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Corporate Presentation

August 2023

Nasdaq: ZNTL

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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 unmet need across an array of cancers; potential benefits of intermittent dosing for our product candidates; 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 ZN-d5; 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 initiating Phase 3 trial of azenosertib in combination with chemotherapy in Cyclin E1+ platinum sensitive ovarian cancer; 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 “continue,” “design,” “estimate,” “expect,” “may,” “milestone,” “opportunity,” “plan,” “potential,” “predicts,” “strategy,” “will” and similar statements of a future or forward-looking nature. 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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.

We Are a Clinical-Stage Oncology Company Focused on Difficult-to-Treat Cancers

Azenosertib: First-in-Class WEE1i Candidate with Broad Franchise Potential

Accelerating Development

- High levels of monotherapy anti-tumor activity
- Best-in-class safety and tolerability to date supports use in earlier lines and maintenance settings
- Demonstrated synergistic activity with chemotherapy and molecularly targeted agents
- Enriched activity in tumors with high genomic instability including Cyclin E1+ and HRD+ cancers
- 8 trials; large indications; 400+ patients dosed

Blockbuster Commercial Opportunity

- Direct registrational path with multiple shots on goal across monotherapy and chemotherapy combination
- Potential to cover 88% of ovarian cancer across multiple lines of therapy
- Ovarian + USC treatable population of ~58K patients / year
- Potential to expand to broad set of tumors as monotherapy or in combination, addressing ~140K per year
- Global commercial rights
- IP – U.S. composition of matter 2039

Highly Selective BCL-2 Inhibitor

- Multiple indications; Best-in-class potential in heme malignancies
- 100+ patients dosed across 3 ongoing studies
- Positioned to potentially demonstrate monotherapy activity in AL amyloidosis
- Attractive commercial opportunity as potential first registered drug in AL amyloidosis

Promising Preclinical Programs

- Discovering assets leveraging distinctive chemistry expertise

Positioned to Execute and Deliver

- Deep oncology experience
- Veteran scientific, clinical advisors
- Partnerships with Pfizer, GSK
- Cash runway into 2026

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Pipeline Addresses Difficult to Treat Cancers with Large Commercial Opportunities

COMPOUND	INDICATION + DEVELOPMENT APPROACH	PRECLINICAL	Phase 1	Phase 1b	Phase 2	Phase 3	STATUS / EXPECTED MILESTONES
Azenosertib WEE1 Inhibitor	**Platinum Sensitive Ovarian Cancer** + Paclitaxel or Carboplatin						Initiate Q1 2024
	Cyclin E1+ Ovarian Cancer Monotherapy						Enrolling
	Uterine Serous Carcinoma Monotherapy						Enrolling; FDA Fast Track Designation
	PARP Resistant Ovarian Cancer Azenosertib monotherapy, alternating with niraparib or concurrent with niraparib				GSK		Enrolling
	Dose Optimization in Solid Tumors Monotherapy						Enrolling
	Osteosarcoma + gemcitabine						Enrolling
	BRAF Mutant Colorectal Cancer + encorafenib and cetuximab			Pfizer			Enrolling
	Pancreatic Cancer + gemcitabine						Dana Farber Cancer Institute, funded by SU2C/Lustgarten
ZN-d5 BCL-2 Inhibitor	**Light Chain (AL) Amyloidosis** Monotherapy						Enrolling; Provide interim clinical data and declare RP2D for monotherapy 2H23
	Non-Hodgkins Lymphoma (NHL) Monotherapy						Enrolling
	Acute Myeloid Leukemia (AML) + azenosertib						Enrolling; Provide preliminary data from clinical trial 2H23
BCL-xL Degrader	**Solid Tumors and Heme Malignancies**						Declared development candidate; IND enabling activities initiated

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Azenosertib

WEE1 Inhibitor with Potential to Address Large Unmet Need Across Array of Cancers

Azenosertib Monotherapy Dose Optimization Supports Advancement into Multiple Difficult-to-Treat Tumor Types

37% Objective Response Rate with durable responses using intermittent dosing in ovarian and USC patients

Monotherapy **RP2D** established: 400 mg 5:2

Doubled steady state drug exposure compared to continuous dosing

Maintained safety and improves tolerability compared to continuous dosing

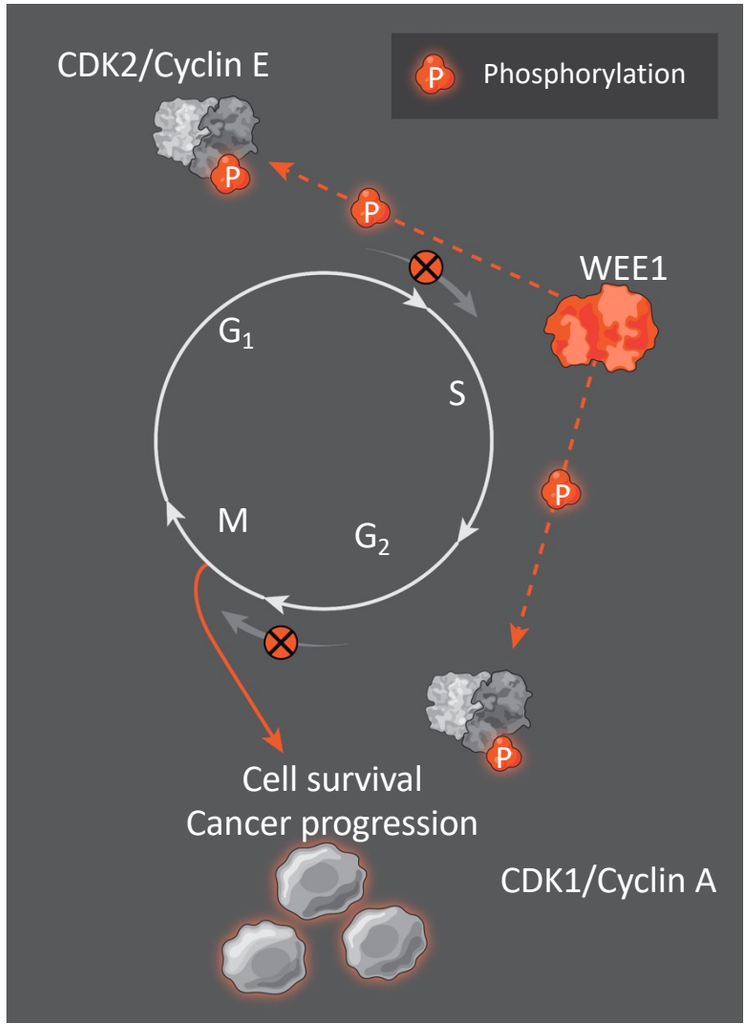
No treatment-related discontinuations in patients who were administered intermittent dosing

Three ongoing Phase 2 monotherapy trials have the potential to support rapid paths to registration in ovarian cancer and USC

Abbreviations: RP2D: recommended phase 2 dose; 5:2 refers to administration schedule of five days on therapy and two days off; USC, uterine serous carcinoma

Azenosertib Targets WEE1, a Critical Protein for Cancer Cell Survival

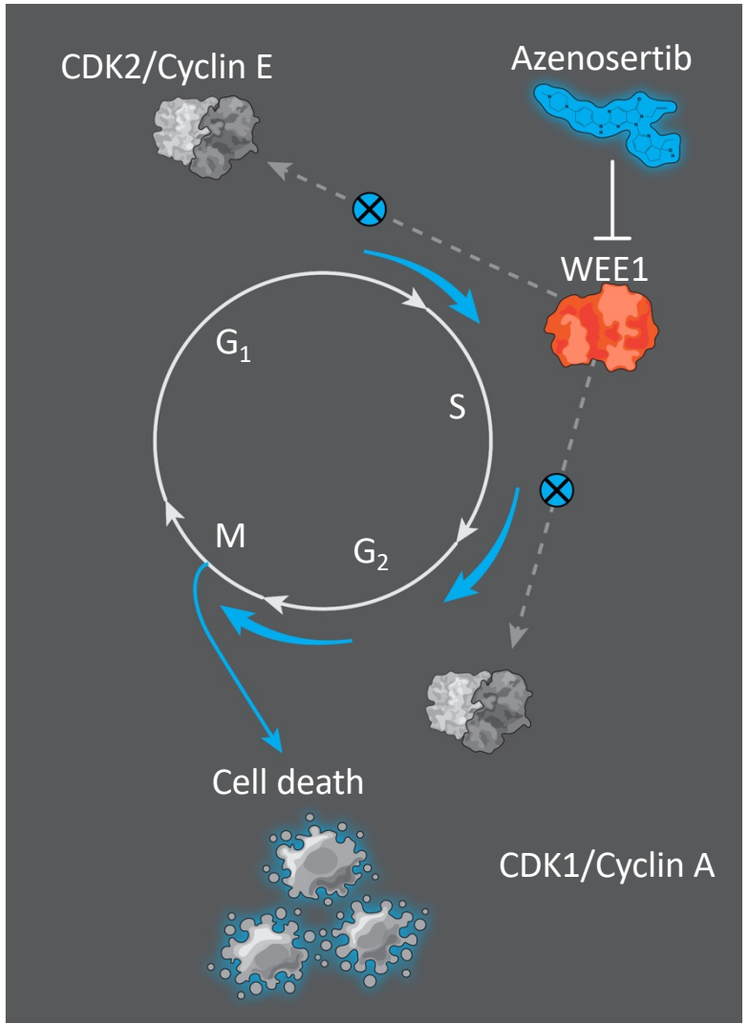
WEE1 activity in untreated cancer cell



- **WEE1 phosphorylates CDK/Cyclin complexes to engage cell cycle checkpoints, allowing DNA repair to occur**
- **Azenosertib inhibits WEE1:**
  - **Leads to inactivation of CDK 1 and 2**
  - **Removes 2 cell cycle checkpoints: G1/S and G2/M**
  - **Cell cycle progresses without sufficient DNA repair**
  - **Cancer cells accumulate DNA damage, resulting in apoptosis and mitotic catastrophe**

Azenosertib's MOA and early monotherapy clinical activity made dose optimization critical

Azenosertib blocks WEE1 resulting in cancer cell death



Establishing RP2D is significant milestone in path to drugging this high-potential oncology target

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Luserna di Rora, et al. 2020. J Hem Onc. 13:126. Elbaek et al. 2022. Cell Reports. 38:110261. Abbreviation: MOA, mechanism of action

Monotherapy Dose and Biomarker Enrichment Is Foundational To Our Clinical Strategy

Tumors with High Genomic Instability are Sensitive to Azenosertib

High genomic instability can be caused by:

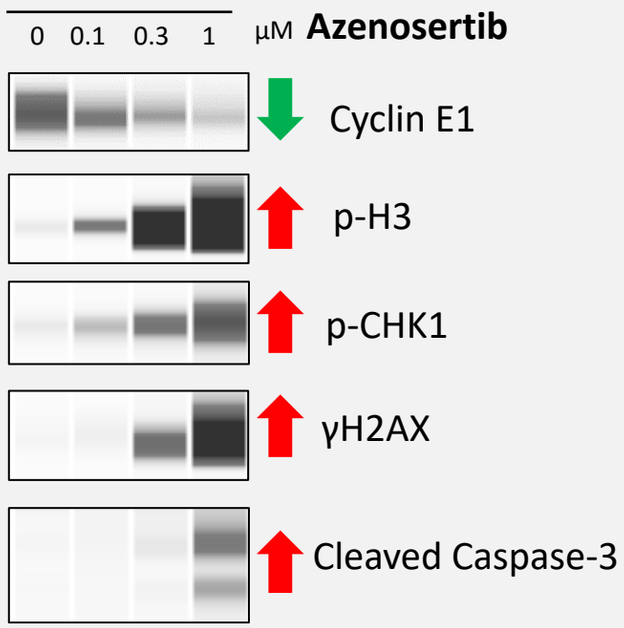
Cyclin E1+ Tumors

- Cyclin E1+ drives accelerated entry into S-phase through its partnership with CDK2
- Replication machinery is overloaded, resulting in genomic instability

Homologous Recombination Repair Defective (HRD+) Tumors

- Results in genomic instability through tumors inability to repair double stranded DNA breaks.

