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Research paper

Canadian real-world experience of asciminib treatment in heavily pre-treated chronic myeloid leukemia (CML) patients who failed multiple lines of tyrosine kinase inhibitor (TKI) therapy

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ABSTRACT

Background: Asciminib is a novel drug specifically targeting *ABL* myristoyl pocket in the *ABL1* protein.
Methods: Forty one patients with chronic myeloid leukemia treated with asciminib from 2018 to 2022 were reviewed and analyzed for the efficacy and tolerability of asciminib using real-world experience data.
Results: The median age was 60 years (range 17–90) with a past history of a cardiovascular event in 21 patients (51%). Patients were pretreated with a median of 3 previous tyrosine kinase inhibitors (range 1–5). After a median of 12 months of asciminib (range 3–41), major molecular response (MMR) rate was 39% (n = 11/28) and 42% (n = 5/12) at 6 and 12 months, respectively. Molecular response with 2 log reduction (MR2) was noted in 54% (n = 15/28) and 50% (n = 6/12) at 6 and 12 months. The cumulative incidence of MMR and MR2 was 46.3% and 66% at 12 months.
Five patients discontinued asciminib due to treatment failure (n = 3) or thrombocytopenia (n = 2). There were no cardiovascular events. Out of 7 patients treated with high dose asciminib for *T315I* mutation, 5 patients achieved MMR or deeper response. The event-free survival was 63% at 12 months.
Conclusion: This study confirmed clinical efficacy and tolerability of asciminib with real-world experience.

1. Introduction

The advent of tyrosine kinase inhibitors (TKIs) has revolutionized the management of chronic myeloid leukemia (CML); and has remarkably improved the long-term outcomes of CML patients including their overall survival. However, a proportion of patients become resistant,

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progress or develop intolerance due to significant toxicity from multiple lines of TKI therapy. Many have no other options for CML treatment except allogeneic stem cell transplantation. About a third of patients do not achieve an optimal response when imatinib is given in the first line setting [1]. Also, a substantial number of patients fail second generation TKIs (2 G-TKIs) due to resistance or intolerance either in the first or second line setting [2,3]. Switching to 2 G-TKIs can still lead to resistance in addition to an increased likelihood of intolerance to the 2 G-TKI [4]. Ponatinib can be considered an alternative option with its exceptional activity against *T315I ABL1* kinase domain mutation. However, concern still remains due to the higher risk of arterial thrombotic/occlusive events which precludes a substantial portion of patients from the use of ponatinib due to their cardiovascular (CV) comorbidities [5].

Asciminib is a novel, first-in-class drug that specifically targets the *ABL* myristate pocket (STAMP inhibitor) by structurally mimicking the N-terminus of *ABL1,* which contains the inhibitory myristate binding site [6,7]. The phase 3 ASCEMBL study reported superior efficacy of asciminib compared to bosutinib with a 6 months' major molecular response (MMR) of 25.5% vs 13.2% with bosutinib, and 6 month complete cytogenetic response of 40.8% vs 24.2% in chronic phase (CP) CML patients who failed at least two lines of TKI therapy with a favorable adverse event profile [8]. Thus, it has been approved in CML patients who previously failed two or more TKIs, and those with a *T315I* mutation by the US-FDA. In Canada, asciminib has been available through a compassionate use program for heavily pre-treated CP CML patients, and was approved by the Health Canada in July 2022.

A previous study of real-world experience (RWE) data for the use of asciminib reported a 41% rate of molecular response of 3 log reduction or deeper (MR3) after a median of 8.8 months of treatment in 31 patients treated with asciminib [9]. Of note, 11 patients who had been previously treated with ponatinib showed lower response rates with asciminib compared to ponatinib-naïve patients.[9] Another study reported a 45% MR3 rate at 6 months in 53 patients which included a higher proportion of patients pre-treated with ponatinib (58%) and also included CML patients in more advanced phases [10].

The present study evaluated the efficacy and tolerability of asciminib in CML patients treated with asciminib across Canada within the compassionate use program.

2. Patients and methods

2.1. Patients and treatment summary including previous TKI therapies as well as asciminib treatment

Clinical data were collected on 41 CML patients treated with asciminib from 2018 to 2022 across Canada. These included patient demographics and comorbidities, disease characteristics, number of previous TKI treatment and TKI drug type, reasons for treatment failure to the latest line of TKI. The initial dose of asciminib, molecular response, and adverse events were captured. The study was approved by the Research Ethics Board at University Health Network, Toronto, Canada.

