

TREATMENT PATTERNS AND OUTCOMES ASSOCIATED WITH THE USE OF PONATINIB IN CLINICAL PRACTICE: A QUALITATIVE SYSTEMATIC LITERATURE REVIEW

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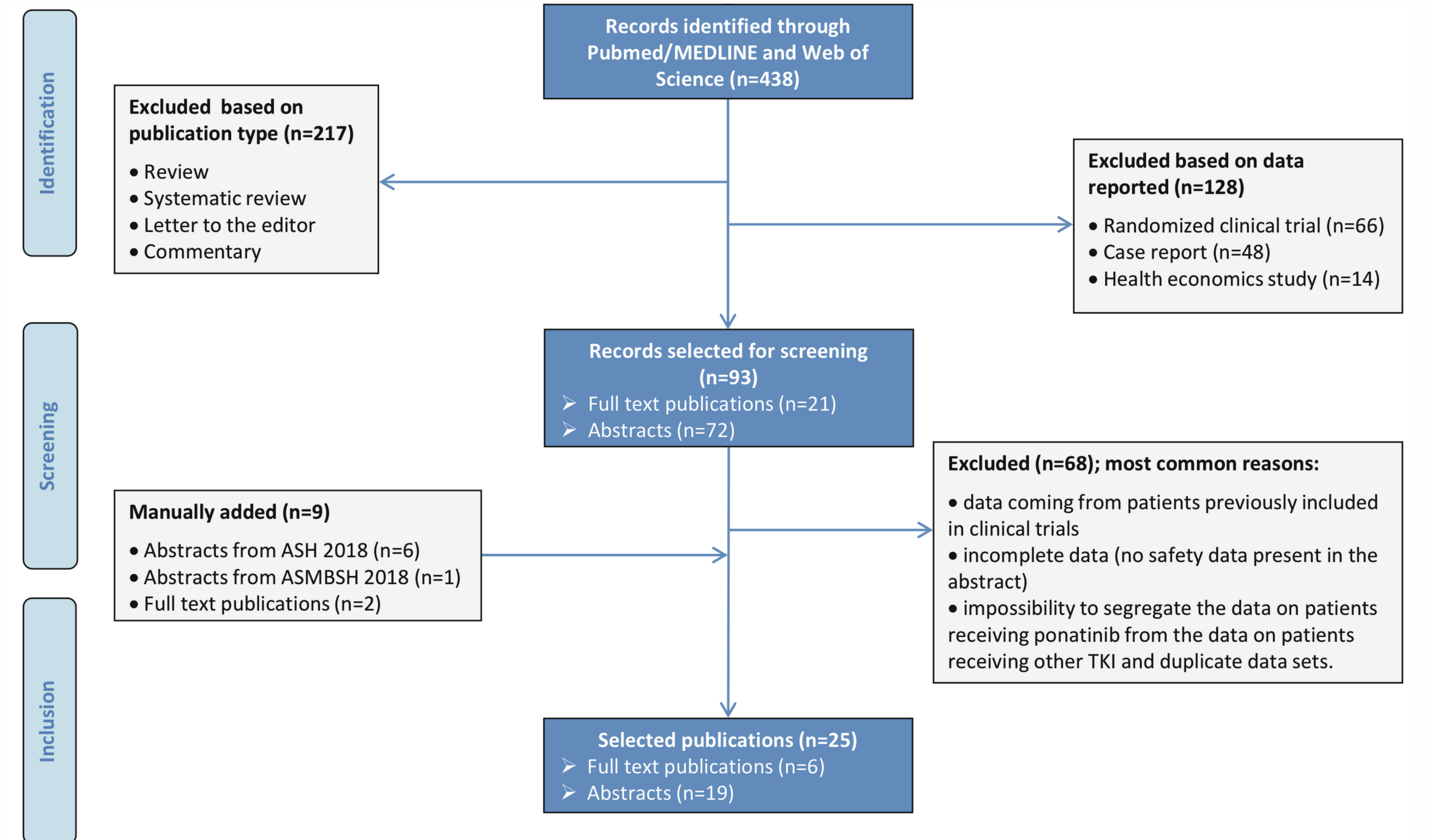
OBJECTIVES

