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): November 9, 2022

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 1710
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 2.02 Results of Operations and Financial Condition.

On November 9, 2022, Zentalis Pharmaceuticals, Inc. (the "Company") announced its financial results for the quarter ended September 30, 2022 and commented on certain business updates. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Item 7.01 Regulation FD Disclosure.

Beginning on November 9, 2022, spokespersons of the Company plan to present the information in the Corporate Presentation attached hereto as Exhibit 99.2 at conferences and in meetings with investors and analysts.

The information contained in Items 2.02 and 7.01 of this Current Report on Form 8-K (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.

By providing the information in Item 7.01 of this Current Report on Form 8-K, including Exhibit 99.2 hereto, the Company is not making an admission as to the materiality of any information herein. The information contained in this Current Report on Form 8-K is intended to be considered in the context of more complete information included in the Company's filings with the U.S. Securities and Exchange Commission (the "SEC") and other public announcements that the Company has made and may make from time to time by press release or otherwise. The Company undertakes no duty or obligation to update or revise the information contained in this Current Report on Form 8-K, although it may do so from time to time as its management believes is appropriate. Any such updating may be made through the filing of other reports or documents with the SEC, through press releases or through other public disclosures.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

The following exhibits relating to Items 2.02 and 7.01 shall be deemed to be furnished, and not filed:

Exhibit No.	Description
99.1	Press Release issued on November 9, 2022
99.2	Corporate Presentation, dated November 2022
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: November 9, 2022

By: /s/ Kimberly Blackwell, M.D.
Kimberly Blackwell, M.D.
Chief Executive Officer

Zentalis Pharmaceuticals Reports Third Quarter 2022 Financial Results and Operational Updates

Six sponsored studies with potentially first-in-class Wee1 inhibitor, ZN-c3, ongoing and continuing dose optimization work, as drug continues to show improved tolerability in initial safety data from monotherapy Phase 2 USC trial announced today

Identified Cyclin E driven high-grade serous ovarian cancer patients as initial expansion population for ZN-c3 biomarker monotherapy trial

Announced first ZN-c3 clinical development collaboration with Pfizer BRAF-mutant mCRC;
Expanded ZN-c3 clinical development collaboration with GSK in PARP resistant ovarian cancer

Declared BCL-xL protein degrader candidate and initiated IND-enabling studies; Molecule has broad potential across multiple tumor types and in combination

Strengthened Board and management team with appointments of Chief Medical Officer, Chief Scientific Officer and Chief Translational Officer

$422 million cash balance as of September 30, 2022, with projected cash runway into 2025

NEW YORK and SAN DIEGO—November 9, 2022 — 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 announced financial results for the third quarter ended September 30, 2022 and highlighted recent corporate accomplishments.

"During the third quarter, we made tremendous progress advancing our clinical strategy and corporate capabilities. We have established a three-pronged development plan for ZN-c3, our potentially first-in-class Wee1 inhibitor investigation as a monotherapy, in combination with chemotherapy and in combination with targeted therapies," said Kimberly Blackwell, MD, Chief Executive Officer of Zentalis. "Building on ZN-c3's favorable safety profile in the monotherapy setting across tumor types, we are pleased to announce Cyclin E gene amplification and protein overexpression as our biomarker strategy in high grade serous ovarian cancer. This biomarker defined trial in ovarian cancer will allow us to demonstrate potential efficacy in an enriched patient population that has shown evidence of clinical sensitivity to Wee1 inhibition. This trial also has the potential to show initial proof of concept for Wee1 inhibition in Cyclin E driven cancers, which have higher levels of chemotherapy and targeted therapy resistance. On the combination front, there is strong data demonstrating Wee1 inhibition's synergy with DNA-damaging therapies, such as PARP inhibitors, and with targeted agents in mutationally driven cancers. There is significant interest in these approaches, and we currently have collaborations with Pfizer, GSK and the Dana-Farber Cancer Institute to explore these combinations in the clinic."

Dr. Blackwell continued, "Our development of ZN-c3 includes ongoing dose optimization activities across the clinical program. Although we have demonstrated a favorable safety profile and monotherapy efficacy when ZN-c3 was given on a continuous daily dosing schedule, data show that higher doses delivered on an intermittent schedule have the potential to lead to higher pharmacokinetic exposures and a more favorable therapeutic index. We believe our dose optimization work will allow us to benefit the broadest range of cancer patients and maximize value for all of our stakeholders. With our strong cash position and strengthened management team, we believe we are well-positioned to execute on our clinical development plans and further our mission to improve the lives of cancer patients."

Wee1 Inhibitor (ZN-c3)Program Highlights

- **Monotherapy in USC safety and enrollment update**: As of a data cutoff on September 14, 2022, a total of 43 patients were enrolled and dosed in the Phase 2 monotherapy uterine serous carcinoma (USC) trial. ZN-c3 was well tolerated and the safety profile was similar or improved relative to previously disclosed data, exhibiting a better hematological and gastrointestinal tolerability profile. The U.S. Food and Drug Administration has granted Fast Track designation to ZN-c3 in this setting.

- **Cyclin E biomarker strategy in high-grade serous ovarian cancer**: The Company announced that Cyclin E overexpression and/or amplification in high-grade serous ovarian cancer will become the focus of its ongoing Phase 1/2 clinical study examining biomarker-driven enrichment strategies for ZN-c3. Cyclin E overexpression acts at the G1-S checkpoint by driving premature entry into S-phase resulting in replicative stress and significantly increases sensitivity to ZN-c3. The Company has generated preclinical data showing that Cyclin E overexpression sensitizes cancer cells to the anti-tumor effects of ZN-c3 as well as preliminary retrospective clinical data that Cyclin E protein levels may be associated with clinical benefit from ZN-c3. The Company plans to present the preclinical data in the first half of 2023. The two new cohorts of patients will be given monotherapy, which will potentially generate meaningful data sets in patients with Cyclin E gene amplification and patients with Cyclin E protein overexpression independent of gene amplification.

- **Dose optimization**: The Company highlighted that it continues to optimize dosing across the ZN-c3 clinical portfolio to maximize exposure, improve normal tissue tolerability and enable maximum probability of success. The Company anticipates that the Phase 2 USC trial dose will be modified based on these ongoing dose optimization studies and that, as a result, the timeline of the USC study will be extended. The Company anticipates providing an update on ZN-c3 dosing in the first half of 2023, including expected program timelines and potential paths to registration.

- **Pfizer collaboration in mCRC**: Zentalis and Pfizer are collaborating on a Phase 1/2 dose escalation study of ZN-c3 in combination with encorafenib and cetuximab (BEACON regimen) in BRAF V600E-mutated metastatic colorectal cancer (mCRC) patients. In preclinical studies, Wee1 inhibition has shown synergy with many targeted agents in mutationally driven cancers and the addition of ZN-c3 to the BEACON regimen enhanced anti-tumor activity in a cell-line-derived xenograft model. Additional information on this clinical development collaboration is available here.

- **GSK collaboration in ovarian cancer:** Zentalis and GSK are expanding their ongoing collaboration looking at the clinical synergy of ZN-c3 and niraparib in PARP resistant ovarian cancer. The Phase 1/2 dose escalation study, currently enrolling with concurrent dosing of the two drugs, will be expanded to include a cohort that will be given ZN-c3 and niraparib on a dose escalating, alternating schedule of one week of ZN-c3 followed by one week of niraparib.

- **Chemotherapy combination in platinum-resistant ovarian cancer**: The Company continues to enroll its dose escalation trial of standard chemotherapy (paclitaxel, gemcitabine, and carboplatin) in platinum-resistant ovarian cancer.

- **Chemotherapy combination in osteosarcoma:** The Company will be presenting initial data from its Phase 1/2 combination trial of ZN-c3 and chemotherapy in osteosarcoma in a poster session at the upcoming Connective Tissue Oncology Society (CTOS) 2022 Annual Meeting, being held November 16-19 in Vancouver. Details for the CTOS poster presentation are as follows:
    - **Title:** Preliminary Data from a Phase 1 Dose Escalation Study of ZN-c3 Plus Gemcitabine in Relapsed/Refractory Osteosarcoma (NCT04833582)
    - **Session:** Medical & Pediatric Oncology and Trials
    - **Date/Time:** November 17, 2022 from 5:00pm to 7:00pm ET
    - **Presenter:** Viswatej Avutu, MD, Assistant Attending Physician at Memorial Sloan Kettering Cancer Center

- **Dana-Farber combination study in platinum-resistant pancreatic cancer**: Zentalis announced an investigator-initiated trial with Dana-Farber Cancer Institute, funded by Stand Up To Cancer and the Lustgarten Foundation, to explore the combination of ZN-c3 with gemcitabine in platinum-resistant advanced pancreatic adenocarcinoma. James Cleary, MD, PhD, Director, Clinical Research, Division of Gastrointestinal Oncology at the Dana-Farber Cancer Institute and Brandon Huffman, MD, Adult Medical Oncology Fellow at the Dana-Farber Cancer Institute, will be running this trial. "We are pleased to announce this important trial which builds on the growing body of clinical evidence supporting the use of ZN-c3 across a range of tumor types," said Dr. Cleary. "Pancreatic cancer continues to be area of high unmet patient need, and we look forward to understanding the potential role of ZN-c3 in helping these patients."

