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): April 17, 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)

1359 Broadway, Suite 1710
New York, New York 10018
(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 April 17, 2023, Zentalis Pharmaceuticals, Inc. (the "Company") issued the press release furnished as Exhibit 99.1 to this Current Report on Form 8-K (this "Current Report") and incorporated herein by reference. In addition, beginning on April 17, 2023, spokespersons of the Company plan to present the information in the Corporate Presentation furnished as Exhibit 99.2 to this Current Report and incorporated herein by reference at conferences and in meetings with investors and analysts.

The information contained in Item 7.01 of this Current Report (including Exhibits 99.1 and 99.2 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 April 17, 2023, the Company announced preclinical data that demonstrated that its potentially first-in-class Wee1 inhibitor product candidate, azenosertib, drove cancer cell death in Cyclin E1-high tumor cells *in vitro* and substantially inhibited the growth of Cyclin E1-high, patient-derived, *in vivo* tumor models at the 2023 American Association for Cancer Research Annual Meeting. These preclinical data support CCNE1 amplification and/or Cyclin E1 expression as a potential marker for the enrichment of patient populations for treatment with azenosertib.

Cautionary Note Regarding Forward-Looking Statements

Statements in this Current Report regarding the Company's strategy, plans, prospects, expectations, beliefs, intentions and goals are forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements regarding the potential for CCNE1 amplification and/or Cyclin E1 expression to be a marker for the enrichment of patient populations for treatment with azenosertib. The terms "potential," "support" and similar references are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause the Company's actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: the Company's limited operating history, which may make it difficult to evaluate the Company's current business and predict the Company's future success and viability; the Company has and expects to continue to incur significant losses; the Company's need for additional funding, which may not be available; the Company's plans, including the costs thereof, of development of any companion diagnostics; the Company's substantial dependence on the success of its lead product candidates; the outcome of preclinical testing and early trials may not be predictive of the success of later clinical trials; failure to identify additional product candidates and develop or commercialize marketable products; potential unforeseen events during clinical trials could cause delays or other adverse consequences; risks relating to the regulatory approval process or ongoing regulatory obligations; failure to obtain U.S. or international marketing approval; the Company's product candidates may cause serious adverse side effects; inability to maintain collaborations, or the failure of these collaborations; the Company's reliance on third parties; effects of significant competition; the possibility of system failures or security breaches; risks relating to intellectual property; the Company's ability to attract, retain and motivate qualified personnel, and risks relating to management transitions; significant costs as a result of operating as a public company; and the other important factors discussed under the caption "Risk Factors" in the Company's most recently filed periodic report on Form 10-K or 10-Q and subsequent filings with the SEC and the Company's other filings with the SEC. These forward-looking statements (except as otherwise noted) speak only as of the date of this Current Report, and the Company does not undertake, and specifically disclaims, any obligation to update any forward-looking statements contained in this Current Report.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

The following Exhibits 99.1 and 99.2 relating to Item 7.01 shall be deemed to be furnished, and not filed:

ExhibitNo.	Description
99.1	Press Release issued on April 17, 2023.
99.2	Corporate Presentation, dated April 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: April 17, 2023

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

Exhibit 99.1

Zentalis announces preclinical data supporting Cyclin E1 as a predictive marker for azenosertib treatment at AACR Annual Meeting 2023

Data suggest Cyclin E1 plays a critical role in high proportion of multiple tumor types including platinum-resistant ovarian cancer

Company anticipates sharing clinical data from ovarian chemotherapy combination study, including data on CCNE1 amplification and / or Cyclin E1 expression, in the first half of 2023, in advance of original guidance

NEW YORK & SAN DIEGO, April 17, 2023 -- Zentalis™ Pharmaceuticals, Inc. (Nasdaq: ZNTL), a clinical-stage biopharmaceutical company focused on discovering and developing clinically differentiated small molecule therapeutics targeting fundamental biological pathways of cancers, today announces preclinical data that supports CCNE1 amplification and / or Cyclin E1 expression as a potential marker for the enrichment of patient populations for treatment with azenosertib, the Company's potentially first-in-class Wee1 inhibitor product candidate. These new preclinical data demonstrate that azenosertib drives cancer cell death in Cyclin E1-high tumor cells *in vitro* and substantially inhibits the growth of Cyclin E1-high, patient-derived, *in vivo* tumor models.

The findings are being presented today at the 2023 American Association for Cancer Research (AACR) Annual Meeting, in a poster entitled "Cyclin E1 protein overexpression sensitizes ovarian cancer cells to azenosertib (ZN-c3), a novel, selective and orally bioavailable inhibitor of Wee1." The poster can be found on the Company's website at this link. The poster presentation details are below.

Session Category: Clinical Research Excluding Trials

Session Title: Biomarkers of Therapeutic Benefit 2

Session Date and Time: Monday, April 17, 2023, 9:00 AM ET - 12:30 PM ET

Location: Section 39

Poster Board Number: 27

Abstract Presentation Number: 2153

"We are excited to present new preclinical data demonstrating the utility of Cyclin E1 as a predictive marker to identify patients likely to respond to azenosertib," said Mark Lackner, Ph.D., Chief Translational Officer of Zentalis. "Our findings suggest that Cyclin E1 expression via gene amplification or independent mechanisms sensitizes ovarian cancer cells to azenosertib alone or in combination with chemotherapy. These data confirm and build upon our prior preclinical work, and the published research of others, and provide additional evidence that supports our ongoing clinical trial studying azenosertib as a monotherapy in patients with Cyclin E1-driven ovarian cancer. These data also support the potential development of companion diagnostics for azenosertib."

The study analyzed data from a panel of patient-derived ovarian cancer cell lines *in vitro* and *in vivo* models of ovarian cancer. The results show that high Cyclin E1 protein expression is significantly associated with sensitivity to azenosertib, and that artificial overexpression of Cyclin E1 in cell lines with low endogenous Cyclin E1 expression sensitizes those cells to azenosertib. In addition, the study

provides foundational details on the mechanistic basis of Cyclin E1 sensitization to Wee1 inhibition, including that Cyclin E1 overexpression results in accumulation of replication stress biomarkers and that azenosertib sensitivity is mediated by CDK2 activity.

The study also provides supportive data for several relevant standard of care chemotherapy combinations based on *in vitro* synergy assays and suggests that Cyclin E1 expression is a relevant clinical predictive marker. The Company is conducting an analysis of CCNE1 copy number and Cyclin E1 protein expression in its Phase 1b study of azenosertib in combination with chemotherapy in patients with platinum-resistant ovarian cancer. The Company now anticipates sharing these clinical data in the first half of 2023, in advance of original guidance.

“These encouraging translational results support the use of CCNE1 copy number and / or Cyclin E1 protein expression as predictive markers that have the potential to significantly improve patient outcomes by enabling us to select the right patients for treatment with azenosertib,” said Gordon Mills, M.D., Ph.D., Professor of Cell, Developmental and Cancer Biology, Oregon Health and Science University School of Medicine. The Company is collaborating with Dr. Mills on preclinical and clinical studies related to the effects of Wee1 inhibition on replicative stress, cell cycle modulation and DNA repair.

Another poster being presented at AACR by the Ivy Brain Tumor Center at Barrow Neurological Institute entitled “Tumor Pharmacokinetics, Pharmacodynamics and Efficacy Analysis of Wee1 inhibitor, Azenosertib in Patient-Derived Xenograft Models of Glioblastoma,” demonstrates that azenosertib can achieve pharmacologically-relevant intracerebral free-drug concentrations, and that pharmacodynamic activity is observed in a preclinical glioblastoma model. This research underscores the potential of azenosertib as a therapy for a more extensive range of tumor types than those presently under clinical investigation. Once presented, the poster can be found on the Company’s website using this link. The poster presentation details are below.

Session Category: Experimental and Molecular Therapeutics, Chemistry

Session Title: Pharmacokinetics, Pharmacodynamics, and Molecular Pharmacology

Session Date and Time: Monday, April 17, 2023, 1:30 PM ET – 5:00 PM ET

Location: Section 18

Poster Board Number: 19

Abstract Presentation Number: 2796

About Azenosertib

Zentalis’ azenosertib (ZN-c3) has been designed to be a highly potent and selective Wee1 inhibitor.
Azenosertib is currently being evaluated in the clinic for advanced solid tumors and hematological malignancies in the following three therapeutic settings of high unmet medical need: (1) as a monotherapy, (2) in combination with traditional chemotherapy and DNA damaging agents, and (3) in combination with molecularly targeted agents. As a monotherapy, azenosertib is currently being evaluated in a Phase 2 clinical trial in adult women with uterine serous carcinoma (USC), an aggressive form of endometrial cancer that accounts for approximately 10-15% of all endometrial cancers. We are also evaluating azenosertib as a monotherapy in a Phase 2 clinical trial in patients with Cyclin E1 driven high-grade serous ovarian cancer (HGSOC). The Company is evaluating azenosertib as a monotherapy in

a Phase 1 dose optimization clinical trial in patients with advanced solid tumors, and plans to declare the recommended Phase 2 monotherapy dose and provide an update on dose optimization activities in the first half of 2023. In chemotherapy combinations, azenosertib is currently being evaluated in combination with each of paclitaxel, carboplatin, pegylated liposomal doxorubicin (PLD) and gemcitabine in four cohorts in a Phase 1b clinical trial in patients with advanced platinum-resistant ovarian, peritoneal or fallopian tube cancer. The Company plans to disclose results from this study in the first half of 2023, in advance of original guidance. Azenosertib is also currently being evaluated in combination with gemcitabine in a Phase 1/2 clinical trial in adult and pediatric patients with relapsed or refractory osteosarcoma. In combination with molecularly targeted agents, the Company is studying azenosertib in combination with GlaxoSmithKline plc's (GSK's) PARP inhibitor, niraparib (ZEJULA®), in a Phase 1/2 clinical trial in platinum-resistant ovarian cancer patients who have failed PARP inhibitor maintenance treatment as part of a clinical collaboration with GSK. The Company is also collaborating with Pfizer Inc. to evaluate azenosertib in combination with encorafenib and cetuximab, an FDA-approved standard of care known as the BEACON regimen, in patients with BRAF V600E mutant metastatic colorectal cancer in a Phase 1/2 clinical trial.

About Zentalis Pharmaceuticals

Zentalis™ Pharmaceuticals, Inc. is a clinical-stage biopharmaceutical company focused on discovering and developing small molecule therapeutics targeting fundamental biological pathways of cancers. Utilizing its Integrated Discovery Engine, the Company is developing a focused pipeline of potentially best-in-class oncology candidates, which include azenosertib (ZN-c3), a Wee1 inhibitor for advanced solid tumors, ZN-d5, a BCL-2 inhibitor for hematologic malignancies and related disorders, and a heterobifunctional degrader of BCL-xL for solid and hematological malignancies. The Company is also leveraging its extensive experience and capabilities across cancer biology and medicinal chemistry to advance its research on protein degraders. Zentalis has operations in both New York and San Diego.