Azenosertib induces markers of DNA damage, replicative stress, and apoptosis*



*OVCAR3 Cyclin E1 positive cells, 16-hour treatment

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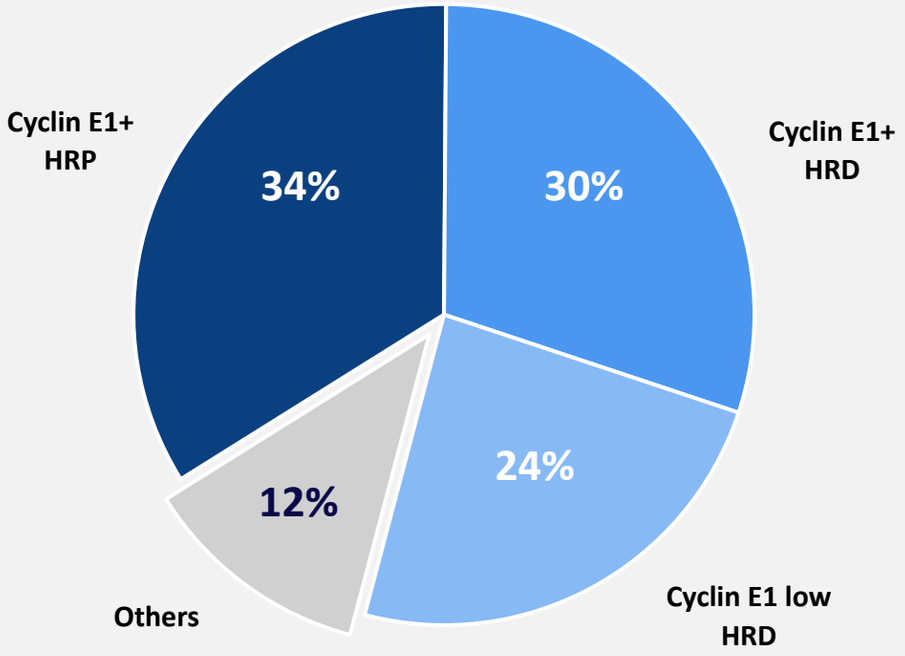
Potential to Transform Treatment Paradigm for Patients and Capture Significant Market Share in Ovarian Cancer

Azenosertib Monotherapy Potentially Addresses 88% Of High Grade Serous Ovarian Cancer

- Ongoing clinical programs address Cyclin E1+ and HRD+ patient populations
  - Opportunity is much larger than recently approved therapies
- Data support potential role for azenosertib at every stage of metastatic therapy:
  - **Platinum sensitive**: combination with chemotherapy
  - **Platinum resistant**: monotherapy and combination with chemotherapy

Potential to transform standard of care

High Grade Serous Ovarian Cancer Patient Segments



HRD: Homologous recombination deficient
HRP: Homologous recombination proficient

Sources:
1. HRD prevalence derived from Konstantinopoulos, et al *Cancer Discov* (2015)
2. CCNE1 amplification prevalence of ~20% reported in Aziz et al *Gynecol Oncol* (2018) and TGCA Network *Nature* volume 474 (2011)
3. Cyclin E1 expression and copy number extracted from the digital analysis of Aziz et al Figure 3B to infer full distribution of Cyclin E1 H-scores and overlap with CCNE1 amplification based on Cyclin E1 high definition of H-score >50
4. HRD prevalence and proportion of overlap with CCNE1 amplification from Konstantinopoulos et al, Figure 2
5. Total HGSOC incidence estimates (US, EU5) sourced from SEER and ECIS are 35, 388 individuals/year

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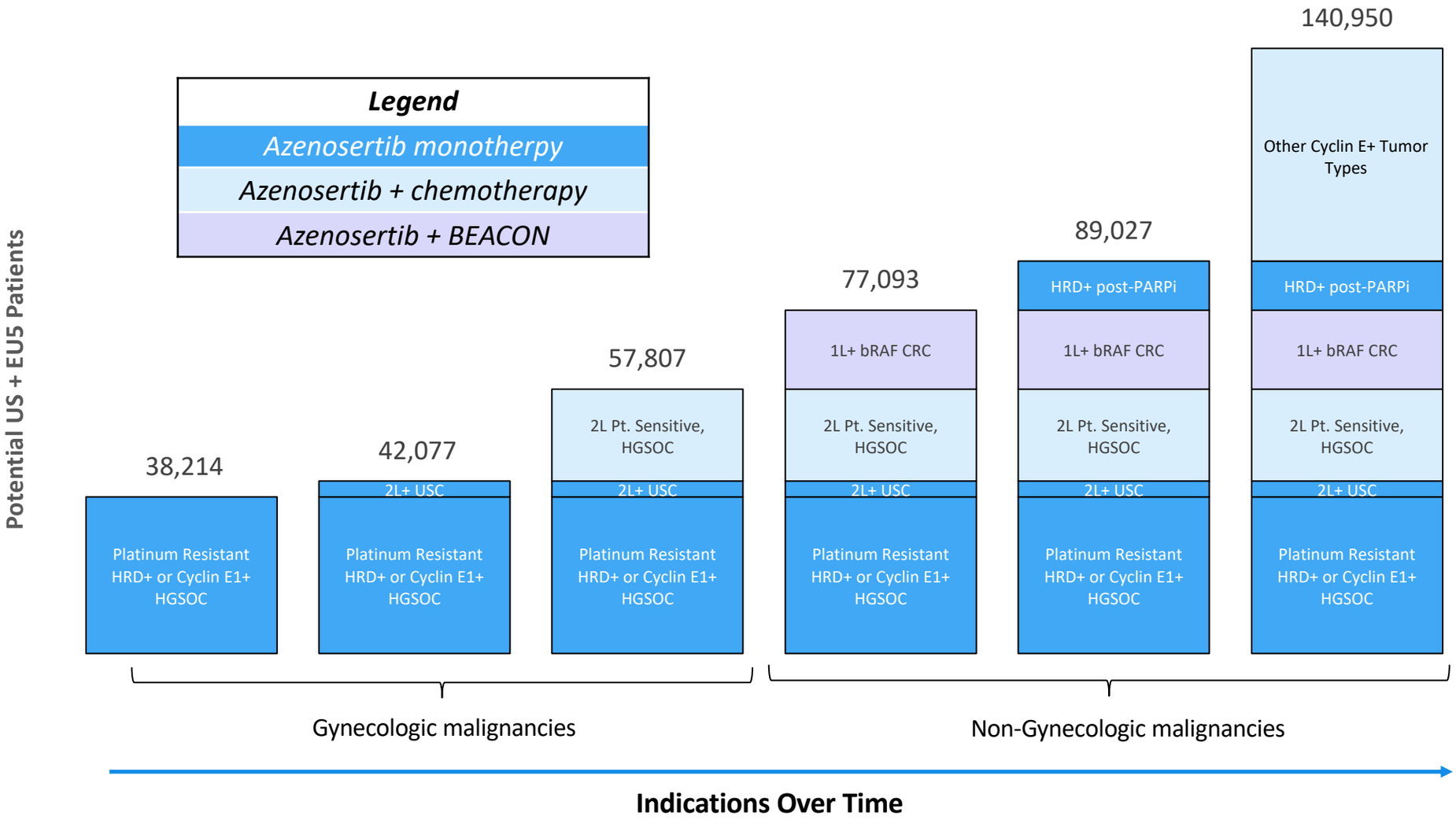
Addressable Patient Population More than Doubles as Franchise Expands to Non-Gynecological Malignancies



Source: Used 'drug-treatable' estimates from DRG Clarivate for all Ovarian, USC, CRC, Breast, Prostate and Pancreatic. For 'Other Cyclin-E1 driven solid tumors' used incidence reported by SEER and ECIS.
Cyclin E1 prevalence in platinum sensitive ovarian cancer derived from Petersen, et al CCNE1 and BRD4 co-amplification in high-grade serous ovarian cancer is associated with poor clinical outcomes, Gynecologic Oncology,Volume 157, Issue 2, 2020
Abbreviations: bRAF+ CRC: bRAF mutant Colorectal Cancer; HRD+ : Homologous Recombinant Repair Deficiency; HGSOC: High Grade Serous Ovarian Cancer; 2L: Second Line
HRD+ Post PARPi tumor types: Prostate, Pancreas and Breast; Other Cyclin E+ Tumor Types include bladder, stomach, esophageal, lung squamous, lung adenocarcinoma, and breast cancer

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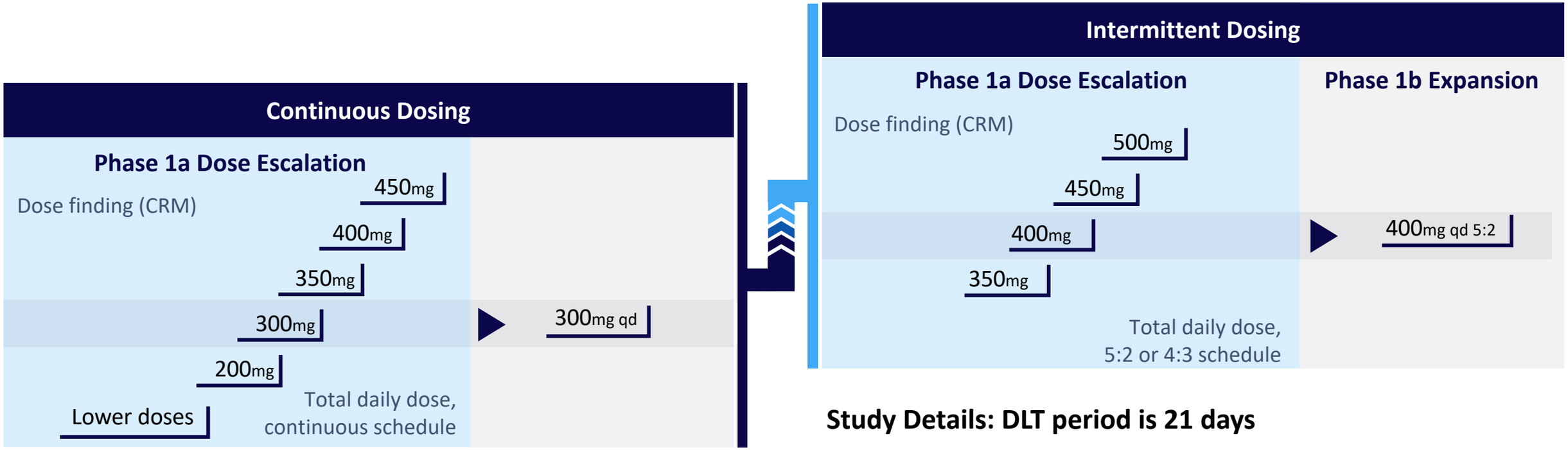
Azenosertib

