561TiP: A Phase 1 dose-escalation study of ZN-d5, a BCL-2 inhibitor with improved selectivity, in subjects with advanced non-Hodgkin lymphoma (NHL) or acute myeloid leukemia (AML)

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Introduction

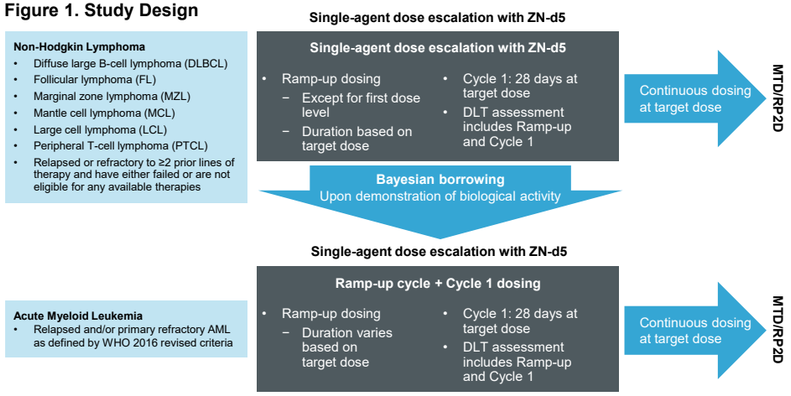
- Anti-apoptotic proteins such as B-cell lymphoma 2 (BCL-2) are commonly utilized by malignant cells to evade signals that would typically induce programmed cell death.[1,2]
- High BCL-2 expression correlates with poor prognosis and poor responses to conventional therapies in subjects with a broad range of malignancies,[3] and dependence on BCL-2 can render cancer cells susceptible to therapy targeting this pathway.[4]
- ZN-d5 is a novel, oral, once-daily BH3 mimetic with improved selectivity for BCL-2 over BCL-xL compared with the commercially available BCL-2 inhibitor venetoclax; this advantage of ZN-d5 could reduce the rate of thrombocytopenia.[5]
- ZN-d5 inhibits tumor cell growth *in vitro* and exhibits significant anti-tumor activity in multiple xenograft models of hematologic malignancies as a single agent and in combination with other anti-tumor drugs.

Methods

Study Design

- The study objectives are to determine the maximum tolerated dose and to establish the recommended phase 2 dose of ZN-d5 for NHL and AML.
- This open-label multicenter phase 1 dose-escalation study (NCT04500587, EudraCT 2020-002525-28) is evaluating the safety, tolerability, clinical activity, pharmacokinetics (PK), and pharmacodynamics (PD) of ZN-d5 in subjects with NHL or AML (**Figure 1**)
- Dose escalation is conducted per indication using a modified Bayesian continuous reassessment method (CRM) design.
- Initially, subjects with NHL will be enrolled; once a dose has been identified that demonstrates biological evidence of activity, subjects with AML will be enrolled. A total enrollment of 85 subjects is expected.

Figure 1. Study Design



- All subjects undergo a screening Period of up to 28 days, a ramp-up cycle (after dose level 1) up to the target dose (ramp-up duration up to 28 days in NHL or 4 days in AML) and treatment cycles of 28 days at the target dose until the patient meets one of the discontinuation criteria.
- Dose-limiting toxicities (DLTs) are assessed during the ramp-up cycle and Cycle 1.

Study sponsored by K-Group Alpha, Inc, a subsidiary of Zentalis Pharmaceuticals, Inc.