BCL-2 Inhibitor (ZN-d5) Update

- **Monotherapy dose optimization continues in NHL and amyloidosis**: Dosing with food is ongoing in patients in non-Hodgkin lymphoma (NHL) and amyloidosis, and the combination study of ZN-d5 and ZN-c3 in acute myeloid leukemia (AML) is scheduled to initiate in the fourth quarter of 2022.

BCL-xL Degrader Update

- **Declared candidate and initiated IND-enabling studies**: BCL-xL degrader candidate demonstrates potent anti-cancer activity in several preclinical models and has the potential to have platelet sparing benefits over clinical-stage BCL-xL targeted inhibitors.

Corporate Highlights

- In September, Zentalis appointed Jan Skvarka, PhD, MBA, to its Board of Directors. Dr. Skvarka is an accomplished biopharmaceutical executive bringing over three decades of extensive operational, strategic and financial expertise to Zentalis. Dr. Skvarka was formerly Chief Executive Officer of Trillium Therapeutics, Inc., which was acquired by Pfizer under his leadership.
- In October, the Company promoted co-founder Kevin Bunker, PhD, to Chief Scientific Officer. In this new role, Dr. Bunker will focus on leading Research and Development, advancing the preclinical pipeline with the Company's Integrated Discovery Engine.
- In October, Zentalis appointed Carrie Brownstein, MD, as Chief Medical Officer. Dr. Brownstein, a leading oncologist and hematologist, joins Zentalis with over two decades of medical and biopharmaceutical experience, successfully executing clinical program strategies across all phases of product development.

- In October, the Company appointed Mark Lackner, PhD, as Chief Translational Officer, Head of Biomarker Strategy. Dr. Lackner, a recognized and respected cancer biologist, joins Zentalis with over two decades of oncology-focused drug development expertise, including significant experience in biomarker discovery and clinical biomarker strategies.

Third Quarter 2022 Financial Results

- **Cash and Marketable Securities Position**: As of September 30, 2022, Zentalis had cash, cash equivalents and marketable securities of $421.7 million. The Company believes that its existing cash, cash equivalents and marketable securities as of September 30, 2022 will be sufficient to fund its operating expenses and capital expenditure requirements into the first quarter of 2025.
- **Research and Development Expenses:** Research and development, or R&D, expenses for the three months ended September 30, 2022 were $42.2 million, compared to $54.0 million for the three months ended September 30, 2021. The decrease of $11.8 million was primarily due to non-recurring R&D impairments and licensing milestones of $8.8 million and $5.0 million, respectively, recorded during the three months ended September 30, 2021. Other decreases in R&D expenses included $4.6 million in decreased manufacturing and collaborative expenses and $0.3 million of additional reimbursement from Zentera under our cost sharing arrangement. These decreases were offset by increases of $3.4 million, $3.1 million and $0.4 million of clinical trial related costs, personnel and consulting costs and overhead allocations, respectively.
- **General and Administrative Expenses**: General and administrative expenses for the three months ended September 30, 2022 were $12.0 million, compared to $8.9 million during the three months ended September 30, 2021. This increase of $3.1 million was primarily attributable to an increase in non-cash stock based compensation expense of $1.8 million and $0.3 million related to other compensation expense. Increases of $1.9 million, $0.6 million and $0.5 million were seen in rent and depreciation expense, external consulting expense and legal expense, respectively. These amounts were partially offset by a decrease in permits and fees and allocation of overhead expenditures to R&D of $1.6 million and $0.4 million, respectively.

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. The Company is developing a focused pipeline of potentially best-in-class oncology candidates, all internally discovered, which include ZN-c3, a potentially first-in-class Wee1 inhibitor for advanced solid and liquid 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 has licensed ZN-c3 and ZN-d5 to its joint venture, Zentera Therapeutics, Ltd. to develop and commercialize these candidates in Greater China, but otherwise retains full economic ownership and control of ZN-c3 and ZN-d5. 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 relating to the potential for a product candidate to be first-in-class and/or best-in-class; the potential benefits of our dose optimization work, including the potential benefit of higher doses delivered on an intermittent schedule; projected cash runway; potential benefits of our product candidates; potential benefits of the Cyclin E biomarker defined trial; our belief we are well-position to execute on our clinical development plans and further our mission to improve the lives of cancer patients; plans to expand our clinical trials, including our Phase 1/2 dose escalation study in ovarian cancer in collaboration with GSK; plans to present preclinical data relating to Cyclin E and the timing thereof; potentially modifying the Phase 2 USC trial dose and the impact of that modification on the timeline of the Phase 2 USC trial; the timing of providing an update on ZN-c3 dosing and the content of that update; the timing of initiation of our clinical trials; and the potential of ZN-c3 to help pancreatic cancer patients. The terms "believe," "look forward," "may," "opportunity," "optimize," "plans," "potential," "scheduled," "will" 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 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; the COVID-19 pandemic has adversely impacted and may continue to adversely impact our business, including our preclinical studies and clinical trials; 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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Zentalis Pharmaceuticals, Inc.
Condensed Consolidated Statements of Operations
(Unaudited)
(In thousands, except per share amounts)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2022	2021	2022	2021
Operating Expenses				
Research and development	$ 42,181	$ 53,998	$ 132,118	$ 137,162
General and administrative	12,012	8,872	43,415	31,187
Total operating expenses	54,193	62,870	175,533	168,349
Operating loss	(54,193)	(62,870)	(175,533)	(168,349)
Other Income (Expense)				
Investment and other income, net	1,905	99	2,755	313
Gain on deconsolidation of Zentera	—	51,582	—	51,582
Net loss before income taxes	(52,288)	(11,189)	(172,778)	(116,454)
Income tax expense (benefit)	(159)	(697)	(109)	(456)
Loss on equity method investment	2,371	—	9,460	—
Net loss	(54,500)	(10,492)	(182,129)	(115,998)
Net loss attributable to noncontrolling interests	(99)	(6,301)	(294)	(7,332)
Net loss attributable to Zentalis	$ (54,401)	$ (4,191)	$ (181,835)	$ (108,666)
Net loss per common share outstanding, basic and diluted	$ (0.96)	$ (0.09)	$ (3.56)	$ (2.59)
Common shares used in computing net loss per share, basic and diluted	56,807	44,609	51,098	41,918

Zentalis Pharmaceuticals, Inc.
Selected Condensed Consolidated Balance Sheet Data
(Unaudited)
(In thousands)

	As of June 30, 2022	As of December 31, 2021
Cash, cash equivalents and marketable securities	$ 421,726	$ 339,887
Working capital [1]	379,829	306,826
Total assets	529,193	454,507
Total liabilities	100,455	90,025
Total Zentalis equity	$ 428,738	$ 364,482

[1] The Company defines working capital as current assets less current liabilities.

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CORPORATE PRESENTATION

November 2022

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 ZN-c3 to address large populations with significant unmet need; our development approach for our product candidates, including ZN-c3; plans for and potential benefits of dose optimization, and the anticipated timing of updates on dosing optimization; 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 strengthen our clinical development plans, including for ZN-c3; timing of discontinuation activities for ZN-c5 and ZN-c4; 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; our anticipated milestones; and the potential of our collaborations, as well as statements that include the words "anticipate," "design," "estimate," "expect," "may," "plan," "opportunity," "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: the outbreak of the novel coronavirus disease, COVID-19, has adversely impacted and may continue to adversely impact our business, including our preclinical studies and clinical trials; 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; 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 (ZN-c3) potentially first- and best-in-class
  - Potential accelerated approval paths for monotherapy in multiple biomarker enriched populations
  - Enriched patient populations including Uterine Serous Carcinoma (USC), Cyclin E driven and post-PARP progression
  - Investigating highly synergistic concurrent combinations, including BRAF/MEK inhibitors in BRAF mutant mCRC and PARP inhibitors in high grade serous 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, including with ZN-c3
- BCL-xL heterobifunctional degrader for liquid and solid tumors (preclinical)
- Additional discovery programs against validated cancer targets
- Integrated Discovery Engine: 4 FDA-cleared INDs within 5 years

