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Update on the use of hydroxyurea for the early management of chronic-phase- chronic myeloid leukemia: data from a real-world cohort

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Title

Update on the use of hydroxyurea for the early management of chronic-phase-chronic myeloid leukemia: data from a real-world cohort

Running title: Pre-TKI hydroxyurea and CML outcome

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Data Sharing Statement: For original data, please contact the corresponding author Marc G. BERGER (mberger@chu-clermontferrand.fr)

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- Prescribing hydroxyurea for a short period before tyrosine kinase inhibitors (TKI) impairs the deep molecular response achievement
- Prescribing hydroxyurea before TKI initiation increases the risk of hematological toxicity with second-generation TKIs.

Novelty: Using real-world data from the French CML Observatory, we discovered that even a short hydroxyurea pretreatment before tyrosine kinase inhibitor initiation negatively influences the deep molecular response achievement and increases hematological toxicity. These findings challenge a long-standing practice and refine the early management recommendations for chronic-phase chronic myeloid leukemia.

Abstract 350 words

Background: Hydroxyurea (HU) is sometimes used before confirmation of the diagnosis of chronic-phase chronic myeloid leukemia (CP-CML) and treatment with tyrosine kinase inhibitors (TKI). The limited literature data suggest that this strategy does not offer any benefit, but no large-scale study has been conducted on this subject.

Methods: From the French CML Observatory (a French registry with real-world data on patients with CP-CML), we identified patients treated with HU before TKI initiation (pre-TKI HU; n=370) and patients treated directly with TKI (direct TKI n=430). First, we compared the frequency of side effects in the two groups. Then, to take into account some factors that could confound the therapeutic response, particularly leukocytosis, we selected patients for whom we had data on baseline leukocytosis and calculated a propensity score to balance the pre-TKI HU and direct TKI groups. Then, we compared the cumulative incidence rates of the different molecular response (MR) levels, mean TKI doses, number of treatment-free days in the first year, and cumulative incidence of first switch in the two weighted patient groups.

Results: Overall, prescribing HU for a short period (median: 16 days) increased the frequency of edema in patients treated with imatinib (23% in the pre-TKI HU vs. 15% in the direct TKI group;

p=0.026) and of hematological toxicity when taking second-generation TKIs (19% vs. 5.5%; p<0.001). Moreover, the likelihood of achieving a deep molecular response was reduced in the pre-TKI HU group, as indicated by the different cumulative incidences of MR4 and MR4.5 between groups and the lower rates of MR4.5in the pre-TKI HU group over time (HR = 0.66 [0.48-0.90]; p=0.008). This effect was observed in both the imatinib and second-generation TKI subgroups. Conversely, the TKI dose, number of days of treatment during the first year, and cumulative incidence of first switch were similar in the pre-TKI HU and direct TKI groups.

Conclusions: Based on these results, we propose to restrict and shorten HU administration before TKI initiation to the minority of patients with suspected leukostasis or symptomatic splenomegaly and to prioritize earlier TKI initiation.

Introduction

Hydroxyurea (HU) is still frequently used at chronic phase-chronic myeloid leukemia (CP-CML) diagnosis to reduce leukocytosis or thrombocytosis, pending diagnosis confirmation by molecular biology analysis. In patients with CP-CML, HU facilitates the rapid reduction of circulating blood cells, while does not have any effect on the *BCR::ABL* transcript load, and on the CML clone(1,2). Importantly, prolonged HU treatment before tyrosine kinase inhibitor (TKI) initiation has been associated with higher risk of CML progression by delaying TKI start(3,4). Therefore, the 2020 European LeukemiaNet (ELN) recommendations suggested to use HU only in patients with high leukocyte or platelet counts until diagnosis confirmation and TKI initiation(5). The 2025 ELN recommendations do not address this issue(6). In 2022, a study showed that HU use for a short period (~2 weeks) before TKI initiation increases TKI-related toxicity and does not provide any therapeutic benefit (7) for the initial molecular response (MR) achievement. However, these findings have not been robustly confirmed. In addition, MR was monitored only up to the achievement of a major MR, and the cohort consisted predominantly of patients treated with first-line imatinib. Consequently, the influence of pre-TKI HU on the deep MR (DMR) achievement and its impact in patients treated front-line with second-generation (2G) TKIs remain unknown. In addition, data monitoring in the French CML Observatory (FCMLO), a large national real-world cohort, revealed HU use heterogeneity across centers (unpublished data). Therefore, the aim of this study was to evaluate the effect of HU use before TKI initiation on MR rates, adverse events, and leukocytosis kinetics in a large real-world CP-CML patient cohort from the FCMLO that included patients treated first-line with 2G-TKIs or imatinib. Analysis of these real-world data showed that HU reduces the likelihood of DMR achievement, persistent in the long term, and increases the risk of initial toxicity, particularly hematological toxicity in patients treated with first-line 2G-TKIs. Moreover, HU did not influence the leukocytosis reduction kinetics. Consequently, we propose an algorithm to limit HU use topatients with high tumor burden pending diagnosis confirmation.

Methods

Data source and patient enrolment

Patient data were from 17 French centers that contribute to the FCMLO (clinicaltrials: # NCT05963061), a multicenter database designed to collect real-world data of patients with CML (supplementary data, additional file 1). Patients who received a diagnosis of CP-CML between 2010 and 2025, aged ≥18 years, and who provided consent for inclusion in the database were included. Patients with missing data at diagnosis or lost to follow-up, patients who received an allograft for CML, or with a non-standard treatment (including ponatinib or asciminib as first-line therapy, HU for >90 days, HU after the first TKI, ara-C or interferon, pegylated interferon outside pregnancy, or concomitant use of two TKIs) were excluded. Then the information on the pre-TKI treatment phase was monitored at each center. If available, patients were included and divided in two groups: pre-TKI

HU group (HU before TKI) and direct TKI group (only TKI) (Fig. 1). The database was closed on April 8, 2026. Adverse events were those recorded in the database by each investigator (>75% of side effects were graded). For the therapeutic response analysis, as leukocytosis at diagnosis may act as a confounding factor(8), a propensity score was applied using relevant variables on the subgroup of patients with complete data at diagnosis for *BCR::ABL1* and leukocytosis (see the Statistical analysis section).

Molecular response

The MR2, MR3, MR4 and MR4.5 levels correspond to the *BCR::ABL1/ABL1* transcript ratio thresholds defined by ELN (additional file 1).

Statistical analyses

Descriptive statistics

The baseline covariates were described using percentages and numbers for categorical variables, medians and interquartile ranges for continuous variables. The Pearson's chi-square and Fisher's exact tests were used to compare categorical covariates. The Mann-Whitney U test was used to compare continuous covariates.

Molecular response analysis

The cumulative incidence of MRs in the pre-TKI HU and direct TKI groups was assessed using Kaplan-Meier survival curves and compared with the log-rank test. Univariate Cox models were used to compute hazard ratios (HR) with their 95% confidence intervals (CI) and differences between groups were assessed with the Wald test.

Propensity weighting

To take into account differences in baseline characteristics between groups, a propensity score was calculated using logistic regression to determine the assignment to the treatment group, by considering age at diagnosis, sex, ELTS and Sokal groups, white blood cell count, first-line TKI, initial *BCR::ABL1/ABL* ratio, and center. The calculated inverse probability of treatment weights (IPTW) were truncated to 10 to avoid over-representation of few patients in the propensity-weighted cohort. Groups were weighted using inverse probability of treatment weighting. The distribution of propensity scores and IPTWs and the standardized mean differences were inspected to assess the quality of the propensity weighting.

Initial leukocytosis kinetics

The initial leukocytosis kinetics were studied based on repeated white blood cell measurements from treatment start (HU or TKI) to day 60 after treatment initiation. A mixed-effect model was constructed to represent the white blood cell count (log-scale) in function of the treatment group and time since treatment start (taken as a second-degree polynomial), with a random slope per patient and baseline covariates (fixed effects). The model with the best Akaike Information Criterion (stepwise selection) was selected: this included age at diagnosis and initial leukocytosis as covariates.

R version 4.5.0 (R Core Team, Vienna, Austria) was used for the statistical analyses and graph generation.

Results

Patients' characteristics

A total of 800 patients were analyzed in this study. Among them, The direct TKI group included 430 patients (295 imatinib, 74 nilotinib, 45 bosutinib, and 16 dasatinib) and the pre-TKI HU group included 370 patients (200 imatinib, 111 nilotinib, 35 bosutinib, and 24 dasatinib) (Fig. 1). HU was more frequently prescribed to younger patients (median age [interquartile range, IQR]: 56 [47, 68] vs. 61 [48, 71] years), with higher proportion of high-risk Sokal (29% vs. 9.5%) and EUTOS long-term survival (ELTS) (17% vs. 9.5%) scores, higher baseline leukocyte count (133 [70, 216] vs. 46 [25, 84] $\times 10^9$/L) and more frequent splenomegaly (48% vs. 14%) (Table 1) reflecting higher disease burden. HU was administered for a median duration of 16 days [IQR: 10, 27], but did not significantly delay TKI initiation. The proportion of patients treated first-line with a 2G-TKI was higher in the pre-TKI HU than direct TKI subgroup (46% vs 31%, $p < 0.001$).

Pre-TKI HU impact on TKI tolerance

Most of the reported TKI adverse events in the whole cohort occurred early: 55% in the first 6 months of treatment. Hematological toxicity was significantly more frequent in the pre-TKI HU group, whereas pulmonary side effects were less frequent (Fig. 2A). Moreover, during the first 12 months of TKI treatment, grade 3-4 adverse events were more frequent in the pre-TKI HU group (11% vs. 8.4%; $p = 0.019$). Analysis of adverse event occurrence in the TKI subgroups by month 12 showed that HU pretreatment increased the rate of edema (23% vs. 15%; $p=0.026$) with imatinib and of hematological toxicity with 2G-TKIs (19% vs. 5.5%; $p<0.001$) (Fig. 2B, C). Similar results were obtained for the nilotinib, bosutinib, and dasatinib subgroups (Additional file 2, Supplemental Fig. 1). In the first 12 months, grade 3 and 4 adverse events were more frequent in the pre-nilotinib HU than direct nilotinib subgroup (13% vs. 1.2%, $p=0.003$).