For more information, please visit www.zentalis.com. Follow Zentalis on Twitter at @ZentalisP and on LinkedIn at www.linkedin.com/company/zentalis-pharmaceuticals.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including statements regarding the potential of Cyclin E1 as a predictive marker for azenosertib treatment, including its potential to significantly improve patient outcomes by enabling selection of the right patients for azenosertib treatment; the role Cyclin E1 may play in a high proportion of multiple tumor types; the timing of disclosure of preclinical and clinical data, the timing of declaration of the recommended Phase 2 monotherapy dose for azenosertib, and the timing of providing an update on the dose optimization activities for azenosertib; the potential for azenosertib to be first-in-class; the potential for our product candidates to be best-in-class; the potential for Cyclin E1 expression to sensitize ovarian cancer cells to azenosertib alone or in combination; the potential to develop companion diagnostics for azenosertib; the potential of azenosertib as a therapy for a more extensive range of tumor types than those presently under clinical investigation; the potential benefits of azenosertib, including the potential benefits of the design of azenosertib; and the market opportunity for azenosertib. The terms “anticipates,” “can,”

“designed,” “likely,” “plan,” “potential,” “provide,” “suggest,” “support” and similar references are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: our limited operating history, which may make it difficult to evaluate our current business and predict our future success and viability; we have and expect to continue to incur significant losses; our need for additional funding, which may not be available; our plans, including the costs thereof, of development of any companion diagnostics; our substantial dependence on the success of our lead product candidates; the outcome of preclinical testing and early trials may not be predictive of the success of later clinical trials; failure to identify additional product candidates and develop or commercialize marketable products; potential unforeseen events during clinical trials could cause delays or other adverse consequences; risks relating to the regulatory approval process or ongoing regulatory obligations; failure to obtain U.S. or international marketing approval; our product candidates may cause serious adverse side effects; inability to maintain our collaborations, or the failure of these collaborations; our reliance on third parties; effects of significant competition; the possibility of system failures or security breaches; risks relating to intellectual property; our ability to attract, retain and motivate qualified personnel, and risks relating to management transitions; significant costs as a result of operating as a public company; and the other important factors discussed under the caption “Risk Factors” in our most recently filed periodic report on Form 10-K or 10-Q and subsequent filings with the U.S. Securities and Exchange Commission (SEC) and our other filings with the SEC. Any such forward-looking statements represent management’s estimates as of the date of this press release. While we may elect to update such forward-looking statements at some point in the future, we disclaim any obligation to do so, even if subsequent events cause our views to change.

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Exhibit 99.2

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CORPORATE PRESENTATION

April 2023

Forward-Looking Statements and Disclaimer

Zentalis Pharmaceuticals, Inc. ("we," "us," "our," "Zentalis" or the "Company") cautions that this presentation (including oral commentary that accompanies this presentation) contains forward-looking statements within the meaning of the U.S. Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding potential for our product candidates to be first-in-class and/or best-in-class; potential for accelerated approval paths; potential for our product candidates to be developed as monotherapies and in combination; potential for azenosertib (ZN-c3) to address large populations with significant unmet need; our development approach for our product candidates, including azenosertib and ZN-d5; plans for and potential benefits of dose optimization, and the anticipated timing of updates on dosing optimization, including timing of declaring a monotherapy RP2D for azenosertib; timing of providing updates on azenosertib program timelines and potential paths to registration; timing of preclinical and clinical program updates; the potential unmet need in a particular indication and/or patient population; potential for combinations including our product candidates and the potential benefits thereof; the target profiles and potential benefits of our product candidates and their mechanisms of action, including as a monotherapy and/or in combination; our belief that we have strengthened our clinical development plans, including for azenosertib; clinical and regulatory progress of our product candidates, including the estimated timing of IND-enabling studies, enrollment, initiation of clinical trials and data announcements; the market opportunities for and market potential of our product candidates; timing of providing preclinical rationale for our Cyclin E1 enrichment strategy for azenosertib; the potential of Cyclin E1 as a predictive marker for azenosertib treatment; timing of advancement of our preclinical programs, including BCL-xL and protein degrader programs; our anticipated milestones, as well as statements that include the words "design," "estimate," "expect," "may," "milestone," "opportunity," "plan," "potential," "strategy," "to come," "will" and similar statements of a future or forward-looking nature. These statements are neither promises nor guarantees, but involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements, including, but not limited to, the following: our limited operating history, which may make it difficult to evaluate our current business and predict our future success and viability; we have and expect to continue to incur significant losses; our need for additional funding, which may not be available; our substantial dependence on the success of our lead product candidate; failure to identify additional product candidates and develop or commercialize marketable products; the early stage of our development efforts; potential unforeseen events during clinical trials could cause delays or other adverse consequences; risks relating to the regulatory approval process or ongoing regulatory obligations; failure to obtain U.S. or international marketing approval; our product candidates may cause serious adverse side effects; interim, initial, "topline", and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data; inability to maintain our collaborations, or the failure of these collaborations; our reliance on third parties; our plans, including the costs thereof, of development of any companion diagnostics; effects of significant competition; the possibility of system failures or security breaches; risks relating to intellectual property; our ability to attract, retain and motivate qualified personnel; and significant costs as a result of operating as a public company. Other risks and uncertainties include those identified under the caption "Risk Factors" in our most recently filed periodic reports on Forms 10-K and 10-Q and subsequent filings with the U.S. Securities and Exchange Commission in the future could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. While we may elect to update these forward-looking statements at some point in the future, we assume no obligation to update or revise any forward-looking statements except to the extent required by applicable law. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. Neither we nor our affiliates, advisors or representatives makes any representation as to the accuracy or completeness of that data or undertake to update such data after the date of this presentation.

ZENTALIS™ and its associated logos are trademarks of Zentalis and/or its affiliates. All other trademarks, trade names and service marks appearing in this presentation are the property of their respective owners. All website addresses given in this presentation are for information only and are not intended to be an active link or to incorporate any website information into this document.

Zentalis' product candidates are investigational drugs and have not yet been approved by the U.S. Food and Drug Administration or any other regulatory authority.

Company Overview

Lead Program: Wee1i azenosertib potentially first- and best-in-class

- Monotherapy in multiple biomarker enriched populations enrolling
  - Enriched patient populations including Uterine Serous Carcinoma (USC), Cyclin E1 driven and post-PARP progression
- Investigating highly synergistic combinations, including BRAF/MEK inhibitors in BRAF mutant metastatic colorectal cancer and PARP inhibitors in high grade serous PARP resistant ovarian cancer
- Fast Track designation granted in USC

BCL-2 inhibitor ZN-d5: broad applicability as anti-apoptotic target; potential as monotherapy and in combination

- Single agent activity in AL amyloidosis
- Potential combinations including with azenosertib in AML

BCL-xL heterobifunctional degrader for liquid and solid tumors (preclinical)

Additional discovery programs against validated cancer targets

Integrated Discovery to Clinical Engine: 4 FDA-cleared INDs within 5 years

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Advancing Focused Pipeline with Multiple Clinical Opportunities

COMPOUND	INDICATION	DEVELOPMENT APPROACH	PRECLINICAL	EARLY CLINICAL DEVELOPMENT	LATE CLINICAL DEVELOPMENT	STATUS / EXPECTED MILESTONES
Azenosertib (ZN-c3) Wee1 Inhibitor	Uterine Serous Carcinoma	Monotherapy				FDA Fast Track Designation
	Dose Optimization for Solid Tumors	Monotherapy				Update on azenosertib dosing 1H 2023 including RP2D
	Cyclin E1 Driven Ovarian Cancer	Monotherapy				Enrolling; preclinical update presented at AACR 2023
	PARP Resistant Ovarian Cancer	Azenosertib alternating with niraparib or concurrent with niraparib				Enrolling
	Ovarian Cancer	+ Multiple Chemotherapy Backbones				Enrolling; Phase 1 dose escalation results in 1H 2023
	Osteosarcoma	+ gemcitabine				Enrolling
	BRAF Mutant Colorectal Cancer	+ encorafenib and cetuximab				Initiated enrollment in Q1 2023
	Pancreatic Cancer	+ gemcitabine				Dana Farber Cancer Institute, funded by SU2C/Lustgarten
ZN-d5 BCL-2 Inhibitor	AL Amyloidosis	Monotherapy				Provide clinical data and declare RP2D for monotherapy 2H 2023
	NHL	Monotherapy				Continues to enroll
	AML	+ azenosertib				Provide preliminary data from clinical trial 2H2023
BCL-xL Degrader	Solid Tumors and Heme Malignancies					Declared development candidate; IND enabling activities initiated

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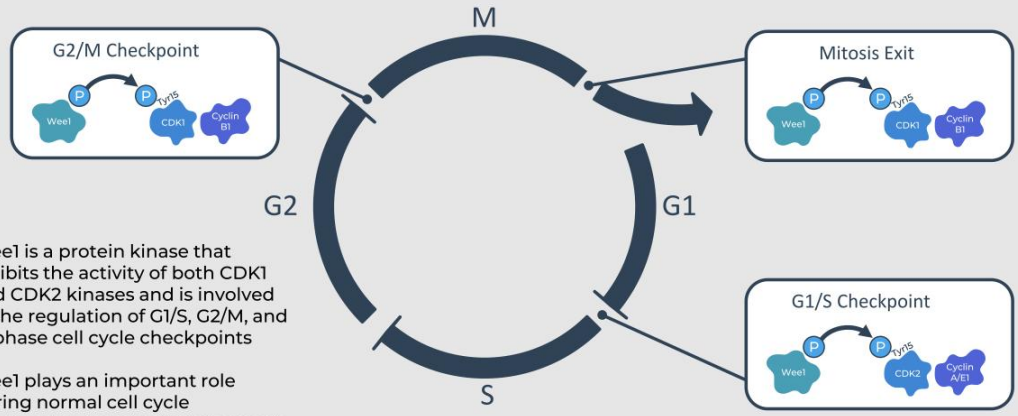
Azenosertib (ZN-c3)

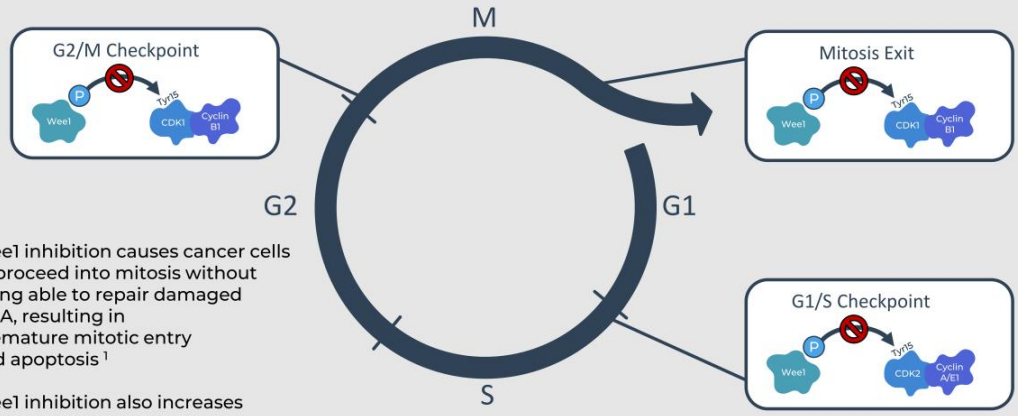
Wee1 Inhibitor

Wee1: A Critical Cell Cycle Regulation Target



- 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
- Wee1 plays an important role during normal cell cycle progression but also in response to DNA damage and interacts with DNA damage response (DDR) pathways