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Q3 2022 Highlights

Broad progress across ZN-3 program as we optimize dosing across exposure, efficacy and tolerability in both monotherapy and combination settings	Multiple dose optimization studies ongoing; USC trial enrolled 43 patients as of September 2022; consistently demonstrating favorable tolerability; osteosarcoma safety and efficacy update to be presented at CTOS Conference
Cyclin E overexpression / amplification as our biomarker strategy for enriching patient populations for ZN-c3	Potential to address large populations with significant unmet need with accelerated monotherapy path to registration
Expanded relationship with Pfizer, building on equity investment and SAB appointment earlier this year	Strategic collaboration now includes ZN-c3 combination study in BRAF mutant colorectal cancer
ZN-d5 efforts focused on amyloidosis monotherapy and combination with ZN-c3 study	Enrollment in dose optimization, first-in-class indication for amyloidosis and ZN-c3 combination in AML studies
Advanced preclinical pipeline	Declared development candidate for BCL-xL protein degrader; IND enabling studies initiated
Cash position of $422 million	Operating runway into 2025 enabling achievement of multiple data readouts and catalysts

Advancing Focused Pipeline with Multiple Clinical Opportunities

COMPOUND	INDICATION	DEVELOPMENT APPROACH	PRECLINICAL	EARLY CLINICAL DEVELOPMENT	LATE CLINICAL DEVELOPMENT	STATUS / EXPECTED MILESTONES
ZN-c3 Wee1 Inhibitor	Uterine Serous Carcinoma	Monotherapy				FDA Fast Track Designation
	Solid Tumors	Monotherapy				Update on ZN-c3 dosing 1H 2023
	Cyclin E Driven Ovarian Cancer	Monotherapy				Enrolling, preclinical update to come in 1H 2023
	PARP Resistant Ovarian Cancer	Monotherapy alternating with niraparib or concurrent with niraparib				Enrolling, opened alternating cohort in 4Q 2022
	Ovarian Cancer	+ Multiple Chemotherapy Backbones				Enrolling; Phase 1 dose escalation results in 2023
	Osteosarcoma	+ gemcitabine				Presenting data CTOS Conf Nov 2022
	BRAF Mutant Colorectal Cancer	+ encorafenib and cetuximab				Plan patient initiation Q1 2023
	Pancreatic Cancer	+ gemcitabine				Dana Farber Cancer Institute, funded by SU2C/Lustgarten
ZN-d5 BCL-2 Inhibitor	AL Amyloidosis	Monotherapy				Continues to enroll
	NHL	Monotherapy				Continues to enroll
	AML	+ ZN-c3				Anticipate trial initiation 4Q 2022
BCL-xL Degrader	Solid Tumors and Heme Malignancies					Declared development candidate; IND enabling activities initiated

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New/Revised Disclosure

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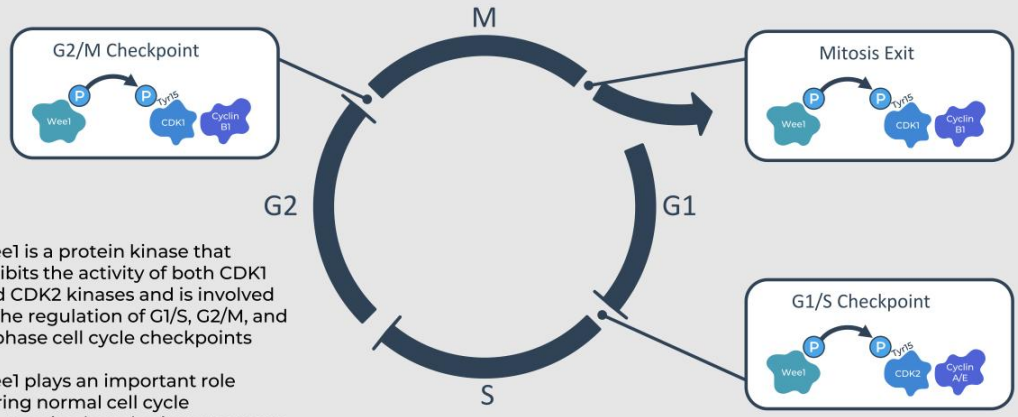
ZN-c3

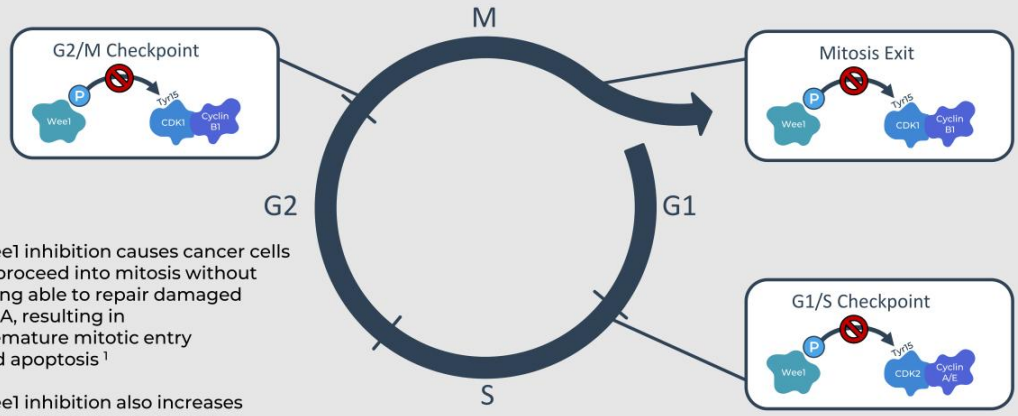
Wee1 Inhibitor

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 ZN-c3 Forces Cancer Cells to Proceed into Mitosis

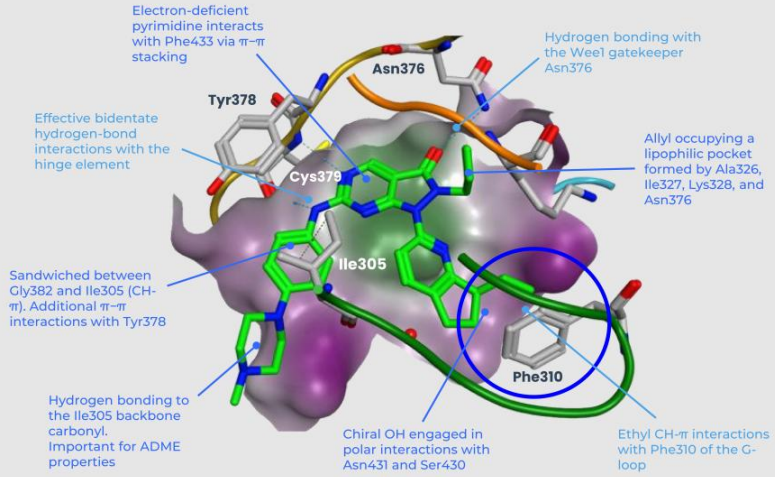


- Wee1 inhibition causes cancer cells to proceed into mitosis without being able to repair damaged DNA, resulting in premature mitotic entry and apoptosis [1]
- Wee1 inhibition also increases replication stress by inducing aberrant firing of replication origins and depletion of nucleotide pools [1]

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 ZN-c3 with Improved ADME Properties

ZN-c3 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

ZN-c3: 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]	Initial ongoing studies combining ZN-c3 with both common chemotherapy backbones and PARP inhibitor in platinum resistant populations as part of GSK development partnership
Cyclin E Driven Ovarian Cancer (~25% of HGSOC)	8,800 [3]	Ongoing Biomarker study with monotherapy regimen exploring Cyclin E protein overexpression and gene amplification
Other Cyclin E 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]	Anticipate initiation of ZN-c3 + BEACON regimen in Q1 2023 as part of Pfizer development partnership
Osteosarcoma	4,300 [6]	ZN-c3 + gemcitabine combination. Initial data readout at 2022 CTOS Conference
Pancreatic Cancer	108,000 [7]	ZNc3 + gemcitabine combination. Demonstrate POC via investigator sponsored trial at Dana Farber
AML	25,600 [8]	Combine ZN-c3 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 and ECIS - European Cancer Information System 2. Ovarian Cancer Research Alliance. Retrieved November 4, 2022. https://ocrahope.org/2021. 3. Chen at al Mol Cell Proteomics. 2019 Aug 9:18(8 suppl 1):S15-S25 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 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 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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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