2.2. Molecular monitoring using BCR::ABL1 quantitative PCR during therapy

Peripheral blood *BCR::ABL1* transcript level was evaluated every 3 months by polymerase chain reaction (PCR) at each institution. *BCR::ABL1* transcript levels were measured and reported according to the international scale (%^{IS}) as well as the log reduction scale: RNA was extracted and reverse transcribed into cDNA then amplified by real-time quantitative PCR for the *BCR::ABL1* fusion transcript. Sanger sequencing-based *ABL1* kinase domain mutation (KDM) analysis was performed as a part of standard practice per physician discretion prior to asciminib start to detect any *ABL1* KDM which confers TKI-resistance: RNA was extracted and reverse transcribed into cDNA then amplified by PCR using primers specific for the detection of *ABL1* KDMs present in the *BCR-ABL1* fusion transcript. PCR products were purified and sequenced and then compared with NCBI reference sequence (*ABL1*: NM_005157.6).

2.3. Response criteria and treatment outcomes

Response criteria were applied as previously defined [11,12]. A major molecular response (MMR) or molecular response of log3 reduction (MR3) was defined as $\leq 0.1\%^{IS}$ of *BCR::ABL1* fusion gene transcripts, equivalent to a 3 log reduction or deeper, and molecular response of log2 reduction (MR2) was defined as $\leq 1\%^{IS}$, equivalent to a 2 log reduction of *BCR::ABL1* transcript levels or deeper. In addition, a molecular response of 4 log reduction or deeper (MR4) was defined as $\leq 0.01\%^{IS}$ of *BCR::ABL1* fusion gene transcripts.

The primary outcome of the study was achievement of MR3 and MR2 at 6 months, which were the primary and secondary endpoints in the ASCEMBL trial, respectively. Molecular responses at 12 months, as well as at the most recently reported molecular assessments were also captured. The secondary outcomes included toxicities, discontinuation events, as well as achievement of MR4. Events for calculating event-free survival (EFS) were defined as 1) treatment failure as per the ELN recommendation 2013 for second-line CML treatment failure such as *BCR::ABL1* transcript > 10% at 6 months [13], 2) disease progression to advanced phase and 3) discontinuation of asciminib due to toxicity. In addition to the initial dose of asciminib, the dose was also captured every 3 months. The reasons for the TKI failure were divided into three categories: intolerance (defined as inability to continue using asciminib due to an adverse event despite achieving a MR3 or deeper response), resistance/suboptimal response (defined as inability to achieve a MR3 regardless of occurrence of adverse event) or both. Toxicities were also captured.

2.4. Statistical analysis

The data were locked as of July 2022. Demographic and disease characteristics, and previous treatment history were analyzed and plotted with median values for continuous variables. The cumulative incidence of MR3 and MR2 on asciminib therapy was calculated using a cumulative incidence method considering competing events of asciminib discontinuation for any reason, or death. Event-free survival was calculated using a Kaplan-Meier analysis. The proportion of the patients achieving MR3 and MR2 was calculated at 6 and 12 months. Several clinical variables such as past history of ponatinib treatment, reason of failure to the latest line of TKI therapy, presence of *T315I* mutation, and past history of a CV event were included in the risk factor analysis for attaining MR3 and M2 at 6 and 12 months. All P values were two-sided and $P < 0.05$ was considered as statistically significant. For statistical analyses, version 16.32 of Excel for Mac, R statistical software 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria; available at http://www.r-project.org) and EZR (version1.54) [14] were used.

3. Results

3.1. Summary of patient, disease and previous treatment characteristics

The median age of the patients at asciminib start was 60 years (range 17–90), and 23 of 41 patients (56%) were female (Table 1). Twenty-one patients (51%) had a past history of a clinically documented CV event including stroke, myocardial infarction, or peripheral arterial occlusive disease Table 2.

The median number of previous TKI lines was 3 (range 1–5). Twenty-eight patients (68%) had been previously treated with 3 or more lines of TKI drugs. The median interval from the start of the first TKI to the start of asciminib was 89 months (range 11–233). *ABL1* kinase domain mutations were noted in 12 patients including *T315I* mutation (n = 7) and

Table 1
Patient and Disease Demographics, N of Patients (%).

