Poster PS1593

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ASC4OPT Study: High Efficacy and Favorable Tolerability of Asciminib Once or Twice Daily in CML Patients with Suboptimal Response, Resistance or Intolerance of 2 or More Tyrosine Kinase Inhibitors

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KEY FINDINGS & CONCLUSIONS

- Asciminib at both 40 mg BID and 80 mg QD doses is highly efficacious and shows favorable safety and tolerability profiles in patients with CML-CP previously treated with ≥2 TKIs
- The safety profile of asciminib at 80 mg QD was similar to that of 40 mg BID, with no new or unexpected safety signals observed. Treatment discontinuation due to AEs was infrequent
- Patients in the exploratory cohort, who had discontinued previous TKIs due to intolerance, were able to maintain or deepen responses on asciminib regardless of dosing schedule
- The more convenient 80 mg QD regimen may enhance treatment adherence and ultimately improve patient outcomes
- These findings strengthen those of the ASCEMBL study,[6,7] supporting asciminib as a standard of care for patients with CML-CP pretreated with ≥2 TKIs.

Scan to obtain:
- Supplementary slides

https://tinyurl.com/HochhausPS1593

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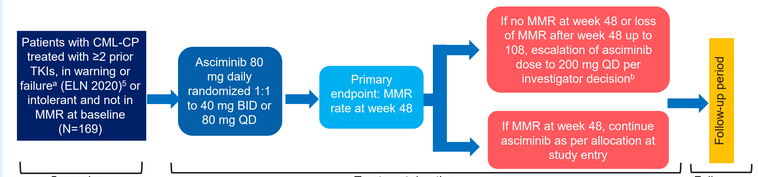
INTRODUCTION

- Asciminib is approved worldwide for adult patients with CML-CP previously treated with ≥2 TKIs at a total dose of 80 mg daily[1-3]
- Clinical and PK studies have shown that BID and QD asciminib regimens had similar and substantial efficacy in patients with CML-CP without the T315I mutation[4]
- Asciminib is given under fasting conditions: therefore, a QD schedule may improve quality of life and increase treatment adherence, potentially resulting in better outcomes[4]
- The ASC4OPT study (NCT04948333) aims to optimize asciminib usage in 3L+ CML-CP by investigating a BID and a QD dosing schedule, re-evaluating efficacy in an expanded population (compared to previous 3L+ studies), and exploring outcomes for patients already in MMR at study entry

METHODS

- ASC4OPT is an international, multi-center, non-comparative phase 3b study in adults with CML-CP not harboring the T315I mutation and previously treated with ≥2 TKIs (i.e., imatinib, nilotinib, dasatinib, bosutinib, radotinib, or ponatinib) (**Figure 1**)
- Eligible patients were in treatment failure or warning categories according to ELN 2020 criteria,[5] or intolerant to their most recent TKI and not in MMR at baseline (main cohort). An exploratory cohort of patients intolerant to their most recent TKI and in MMR at baseline was also enrolled and analyzed separately
- Patients were randomized 1:1 to receive asciminib 40 mg BID or 80 mg QD under fasting conditions
- The primary endpoint was MMR rate at week 48 in patients not in MMR at baseline (main cohort); MMR rates for patients already in MMR at baseline (exploratory cohort) were analyzed separately
- As the study was not powered to assess differences between arms, the Propensity Scores Weighting method was used to compare the difference in MMR rate between the different dosing regimens in ASC4OPT

Figure 1. ASC4OPT study design



An exploratory group of patients intolerant to their most recent TKI and in MMR at baseline was also enrolled (N=30); these patients were not included in the primary endpoint analysis

[a]Based on ELN 2020 recommendations. [b]In addition, there must not be any grade 3 or 4 toxicity while on therapy, or persistent grade 2 toxicity, possibly related to asciminib and unresponsive to optimal management.