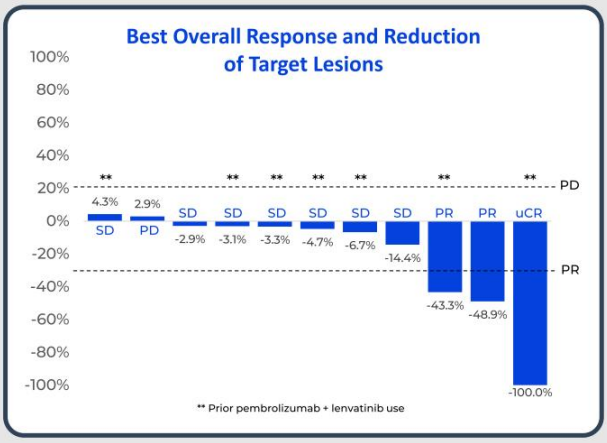
- Current standards of care for USC:
  - First line: Platinum based chemotherapy
  - Second line: Pembro + Lenvatinib
  - Third Line: No specific recommendations, single-agent chemotherapy (4-9%) and some limited use of bevacizumab [6]
- There is a high need for a therapeutic option in later line patients after prior platinum containing chemotherapy and pembrolizumab + lenvatinib treatment
- ZN-c3 is potentially a first-in-class treatment option for USC

ZN-c3'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 ZN-c3, 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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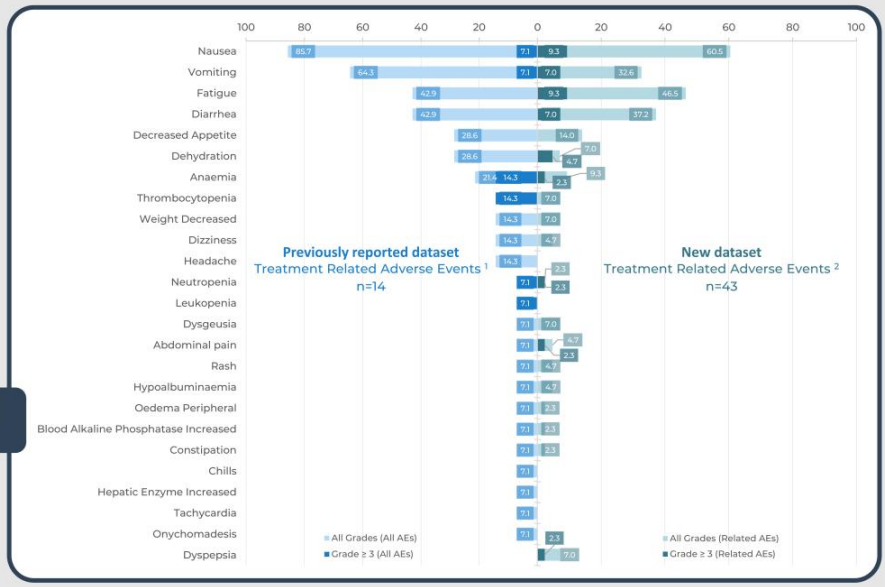
* Best overall response for this subject is PR. † N=11 subjects with measurable disease and at least 1 post-baseline tumor assessment. At time of data cutoff 2 SDs were ongoing on study DCR=disease control rate; uCR=unconfirmed complete response.

ZN-c3 Continues to Show Favorable Tolerability Profile in Monotherapy USC Setting

Patients with Adverse Events (%)



1. Data as of 21 Jan 2022, Presented at AACR 2022 by F. Meric-Bernstam 2. Data as of 14 Sep 2022

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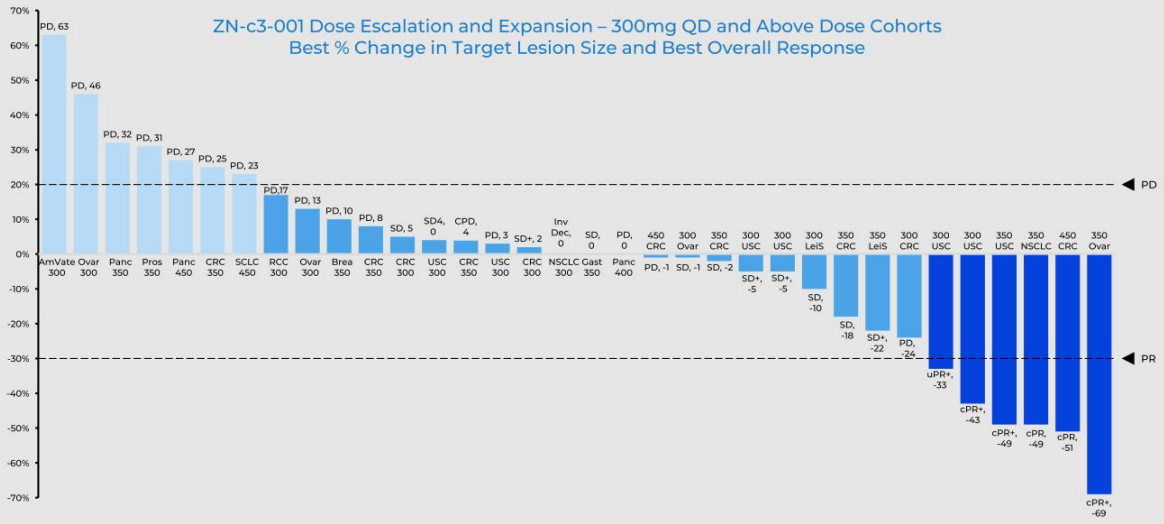
ZN-c3

Dose Optimization

ZN-c3: Multiple PRs Across Tumor Types as Monotherapy

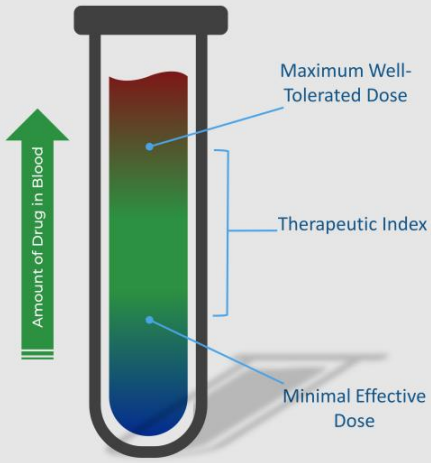


Waterfall as of 05/15/2021; 3 subjects with no treatment scans (CRC, USC, Pancreas), and experienced clinical progressive disease (CPD) + denotes treatment ongoing.
Newly reported uPR in USC is included. ORR based on radiographic responses. Both uPRs reported at AACR 2021 as of 03/15/2021 in USC were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

Optimizing the Therapeutic Index of ZN-c3

- Only set dose of ZN-c3 has been in the 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



Accelerating Our Approach to Optimizing Dosing

ENCOURAGING DEMONSTRATION OF CLINICAL ACTIVITY

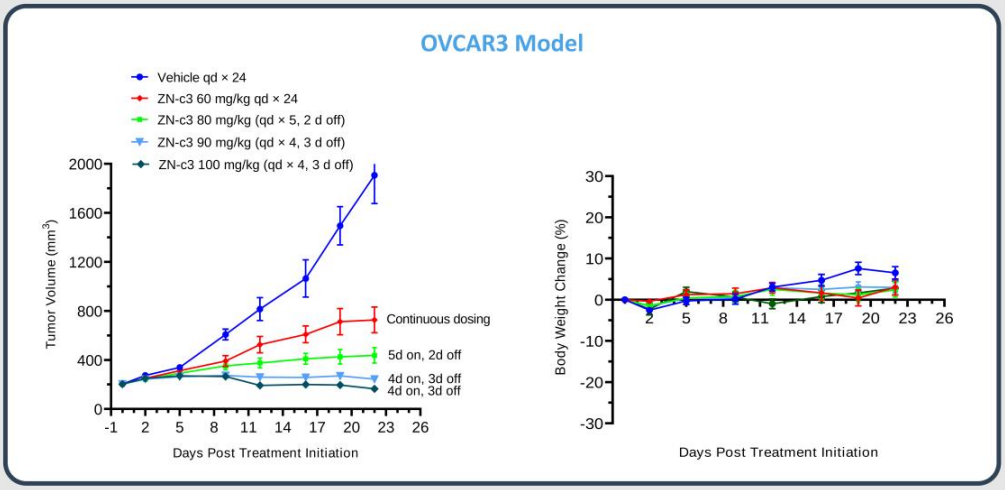
- Preclinical and clinical evidence demonstrates that exposure drives activity, which is key to addressing as many patients and dosing regimens as possible
- Large clinical data set (n>200 treated patients to date) with established activity as a continuous dose and ongoing studies examining combination regimens and dose optimization
- Patients already treated form strong basis for ongoing work

PLAN TO ESTABLISH OPTIMAL DOSING

- Strategy is to demonstrate strong monotherapy efficacy in high unmet need tumors, optimizing for activity and maintaining or improving tolerability
- Three monotherapy trials, including a two-arm trial with Cyclin E biomarker
- Anticipate providing update on dosing in H1 2023

Establishing the optimal monotherapy dose will lead to broadest benefit across tumor types, shortest path to registration and strongest clinical profile

