AZURE: A Phase 1/2 Study of BLU-263 as Monotherapy and in Combination With Azacitidine in Patients With Advanced Systemic Mastocytosis

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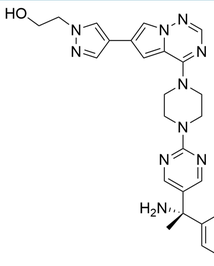
Background

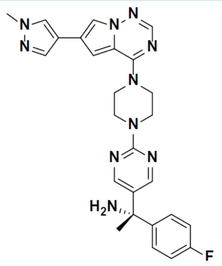
- Systemic mastocytosis (SM) is a rare clonal hematologic neoplasm, driven by the *KIT* D816V mutation in approximately 95% of patients and characterized by proliferation and accumulation of mast cells causing debilitating symptoms and end-organ damage[1,2]
- Advanced SM (AdvSM) consists of aggressive SM (ASM), mast cell leukemia (MCL), and SM with an associated hematologic neoplasm (SM-AHN)[3,4]
- Avapritinib, an oral, highly potent and selective inhibitor of KIT D816V, is approved in the USA and in Europe (after ≥1 systemic therapy) for treatment of adult patients with AdvSM with platelet counts of ≥50×10^9/L, and midostaurin is also approved in this indication[5–8]
- SM-AHN, the main AdvSM subtype seen in about 75% of cases, has a high degree of genetic heterogeneity and some patients with high-risk and very high-risk AHNs require additional AHN-specific therapeutic agents, such as hypomethylating agents (HMAs)[1,9]
- Patients with SM with high-risk and very high-risk AHNs have not been studied for treatment with midostaurin or avapritinib alone due to the aggressive course of their disease.[10,11] Many of these patients may benefit from combination therapy of a selective KIT D816V inhibitor with an HMA. Low central nervous system (CNS) penetration may allow safer dosing, especially in combination with HMAs with a reduced risk of CNS adverse events

Chemical structure

BLU-263



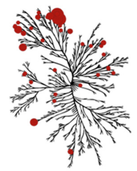
Avapritinib[12]



- BLU-263 is an investigational, novel, orally administered tyrosine kinase inhibitor (TKI) with high potency and selectivity towards the *KIT* D816V mutation and high *in vitro* potency in both the biochemical (dissociation constant, Kd=0.24 nM) and cellular (half-maximal inhibitory concentration, IC_{50}=4.3 nM) settings
- BLU-263 has a high degree of selectivity for KIT D816V with minimal CNS penetration, as demonstrated in preclinical studies and two phase 1 studies in healthy volunteers[13]
- Overall, the results from the preclinical as well as clinical studies in volunteers indicate a benefit/risk profile that allows the clinical evaluation of BLU-263 alone and in combination with azacitidine in patients with AdvSM, including high- and very high-risk SM-AHN

BLU-263 – A next-generation KIT inhibitor

Equivalent potency	
Compound	**KIT D816V IC_{50} (nM)**
BLU-263	0.20
Avapritinib	0.22
Imatinib	>10,000



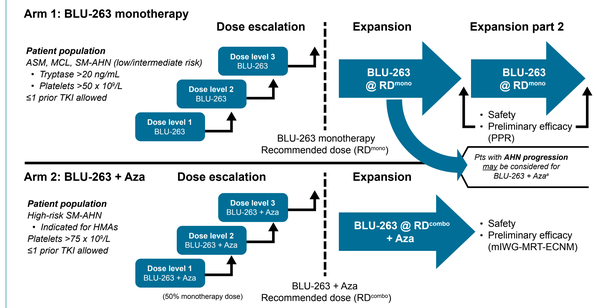
BLU-263 kinome[a]

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)(CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content.

Study objectives and design

- AZURE (NCT05609942) is an international, phase 1/2, open-label, 2-arm study designed to evaluate the safety and efficacy of BLU-263 as monotherapy and in combination with azacitidine in patients with AdvSM, including those with high-risk and very high-risk SM-AHN in whom HMAs, including azacitidine, are the standard of care
- The study has 2 arms: Arm 1 will evaluate BLU-263 monotherapy in all patients with AdvSM, while Arm 2 will evaluate BLU-263 in combination with azacitidine in a selected population of high- and very high-risk SM-AHN patients

Study design

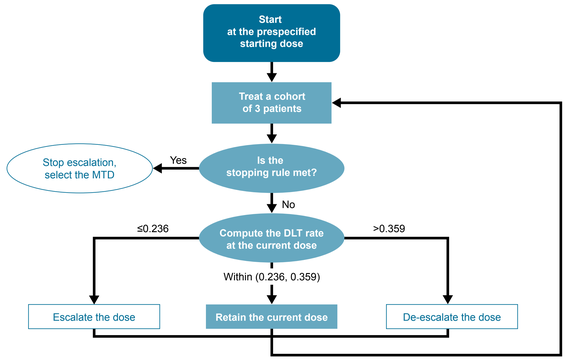


[a]The decision on the need for combination therapy will be adjudicated by the Safety Review Committee.
AHN, associated hematologic neoplasm; ASM, aggressive systemic mastocytosis; Aza, azacitidine; HMA, hypomethylating agent; MCL, mast cell leukemia; mIWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment-European Competence Network on Mastocytosis; PPR, pure pathological response; Pts, patients; RD^{mono}, recommended monotherapy dose; RD^{combo}, recommended combination dose; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; TKI, tyrosine kinase inhibitor.

