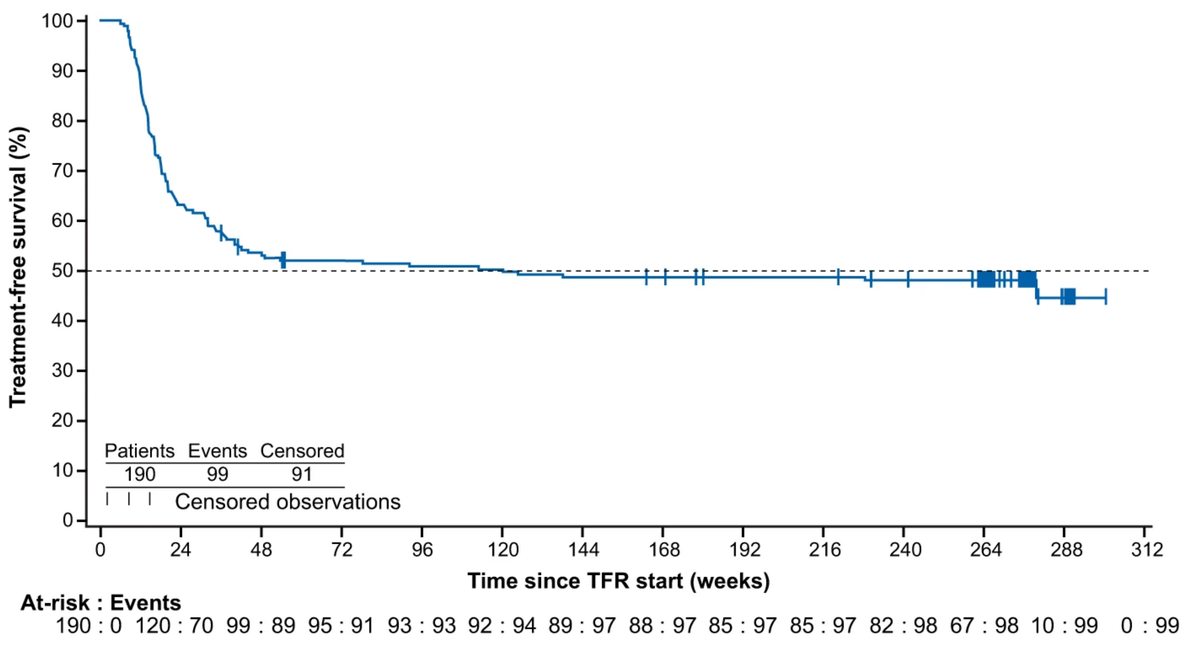
- Overall, 34 studies were identified, out of which twelve randomized-clinical-trial studies reported outcomes on efficacy and safety, and two on QOL. A further twenty-four observational and non-randomized studies reported TFR
- Of the studies which reported TFR outcomes, only three studies were identified for inclusion in this analysis, having met the predefined criteria
- All three studies had a long study follow up of =>5 years and showed promising results, indicating that many patients remain in TFR at 60 months

### ENESTfreedom[5]

ENESTfreedom was a prospective, single-arm study evaluating TFR after frontline nilotinib in adults with chronic-phase CML who achieved and sustained a DMR (MR4.5). To be eligible for TFR a patient had to be previously treated for at least 3 years with nilotinib and achieved sustained DMR (defined as MR4.5 in the most recent assessment, ≤2 assessments between MR4 [BCR-ABL1IS ≤ 0.01%] and MR4.5, and no assessment worse than MR4 in the last 4 quarterly RQ-PCR assessments)

- Individual patient data (IPD) from the ENESTfreedom trial (cut-off date of 3rd February 2020) was analysed to estimate the mean TFR duration and restricted mean TFR duration that patients spent in TFR. For patients ongoing in the TFR phase, cut-off date is used as the end date of TFR phase
- Restricted mean TFR duration was used to compare available data from ENESTfreedom with the selected studies at 5 years (60 months / 260 weeks)
- Analysis of ENESTfreedom patient data at 260 weeks revealed a mean TFR duration of 30 months compared to the reported median TFR duration of 28 months

**Figure 1. Kaplan–Meier estimate from ENESTfreedom trial of treatment free survival for all patients who entered the TFR phase[5]**