Assessment of pre-TKI HU impact on the therapeutic response

In the whole cohort, the DMR rates were lower in the pre-TKI HU than direct TKI group ($p <0.001$ for MR4 and $p <0.001$ for MR4.5) (Additional file 2, Supplemental Fig. 2). As higher leukocytosis in the pre-TKI subgroup could been associated with lower DMR probability(8), it is considered a confounding factor. Consequently, patients with documented white blood cell (WBC) count at diagnosis were selected: 274 patients in the direct TKI group and 218 patients in the pre-TKI HU group (Fig. 3, Table 2). Most baseline characteristics were similar in patients with known WBC count at diagnosis and in the whole cohort. The additional differences in patients with known WBC counts

were higher platelet count in the pre-TKI HU subgroup (422 [IQR: 250, 657] vs. 359 [IQR: 245, 541] x10⁹/L; p=0.027) and a longer interval between diagnosis and first-line treatment in the direct TKI subgroup [mean (SD) number of days; 21 (13, 32) vs. 17 (10, 30); p=0.023]. In this population with documented WBC at diagnosis, 48% and 31% of pre-TKI and direct TKI patients were treated with 2G-TKI respectively. Then, a propensity score matching strategy was applied to this population (Fig. 4A-C) before comparing the cumulative incidences of the different response levels. The cumulative incidence rates of MR3 (Fig. 4D) were not different in the propensity score-matched direct TKI and pre-TKI HU groups. However, HU use was associated with a reduced likelihood of DMR achievement (Fig. 4E, F) over time. Specifically, the cumulative incidence rates (95% CI) of MR4 at 12, 48 and 96 months were 21.8% (13.8%-29.1%), 62.4% (52.7%-70.1%) and 79.1% (71.1%-84.9%) in the pre-TKI HU group and 22.6% (16.7%-28.2%), 74.1% (64.9%-80.9%) and 91.7% (82.3%-96.1%) in the direct TKI group (p<0.001), respectively. The Cox model analysis was almost significant (HR = 0.78 [0.60-1.02]; p=0.072). The cumulative MR4.5 incidence rates at 12, 48 and 96 months were 10.9% (4.1%-17.2%), 47.4% (37.3%-56%) and 58.2% (47.5%-66.7%) in the pre-TKI HU group and 13.7% (9.6%-17.6%), 58.8% (49.2%-66.7%) and 91.1% (82.5%-95.4%) in the Direct TKI group, respectively (p<0.001) (HR = 0.66 [0.48-0.90] (p=0.008).

By considering the first-line TKI, HU negatively affected the MR4 and MR4.5 incidence rates in the imatinib subgroup (Figure 4 H-I) and the MR3 up to MR4.5 incidence rates in the 2G-TKI subgroup and this effect persisted in the long term (Fig. 4J-L).

Indeed, for patients treated with 2G-TKIs, the cumulative incidence rates (95% CI) of MR4 at 48 and 96 months were 59.2% (46.2%-69.0%) and 67.3% (54.2%-76.7%) in the pre-TKI HU group and 88.0% (66.7%-95.7%) and 97.7% (83.2%-99.7%) in the direct TKI group (p<0.001), respectively. The HR was 0.68 [0.45-1.04] (p=0.072). Similarly, the cumulative MR4.5 incidence rates at 48 and 96 months were 47.2% (33.6%-58.0%) and 54.9% (40.5%-65.9%) in the pre-TKI HU group and 73.0% (49.4%-85.5%) and 96.1% (69.8%-99.5%) in the direct TKI group, respectively (p<0.001). The Cox model analysis showed a similar trend (HR = 0.62 [0.38-1.00]; p=0.050).

Adverse events may influence TKI treatment (dose reduction, temporary treatment interruption), possibly reducing the therapeutic exposure and negatively affecting the response. However, the mean dose received and the number of treatment-free days in the first 12 months did not differ between groups regardless of the first-line TKI (Additional file 3, Supplemental Tables 1, 2). Analysis of treatment switches (likely due to intolerance or therapeutic resistance) showed that the proportion of patients who switched treatment at least once, regardless of timing or reason, was higher in the pre-TKI HU group than direct TKI group, particularly for first-line 2G-TKIs (53.5% vs. 32.6%) compared with imatinib (49.5% vs. 44.1%) (Fig. 5). No obvious bias in TKI distribution between groups was observed; the choice of dasatinib or bosutinib from the second line onwards and of asciminib from the third line onwards was consistent with their marketing authorizations.

However, it could be argued that only early switches might be linked to the first-line TKI. Therefore, the cumulative first switch incidence was analyzed by distinguishing treatment changes due to intolerance and due to therapeutic resistance (Fig. 6). The first switch was more frequently explained by intolerance than by resistance and occurred early in both groups. Intolerance-related switches mainly occurred during the first year of follow-up, whereas resistance-related switches were mostly distributed over the first 24 months. The cumulative incidence of switches due to intolerance was similar between groups (Fig. 6A). Conversely, the cumulative incidence of switches due to resistance tended to be higher in the pre-TKI HU group during the whole follow-up period, although the difference was not significant because of the small sample size (Fig. 6B). This difference became significant in the whole cohort before the application of the propensity score (p=0.025; Additional file 2, Supplemental Fig. 3). Overall, these results indicate the absence of a potential HU-linked bias on switches due to intolerance, but a trend towards higher rates of resistance in the pre-TKI HU group.

Discussion

To refine the initial place of hydroxyurea before TKI in routine CML management, we performed a large analysis using data from a real-world CP-CML cohort issued from the FCMLO registry.

Our study confirms the observations by Kockerols et al(7) on the increased TKI toxicity after HU use. However, unlike this previous study, only higher rates of edema in the subgroup treated with imatinib and increased hematological toxicity essentially in the subgroup treated with 2G-TKIs, regardless of TKI dose reductions or interruptions. One potential bias in the former study is the longer delay in patients pre-treated with HU. Moreover, this difference in toxicity rates could be explained by the higher proportion of patients treated with first-line 2G-TKIs in our study (31% and 48% in the direct TKI group and pre-TKI HU group vs. ~22% in both groups in the study by Kockerols et al(7)). This may reflect a more aggressive therapeutic approach for younger patients with higher prognostic risk score and greater tumor burden[6]. We do not currently have a pathophysiological explanation for this higher hematotoxicity, We could hypothesize that HU-related changes in non-leukemic hematopoiesis before TKI initiation make cells sensitive to the TKI off-target effects. In any case, hematotoxicity may challenge the initial TKI treatment plan (9).

To better understand the impact of pre-TKI HU use on the therapeutic response, we took into account the differences in patient characteristics between groups, some of which could represent confounding factors. After balancing the two groups using propensity score matching, we could confirm the lack of benefit of HU use before TKI initiation for MR2 or MR3 achievement(7), and also demonstrate for the first time a detrimental impact on the likelihood of achieving MR4 and MR4.5 over time. We found that HU has this deleterious effect also when 2G-TKIs are used as first-line therapy. Therefore, this effect is not offset by more potent TKIs, for which earlier and more in-depth molecular responses are expected than with imatinib. This must be kept in mind during TKI decision-making in view of a future treatment-free remission.

Given the impact of HU on TKI tolerability, one could ask whether changes in TKI prescribing may have played a role. Unlike in the study by Kockerols et al(7), HU treatment duration did not delay TKI initiation. To distinguish more clearly between a direct effect of HU and an indirect effect mediated by possible changes in dose or treatment, we first examined the therapeutic sequences in the two groups. This revealed complex real-world therapeutic sequence patterns, without evidence of treatment allocation bias between groups. Nevertheless, first-line switches were more common in the pre-TKI HU group, regardless of the TKI used and the timing of the switch. In this context, it is more informative to compare the cumulative incidence of the first switch. Overall, switches due to intolerance were more frequent and occurred earlier, in agreement with a study based on the Quebec CML registry(10). Conversely, resistance-related switches were observed throughout the first 24 months. The cumulative incidence of intolerance-related switches was similar between groups, whereas resistance-related switches tended to be higher in the pre-TKI HU group, suggesting a trend towards increased resistance rather than intolerance. We did not find any differences in the mean dose received and number of days without treatment during the first year. Taken together, these findings argue against the hypothesis that the poorer response in the pre-TKI HU group is related to an effect on TKI exposure, and rather suggest that HU has a direct negative effect. The underlying pathophysiological mechanism on hematopoiesis remains unknown. Interestingly, a recent single-cell proteomic-transcriptomic study showed that after HU administration, the proportion of stem progenitor cells in the S/G2/M phase increases(11), and that patients with a larger fraction of immature leukemic stem cells in the S/G2/M phase respond poorly to TKIs. This observation, combined with the previously reported deleterious effect of longer HU exposure (6 to 12 months) on CML progression(3,4), confirms that HU fails to reduce the *BCR::ABL*-positive clone burden, and may promote disease aggressiveness through mechanisms that remain to be explored.

Overall, these results confirm that HU use should be limited as much as possible for the early management of CP-CML. To better define the patients for whom its prescription is essential, we reviewed the main reasons reported by physicians in clinical practice.