- Chronic myeloid leukemia (CML) is a neoplastic disease that affects 1-2 in 100,000 adults, accounting for about 15% of newly diagnosed adult leukemia cases.¹
- The introduction of small molecule tyrosine kinase inhibitors (TKIs) such as ponatinib opened new therapeutic possibilities for CML patients, dramatically increasing the 10-year survival rate;² Ponatinib is a 3rd generation TKI currently indicated for the treatment of CML and Philadelphia positive acute lymphoblastic leukemia patients resistant and/or intolerant to other TKIs, and patients with the T315I mutation.³
- Treatment with TKIs is associated with adverse events (AEs), including cardiovascular (CV) AEs. Recent publications have reported on ponatinib use and outcomes in CML patients treated in “real-world” clinical practice (RW). To understand the patient benefits and risks associated with the use of ponatinib, data collected in RW are of potentially greater value than, or at least complementary to, those collected in trials (e.g. the pivotal phase II trial PACE [NCT01207440]).
- This review describes ponatinib patient demographics, prescription patterns, effectiveness, and CV safety, given the impact of these parameters on survival, quality of life, and healthcare resource utilization.

METHODS

- We performed a systematic literature search of publications (peer-reviewed articles, non-peer-reviewed articles, abstracts) available in Pubmed/MEDLINE and Web of Science, during 01/2012-04/2019, using a pre-established protocol defining the search criteria and search terms; PRISMA guidelines were followed as closely as possible.
- 25 publications (6 manuscripts and 19 abstracts) were selected.

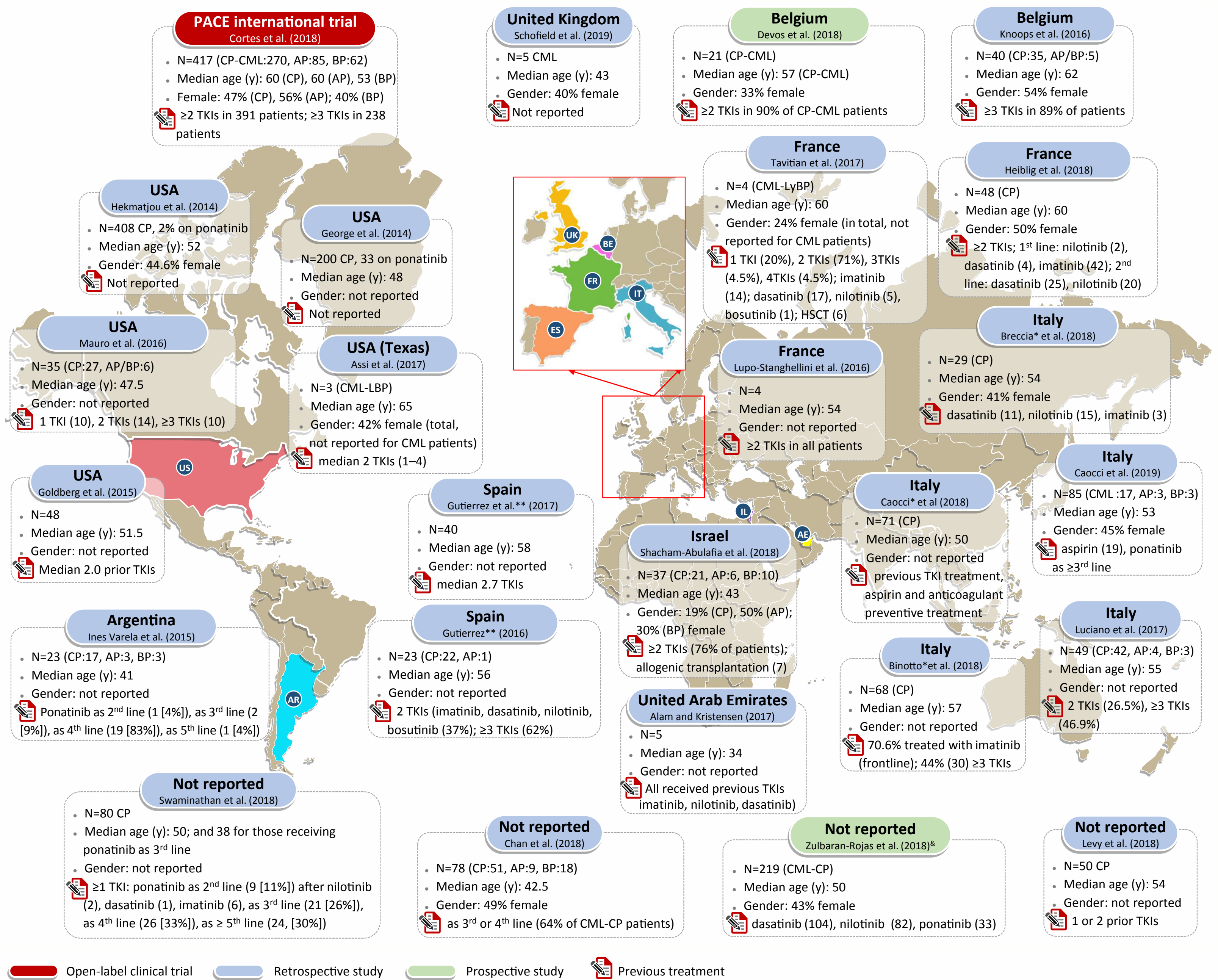
All publications reporting safety and/or efficacy of ponatinib in CML patients not enrolled in clinical trials were included



