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# Clinical Outcomes of Interventions in Patients with Newly Diagnosed Chronic Myeloid Leukemia - A Systematic Literature Review

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## CONCLUSIONS

- Reported evidence supported better effectiveness of dasatinib, nilotinib, and bosutinib over imatinib in front-line CML-CP.
- Among safety outcomes, AE related treatment-discontinuation was lower with imatinib and nilotinib.
- Initiating TFR benefited patients by controlling disease progression without treatment and eliminated treatment-related-AEs. However, further research is needed to compare overall incremental and sustained benefit of TKIs as front-line CML-CP treatment.

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## INTRODUCTION

- Chronic myeloid leukemia (CML) is a rare type of cancer and accounts for approximately 30% of adult leukemia cases worldwide.[1]
- Tyrosine kinase inhibitors (TKIs) revolutionized treatment of chronic myeloid leukemia in chronic-phase (CML-CP)[2], however, long-term benefit depends on treatment tolerability, quality-of-life (QOL) improvement, and sustained deep molecular response (DMR), which impacts patients' future treatment free remission (TFR) eligibility.[3]
- This systematic literature review summarized clinical evidence of interventions in front-line CML-CP.

## METHODS

- 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 and QOL.
- The searches were extended to include observational studies published until 08-February-2024 to retrieve evidence on TFR.

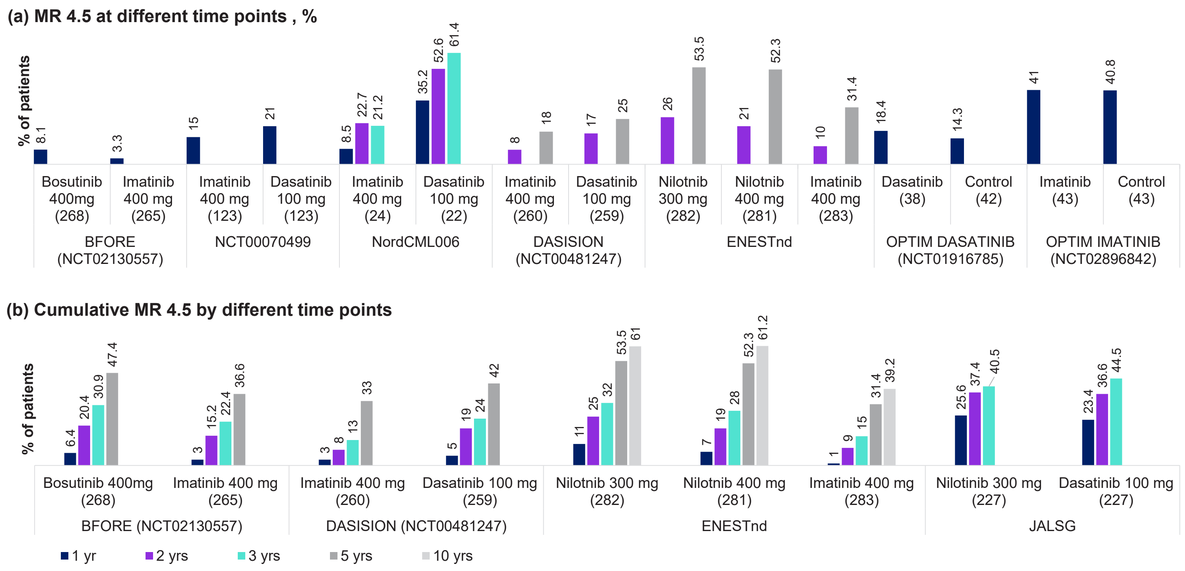
## RESULTS

- Overall, 34 studies were included, out of which twelve randomized-clinical-trial studies reported outcomes on efficacy and safety, and two on QOL.
- Twenty-four observational and non-randomized studies reported TFR.