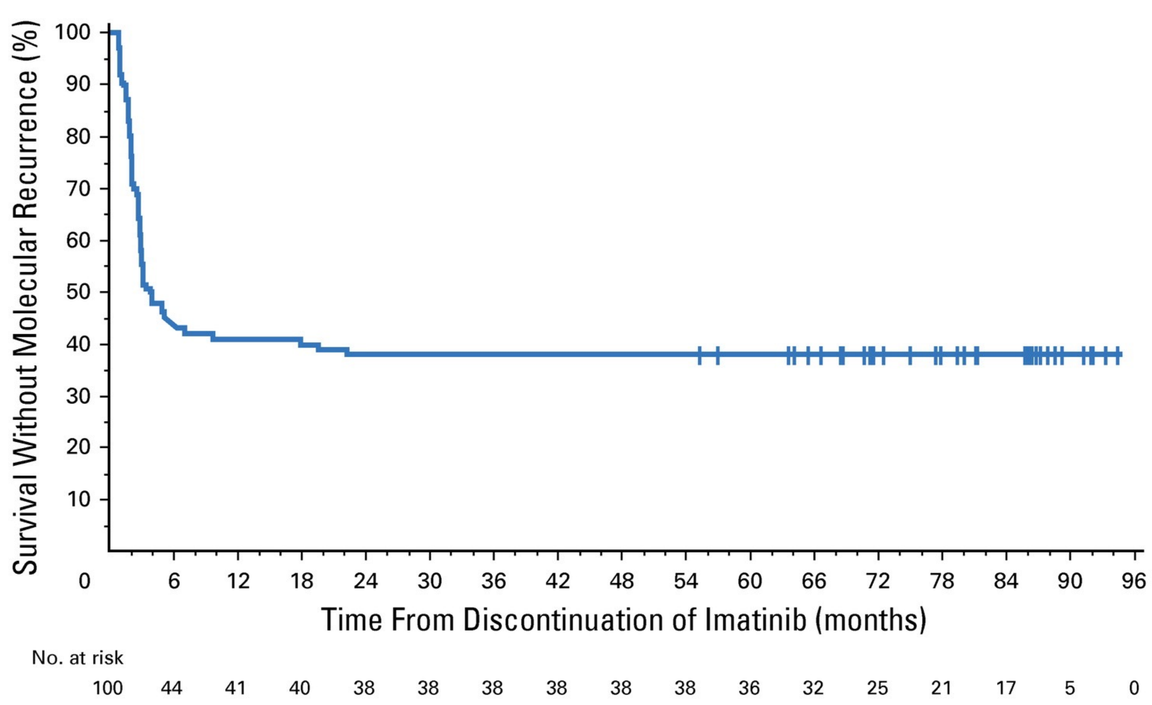

### STIM-1[6] & STIM-2[7]

The STIM-1 study was the first prospective trial designed to assess TFR efficacy in patients who had been treated with Imatinib. To be eligible for inclusion, patients had to be treated for at least 3 years and in sustained undetectable molecular residual disease (UMRD) for at least 2 years

STIM-2 study was a follow up prospective trial based on the STIM-1 trial where cessation of imatinib treatment was proposed for patients in sustained DMR who were treated only with imatinib

- KM curves from each study were digitized using WebPlotDigitizer 5.2 software[8] and an area under the survival curve (AUC) analysis was then conducted to effectively capture the plateau presence in survival curves to estimate the MST and RMST
- Based on the analysis, results were in line with the IPD analysis with restricted mean (RMST) TFR duration values of 25 months and 31 months, respectively
- When full study follow up is considered from the STIM-1 and STIM-2 trials, MST results illustrated a longer expected time in TFR of 38 months and 51 months

**Figure 2. Molecular recurrence–free survival after imatinib discontinuation from the STIM-1 trial[6]**




### Discussion

- Overall, our findings emphasize the relative safety of attempting TFR for eligible patients. Whilst 50% of patients may lose response during the first year of TFR, according to the European Leukemia Net (ELN) 2020 guidelines, those patients will be able to reinitiate their previously successful TKI therapy with approximately 95% of patients regaining pre-discontinuation levels of response
- When the analysis of ENESTfreedom patient data is extended beyond the 5 years (260 weeks) to 5.8 years (300 weeks) the MST increased to 36 months in TFR, however this estimate may be uncertain due to the level of censoring present after week 260. Censoring occurred at the date of last assessment
- This highlights the need for future analysis which is planned as further longer-term trial readouts are published from ENESTfreedom, with estimates of MST expected to increase, reflecting the tail-end plateau of the time-to-event curves as present in STIM-1 & STIM-2 studies. Future analysis could potentially integrate real world data, to extrapolate a more accurate estimate of real world TFR by applying parametric modelling with real world evidence

### Limitations

- Efficacy outcomes varied across the reported time-points and studies with sufficient follow up were limited
- The definitions for eligibility criteria for TFR varied significantly across studies with a stricter criteria such the ELN 2020[9] guidelines expected to result in a more successful period of TFR

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### Disclosures

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