Methods (continued)

Inclusion Criteria

- Age ≥18 years
- White blood cell count <25 × 10^9/L (cytoreduction allowed)
- Eastern Cooperative Oncology Group Performance Status ≤1
- Adequate organ function (based on baseline liver enzymes, bilirubin, and creatinine)
- Not pregnant and agrees to use adequate contraception

Subjects with NHL

- Histologically or cytologically confirmed NHL, including diffuse large B-cell lymphoma, follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, large cell lymphoma, and peripheral T-cell lymphoma
- Received ≥2 prior lines of therapy and have either failed or are not eligible for any available therapies expected to provide clinical benefit
- Measurable disease (≥1 lesion accurately measurable in ≥2 dimensions; longest diameter >15 mm if nodal and >10 mm if extranodal)
- Adequate hematologic function (based on absolute neutrophil count, platelet count, and hemoglobin)

Subjects with AML

- Relapsed and/or primary refractory AML as defined by WHO 2016 revised criteria

Exclusion Criteria

Any of the following treatment interventions within the specified time frame prior to first dose:

- Major surgery ≤28 days
- Radiation therapy ≤14 days if >5% of marrow reserve
- Clinically significant, unresolved nonhematologic toxicity of prior chemotherapy
- Stem cell transplantation within 2 months and not receiving immunosuppression or having active graft-versus-host disease or fungal disease
- Use of an investigational agent that is not expected to be cleared by the time of first dosing of study drug or that has been demonstrated to have prolonged side effects

- Any serious medical condition including (but not limited to) CNS disease, significant cardiac impairment, QTcF >480 msec, gastrointestinal abnormalities, HIV, hepatitis B or C, and active or uncontrolled infection
- Prior therapy with venetoclax
- Administration of strong CYP3A4 inhibitors or strong or moderate CYP3A4 inducers

Subjects with AML

- Any prior systemic neoplastic agent within 14 days or ≥5 half-lives (excluding permitted cytoreductive therapies)

Treatment

- For subjects with NHL, the first ZN-d5 dose cohort will receive 100 mg; subsequent dose cohorts will be determined by the CRM model
- For subjects with AML, ZN-d5 dosing will be selected based on the dose that demonstrated biological activity in the participants with NHL
- Dosing in the NHL and AML cohorts will be escalated independently
- ZN-d5 is administered orally, once or twice daily, in continuous 28-day cycles

Endpoints

Table 1. Endpoints

Primary
• Observed DLTs in DLT-evaluable subjects • Incidence and severity of adverse events (AEs), graded according to NCI CTCAE v 5.0
Secondary
• For NHL, efficacy as defined by the Lugano response criteria for NHL: – Complete response (CR), partial response (PR), stable disease (SD), overall response rate (CR + PR + SD), duration of response • For AML, efficacy as defined by the European LeukemiaNet Response Criteria: – Complete remission (CR), CR with incomplete hematologic recovery, morphologic leukemia-free state, partial remission. • Plasma PK parameters for ZN-d5
Exploratory
• To characterize the PD effects of ZN-d5 • To evaluate the PK/PD relationship of ZN-d5

Characteristics of Subjects Enrolled

Characteristics of subjects enrolled as of 1 Aug 2021 are provided in **Table 2**.

Table 2. Subject Characteristics

Female/Male	**11/9**	**55%/45%**
Mean Age (range)	**68**	**(33-82)**
Diagnosis		
DLBCL	9	45%
MCL	3	15%
FL	3	15%
MZL	2	10%
AML	3	15%

Currently Active Sites

Australia: Liverpool Hospital, Royal Hobart Hospital, Ashford Cancer Center, Kinghorn Cancer Center. **Bulgaria:** National Hematology Hospital, Sveta Marina Multiprophy Hospital. **Croatia:** University Hospital CHC Zagreb. **Poland:** Medical University Gdansk. **S. Korea:** Pusan National University Hospital, Seoul National University Hospital. **Spain:** Hospital Vall d'Hebron, Hospital La Fe. **Ukraine:** Arensia Exploratory Medicine Clinic.

Conclusions

- The trial is ongoing.

References

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Disclosure

Dr Zaucha: Speaker and consultant for Roche, Abbvie, Takeda, Janssen, Novartis, and Bristol-Myers Squibb.