UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of report (Date of earliest event reported): June 5, 2023

ZENTALIS PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-39263**	**82-3607803**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

1359 Broadway, Suite 801
New York, New York 10018
(Address of principal executive offices) (Zip Code)

(212) 433-3791
(Registrant's telephone number, include area code)

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	ZNTL	The Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On June 5, 2023, Zentalis Pharmaceuticals, Inc. (the "Company") presented a poster titled "A Phase 1/2 Dose Escalation Study of the BCL-2 Inhibitor ZN-d5 and the WEE1 Inhibitor Azenosertib (ZN-c3) in Patients (Pts) With Acute Myeloid Leukemia (AML)" (the "ZN-d5 Poster") at the 2023 American Society of Clinical Oncology Annual Meeting ("ASCO"). A copy of the ZN-d5 Poster is furnished as Exhibit 99.1 to this Current Report on Form 8-K (this "Current Report") and incorporated herein by reference.

The information contained in Item 7.01 of this Current Report (including Exhibit 99.1 attached hereto) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, whether made before or after the date hereof, except as expressly provided by specific reference in such a filing.

Item 8.01 Other Events.

On June 5, 2023, the Company presented at ASCO a poster titled "Correlation of Cyclin E1 Expression and Clinical Outcomes in a Phase 1b Dose-Escalation Study of Azenosertib (ZN-c3), a WEE1 inhibitor, in Combination with Chemotherapy (CT) in Patients (pts) with Platinum-Resistant or Refractory (R/R) Epithelial Ovarian, Peritoneal, or Fallopian Tube Cancer (EOC)" (the "Azenosertib Poster"). A copy of the Azenosertib Poster is filed as Exhibit 99.2 to this Current Report and incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following Exhibit 99.1 relating to Item 7.01 shall be deemed to be furnished, and not filed:

Exhibit No.	Description
99.1	ZN-d5 Poster Presentation at the ASCO Annual Meeting on June 5, 2023
99.2	Azenosertib Poster Presentation at the ASCO Annual Meeting on June 5, 2023
104	Cover Page Interactive Data File (embedded within the inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ZENTALIS PHARMACEUTICALS, INC.

Date: June 5, 2023

By: /s/ Melissa Epperly
Melissa Epperly
Chief Financial Officer

Poster# TPS7077

A Phase 1/2 Dose Escalation Study of the BCL-2 Inhibitor ZN-d5 and the WEE1 Inhibitor Azenosertib (ZN-c3) in Patients (Pts) With Acute Myeloid Leukemia (AML)

Catherine Smith[1], Pankit Vachhani[2], Guillermo Garcia Manero[3], Nicole Grieselhuber[4], Guru Subramanian Guru Murthy[5], Astha Bhatia[6], Jatinder Arora[6], Hooman Izadi[7], Anthony Fiorino[7], Raajit Rampal[8]

[1]Division of Hematology/Oncology, Department of Medicine, Helen Diller family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA; [2]Division of Hematology and Oncology, Heersink School of Medicine, University of Alabama Birmingham, Birmingham, AL; [3]Department of Leukemia, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX; [4]The James Cancer Hospital and Solove Research Institute, The Ohio State University, Columbus, OH; [5]Cancer Center - Froedtert Hospital, Medical College of Wisconsin, Milwaukee, WI; [6]Zentalis Pharmaceuticals, New York, NY; [7]Formerly Zentalis Pharmaceuticals, New York, NY; [8]Memorial Sloan Kettering Cancer Center, New York, NY

BACKGROUND

- B-cell lymphoma 2 (BCL-2) is an anti-apoptotic protein and pathway inhibition combined with chemotherapy and/or targeted therapeutics has led to significant clinical benefit in pts with AML[1]
- Disruption of cell cycle regulation may complement BCL-2 inhibition as many malignant cells are dependent on proteins that regulate cell cycle progression[2]
- The cell cycle checkpoint protein, WEE1, is highly expressed in genomically unstable malignancies and inhibition of WEE1 induces tumor cell apoptosis[3,4]
- It has been previously reported that the combination of ZN-d5 (an oral, selective BCL-2 inhibitor) and azenosertib (an oral, highly potent WEE1 inhibitor) synergistically enhance killing of AML cells both *in vitro* and *in vivo*, as well as in TP53-mutated models[5]
- Based on this strong pre-clinical rationale, a Phase 1/2 study was designed to evaluate the novel combination of ZN-d5 and azenosertib in pts with relapsed/refractory (R/R) AML

