A Phase I/II Study to Investigate the Safety and Clinical Activity of the Protein Arginine Methytransferase 5 Inhibitor GSK3326595 in Subjects with Myelodysplastic Syndrome and Acute Myeloid Leukemia

Background

Myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), and acute myeloid leukemia (AML) are closely related neoplastic diseases of hematopoietic myeloid progenitors. Despite current therapies, overall long-term survival is poor.1

Protein arginine methytransferase 5 (PRMT5) is a phase I enzyme responsible for symmetric arginine dimethylation of multiple proteins that impact cell proliferation.2 Its substrates include proteins involved in mRNA splicing, signal transduction, gene transcription, and DNA repair.3

Myelodysplastic syndrome (MDS) is a neoplastic disease that is characterized by ineffective hematopoiesis. It is a progressive disease with a high risk of transformation to acute myeloid leukemia (AML).4 The pathogenesis of MDS and AML involves complex genetic and epigenetic alterations.5

Table 1. Study Objectives

<table>
<thead>
<tr>
<th>Objective</th>
<th>Primary Endpoint</th>
<th>Frequency and severity of AEs</th>
<th>Frequency of DLTs</th>
<th>CR/PR/SRD</th>
<th>ORR</th>
<th>Time to disease progression (months)</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>Safety evaluation and single-arm dose expansion to identify a tolerated dose and establish preliminary evidence of efficacy in patients with relapsed/refractory MDS, CMML, and hypoproliferative AML.</td>
<td>No DLTs identified</td>
<td>1-2 DLTs</td>
<td>CR/PR/SRD</td>
<td>ORR</td>
<td>Time to disease progression (months)</td>
<td>Median overall survival (months)</td>
</tr>
<tr>
<td>Part 2A</td>
<td>Phase II, head-to-head comparison to evaluate efficacy, safety, and health-related quality of life of GSK326595 monotherapy vs best available care (BAC) in patients with relapsed/refractory MDS, CMML, and hypoproliferative AML.</td>
<td>No DLTs identified</td>
<td>1-2 DLTs</td>
<td>CR/PR/SRD</td>
<td>ORR</td>
<td>Time to disease progression (months)</td>
<td>Median overall survival (months)</td>
</tr>
<tr>
<td>Part 2B</td>
<td>Single-arm investigation of GSK326595 plus 5-azacitidine to evaluate the efficacy and safety of GSK326595 plus 5-azacitidine in patients with relapsed/refractory AML.</td>
<td>No DLTs identified</td>
<td>1-2 DLTs</td>
<td>CR/PR/SRD</td>
<td>ORR</td>
<td>Time to disease progression (months)</td>
<td>Median overall survival (months)</td>
</tr>
</tbody>
</table>

Study Design

Phase I open-label, multi-part study of GSK326595 as monotherapy and in combination with other agents in patients with myeloid malignancies

Part 1: Dose confirmation and single-arm dose expansion in relapsed/refractory MDS, CMML, and hypoproliferative AML

- Dose confirmation (safety run-in cohort)
- Dosing will start at 400mg GSK326595 daily
- Neusschneider-continual reassessment method (N-CRM) and guide dose escalation/escalation decisions
- 28-day dose-limiting toxicity (DLT) window
- Dose confirmed if posterior probability of excessive or unacceptable toxicity is no more than 25%
- The excessive or unacceptable toxicity is defined as DLT rate exceeding 33%

Part 2: Further exploration of efficacy in myelodysplasia neoplasms

Part 2A: Head-to-head comparison of GSK326595 vs best available care (BAC) in patients with relapsed/refractory MDS, CMML, and hypoproliferative AML

- Participants randomized 2:1 to GSK326595 at the recommended dose identified in dose confirmation phase vs best available care (BAC)
- Participants randomized 2:1 to GSK326595 at the recommended dose from Part 1 vs best available care (BAC)

Part 2B: Single-arm dose escalation and expansion study to evaluate clinical activity and safety of GSK326595 monotherapy in patients with relapsed/refractory AML, whose tumors harbor mutations in components of the pre-mRNA splicing machinery (eg, U2AF1, or ZRSR2) and 5-azacitidine for patients with relapsed/refractory AML.

- Participants randomized 2:1 to GSK326595 at the recommended dose from Part 1 vs 5-azacitidine
- Participants randomized 2:1 to GSK326595 at the recommended dose from Part 2 vs 5-azacitidine

Additional Analyses

- Evaluation of safety of arginine dimethylated arginines (SDMA), the enzymatic product of PRMT5
- PD marker of PRMT5 inhibition in plasma and tissue
- Evaluation of the presentation on the safety of the dose of the study on MDS or AML
- Measurement of transcriptome to elucidate known and novel mechanisms of action and inform future developments

Disclosures

References


Table 2. Study Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Part 1</th>
<th>Part 2A</th>
<th>Part 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical efficacy</td>
<td>CR/PR/SRD</td>
<td>CR/PR/SRD</td>
<td>CR/PR/SRD</td>
</tr>
<tr>
<td>Safety</td>
<td>No DLTs identified</td>
<td>1-2 DLTs</td>
<td>No DLTs identified</td>
</tr>
<tr>
<td>Death</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 3. Key Eligibility Criteria – Overall Study

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Part 1</th>
<th>Part 2A</th>
<th>Part 2B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥18 years</td>
<td>≥18 years</td>
<td>≥18 years</td>
</tr>
<tr>
<td>MDS, CMML, or AML diagnosis (low or intermediate-risk by criteria)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior history of stem cell transplant</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>≤8</td>
<td>≤8</td>
<td>≤8</td>
</tr>
<tr>
<td>No prior therapy</td>
<td>≤6</td>
<td>≤6</td>
<td>≤6</td>
</tr>
<tr>
<td>No history of severe cardiac disease</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>No history of secondary malignancy</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of a second malignancy</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of acute coronary disease</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of uncontrolled hypertension</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of uncontrolled diabetes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>History of uncontrolled hyperlipidemia</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 4. Eligibility Criteria by Study Part

Part 1 and 2A

- MDS: intermediate/high-risk by criteria
- CMML: intermediate-2 or high-risk per CPS1 or CMML-risk criteria
- AML: measured blast percentage in the bone marrow ≥35% or peripheral white blood cell count ≥20,000 cells/μL
- No prior therapy
- Age: ≥18 years
- MDS, CMML, or AML diagnosis (low or intermediate-risk by criteria)
- No history of severe cardiac disease
- No history of secondary malignancy
- No history of acute coronary disease
- No history of uncontrolled hypertension
- No history of uncontrolled diabetes
- No history of uncontrolled hyperlipidemia

Part 2C

- MDS: high-risk high-risk by criteria
- CMML: intermediate-2 or high-risk per CPS1 or CMML-risk criteria
- AML: high-risk by criteria
- No prior therapy
- Age: ≥18 years
- MDS, CMML, or AML diagnosis (low or intermediate-risk by criteria)
- No history of severe cardiac disease
- No history of secondary malignancy
- No history of acute coronary disease
- No history of uncontrolled hypertension
- No history of uncontrolled diabetes
- No history of uncontrolled hyperlipidemia

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