Patient Characteristics	
Total Patients	41 (100)
Female	23 (56)
Median Age in Years at Diagnosis (Range)	60 (17–90)
Hypertension	25 (61)
Diabetes	10 (24)
Dyslipidaemia	17 (41)
Cardiovascular Disease (Stroke, CAD, PVD)	21 (51)
Smoking	6 (15)
Disease Characteristics	
Low Risk Sokal	7
Intermediate Risk Sokal	14
High Risk Sokal	7
Sokal Score Not Reported	14
CML Phase at Diagnosis	
Chronic Phase	38 (93)
Accelerated Phase	2 (5)
Blast Phase	1 (2)
ABL1 Kinase Domain Mutations	14 (34)
T3151 mutation	7 (17)
Non-*T315I* Mutations	7 (17) N = 3 of M244V; N = 2 of E255K and F312L; N = 1 of G250E, F359V, Y253H, Lys262_Arg332del.
Additional Cytogenetic Abnormality	N = 1 of Trisomy 8; N = 1 of del(6) in Ph(-) cells; N = 1 of 46,XY,− 6,t(9;22),+mar
Treatment Characteristics	
Median Lines of Treatment (Range)	3 (1–5)
Patients with ≥ 3 TKIs	28 (68)
Imatinib Pre-treatment	33 (81)
Dasatinib Pre-treatment	30 (73)
Nilotinib Pre-treatment	22 (54)
Bosutinib Pre-treatment	27 (66)
Ponatinib Pre-treatment	14 (34)
Reasons for Starting Asciminib	
Resistant/Suboptimal to Previous TKI	28 (68)
Intolerance to Previous TKI	13 (32)

*Abbreviation: CAD, coronary artery disease; PVD, peripheral vascular disease; CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitior

non-*T315I* mutation (n = 7) including *F359V* (n = 1), *Y235H (n = 1), G250E* (n = 1), *E255K* (n = 1), *Lys262_Arg332del*(n = 1) and two patients with three mutations: *M244V, F317L,* and *E255K*. (Table 1 and Table 3).

3.2. Asciminib treatment and dosage

The median duration of asciminib treatment was 12 months (range 3–41 months). Thirteen patients (32%) started asciminib due to intolerance but had achieved MR3 or deeper response prior to asciminib therapy start. The remainder included resistant patients or suboptimal responders (less than MR3). Thirty-eight patients (93%) were in CP before starting asciminib, of these the majority (n = 33/38) were started at a dose of 40 mg twice daily. One patient started at 20 mg twice daily as the patient had just recovered from elevated liver enzymes secondary to imatinib; another four patients in CP with *T315I* mutations, started at higher doses of asciminib with quick escalation to 200 mg twice daily. The two AP patients were also started on higher doses with a target of 200 mg twice daily, and the blast phase patient started at 20 mg twice daily with quick escalation.

3.3. Molecular response to asciminib treatment

After a median follow-up of 12 months, MR3 was achieved in 11/28 (39%) and 5/12 patients (42%) at 6 and 12 months, respectively. MR2 was noted in 15/28 (54%) and 6/12 patients (50%) at 6 and 12 months. Similar rates were seen in most subgroups except for patients who had been treated with ponatinib. (Table 2).

Table 2
Summary of 12-months' event-free survival and MMR and MR2 rates at 6 and 12 months in overall cohort (n = 41) and in the subgroups.

Number of Pts (%)	MR2, 6 mon	MR2, 12 mon	MR3, 6 mon	MR3, 12 mon	EFS, 12 mon
Overall cohort (n = 41)	15/28 (54)	6/12 (50)	11/28 (39)	5/12 (42)	61.3% [8.9–77.6%]
Chronic phase CML	15/27 (56)	6/11 (55)	11/27 (41)	5/11 (45)	65.0% [40.8–81.3%]
Non-chronic phase CML	0/1	-	0/1	-	33.3 [0.09–77.4%]
Ponatinib naïve (n = 27)	14/18 (78)	5/7 (71)	10/18 (56)	4/7 (57)	77.9% [42.0–93.0%]
Ponatinib pre-treated (n = 14)	1/10 (10)	1/5 (20)	1/10 (10)	1/5 (20)	41.7% [15.2–66.5%]
Without *T315* mutation (n = 34)	14/25 (56)	5/10 (50)	10/25 (40)	4/10 (40)	61.7% [34.8–80.1%]
With *T315I* mutation (n = 7)	1/3 (33)	1/2 (50)	1/3 (33)	1/2 (50)	53.6% [13.2–82.5%]
No *ABL1* KD mutation (n = 27)	13/20 (65)	4/8 (50)	10/20 (50)	3/8 (38)	71.6% [38.9–82.7%]
ABL1 KD mutation (n = 14)	2/8 (25)	2/4 (50)	1/8 (13)	2/4 (50)	48.2% [18.4–73.0%]
Resistant/suboptimal (n = 28)	11/21 (52)	4/9 (44)	8/21 (38)	4/9 (44)	59.1% [15.3–71.8]
Intolerant (n = 13)	4/7 (57)	2/3 (67)	3/7 (43)	1/3 (33)	71.4% [42.5–89.7%]
Pts having past history of cardiovascular event (n = 21)	5/14 (36)	4/7 (57)	3/14 (21)	3/7 (43)	44.0% [19.2–66.5%]