Wee1 Inhibition by Azenosertib Forces Cancer Cells to Proceed into Mitosis

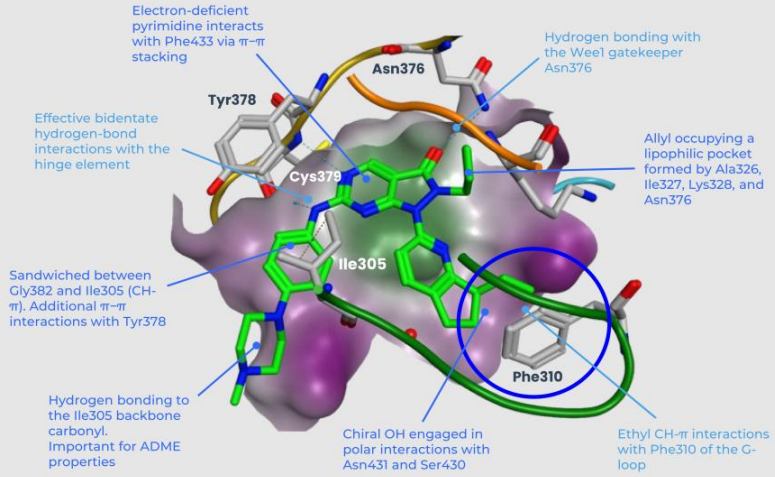


- Wee1 inhibition causes cancer cells to proceed into mitosis without being able to repair damaged DNA, resulting in premature mitotic entry and apoptosis [1]
- Wee1 inhibition also increases replication stress by inducing aberrant firing of replication origins and depletion of nucleotide pools [1]

1. Kok, *et al.* Overexpression of Cyclin E1 or Cdc25A leads to replication stress, mitotic aberrancies, and increased sensitivity to replication checkpoint inhibitors. *Oncogenesis* 9, 88 (2020)

Structure-Based Drug Design (SBDD) Led to the Discovery of a Highly Potent and Selective Wee1 Inhibitor Azenosertib with Improved ADME Properties

azenosertib potency and ADME	
Wee1 IC_{50}	3.8 nM
H23 IC_{50}	103 nM
A427 IC_{50}	75 nM
Log *D*	2.4
*h*PPB	66%
*h*Hep	<18 mL/min/kg
solubility	> 2000 µM
CYP3A4	7 µM
hERG	> 30 µM



Huang, PQ; *et al.* J. Med. Chem. **2021**, *64*, 13004-13024

Azenosertib: Significant Market Opportunity Across a Broad Range of Solid and Liquid Tumors

Indication	Incidence Estimates (US+EU)	Development Approach
Ovarian Cancer	46,700 [1]	Strategic commitment to patients with multiple ongoing studies in monotherapy and combination settings
High Grade Serous Ovarian Cancer (HGSOC) (75% of Ovarian Cancer)	35,000 [2]	Ongoing study combining azenosertib with common chemotherapy backbones in platinum resistant populations. Additional ongoing study examining PARP inhibition in PARP resistant populations with GSK
Cyclin E1 Driven Ovarian Cancer (~25% of HGSOC)	8,800 [3]	Ongoing biomarker study with monotherapy regimen exploring high Cyclin E1 protein expression and CCNE1 gene amplification
Other Cyclin E1 Driven Solid Tumors	80,000+ [3]	Potential follow-on opportunities including prostate, lung, breast, etc.
Uterine Serous Carcinoma	10,100 [4]	Fast track designation monotherapy program
Colorectal (BRAF mutant)	36,300 [5]	Initiated enrollment of azenosertib + BEACON regimen in Q1 2023 as part of Pfizer development partnership
Osteosarcoma	4,300 [6]	Azenosertib + gemcitabine combination. Initial data readout at 2022 CTOS Conference
Pancreatic Cancer	108,000 [7]	Azenosertib + gemcitabine combination. Potential to demonstrate POC via investigator sponsored trial at Dana Farber.
AML	25,600 [8]	Combine azenosertib with ZN-d5, BCL-2 inhibitor

1. Cancer of the Ovary - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/ovary.html for US and ECIS - European Cancer Information System for EU (applying EU27 female population to incidence cited) 2. Ovarian Cancer Research Alliance. Retrieved November 4, 2022, https://ocrahope.org/2021. 3. Chen et al Mol Cell Proteomics. 2019 Aug 9:18(8 suppl 1):S15-S25 and TCGA dataset 4. Trastuzumab for Rare Form of Endometrial Cancer. (2020, August 13). National Cancer Institute. https://www.cancer.gov/news-events/cancer-currents-blog/2020/endometrial-cancer-usc-her2-trastuzumab (US only). 5. Cancer of the Colon and Rectum - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/colorect.html and ECIS - European Cancer Information System and applying estimated BRAF V600E proportion. 6. Cancer of the Bones and Joints - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/bones.html and Annals of Oncology, VOLUME 32, ISSUE 12, P1520-1536, DECEMBER 01, 2021. 7. Cancer of the Pancreas - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/pancreas.html and ECIS - European Cancer Information System. 8. Acute Myeloid Leukemia - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/amyl.html and Acute Myeloid Leukaemia: Mapping the Policy Response to an Acute Cancer in France, Germany, Italy, Spain, and the UK. (2019). The Economist Intelligence Unit.

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Azenosertib (ZN-c3)

Uterine Serous Carcinoma

Unmet Need in Uterine Serous Carcinoma is Significant

UNMET NEED

- USC is an aggressive form of endometrial cancer that accounts for 10-15% of all endometrial cancers [1]
- The 5-year survival for late-stage is approx. 41% compared to 75% in women with the most common form of endometrial cancer [2]
- USC is responsible for ~40% of endometrial cancer deaths [3]

UNIQUE BIOLOGY

- USC is molecularly distinct from endometrial cancer with frequent alterations in p53 (90%), CCNE1 (25%) and HER2 (25%) [4]
- High amounts of oncogene-driven replicative stress
- Wee-1 is a validated target in USC with reported ORR of 29.4% and a PFS6 rate of 47.1% with adavosertib [5]

COMPETITIVE LANDSCAPE

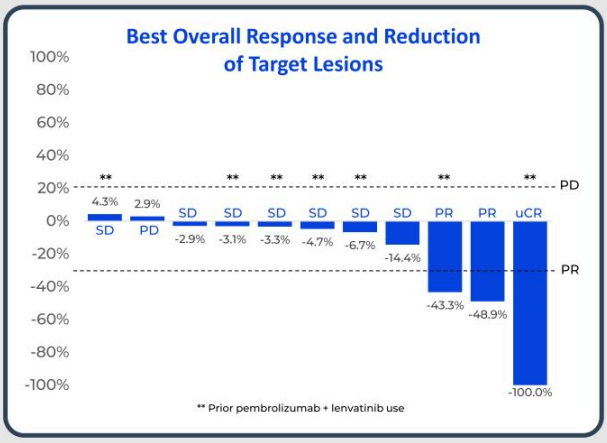
- Current standards of care for USC:
  - First line: Platinum based chemotherapy
  - Second line: Pembro + Lenvatinib
  - Third Line: No specific recommendations, single-agent chemotherapy (4-9%) and some limited use of bevacizumab [6]
- There is a high need for a therapeutic option in later line patients after prior platinum containing chemotherapy and pembrolizumab + lenvatinib treatment
- Azenosertib is potentially a first-in-class treatment option for USC

Azenosertib's emerging efficacy and tolerability profile show promise in addressing unmet need in USC

1. https://www.cancer.gov/news-events/cancer-currents-blog/2020/endometrial-cancer-usc-her2-trastuzumab 2. Boruta DM II, Cancer 101:2214-2221, 2004. 3. McGunigal M. Int J Gynecol Cancer 27:85-92, 2017.
4. Cancer Genome Atlas Research Network, Kandoth C. Nature 497:67-73, 2013. 5. Liu J. J Clin Oncol 39, 14:1531-1539, 2021. 6. CancerMPact, Future Trends and Insights Endometrial cancer June 2021; data on file.

ZN-c3-001: Summary of Clinical Activity – Meaningful and Durable Responses Seen in USC

Best Overall Response	N = 11†; n (%)
Complete Response (unconfirmed)*	1 (9.1)
Partial Response (confirmed)	2 (18.2)
Stable Disease	7 (63.6)
≥ 12 weeks	4 (36.3)
< 12 weeks	3 (27.3)
Progressive Disease	1 (9.1)
Overall Response Rate (95% CI = 6.0%, 61.0%)	3 (27.3)
DCR (CR + PR + SD) (95% CI = 58.7%, 99.8%)	10 (90.9)
Median Duration of Response	5.6 months
mPFS	4.2 months



Meric-Bernstam et al. Presentation at American Association for Cancer Research 2022 Meeting. Safety and clinical activity of single-agent azenosertib, an oral Wee1 inhibitor, in a Phase 1 trial in subjects with recurrent or advanced uterine serous carcinoma (USC). Data cutoff January 21, 2022.

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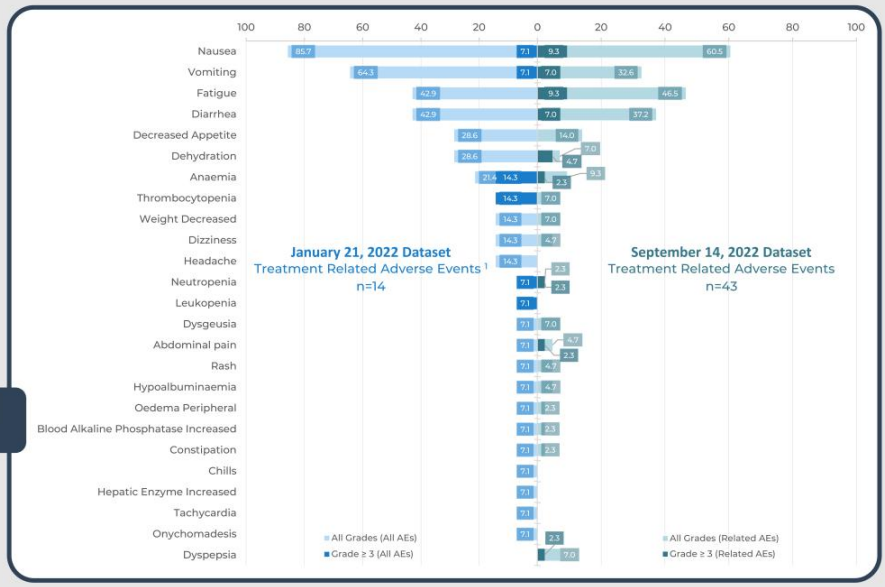
* Best overall response for this subject is PR. † N=11 subjects with measurable disease and at least 1 post-baseline tumor assessment. At time of data cutoff 2 SDs were ongoing on study
DCR=disease control rate; uCR=unconfirmed complete response.