Azenosertib Intermittent Monotherapy Dose Substantially Improves Antitumor Activity and Tolerability

Zentalis 001 Study Enabled Rapid and Efficient Approach to Dose Optimization



Study Details: DLT period is 21 days

- Tumor assessments (per RECIST 1.1) occur every 2 cycles (6 weeks)
- Protocol permits "Backfill" enrollment of additional patients at the highest previously cleared dose level

NCT04158336

Primary objectives: Safety, PK (Steady State Exposure (AUC_{0-24}) & Concentration Maximum (C_{max}))

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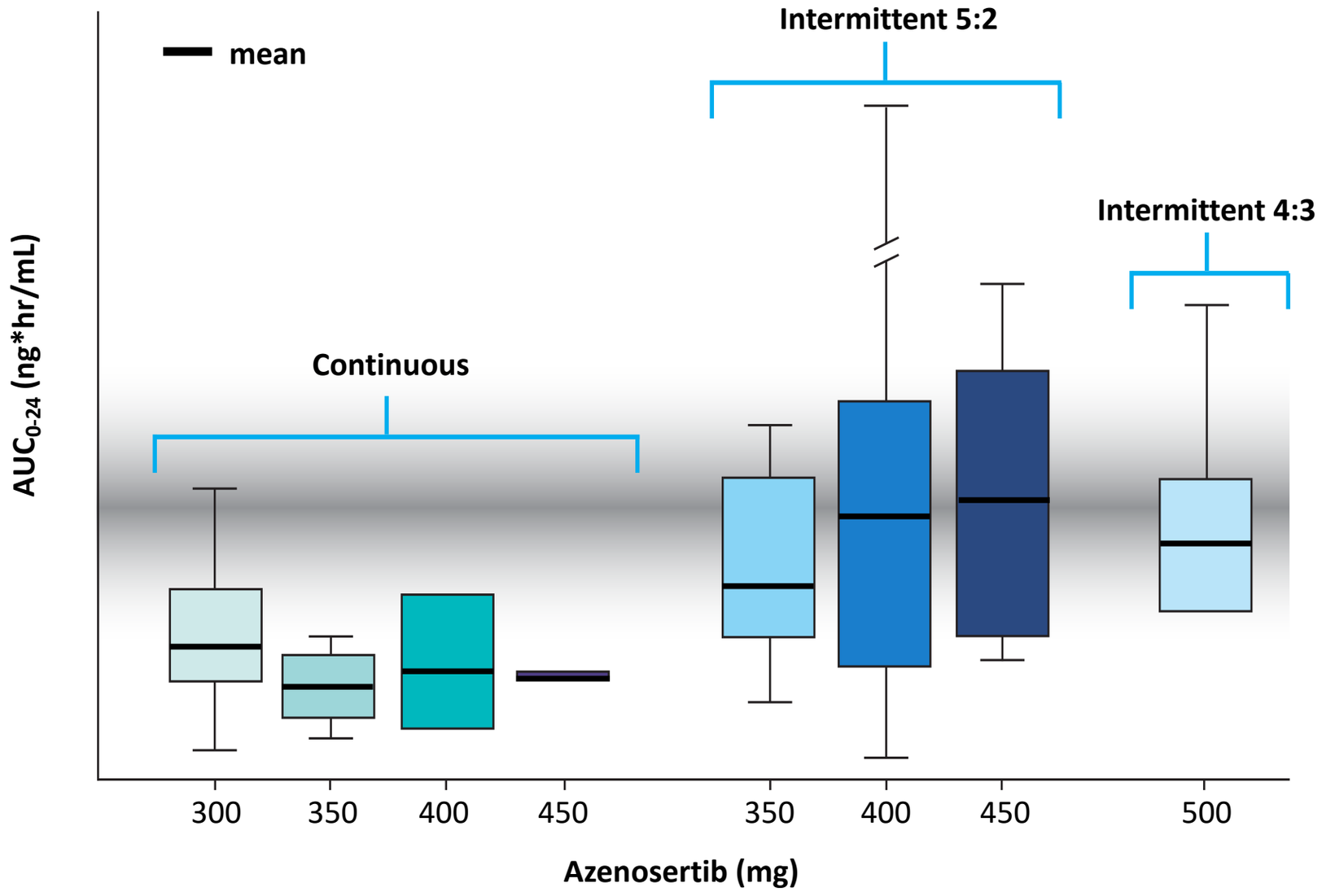
Abbreviations: CRM, continual reassessment method; qd, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; 4:3, 4-days of treatment followed by 3-days off treatment; DLT, dose limiting toxicity; RECIST, response evaluation criteria in solid tumors; PK, pharmacokinetics; AUC, area under the curve

Intermittent Dosing Resulted In A Significant Increase In Steady State Exposure



With intermittent dosing, more patients reach the projected target efficacious steady state exposure (AUC_{0-24})

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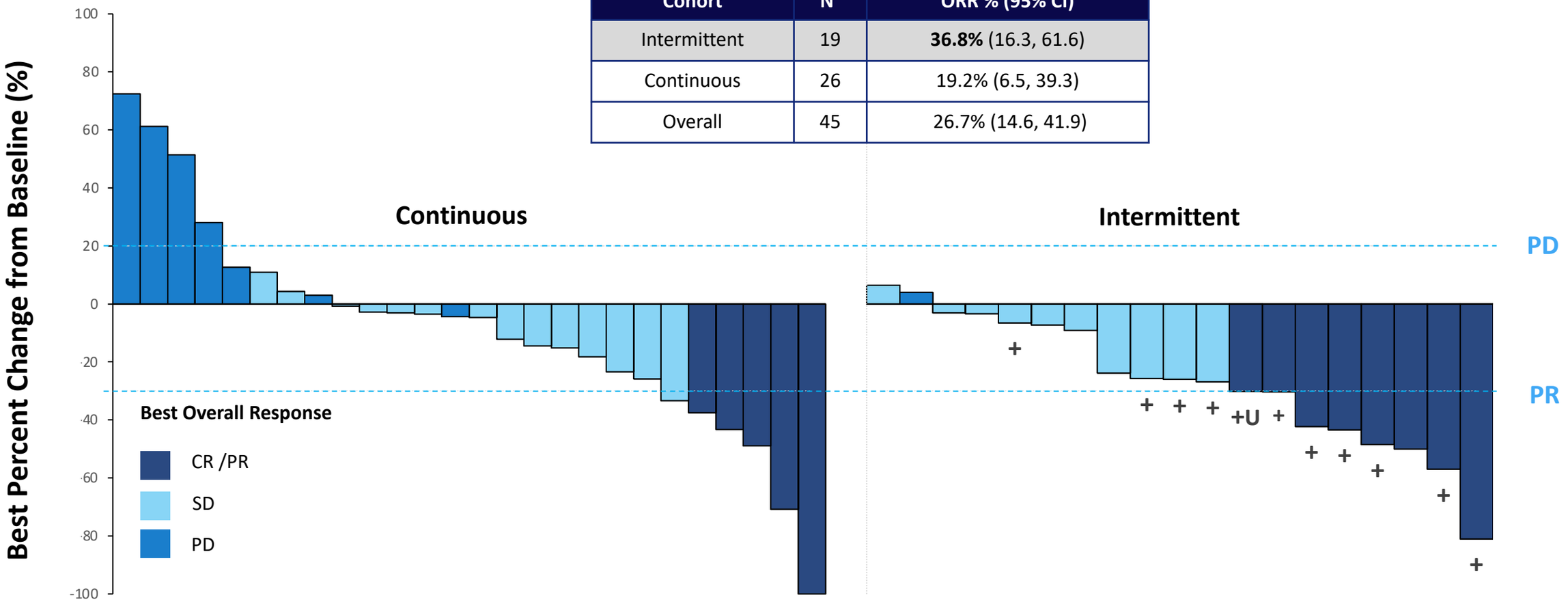
Patients who received ≥300 mg; Abbreviations: 5:2, 5-days of treatment followed by 2-days off treatment; AUC, area under the curve

Data cut-off: April 24, 2023

Azenosertib Intermittent Dosing Schedule Doubles Objective Response Rate In Ovarian/USC Populations

Cohort	N*	ORR % (95% CI)
Intermittent	19	**36.8%** (16.3, 61.6)
Continuous	26	19.2% (6.5, 39.3)
Overall	45	26.7% (14.6, 41.9)



*Response evaluable: have baseline measurable disease by RECIST 1.1, at least one post baseline scan, and received at least one dose of drug
Patients who received ≥300 mg. Abbreviations: USC, uterine serous carcinoma; CR, complete response; PR, partial response;
SD, stable disease; PD, progressive disease; ORR, objective response rate; CI, confidence interval; +: Patients remain on therapy at the time of data cut-off