Leukostasis prevention is the first reason reported by clinicians for HU use, although it does not reduce the leukemia burden(1,2). The leukostasis risk threshold varies according to the hematological malignancy type(12–16): 100×10^9/L for acute myeloid leukemia, ~400×10^9/L for acute lymphoid leukemia, no threshold for chronic lymphoid leukemia, and ≥250×10^9/L in children with CP-CML (although no robust threshold has been established) and was not determined for adult CP CML patients. In fact, leukostasis is infrequent in CP-CML: 9.7–16.5% of pediatric and adolescent patients and <10% of adult patients(12,17,18), compared with up to 35% of patients with Ph1-negative myeloproliferative syndromes(19). Consequently, clinical symptoms are important when assessing the risk of leukostasis. Although classical pulmonary and cerebral manifestations(20–22) are unusual in CML, the occurrence of visual disturbances with a risk of retinal hemorrhage is sometimes a concern. Moreover, priapism (1–3% of pediatric and young male patients with CP-CML) is a medical and

surgical emergency(18,23). These clinical features should be considered during CP-CML diagnostic work-up.

Starting HU treatment may also be motivated by very high platelet count. In our cohort, some patients in the pre-TKI HU group had high thrombocytosis (>1000 x10^9/L) (Tables 1 and 2), but the risk of complication is clearly lower compared with essential thrombocythemia(24). The small number of cases did not allow a reliable analysis.

The last urgent situation that explains HU use is acute abdominal pain due to symptomatic splenomegaly with the risk of spleen infarct or atraumatic rupture. Although rare in CP-CML, this complication is associated with an estimated mortality rate of ~12%.

In all these cases, HU is used for its rapid cytoreductive effect. However, in the TKI era, this rationale is less obvious because TKIs lead rapidly to a complete hematologic response. In our cohort, no significant difference was observed between the pre-TKI HU and direct TKI groups concerning the initial leukocytosis reduction (Additional file 2, Supplemental Fig. 4). Furthermore, 2G-TKIs induce a more rapid initial decline in disease burden than imatinib, including for reaching the hematologic response(26). Consequently, 2G-TKIs or imatinib start should be prioritized even in patients at high risk of leukostasis. In these patients, rapid molecular testing with the automated GeneXpert system, when available, can shorten the time to CML diagnosis confirmation. As CP-CML typically evolves over months and is often minimally symptomatic at diagnosis, TKI treatment should be also directly started for these patients.

Consequently, we propose a pragmatic approach in which HU use is restricted to patients with leukostasis or symptomatic splenomegaly (Fig. 7). To date, only Novotny et al. proposed a leukostasis grading score(12) in which higher scores correlate with mortality(27). We suggest to integrate this score into this management strategy.

A limitation of this study is its retrospective design; however, it would have been difficult to establish comparable groups given the gradual decline, between 2010 and 2025, in the number of patients who received HU before TKI initiation, consistent with the decreasing use of this strategy (Additional file 2, Supplemental Fig. 5).

Conclusions

In conclusion, our study highlights that pre-TKI HU negatively influences the likelihood of DMR achievement with first-line imatinib or 2G-TKIs and increases the risk of hematological toxicity by first-line 2G-TKIs. We propose an algorithm for HU treatment decision-making in CP-CML and starting TKI treatment as soon as possible.

List of abbreviations

2G-TKI: second-generation tyrosine kinase inhibitor
AE: adverse event
AML: acute myeloid leukemia
ARA-C: cytosine arabinoside (cytarabine)
ASR: atraumatic splenic rupture
BCR::ABL1: breakpoint cluster region–Abelson 1 fusion gene/transcript
BOSU: bosutinib
CI: confidence interval
CML: chronic myeloid leukemia
CNIL: Commission Nationale de l'Informatique et des Libertés (French data protection authority)
CP-CML: chronic-phase chronic myeloid leukemia
DASA: dasatinib
DMR: deep molecular response
ELN: European LeukemiaNet
ELTS: EUTOS long-term survival
EUTOS: European Treatment and Outcome Study
FCMLO: French Chronic Myeloid Leukemia Observatory
HR: hazard ratio
HU: hydroxyurea
IFN: interferon
IMA: imatinib
IPTW: inverse probability of treatment weighting
IQR: interquartile range
MR: molecular response
MR2: molecular response with BCR::ABL1 ≤1% on the International Scale
MR3: molecular response with BCR::ABL1 ≤0.1% on the International Scale
MR4: molecular response with BCR::ABL1 ≤0.01% on the International Scale
MR4.5: molecular response with BCR::ABL1 ≤0.0032% on the International Scale
NILO: nilotinib
PEG-IFN: pegylated interferon
Ph: Philadelphia chromosome
SD: standard deviation
SI: splenic infarction
TFR: treatment-free remission
TKI: tyrosine kinase inhibitor
WBC: white blood cell count

Declarations

Ethics approval and consent to participate:

The French CML Observatory was established in accordance with the French regulatory framework applicable to health-data research at that time. The project received a favourable opinion from the *Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé* (CCTIRS) on 16 April 2014. The CCTIRS was an independent national multidisciplinary committee established under French law to review health-research projects involving the processing of personal health data before authorisation by the French Data Protection Authority. Its assessment included the scientific and methodological justification of the research, the necessity of the proposed data processing, and the measures implemented to protect participants' rights, confidentiality, and personal data. Following this favourable opinion, the French CML Observatory was authorised by the *Commission nationale de l'informatique et des libertés* (CNIL; authorisation No. 914456), with approval of its extension on 11 July 2016.

All patients were informed and consented to the collection and subsequent reuse of their pseudonymised clinical data. The present study consisted exclusively of the secondary analysis of pseudonymised data previously collected in the French CML Observatory as part of routine clinical care, without any study-specific intervention, examination, biological sampling, or contact with patients. Under the French regulatory framework applicable to this study, no separate approval from a *Comité de Protection des Personnes* or institutional ethics committee/IRB was required for this secondary analysis. Data processing complied with the applicable CNIL requirements and with Regulation (EU) 2016/679, the General Data Protection Regulation.

Consent for publication: not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: MGB designed the study, participated in the data analysis, and participated in the writing of the manuscript. LR, GR-G, CD, FR-H formed the study scientific advisory board and participated in interpreting the results and reviewing the manuscript. SM carried out all statistical analyses and participated in the writing of the manuscript. TL extracted the data, and participated in the analysis of the results. BL participated in the data analysis. LR, GR-G, CD, FR-H, AP, MM, HJ-A, AP, MEB, VP, HM, GD, PR, LL, and MGB (investigators in the partner centers of the CML Observatory) included patients, and recorded data. JB and AK participated in the data analysis. DH and

MGB developed the computer database; DH maintains it and is responsible for data security and data protection. All authors validated the submitted manuscript.

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Figure Legends

Figure 1: Flowchart of patient selection from the French CML Observatory database. Exclusion criteria were: diagnosis of chronic phase-chronic myeloid leukemia (CP-CML) before 2010 (*BCR::ABL1* transcript standardized quantification became available only in 2010), patients with missing data at diagnosis or lost to follow-up, patients younger than 18 years, patients who received an allograft for CML, and patients with non-standard treatment. This led to the selection of 1096 patients among the 1,879 patients with CP-CML included in the database. Subsequently, 296 patients were excluded because the use or not of hydroxyurea could not be ascertained. ARA-C: Cytosine Arabinoside, HU: Hydroxyurea, IFN: Interferon, PEG-IFN: Pegylated Interferon, TKI: Tyrosine Kinase Inhibitor. BOSU: bosutinib, DASA: dasatinib, IMA: imatinib, NILO: nilotinib.

Figure 2. TKI-related adverse events in the direct TKI and pre-TKI HU groups
Percentage of patients with adverse events that occurred in the first 12 months of TKI treatment in the direct TKI group (blue bars) and pre-TKI HU group (red bars) in (A) the whole cohort, and according to the prescribed first-line TKI: (B) imatinib, (C) second-generation (2G) – TKI (nilotinib, bosutinib or dasatinib). Direct TKI group = 430 patients (295 imatinib, 135 2G-TKI) and pre-TKI HU group = 370 patients (200 imatinib, 170 2G-TKI). *$p < 0.05$ (Pearson's chi-square test).

Figure 3: Flowchart of patient selection from the French CML Observatory database for the propensity score. Only patients with complete data at diagnosis (*BCR::ABL1* and leukocytosis) were selected. ARA-C: Cytosine Arabinoside, HU: Hydroxyurea, IFN: Interferon, PEG-IFN: Pegylated Interferon, TKI: Tyrosine Kinase Inhibitor, WBC: White Blood Cells. BOSU: bosutinib, DASA: dasatinib, IMA: imatinib, NILO: nilotinib.

Figure 4. Cumulative incidence of the different molecular response levels in the direct TKI and pre-TKI HU groups
Propensity scores (A) and Inverse Probability Treatment Weights (IPTW) (B) for the two treatment groups. In this sub-cohort, 218 patients received HU before TKI initiation and 274 started directly with a TKI. (C) Standardized Mean Differences of the indicated baseline covariates between groups before and after propensity weighting. The center effect was not taken into account for the propensity weighting. (D-L) Kaplan-Meier curves showing the cumulative incidence of MR3, MR4 and MR4.5 in patients pretreated (HU) or not (no HU) before TKI initiation in the whole sub-cohort (D-F), and in the subgroups who received first-line imatinib (G-I) or a 2G-TKI (J-L) after application of the propensity score to take into account leukocytosis at diagnosis (confounding variable). Differences were assessed with the log-rank test. Direct TKI group = 274 patients (190 imatinib, 45 nilotinib, 34 bosutinib, and 5 dasatinib) and pre-TKI HU group = 218 patients (113 imatinib, 74 nilotinib, 25 bosutinib, and 6 dasatinib). Red: HU pretreatment; Blue: TKI without HU pretreatment; WBC: White Blood Cells.

Figure 5: Changes in treatment lines.
Sankey plots of treatment lines in the pre-TKI HU group (A) and Direct TKI group (B) showing all TKI switches in the cohort, irrespective of timing or reason. Each flow represents the proportion of patients transitioning from one treatment line to another, and the flow width is proportional to the number of patients. Percentages refer to proportions within the entire group. For first-line TKIs, the percentages of patients remaining on first line (black) and those who switched treatment at least once (red) are shown.
[a]The percentage concerns all second-generation (2G) TKIs used as first-line treatment.