Azenosertib Continues to Show Favorable Tolerability Profile in Monotherapy USC Setting

Patients with Adverse Events (%)



1. Presented at AACR 2022 by F. Meric-Bernstam

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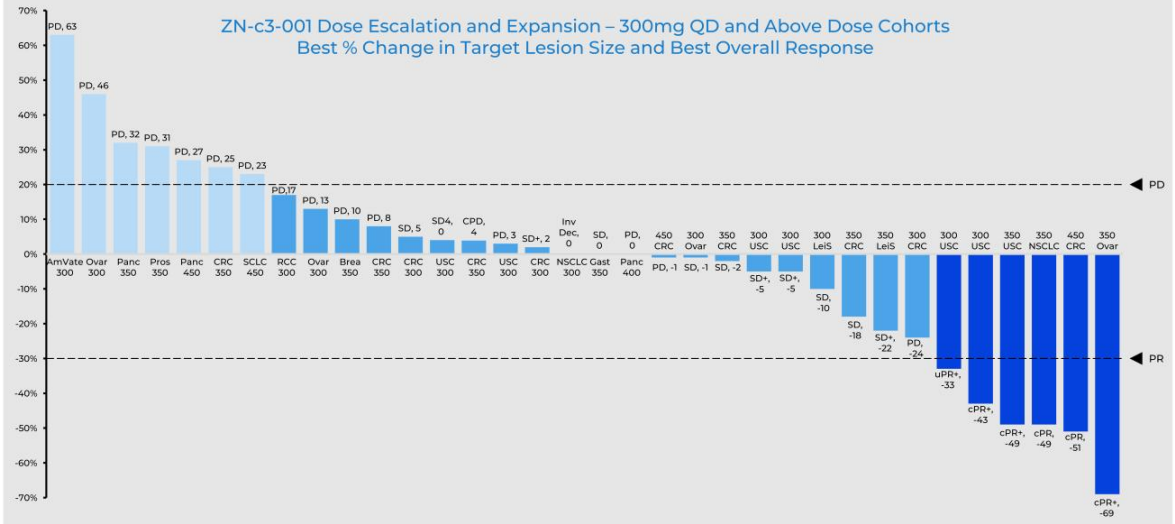
Azenosertib (ZN-c3)

Dose Optimization

Azenosertib: Multiple PRs Across Tumor Types as Monotherapy

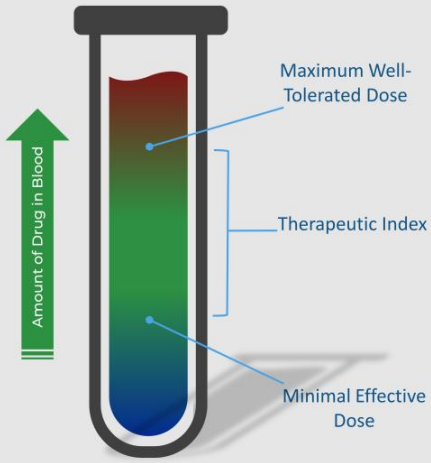


Waterfall as of 05/15/2021; 3 subjects with no treatment scans (CRC, USC, Pancreas), and experienced clinical progressive disease (CPD) + denotes treatment ongoing.
Newly reported uPR in USC is included. ORR based on radiographic responses. Both uPRs reported at AACR 2021 as of 03/15/2021 in USC were confirmed.

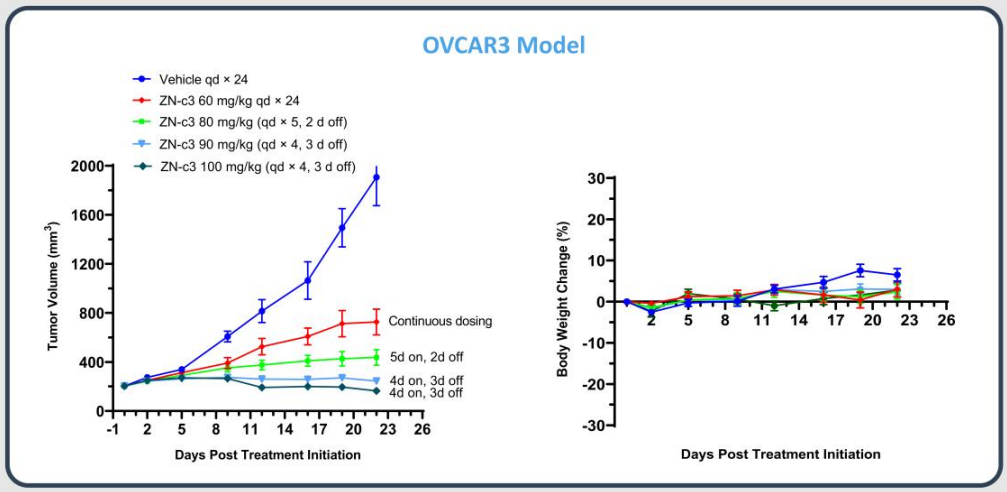
Optimizing the Therapeutic Index of Azenosertib

- Only set dose of azenosertib has been in USC (004 trial) at 300mg QD continuous daily dosing
  - Monotherapy activity demonstrated
  - Well tolerated safety profile
- From 300mg QD dosing, we will examine pushing the therapeutic index for monotherapy dosing across three trials as this represents the fastest path to regulatory approval considerations and meaningful clinical evidence
- Our experience to date (>200 patients) is that exposure and maintenance of exposure drives efficacy (both response and duration of response)
- Alternative dosing to date (>60 patients):
  - Less dose interruptions and modifications

Dosing update planned 1H 2023



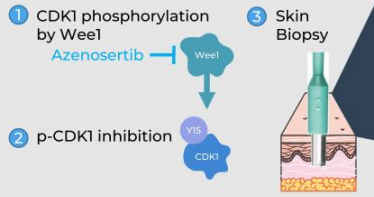
Azenosertib: Intermittent Dosing Increases Efficacy and Maintains Tolerability in Ovarian Cancer Models



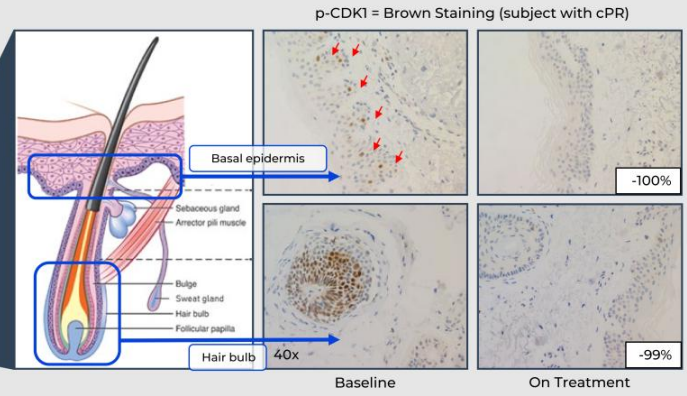
Decreases in p-CDK1 Show Target Engagement for Wee1 Inhibition

Confirmation of Wee1 Target Engagement in Surrogate Tissue [1]

1. CDK1 phosphorylation (p-CDK1) is mediated by Wee1
2. Inhibition of Wee1 will lead to inhibition of p-CDK1
3. Skin biopsies were performed at baseline and on treatment to verify p-CDK1 levels and level of target engagement of Wee1

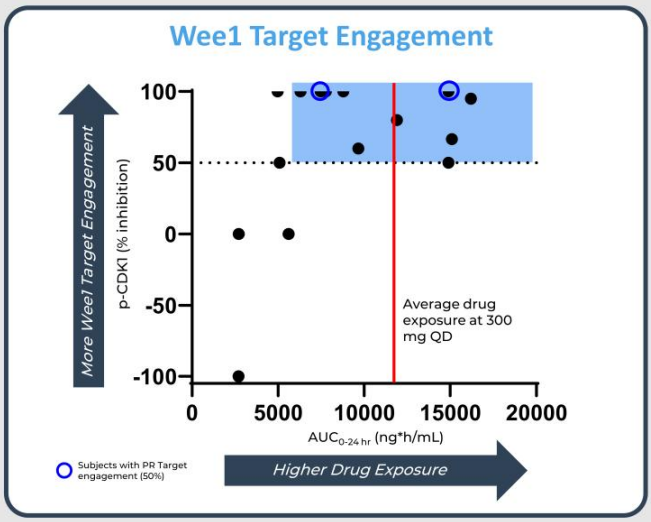


Decreases in p-CDK1 at Baseline vs on Treatment



1. Chalasani, P; *et al.* 526P Pharmacodynamic evidence for WEE1 target engagement in surrogate and tumor tissues from a phase I study of the WEE1 inhibitor ZN-c3. Annals of Onc. **2021**, 526P

Azenosertib: PK/PD Correlation Shows Active Target Engagement



- Inhibition of p-CDK1 demonstrated Wee1 target engagement
- Increase in dose / drug exposure directly related to Wee1 target engagement
- ≥300 mg QD showed highest AUC, with excellent target engagement and p-CDK1 levels decreased at least by 50%

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1. Chalasani, P; *et al.* 526P Pharmacodynamic evidence for WEE1 target engagement in surrogate and tumor tissues from a phase I study of the WEE1 inhibitor ZN-c3. Annals of Onc. **2021**, 526P

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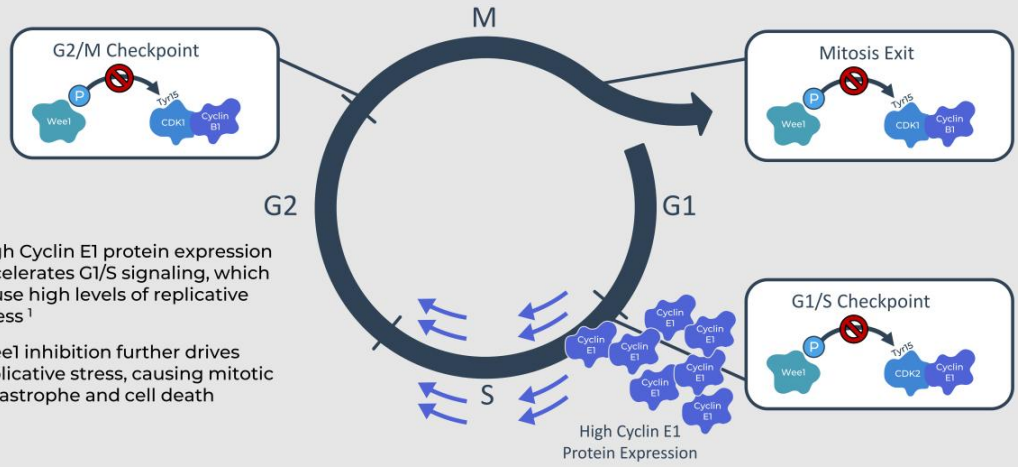
Azenosertib (ZN-c3)

Biomarker Approach: Cyclin E1 Driven Cancers

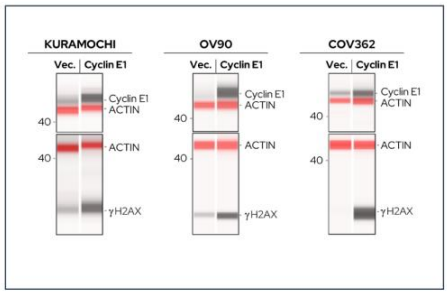
High Cyclin E1 Expressing Cancer Cells are Highly Sensitive to Wee1 Inhibition



