Check for updates

ELSEVIER

Blood 142 (2023) 6389–6391

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

ASC2ESCALATE: A US Phase 2, Open-Label, Single-Arm, Dose-Escalation Study of Asciminib (ASC) Monotherapy in Patients (Pts) with Chronic Myeloid Leukemia in Chronic Phase (CML-CP) As Second-Line (2L) and First-Line (1L) Treatment

Ehab L. Atallah, MD[1], *Michael Mauro, MD*[2], *Koji Sasaki, MD*[3], *Moshe Levy*[4], *Paul B. Koller, MD*[5], *Daisy Yang, PharmD, BCOP*[6], *Dramane Laine, PhD*[6], *John Sabo*[6], *Ennan GU*[7], *Jorge Cortes, MD*[8]

[1] Division of Hematology/Oncology, Medical College of Wisconsin, Milwaukee, WI
[2] Memorial Sloan Kettering Cancer Center, New York, NY
[3] Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[4] Baylor Scott & White Health, Dallas, TX
[5] Hematology/HCT, City of Hope National Medical Center, Duarte, CA
[6] Novartis Pharmaceuticals Corporation, East Hanover, NJ
[7] Novartis Pharmaceuticals Corporation, Cambridge, MA
[8] Georgia Cancer Center, Augusta University, Augusta, GA

BACKGROUND AND SIGNIFICANCE Adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs) have increased survival in CML, although resistance and intolerance remain challenges, which often necessitate switch to another TKI. Many pts discontinue 1L treatment due to resistance/intolerance and switch to 2L therapy, to which resistance is typically higher. A need exists for effective, safe treatment options for pts in 1L and 2L. ASC is thefirst approved BCR::ABL1 inhibitor that Specifically Targets the ABL Myristoyl Pocket (STAMP), with activity against most *BCR::ABL1* kinase domain mutations conferring resistance to ATP-competitive TKIs, potentially providing a new early-line treatment option.
ASC was first approved in the United States for pts with CML-CP after ≥2 TKIs at 80 mg once daily (QD) or 40 mg twice daily (BID) and for pts with CML-CP with the T315I mutation at 200 mg BID. A large, phase 1, dose-escalation trial (NCT02081378) demonstrated efficacy and tolerability of ASC across a broad range of dosages. Also, with >2 years of follow-up, ASC demonstrated superior efficacy and better safety and tolerability compared with bosutinib in pts with CML-CP without the T315I mutation after ≥2 prior TKIs in the phase 3 ASCEMBL study (NCT03106779). We describe the phase 2 ASC2ESCALATE trial investigating efficacy and safety of ASC with dose escalation in pts with CML-CP receiving ASC as their 2L or 1L therapy.

STUDY DESIGN AND METHODS This is a phase 2, open-label, multicenter, single-arm, dose-escalation study with sites in the United States (NCT05384587) (Figure). Pts receiving ASC as their 2L TKI must be adults with non-T315I CML-CP who discontinued their first ATP-competitive TKI for warning response (*BCR::ABL1* ^{IS} >1%-10% after 6 months or >0.1%-1% after 12 months of 1L treatment), resistance (*BCR::ABL1* ^{IS} >10% after 6-12 months or >1% or loss of major molecular response [MMR] after >12 months of 1L treatment), or intolerance (with *BCR::ABL1* ^{IS} >0.1% at screening). In addition to pts receiving ASC as their 2L TKI, a separate cohort of newly diagnosed pts will be included, and these pts may receive up to 4 weeks of prior treatment with imatinib or an approved second-generation TKI (Table).
All pts will start treatment with ASC 80 mg QD. Pts achieving *BCR::ABL1* ^{IS} ≤1% at 6 months will continue at the same dose; pts not achieving *BCR::ABL1* ^{IS} ≤1% at 6 months will have their dose escalated to 200 mg QD. In pts not achieving MMR at 12 months, dose escalation from 80 to 200 mg QD or from 200 mg QD to 200 mg BID will occur or the pt will be taken off the study. If pts have grade ≥3 or persistent grade 2 toxicity refractory to optimal management, no dose escalation will occur, and pts will remain on ASC at their most current dose. This dose-escalation strategy applies to both the 2L and 1L cohorts.
The primary endpoint is MMR rate at 12 months in pts using ASC as their 2L TKI. As all primary and secondary endpoints for the 2L cohort will be measured for the 1L cohort as secondary endpoints, the MMR rate at 12 months in pts receiving ASC as their 1L TKI is a secondary endpoint. Additional secondary endpoints are the same for both 2L and 1L cohorts and include MMR rates at 3, 6, 18, and 24 months; MMR rates by all scheduled time points; MR ^{2} (*BCR::ABL1* ^{IS} ≤1%), MR ^{4} (*BCR::ABL1* ^{IS} ≤0.01%), and MR $^{4.5}$ (*BCR::ABL1* ^{IS} ≤0.0032%) at and by scheduled time points; time to and duration of MMR; time to