n, number of publications; ASH, American Society for Hematology, ASMBSH, Annual Scientific Meeting of the British Society for Haematology.

PUBLICATIONS INCLUDED IN THE REVIEW

Demographic characteristics of the CML patients, design and countries of the studies included



*. **possible duplicate datasets; *the patients in this study were previously treated in a clinical trial, but the safety data was presented in this study; PACE, the pivotal phase 2 Ponatinib Ph+ ALL and CML Evaluation; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia; CML, chronic myeloid leukemia; CP, chronic phase; AP, accelerated phase; BP, blast phase; LyBP, lymphoid blastic phase; N, number of CML patients treated with ponatinib; y, years; HSCT, hematopoietic stem cell transplantation.

Frequency of standard vs reduced starting dosage in clinical practice: results were not sensitive to number of studies included, overlapping data, or inclusion of small subsets of ALL patients

	% of patients starting at a mean dose of 45 mg ponatinib/day	% of patients starting at a mean dose of 30 mg or 15 mg ponatinib/day
Removing partially overlapping studies and those where ALL and CML patient data could not be separated	52%	48%
Dropping studies pair-wise (average % of patients calculated over all possible study-dropping scenarios)	55%	45%
Dropping each study once (average % of patients calculated over all possible study-dropping scenarios)	55%	45%
Base case	54%	46%

CONCLUSIONS

- Published RW studies suggest a positive impact of personalized selection of ponatinib starting dose on reducing cardiovascular events and achieving response to treatment.
- However, they are too heterogeneous and few to disentangle the effect of potential confounders and effect modifiers.