RESULTS

Patients

- At data cutoff (12 March 2024; median follow-up, 17.5 months), 136/169 patients (80.5%) in the main cohort remained on treatment (**Figure 2**)
- Among patients already in MMR at baseline (40 mg BID, n=14; 80 mg QD, n=16), 3/30 patients had discontinued treatment (AEs, n=2; patient decision, n=1), all in the 80 mg QD arm
- Patient demographics and baseline characteristics for both cohorts are presented in **Table 1**

Efficacy

- For patients in the main cohort, MMR rates are shown in **Table 2** and cumulative incidence of MMR in **Figure 3**. Four patients in this cohort had the T315I mutation detected after enrollment and were excluded from efficacy analyses
  - A propensity score weighting analysis found no significant differences in MMR rates between the two dosing schedules among patients in the main cohort (p=0.763)
- In the exploratory cohort, most patients maintained MMR at 48 weeks (**Table 2**). Two patients in this cohort (both in the 80 mg QD arm) discontinued asciminib before week 48 due to AEs and were considered non-responders
  - Among these patients, 3/14 (21.4%) patients on 40 mg BID were in MR[4] at baseline and 7/14 (50.0%) at week 48; the corresponding numbers for patients on 80 mg QD were 5/16 (31.3%) and 8/16 (50.0%), respectively

PROs

- MDASI-CML Symptom and Interference Total scores decreased quickly for patients in the main cohort at Weeks 4 to 12, denoting improvement in patients' symptoms and reduced interference with their daily life activities; scores then stabilized before decreasing again towards week 96 of the study
- Similar results were observed for patients in the exploratory cohort, although the reduction in scores appeared larger

Safety

- An overview of AEs reported in the main and exploratory cohorts is shown in **Table 3**
  - In the main cohort, the most frequent any-grade AEs were thrombocytopenia (15.5%), arthralgia (13.7%), COVID-19 (11.9%), and pruritus (10.1%)
  - In the exploratory cohort, the most common any-grade AEs were pruritus (26.7%), arthralgia (23.3%), myalgia, COVID-19, and headache (20.0% each)
- One on-treatment death was reported (main cohort patient on 80 mg QD, due to cerebrovascular accident), which was not suspected by investigators to be related to study drug

Figure 2. Patient disposition

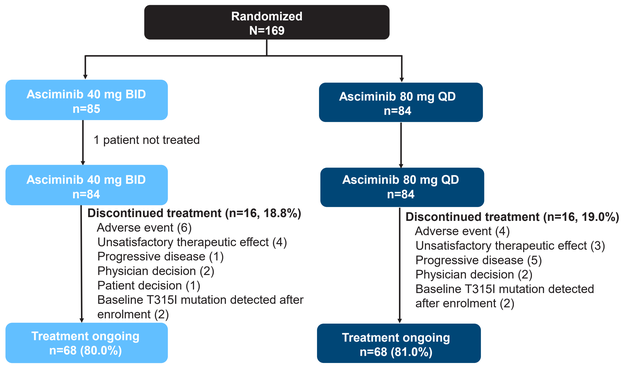
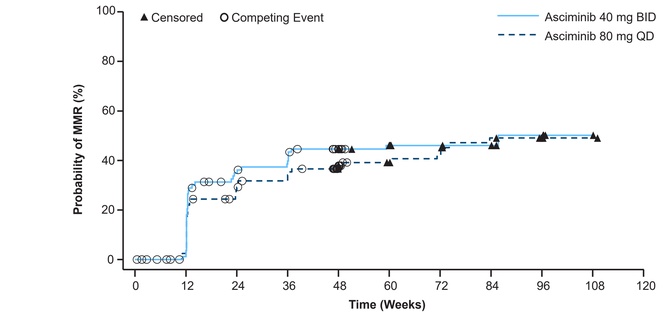


Table 1. Patient demographics and disease characteristics

	Main cohort			Exploratory cohort		
	Asciminib 40 mg BID n=85	Asciminib 80 mg QD n=84	All patients N=169	Asciminib 40 mg BID n=14	Asciminib 80 mg QD n=16	All patients N=30
Median age, years (range)	54.0 (24–86)	56.0 (18–84)	55.0 (18–86)	56.5 (37–81)	63.0 (32–77)	59.0 (32–81)
Male, n (%)	48 (56.5)	57 (67.9)	105 (62.1)	8 (57.1)	10 (62.5)	18 (60.0)
Median time since initial diagnosis of CML, years (range)	3.8 (0.2–29.6)	3.7 (0.6–28.1)	3.7 (0.2–29.6)	4.4 (1.7–21.2)	5.2 (1.3–18.0)	4.5 (1.3–21.2)
Number of lines of prior TKI therapy, n (%)						
2	45 (52.9)	39 (46.4)	84 (49.7)	6 (42.9)	8 (50.0)	14 (46.7)
3	23 (27.1)	27 (32.1)	50 (29.6)	3 (21.4)	3 (18.8)	6 (20.0)
4	9 (10.6)	17 (20.2)	26 (15.4)	3 (21.4)	3 (18.8)	6 (20.0)
≥5	7 (8.2)	1 (1.2)	8 (4.7)	2 (14.3)	2 (12.5)	4 (13.3)
Cytogenetic response, n (%)						
CCyR	27 (31.8)	29 (34.5)	56 (33.1)			
PCyR	18 (21.2)	9 (10.7)	27 (16.0)			
***BCR::ABL1*[IS] >10%, n (%)**	36 (42.4)	31 (36.9)	67 (39.6)			