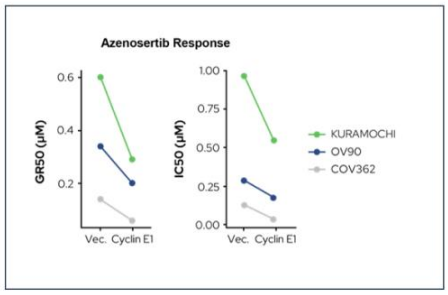
- High Cyclin E1 protein expression accelerates G1/S signaling, which cause high levels of replicative stress [1]
- Wee1 inhibition further drives replicative stress, causing mitotic catastrophe and cell death

1. Kok, *et al.* Overexpression of Cyclin E1 or Cdc25A leads to replication stress, mitotic aberrancies, and increased sensitivity to replication checkpoint inhibitors. *Oncogenesis* 9, 88 (2020)

Cyclin E1 Overexpression Sensitizes Isogenic HGSOC Cell Lines to Azenosertib

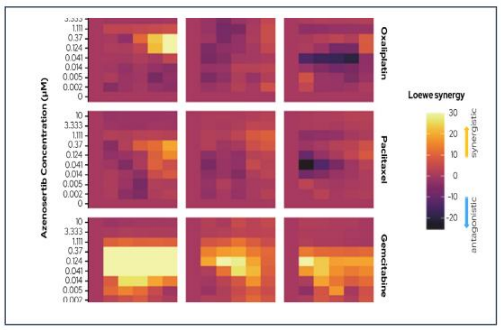


- Cyclin E1 over expression induced by lentiviral transduction was confirmed by Western Blot
- Cyclin E1 over expression significantly increases gamma H2AX in all cell lines, suggesting that Cyclin E1 over expression can induce DNA damage response

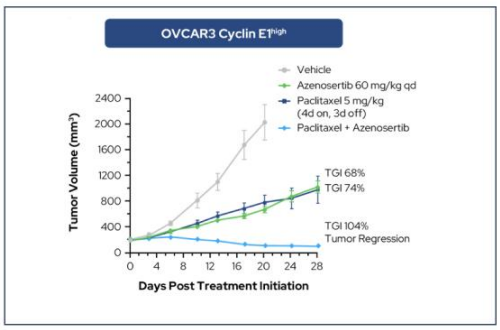


- Cyclin E1 over expression sensitizes HGSOC cell lines to azenosertib by further decreasing growth rate and cell viability compared to control vector (Vec) cell lines
- GR50 and IC50 of azenosertib were determined by CellTiter-Glo assay and the GR calculator

Increased Synergy Between Azenosertib and Chemotherapy is Observed in Cyclin E1^{high} HGSOC *in vitro* and *in vivo*



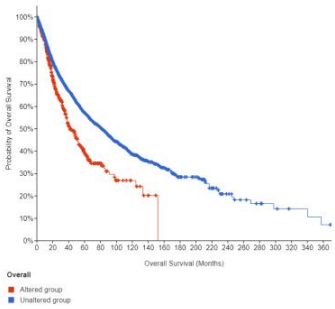
- Cyclin E1^{high} OVCAR3 cells show greater synergistic effects (Loewe synergy score > 10 is synergistic, Loewe synergy score <10 is antagonistic) in all chemotherapy and azenosertib combinations than Cyclin E1^{low} OV90 and TYK-nu cells (calculated following SynergyFinder guidelines, see https://synergyfinder.org)



- NOD/SCID mice bearing OVCAR3 tumors were treated with azenosertib orally every day and paclitaxel intraperitoneally as a single agent or in combination as indicated
- All treatments were well tolerated

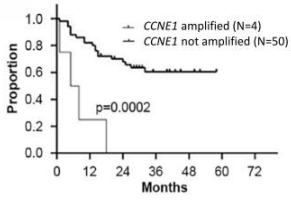
CCNE1 Gene Amplification is Associated with Poor Prognosis and Chemotherapy Response Across Tumor Types

TCGA Pan Cancer Atlas [1]

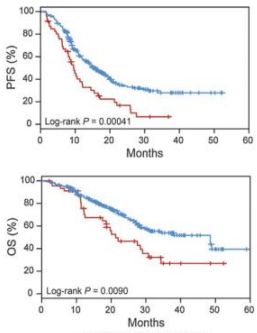


CCNE1 amplified (N=410)
CCNE1 not amplified (N=10,305)
Log-rank test p-value=1.06 10^{-13}

Triple Negative Breast Cancer (TNBC) [2]



Carboplatin-treated Ovarian Cancer [3]

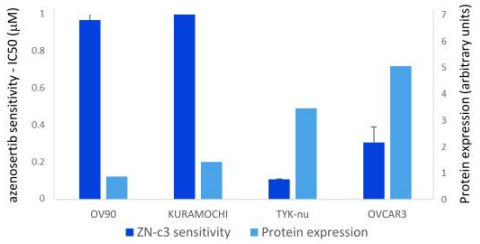


CCNE1 amplified (N=47)
CCNE1 not amplified (N=201)

1. Liu, J. et al., Cell, 2018, 173, 400-416; (figure generated using cBioPortal.org, see Cerami et al. Cancer Discovery. 2012 2; 401 and Gao et al. Sci. Signal. , 2013, 6, pl1). 2. Huang, X. et al., Frontiers in Oncology, 2020, 10, Article 583314, 1-16 3. Stronach, E., et al., Molecular Cancer Research, 2018, 1103-1111.

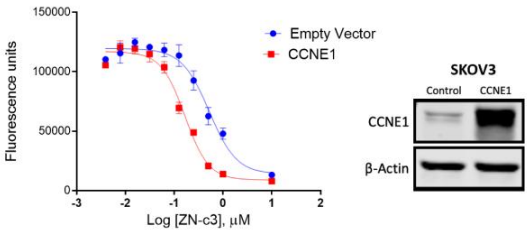
High Cyclin E1 Protein Expression is Associated with Increased Sensitivity to Azenosertib in Ovarian Cell Lines

Azenosertib Sensitivity and Cyclin E1 Protein Expression [1]



- Ovarian cell lines with high Cyclin E1 protein expression are more sensitive to azenosertib
- High Cyclin E1 protein expression sensitizes the low-sensitive cell line SKOV-3 to azenosertib

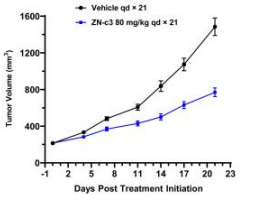
Azenosertib Sensitivity in SKOV3 High Expressing Cyclin E1 [2]

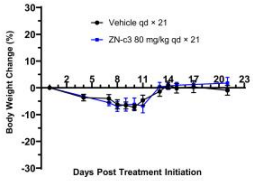


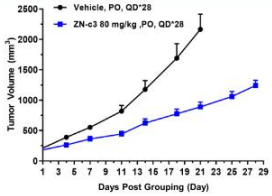
1. Azenosertib sensitivity is assessed by CellTiter Glo after 96 hours of culture. Data represent an average of at least 2 independent studies. Protein expression was assessed by Western Blot and is representative of 2 independent experiments.
2. Cyclin E1 was over-expressed in SKOV3 by lentivirus transduction followed by puromycin selection. Empty vector control was generated simultaneously.

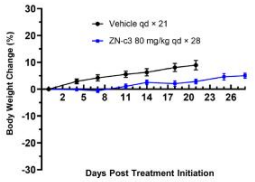
CCNE1 Gene Amplification is Associated with Poor Prognosis and Chemotherapy Response Across Tumor Types

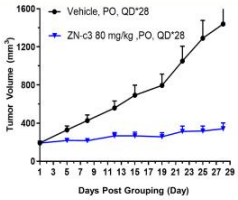
SKOV3 CCNE1 not amplified, TP53 mut	HCC1806 CDX CCNE1 amp (CN=7), TP53 mut	OVCAR3 CDX CCNE1 amp (CN=14)
$TGI_{(80\ mpk,\ Day\ 28)}$ = 51.5%	$TGI_{(80\ mpk,\ Day\ 28)}$ = 63.5%	$TGI_{(80\ mpk,\ Day\ 28)}$ = 88%

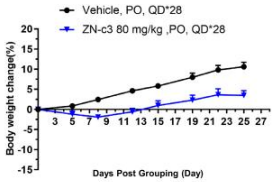




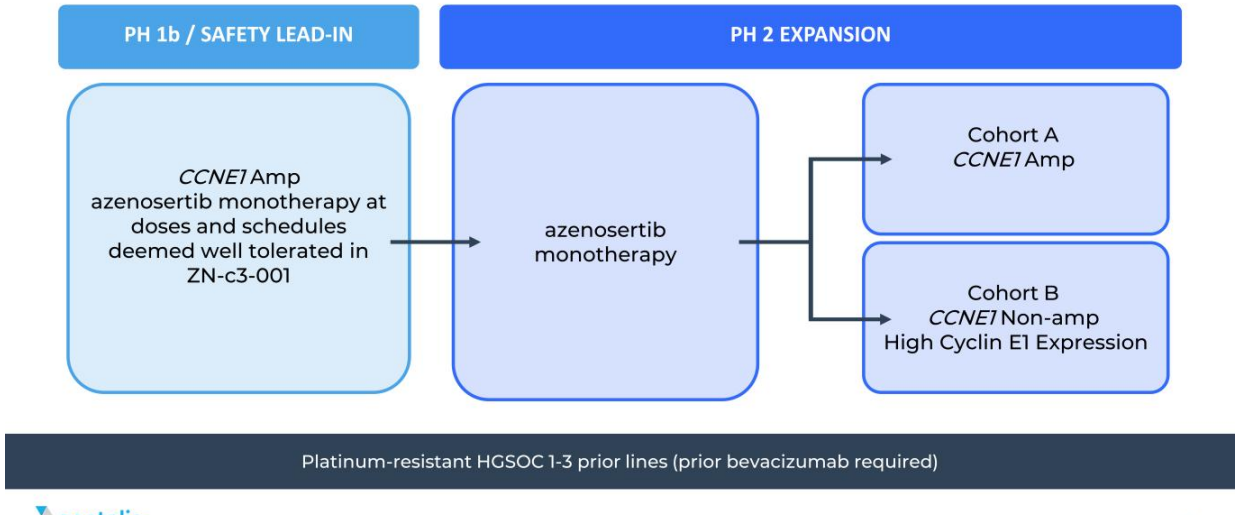








Moving Forward with Cyclin E1 patient enrichment in HGSOC: Revised ZN-c3-005 Study Design



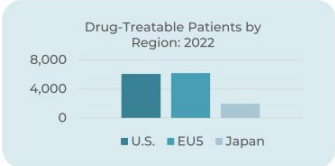
Platinum-Resistant/Refractory Ovarian Cancer Remains an Unmet Need

UNMET NEED

- Platinum-resistant and -refractory ovarian cancer represents a high unmet need
- It is associated with a poor prognosis and limited treatment options
  - ORR of 11.8% with standard of care [1] for platinum-resistant patients
- Improvement in efficacy with acceptable safety profile would make a meaningful difference for patients

PATIENT POPULATION

- In 2022, the total number of drug-treatable second line platinum-resistant ovarian cancer patients is estimated to be >14,000 in the United States, EU5 and Japan [2]



COMPETITIVE LANDSCAPE

- Current standard of care for second line platinum-resistant ovarian patients is single-agent chemotherapy ± bevacizumab [3]
- Ongoing pivotal trials focus on novel MOAs, including ADCs, and combinations with either PARPi or chemotherapy [3]
- Azenosertib is potentially a first-in-class treatment option that works synergistically with other anticancer therapies

Azenosertib's efficacy and tolerability profile are well-positioned for the platinum-resistant/refractory ovarian population

1. Pujade-Lauraine et al. J Clin Oncol 2014; 32:1302-1308; AURELIA study 2. Decision Resources Group; data on file. 3. CancerMPact Treatment Architecture Ovarian cancer July 2021; data on file.