Figure 6: Cumulative incidence of first switches.
Cumulative incidence of first TKI switches during the 60 months of follow-up according to the reason in the pre-TKI HU group (red) and direct TKI group (blue). Switches were classified as due to resistance (A) or intolerance (B). These reasons were considered as competing risks with other switch types and death also was treated as a competing event. (C) Percentages (and 95% Confidence Interval) of patients in the two groups who switched TKI at months 12, 24, 36, and 60. AE: adverse event.

Figure 7. Recommendations for prescribing HU before TKI initiation
As HU has a negative effect on the chances of achieving an optimal therapeutic response and on TKI tolerance in CP-CML, we recommend: (A) In patients with asymptomatic presentation or minimal symptoms at diagnosis, HU should not be prescribed while awaiting the molecular biology test results. (B) Patients with suspected/at risk of leukostasis. This risk can be evaluated using the symptom grading proposed by Novotny et al. For grade 1 patients, hydration and regular re-evaluation should be proposed. For grade 2 and 3 patients, cytoreduction with HU, possibly associated with other specific therapeutic strategies is indicated. (C) Patients with symptomatic splenomegaly at high risk of infarct or atraumatic splenic rupture. Acute abdominal pain of variable location, sometimes radiating to the left shoulder (Kehr's sign), rarely associated with signs of intra-abdominal hemorrhage (hypotension, fever, tachycardia, nausea, and vomiting), requires urgent spleen scan/echography and rapid cytoreduction with HU, possibly associated with other specific therapeutic strategies
ASR: Atraumatic splenic rupture; SI: spleen infarct.
[1]: The table has been proposed by Novotrony et al(12) to categorize leukostasis in other hematologic diseases. Pulmonary manifestations range from cough, dyspnea, tachypnoea, hypoxemia, and bronchial rales to severe presentations, such as diffuse alveolar hemorrhage and respiratory failure(22). Neurological symptoms begin with dizziness or blurred vision due to microvascular injury, and progress to headache, somnolence, confusion, delirium, or coma. Rare, but severe complications include intracerebral or retinal hemorrhage, renal vein thrombosis, and myocardial ischemia. Although classical pulmonary or cerebral presentation are unusual in CP-CML, the occurrence of retinal hemorrhage and priapism, a medical and surgical emergency, is sometimes observed(18).
[2]: Blurred vision, diplopia, hemianopsia.
[3]: Surgery for priapism, critical care unit, multidisciplinary management.

Table 1: Characteristics of patients

Characteristics[1]	**Whole cohort** N = 800[1]	**Pre-TKI hydroxyurea** N = 370[1]	**Direct TKI** N = 430[1]	**p-value**[2]
Sex, male	432 (54%)	213 (58%)	219 (51%)	0.060
Age at diagnosis (years)	59 (47, 69)	56 (47, 68)	61 (48, 71)	0.011
Sokal score				<0.001
Low	242 (30%)	82 (22%)	160 (37%)	
Intermediate	347 (43%)	162 (44%)	185 (43%)	
High	147 (18%)	106 (29%)	41 (9.5%)	
Unknown	64 (8.0%)	20 (5.4%)	44 (10%)	
ELTS group				<0.001
Low	393 (49%)	167 (45%)	226 (53%)	
Intermediate	229 (29%)	117 (32%)	112 (26%)	
High	105 (13%)	64 (17%)	41 (9.5%)	
Unknown	73 (9.1%)	22 (5.9%)	51 (12%)	
Leukocytosis at diagnosis, x10⁹/L	72 (35, 147)	133 (70, 216)	46 (25, 84)	<0.001
Unknown	272	133	139	
Leukocytosis >100 x10⁹/L	203 (38%)	145 (61%)	58 (20%)	<0.001
Unknown	272	133	139	
Platelets, x10⁹/L	381 (251, 602)	397 (262, 636)	375 (247, 561)	0.14
Unknown	96	25	71	
Thrombocytosis ≥1000 x10⁹/L	54 (7.7%)	37 (11%)	17 (4.7%)	0.003
Unknown	96	25	71	
Splenomegaly	239 (30%)	177 (48%)	62 (14%)	<0.001
Time from diagnosis to first-line TKI (days)	20 (12, 35)	19 (11, 33)	21 (13, 35)	0.13
HU pretreatment (days)	-	16 (10, 27)	-	-
Unknown	34	34	0	
First-line TKI				<0.001

Characteristics[1]	**Whole cohort** N = 800[1]	**Pre-TKI hydroxyurea** N = 370[1]	**Direct TKI** N = 430[1]	**p-value**[2]
Imatinib	495 (62%)	200 (54%)	295 (69%)	
Nilotinib	185 (23%)	111 (30%)	74 (17%)	
Bosutinib	80 (10%)	35 (9.5%)	45 (10%)	
Dasatinib	40 (5.0%)	24 (6.5%)	16 (3.7%)	
Hematotoxicity with first-line TKI	163 (20%)	82 (22%)	81 (19%)	0.2
Hematotoxicity (first year of TKI)	146 (18%)	81 (22%)	65 (15%)	0.013
First-line TKI reduction/interruption for any reason	298 (37%)	136 (37%)	162 (38%)	0.8
First-line TKI reduction/interruption due to hematotoxicity	87 (11%)	44 (12%)	43 (10%)	0.4

[1]n (%); Median (Q1, Q3)

[2]Pearson's Chi-square test; Wilcoxon rank sum test

Table 2: Characteristics of patients with leukocyte count at diagnosis

Characteristics[1]	**Whole cohort** N = 492[1]	**Pre-TKI hydroxyurea** N = 218[1]	**Direct TKI** N = 274[1]	**p-value**[2]
Sex, male	264 (54%)	126 (58%)	138 (50%)	0.10
Age at diagnosis (years)	60 (47, 70)	56 (47, 68)	63 (50, 72)	0.009
Sokal score				<0.001
Low	157 (32%)	47 (22%)	110 (40%)	
Intermediate	235 (48%)	102 (47%)	133 (49%)	
High	95 (19%)	66 (30%)	29 (11%)	
Unknown	5 (1.0%)	3 (1.4%)	2 (0.7%)	
ELTS group				0.051
Low	257 (52%)	100 (46%)	157 (57%)	
Intermediate	151 (31%)	72 (33%)	79 (29%)	
High	78 (16%)	43 (20%)	35 (13%)	
Unknown	6 (1.2%)	3 (1.4%)	3 (1.1%)	
Leukocytosis at diagnosis, x10⁹/L	75 (35, 146)	133 (71, 219)	46 (26, 85)	<0.001
Leukocytosis >100 x10⁹/L	190 (39%)	135 (62%)	55 (20%)	<0.001
Platelets, x10⁹/L	377 (247, 583)	422 (250, 657)	359 (245, 541)	0.027
Unknown	19	5	14	
Thrombocytosis ≥1000 x10⁹/L	31 (6.6%)	21 (9.9%)	10 (3.8%)	0.009
Unknown	19	5	14	
Splenomegaly	154 (31%)	108 (50%)	46 (17%)	<0.001
Time from diagnosis to first-line TKI (days)	20 (11, 31)	17 (10, 30)	21 (13, 32)	0.023
HU pretreatment (days)	-	15 (10, 22)	-	-
Unknown	5	5	0	
First-line TKI				<0.001
Imatinib	303 (62%)	113 (52%)	190 (69%)	
Nilotinib	119 (24%)	74 (34%)	45 (16%)	
Bosutinib	59 (12%)	25 (11%)	34 (12%)	
Dasatinib	11 (2.2%)	6 (2.8%)	5 (1.8%)	

Characteristics[1]	Whole cohort N = 492[1]	Pre-TKI hydroxyurea N = 218[1]	Direct TKI N = 274[1]	p-value[2]
Unknown	19	8	11	

[1]n (%); Median (Q1, Q3)