### Clinical Efficacy

- Evidence on molecular response rates was reported at different time-points across the studies, wherein, results at 12-24 months are commonly reported (**Table 1**).
  - Most studies reported favourable major molecular response (MMR) rates at 12 months of treatment with the second-generation TKIs compared with imatinib (dasatinib: 36.8%-81.8%; bosutinib: 41.0%-47.2%, and nilotinib: 44.0%-52.2%; versus imatinib: 22.0%-67.0%).
  - Deeper responses, such as MR4.5, were notably higher for dasatinib and nilotinib when compared with other TKIs (**Figure 1**).
  - Early molecular response (EMR) was reported at 3 months and was similar for dasatinib (84.0%-95.5%), nilotinib (82.0%-91.0%), and bosutinib (75.2%-86.0%). These results were consistently higher than imatinib (57.3%-70.8%) across all studies.

**Figure 1. Long term results of MR4.5 in different studies**




- Survival outcomes were observed close to the general population and were consistently >90% across all treatments at 1- to 2-years of follow-up time-point (**Table 1**).
  - Overall-survival (OS) rate at 5-years was reported in three studies, while only one study (ENESTnd) reported OS at 10 years.
  - At 5-years, the OS for imatinib ranged from 90.0% to 94.6%, whereas it was 91.0% for dasatinib, 94.5 for bosutinib, and 96.3% for nilotinib.

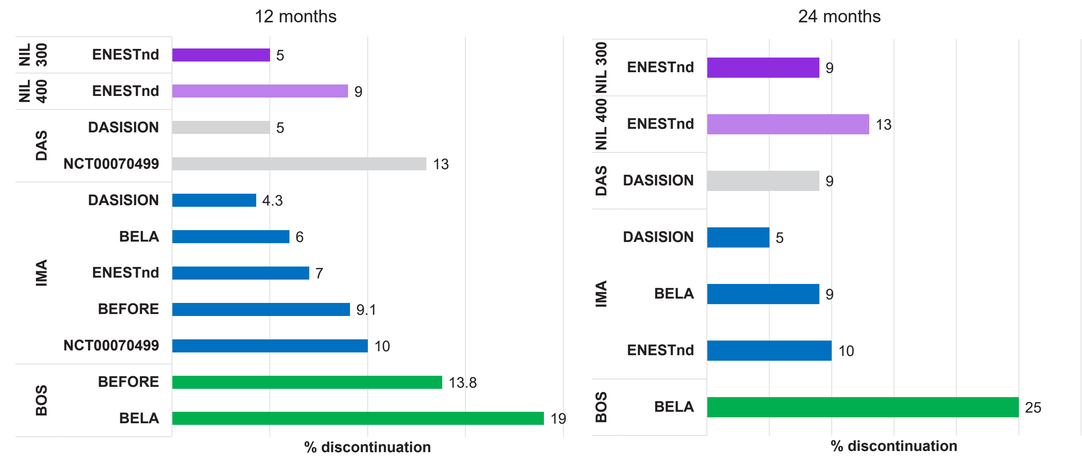
**Table 1. Overview of evidence on key efficacy outcomes in the included studies**