METHODS

Azenosertib (ZN-c3): A Novel, Selective, and Orally Bioavailable WEE1 Inhibitor

- WEE1 is a protein kinase that inhibits the activity of both CDK1 and CDK2 kinases and is involved in the regulation of G1/S, G2/M, and M phase cell cycle checkpoints[4] (**Figure 1A**)
  - WEE1 plays an important role during normal cell cycle progression but also in response to DNA damage and interacts with DNA damage response pathways[4]
- WEE1 inhibition causes cancer cells to proceed into mitosis without being able to repair damaged DNA, resulting in premature mitotic entry and apoptosis[4] (**Figure 1B**)
  - WEE1 inhibition also increases replication stress by inducing aberrant firing of replication origins and depletion of nucleotide pools[3]

Figure 1: WEE1 Inhibition by Azenosertib Forces Cancer Cells to Proceed Into Mitosis, Resulting in Apoptosis

Figure 1A: WEE1 Activity in Cell Cycle Progression

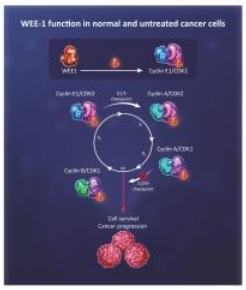
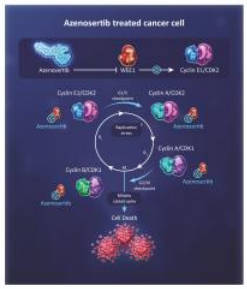


Figure 1B: WEE1 Inhibition by Azenosertib Resulting in Cancer Cell Death

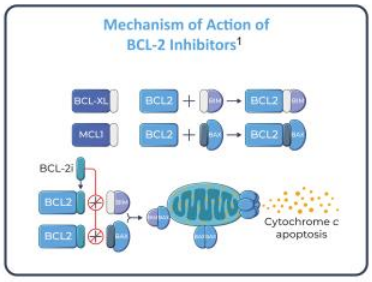


ZN-d5: A Potent BCL-2 Inhibitor Designed With Improved Selectivity for BCL-2

- The intrinsic apoptotic pathway is controlled by the BCL-2 protein family on the mitochondrial outer membrane[6,7]
- BCL-2 inhibitors may restore the normal apoptosis process, making it an important target for cancer treatments (**Figure 2**)
- BH3 mimetics bind to BCL-2 proteins and displace pro-apoptotic factors to trigger apoptosis
- ZN-d5 is highly selective for BCL-2 over BCL-xL, resulting in reduced platelet toxicity in vitro

Figure 2: BCL-2 Inhibition and Apoptosis

- BCL-2 is an anti-apoptotic protein involved in tumor survival and chemo resistance[1]
- The intrinsic apoptotic pathway is controlled by the BCL-2 protein family on the mitochondrial outer membrane[2, 3]
- BCL-2 inhibitors may restore the normal apoptosis process, making it an important target for cancer treatments

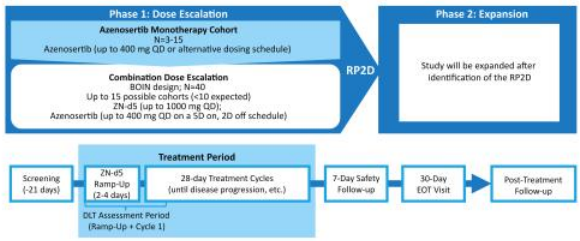


Study Design

- This phase 1/2 open-label study (ZN-d5-004C, NCT05682170) is determining the maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), pharmacokinetics (PK), and clinical activity of ZN-d5 + azenosertib in pts with AML (**Figure 3**)
- The phase 1 dose-escalation stage is based on a Bayesian Optimal Interval design
- Phase 2 is an open-label expansion to be conducted if supported by safety and efficacy data from the dose-escalation stage
- Prior to initiating dose-escalation for the ZN-d5 + azenosertib combination, an azenosertib monotherapy cohort is being enrolled, as it has not been previously administered to pts with hematologic malignancies.