ZN-c3-002: Summary of Clinical Activity

Summary of Clinical Activity (All Cohorts)							
Group	N	Evaluable* (n)	PR/uPR (n)	SD (n)	PD (n)	DCR (%)	ORR (%)
Azenosertib + Paclitaxel	9	8	5	3	–	100	62.5
Azenosertib + Carboplatin	17	11	5	4	2	81.8	45.5
Azenosertib + PLD	30	24	3	17	4	83.3	12.5
Total	56	43	13	24	6	86.0	30.2

Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1
* Patients with measurable disease and at least one post-baseline scan
Of evaluable subjects, ORR is percentage with PR/uPR; DCR = disease control rate, percentage of ORR + SD; uPR = unconfirmed partial response
Data cutoff January 28, 2022

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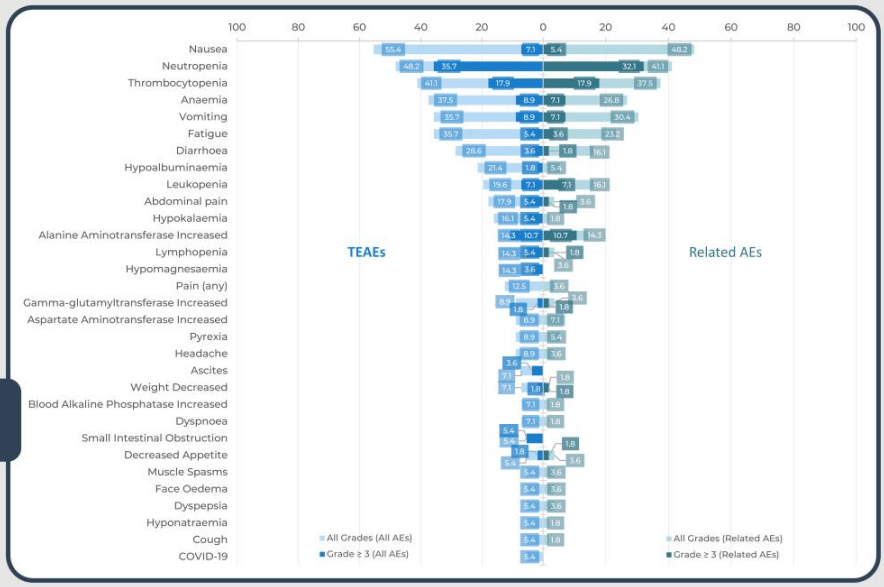
Pasic, et al. Poster Presented at American Association for Cancer Research Annual Meeting (2022): Abstract CT148: A phase 1b dose-escalation study of ZN-c3, a WEE1 inhibitor, in combination with chemotherapy (CT) in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer.

ZN-c3-002: TEAEs ≥5% for All Patients (N=56)

Adverse Events



January 28, 2022 data cutoff

Pasic, et al. Poster Presented at American Association for Cancer Research Annual Meeting (2022): Abstract CT148: A phase 1b dose-escalation study of ZN-c3, a WEE1 inhibitor, in combination with chemotherapy (CT) in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer

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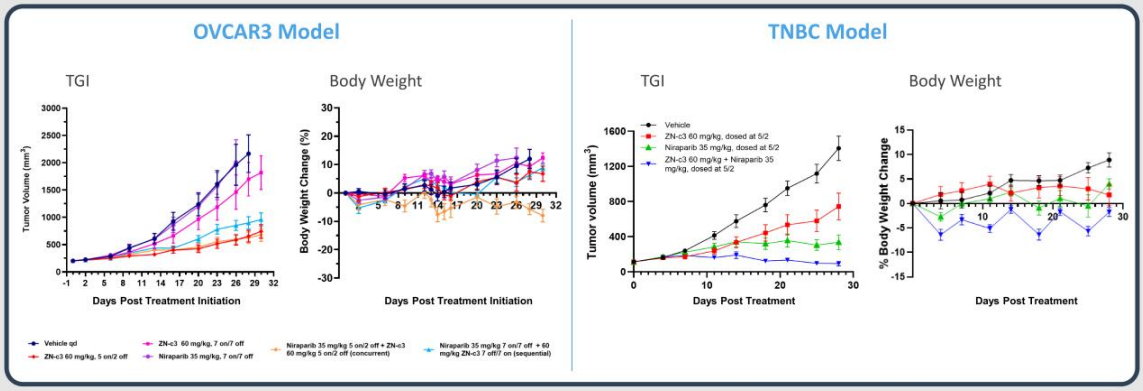
Azenosertib (ZN-c3)

PARP-Refractory Ovarian Cancer

Azenosertib + PARP Inhibitor Combinations are Active in both Ovarian CDX and TNBC PDX Models



- Combination of PARP and Wee1 inhibitors in TNBC results in synergistic cell killing in preclinical models with either BRCA1 mutations or high levels of cyclin E1 [1]
- The combination of azenosertib and niraparib shows efficacy in both ovarian and TNBC in vivo models
- Preclinically, sequential administration of PARP and azenosertib is efficacious but is better tolerated than concurrent based on body weight loss
- Wee1 inhibition may broaden the application range of PARP inhibitors in ovarian cancer and TNBC, consistent with results from the EFFORT [2] and STAR trials [3]

1. Chen X Cancers (Basel). 2021 Apr 1;13(7):1656 2. Westin, S.; J Clinical Oncology, 39, N15 (Supplement). 2021, 5505. 3. Yap T. Eur J Cancer. Vol 174 (Supplement 1), S7: 2022.

ZN-c3-006: Phase 1/2 Study of Azenosertib In Combination with Niraparib in Patients with PARP-Resistant Ovarian Cancer

KEY ELIGIBILITY

Key Eligibility:

- Recurrent high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer (serous, clear cell or endometrioid).
- Prior therapy: 1 – 5 prior lines for advanced/metastatic disease
- Disease progression while taking a PARPi as maintenance treatment (minimum of 3 months of treatment required).

Primary Endpoint

- Determine MTD/RP2D and optimal administration schedule

PHASE 1: SAFETY LEAD-IN

3+3 dose escalation design

azenosertib + niraparib administered concurrently

azenosertib + niraparib administered in an alternating schedule

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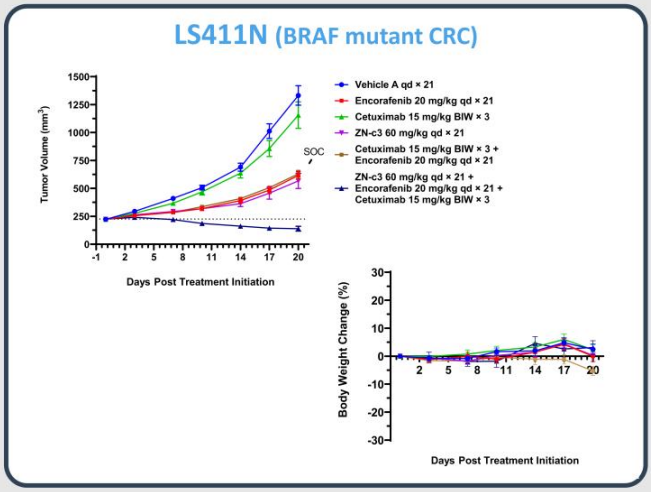
Azenosertib (ZN-c3)

BRAF Metastatic Colorectal Cancer

Preclinical Data Supports the Combination of Azenosertib with Encorafenib and Cetuximab: BEACON REGIMEN



- Oncogene-induced replication stress in mutationally driven cancers such as BRAF mutant colorectal cancer leads to DNA damage and genomic instability
- Oncogene activation disrupts replication regulation leading to slow and stalled replication forks and other defects and leads to DNA damage
- Dependency of cancers with replication stress on Wee1 signaling provides a mechanistic basis for synergy with EGFR/BRAF inhibition
- Addition of azenosertib to the BEACON regimen is well tolerated and provides superior efficacy in an *in vivo* model of BRAF mutant CRC

BRAF mCRC Study in Collaboration with Pfizer

Large Patient Population…

- Up to 21% of mCRC patients have BRAF mutations (~15,000 patients per year, U.S.) with over 90% V600E[1]
- Testing for BRAF mutations is routine, providing opportunity to identify patients

With Significant Unmet Need

- Median OS in BRAF mutant CRC patients <1 year, vs. BRAF WT >2 years[2]
- While targeted BRAF inhibition (e.g., vemurafenib) has been successful in melanoma with response rates >80%, this strategy has failed in CRC (OR ~5%) due to innate resistance[3]
- Encorafenib in combination with cetuximab (BEACON) was approved for BRAF V600E mCRC in April 2020 and is now the standard of care

Phase 1/2, Open-Label, Multi-center Study Of Azenosertib In Adults With Metastatic Colorectal Cancer Pfizer

PHASE 1: DOSE FINDING

- Patients with mCRC and documented BRAFV600E mutation
- Disease progression after 1 or 2 previous regimens for metastatic disease
- Prior therapy may include BRAF and/or EGFR directed therapy (e.g. may have progressed after BEACON regimen)

→ Encorafenib + Cetuximab + Escalating Dose Levels of azenosertib →

PHASE 2: DOSE EXPANSION

N: Up to 80 patients

- Phase 1 Endpoints: Safety, tolerability, MTD, RP2D
- Phase 2 Endpoint(s): ORR, DOR, DCR, PFS, TTP

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1 Sorbye H, Dragomir A, Sundström M, et al. High BRAF Mutation Frequency and Marked Survival Differences in Subgroups According to KRAS/BRAF Mutation Status and Tumor Tissue Availability in a Prospective Population-Based Metastatic Colorectal Cancer Cohort. PLoS One. 2015;10(6):e0131046. 2 Corcoran et al. Combined BRAF and MEK Inhibition With Dabrafenib and Trametinib in BRAF V600–Mutant Colorectal Cancer. J Clin Oncol (2015) Dec 1; 33(34): 4023-4031
3 Kopetz et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer. NEJM (2019) 381: 1632-1643 Zentalis maintains full economic ownership and control of azenosertib, apart from Greater China rights (Zentara).