*Abbreviation: MR2 (Molecular response of 2 log reduction or deeper); MR3 (Molecular response of 3 log reduction or deeper); EFS (Event-free survival); KD (Kinase domain)

The cumulative incidence rates of MR3 were 39.0% and 46.2% at 6 months and 12 months respectively with a median of 24 months to achieve MR3 in the overall cohort. In the patients who achieved MMR, MMR was achieved a median of 9.4 months after asciminib start. The cumulative incidence rate of MR2 was 57.1% and 66.0% at 6 and 12 months respectively with a median of 4.5 months to achieve MR2. (Fig. 1A). Meanwhile, the event-free survival rate was 61.3% at 12 months (Fig. 1B) with a trend of superior EFS in the patients receiving asciminib for intolerance to the previous TKI compared to those who were resistant to the last TKI (71.4% vs 59.%; p = 0.985). In order to reach a clearer conclusion, further study is strongly warranted in a larger number of patients treated with asciminib. The cumulative incidence of MR4 was 32.1% at 24 months. No patient had received an allogeneic stem cell transplant at the time of last follow-up.

3.4. ABL1 kinase domain mutation prior to asciminib therapy

As shown in Table 3, 14 patients had *ABL1* kinase domain mutation (KDM) including 7 patients with *T315I* mutation and other 7 patients with non-*T315I* mutations. Five of the seven patients with a *T315I* mutation were in CP with one case in accelerated phase (AP) and another in lymphoid blast phase. Five of the patients with *T315I* mutations had previously failed ponatinib. Two experienced intolerance (due to coronary artery event and peripheral vascular disease) and the remaining were resistance or suboptimal responders to ponatinib. Follow-up *BCR::ABL1* qPCR was not available for the blast phase patient but the patient was alive at 15 months of follow-up; the patient in AP was resistant to therapy and treatment was discontinued. The remaining 5 CP patients were in MR3 or deeper response at last follow-up, with one patient discontinuing therapy at 6 months due to thrombocytopenia.

As presented in the Table 3, 6 of the 7 patients with non-*T315I ABL1* kinase domain mutations were in CP at the time of asciminib start, with one patient in AP. This patient had 3 KD mutations simultaneously

Table 3
Summary of the patients harboring *ABL1* kinase domain mutation prior to asciminib therapy start and the treatment outcomes following asciminib therapy.

Disease Phase Prior Asciminib	ABL1 KD mutations	Previous treatment					Starting Dose of Asciminib (mg/day)	Latest dose of Asciminib (mg/day)	Response to Asciminib therapy
		Ponatinib	**Imatinib**	**Dasatinib**	**Nilotinib**	**Bosutinib**			
CP	G250E	No	Yes	Yes	No	Yes	80	80	achieved MR4
CP	Y253H	No	Yes	No	Yes	No	80	80	achieved MR2
CP2	Lys262_Arg332del	Yes	No	Yes	No	No	80	240	achieved hematologic response
CP	F359V	Yes	No	Yes	Yes	Yes	80	80	failed to achieve MR2
CP	M244V, F317L, E255K	No	Yes	Yes	Yes	Yes	80	80	achieved MR2
CP	M244V	Yes	Yes	Yes	No	Yes	80	80	failed to achieve MR2
AP	M244V, F317L, E255K	Yes	Yes	Yes	Yes	Yes	200	200	failed to achieve MR2
CP	T315I	No	Yes	No	No	No	320	240	achieved MR4
CP	T315I	No	Yes	No	No	Yes	320	240	achieved MR4
CP	T315I	Yes	Yes	No	No	No	320	320	achieved MR4
CP	T315I	Yes	Yes	No	No	No	80	160	achieved MR4
CP	T315I	Yes	Yes	Yes	Yes	Yes	300	240	achieved MR3
AP	T315I	Yes	Yes	No	No	No	160	400	resistant to therapy
BP	T315I	Yes	No	Yes	Yes	No	40	160	achieved hematologic response

(*M244V, F317L, E255K)* and had not achieved a MR2 at 9 months of asciminib despite being on the higher dose of 200 mg po bid. However, another patient in CP with the same 3 KD mutations achieved MR2 after 3 months of asciminib. Another patient with *G250E* mutation quickly achieved and maintained MR3 on asciminib. Two patients with a single *F359V* and *M244V* mutation failed to achieve MR2 with asciminib despite more than 18 months of treatment at standard 40 mg twice daily dosing.

