

Systematic literature review of treatment patterns, long-term efficacy, and safety of dasatinib therapy for patients with chronic myeloid leukemia

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Introduction

- Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm with an incidence rate of 1-2 cases per 100,000 adults¹
 - In the United States, in 2020, 8450 new CML cases were estimated to have been diagnosed, with an estimated 1080 deaths due to CML¹
- Tyrosine kinase inhibitors (TKIs) imatinib, dasatinib, and nilotinib are approved for the treatment of CML; however, each TKI displays differences in discontinuation/switching rates, efficacy, and safety
 - Therefore, it is important to evaluate these differences to help guide first-line (1L) treatment decisions

Objective

- A systematic literature review (SLR) was conducted to:
 - Evaluate treatment and switching patterns of dasatinib in the context of other TKIs
 - Identify long-term efficacy and safety outcomes of 1L treatment with dasatinib

Methods

Study design

- The SLR was conducted using Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) guidelines; inclusion/exclusion criteria were defined using the Patient population, Intervention, Comparators, Outcome measures, and Study design (PICOS) statement (Table 1). The Ovid platform was used to conduct searches in the literature databases mentioned

Table 1. PICOS criteria for systematic literature review

PICOS	Criteria for inclusion
Patient population	Adult patients with previously untreated CML receiving treatment with dasatinib
Intervention and comparators	- Dasatinib - Comparators, if present, were not restricted
Outcomes measures	- Survival (PFS, OS) - Response rate (molecular, cytogenetic, or any other form of response) - All other efficacy outcomes (eg, duration of response, time to response) - Switching/treatment patterns^a - Safety - QoL/utility (eg, EORTC QLQ-C30, FACT-G, EQ-5D-5L)^b - Adherence^a
Study design	- RCTs (including extension studies) - Subgroup analyses of previously published studies - Retrospective or prospective RWE studies - Systematic reviews and meta-analyses (for cross-checking only)

^aFor switching/treatment pattern outcomes, patients receiving dasatinib in the 2L+ setting were considered; ^bOutcomes were considered in the context of switching/discontinuation. 2L, second-line; EQ-5D-5L, European Quality of Life 5-dimension 5-level; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FACT-G, Functional Assessment of Cancer Therapy - General; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial; RWE, real-world evidence.

- Databases searched:
 - Medical Literature Analysis and Retrieval System Online (MEDLINE[®]), Excerpta Medica Database (Embase[®]), EconLit, and Cochrane for records dated between January 1, 2010, and June 30, 2020
 - MEDLINE[®] Epub Ahead of Print, In-Process & Other Non-Indexed Citations via the Ovid platform for nonindexed records
 - Congress abstracts published in 2017-2020 (American Society of Clinical Oncology and European Hematology Association) or in 2017-2019 (European Society of Medical Oncology and American Society of Hematology) as 2020 abstracts were not available at the time of searches
- To identify key studies, bibliographies of relevant systematic reviews and meta-analyses identified through database searches were used. Bibliographies from selected studies were also reviewed to identify any relevant additional studies