| Trial name (NCT) | Intervention / comparator (N) | Survival outcomes, % (95%CI) | | | | | |
|---|---|---|---|---|---|---|---|
| | | EFS | | PFS | | OS | |
| | | 1 yr | 5 yrs | 1 yr | 5 yrs | 1 yr | 5 yrs |
| **BELA (NCT00574873)** | Bosutinib 500mg (250) | 94.0 (-) | - | - | - | >99.0 (-) | - |
| | Imatinib 400 mg (252) | 93.0 (-) | - | - | - | 97.0 (-) | - |
| **BFORE (NCT02130557)** | Bosutinib 400mg (268) | 3.7 (1.8-6.7) | 6.7 (4.1-10.1) | - | - | 99.6 (97-99.9) | 94.5 (90.8-96.7) |
| | Imatinib 400 mg (265) | 6.4 (3.7-10) | 9.3 (6.2-13.2) | - | - | 97.9 (95-99.1) | 94.6 (91-96.8) |
| **NCT00070499** | Imatinib 400 mg (123) | - | - | 90.0 (82-95) | - | 97.0 (90-99) | - |
| | Dasatinib 100 mg (123) | - | - | 93.0 (86-96) | - | 97.0 (91-99) | - |
| **DASISION (NCT00481247)** | Imatinib 400 mg (260) | - | - | 97.0 (-) | 86.0 (-) | 99.0 (-) | 90.0 (-) |
| | Dasatinib 100 mg (259) | - | - | 96.0 (-) | 85.0 (-) | 97.0 (-) | 91.0 (-) |
| **ENESTnd** | Nilotnib 300 mg (282) | - | 95.0 (92.1-97.8) | - | 92.3 (89.1-95.4) | - | 93.7 (90.8-96.6) |
| | Nilotnib 400 mg (281) | - | 96.9 (94.6-99.2) | - | 95.9 (93.5-98.3) | - | 96.3 (94-98.5) |
| | Imatinib 400 mg (283) | - | 92.6 (89.3-95.9) | - | 91.2 (87.8-94.5) | - | 91.8 (88.5-95.1) |

### Clinical Safety

- Safety outcomes were comparable across all treatments; however, adverse-event (AE) related treatment-discontinuation was higher with bosutinib and dasatinib versus imatinib (13.8%-19.0%, 5.0%-13.0% versus 1.5%-10.0%) (**Figure 2**).
  - The most frequent AEs commonly (≥1%) leading to treatment discontinuation included elevated levels of alanine aminotransferase/aspartate aminotransferase, thrombocytopenia, neutropenia, vomiting, increased lipase and pleural effusion for bosutinib; pleural effusion and drug-related cytopenia with dasatinib; diarrhea, thrombocytopenia, neutropenia, muscle spasms and myalgia with imatinib; and thrombocytosis with nilotinib.

**Figure 2. Patients with treatment discontinuation due to AEs**




### Quality of life outcomes

- There is very limited evidence on patients' QOL reported in clinical trials.
- The included studies measured the patient reported outcomes using FACT-Leu, EQ-5D, and SF-36.
- Based on the two studies, QOL scores after treatment with bosutinib, nilotinib, and imatinib showed improvement but the change-from-baseline was not clinically meaningful.

### Treatment free remission

- Criteria for patients to be eligible for TFR attempt varied across different studies (**Table 2**).
  - The most commonly used criteria were having a treatment duration of 3 years or more and MR4.5 maintained for ≥2 years with a follow-up till loss of MMR after treatment discontinuation.
- Data on patients still in TFR was reported at varying follow-up periods in different studies.
  - At 12 months, patients in TFR were reported only for dasatinib (59.2%) and nilotinib (51.6% to 76.5%) (**Table 2**).
  - Long-term data on TFR was limited, but overall proportion of patients in TFR decreased with increased follow-up duration (**Table 2**).
  - Out of patients who attempted TFR, 43.4% of imatinib treated patients and 42.6% of nilotinib treated patients remained in TFR after five-years.

**Table 2. Overall eligibility criteria reported in different studies for attempting TFR with sub-categorization of studies that include sustained MR4.5 as a criteria**