- Each study arm will involve a dose escalation and expansion phase
  - Dose escalation will involve a cohort-based administration of incremental doses of BLU-263 to identify the recommended dose (RD) of BLU-263 monotherapy (RD^{mono}) in Arm 1, and the RD of BLU-263 + azacitidine (RD^{combo}) in Arm 2[a]
  - Dose expansion will further characterize the safety and preliminary efficacy of BLU-263 RD^{mono} and RD^{combo} in patients with AdvSM
- After determining RD^{mono} in Arm 1 dose escalation and RD^{combo} in Arm 2 dose escalation, patients may be enrolled in the respective dose expansion phases
- Once safety has been established in the BLU-263 monotherapy dose escalation, BLU-263 + azacidine combination dose escalation will be initiated
  - Patients will receive azacitidine 75 mg/m^2/day on days 1–7 (or days 1–5, and days 8 and 9 [5+2+2 schedule]) of each 28-day cycle
- Patients with SM-AHN receiving BLU-263 monotherapy who experience AHN progression may be considered to receive azacitidine, in addition to BLU-263 at the RD^{combo}
- Dose escalation of monotherapy and combination therapy in both arms will follow the rules of Bayesian optimal interval design (BOIN)
  - Using a cohort size of approximately 3 patients, the study will aim for a dose-limiting toxicity rate of ≤30% until a safe and efficacious dose of BLU-263 is reached
  - The Arm 2 starting dose will not exceed 50% of the highest BLU-263 monotherapy dose determined to be safe in Arm 1

[a]Only one-third of patients in each dose escalation cohort may have received prior selective KIT inhibitors

BOIN dose escalation design



DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

Key eligibility criteria

Exclusion criteria

- Age ≥18 years
- Eastern Cooperative Oncology Group performance status 0–3
- Patients must have a BM biopsy taken within 35 days prior to C1D1
- Patients receiving antineoplastic therapy 12 weeks prior to initiation of the study drug must have discontinued therapy due to disease progression, refractory disease, lack of efficacy, or intolerance
- For Arm 1 (monotherapy), patients must have a centrally confirmed pathologic diagnosis of AdvSM (ASM, SM-AHN[a], MCL[b])[c] via BM assessment and per WHO criteria
- For Arm 2 (combination therapy), patients must have 1 of the following centrally confirmed pathologic diagnoses of SM-AHN via BM assessment and per WHO criteria:
  - CMML-2
  - High- or very high-risk MDS per IPSS-R scoring
  - MDS/accelerated phase myeloproliferative neoplasm[d]
  - MDS with excessive blasts-2[e]
  - Complex karyotype/mutational profile
  - A hematologic neoplasm which is felt to have high-risk disease and has a strong rationale for combination treatment following consultation with the sponsor

Exclusion criteria

- A diagnosis of philadelphia chromosome positive malignancy
- A diagnosis of AML
- Received antineoplastic therapy or an investigational agent within 14 days prior to enrollment
- Received the following therapy within 14 days of screening BM biopsy:
  - Radiotherapy[f]
  - Any hematopoietic growth factor (except erythropoietin), or requiring growth factors to maintain adequate neutrophil or platelet levels[g]
- Received >1 prior selective KIT inhibitor[h]
- Having the following lab abnormalities within 14 days prior to initiation of study drug:
  - Alanine aminotransferase and aspartate aminotransferase >3 × ULN[i]
  - Total bilirubin >1.5 × ULN[i]
  - Serum creatinine clearance <40 mL/min
  - Absolute neutrophil count <0.5 × 10^9/L
- Received prior HMA therapy for the current diagnosis
- Platelet count <50 × 10^9/L for monotherapy or <75 × 10^9/L for combination therapy within 4 weeks prior to the first dose of study drug; or receiving platelet transfusions or thrombopoietin receptor agonists within the prior 14 days
- In the monotherapy arm, a myeloid AHN with ≥10% blasts in BM or PB