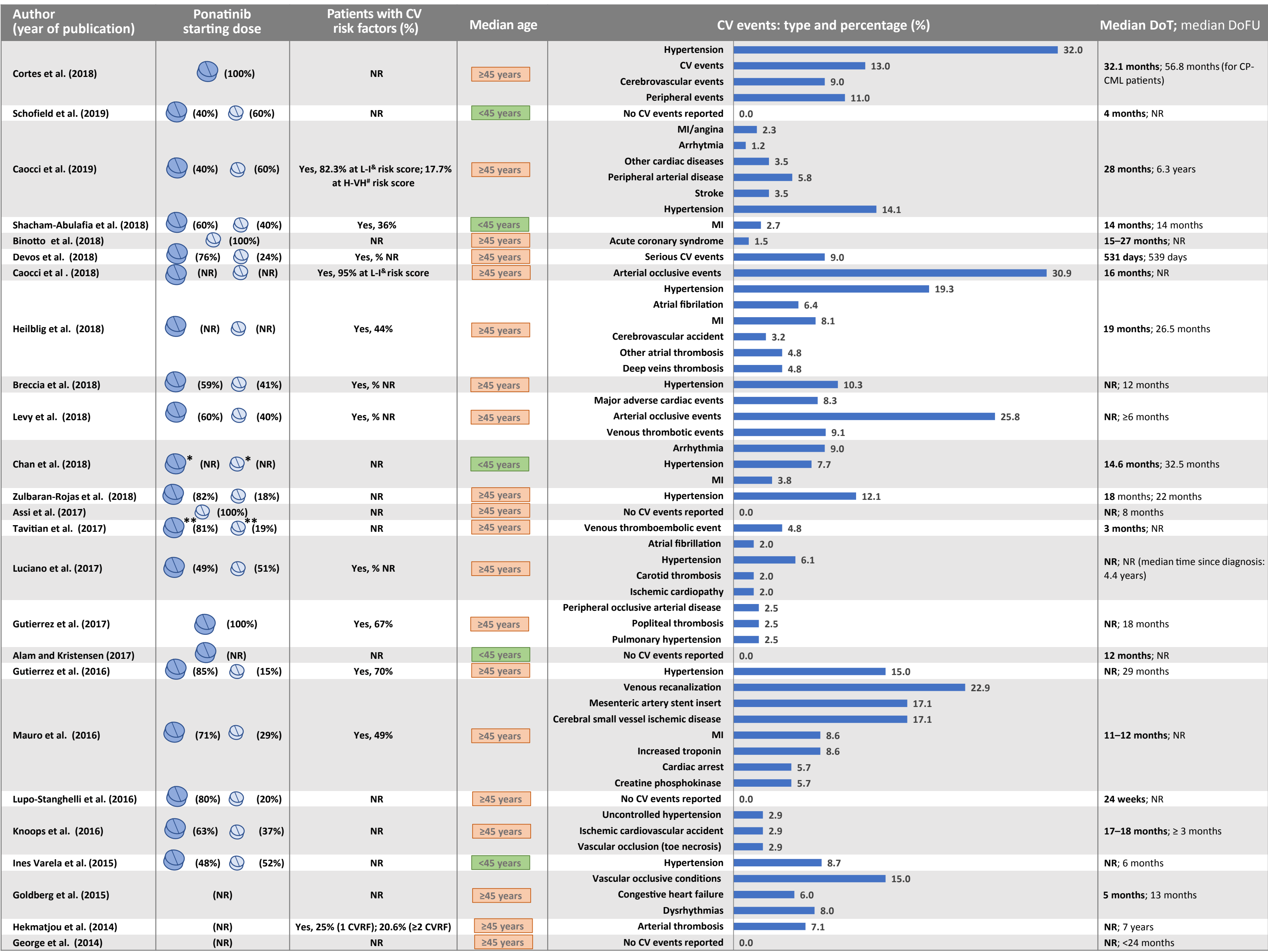
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RESULTS