| Study | Eligibility criteria for attempting TFR | | | | | | | | | | TFR results | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total duration of treatment | | | | | Sustained MR4.5 | | Sustained MR4.0 | | | Intervention | Patients still in TFR at different time points, % | | | |
| | Since diagnosis | > 3 yrs | >4 yrs | > 5 yrs | > 8 yrs | >1 yrs | >2 yrs | >1 yrs | >2 yrs | >3 yrs | | 1 yr | 2 yrs | 3 yrs | 5 yrs |
| **Studies using sustained MR4.5 for >1 year as a criteria** | | | | | | | | | | | | | | | |
| **EURO-SKI** | - | ✓ | - | - | - | ✓ | - | - | - | - | - | - | - | - | - |
| **Studies using sustained MR4.5 for >2 year as a criteria** | | | | | | | | | | | | | | | |
| **STIM1** | - | ✓# | - | - | - | - | ✓# | - | - | - | - | - | - | - | - |
| **STIM2** | - | - | - | - | - | - | ✓Y | - | - | - | Imatinib | - | - | - | 43.4 |
| **JALSG** | - | ✓ | - | - | - | - | ✓ | - | - | - | Nilotinib | 76.5 | - | - | - |
| | - | ✓ | - | - | - | - | ✓ | - | - | - | Dasatinib | 59.2 | - | - | - |
| **NILSt** | - | - | - | - | - | - | ✓ | - | - | - | Nilotinib | - | 60.9 | 60.9 | - |
| **Hoosen, 2023** | - | - | - | ✓ | - | - | ✓† | - | - | - | Nilotinib | - | - | 100** | |
| | - | - | - | ✓ | - | - | ✓ | - | - | - | Imatinib | - | - | 72.7** | |
| **Cheng, 2023** | - | - | - | - | - | - | ✓^ | - | ✓^ | - | - | - | - | - | - |
| **Nicolini, 2021** | ✓ | - | - | - | - | - | ✓* | - | - | - | - | - | - | - | - |
| **DADI** | - | - | - | - | - | - | ✓ | - | - | - | - | - | - | - | - |
| **D-FREE** | ✓ | - | - | - | - | - | ✓ | ✓ | - | - | - | - | - | - | - |
| **Saugues, 2022** | - | - | - | ✓ | - | - | ✓^ | - | ✓^ | - | - | - | - | - | - |
| **Hughes, 2016 ‡** | - | - | - | - | ✓ | - | ✓ | - | - | - | - | - | - | - | - |
| **Rea, 2018** | - | - | - | ✓ | - | - | ✓ | - | - | - | - | - | - | - | - |
| **Hochhaus, 2020** | - | - | - | ✓ | - | - | ✓^ | - | - | ✓^ | - | - | - | - | - |
| **Studies using other criteria** | | | | | | | | | | | | | | | |
| **DANTE** | - | ✓ | - | - | - | - | - | ✓ | - | - | Nilotinib | 67.5 | - | - | - |
| **JALSG-STIM213** | - | ✓ | - | - | - | - | - | - | ✓ | - | Imatinib | 67.6 | - | - | - |
| **D'adda, 2019** | - | - | - | ✓ | - | - | - | - | ✓ | - | - | - | - | - | - |
| **DOMEST trial** | - | - | - | - | - | - | - | - | ✓ | - | - | - | - | - | - |
| **GIMEMA CML 0307** | - | - | ✓ | - | - | - | - | - | ✓ | | - | - | - | - | - |
| **Radich, 2018** | - | ✓ | - | - | - | - | - | - | ✓ | - | - | - | - | - | - |
| **DESTINY** | - | ✓ | - | - | - | - | - | - | ✓ | - | - | - | - | - | - |
| **ENESTfreedom** | - | ✓ | - | - | - | - | - | - | - | - | Nilotinib | 51.6 | 48.9 | | 42.6 |
| **Claudiani 2021** | - | - | - | - | - | - | - | - | - | - | Imatinib | - | 79.2 | - | - |
| **Pacelli, 2023** | - | - | - | - | - | - | - | - | - | - | Imatinib | - | 51.3** | - | - |

✓: Criteria reported by the study
*Sustained MR4.5 on ≥4 data points; ʏSustained MR4.5 on ≥5 data points; ^DMR included either MR4.0 or MR4.5; †3 years for first-generation TKI and 2 years for second-generation TKIs; ‡Additional criteria includes sokal non-high.
** Median follow-up time reported; #treatment duration of >2years and CMR with >5 log reduction which is considered equivalent to MR4.5

## Limitations

- Efficacy outcomes varied across the reported time-points however, for ease of representation and comparison, only data from selected timepoints are presented here.
- The definitions for eligibility criteria for TFR varied significantly across studies and greatly reduce the number of studies which could be analysed for relative comparison.

## References

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## Disclosures

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