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/6389/2204955/blood-2986-main.pdf by guest on 18 May 2024

© 2023 by The American Society of Hematology

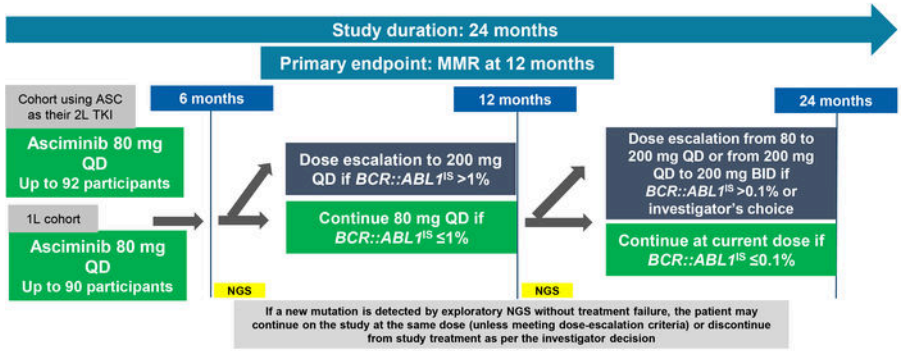
treatment failure; progression-free survival; overall survival; and safety/tolerability. Exploratory endpoints include assessment of *BCR::ABL1* mutations.

CONCLUSIONS ASC2ESCALATE is the first clinical trial designed to assess pts with CML-CP using ASC as their 2L TKI and will provide critical information on efficacy and safety of dose escalation in pts for whom certain response milestones are not met in 2L and 1L. Dose escalation of ASC in 2L and 1L is another treatment strategy and results from ASC2ESCALATE will add to the growing body of evidence for using ASC to treat pts with CML-CP. Recruitment for pts using ASC as their 2L TKI began November 2022, and as of July 10, 2023, 5 pts have been enrolled in this cohort; Up to 92 and 90 pts are estimated to enroll in the 2L and 1L cohorts, respectively, across 90 sites.