Safety

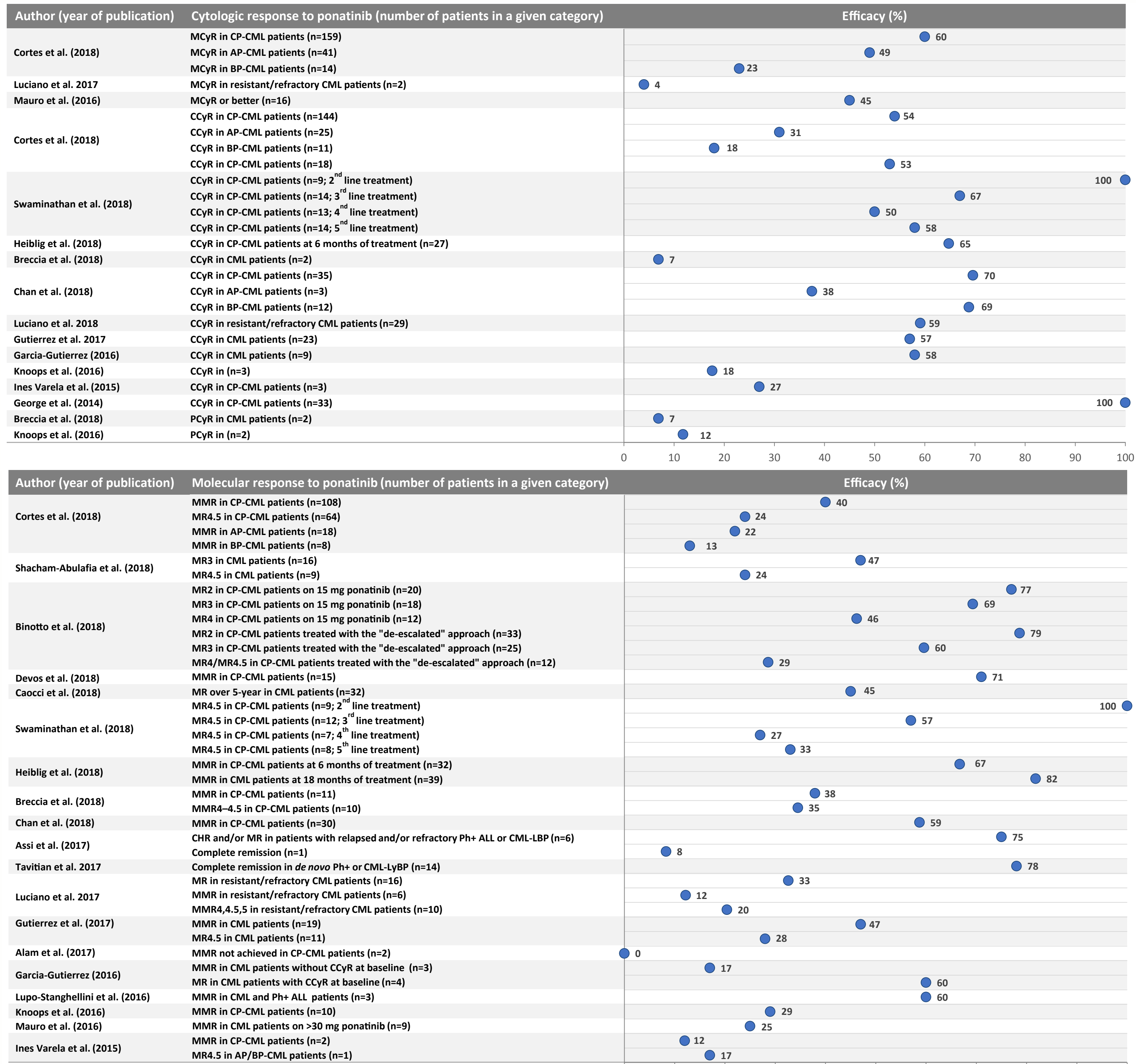
- In most RW studies, the recorded incidence of CV AEs was relatively low (<9%), except for hypertension whose incidence was reported more frequently (in 9 out of 24 RW studies included, any grade, but not necessarily treatment-related). Thrombosis-related events ranged between 2.0% and 9.1% and myocardial infarction (MI) between 2.3% and 8.6% of reported events. The study of Mauro et al. (2016)⁴ showed a higher incidence of CV events compared to the other studies included in this review.
- CV events were less frequent or absent in studies with patients that had no CV history. There were 10 serious CV events (SCVEs) reported in the reviewed publications, i.e. 1 (1.5%) fatal CV event (Binotto et al., 2018), 3 SCVEs (3%) in 1 patient with history of congenital cardiomyopathy and aortic prosthesis (Devos et al., 2018), 1 (1.6%) fatal MI and 1 (1.6%) fatal peripheral arterial obstructive disease-related complication (Heiblig et al., 2018), 1 SCVE (Tavittian et al., 2017), 1 (0.9%) serious MI (Alam and Kristensen, 2017), 1 (2.9%) cardiac death (Knoops et al., 2016) and 1 (4.4%) fatal arterial thrombosis (Ines Varela et al., 2015).
- The reported frequency of CV events was lower than average in studies with a median population age under 45 years.



ponatinib dose of 45 mg/day; ponatinib dose of 30 or 15 mg/day; *ponatinib was 3rd or 4th line therapy in 65% of chronic phase (CP) patients, with a mean starting dose of 39.65 mg/day; **doses reported for all patients (17 *de novo* ALL and 4 LyBP-CML), not only for CML ones; *SCORE risk ≤5%; *SCORE risk >5%; *patient with history of congenital cardiomyopathy and aortic prosthesis; NR, not reported; L-I, low-intermediate; H-VH, high-very high; MI, myocardial infarction; CVRF, cardiovascular risk factor; DoT, duration of treatment with ponatinib; DoFu, duration of follow-up.

Efficacy

- The proportion of patients who responded to ponatinib treatment are summarized in the figures below.
- The majority of responders achieved complete cytogenetic (CCyR) or major molecular response (MMR). Deep molecular response (MR4.5) was achieved in 17%-57% of CML patients included in studies that reported this specific outcome.



%, percentage of patients who responded to ponatinib treatment; CCyR, complete cytogenetic response; MCyR, major cytogenetic response; PCyR, partial cytogenetic response; CHR, complete hematologic response; MR, molecular response.

References: 1. Jabbour and Kantarjian. Am J Hematol. 2018;93:442-59; 2. Huang, Cortes and Kantarjian. Cancer. 2012;118:3123-7; 3. Breccia et al. Ann Hematol. 2018;97:1577-80; 4. Mauro et al. Haematologica. 2016;101:458-9.

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