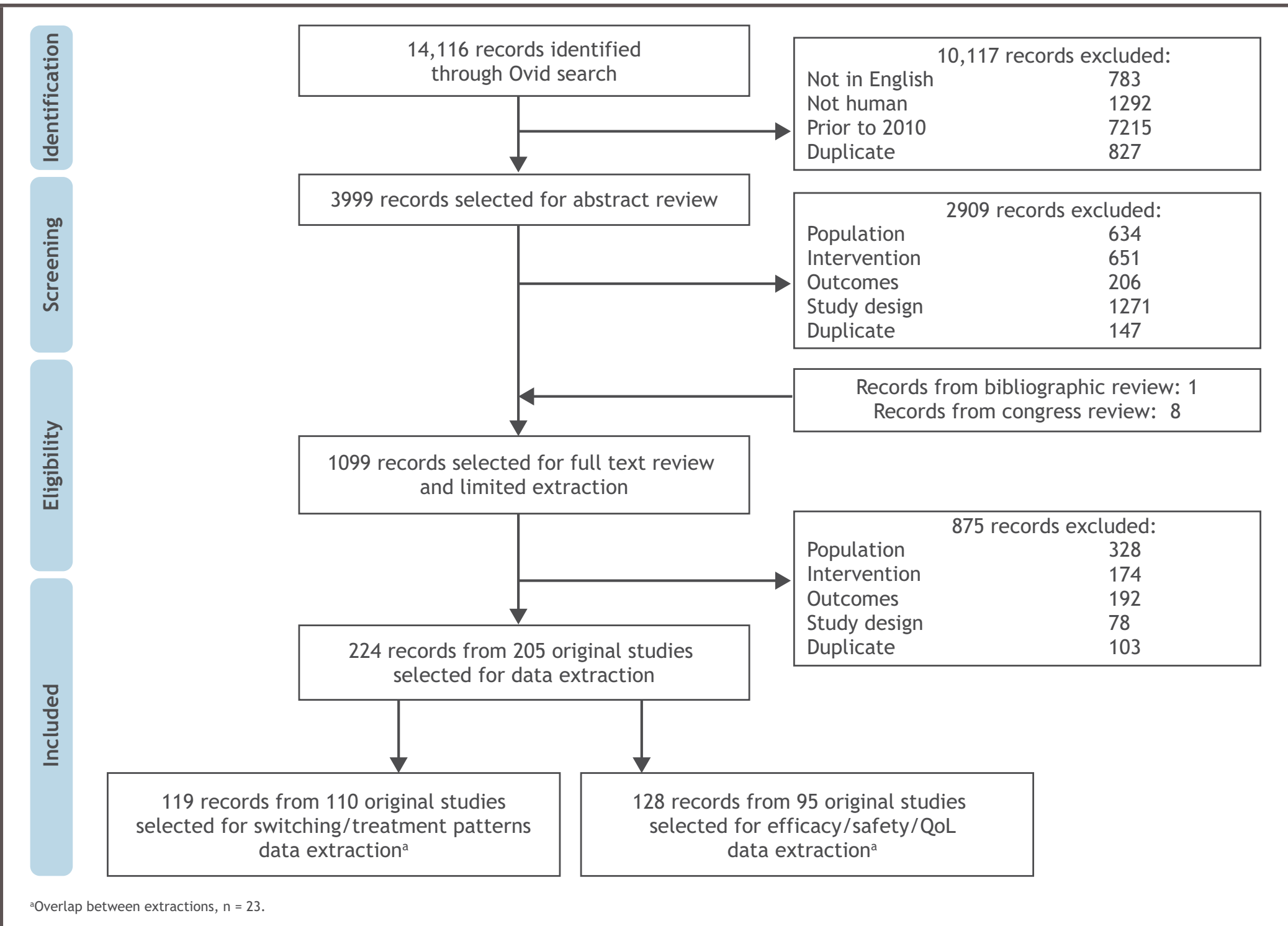
Results

- A total of 3999 records were identified using the Ovid platform (Figure 1)
 - 1099 records were selected for full-text review and limited extraction
 - 224 records from 205 original studies fulfilled the eligibility criteria and were selected for data extraction
 - Of these 224 records, 55 were interventional studies and 169 were real-world studies
- Data extraction occurred in two parts
 - Part 1 focused on the outcome of switching and/or treatment patterns and discontinuation
 - 119 records from 110 original studies were included (44 reported switching only and 52 included 2L+ populations)
 - Part 2 considered efficacy, safety, and health-related quality of life (HRQoL) of patients treated with dasatinib in the 1L setting
 - 128 records from 95 studies were included