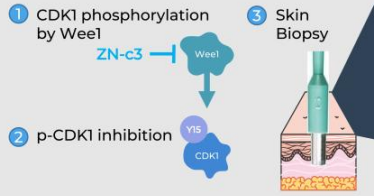
ZN-c3: Intermittent Dosing Increases Efficacy and Maintains Tolerability in Ovarian Cancer Models



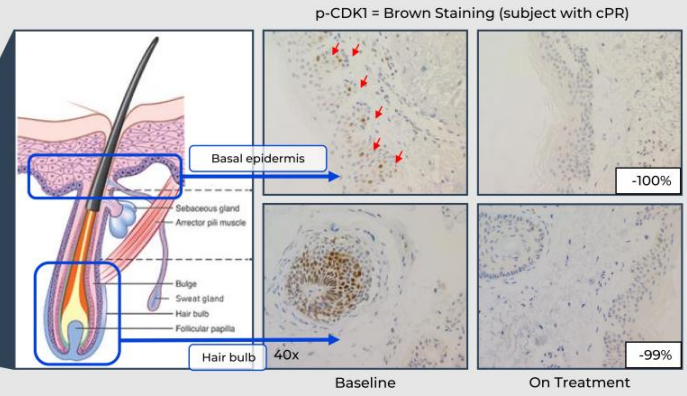
Decreases in p-CDK1 Show Target Engagement for Wee1 Inhibition

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

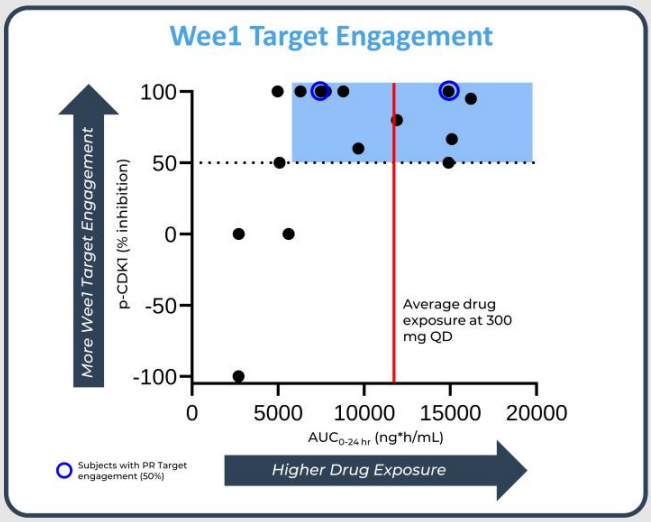


Decreases in p-CDK1 at Baseline vs on Treatment



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

ZN-c3: 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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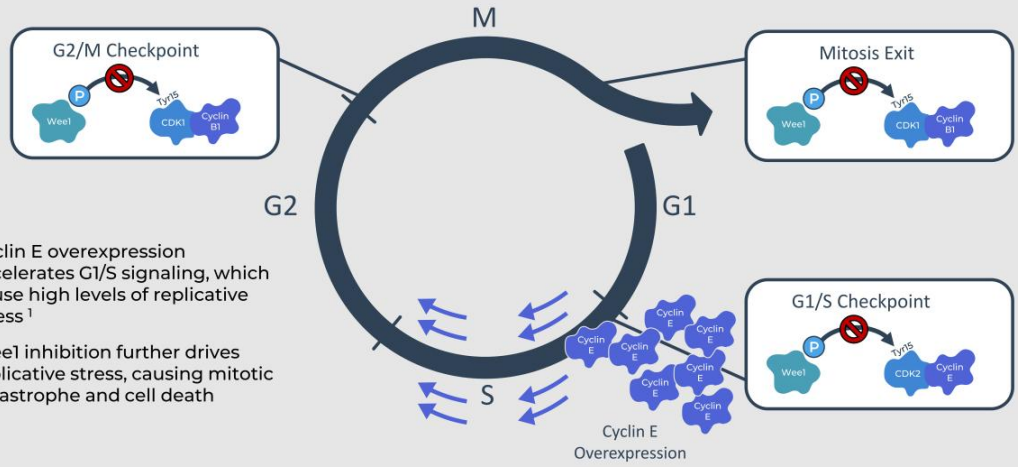
ZN-c3

Biomarker Approach: Cyclin E Driven Cancers

Cyclin E Overexpressing Cancer Cells are Highly Sensitive to Wee1 Inhibition

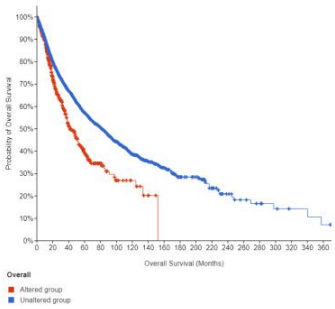


- Cyclin E overexpression accelerates G1/S signaling, which cause high levels of replicative stress [1]
- Wee1 inhibition further drives replicative stress, causing mitotic catastrophe and cell death

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)

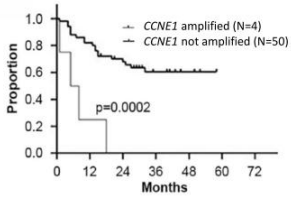
Cyclin E Amplification is Associated with Poor Prognosis and Chemotherapy Response Across Tumor Types

TCGA Pan Cancer Atlas [1]

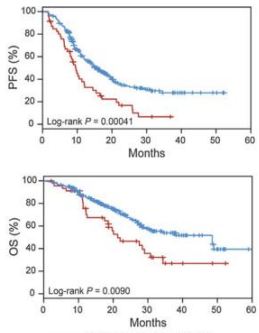


CCNE1 amplified (N=410)
CCNE1 not amplified (N=10,305)
Log-rank test p-value=1.06 10^{-13}

Triple Negative Breast Cancer (TNBC) [2]



Carboplatin-treated Ovarian Cancer [3]

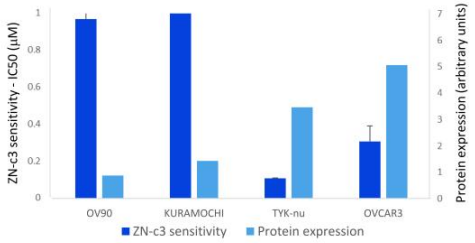


CCNE1 amplified (N=47)
CCNE1 not amplified (N=201)

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.

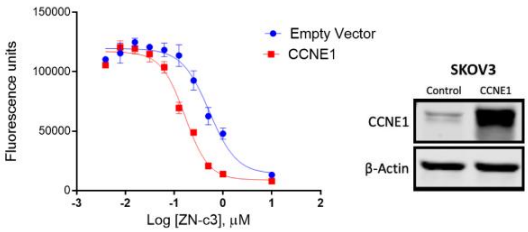
Cyclin E Overexpression is Associated to Increased Sensitivity to ZN-c3 in Ovarian Cell Lines

ZN-c3 Sensitivity and Cyclin E Protein Expression [1]



- Ovarian cell lines overexpressing Cyclin E are more sensitive to ZN-c3
- Cyclin E overexpression sensitizes the low-sensitive cell line SKOV-3 to ZN-c3

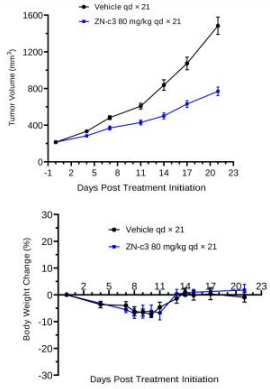
ZN-c3 Sensitivity in SKOV3 Overexpressing Cyclin E [2]

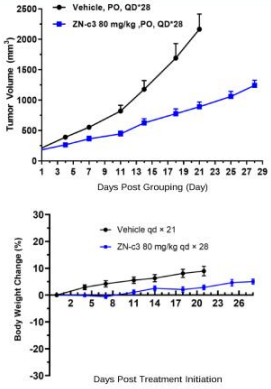


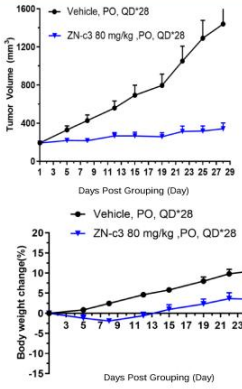
1. ZN-c3 sensitivity is assessed by CellTiter Glo after 96 hours of culture. Data represent an average of at least 2 independent studies. Protein expression was assessed by Western Blot and is representative of 2 independent experiments.
2. CCNE1 was overexpressed in SKOV3 by lentivirus transduction followed by puromycin selection. Empty vector control was generated simultaneously.