[a]SM-AHN deemed not to be a candidate for HMA monotherapy by the investigator; incidental indolent, low-grade lymphoid AHNs (e.g., chronic lymphocytic leukemia) not requiring treatment are eligible. [b]MCL, including those with an AHN component diagnosis, which do not require a C-finding. [c]Other relapsed or refractory, potentially BLU-263-responsive hematologic neoplasms (e.g., those with evidence of aberrant KIT) may be considered for enrollment upon discussion with the sponsor. [d]Defined by blast count >10% in BM OR peripheral blood but not meeting diagnostic criteria of AML. [e]10–19% in BM or 5–19% in peripheral blood. [f]Prior radiotherapy to palliate specific sites of disease may be allowed with the sponsor's approval. [g]Patients on chronic erythropoietin doses, with stable hemoglobin, and whose dose of erythropoietin has not been changed in the prior 28 days are eligible. [h]Refers to prior use of avapritinib or bezuclastinib, but not midostaurin. [i]>5 × ULN if associated with clinically suspected liver infiltration by mastocytosis or another disease for which a patient was enrolled. [j]>3 × ULN if associated with liver infiltration by the disease being treated or in the presence of Gilbert's Disease, in which case a direct bilirubin >2 × ULN would result in exclusion.
AdvSM, advanced systemic mastocytosis; AHN, associated hematologic neoplasm; AML, acute myeloid leukemia; ASM, aggressive systemic mastocytosis; BM, bone marrow; C, cycle; CMML-2, chronic myelomonocytic leukemia-2; D, day; HMA, hypomethylating agent; IPSS-R, International Prognostic Scoring System for Myelodysplastic Syndromes-Revised; MCL, mast cell leukemia; MDS, myelodysplastic syndrome; PB, peripheral blood; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; ULN, upper limit of normal; WHO, World Health Organization.

Key study endpoints

Monotherapy Arm 1: BLU-263

Primary endpoints	Secondary endpoints
• **Dose escalation** – RD^{mono} • **Dose escalation & expansion** – Safety and tolerability – Preliminary efficacy at RD via PPR	• **Dose escalation & expansion** – ORR for AdvSM, per modified IWG-MRT-ECNM – PK – Time-to-response, OS, DOR, PFS – Proportion of patients pursuing stem cell transplant

Exploratory endpoints

- **Dose escalation & expansion**
  - Changes in *KIT* D816V MAF and other pathway genes in PB and BM
- **Dose expansion**
  - Changes in PROs based on the AdvSM-SAF, PGIS, and EORTC QLQ-C30 tools

AdvSM, advanced systemic mastocytosis; AdvSM-SAF, AdvSM Symptom Assessment Form; BM, bone marrow; DOR, duration of response; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Core QoL Questionnaire; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MAF, mutant allele fraction; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PGIS, Patient's Global Impression of Symptom Severity; PK, pharmacokinetic; PPR, pure pathological response; PRO, patient reported outcome; RD^{mono}, recommended monotherapy dose.

Combination Arm 2: BLU-263 + azacitidine

Primary endpoints	Secondary endpoints
• **Dose escalation** – RD^{combo} • **Dose escalation & expansion** – Safety and tolerability	• **Dose escalation & expansion** – ORR for AdvSM, per modified IWG-MRT-ECNM – PPR – PK

Exploratory endpoints

- **Dose escalation & expansion**
  - Changes in *KIT* D816V MAF and other pathway genes in PB and BM
  - Time-to-response, OS, DOR, PFS
  - Proportion of patients transferring to stem cell transplant
- **Dose expansion**
  - Changes in PROs based on the AdvSM-SAF, PGIS, and EORTC QLQ-C30 tools

AdvSM, advanced systemic mastocytosis; AdvSM-SAF, AdvSM Symptom Assessment Form; BM, bone marrow; DOR, duration of response; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Core QoL Questionnaire; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; MAF, mutant allele fraction; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PFS, progression-free survival; PGIS, Patient's Global Impression of Symptom Severity; PK, pharmacokinetic; PPR, pure pathological response; PRO, patient reported outcome; RD^{combo}, recommended combination therapy dose.

Summary

- AZURE, a phase 1/2 study, will evaluate the safety and efficacy of BLU-263 given orally as monotherapy in patients with AdvSM, as well as in combination with azacitidine in a selected population of patients with SM-AHN
- BLU-263 is also being studied in HARBOR, a phase 2/3 study comparing the efficacy and safety of BLU-263 + best supportive care (BSC) with placebo + BSC in patients with indolent SM whose symptoms are not adequately controlled by BSC
- To learn more about our clinical trials in the USA, visit blueprintclinicaltrials.com or contact us in the USA at medinfo@blueprintmedicines.com or 1-888-BLU-PRNT (1-888-258-7768), and in Europe at medinfoeurope@blueprintmedicines.com or +31 85 064 400118015445
- For more information visit:

https://clinicaltrials.gov/ct2/show/NCT05609942

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