Figure 3: ZN-d5-004C – Inhibition of BCL-2 and WEE1 in R/R AML:

A Phase 1/2 Dose Escalation Study of the BCL-2 Inhibitor ZN-d5 and the WEE1 Inhibitor Azenosertib (ZN-c3) in Subjects with Relapsed or Refractory Acute Myeloid Leukemia



Study Endpoints

	Objectives	Endpoints
Primary	Assess the safety and tolerability of ZN-d5 and azenosertib in combination and azenosertib monotherapy	Incidence, severity, and relatedness of AEs
	Determine the MTD and RP2D for ZN-d5 and azenosertib in combination	Observed DLTs
Secondary	Assess the clinical activity of ZN-d5 and azenosertib in combination and azenosertib monotherapy	Rate of and duration of remission (ELN 2017 criteria), relapse rate, time to relapse
	Characterize the PK of ZN-d5 and azenosertib in combination and the PK of azenosertib when administered as a monotherapy	Plasma PK parameters for ZN-d5 and azenosertib

Patient Population

Key Inclusion Criteria

- Adults ≥ 18 years of age
- Histologically or cytologically confirmed AML, as defined by World Health Organization (WHO) 2016 revised criteria[8], including secondary and therapy-related AML
- Subjects must be relapsed from or refractory to ≥1 prior lines of therapy which can include venetoclax-based regimens, induction chemotherapy, stem cell transplant, or salvage therapy
- Adequate organ function:
  - ALT and AST ≤3 × ULN (≤5 × ULN if leukemic disease in the liver)
  - Alkaline phosphatase ≤5 × ULN
  - Total bilirubin ≤1.5 × ULN (≤3 × ULN if Gilbert syndrome or if leukemic disease in the liver)
  - eGFR (CKD-EPI) ≥60 mL/min and adjusted for body surface area
- Use of an acceptable form of contraception

Key Exclusion Criteria

- Prohibited treatments or procedures from the specified time frame prior to the initiation of treatment until EOT:
  - Systemic anti-neoplastic agents within 5 half-lives
  - Hematopoietic stem cell transplant within 60 days
    - If no GVHD ≥ Grade 2 or that has required treatment with immunosuppressive agents within 28 days
  - Radiation therapy within 14 days
- Presence of a clinically significant non-hematologic toxicity related to prior AML therapy (other than alopecia, neuropathy, or skin pigmentation) that has not returned to baseline or resolved to Grade ≤2
- Active CNS involvement
- Diagnosis of acute PML
- Peripheral WBC count of >25 × 10^9 /L (cytoreduction permitted during screening)
- Significant cardiovascular disease

Study Sites

- This study is open and enrolling at 7 sites in the United States (**Figure 4**)

Figure 4: Currently Enrolling Study Site

REFERENCES

1. Konopleva M, et al. *Cancer Discov.* 2016;6:1106-1117.
2. de Jong MRW, et al. *Cancers.* 2019;11:1742.
3. Kok HT, et al. *Oncogenesis.* 2020;9:88.
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5. Izadi H, et al. AACR 2022. Poster Presentation. Konopleva M and Letai A. *Blood.* 2018;132:1067-1012.
6. Bhatia PD and Lane A. *Mol Cell.* 2016;61:695-704.
7. Peckman JR, et al. ESMO. 2021. Poster 528P.
8. Dohner H, et al. *Blood.* 2017;140:1345-1377.