Cyclin E Amplification is Associated with Poor Prognosis and Chemotherapy Response Across Tumor Types

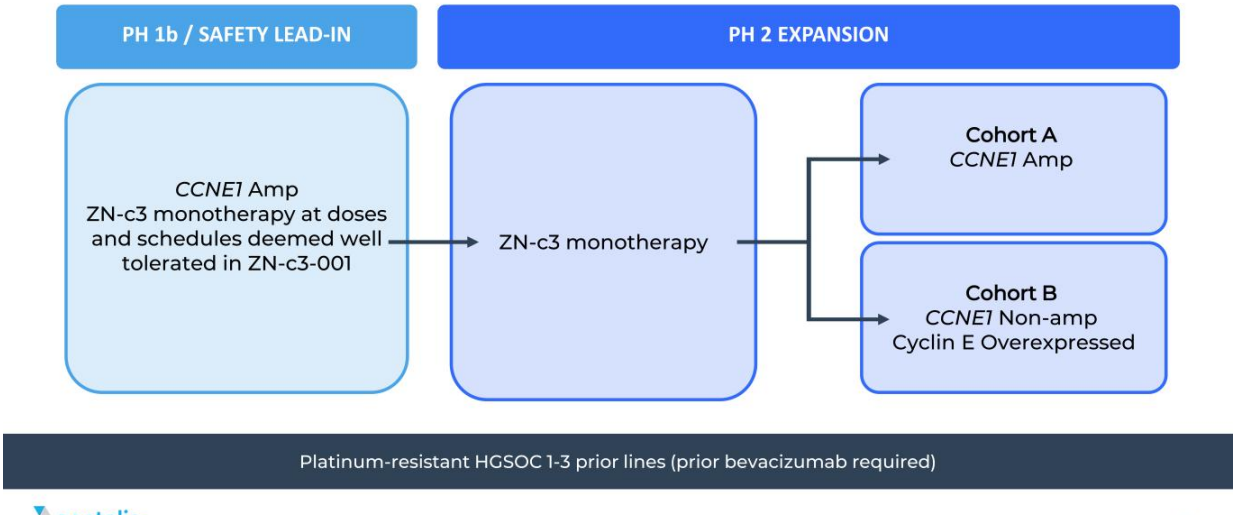
SKOV3 CCNE1 not amplified, TP53 mut	HCC1806 CDX CCNE1 amp (CN=7), TP53 mut	OVCAR3 CDX CCNE1 amp (CN=14)
$TGI_{(80\ mpk,\ Day\ 28)}$ = 51.5%	$TGI_{(80\ mpk,\ Day\ 28)}$ = 63.5%	$TGI_{(80\ mpk,\ Day\ 28)}$ = 88%







Moving Forward with CCNE1 in HGSOC: Revised ZN-c3-005 Study Design



Platinum-resistant HGSOC 1-3 prior lines (prior bevacizumab required)

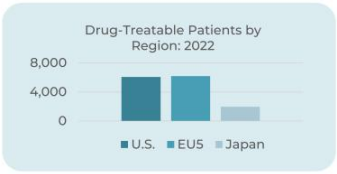
Platinum-Resistant/Refractory Ovarian Cancer Remains an Unmet Need

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]
- ZN-c3 is potentially a first-in-class treatment option that works synergistically with other anticancer therapies

ZN-c3'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 (%)
ZN-c3 + Paclitaxel	9	8	5	3	–	100	62.5
ZN-c3 + Carboplatin	17	11	5	4	2	81.8	45.5
ZN-c3 + 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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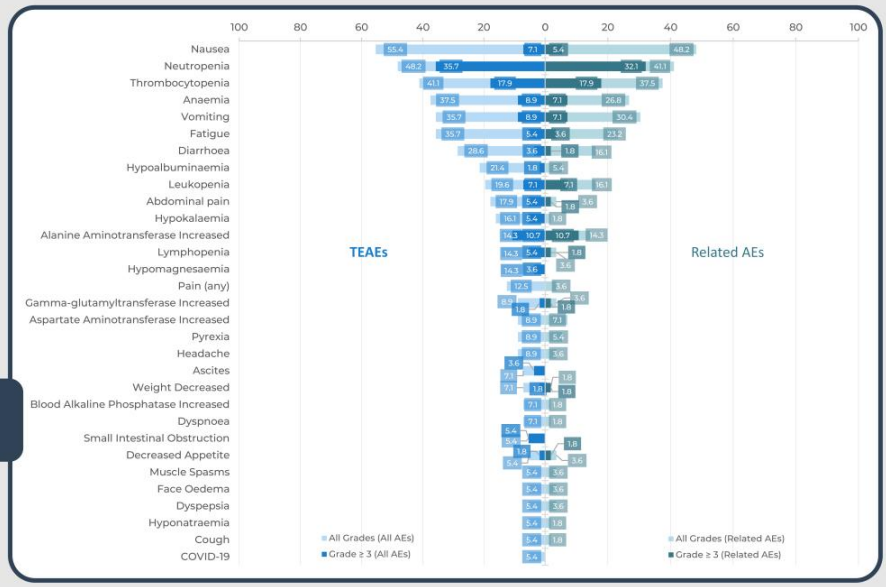
Pasic, et al. Poster Presented at American Association for Cancer Research Annual Meeting (2022): Abstract CT148: A phase 1b dose-escalation study of ZN-c3, a WEE1 inhibitor, in combination with chemotherapy (CT) in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube 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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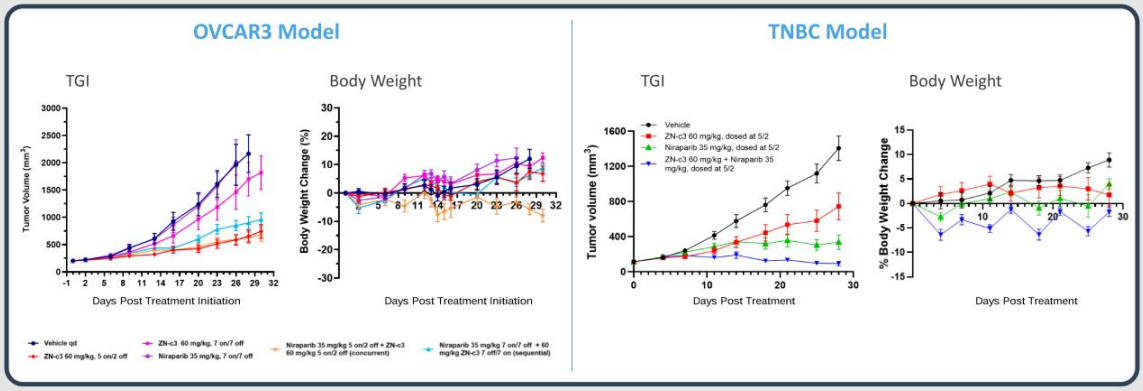
ZN-c3

PARP-Refractory Ovarian Cancer

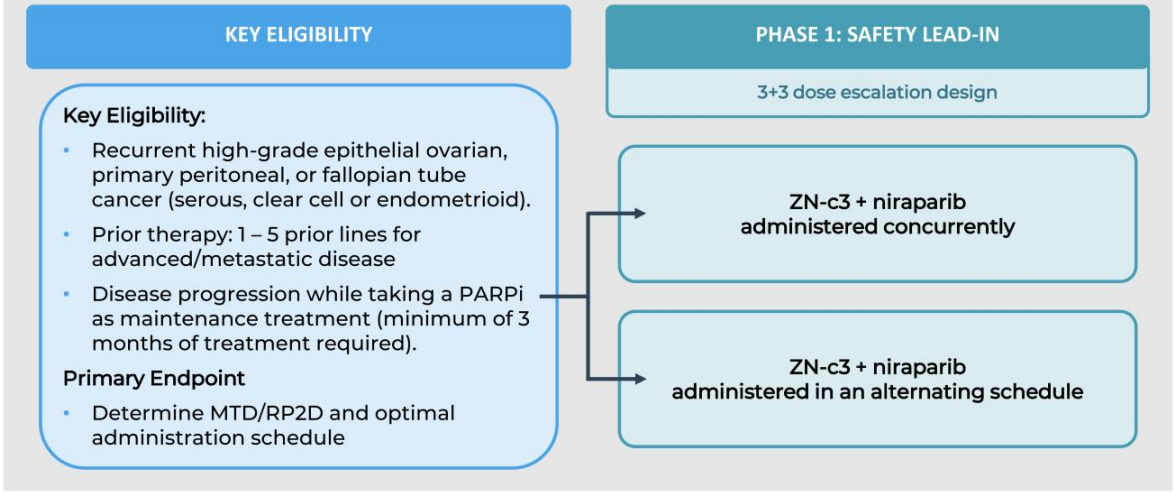
ZN-c3 + PARP Inhibitor Combinations are Active in both Ovarian CDX and TNBC PDX Models



