650 Asciminib, a First-in-Class STAMP Inhibitor, Provides Durable Molecular Response in Patients (pts) with Chronic Myeloid Leukemia (CML) Harboring the T315I Mutation: Primary Efficacy and Safety Results from a Phase 1 Trial

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Introduction: Tyrosine kinase inhibitors (TKIs) are an effective therapy for pts with CML. However, resistance to treatment driven by point mutations in the ABL kinase domain, particularly the T315I mutation, represents a clinical challenge. The T315I mutation confers resistance to all approved ATP-competitive TKIs except ponatinib (PON) and is associated with significantly worse clinical outcomes. PON use, however, is limited in many patients by its safety profile. Asciminib has a distinct mechanism of action and is the first-in-class STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor. Asciminib demonstrated clinical activity in heavily pretreated CML pts with or without mutations, with promising efficacy in pts with T315I, including those resistant to/intolerant of (R/I) PON.

Methods: This phase 1 study enrolled adults with CML in chronic phase (CP) or accelerated phase (AP) R/I ≥ 2 TKIs; pts with T315I were eligible after receiving ≥ 1 TKI if no other effective therapy was available. Pts with uncontrolled cardiovascular conditions were excluded. Pts with T315I were assigned to varying dose levels in phase 1, and 200 mg twice daily (BID) was selected for cohort expansion. Here, we report updated efficacy and safety results in pts with T315I who received 200 mg BID (data cutoff: April 2, 2020).

Results: A total of 52 pts with T315I received asciminib 200 mg BID. At the data cutoff, treatment was ongoing in 35/52 pts (67.3%); 17 (32.7%) discontinued treatment, a majority of whom (10 [19.2%]) discontinued due to physician's decision, mainly for unsatisfactory response (Table 1). Of pts still on treatment, 31/35 (88.6%) received treatment for > 48 wk. The median duration of exposure was 68.4 wk (range, 2-175 wk) and median dose intensity was 399.0 mg/day (range, 188-400 mg/day). Among evaluable pts not in major molecular response (MMR) at baseline, 23/49 (46.9%) achieved MMR and 21 of these responders were still in MMR at the time of data cutoff; 40.8%, 42.9%, 44.9%, and 46.9% had MMR by 24, 48, 72, and 96 wk, respectively. The Kaplan-Meier-estimated rate of durable first MMR among pts who achieved MMR was 87% (95% CI, 68.4-100.0) at 96 wk and remained unchanged until 144 wk. The median time to MMR was 12.1 wk (range, 4-84 wk). By 24 wk, 57.1% of PON-naive pts and 28.6% of PON-pretreated pts achieved MMR (Table 2). Three additional pts achieved MMR after 24 wk: 2 PON naive and 1 PON pretreated. The estimated cumulative MMR rate at 60 wk increased to 66% and 32% in PON-naive and PON-pretreated pts, respectively (Figure). Among 26 pts who did not achieve MMR, 3 had additional mutations (E255K, E355G, F359I) at baseline and 6 acquired new mutations after baseline (F359I [n = 2], A337T/F359V, M351T, M244V, E453Q). Among 2 pts who lost MMR, 1 acquired a new F359V mutation. Among evaluable pts without MMR at baseline, 13/49 (26.5%) and 10/49 (20.4%) achieved MR^4 and $MR^{4.5}$, respectively.

Treatment-related adverse events (AEs) were reported in 45/52 pts (86.5%) and were mainly mild in severity; grade ≥ 3 AEs were reported in 17/52 pts (32.7%). All-grade serious AEs were reported in 12 pts (23.1%), with 2 (3.8%) deemed treatment related. No on-treatment deaths were reported. On-treatment AEs leading to discontinuation were reported in 4 pts (7.7%; disease progression, grade 2 thrombocytosis, grade 3 lipase elevation, and grade 4 pancytopenia, 1 pt each). Dose reductions and interruptions (excluding dosing errors) were reported in 21 (40.4%) and 22 (42.3%) pts, respectively (reduction and/or interruption in 29 pts total); they were mainly due to AEs (13 [25.0%] and 18 [34.6%] pts, respectively). The most frequent any-grade AEs of special interest (occurring in ≥ 10% of pts) were gastrointestinal toxicity (48.1%), hypersensitivity (26.9%), myelosuppression (25.0%), pancreatic toxicity (25.0%), hepatotoxicity (23.1%), thrombocytopenia (21.2%), hemorrhage (17.3%), leukopenia (15.4%), and edema and fluid

retention (13.5%). Ischemic stroke and peripheral arterial occlusive disease were each reported in 1 pt; both pts had underlying cardiovascular disease.