3.5. Ponatinib naïve vs pre-treated patients

In the 14 ponatinib pre-treated patients, 9 were resistant to ponatinib, while the remaining 5 were intolerant. At 6 months, 10/18 (56%) in the ponatinib naïve subgroup achieved MR3 while 1/10 (10%) in ponatinib pre-treated patients achieved MR3 (Table 2). However, *ABL1* kinase domain mutations were more frequently detected in ponatinib pre-treated subgroup (9/14; 64%) compared to the ponatinib naïve subgroup (5/27; 19%).

When analysis was confined to the patients with *T315I* mutation, even though they had been previously treated with ponatinib, at least 3 out of 5 (60%) achieved MR3 or deeper response, which would suggest asciminib therapy is still active in ponatinib-pretreated patients if they have *T315I* mutation.

3.6. Side effects, discontinuations, and deaths during asciminib therapy

The most commonly observed toxicity of asciminib therapy in our study was generalized muscle aches observed in seven patients (17%). This necessitated dose reductions in all except one. The two patients with elevated lipase (grade 2 and grade 4) had to temporarily interrupt asciminib, and the medication was carefully reintroduced and gradually escalated without recurrence. One patient, who had a pre-existing history of pleural effusion secondary to multiple TKIs, had another episode of pleural effusion while on asciminib, but this did not require discontinuation at the latest follow up. Another patient developed both pericardial and pleural effusions with cardiac tamponade. This patient was in AP at asciminib start and remained resistant to treatment despite being on asciminib at 200 mg po bid for greater than 9 months. Eventually, the drug was discontinued.

Overall, five patients discontinued asciminib treatment: 3 patients due to disease resistance including one having AP with *M244V*, *F312L,* and *E255K* mutation, previously treated with ponatinib, had been treated with 200 mg per day of asciminib but failed to have any reduction of *BCR::ABL1* transcript level; Another patient also had AP with *T315I* mutation, and treated with 320 mg per day of asciminib, but progressed to blast phase; The last patient was in CP but without any detectable *ABL1* KDM and was treated with 80 mg per day of asciminib but failed to show a reduction in *BCR::ABL1* transcript level. Two patients discontinued asciminib due to grades 3/4 thrombocytopenia: One patient developed thrombocytopenia without any evidence of cytopenia prior to asciminib start, while another developed anemia/thrombocytopenia with previous episodes of recurrent cytopenia with other TKIs.

The most common event was treatment failure seen in eight patients, followed by three events of disease progression to advanced phases, and the two patients who discontinued due to drug toxicity as described above.

3.7. Asciminib therapy in patients with a previous history of clinically significant CV events

Twenty-one patients out of 41 (51%) had a past history of clinically documented CV events including stroke, myocardial infarction, or peripheral arterial occlusive disease. We did not observe any CV events during their asciminib treatment with a median duration of 15 months (range 3–41).

We performed an analysis to look at possible predictors for asciminib failures but did not find any clinically significant risk factors for EFS in our cohort. Ponatinib pre-treatment may be associated with lower EFS compared to patients who were ponatinib naïve. (Fig. 1C).

4. Discussion

In this first North American RWE result of asciminib treatment, most patients were heavily-pretreated CML patients, of whom 51% of patients had a clinically documented CV event in the past. Such patients are often excluded from clinical trials due to their comorbidities. However, their treatment outcome with respect to MR3 and MR2 rates were comparable to that from the clinical trial [15,16]. In 21 patients with a past history of a CV event, none developed clinically significant CV toxicities nor discontinued asciminib due to a CV event after a median duration of 15 months on asciminib (range 3–41).