[2]Pearson's Chi-square test; Wilcoxon rank sum test; Fisher's exact test

Figure 1

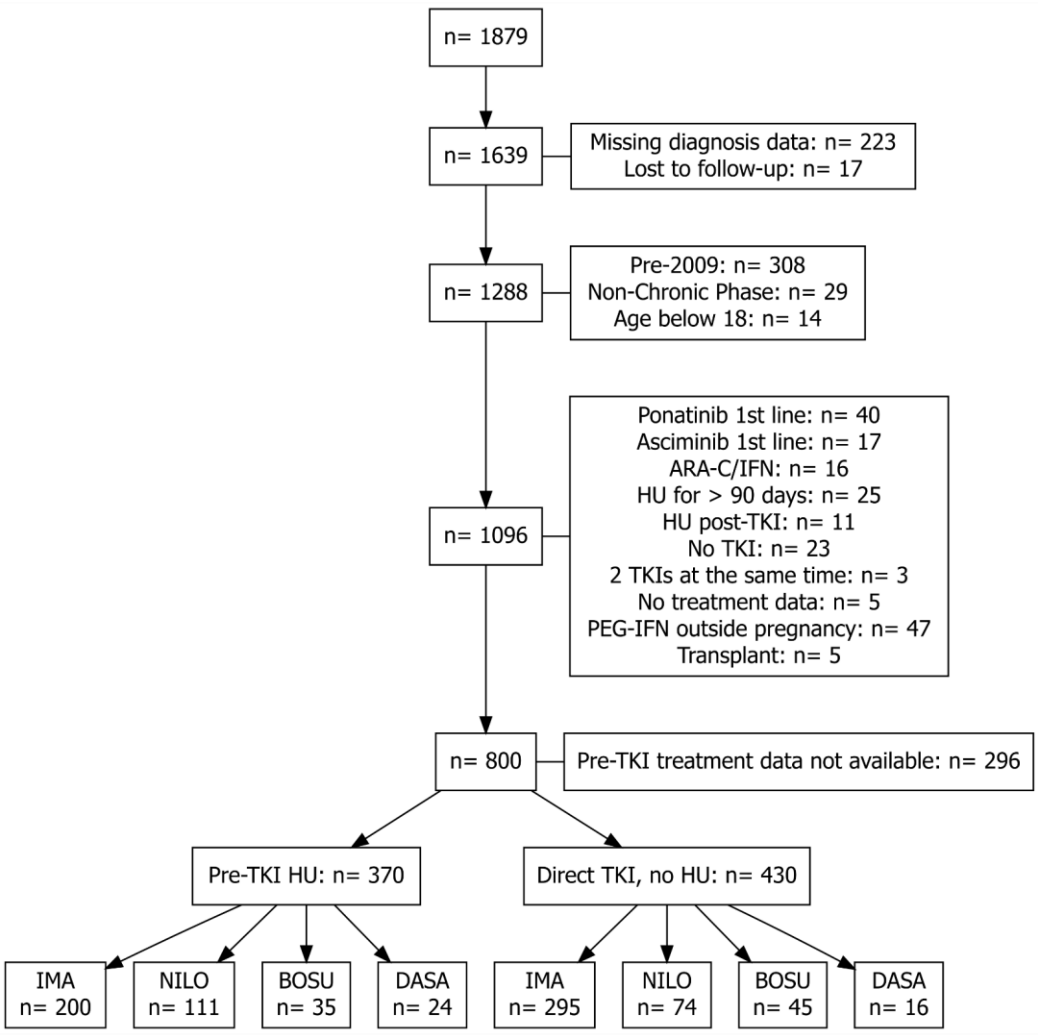
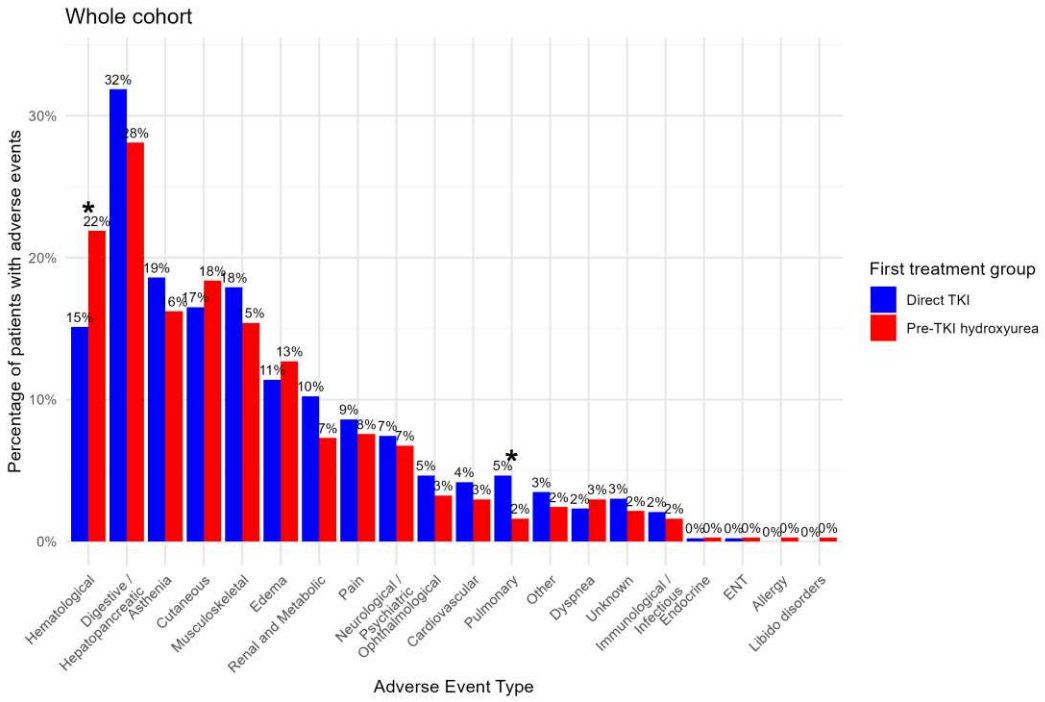
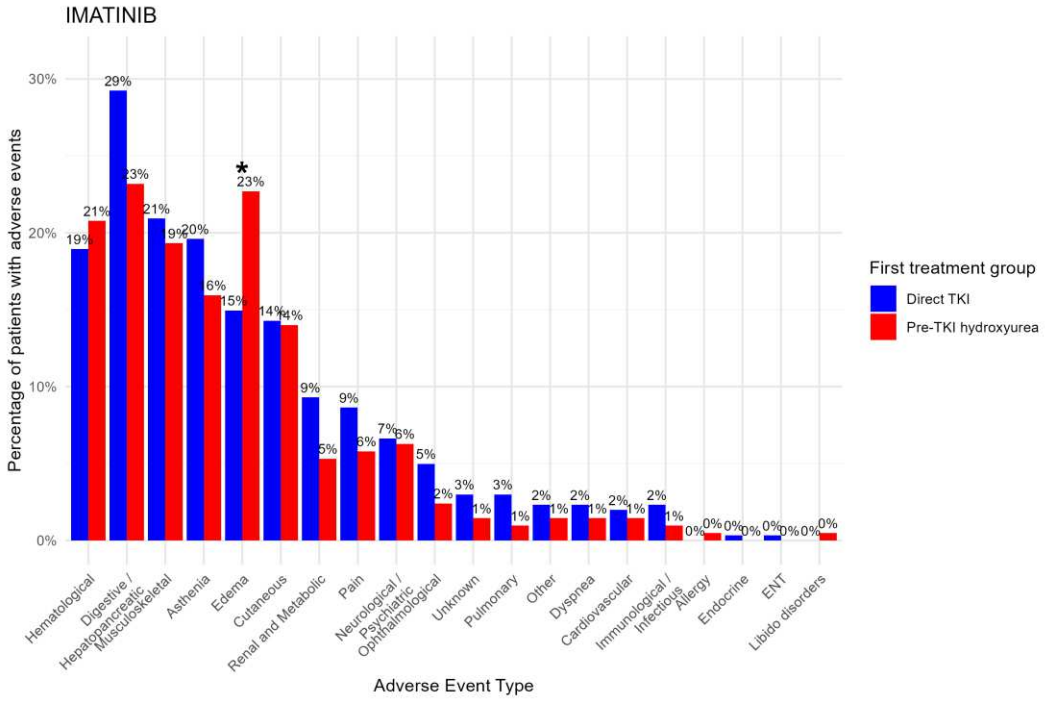


Figure 2

A


Whole cohort
Percentage of patients with adverse events
30%
20%
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0%
32%
28%
22%
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18%
17%
15%
15%
13%
11%
10%
9%
8%
7%
7%
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0%
Hematological
Digestive / Hepatopancreatic
Asthenia
Cutaneous
Musculoskeletal
Edema
Renal and Metabolic
Pain
Neurological / Psychiatric Ophthalmological
Cardiovascular
Pulmonary
Other
Dyspnea
Unknown
Immunological / Infectious
Endocrine
ENT
Allergy
Libido disorders
Adverse Event Type
First treatment group
Direct TKI
Pre-TKI hydroxyurea

B


IMATINIB
Percentage of patients with adverse events
30%
20%
10%
0%
29%
23%
23%
21%
21%
20%
19%
16%
15%
14%
14%
9%
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Hematological
Digestive / Hepatopancreatic
Musculoskeletal
Asthenia
Edema
Cutaneous
Renal and Metabolic
Pain
Neurological / Psychiatric Ophthalmological
Unknown
Pulmonary
Other
Dyspnea
Cardiovascular
Immunological / Infectious
Allergy
Endocrine
ENT
Libido disorders
Adverse Event Type
First treatment group
Direct TKI
Pre-TKI hydroxyurea

C

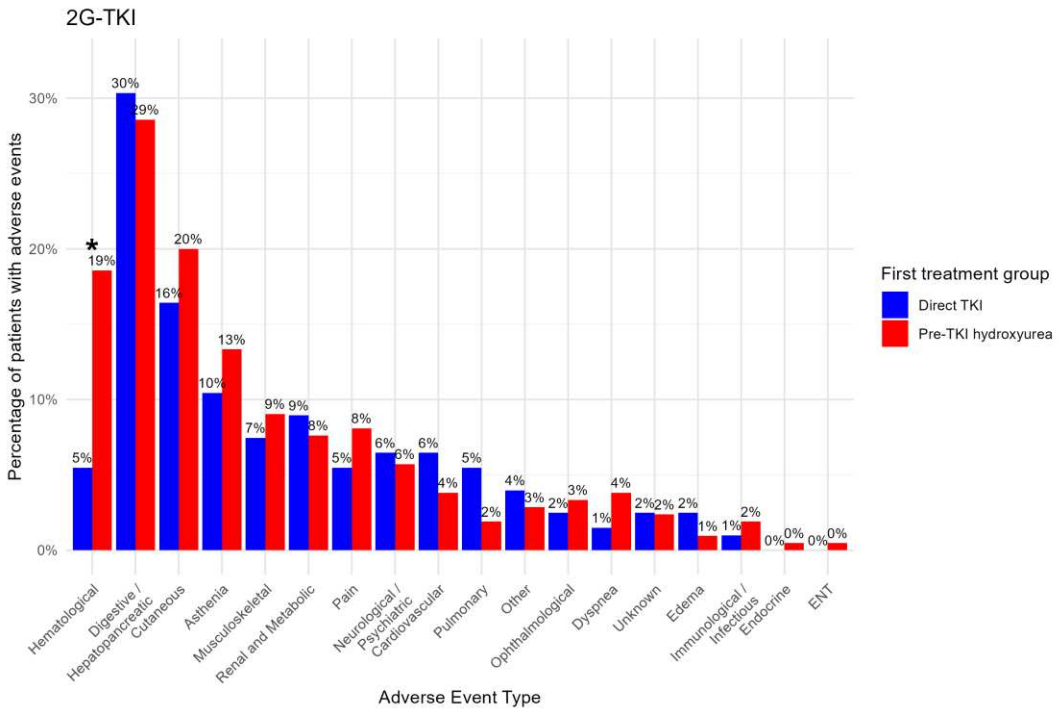

2G-TKI
Percentage of patients with adverse events
30%
20%
10%
0%
*
19%
5%
30%
29%
16%
20%
10%
13%
7%
9%
9%
8%
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Hematological
Digestive / Hepatopancreatic
Cutaneous
Asthenia
Musculoskeletal
Renal and Metabolic
Pain
Neurological / Psychiatric
Cardiovascular
Pulmonary
Other
Ophthalmological
Dyspnea
Unknown
Edema
Immunological / Infectious
Endocrine
ENT
Adverse Event Type
First treatment group
Direct TKI
Pre-TKI hydroxyurea