Switching and treatment patterns: HRQoL and adherence

- A total of 6 studies evaluated HRQoL among 1L TKIs (dasatinib, imatinib, nilotinib)
 - Fatigue was the most common adverse event (AE) among 1L TKIs, with work interference the most affected activity
 - Four studies comparing 1L TKIs reported minor differences among 1L dasatinib, imatinib, or nilotinib, despite the different safety profiles of these drugs^{2,3}
 - Two studies reported an improvement in HRQoL with 1L dasatinib compared with 1L imatinib,^{6,7} although the improvement was lessened when age was taken into consideration⁷
- All 3 studies evaluating symptom burden observed numerically lower symptom scores in patients treated with 1L dasatinib versus 1L imatinib or nilotinib^{2,3,6}; disease-related symptoms peaked during the first 3 months of 1L nilotinib treatment, while 1L dasatinib resulted in more stable symptom scores over 24 months of treatment^{2,3,6}

Figure 1. PRISMA flow diagram for SLR findings



- Overall, 6 studies compared adherence rates
 - Four studies reported higher adherence rates for dasatinib versus imatinib or nilotinib⁸⁻¹¹
 - Two studies suggested the administration of dasatinib (once daily [QD] with/without food) is more convenient than imatinib or nilotinib^{8,12}
 - In 1 study, adherence was related to patient experience of AEs, with some patients deliberately not taking their medication¹²

Discontinuations, switching, and treatment patterns

- A total of 22 studies reported short-term (< 3 years; 10 studies) or long-term (≥ 3 years; 12 studies) discontinuation rates with dasatinib, imatinib, and/or nilotinib
 - Discontinuation rates were lower for patients treated with dasatinib versus imatinib and nilotinib in 8 of 10 short-term and 9 of 12 long-term studies (Figures 2A and 2B)¹³⁻³⁴
 - Time on sustained dasatinib and time to discontinuation were observed to be numerically longer with 1L dasatinib compared with other TKIs^{14,17,35}
 - A similar trend was observed when the US population was analyzed alone: 3 of the 4 short-term studies reported lower discontinuation rates with dasatinib^{17,19,28,33}
- In total, 73 studies reported switching to 2L dasatinib or nilotinib
 - 42 studies (58%) had a higher proportion of patients switching to dasatinib

Efficacy with 1L dasatinib

- Treatment with dasatinib was compared with imatinib in 3 RCTs and nilotinib in 6 RWE studies
 - Treatment with dasatinib resulted in a faster, deeper molecular response compared with imatinib in all 3 RCTs^{23,26,32} but a comparable response versus nilotinib in all 6 RWE studies^{22,24,29,36-38}
- Two studies compared efficacy outcomes for patients who remained on 1L dasatinib compared with those who switched to 2L dasatinib: DASCERN multinational trial and SIMPLICITY real-world study
 - DASCERN: 52% of patients randomized to imatinib crossed over to the dasatinib arm when an early molecular response (EMR; ≤ 10% BCR-ABL1 [International scale] at 3 or 6 months) was not achieved. Three-year major molecular response (MMR) rates were highest (75%) in patients who initiated and remained on 1L dasatinib versus those who switched from imatinib to dasatinib (58%) or remained on 1L imatinib (43%)³⁹⁻⁴⁰
 - SIMPLICITY: patients in the United States and Europe who initiated and remained on 1L dasatinib had higher survival rates (97%) than those who switched to dasatinib after imatinib or nilotinib treatment (91%)³⁴
- Response and survival rates were reported in 37 studies
 - Six studies reported both EMR and 5-year OS rate in patients (N = 107 to 406) treated with 1L dasatinib, with a positive correlation between 3-month EMR and survival up to 5 years (R² = 0.5946; Figure 3A)^{23,26,29,41-43}
 - Seven studies reported both the achievement of MMR at 12 months and 5-year OS rate, with a strong correlation between 12-month MMR and 5-year OS rate (R² = 0.8415; Figure 3B)^{23,26,29,41-44}
- Both time to MMR and 5-year OS rate were reported in 3 studies^{26,43,45}
 - DASISION (phase 3 RCT): median time to MMR was 9.3 months and 5-year OS rate was 91%²⁶
 - Study by Maiti et al. (phase 2 RCT): median time to MMR was 6 months and 5-year OS rate was 96% in a cohort of patients of whom ≥ 50% received dasatinib at 100 mg QD⁴³
 - A Taiwanese prospective observational study: median time to MMR was 6.0-7.3 months and 5-year OS rate was 90%-96%⁴⁵