- 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 E [1]
- The combination of ZN-c3 and niraparib shows efficacy in both ovarian and TNBC in vivo models
- Sequential administration of PARP and ZN-c3 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 ZN-c3 in combination with niraparib in patients with platinum-resistant ovarian cancer



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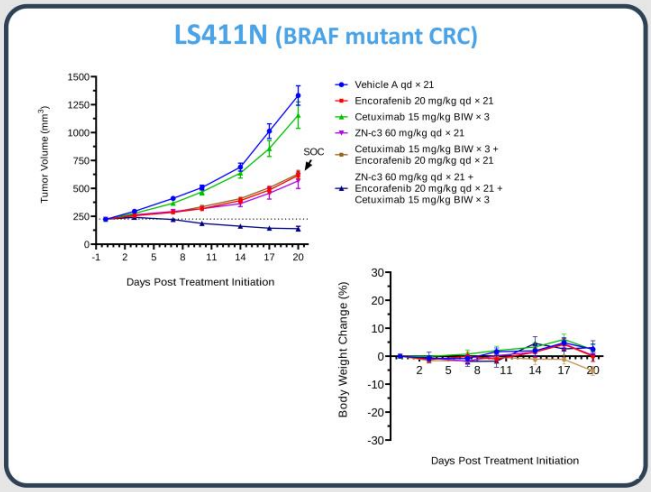
ZN-c3

BRAF Metastatic Colorectal Cancer

Preclinical Data Supports the Combination of ZN-c3 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 ZN-c3 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 ZN-c3 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 ZN-c3 →

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 ZN-c3, apart from Greater China rights (Zentara).

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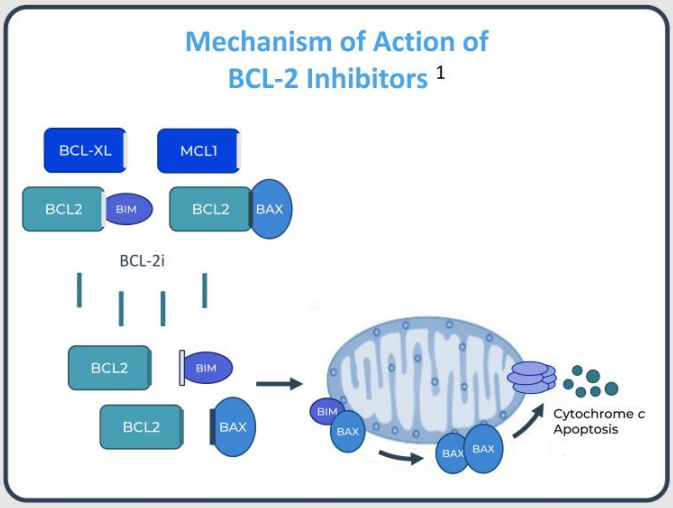
ZN-d5

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

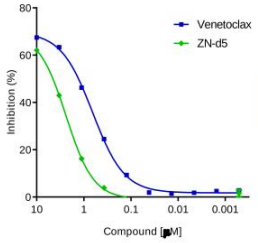
ZN-d5 has >14x Improved Selectivity for BCL-2 vs BCL-xL and Binds With Higher Affinity to BCL-2 Mutants than Venetoclax

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

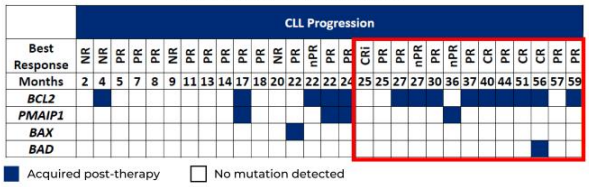
ZN-d5 shows activity in preclinical models of ALL, NHL and AML

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

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

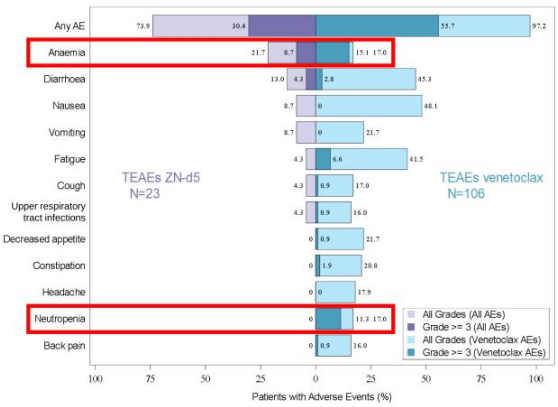
- Improved *in vitro* potency and has 10x improved selectivity for BCL-2 vs BCL-xL compared to venetoclax
- Observed to bind with higher affinity to BCL-2 mutants than venetoclax in *in vitro* assay
  - Mutations in BCL-2 may be driving sub-clonal pockets of resistance to venetoclax
- Preclinical combination data of ZN-d5 + ZN-c3 utilizing novel biology showed synergistic an 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 & ZN-c3	Anticipate trial initiation in 4Q 2022

ZN-d5: Favorable Early Comparison to Venetoclax in NHL

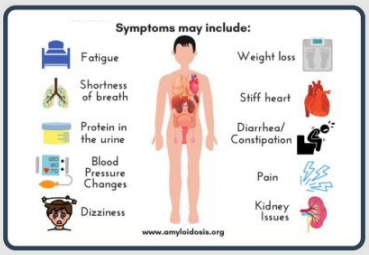
- ZN-d5 100-1200mg, empty stomach
- Venetoclax 200-1200mg with food
- Early toxicity profile in NHL favorable vs. published venetoclax data [1]
  - Fewer AEs of any Grade, Grade ≥3
  - No TLS observed
  - Venetoclax AEs not dose-dependent

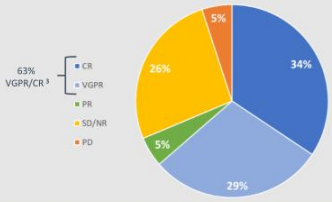
Adverse Event	Any Grade			
	All Doses (N = 106)	≤ 400 mg (n = 22)	600 to 900 mg (n = 33)	1,200 mg (n = 51)
Emergent*				
Any event	103 (97)	21 (96)	33 (100)	49 (96)
Nausea	51 (48)	9 (41)	15 (45)	27 (53)
Diarrhea	48 (45)	7 (32)	14 (42)	27 (53)
Fatigue	44 (42)	10 (45)	9 (27)	25 (49)
Decreased appetite	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.

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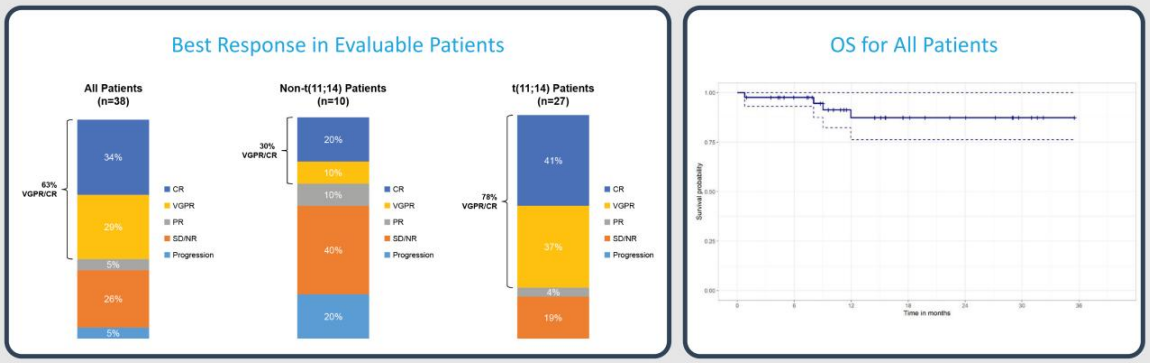
BCL-2 Inhibition has Shown Robust Clinical Activity in AL Amyloidosis

- 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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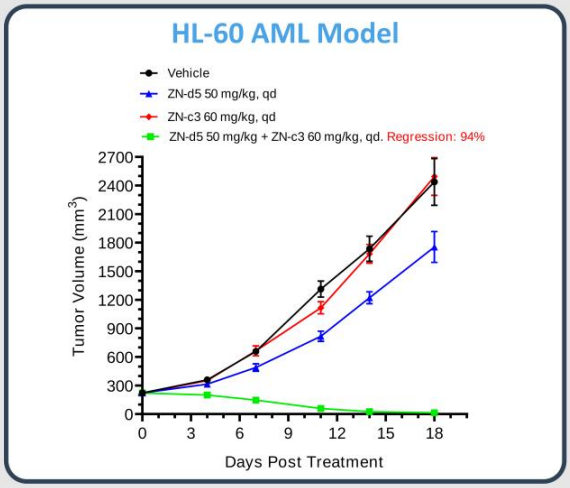
Potential Combination of ZN-c3 and ZN-d5

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

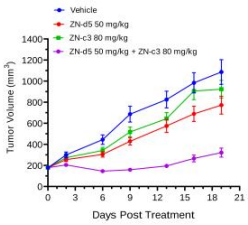


- ZN-d5 and ZN-c3 combination represents a novel therapeutic approach
- Significant enhancement of activity than single agent in several indications, including AML
- Combination regimen was well-tolerated in mice
- Zentalis is the only company known to have both inhibitors in clinical development

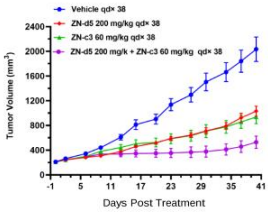
Presented at AACR 2022 by Izadi, H.; et. al. Cancer Res (2022) 82 (12_supplement): 2591.