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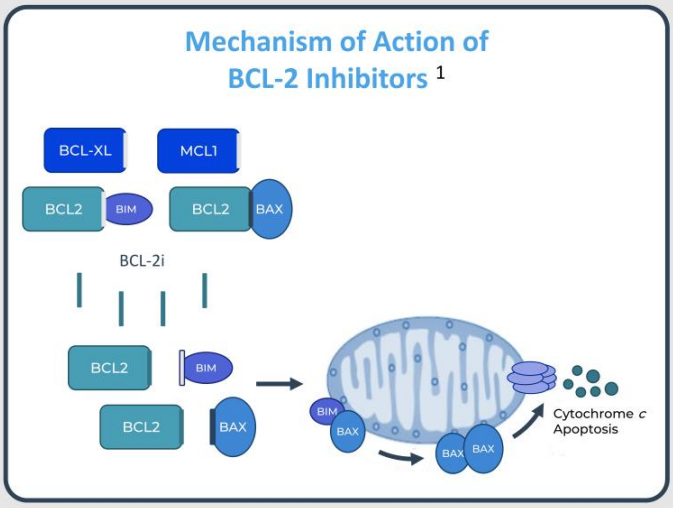
ZN-d5

BCL-2 Inhibitor

BCL-2: A Clinically Validated Oncology Target

- 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



1. Konopleva M et al. Cancer Discov. 2016 Oct;6(10):1106-1117 2. Konopleva M and Letai A. Blood. 2018 Sep 6;132(10):1007-1012 3. Bhola PD and Letai A. Mol Cell. 2016;61(5):695-704

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

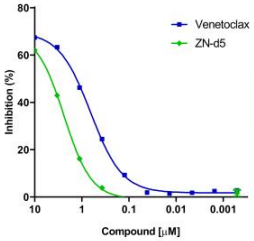
ZN-d5 has 10x Improved Selectivity for BCL-2 vs BCL-xL and Binds With Higher Affinity to BCL-2 Mutants than Venetoclax

Compound ID	Affinity (Kd, nM)			IC_{50} (nM) BCL-2 Type			
	BCL-2	BCL-xL	MCL-1	WT	G101V	F104L	D103Y
Venetoclax	0.41	28	>30000	1.3	7.3	8.4	18.3
ZN-d5	0.29	190	>30000	1.4	3.7	1.4	5.0

ZN-d5 Exhibits Potent *In Vitro* Activity Across Multiple Tumor Cell Lines

Compound ID	CTG IC_{50} (nM)							
	ALL	MCL		DLBCL		AML		
	RS4;11	Mino-1	Granta-519	DOHH-2	Toledo	HL-60	Molm-13	MV4-11
Venetoclax	2.9	1.1	161	43	191	26	18	3.8
ZN-d5	5.1	0.1	89	50	92	21	39	5.1

ZN-d5: Less Human Platelet Toxicity Compared to Venetoclax in an *In Vitro* Assay



Compound ID	CTG (24 h) IC_{50} (mM)
Venetoclax	0.6
ZN-d5	2.4

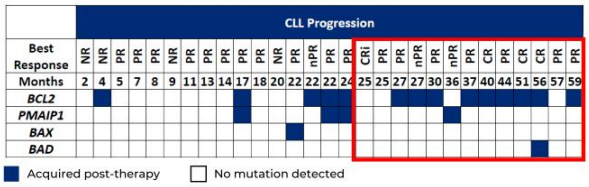
ZN-d5 shows activity in preclinical models of ALL, NHL and AML

Venetoclax data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound

ZN-d5: May Bind with Higher Affinity to BCL-2 Mutants than Venetoclax

Mutations in BCL-2 May be Driving Sub-Clonal Pockets of Resistance to Venetoclax in CLL

CLL Progression on Venetoclax



Acquired post-therapy ☐ No mutation detected

55% (16/29) patients acquired mutations in BCL-2 family members

- 41% (14/29) with mutations in BCL-2
- 21% (6/29) with mutations in PMAIP1 (NOXA), BAX or BAD

Majority (9/14) were detected with BCL-2 mutations after 24 months on venetoclax

- 55% (16/29) of patients with CLL progression

Compound ID	IC_{50} (nM) BCL-2 Type			
	WT	G101V	F104L	D103Y
Venetoclax	1.3	7.3	8.4	18.3
ZN-d5	1.4	3.7	1.4	5.0

Note: Competition assay for displacing BAK peptide bound to BCL-2

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Source: Chyla, B. ASH Presentation (2019)
Venetoclax data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound.

ZN-d5 Clinical Development Plan

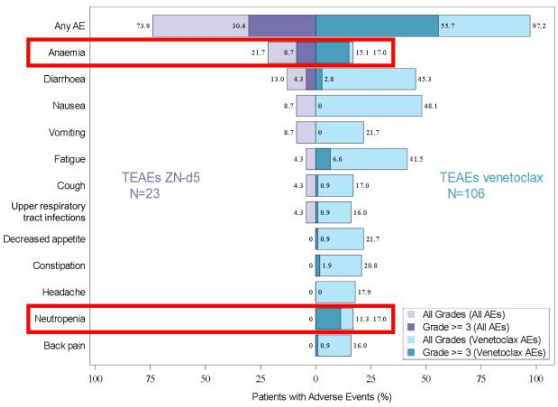
- Improved *in vitro* potency and has 10x improved selectivity for BCL-2 vs BCL-xL compared to venetoclax
- Observed to bind with higher affinity to BCL-2 mutants than venetoclax in *in vitro* assay
  - Mutations in BCL-2 may be driving sub-clonal pockets of resistance to venetoclax
- Preclinical combination data of ZN-d5 + azenosertib (ZN-c3) utilizing novel biology showed synergistic and additive activity across multiple indications in both solid and liquid tumors, often at subtherapeutic doses

Ongoing and Planned Clinical Programs		
Indication	Treatment	Trial Updates
Non-Hodgkin's Lymphoma	ZN-d5	Continues to enroll
AL Amyloidosis	ZN-d5	Continues to enroll
AML	ZN-d5 & azenosertib	Trial initiated in 4Q 2022

ZN-d5: Favorable Early Comparison to Venetoclax in NHL

- ZN-d5 100-1200mg, empty stomach
- Venetoclax 200-1200mg with food
- Early toxicity profile in NHL favorable vs. published venetoclax data [1]
  - Fewer AEs of any Grade, Grade ≥3
  - No TLS observed
  - Venetoclax AEs not dose-dependent

Adverse Event	Any Grade			
	All Doses (N = 106)	≤ 400 mg (n = 22)	600 to 900 mg (n = 33)	1,200 mg (n = 51)
Emergent*				
Any event	103 (97)	21 (96)	33 (100)	49 (96)
Nausea	51 (48)	9 (41)	15 (45)	27 (53)
Diarrhea	48 (45)	7 (32)	14 (42)	27 (53)
Fatigue	44 (42)	10 (45)	9 (27)	25 (49)
Decreased appetite	23 (22)	4 (18)	4 (12)	15 (29)
Vomiting	23 (22)	5 (23)	6 (18)	12 (24)
Constipation	22 (21)	6 (27)	7 (21)	9 (18)
Headache	19 (18)	2 (9)	7 (21)	10 (20)
Anemia	18 (17)	7 (32)	6 (18)	5 (10)
Cough	18 (17)	7 (32)	6 (18)	5 (10)
Neutropenia	18 (17)	4 (18)	8 (24)	6 (12)
Back pain	17 (16)	3 (14)	6 (18)	8 (16)
Upper RTI	17 (16)	5 (23)	8 (24)	4 (8)



1. Davids et al, J Clin Oncol 2017;35:826-833; emergent AEs reported in ≥15% of subjects. ZN-d5 results as of 03 Nov 2021 data cutoff. Not a head-to-head study

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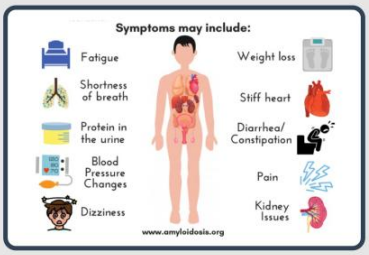
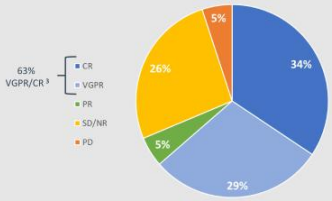
ZN-d5 in AL (Primary) Amyloidosis





- AL Amyloidosis: Deposition of immunoglobulin light chains
  - Clonal plasma cell population secretes misfolding light chain
  - Progressive systemic amyloid accumulation causes widespread organ damage
  - High morbidity and mortality
- Orphan disease
  - Estimated worldwide prevalence is 75,000 [1]
  - About 4k new cases/year in the US [2]
- Not a cancer, but treated like one
  - Agents active in multiple myeloma used in first-line and relapsed/refractory settings
  - Daratumumab only approved therapy, for first-line use with CyBorD
- Relapsed/refractory setting is a high unmet medical need

AL Amyloidosis study is currently enrolling patients

1. Zhang et al. Clin Lymphoma Myeloma Leuk. 2019;19(suppl 10):e339 2. Kyle et al, Mayo Clin Proc. 2019;94:465-471 3. Premkumar et al, Blood Cancer J 2021;11:10; hematologic response rate in 38 evaluable patients.

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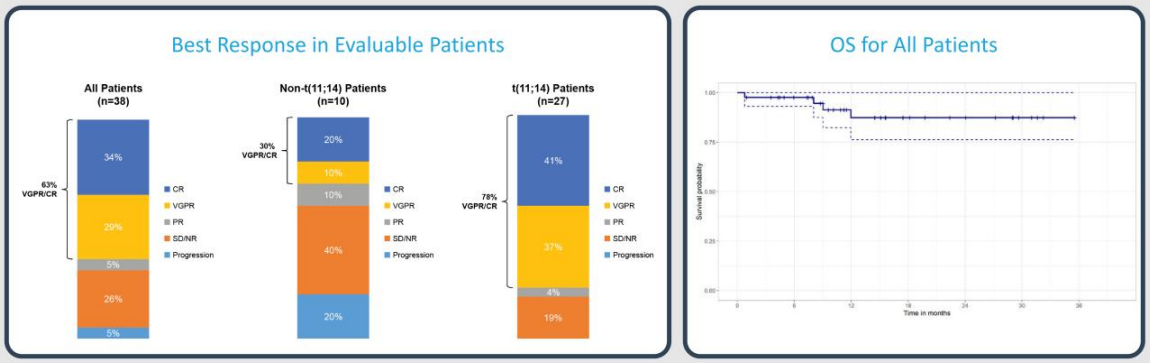
BCL-2 Inhibition has Shown Robust Clinical Activity in AL Amyloidosis

- Patients with the t(11;14) translocation have a worse prognosis than the general AL amyloidosis population [1]
- BCL-2 inhibition showed an improved response rate in the t(11;14) cohort with a trend towards better survival



1. Premkumar et al, Blood Cancer J 2021;11:10; hematologic response rate in 38 evaluable patients.

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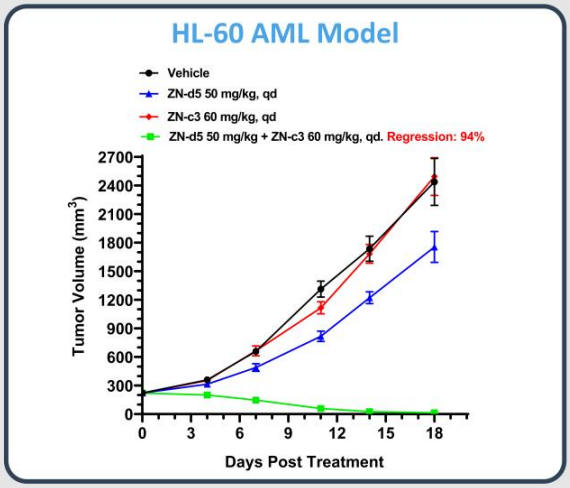
Potential Combination of Azenosertib (ZN-c3) and ZN-d5

The Combination of BCL-2 and Wee1 Inhibitors Results in Synergy in Several Tumor Models Including AML

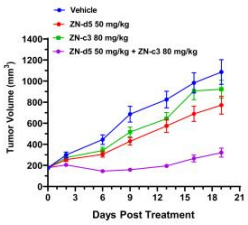


- ZN-d5 and azenosertib combination represents a novel therapeutic approach
- Significant enhancement of activity than single agent in several indications, including AML
- Combination regimen was well-tolerated in mice
- Zentalis is the only company known to have both inhibitors in clinical development

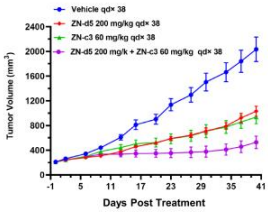
Presented at AACR 2022 by Izadi, H.; et. al. Cancer Res (2022) 82 (12_supplement): 2591.