Figure 3

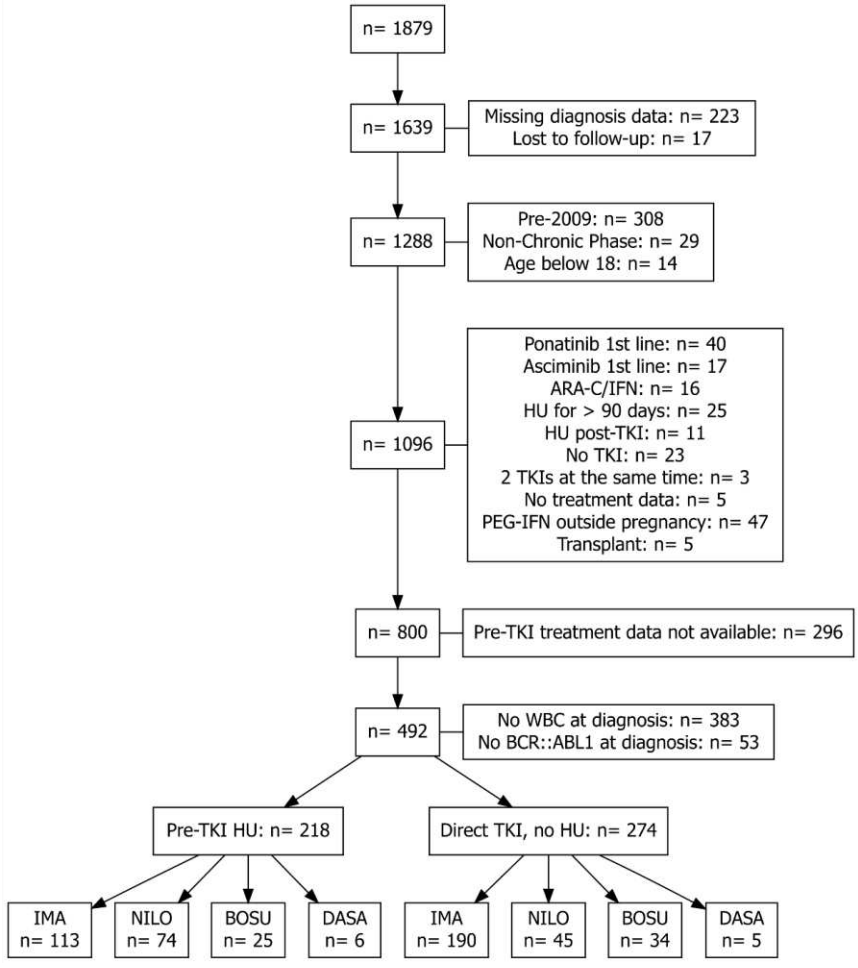

n= 1879
n= 1639
Missing diagnosis data: n= 223
Lost to follow-up: n= 17
n= 1288
Pre-2009: n= 308
Non-Chronic Phase: n= 29
Age below 18: n= 14
n= 1096
Ponatinib 1st line: n= 40
Asciminib 1st line: n= 17
ARA-C/IFN: n= 16
HU for > 90 days: n= 25
HU post-TKI: n= 11
No TKI: n= 23
2 TKIs at the same time: n= 3
No treatment data: n= 5
PEG-IFN outside pregnancy: n= 47
Transplant: n= 5
n= 800
Pre-TKI treatment data not available: n= 296
n= 492
No WBC at diagnosis: n= 383
No BCR::ABL1 at diagnosis: n= 53
Pre-TKI HU: n= 218
Direct TKI, no HU: n= 274
IMA n= 113
NILO n= 74
BOSU n= 25
DASA n= 6
IMA n= 190
NILO n= 45
BOSU n= 34
DASA n= 5