Disclosures Atallah: *Abbvie:* Consultancy, Research Funding, Speakers Bureau; *Takeda:* Consultancy, Research Funding; *BMS:* Consultancy, Speakers Bureau; *Novartis:* Consultancy, Research Funding. **Mauro:** *Bristol Myers Squibb:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding; *Takeda:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding; *Novartis:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding; *Pfizer:* Consultancy, Honoraria, Other: Travel, accommodation, and expenses, Research Funding; *Sun Pharma/SPARC:* Research Funding. **Levy:** *Jazz:* Consultancy, Honoraria, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Speakers Bureau; *Genmab:* Consultancy, Honoraria, Speakers Bureau; *Gilead:* Consultancy, Honoraria, Speakers Bureau; *Karyopharm:* Consultancy, Honoraria, Speakers Bureau; *Morphosys:* Consultancy, Honoraria, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Seagen:* Consultancy, Honoraria, Speakers Bureau; *Sanofi:* Consultancy, Honoraria, Speakers Bureau; *Sobi:* Consultancy, Honoraria, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Speakers Bureau; *Sellas:* Membership on an entity's Board of Directors or advisory committees; *Bristol Meyer Squibb:* Consultancy, Honoraria, Speakers Bureau; *Beigene:* Consultancy, Honoraria, Speakers Bureau; *AZ:* Consultancy, Honoraria, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Speakers Bureau; *Amgen:* Consultancy, Honoraria, Speakers Bureau. **Koller:** *treadwell therapuetics:* Consultancy, Other: safety review committee; *NOVARTIS:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *takeda:* Consultancy, Speakers Bureau. **Yang:** *Novartis:* Current Employment. **Laine:** *Novartis Pharmaceuticals Corporation:* Current Employment. **Sabo:** *Novartis:* Current Employment. **GU:** *Novartis:* Current Employment. **Cortes:** *Biopath Holdings:* Consultancy, Current holder of *stock options* in a privately-held company, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Gilead:* Consultancy; *Pfizer:* Consultancy, Research Funding; *Abbvie:* Consultancy, Research Funding; *Takeda:* Consultancy, Honoraria; *Forma Therapuetic:* Consultancy; *Novartis:* Consultancy, Research Funding.

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/6389/2204955/blood-2986-main.pdf by guest on 18 May 2024

Figure. ASC2ESCALATE Study Design



1L, first line; 2L, second line; ASC, asciminib; BID, twice daily; QD, once daily; MMR, major molecular response; NGS, next-generation sequencing; TKI, tyrosine kinase inhibitor.

Table. Key Eligibility Criteria for the Phase 2 ASC2ESCALATE Study of ASC Monotherapy in Pts with CML-CP as 2L and 1L Treatment

Common to both 2L and 1L cohorts	Specific to the 2L cohort	Specific to the 1L cohort
Key inclusion criteria		
• Diagnosis of CML-CP • Age ≥18 years • ECOG performance status of 0-2 • Adequate end-organ function within 14 days before the first dose of ASC	• Warning response to 1L TKI, defined as: ◦ *BCR::ABL1*^{IS} >1%-10% at 6 months after treatment initiation ◦ *BCR::ABL1*^{IS} >0.1%-1% at 12 months after treatment initiation • Failure of 1L TKI, defined as: ◦ *BCR::ABL1*^{IS} >10% if 1L treatment duration was between 6 and 12 months ◦ *BCR::ABL1*^{IS} >1% if 1L treatment duration was >12 months ◦ Loss of MMR >12 months after treatment initiation • Intolerance of 1L TKI, defined as: ◦ *BCR::ABL1*^{IS} >0.1% at screening	• No prior therapy or a maximum of 4 weeks of prior therapy with imatinib or an approved 2G TKI (nilotinib, dasatinib, or bosutinib)
Key exclusion criteria		
• Previous treatment with ASC • Known T315I mutation • Known second chronic phase of CML after progression to AP/BC • Previous hematopoietic stem cell transplant or planned allogeneic hematopoietic stem cell transplant • Cardiac or cardiac repolarization abnormality or history of acute pancreatitis within 1 year of study entry or past medical history of chronic pancreatitis • Pregnant or lactating women, women of childbearing potential not on highly effective contraception, or sexually active men unwilling to use barrier contraception while taking study treatment and for 7 days after stopping study	• Previous treatment with ≥2 ATP-competitive TKIs	• Previous treatment of >4 weeks with 1 ATP-competitive TKI

1L, first line; 2G, second generation; 2L, second line; AP, accelerated phase; ASC, asciminib; ATP, adenosine triphosphate; BC, blast crisis; CML-CP, chronic myeloid leukemia in chronic phase; ECOG, Eastern Cooperative Oncology Group; pt, patient; TKI, tyrosine kinase inhibitor.

Figure 1

https://doi.org/10.1182/blood-2023-186974

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/6389/2204955/blood-2986-main.pdf by guest on 18 May 2024