ACKNOWLEDGMENTS

We would like to thank all the patients, families, and caregivers as well as the investigators and study site staff for their invaluable contributions to this study. This study is funded by Zentalis Pharmaceuticals.

Presented at the ASCO Annual Meeting, Chicago, IL. June 2-6

GOG-3072

Correlation of Cyclin E1 Expression and Clinical Outcomes in a Phase 1b Dose-Escalation Study of Azenosertib (ZN-c3), a WEE1 inhibitor, in Combination with Chemotherapy (CT) in Patients (pts) with Platinum-Resistant or Refractory (R/R) Epithelial Ovarian, Peritoneal, or Fallopian Tube Cancer (EOC)

Abstract # 5513
Poster Bd # 208

Joyce Liu[1], Siqing Fu[2], Gary Richardson[3], Zivko Vranjes[4], Tarek Meniawy[5], Catherine Shannon[6], Erika P. Hamilton[7], Stephanie Blank[8], Cara Mathews[9], Jasmina Alidzanovic[10], Rossitza Krasteva[11], Qing Shi[12], Olivier Harismendy[12], Mieke Ptaszynski[13], Shannon N. Westin[2], Funda Meric-Bernstam[2], Premal H. Thaker[14]

[1]Dana Farber Cancer Institute, Boston, MA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Cabrini Hospital, Malvern, Australia; [4]University Clinical Center of Republic of Srpska, Bosnia and Herzegovina; [5]Linear Cancer Research, University of Western Australia, Perth, Australia; [6]Mater Hospital, Brisbane, Australia; [7]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN; [8]Icahn School of Medicine at Mount Sinai, New York City, NY; [9]Women & Infants Hospital of Rhode Island, Providence, RI; [10]University Clinical Center Tuzla, Bosnia and Herzegovina; [11]Uni Hospital, Panagyurishte, Bulgaria; [12]Zentalis Pharmaceuticals, New York, NY; [13]Formerly Zentalis Pharmaceuticals, New York, NY; [14]Siteman Cancer Center, Washington University, St Louis, MO

INTRODUCTION

- Azenosertib is an oral, highly specific, potent inhibitor of WEE1 kinase. Preclinical and clinical data have shown it to be highly synergistic with multiple chemotherapies (**Figure 1**).
- Cyclin E1 positivity accelerates the G1/S transition, resulting in replication stress and rendering cells even more sensitive to WEE1 inhibition (**Figure 2**).
- Cyclin E1 positivity is also strongly correlated with platinum resistance and worse ovarian cancer outcomes (**Figure 3**).
- Zentalis 002 was a Phase 1b dose escalation study to define the recommended Phase 2 dose and early clinical activity of azenosertib in combination with chemotherapy.
- The purpose of this analysis was to describe the results of Zentalis 002 to date and determine if Cyclin E1 status was associated with benefit from azenosertib.

RESULTS

Figure 1: Multiple Chemotherapeutic Agents Induce DNA or Mitotic Machinery Damage, with Mechanistic Potential to Synergize with Azenosertib

Figure 2: Synergy between Azenosertib and Chemotherapy in Non-Clinical *CCNE1* Amplified Ovarian Cancer Models

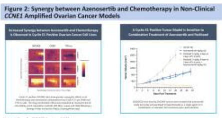


Figure 3: Ovarian Cancer Patients with *CCNE1* Amplified and/or Cyclin E1 Positive Cancers have a Worse Outcome Following Platinum-Based Chemotherapy Treatment

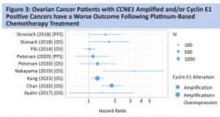


Figure 4: Zentalis 002/GOG-3072 Trial Schema

Table 1: Baseline Characteristics

Characteristic		Azenosertib + Paclitaxel	Azenosertib + Carboplatin	Azenosertib + Gemcitabine	Azenosertib + PLD	Total
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 2: Treatment-Related Adverse Events ≥20%

Treatment-Related Adverse Events	Azenosertib + Paclitaxel	Azenosertib + Carboplatin	Azenosertib + Carboplatin	Azenosertib + Gemcitabine	Azenosertib + PLD	Total
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 3: Clinical Activity of Azenosertib Doublets