Figure 4

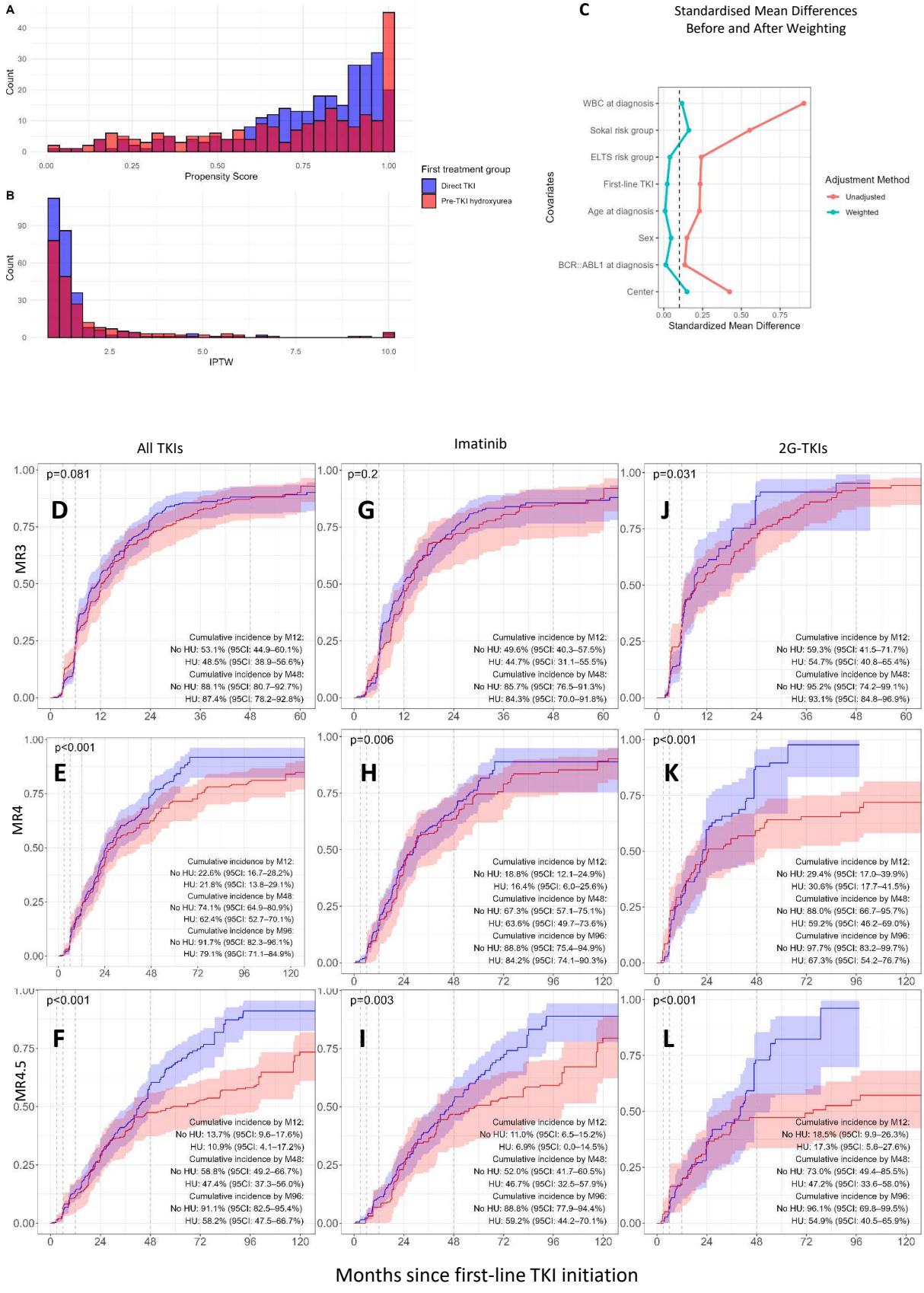

A
Count
Propensity Score
First treatment group
Direct TKI
Pre-TKI hydroxyurea
B
Count
IPTW
C
Standardised Mean Differences
Before and After Weighting
WBC at diagnosis
Sokal risk group
ELTS risk group
First-line TKI
Age at diagnosis
Sex
BCR::ABL1 at diagnosis
Center
Covariates
Standardized Mean Difference
Adjustment Method
Unadjusted
Weighted
All TKIs
Imatinib
2G-TKIs
MR3
MR4
MR4.5
p=0.081
p=0.2
p=0.031
p<0.001
p=0.006
p<0.001
p<0.001
p=0.003
p<0.001
D
G
J
E
H
K
F
I
L
Cumulative incidence by M12:
No HU: 53.1% (95CI: 44.9–60.1%)
HU: 48.5% (95CI: 38.9–56.6%)
Cumulative incidence by M48:
No HU: 88.1% (95CI: 80.7–92.7%)
HU: 87.4% (95CI: 78.2–92.8%)
Cumulative incidence by M12:
No HU: 49.6% (95CI: 40.3–57.5%)
HU: 44.7% (95CI: 31.1–55.5%)
Cumulative incidence by M48:
No HU: 85.7% (95CI: 76.5–91.3%)
HU: 84.3% (95CI: 70.0–91.8%)
Cumulative incidence by M12:
No HU: 59.3% (95CI: 41.5–71.7%)
HU: 54.7% (95CI: 40.8–65.4%)
Cumulative incidence by M48:
No HU: 95.2% (95CI: 74.2–99.1%)
HU: 93.1% (95CI: 84.8–96.9%)
Cumulative incidence by M12:
No HU: 22.6% (95CI: 16.7–28.2%)
HU: 21.8% (95CI: 13.8–29.1%)
Cumulative incidence by M48:
No HU: 74.1% (95CI: 64.9–80.9%)
HU: 62.4% (95CI: 52.7–70.1%)
Cumulative incidence by M96:
No HU: 91.7% (95CI: 82.3–96.1%)
HU: 79.1% (95CI: 71.1–84.9%)
Cumulative incidence by M12:
No HU: 18.8% (95CI: 12.1–24.9%)
HU: 16.4% (95CI: 6.0–25.6%)
Cumulative incidence by M48:
No HU: 67.3% (95CI: 57.1–75.1%)
HU: 63.6% (95CI: 49.7–73.6%)
Cumulative incidence by M96:
No HU: 88.8% (95CI: 75.4–94.9%)
HU: 84.2% (95CI: 74.1–90.3%)
Cumulative incidence by M12:
No HU: 29.4% (95CI: 17.0–39.9%)
HU: 30.6% (95CI: 17.7–41.5%)
Cumulative incidence by M48:
No HU: 88.0% (95CI: 66.7–95.7%)
HU: 59.2% (95CI: 46.2–69.0%)
Cumulative incidence by M96:
No HU: 97.7% (95CI: 83.2–99.7%)
HU: 67.3% (95CI: 54.2–76.7%)
Cumulative incidence by M12:
No HU: 13.7% (95CI: 9.6–17.6%)
HU: 10.9% (95CI: 4.1–17.2%)
Cumulative incidence by M48:
No HU: 58.8% (95CI: 49.2–66.7%)
HU: 47.4% (95CI: 37.3–56.0%)
Cumulative incidence by M96:
No HU: 91.1% (95CI: 82.5–95.4%)
HU: 58.2% (95CI: 47.5–66.7%)
Cumulative incidence by M12:
No HU: 11.0% (95CI: 6.5–15.2%)
HU: 6.9% (95CI: 0.0–14.5%)
Cumulative incidence by M48:
No HU: 52.0% (95CI: 41.7–60.5%)
HU: 46.7% (95CI: 32.5–57.9%)
Cumulative incidence by M96:
No HU: 88.8% (95CI: 77.9–94.4%)
HU: 59.2% (95CI: 44.2–70.1%)
Cumulative incidence by M12:
No HU: 18.5% (95CI: 9.9–26.3%)
HU: 17.3% (95CI: 5.6–27.6%)
Cumulative incidence by M48:
No HU: 73.0% (95CI: 49.4–85.5%)
HU: 47.2% (95CI: 33.6–58.0%)
Cumulative incidence by M96:
No HU: 96.1% (95CI: 69.8–99.5%)
HU: 54.9% (95CI: 40.5–65.9%)
Months since first-line TKI initiation

Figure 5

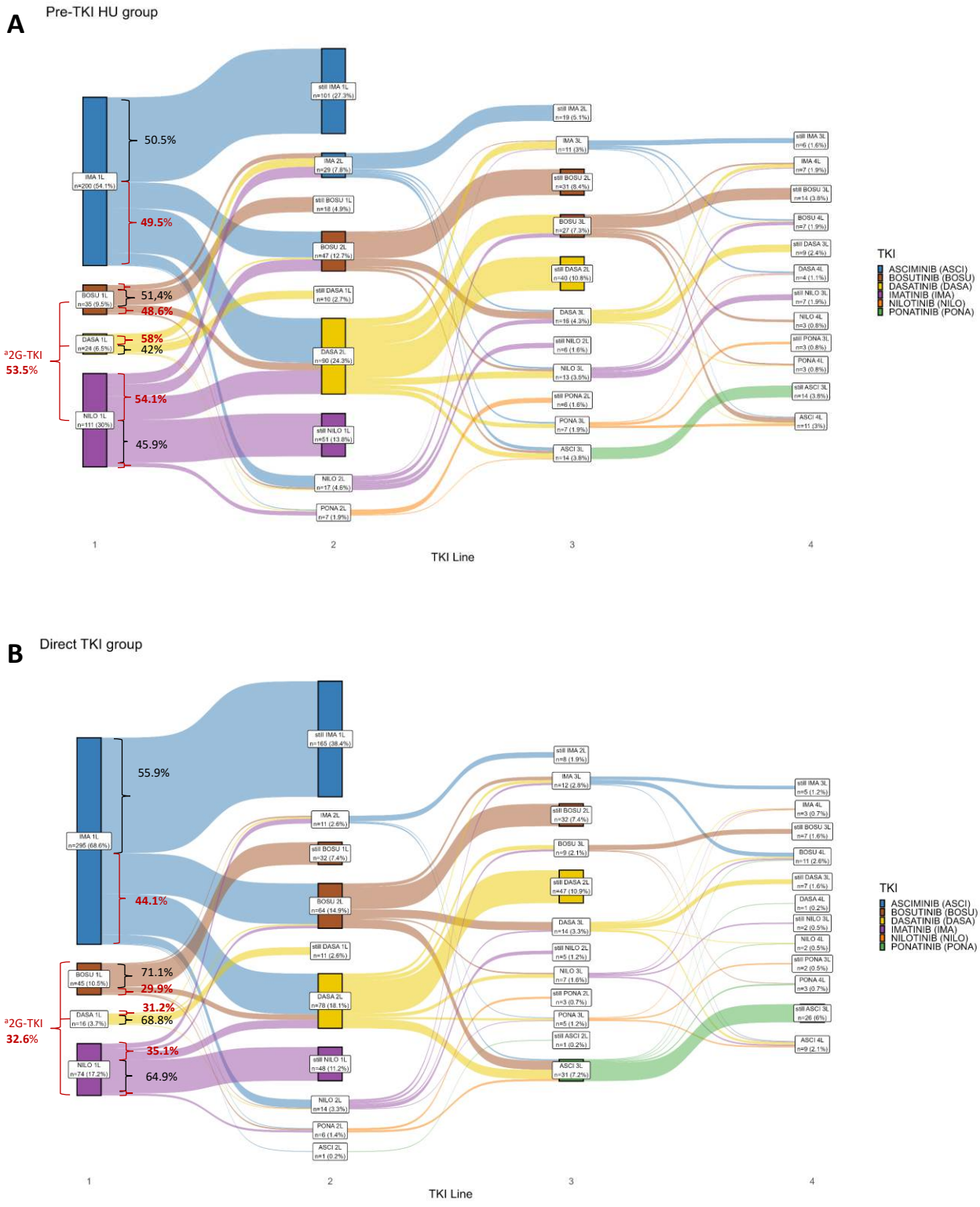
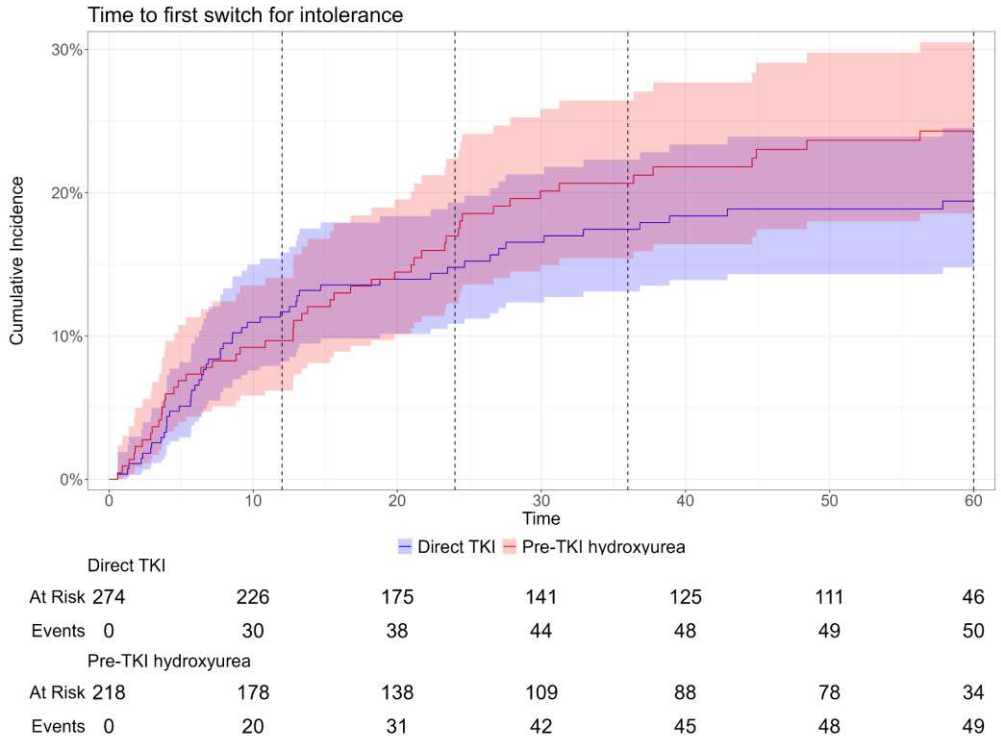