Data from the phase 3 ASCEMBL trial revealed an almost 2-fold

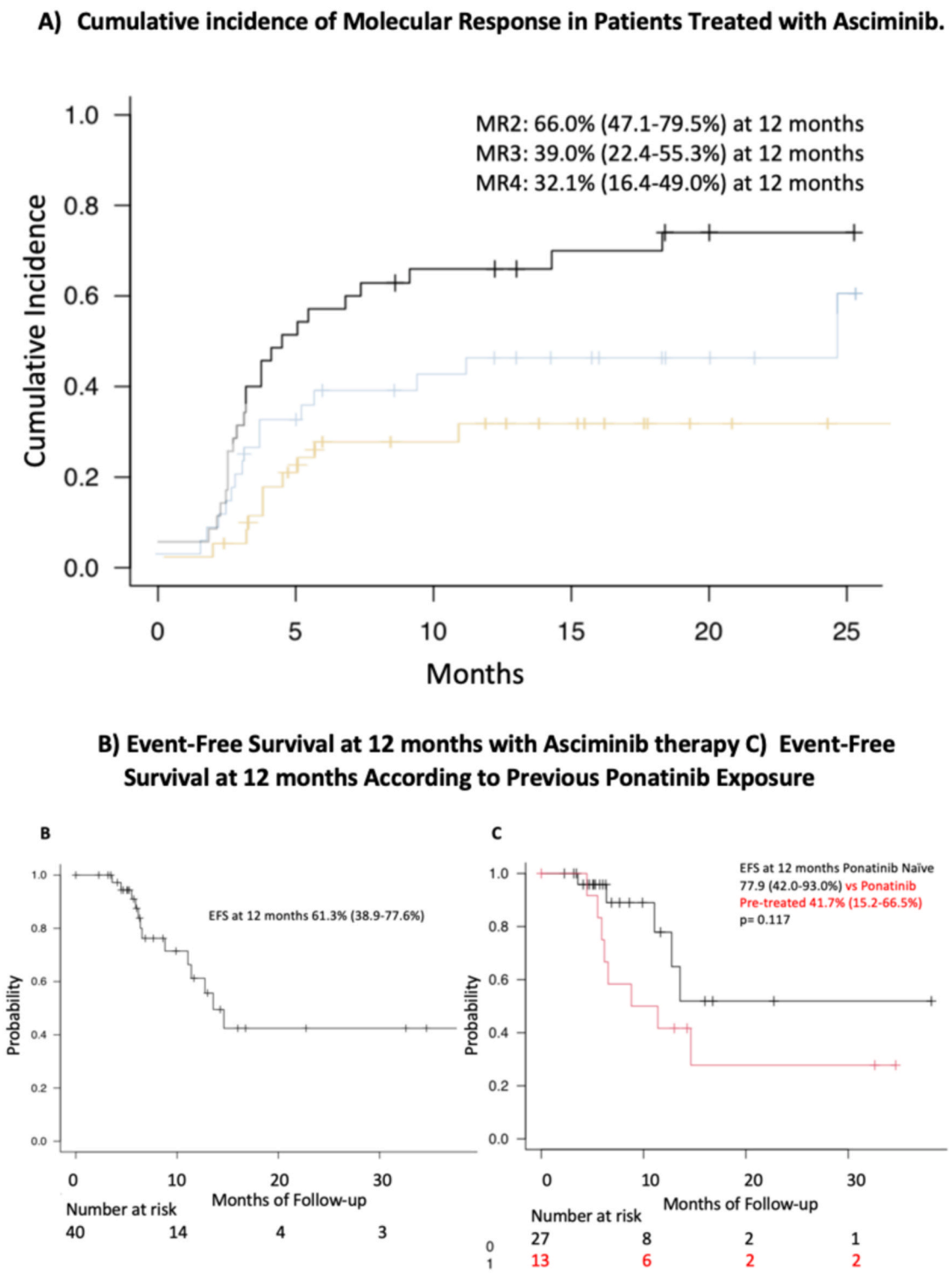

Fig. 1. A) Cumulative incidence of Molecular Response in patients Treated With Asciminib. B) Event-Free Survival at 12 months with Asciminib therapy C) Event-Free Survival at 12 months According to previous ponatinib Exposure.

increased MR3 rate at 6 months with asciminib compared to bosutinib (25% vs 12%) in patients who had failed at least 2 previous TKIs [16], and follow-up from that trial revealed MR3 rates at 96-weeks of 37.6% with asciminib vs 15.8% in the bosutinib arm [16]. This MR3 rate is compatible with that in our cohort with 50% achieving MR3 at 6 months in the overall cohort, especially as our cohort was more heavily pre-treated, included non-CP patients, and most patients had failed 3 or more TKIs prior to asciminib therapy. Our data also included a higher proportion of patients who had received ponatinib (34%) or with *ABL1* kinase domain mutations (34%), compared to lower frequencies in previous studies[17]. Additionally, at baseline, more than half of our patients (23/41; 56%) had not achieved a MR2 (Fig. 2).