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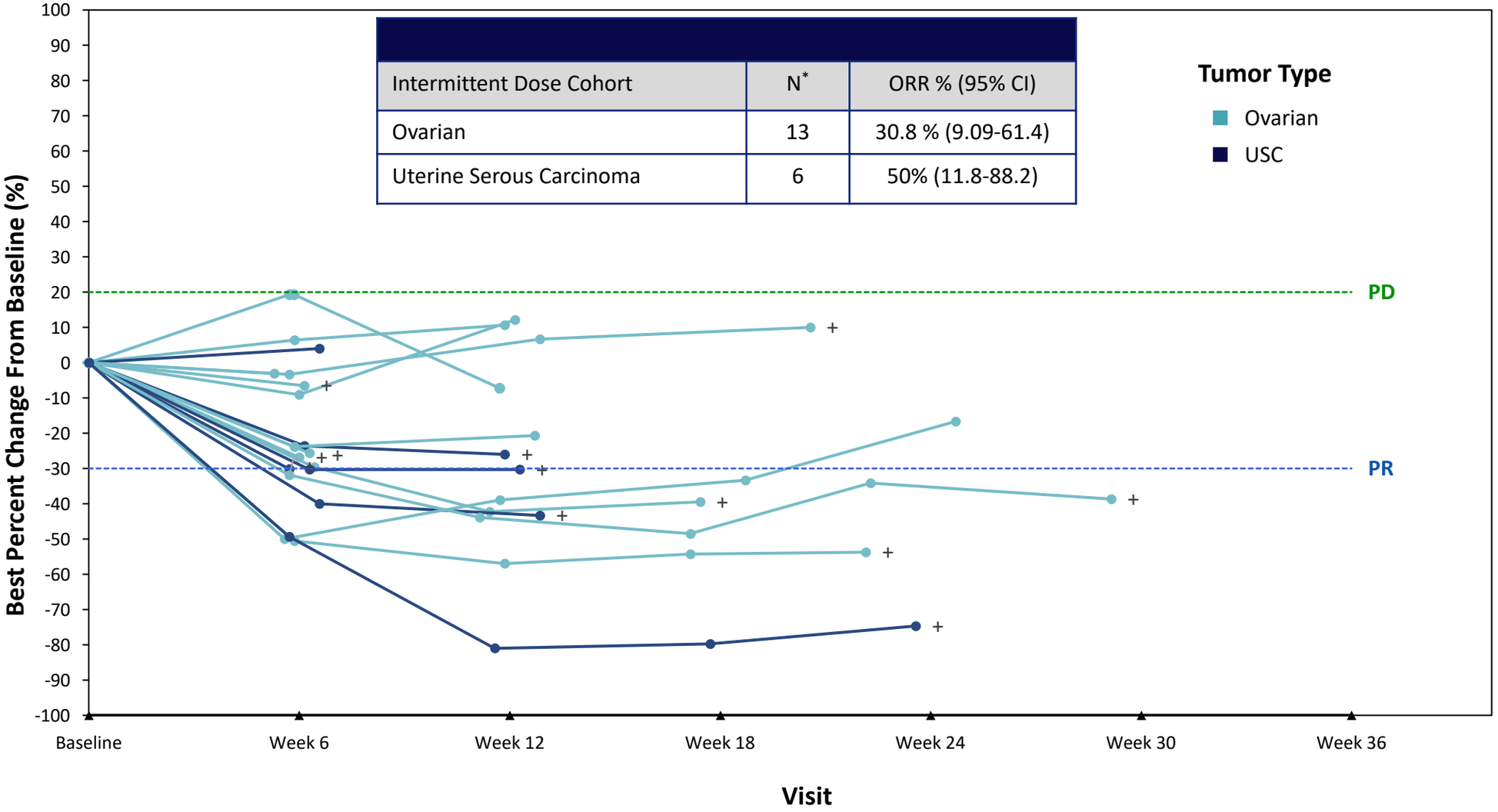
Data cut-off: June 2, 2023

Azenosertib Monotherapy Intermittent Dosing: 89% of Ovarian and USC Patients Had Target Lesion Reductions from their Baseline Scans



Intermittent Dose Cohort	N*	ORR % (95% CI)
Ovarian	13	30.8 % (9.09-61.4)
Uterine Serous Carcinoma	6	50% (11.8-88.2)

- 12/19 (63%) patients remain on therapy
- Median follow up of 4.4 months
- mPFS of 5.68 months (2.79, NR)
- 10/13 (77%) of ovarian cancer patients had received a prior PARP inhibitor

*Response evaluable: have baseline measurable disease by RECIST 1.1, at least one post baseline scan, and received at least one dose of drug; Patients who received ≥300 mg.
Abbreviations: USC, uterine serous carcinoma; HGSOC, high-grade serous ovarian cancer SD, stable disease; PR, partial response; ORR, confirmed objective response rate; mPFS, median progression free survival; complete response; NR, Not reached, +: Patients remain on therapy at the time of data cut-off

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Data cut-off: June 2, 2023

Intermittent Dosing Maintains Safety And Tolerability

Treatment Related AEs, N (%)	Continuous (n=67)		Intermittent (n=27)		Total* (n=94)	
	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4
Gastrointestinal						
Nausea	46 (68.7)	2 (3.0)	9 (33.3)	-	55 (58.5)	2 (2.1)
Diarrhea	31 (46.3)	4 (6.0)	11 (40.7)	3 (11.1)	42 (44.7)	7 (7.4)
Vomiting	28 (41.8)	-	3 (11.1)	-	31 (33.0)	-
Decreased appetite	20 (29.9)	1 (1.5)	4 (14.8)	1 (3.7)	24 (25.5)	2 (2.1)
Dehydration	6 (9.0)	-	3 (11.1)	-	9 (9.6)	-
Fatigue	30 (44.8)	8 (11.9)	11 (40.7)	2 (7.4)	41 (43.6)	10 (10.6)
Hematologic						
Anemia	6 (9.0)	2 (3.0)	6 (22.2)	3 (11.1)	12 (12.8)	5 (5.3)
Thrombocytopenia	4 (6.0)	3 (4.5)	2 (7.4)	-	6 (6.4)	3 (3.2)
Neutropenia**	1 (1.5)	1 (1.5)	4 (14.8)	3 (11.1)	5 (5.3)	4 (4.3)

*Safety Evaluable Population: Received at least one dose of drug;
**No incidence of febrile neutropenia in either dosing group
Continuous 300, 350, 400; Intermittent 350 5:2 and 400 5:2
Treatment Related AEs > 10% and treatment related AEs of interest: All Tumor Types
Abbreviations: AE, adverse event

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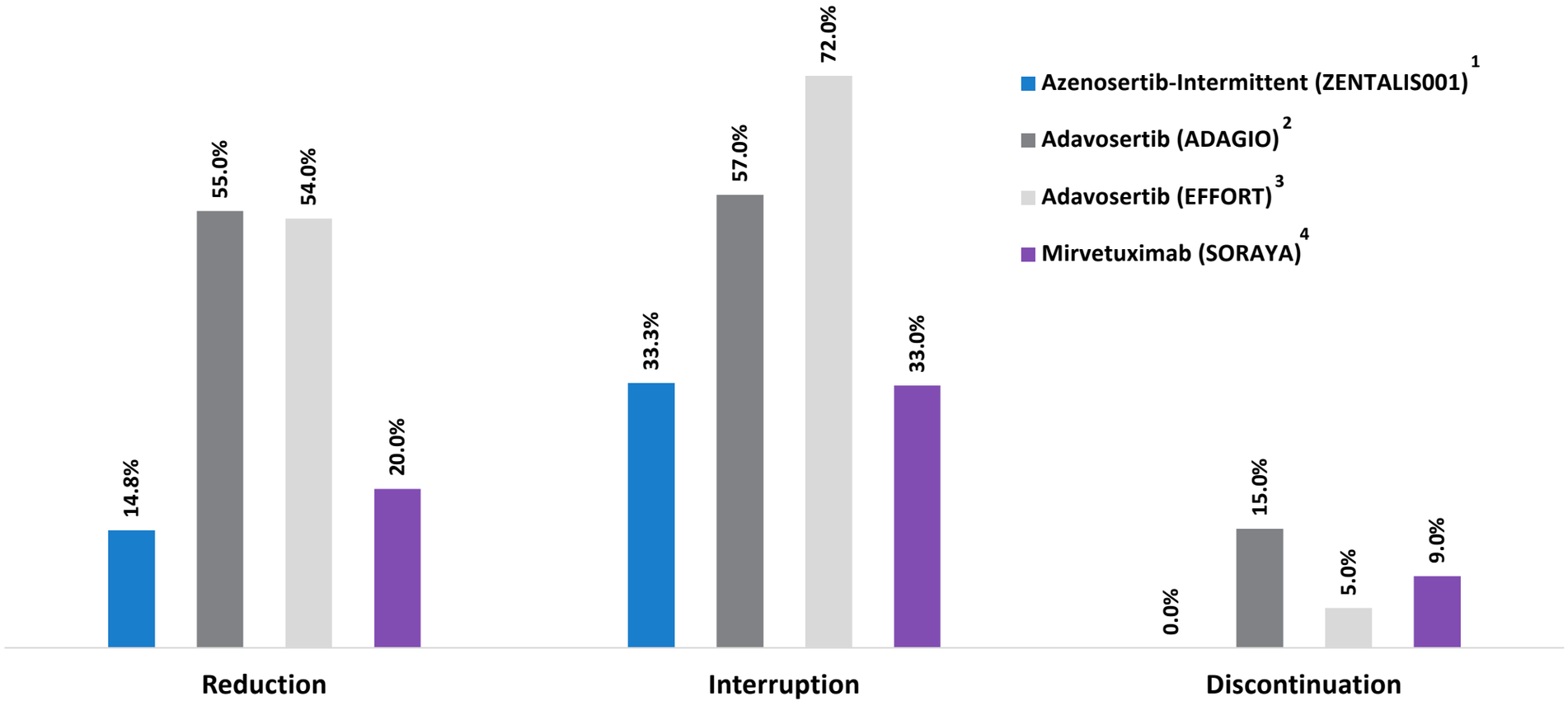
Data cut-off: April 24, 2023

Azenosertib: Improved Tolerability Compared To Other Agents



1. ZENTALIS 001: data on file
2. (ADAGIO Phase 2b Study) Liu et. al. Presented at the Society of Gynecologic Oncology Annual Meeting, March 23–28, 2023
3. (EFFORT Phase 2 Study) Westin et. al. DOI: 10.1200/JCO.2021.39.15_suppl.5505 Journal of Clinical Oncology 39, no. 15_suppl (May 20, 2021) 5505-5505.
4. (SORAYA Phase 2 Study) Matulonis et al. DOI: 10.1200/JCO.22.01900 Journal of Clinical Oncology 41, no. 13 (May 01, 2023) 2436-2445.

Comparisons to adavosertib and Mirvetuximab are not head-to-head comparisons

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Data cut-off: April 24, 2023

Azenosertib Monotherapy

Paving Path to Registration with Three Ongoing Trials Accruing at New Intermittent Dose

Zentalis 004 (TETON): Azenosertib Monotherapy In Women With ≥2L Advanced Uterine Serous Carcinoma

CURRENTLY ACCRUING- FDA Fast track designation

Key Eligibility: Recurrent or persistent USC; ≥1 prior platinum-based chemotherapy regimen; Prior HER-2 directed therapy for known HER-2+; Prior anti-PDL-1; Measurable disease; ECOG PS 0-1; No prior WEE1 inhibitor; No prior cell cycle checkpoint inhibitor.

Patients (N=130)
Azenosertib
400 mg QD 5:2

Endpoints

- **ORR**
- **DOR**
- **Safety and Tolerability**

NCT04814108

Abbreviations: 2L, two lines; USC, uterine serous carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance score;
QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; ORR, objective response rate; DOR, duration of response
The FDA granted Fast Track designation in November 2021 to azenosertib in patients with advanced or metastatic USC who have received at least one prior platinum-based chemotherapy regimen for management of advanced or metastatic disease.