Figure 3. Cumulative incidence of MMR



Number of patients still at risk

Asciminib 40 mg BID	83	75	45	40	31	13	10	9	4	1	0
Asciminib 80 mg QD	82	77	53	47	33	14	11	5	2	1	0

Cumulative number of competing events

Asciminib 40 mg BID	0	5	9	10	15	27	27	27	27	27	27
Asciminib 80 mg QD	0	2	5	7	18	33	33	33	33	33	33

Table 2. MMR rates over time

Main Cohort: Patients not in MMR at baseline						
	Asciminib 40 mg BID N=83		Asciminib 80 mg QD N=82		All patients N=165	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Week 48	36 (43.4)	(32.53, 54.71)	29 (35.4)	(25.12, 46.70)	65 (39.4)	(31.89, 47.29)

Exploratory Cohort: Patients in MMR at baseline						
	Asciminib 40 mg BID N=14		Asciminib 80 mg QD N=16		All patients N=30	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Week 48[a]	14 (100)	(76.84, 100.0)	14 (87.5)	(61.65, 98.45)	28 (93.3)	(77.93, 99.18)

Pearson-Clopper 95% 2-sided CI for response rate. [a] Before week 12, two patients in the 80 mg QD arm discontinued from the study due to AEs and were considered as non-responders. Patients without RT-qPCR assessment at a time point are considered as non-responders at that time point.

Table 3. Overview of AEs

Main Cohort: Patients not in MMR at baseline						
n (%)	Asciminib 40 mg BID N=84		Asciminib 80 mg QD N=84		All patients N=164	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Adverse events	76 (90.5)	21 (25.0)	74 (88.1)	29 (34.5)	150 (89.3)	50 (29.8)
Treatment-related	46 (54.8)	13 (15.5)	53 (63.1)	16 (19.0)	99 (58.9)	29 (17.3)
AEs leading to discontinuation	6 (7.1)	3 (3.6)	4 (4.8)	3 (3.6)	10 (6.0)	6 (3.6)
Treatment-related	4 (4.8)	2 (2.4)	3 (3.6)	2 (2.4)	7 (4.2)	4 (2.4)
AEs leading to dose adjustment/interruption	25 (29.8)	17 (20.2)	26 (31.0)	21 (25.0)	51 (30.4)	38 (22.6)

Exploratory Cohort: Patients in MMR at baseline						
n (%)	Asciminib 40 mg BID N=14		Asciminib 80 mg QD N=16		All patients N=30	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Adverse events	13 (92.9)	6 (42.9)	16 (100)	6 (37.5)	29 (96.7)	12 (40.0)
Treatment-related	7 (50.0)	4 (28.6)	12 (75.0)	3 (18.8)	19 (63.3)	7 (23.3)
AEs leading to discontinuation	0	0	2 (12.5)	2 (12.5)	2 (6.7)	2 (6.7)
Treatment-related	0	0	2 (12.5)	2 (12.5)	2 (6.7)	2 (6.7)
AEs leading to dose adjustment/interruption	5 (35.7)	4 (28.6)	4 (25.0)	2 (12.5)	9 (30.0)	6 (20.0)

A patient with multiple severity grades for an AE is only counted under the maximum grade. AEs occurring during treatment or within 30 days of last study medication are summarized. MedDRA version 26.1, CTCAE version 5.0.

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Abbreviations

3L+, third line or later; AE, adverse event; BID, twice daily; CCyR, complete cytogenetic response; CML, chronic myeloid leukemia; COVID-19, coronavirus disease of 2019; CP, chronic phase; ELN, European LeukemiaNet; IS, international scale; MMR, major molecular response (*BCR::ABL1*[IS] ≤0.1%); PCyR, partial cytogenetic response; PK, pharmacokinetics; QD, once daily; RT-qPCR, real-time quantitative polymerase chain reaction; TKI, tyrosine kinase inhibitor.