Endpoint	Azenosertib + Paclitaxel	Azenosertib + Carboplatin	Azenosertib + Gemcitabine	Azenosertib + PLD	Total
Response Evaluable (N)	22	28	13	31	94
ORR (confirmed), N (%)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Median DOR (95% CI) in months	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Clinical Benefit Rate (CR + PR + SD for ≥ 16 weeks), N (%)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Median PFS (95% CI) in months	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Figure 5: Waterfall Plots

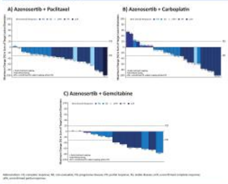


Figure 6: Kaplan-Meier Curves of Progression-Free Survival

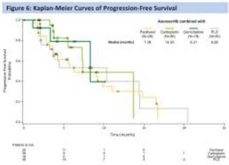
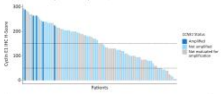


Figure 7: Cyclin E1 Immunohistochemistry (IHC)

- Anti-Cyclin E1 mouse monoclonal antibody (Abcam CCNE1/2460)
- H-score > 50 includes all CCNE1 amplified tumors
- Prevalence of Cyclin E1-IHC positive, H-score > 50 in this data set is 87%



H-Score*	≥ 150	< 150 to > 50	≤ 50
CCNE1 Amplified	5	0	0
CCNE1 Not Amplified	25	15	6
Tissue Not Evaluated for Amplification	16	21	6

Table 4: Objective Responses by Cyclin E1 IHC-Status

Endpoints	Azenosertib + Paclitaxel	Azenosertib + Carboplatin	Azenosertib + Gemcitabine	Azenosertib + PLD	Total
Response Evaluable with IHC (N)*	19	23	13	28	83
Overall Response Rate, n (%)	[illegible]	[illegible]	[illegible]	[illegible]	29 (35.4)
Response Evaluable IHC H-Score >50 (N)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Overall Response Rate, n (%)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Response Evaluable IHC H-Score ≤50 (N)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Overall Response Rate, n (%)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Figure 8: Kaplan-Meier Curve of Progression-Free Survival by Cyclin E1 IHC-Status

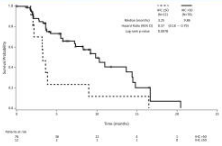


Figure 9: Proposed Randomized Phase 3 Trial Design of Azenosertib + Chemotherapy in Cyclin E1+ Recurrent Platinum-Sensitive Ovarian Cancer

CONCLUSIONS

- **Azenosertib is active with chemotherapy and can be safely combined. RP2Ds are:**
  - **Paclitaxel 80 mg/m² on D1, D8, D15 (28-day cycles) + Azenosertib 300 mg QD 5:2**
  - **Carboplatin AUC 5 mg/mL*min on D1 (21-day cycles) + Azenosertib 200 mg QD 5:2**
  - **PLD 40 mg/m² D1 (28-day cycles) + Azenosertib 400 mg QD 5:2**
  - **Gemcitabine + Azenosertib has exciting and durable activity, a MTD has not been determined, further dose cohorts are ongoing**
- **Azenosertib-chemotherapy doublet combinations have a longer ORR, mDOR, and mPFS compared to historic control data for single-agent chemotherapy**
- **Cyclin E1 status predicts the benefit from the addition of azenosertib to single-agent chemotherapy suggesting that azenosertib restores chemotherapy sensitivity in heavily pre-treated platinum-resistant ovarian cancer**
- **Azenosertib + chemotherapy has a high level of clinical activity and safety, supporting a randomized study comparing this combination to carboplatin-doublet chemotherapy in platinum sensitive ovarian cancer**

ACKNOWLEDGMENTS

We are grateful to all the patients, their families, and the investigators that participated in this study. We would also like to thank the GOG for extraordinary development and operational support for this study.

Presented at the ASCO Annual Meeting, Chicago, IL, June 2-6