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Zentalis 005 (DENALI): Evaluating Impact of *CCNE1* Amplification and Cyclin E1+ in Platinum-Resistant High-Grade Serous Ovarian Cancer

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Key Eligibility: High-Grade Serous Ovarian Cancer; ECOG PS 0-1; Platinum-resistant (excluding Platinum-refractory); 1-3 prior lines of chemotherapy; Measurable disease per RECIST v 1.1

Cohort 1 (N=30)
CCNE1 Amplified and/or Cyclin E1+

Azenosertib
400 mg QD 5:2

Cohort 2A (N=60)
CCNE1 Amplified

Cohort 2B (N=80)
CCNE1 Non-Amplified & Cyclin E1+

Cohort 2C (N=40)
CCNE1 Non-Amplified & Cyclin E1-

Endpoints (ICR)

ORR
DOR

ORR
DOR

ORR
DOR

NCT05128825

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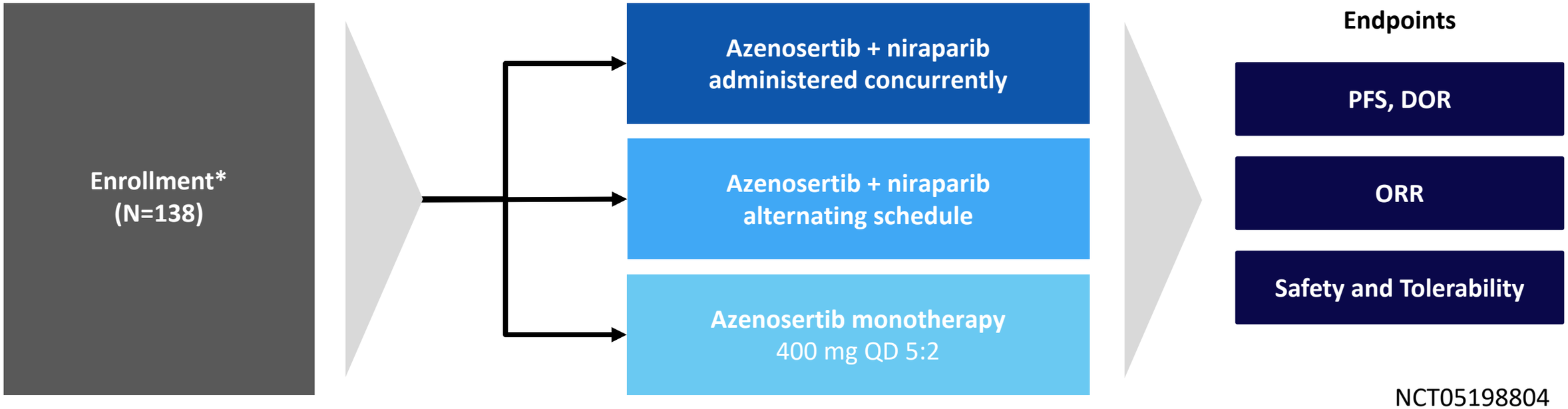
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; RECIST, response evaluation criteria in solid tumors; QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; ORR, objective response rate; DOR, Duration of Response; ICR, Independent Central Review

Zentalis 006 (MAMMOTH): Revised Phase 1/2 Study Of Azenosertib In Combination With Niraparib Or Alternating With Niraparib Or As A Monotherapy in Patients With PARP-resistant Ovarian Cancer

CURRENTLY ACCRUING

Key Eligibility: Recurrent high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer (serous, clear cell or endometrioid); 1 – 5 prior lines for advanced/metastatic disease; Relapsed within 6 months of platinum therapy (platinum resistant), progressed after taking at least 3 months of PARPi as maintenance treatment.



NCT05198804

* Enrollment Based on Slot Availability

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Abbreviations: PARPi, poly-ADP ribose polymerase inhibitor; QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; PFS, progression free survival; ORR, objective response rate

Azenosertib Combination with Chemotherapy

Strong and Durable Efficacy Signals and Favorable Safety Profile Across Chemotherapy Backbones Enable Advancement into Phase 3 in Ovarian Cancer

Addition of Azenosertib to Chemotherapies Increases Response Rates and Durability of Response in Ovarian Cancer Compared to Chemotherapy Alone

50%

50% Objective Response Rate with 7.4-month Progression Free Survival in paclitaxel combination

Superior durability in carboplatin combination with **10.4-month Progression Free Survival** and 36% Objective Response Rate

Overall tolerability of paclitaxel and carboplatin combinations **compares favorably to SOC** chemotherapy doublets paclitaxel-carboplatin or PLD-carboplatin

Cyclin E1+ status associated with **superior Objective Response Rate and longer Progression Free Survival** across response-evaluable patient population

Registrational Phase 3 Trial Announced in Platinum Sensitive Ovarian Cancer

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SOC, standard of care; PLD, pegylated liposomal doxorubicin

Zentalis 002: Phase 1b Combination Study To Define RP2D Dosing

Key Eligibility: High-Grade Serous Ovarian Cancer; ECOG Performance Status 0-2; Platinum-resistant/refractory; Up to 3 prior lines of chemotherapy; Measurable disease per RECIST v 1.1

Dose Finding guided by a CRM

Cohort assignment by availability and investigator preference

Azenosertib + Paclitaxel

Paclitaxel: 80 mg/m^2 on D1, D8, D15 (28-day cycles)

200 mg QD 5:2 → 2 dose levels → 300 mg QD 5:2

Azenosertib + Carboplatin

Carboplatin: AUC 5 mg/mL*min on D1 (21-day cycles)

300 mg QD → 4 dose levels → 200 mg QD 5:2

Azenosertib + Gemcitabine

Gemcitabine: D1, D8 (21-day cycles)

G: 1000 mg/m^2 A: 200 mg QD → 3 dose levels → G: 600 mg/m^2 A: 200 mg QD 5:2

Azenosertib + PLD

PLD: 40 mg/m^2 D1 (28-day cycles)

200 mg QD → 3 dose levels → 400 mg QD 5:2

Objectives

Primary: Safety and Tolerability MTD and/or RP2D

Key Secondary: Clinical Activity (Endpoints: ORR, DOR, PFS, CA125)

NCT04516447

Abbreviations: ; ECOG, Eastern Cooperative Oncology Group; RECIST, response evaluation criteria in solid tumors; 5:2, 5-days of treatment followed by 2-days off treatment; CRM, continuous reassessment model; QD, once daily; D, day; AUC, area under the curve; G, gemcitabine; A, azenosertib; PLD, pegylated liposomal doxorubicin; MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival;

Liu, J., et al. "Correlation of Cyclin E1 expression and clinical outcomes in a Phase 1b dose-escalation study of Azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC)." Poster presented ASCO 2023

Encouraging Efficacy and Durability in Azenosertib Chemotherapy Doublets

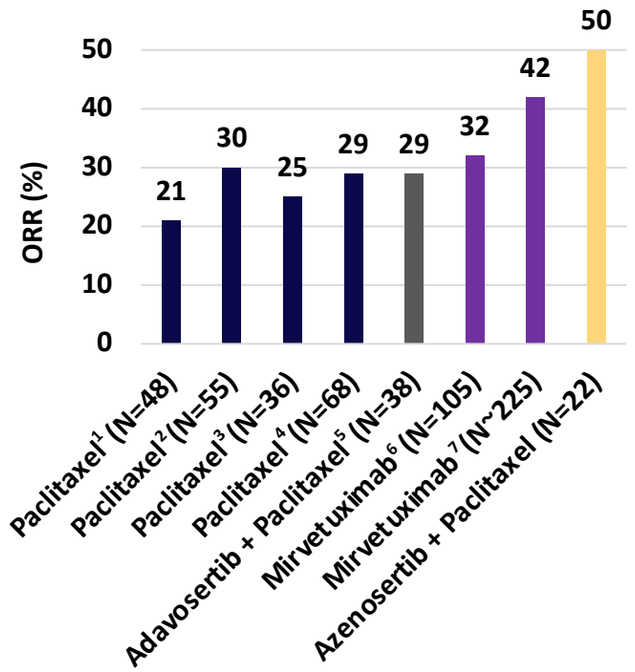
Endpoint	Azenosertib + Paclitaxel (N=26)	Azenosertib + Carboplatin (N=36)	Azenosertib + Gemcitabine (N=18)	Azenosertib + PLD (N=35)	Total (N=115)
Response-Evaluable* (N)	22	28	13	31	94
ORR (confirmed), N (%)	11 (50.0)	10 (35.7)	5 (38.5)	6 (19.4)	32 (34.0)
Median DOR (95% CI) in months	5.6 (3.8-NE)	11.4 (8.3-NE)	6.2 (NE)	7.3 (1.5-NE)	8.3 (5.6-12.4)
Clinical Benefit Rate (CR + PR + SD for ≥ 16 weeks), N (%)	18 (81.8)	16 (57.1)	6 (46.2)	24 (77.4)	64 (68.1)
Median PFS (95% CI) in months	7.4 (5.5-NE)	10.4 (3.3-14.5)	8.3 (3.3-NE)	6.3 (3.7-11.0)	9.0 (5.8-13.7)

*Response evaluable subjects are treated subjects with baseline measurable disease per RECIST version 1.1 and at least one post-baseline assessment.
All objective responses were confirmed per RECIST v 1.1.
Abbreviations: ; PLD, pegylated liposomal doxorubicin; ORR, objective response rate; DOR, duration of response; CI, confidence interval; NE, not estimable; CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors

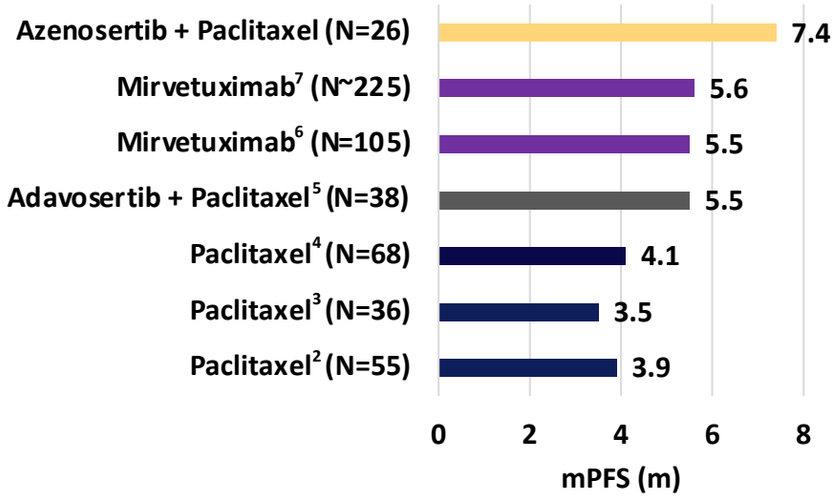
Liu, J., et al. "Correlation of Cyclin E1 expression and clinical outcomes in a Phase 1b dose-escalation study of Azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC)." Poster presented ASCO 2023

Activity of Azenosertib + Paclitaxel is Robust and Competitively Favorable

Objective Response Rate (ORR)



Median Progression Free Survival (mPFS)



References: 1. Markman et al. Gynecol Oncol 2006;101:436-40. 2. AURELIA: Avastin USPI 3. MITO11: Pignata et al. Lancet Oncol 2015;16:561-68. 4. OCTOPUS: Banerjee et al. ESMO 2019. 5. GYN49: Moore et al. Clin Cancer Res 2022;28:36-44. 6. SORAYA: Matulonis et al. J Clin Oncol 2023;41:2436-45. 7. MIRASOL: Immunogen Press Release May 3, 2023.