Antitumor Activity in Solid Tumor Models with the ZN-d5 + Azenosertib Combination Represents Market Expansion Opportunities

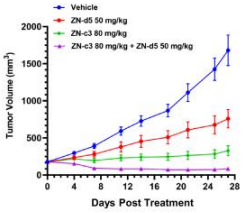
SCLC Model (DMS53)[1]



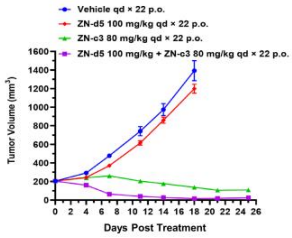
TNBC Model (MDA-MB-436)



NSCLC Model (H146)



Neuroendocrine Prostate Model (H660)



1. Izadi, H. et. al. Cancer Res (2022) 82 (12_Supplement): 2605.

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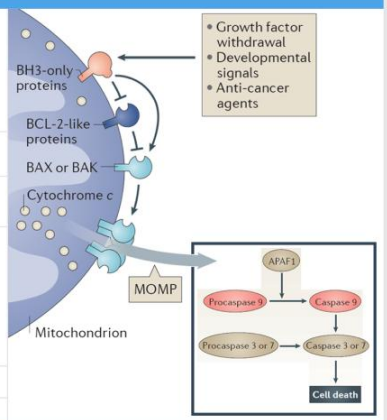
BCL-xL Protein Degrader

BCL-xL Degrader Background and Rationale

Background, Clinical Relevance, and Approach	
Therapeutic Hypothesis	• BCL-xL is a member of the anti-apoptotic BCL-2 proteins and is clinically validated. [1,2] • Expression of BCL-xL contributes to therapeutic resistance mechanisms. [3,4,5] • Degrading BCL-xL will induce cell death and overcome resistance mechanisms in multiple cancer types, while reducing the possibility of on-target thrombocytopenia.
Patient Selection	• Heme malignancies. • Solid tumors.
Internal Combination Opportunities	• Azenosertib (ZN-c3; Wee1 inhibitor) and ZN-d5 (BCL-2 inhibitor)
Therapeutic Window	• BCL-xL is required for platelet viability and BCL-xL inhibitors (e.g. navitoclax) are dose limited in the clinic due to on-target thrombocytopenia. [6] • A degradation approach with a E3 ligase low expressed in platelets could help mitigate thrombocytopenia. [7,8] • Efficacy may be achieved at lower doses and frequencies due to the catalytic MOA of degraders, further reducing the chance of thrombocytopenia and increasing TI.
Chemical Modality	• Heterobifunctional degrader linking BH3-binding moiety.
Competitive Landscape	• Multiple inhibitors and one degrader in the clinic (Ph1/2).

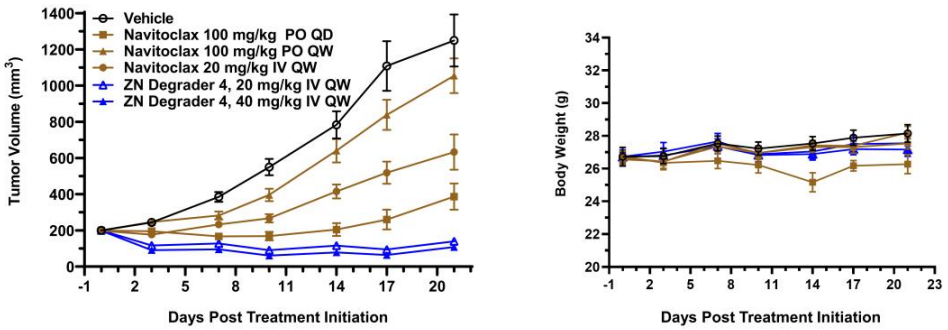


Declared development candidate and initiated IND enabling activities

1. Bhola PD and Letai A. Mol Cell. 2016;61(5):695-704 2. Konopleva M and Letai A. Blood. 2018 Sep 6;132(10):1007-1012 3. Rahman SFA et al., Future Oncology, 2020, 16(28) 4. Yue et al., Cnacer Cell Int., 2020, 20(254)
5. cbioportal.org 6. Wilson WY et al., Lancet Oncol., 2010; 11(12):1149-1159 7. Khan et al. Nature Med 12, 1938-1947 (2019) 8. He et al. Nature Comm 11, (2020)

Figure from: Delbridge, A. R. D., et. al. Nat Rev Cancer 16, 99-109 (2016)

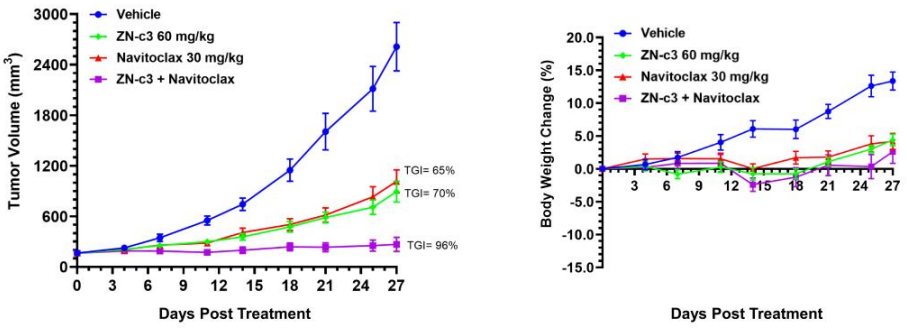
BCL-xL IV Degrader is More Efficacious than BCL-xL Inhibitor (Navitoclax) in MOLT4 (T-ALL) Models



- BCL-xL degrader demonstrates excellent efficacy in the MOLT4 tumor model (T-ALL) and is well-tolerated at efficacious doses
- BCL-xL degrader is more efficacious than Navitoclax

Navitoclax data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound

Azenosertib Combined with a Low Dose of Navitoclax (BCL-xL Inhibitor) Results in Synergistic Anti-tumor Activity in the T-ALL model MOLT-4[1]



- The MOA of the combination of the BCL-xL therapeutic and azenosertib represents a novel approach which results in synergistic anti-tumor activity.
- Development of the BCL-xL degrader offers an opportunity to combine with other anti-cancer agents, such as azenosertib.

1. Izadi, H.; et. al. Cancer Res (2022) 82 (12_Supplement): 2605.
TGI: Tumor Growth Inhibition ALL: Acute Lymphoblastic Leukemia MOLT-4 model is BCL-xL dependent, but is not on BCL-2
Navitoclax data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound

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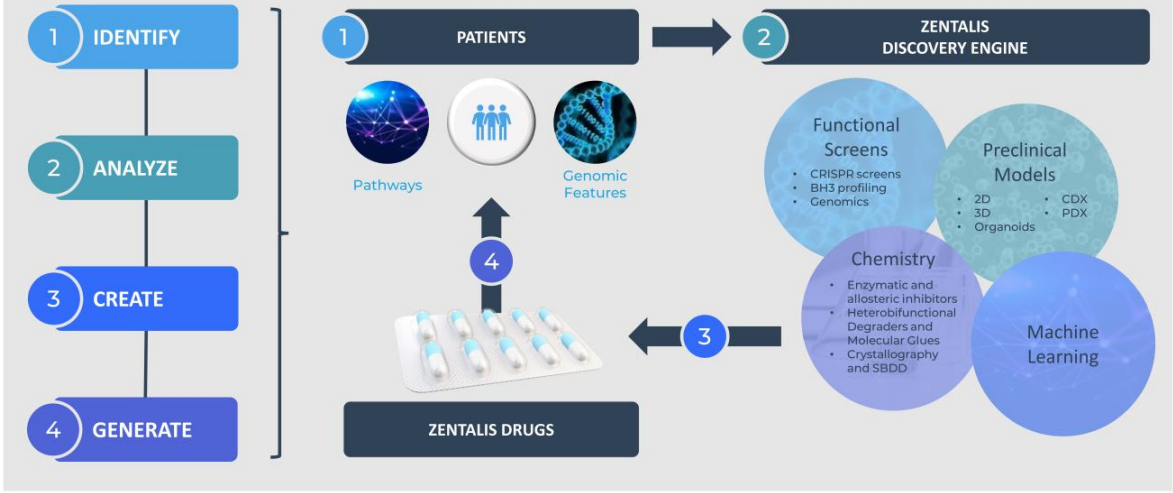
Conclusions

Utilizing the Highly Efficient Integrated Discovery Engine to Generate Potentially Best-In-Class Drugs



2023 Key Milestones

Azenosertib (ZN-c3) Wee1 Inhibitor

✓ 1Q 2023	Initiate enrollment in the BRAF mutant colorectal cancer BEACON regimen combination clinical trial in collaboration with Pfizer
✓ 1H 2023	Provide preclinical rationale for Cyclin E1 enrichment strategy at a scientific conference
1H 2023	Declare monotherapy RP2D and provide update on dose optimization activities, program timelines and potential paths to registration
1H 2023 (updated)	Results from Phase 1b ovarian chemotherapy combination trial, including clinical translational data on Cyclin E1 amplification / overexpression

ZN-d5 BCL-2 Inhibitor

2H 2023	Provide interim clinical data and declare RP2D for Phase 1/2 monotherapy trial in amyloidosis
2H 2023	Provide preliminary data from clinical trial of azenosertib + ZN-d5 in relapsed / refractory acute myeloid leukemia

Integrated Discovery Engine

2023	Continue to advance the BCL-xL protein degrader program through IND enabling studies
2023	Advance ongoing research on protein degrader programs of undisclosed targets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