The response to asciminib was seen across all the subgroups reported in Table 2 including in the seven patients who had a *T315I* mutation. This finding is consistent with the report from the phase 1 study. Hughes et al.[15] reported antileukemic activity of asciminib in 28 CML patients

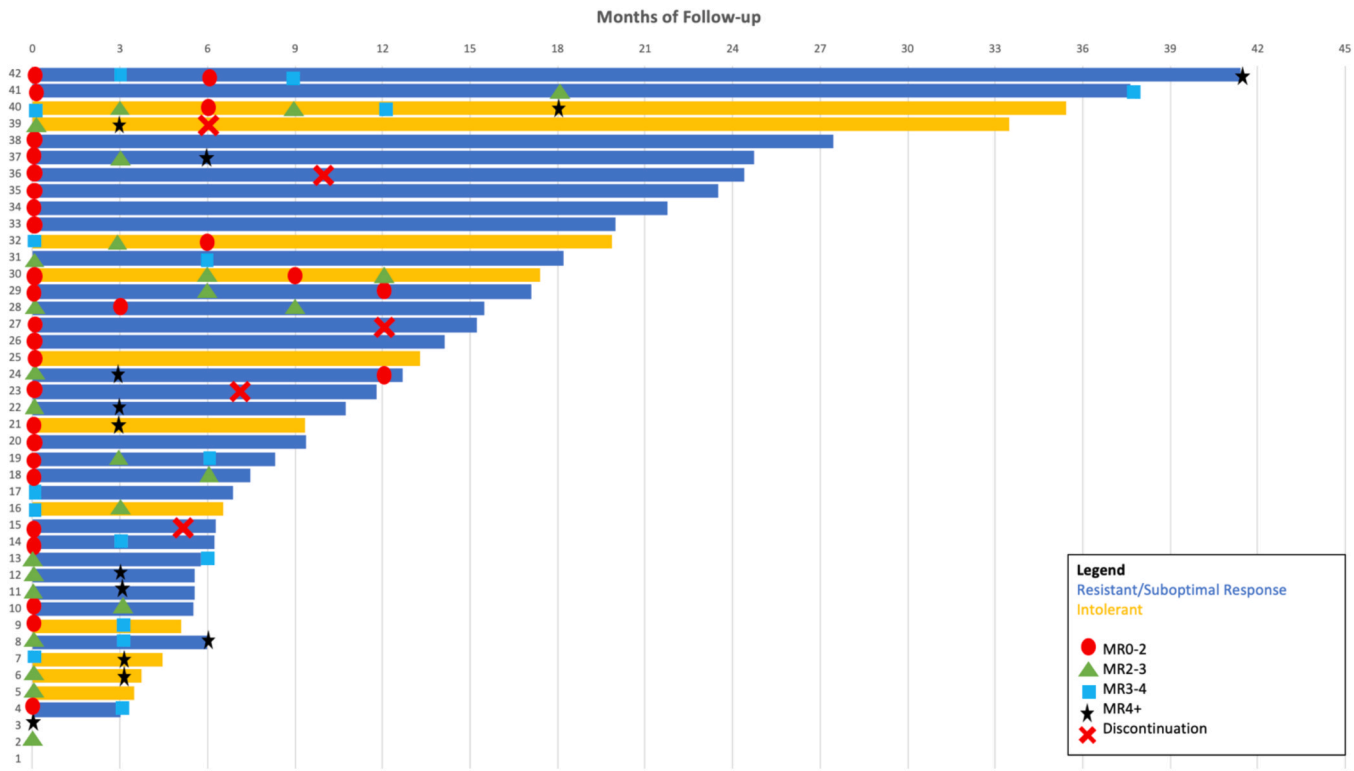

Fig. 2. swimmer's Plot of Patients on Asciminib.

with a *T315I* mutation. 41% of patients achieved a complete cytogenetic response, while 24% of patients achieved MMR with asciminib, similar to our result. In the phase 1 study, 3 of 4 CML patients (75%) with a *T315I* mutation who had MR3 received a dose of more than 150 mg twice daily. Due to a past history of clinically documented prior CV events, we started asciminib at lower dose of 80 mg twice daily in *T315I* mutant cases, aiming to escalate it up to 200 mg twice daily. Although these patients were commenced on a lower dose of asciminib in the beginning, their achievement of MR3 (n = 1) and MR4 (n = 1) was not impeded. The optimal dose of asciminib in *T315I* mutant CML should be analyzed further.