Abbreviations: ORR, objective response rate; mPFS, median progression free survival; m, months

Comparisons to historic benchmarks on this slide are not head-to-head comparisons

Liu, J., et al. "Correlation of Cyclin E1 expression and clinical outcomes in a Phase 1b dose-escalation study of Azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC)." Poster presented ASCO 2023

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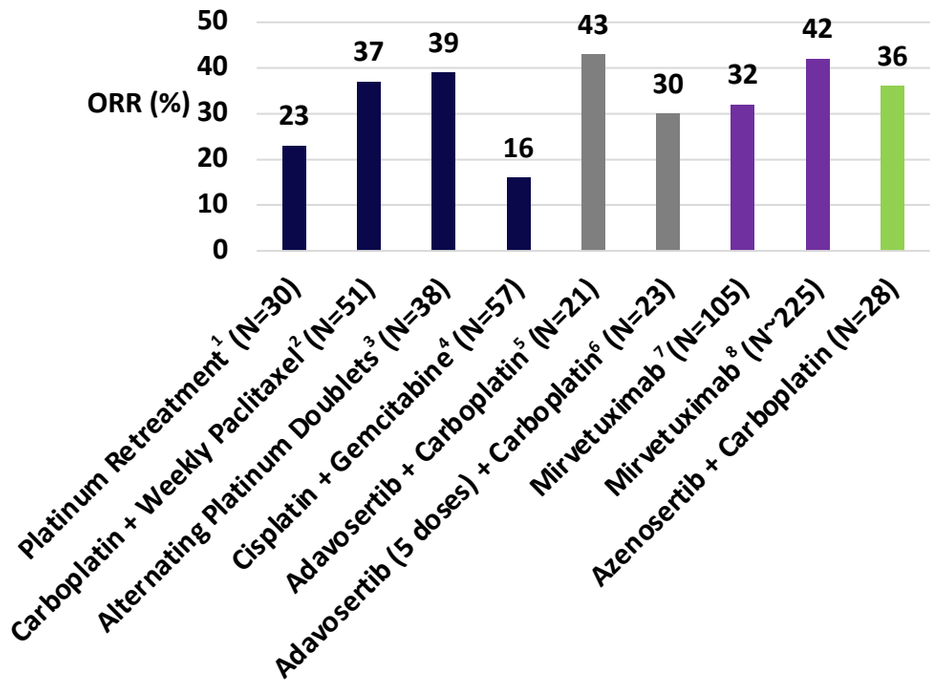
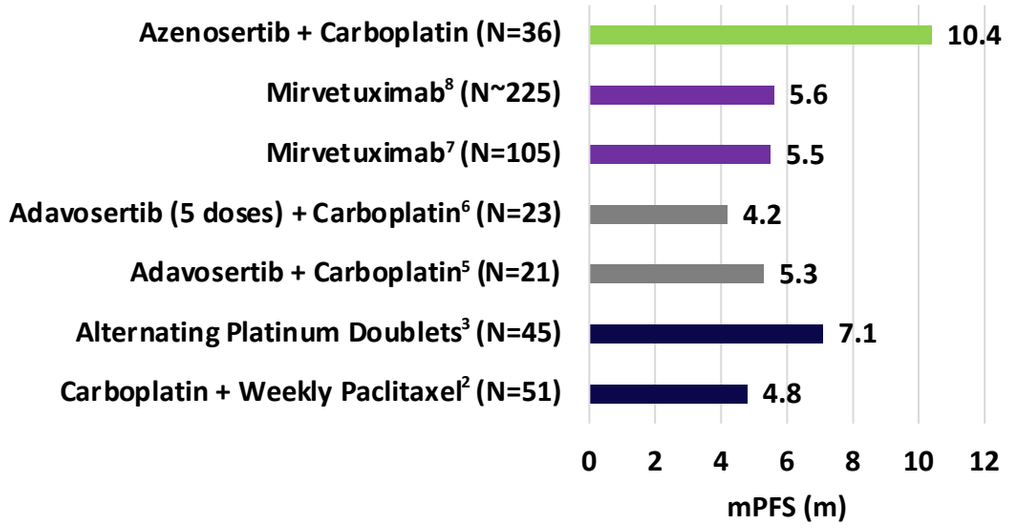
Data cut-off: April 10, 2023

Activity of Azenosertib + Carboplatin is Robust and Highly Differentiated on Durability

Objective Response Rate (ORR)



Median Progression Free Survival (mPFS)



References: 1. Leitao et al. Gynecol Oncol 2003;91:123-9. 2. CARTAXHY: Lortholary et al. Ann Oncol 2012;23:346-52. 3. Pectasides et al. Gynecol Oncol 2010;118:52-7. 4. Brewer et al. Gynecol Oncol 2006;103:446-50. 5. MK-1775-009: Leijen et al. J Clin Oncol 2016;34:4354-61. 6. GYN-49: Moore et al. Clin Cancer Res 2022;28:36-44. 7. SORAYA: Matulonis et al. J Clin Oncol 2023;41:2436-2445. 8. MIRASOL: Immunogen Press Release May 3, 2023.
Abbreviations: ORR, objective response rate; mPFS, median progression free survival; m, months
Comparisons to historic benchmarks on this slide are not head-to-head comparisons
Liu, J., et al. "Correlation of Cyclin E1 expression and clinical outcomes in a Phase 1b dose-escalation study of Azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC)." Poster presented ASCO 2023

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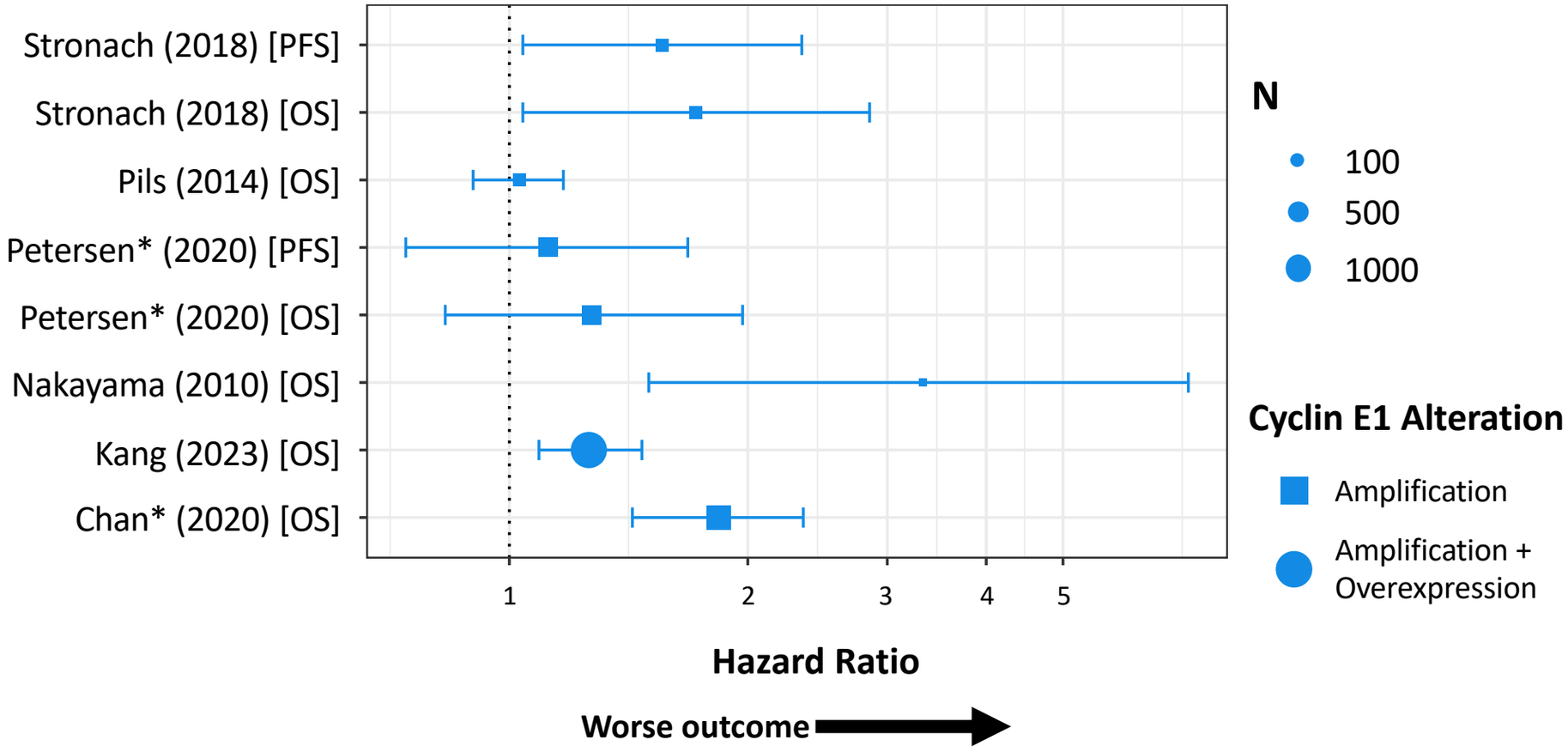
Ovarian Cancer Patients with CCNE1 Amplified and/or Cyclin E1 Positive Cancers have a Worse Outcome Following Platinum-Based Chemotherapy Treatment Independent of Platinum-Sensitivity Status



- 6 Studies; n=5404
- 4 Studies where timing of tissue collection was available-all were platinum sensitive tissue collected after ≤ 1 course of chemotherapy); 3533/5404 (65%)
- Other 2 Studies did not disclose timing of tissue collection

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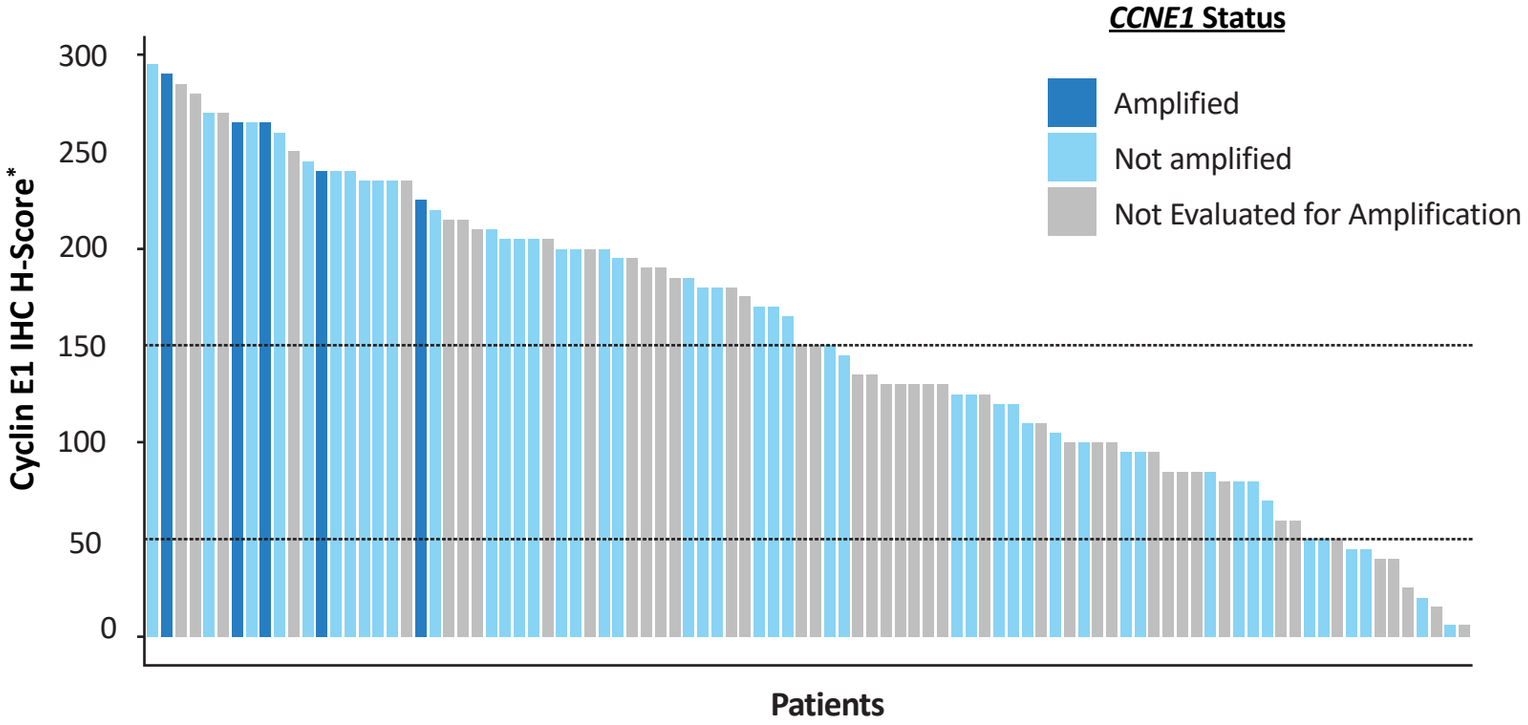
*Timing of tissue collection was not disclosed. Abbreviations: PFS: progression free survival, **OS; overall survival**