Figure 2. Switching or discontinuation rates of first-line TKIs in short-term (< 3 years) or long-term (≥ 3 years) settings

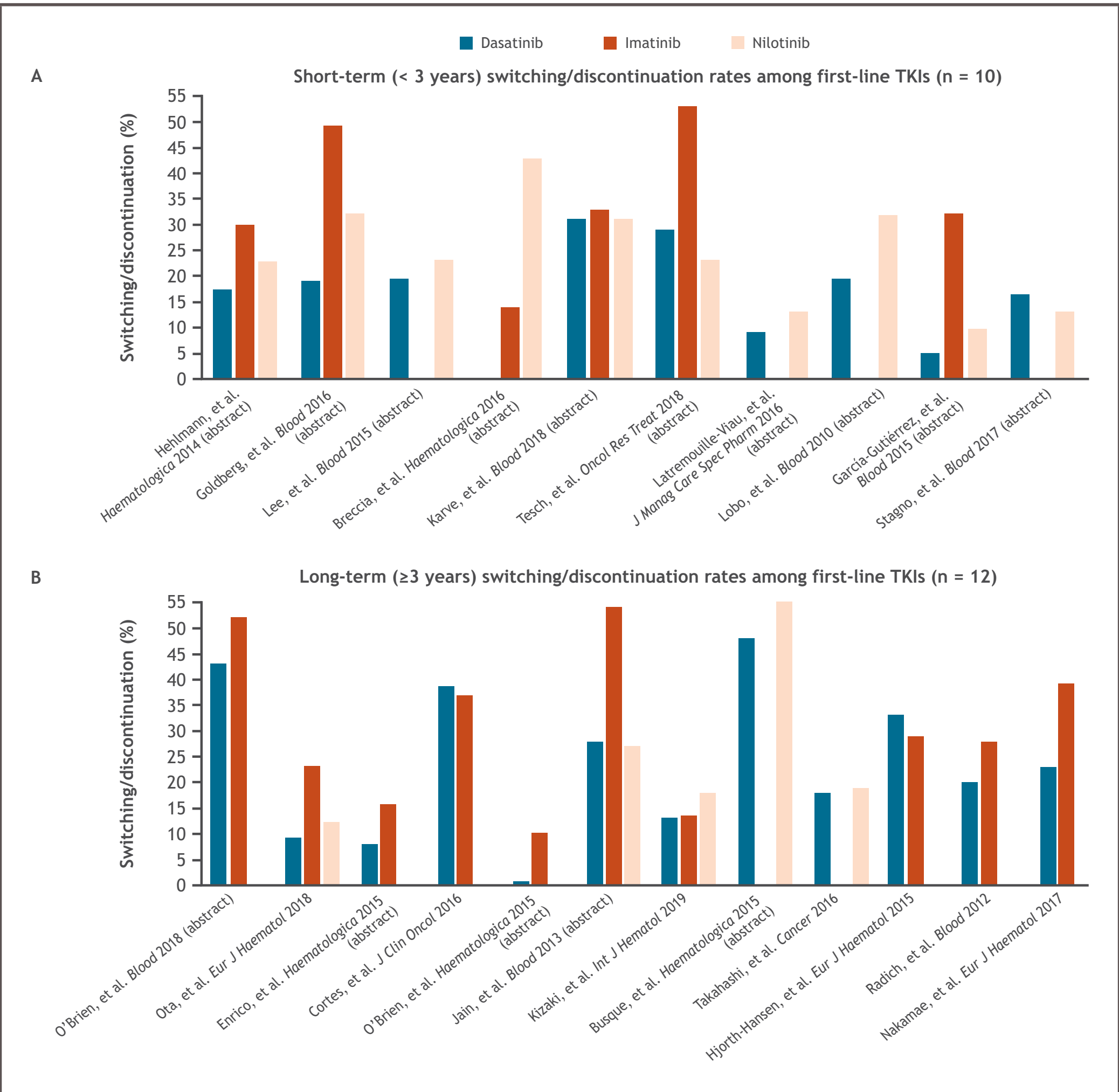
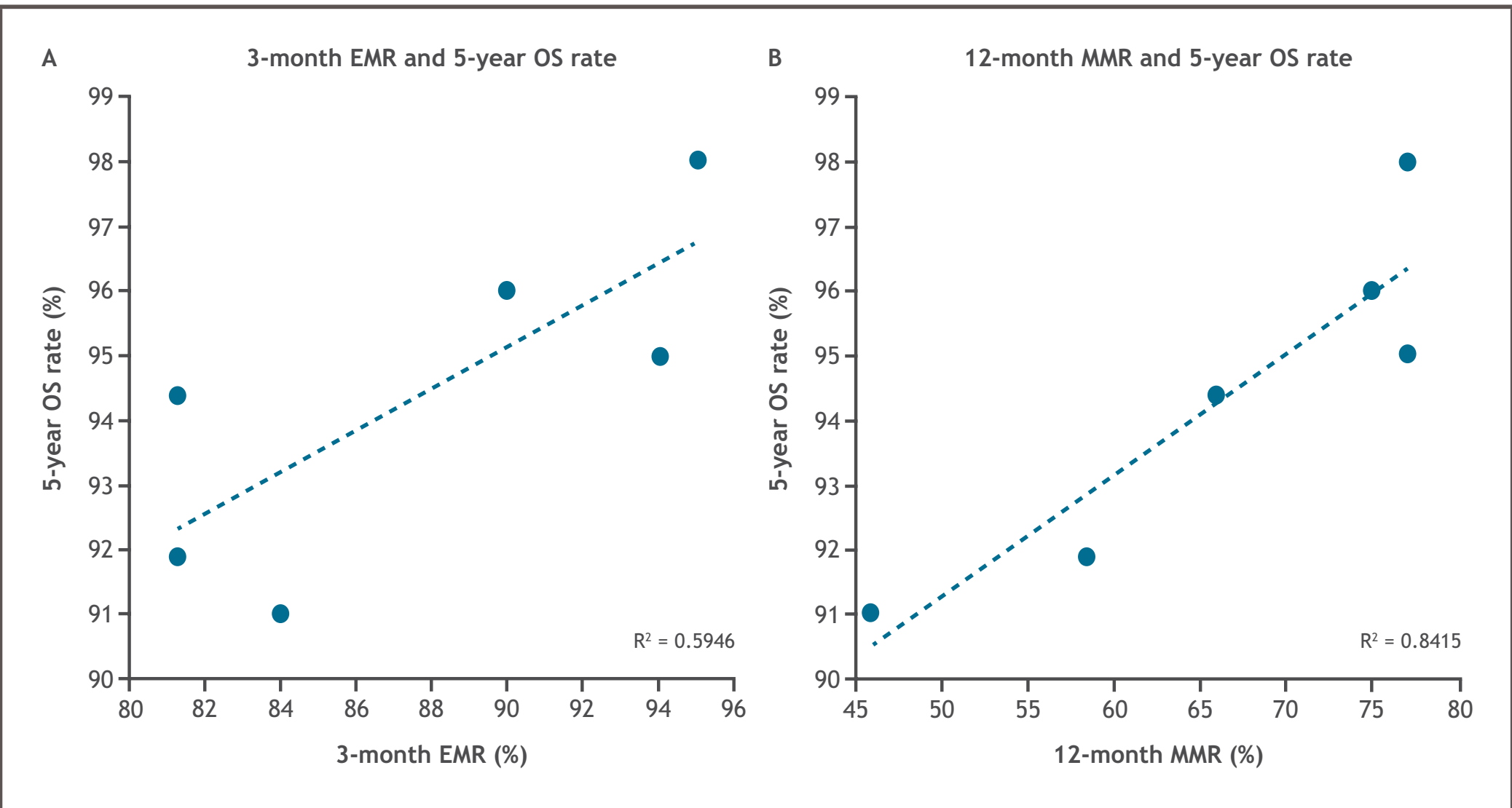