A
Pre-TKI HU group
IMA 1L n=200 (54.1%)
BOSU 1L n=35 (9.5%)
DASA 1L n=24 (6.5%)
NILO 1L n=111 (30%)
50.5%
49.5%
51,4%
48.6%
58%
42%
54.1%
45.9%
a2G-TKI
53.5%
still IMA 1L n=101 (27.3%)
IMA 2L n=29 (7.8%)
still BOSU 1L n=18 (4.9%)
BOSU 2L n=47 (12.7%)
still DASA 1L n=10 (2.7%)
DASA 2L n=90 (24.3%)
still NILO 1L n=51 (13.8%)
NILO 2L n=17 (4.6%)
PONA 2L n=7 (1.9%)
still IMA 2L n=19 (5.1%)
IMA 3L n=11 (3%)
still BOSU 2L n=31 (8.4%)
BOSU 3L n=27 (7.3%)
still DASA 2L n=40 (10.8%)
DASA 3L n=16 (4.3%)
still NILO 2L n=6 (1.6%)
NILO 3L n=13 (3.5%)
still PONA 2L n=6 (1.6%)
PONA 3L n=7 (1.9%)
ASCI 3L n=14 (3.8%)
still IMA 3L n=6 (1.6%)
IMA 4L n=7 (1.9%)
still BOSU 3L n=14 (3.8%)
BOSU 4L n=7 (1.9%)
still DASA 3L n=9 (2.4%)
DASA 4L n=4 (1.1%)
still NILO 3L n=7 (1.9%)
NILO 4L n=3 (0.8%)
still PONA 3L n=3 (0.8%)
PONA 4L n=3 (0.8%)
still ASCI 3L n=14 (3.8%)
ASCI 4L n=11 (3%)
1
2
3
4
TKI Line
TKI
ASCIMINIB (ASCI)
BOSUTINIB (BOSU)
DASATINIB (DASA)
IMATINIB (IMA)
NILOTINIB (NILO)
PONATINIB (PONA)
B
Direct TKI group
IMA 1L n=295 (68.6%)
BOSU 1L n=45 (10.5%)
DASA 1L n=16 (3.7%)
NILO 1L n=74 (17.2%)
55.9%
44.1%
71.1%
29.9%
31.2%
68.8%
35.1%
64.9%
a2G-TKI
32.6%
still IMA 1L n=165 (38.4%)
IMA 2L n=11 (2.6%)
still BOSU 1L n=32 (7.4%)
BOSU 2L n=64 (14.9%)
still DASA 1L n=11 (2.6%)
DASA 2L n=78 (18.1%)
still NILO 1L n=48 (11.2%)
NILO 2L n=14 (3.3%)
PONA 2L n=6 (1.4%)
ASCI 2L n=1 (0.2%)
still IMA 2L n=8 (1.9%)
IMA 3L n=12 (2.8%)
still BOSU 2L n=32 (7.4%)
BOSU 3L n=9 (2.1%)
still DASA 2L n=47 (10.9%)
DASA 3L n=14 (3.3%)
still NILO 2L n=5 (1.2%)
NILO 3L n=7 (1.6%)
still PONA 2L n=3 (0.7%)
PONA 3L n=5 (1.2%)
still ASCI 2L n=1 (0.2%)
ASCI 3L n=31 (7.2%)
still IMA 3L n=5 (1.2%)
IMA 4L n=3 (0.7%)
still BOSU 3L n=7 (1.6%)
BOSU 4L n=11 (2.6%)
still DASA 3L n=7 (1.6%)
DASA 4L n=1 (0.2%)
still NILO 3L n=2 (0.5%)
NILO 4L n=2 (0.5%)
still PONA 3L n=2 (0.5%)
PONA 4L n=3 (0.7%)
still ASCI 3L n=26 (6%)
ASCI 4L n=9 (2.1%)
1
2
3
4
TKI Line
TKI
ASCIMINIB (ASCI)
BOSUTINIB (BOSU)
DASATINIB (DASA)
IMATINIB (IMA)
NILOTINIB (NILO)
PONATINIB (PONA)

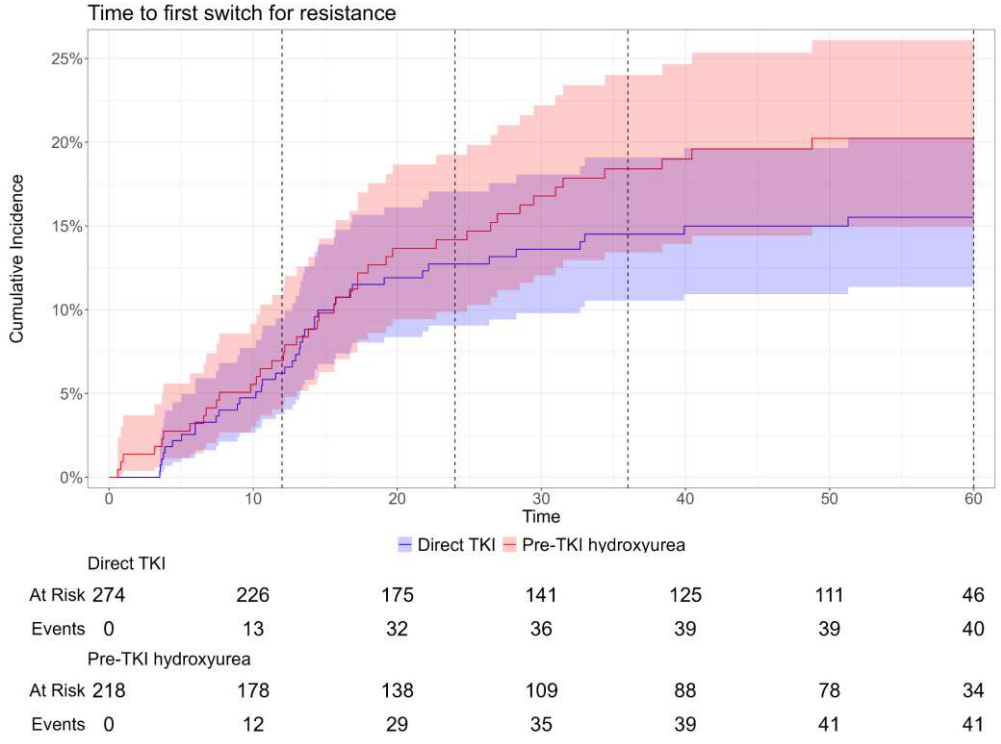
Figure 6

A



Direct TKI							
At Risk	274	226	175	141	125	111	46
Events	0	30	38	44	48	49	50
Pre-TKI hydroxyurea							
At Risk	218	178	138	109	88	78	34
Events	0	20	31	42	45	48	49

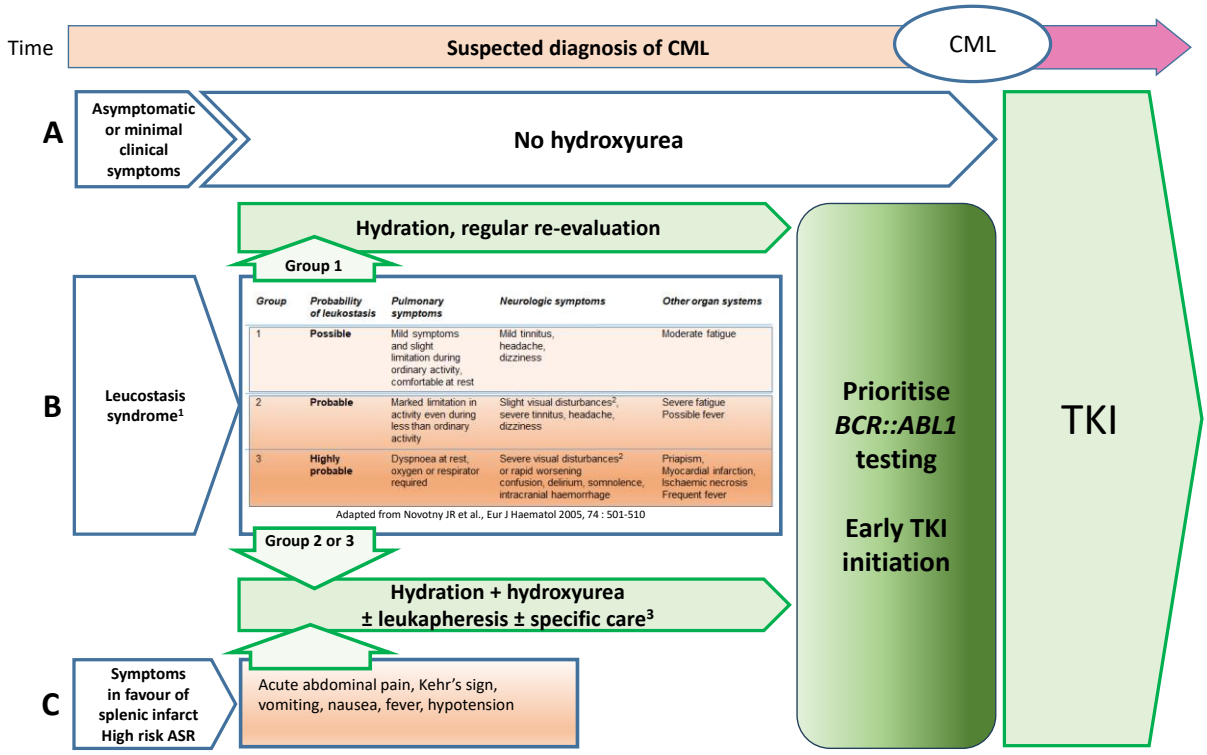
B



Direct TKI							
At Risk	274	226	175	141	125	111	46
Events	0	13	32	36	39	39	40
Pre-TKI hydroxyurea							
At Risk	218	178	138	109	88	78	34
Events	0	12	29	35	39	41	41

Characteristic	Month 12	Month 24	Month 36	Month 60
Switch for intolerance				
group				
Direct TKI	12% (8.2%, 16%)	15% (11%, 19%)	17% (13%, 22%)	19% (15%, 25%)
Pre-TKI hydroxyurea	9.7% (6.2%, 14%)	17% (12%, 22%)	21% (15%, 26%)	24% (19%, 30%)
Switch for resistance				
group				
Direct TKI	6.2% (3.8%, 9.5%)	13% (9.1%, 17%)	15% (11%, 19%)	16% (11%, 20%)
Pre-TKI hydroxyurea	7.0% (4.1%, 11%)	14% (9.9%, 19%)	18% (13%, 24%)	20% (15%, 26%)

Figure 7



Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1Royetal.docx
- Additionalfile2FiguresRoyetal.docx
- Additionalfile3Tables1Royetal.docx