The lower efficacy of asciminib in patients who have failed ponatinib compared to those who are ponatinib-naïve has been previously reported although this is a small cohort [9]. The reason for this is complex, confounded by factors such as the number of lines of prior therapy and/or *ABL1* kinase domain mutation. Thus, it is not evident whether the lower response rate in the ponatinib pre-treated subgroup is from the ponatinib treatment history itself, or from biologically more aggressive disease. Indeed, there is a trend of more lines of pre-treatment in patients who had failed ponatinib, as well as a higher frequency of *ABL1* kinase domain mutation in ponatinib pre-treated patients. This would suggest that the more resistant and advanced CML clones are selected via ponatinib therapy. Out of 14 ponatinib pre-treated patients, 5 patients had a pre-existing *T315I* mutation.

Regarding the *ABL1* KDM and its sensitivity to asciminib, there is a lack of clinical data available. Theoretically, asciminib's therapeutic activity should not be hindered by the presence of the ATP binding pocket site. However, emerging evidence suggests that *ABL1* mutation located in the ATP binding pocket site may indeed inhibit the activity of asciminib. In a recent study by Shah et al. [18], the M244V mutation is reported to be clinically resistant to asciminib 80 mg once daily in 2 patients. Also, BaF3/M244V cell line experiment confirms that M244V mutation confers a surprisingly high degree of resistance to asciminib [18]. Additionally, our group presented preliminary in vitro data supporting in vitro resistance of M244V mutation to asciminib. In the present study, out of 3 patients with M244V mutation, at least 2 did not respond even to high dose asciminib treatment [19]. On a positive note, the patient with the G250E mutation responded favorably to asciminib and achieved a rapid MR4 response, which is consistent with our in vitro data [19].

In our real world experience data, with a significant cohort at high risk for CV events, it was reassuring to note the absence of any cardiac or arterial occlusive events after a median of 15 (range 3–41) months of asciminib. These patients are often precluded from participation in prospective clinical trials, while nilotinib and ponatinib treatment can be challenging. Accordingly the present study is reassuring that the use of asciminib in this cohort yields a good molecular response rate without increasing CV toxicity. Furthermore, these results provide a perspective on the safety of asciminib in earlier lines of therapy (i.e. front line or second line) in patients with a high CV risk, although this question warrants further investigation.

Our study is limited due to its retrospective nature and a relatively smaller sample size. We do not have a centralized laboratory system in Canada for *BCR::ABL1* testing with the potential issue of inter-laboratory variation for *BCR::ABL1* qPCR monitoring. Nevertheless, this is the first reported North American experience of asciminib treatment in a RWE and is therefore valuable in gaining an understanding of asciminib use outside of the context of clinical trials.

In summary we demonstrated that 1) Asciminib treatment is very feasible in the patients with limited treatment options available, 2) The clinical efficacy of asciminib in RWE was similar to that in the clinical trials, including in patients with significant CV risk factors and who were more heavily pre-treated than in previous reports. 3) Asciminib treatment is tolerable and safe, and can be administered to patients with cardiac comorbidities.

Authorship

DK conceived the idea. AX, JD, LB, KJ, SC, HO, PK, RK, BL, and SA collected data from their centres. FK and DK inputted the data and

performed the statistical analysis. FK drafted the manuscript. All authors reviewed the manuscript and approved its final version.

Declaration of Competing Interest

FK provides consultancy for Novartis, SC provides consultancy and has honoraria for Novartis, Pfizer, BMS, Celgene, Incite. AX, NF and LB has honoraria from Novartis. BL provides consultancy, has honoraria and on the advisory board for Novartis, Pfizer, BMS, Abbvie, and AMGEN. RK is on the advisory boards of Sanofi, FORUS Therapeutics, Belgene, Pfizer and has honoraria from Janssen and BMS. SA gets research funding from Novartis and has consultancy/ honoraria from Genentech/Roche, Astra Zeneca, Novartis, BMS, Jazz, Gilead, Amgen, Beigene, Abbvie, Paladin. DK is a consultant, has received research funding, and honoraria from Pfizer, Sanofi, Paladin, and Novartis. The remaining authors have no conflict of interest.

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