Zentalis 002: Majority of Ovarian Cancers are Cyclin E1+

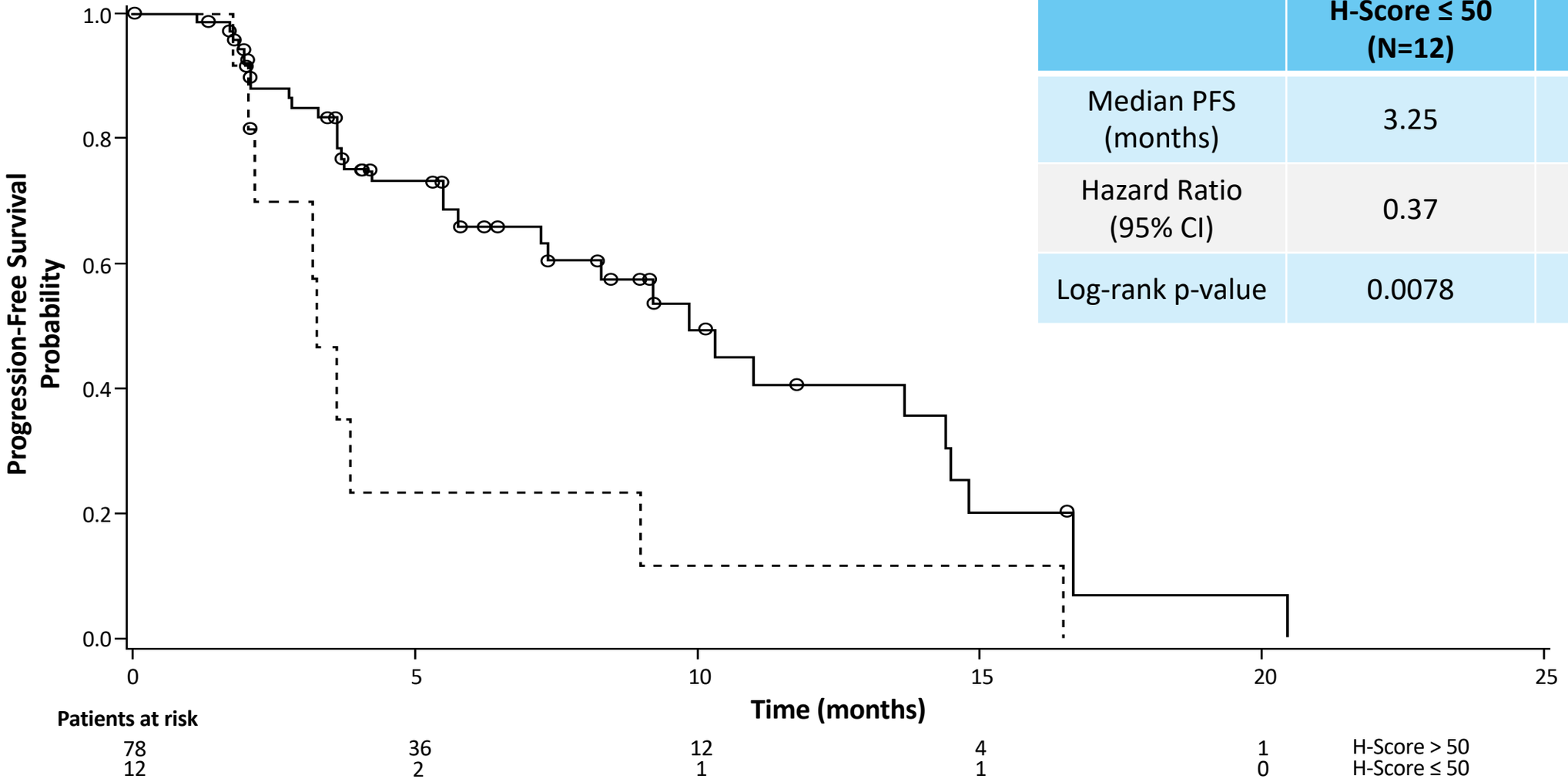


IHC H-Score*	>150	≤ 150 to > 50	≤ 50
CCNE1 Amplified	5	0	0
CCNE1 Not Amplified	25	15	6
Tissue Not Evaluated for Amplification	16	21	6

- H-score > 50 includes all *CCNE1* amplified tumors
- Prevalence of Cyclin E1-IHC+, H-score > 50 of all safety evaluable patients with tissue is 82/94 (**87**%);
- Prevalence of Cyclin E1+ in the response evaluable patients with tissue is 70/82 **(85%).**

*H-scores calculated by multiplying the percentage of cells (0 to 100%) with intensity of Cyclin E1 expression (0 to 3); IHC: Immunohistochemistry
Safety evaluable: received at least one dose of drug; Response evaluable: have baseline measurable disease by RECIST 1.1, at least one post baseline scan, and received at least one dose of drug
Liu, J., et al. "Correlation of Cyclin E1 expression and clinical outcomes in a Phase 1b dose-escalation study of Azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC)." Poster presented ASCO 2023

Durability Triples in Patients with Cyclin E1+ Tumors Independent of Chemotherapy Backbone



	H-Score ≤ 50 (N=12)	H-Score > 50 (N=78)
Median PFS (months)	3.25	9.86
Hazard Ratio (95% CI)	0.37	(0.18 – 0.79)
Log-rank p-value	0.0078	

*Response evaluable patients (having received at least one scan)
Abbreviations: IHC, immunohistochemistry ; CI, confidence interval
Liu, J., et al. "Correlation of Cyclin E1 expression and clinical outcomes in a Phase 1b dose-escalation study of Azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC)." Poster presented ASCO 2023

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Data cut-off: April 10, 2023

Intermittent Dosing Across Chemotherapy Backbones Has Favorable Safety Profile

Treatment-Related Adverse Event ≥20% N (%)			Azenosertib + Paclitaxel (Continuous, N=7; Intermittent, N=19)		Azenosertib + Carboplatin (Continuous, N=22; Intermittent, N=14)		Azenosertib + Carboplatin (Continuous, N=14; Intermittent, N=8)		Azenosertib + Gemcitabine (Continuous N=8; Intermittent, N=10)		Azenosertib + PLD (Continuous N=27; Intermittent, N=8)		Total (Continuous, N=64; Intermittent, N=51)	
			All Doses*		All Doses		Doses ≤ MTD		All Doses**		All Doses*			
Grade			All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3
Hematologic	Neutropenia	C	5 (71.4)	5 (71.4)	9 (40.9)	7 (31.8)	4 (28.6)	3 (21.4)	7 (87.5)	6 (75.0)	19 (70.4)	17 (63.0)	40 (62.5)	35 (54.7)
		I	11 (57.9)	5 (26.3)	7 (50.0)	1 (7.1)	4 (50.0)	-	7 (70.0)	4 (40.0)	3 (37.5)	3 (37.5)	28 (54.9)	13 (25.5)
	Thrombo-cytopenia	C	4 (57.1)	2 (28.6)	16 (72.7)	11 (50.0)	11 (78.6)	6 (42.9)	8 (100.0)	5 (62.5)	9 (33.3)	2 (7.4)	37 (57.8)	20 (31.3)
		I	4 (21.1)	-	9 (64.3)	5 (35.7)	4 (50.0)	2 (25.0)	8 (80.0)	6 (60.0)*	3 (37.5)	3 (37.5)	24 (47.1)	14 (27.5)
	Anemia	C	5 (71.4)	-	10 (45.5)	3 (13.6)	5 (35.7)	1 (7.1)	6 (75.0)	2 (25.0)	11 (40.7)	4 (14.8)	32 (50.0)	9 (14.1)
		I	8 (42.1)	1 (5.3)	10 (71.4)	4 (28.6)	4 (50.0)	1 (12.5)	5 (50.0)	2 (20.0)	2 (25.0)	1 (12.5)	25 (49.0)	8 (15.7)
Gastro-intestinal	Nausea	C	4 (57.1)	-	15 (68.2)	1 (4.5)	10 (71.4)	1 (7.1)	5 (62.5)	-	16 (59.3)	2 (7.4)	40 (62.5)	3 (4.7)
		I	7 (36.8)	1 (5.3)	6 (42.9)	-	3 (37.5)	-	5 (50.0)	-	4 (50.0)	1 (12.5)	22 (43.1)	2 (3.9)
	Vomiting	C	3 (42.9)	1 (14.3)	8 (36.4)	-	6 (42.9)	-	1 (12.5)	-	11 (40.7)	2 (7.4)	23 (35.9)	3 (4.7)
		I	2 (10.5)	1 (5.3)	2 (14.3)	-	2 (25.0)	-	1 (10.0)	-	4 (50.0)	1 (12.5)	9 (17.6)	2 (3.9)
	Diarrhea	C	4 (57.1)	1 (14.3)	4 (18.2)	-	1 (7.1)	-	1 (12.5)	-	8 (29.6)	-	17 (26.6)	1 (1.6)
		I	6 (31.6)	1 (5.3)	5 (35.7)	-	3 (37.5)	-	6 (60.0)	-	2 (25.0)	-	19 (37.3)	1 (2.0)
Other	Fatigue	C	6 (85.7)	1 (14.3)	8 (36.4)	-	3 (21.4)	-	3 (37.5)	1 (12.5)	8 (29.6)	3 (11.1)	25 (39.1)	5 (7.8)
		I	8 (42.1)	2 (10.5)	5 (35.7)	1 (7.1)	4 (50.0)	-	6 (60.0)	2 (20.0)	2 (25.0)	-	21 (41.2)	5 (9.8)

Abbreviations: C, Continuous azenosertib dosing; I, Intermittent azenosertib dosing; MTD, maximum tolerated dose; PLD, pegylated liposomal doxorubicin
*All doses were at or below the MTD
**A MTD for Gemcitabine + Azenosertib has not been determined, further dose cohorts are ongoing.