Antitumor Activity in Solid Tumor Models with the ZN-d5 + ZN-c3 Combination Represents Market Expansion Opportunities

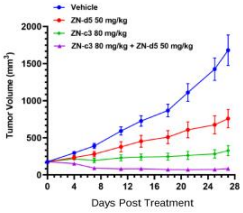
SCLC Model (DMS53)[1]



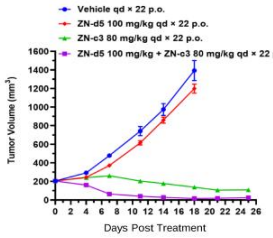
TNBC Model (MDA-MB-436)



NSCLC Model (H146)



Neuroendocrine Prostate Model (H660)



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

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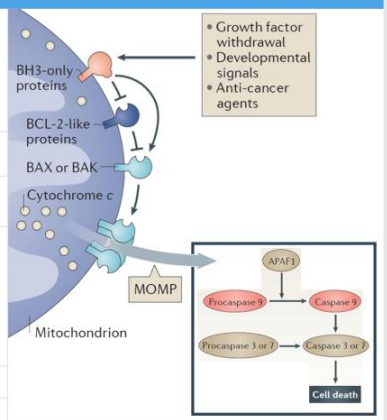
BCL-xL Protein Degrader

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	• 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).

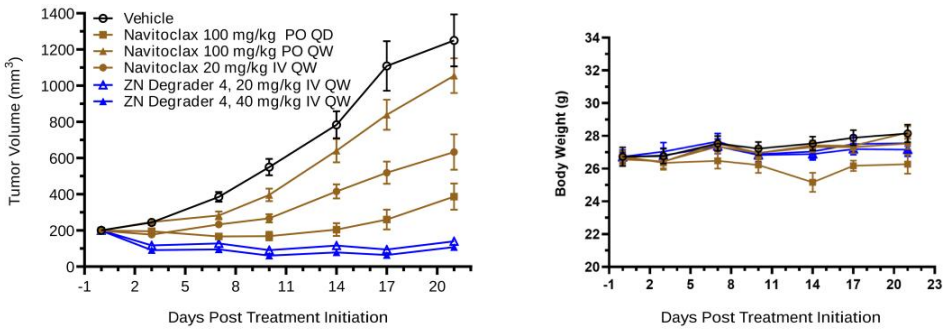


Declared development candidate and initiated IND enabling activities

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)

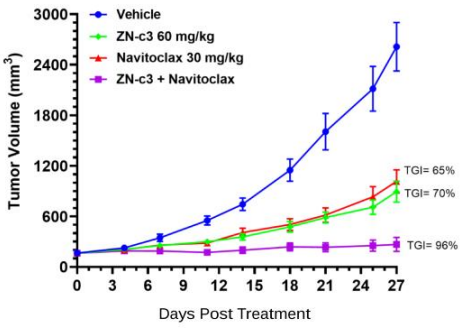
BCL-xL IV Degrader is More Efficacious than BCL-xL Inhibitor (Navitoclax) in MOLT4 (T-ALL) Models

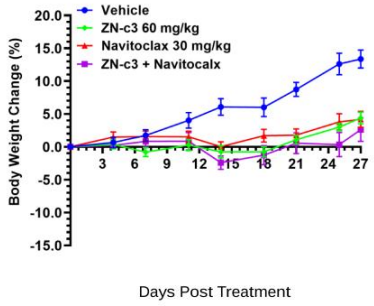


- BCL-xL Degrader demonstrates excellent efficacy in the MOLT4 tumor model (T-ALL) and is well-tolerated at efficacious doses
- BCL-xL degrader is more efficacious than Navitoclax

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

ZN-c3 Combined with a Low Dose of Navitoclax (BCL-xL Inhibitor) Results in Synergistic Anti-tumor Activity in the ALL model MOLT-4 [1]





- The MOA of the combination of the BCL-xL therapeutic and ZN-c3 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 ZN-c3.

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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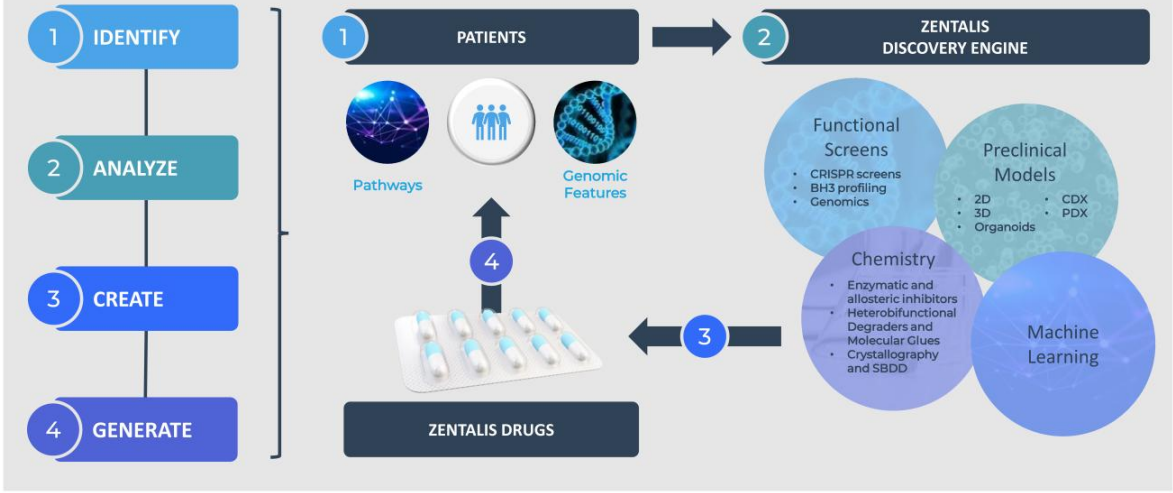
Conclusions

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



Organizational Accomplishments and Progress Since May 2022

	PRIORITY	ACCOMPLISHMENTS / PROGRESS	
1	Strengthen organizational talent and complete executive team build-out	New Board Member and 6 Executive Hires or Promotions including CMO, CSO, CTO, SVP Portfolio Management, General Counsel and President	✓
2	Prioritize and strengthen clinical development plans for ZN-c3	Expanded / continued near-term registrational opportunities in populations most likely to benefit: 6 ongoing sponsored and 2 newly announced studies (one with Pfizer and one with Dana Farber)	✓
3	Evolve ZN-d5 program	Establishing clear clinical strategy around pro-apoptotic asset	✓
4	Advance BCL-xL degrader program	Declared development candidate and initiated IND enabling studies	✓
5	Deprioritize non-strategic assets	Discontinue all activity around SERD (ZN-c5) and EGFR (ZN-d4) by end of 2022	✓
6	Strengthen balance sheet to fund development activities through key catalysts	Successfully completed capital raise in May 2022; cash runway into 2025	✓

Company focused on generating clinical evidence that creates value and delivers new therapies to cancer patients

2022 Key Milestones

ZN-c3 Wee1 Inhibitor

1H 2022	✓ Initial readout on Phase 1 USC expansion cohort
1H 2022	✓ Initial readout on Phase 1b ovarian chemotherapy combo
1H 2022	✓ Initial enrollment/safety update on Phase 2 USC trial [1]
1H 2022	✓ Initial readout on Phase 1/2 chemotherapy combo in osteosarcoma

ZN-d5 BCL-2 Inhibitor

1Q 2022	✓ Initiate Phase 1 / 2 monotherapy study in amyloidosis
1H 2022	Initiate Phase 1 / 2 combination study of ZN-d5 + ZN-c3 in AML
1H 2022	Updated results from Phase 1 dose escalation in AML and NHL

Integrated Discovery Engine

2022	✓ Initiate IND enabling studies for an internal program

Zentera

2022	✓ Maximize value from investment in and partnership with Zentera

1. FDA Fast Track designation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