Conclusions: Asciminib 200 mg BID monotherapy continued to demonstrate a favorable safety profile and clinical efficacy in pts with CML-CP/AP harboring the T315I mutation, with durable MMR seen in almost half of the patients. Asciminib is a promising therapeutic option for pts with CML-CP/AP with T315I, including those for whom PON treatment has failed.

Table 1. Demographics, Baseline Characteristics, and Disposition of Pts with Centrally Confirmed T315I at Screening Treated with Asciminib 200 mg BID Monotherapy

	Pts with Confirmed T315I Treated with Asciminib 200 mg BID (N = 52)
Median age (range), y	54.0 (26-86)
Male, n (%)	39 (75.0)
BCR-ABL1^{IS} at screening, n (%)[a]	
> 0.1% to ≤ 1%	8 (15.4)
> 1% to ≤ 10%	13 (25.0)
> 10%	28 (53.8)
Atypical/p190/unknown transcripts	3 (5.8)
ECOG performance status, n (%)	
0	39 (75.0)
1	13 (25.0)
Pt disposition, n (%)	
Treatment ongoing[b]	35 (67.3)
End of treatment	17 (32.7)
Reasons for end of treatment	
Adverse event	4 (7.7)
Physician decision	10 (19.2)
Progressive disease	3 (5.8)

BID, twice daily; ECOG, Eastern Cooperative Oncology Group; IS, International Scale; pt, patient.

[a] Overall, 49 pts were evaluable for achieving major molecular response, as 3 pts had atypical/unknown transcripts at baseline.

[b] Pts with ongoing treatment at the data cutoff of April 2, 2020.

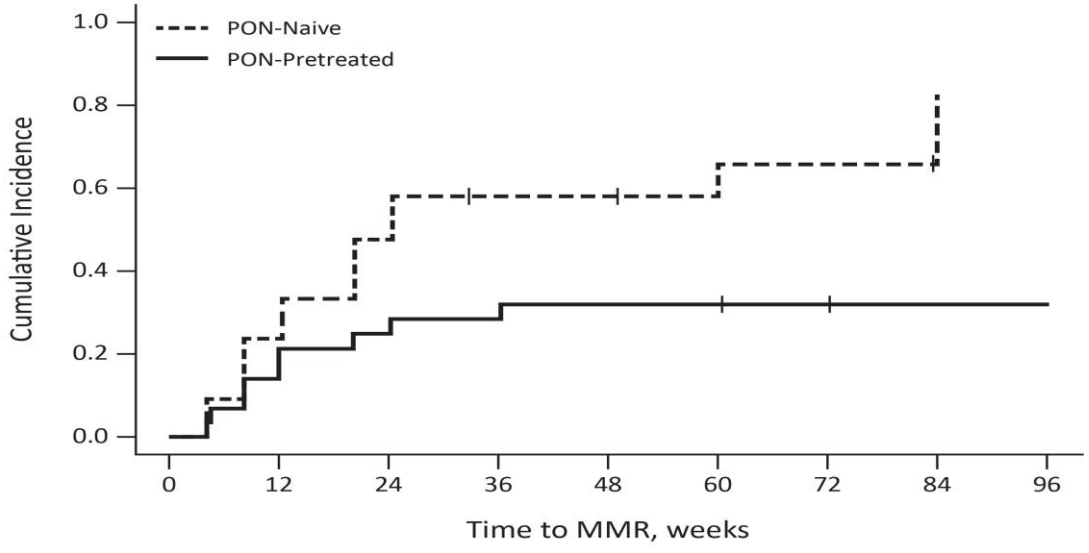
Table 2. Cumulative MMR in Pts with Confirmed T315I and not in MMR at Screening Treated with Asciminib 200 mg BID Monotherapy

n (%)	PON Naive (n = 21)	PON Pretreated (n = 28)[a]
Overall MMR	14 (66.7)	9 (32.1)
MMR by 24 wk	12 (57.1)	8 (28.6)
MMR by 48 wk	12 (57.1)	9 (32.1)
MMR by 72 wk	13 (61.9)	9 (32.1)
MMR by 96 wk	14 (66.7)	9 (32.1)

BID, twice daily; MMR, major molecular response; PON, ponatinib.

[a] Among 28 PON-pretreated pts evaluable for efficacy analyses, 14, 11, and 3 pts, respectively, had discontinued PON due to intolerance, resistance, and other reasons.

Figure. Cumulative MMR in PON-Naive and PON-Pretreated Pts.



Number at Risk									
PON-Naive	21	15	9	5	5	3	2	1	0
PON-Pretreated	28	23	16	12	9	8	6	5	5

MMR, major molecular response; PON, ponatinib.

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