BACKGROUND

Unmet clinical need

- Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are hematologic malignancies arising from immature myeloid progenitor cells in bone marrow
- AML and MDS are highly resistant to most standard therapies, frequently relapse, and have high disease-specific mortality
- Despite the development of several novel therapies, time-limited responses and treatment-related toxicities remain major challenges contributing to an unmet clinical need
- cGAS-STING-TBK1 pathway
- Stimulator of interferon genes (STING) is the key adaptor molecule in the cyclic guanosine monophosphate (cGAMP)/adenosine monophosphate (AMP) synthase (cGAS)/STING/TANK binding kinase 1 (TBK1) pathway, which mediates the sensing of cytosolic DNA derived from viruses, bacteria, or tumor cells
- Activation of STING induces the recruitment of TBK1, driving the transcriptional induction of type I interferon (IFN-I) and proinflammatory cytokines

Preclinical evidence of STING agonist antitumor activity

- STING agonists have demonstrated direct cytotoxic activity against malignant human myeloid cells
- STING agonists stimulate the innate and adaptive immune response, resulting in enhanced T-cell activation and robust antitumor activity in preclinical tumor models
- STING is expressed at a higher level in AML cells than in other tumor types, which may lead to the observed enhanced T-cell-dependent STING activation

Development of the synthetic STING agonist GSK3745417

- GSK3745417 is a novel STING agonist being developed as an immune stimulatory agent for the treatment of cancer
- It has been studied previously in advanced solid tumors (NCT03436795)
- Based on preclinical evidence, GSK3745417 may have efficacy in patients with AML via a dual mechanism of action (Figure 1)

OBJECTIVE

- To evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity, and cytotoxicity of intravenously administered GSK3745417 in patients with relapsed/refractory (r/r) AML and high-risk MDS

METHODS

Study design

- NCT05424305 is a first-in-clinic, open-label, phase 1 trial composed of 2 parts (Figure 2)
- Part 1 is an intrapatient dose-escalation phase with cycles of 28 days
- A 3-cycle induction period (ie, escalating intravenous [IV] dose of GSK3745417 with each cycle) will be followed by a maintenance phase (ie, constant IV dose of GSK3745417)
- Part 2 is a dose-expansion phase using starting doses selected from part 1 based on safety outcomes
- Patients will undergo a 3-cycle induction period followed by maintenance doses until disease progression or intolerance
- Key inclusion and exclusion criteria are listed in Table 1

Part 1: Intrapatient dose-escalation phase

- Approximately 22 patients will be enrolled
- One cycle (28 days) consists of treatment with IV GSK3745417 followed by 2 weeks of observation
- Escalating doses of IV GSK3745417 for 3 cycles (induction) followed by IV GSK3745417 dose (maintenance)

Part 2: Dose-expansion phase

- Approximately 50 patients will be enrolled (25 patients with AML; 25 patients with high-risk MDS)
- Induction regimen at the dose determined by safety assessments in part 1
- Maintenance dosing schedule will be determined
- Patients will receive maintenance dose until disease progression or intolerance

Whole figure text as in figure 2...