Figure 3. Correlation of 3-month EMR (A) and 12-month MMR (B) with 5-year OS rate



Safety

- In all, 69 studies evaluating 1L dasatinib reported safety/toxicity data (34 clinical/interventional, 13 prospective-observational, 21 retrospective-observational, and 1 cross-sectional survey)
 - Pleural effusions were the most common AE associated with dasatinib (all-grade events were reported in 21 studies)
 - Despite the wide range of affected patients between studies (0%-50%), severity of pleural effusion was low (0%-9% grade ≥ 3) and occurrence did not negatively affect achievement of cytogenetic or molecular response⁴⁶
 - Patients treated with dasatinib, nilotinib, and imatinib experienced similar rates of grade ≥ 3 hematologic AEs in 4 RWE studies (Table 2)
 - Specific hematologic AEs (eg, thrombocytopenia) were more frequent in patients treated with dasatinib versus imatinib in 4 RCTs^{28,32,35,39}
 - In all studies, patients receiving nilotinib had a higher incidence of cardiovascular, gastrointestinal, or hepatobiliary AEs than those receiving dasatinib (Table 2)^{21,24,29,47}
 - Patients receiving dasatinib were at a significantly lower risk for developing type 2 diabetes or hyperlipidemia compared with those on nilotinib or imatinib,⁴⁸ and also had a lower incidence of cardiovascular-related hospitalizations, length of stay, and mean hospital costs⁴⁹

Table 2. Real-world studies reporting comparative grade 3/4 AEs between 1L TKIs (dasatinib, imatinib, nilotinib)

Short reference	Study design	Country	Interventions	Grade 3/4 hematologic AEs (%)	Grade 3/4 nonhematologic AEs, n (%)				
					All	Cardiovascular	Hepatobiliary	Gastrointestinal	Respiratory
Lang, et al. J Clin Pharm Ther 2015 ⁵⁷	Retrospective single center	France	Dasatinib (n = 21)	10	NR	9	0	0	3
			Imatinib (n = 62)	15	NR	3	8	2	0
			Nilotinib (n = 29)	7	NR	17	7	3	0
Stagno, et al. Blood 2017 (abstract) ⁴¹	Retrospective multicenter	Italy	Dasatinib (n = 72)	11	17	NR	NR	NR	NR
			Nilotinib (n = 54)	9	19	NR	NR	NR	NR
Kizaki, et al. Int J Hematol 2019 ²⁹	Prospective multicenter	Japan	Dasatinib (n = 144)	Thrombocytopenia: 7	NR	Vascular AEs: 1	NR	Diarrhea: 0	Pleural effusion: 1
			Imatinib (n = 139)	Thrombocytopenia: 1	NR	Vascular AEs: 1	NR	Diarrhea: 0	Pleural effusion: 0
			Nilotinib (n = 169)	Thrombocytopenia: 1	NR	Vascular AEs: 2	NR	Diarrhea: 0	Pleural effusion: 0
Ota, et al. Eur J Haematol 2018 ⁴⁴	Retrospective multicenter	Japan	Dasatinib (n = 95)	15	NR	0	0	1	4
			Imatinib (n = 255)	15	NR	2	3	3	4
			Nilotinib (n = 100)	13	NR	3	10	3	2

NR, not reported.

Conclusions

- Dasatinib is a highly effective 1L treatment option for patients with CML, demonstrating sustained response and long-term survival
- In studies evaluating 1L TKIs, patients treated with dasatinib had superior outcomes than patients who switched to dasatinib from 1L imatinib or who remained on 1L imatinib
- Patients treated with dasatinib experienced lower discontinuation rates, better adherence, and a lower incidence of nonhematologic AEs compared with imatinib or nilotinib

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Disclosures

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