Liu, J., et al. "Correlation of Cyclin E1 expression and clinical outcomes in a Phase 1b dose-escalation study of Azenosertib (ZN-c3), a WEE1 inhibitor, in combination with chemotherapy (CT) in patients (pts) with platinum-resistant or refractory (R/R) epithelial ovarian, peritoneal, or fallopian tube cancer (EOC)." Poster presented ASCO 2023

Data Supports Advancement of Azenosertib-Chemotherapy Combination into Platinum-Sensitive Ovarian Cancer & Earlier Line Therapy

RP2D established for paclitaxel, carboplatin and PLD combinations

RP2D		
	Azenosertib	Chemotherapy
Paclitaxel	300 mg QD 5:2	80 mg/m^2 on D1, D8, D15 (28-day cycles)
Carboplatin	200 mg QD 5:2	AUC=5 on D1 (21-day cycles)
Gemcitabine	TBD*	TBD*
PLD	400 mg QD 5:2	40 mg/m^2 D1 (28-day cycles)

Main Takeaways

- Strong and durable efficacy signal across chemotherapy backbones
- Cyclin E1 status predicts benefit of azenosertib addition to chemotherapy
  - Suggests azenosertib restores chemotherapy sensitivity in heavily pre-treated platinum-resistant ovarian cancer
- **Plans to initiate Phase 3 study of azenosertib in combination with paclitaxel or with carboplatin in Cyclin E1+ platinum sensitive ovarian cancer**

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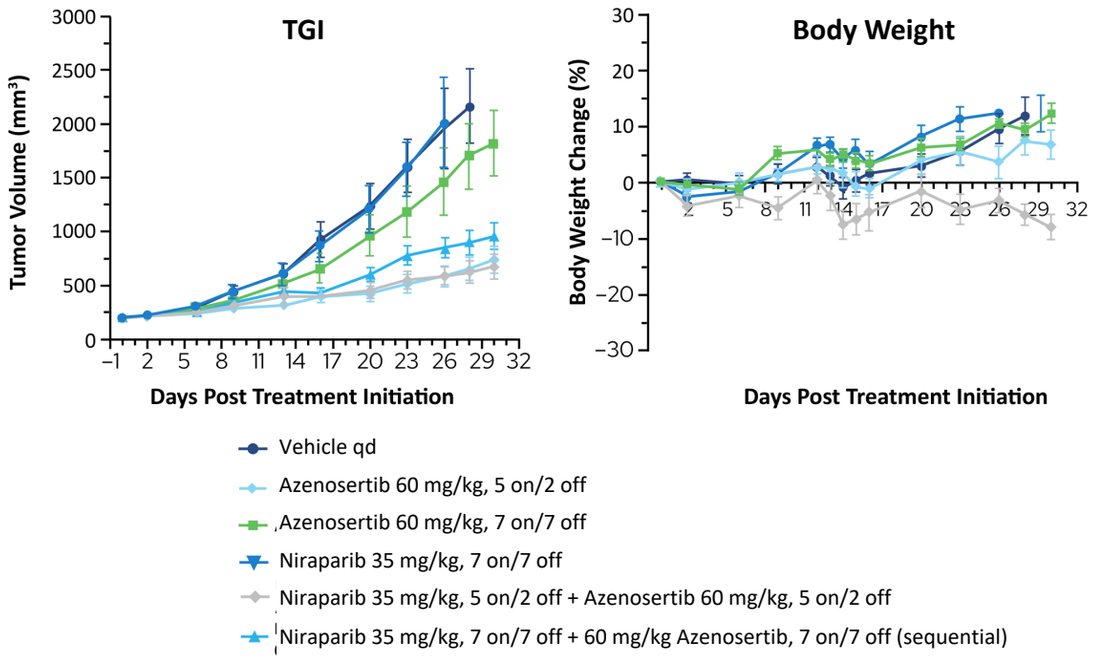
*Gemcitabine + Azenosertib has exciting and durable activity-a MTD has not been determined, further dose cohorts are ongoing.
Abbreviations: RP2D, recommended phase 2 dose; PLD pegylated liposomal doxorubicin; QD, once daily;
5:2, 5-days of treatment followed by 2-days off treatment; D, day; AUC, area under the curve; mg/mL*min

Azenosertib

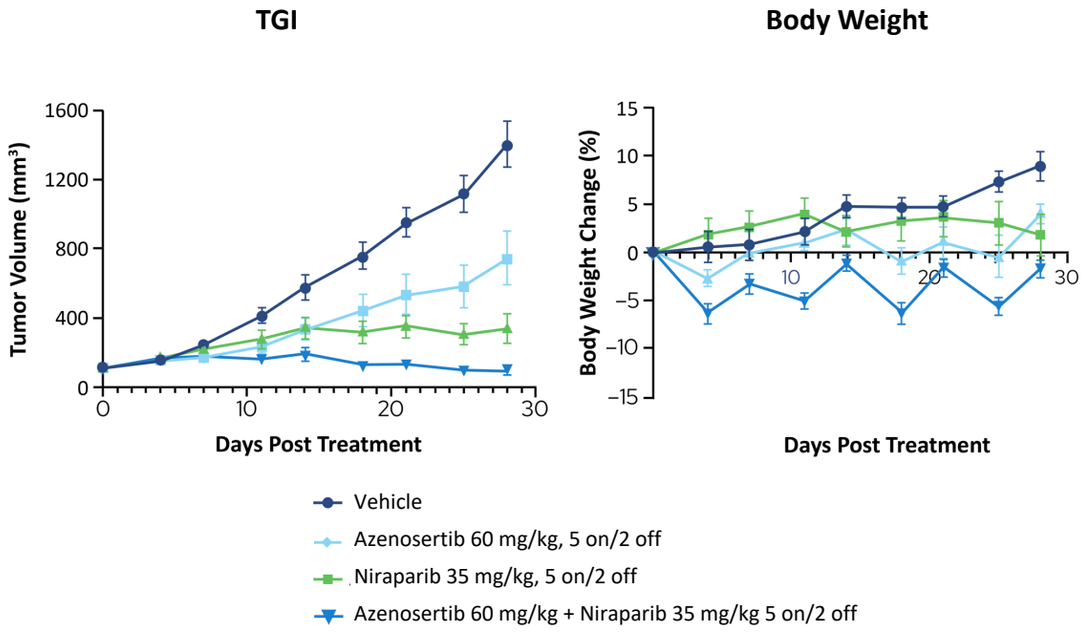
Advancing Programs Investigating Post-PARPi Treatment and Post-BEACON BRAF mCRC, Supported by Strong Body of Preclinical Data

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

CDX Ovarian Cancer Model (OVCAR3; *CCNE1* Amp)



PDX TNBC Model (HBCx-10; *BRCA2*mt)



- Combination of PARP and WEE1 inhibitors in TNBC results in synergistic cell killing in preclinical models with either BRCA mutations or high levels of Cyclin E1 [1]

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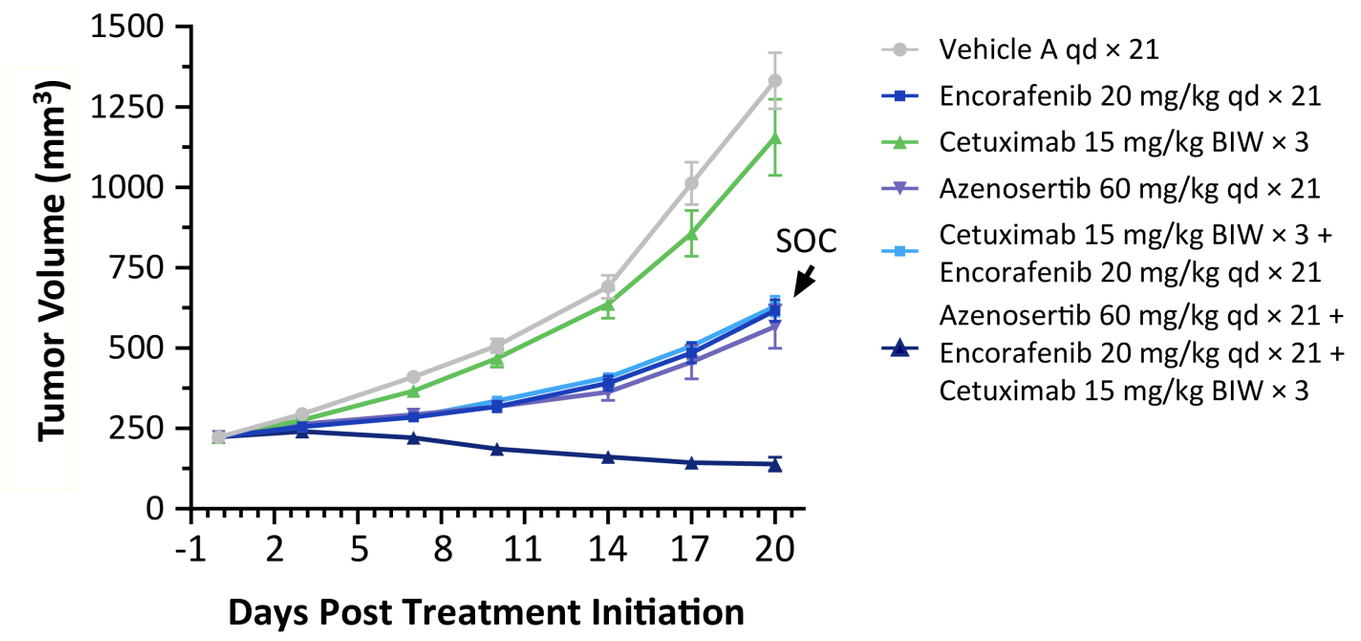
1. Chen X Cancers (Basel). 2021 Apr 1;13(7). Abbreviations: PARP, poly (ADP-ribose) polymerase; CDX, cell line derived xenograft; TNBC, triple-negative breast cancer; PDX, patient derived xenograft; TGI, tumor growth inhibition

Preclinical Data Supports the Combination of Azenosertib with Encorafenib and Cetuximab (BEACON Regimen)

LS411N (BRAF mutant CRC model)



- 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

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Source: Zentalis Data on File

Kotsantis, et al. Cancer Discov. 2018 May; 8(5): 537–555.

BRAF mCRC Study in Collaboration with Pfizer

Key Eligibility: 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)

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

Phase 1: Dose Finding

Escalating Dose Levels of azenosertib + encorafenib + cetuximab

Phase 2: Dose Expansion

N=up to 80 patients

Primary Objectives

Phase 1: Safety, tolerability, MTD, RP2D

Phase 2: ORR, DOR, DCR, PFS, TTP

Triplet Combination to be Investigated in Patients With Significant Unmet Need

- Median OS in BRAF mutant CRC patients <1 year, vs. BRAF WT >2 years2
- 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 resistance3
- Encorafenib in combination with cetuximab (BEACON) was approved for BRAF V600E mCRC in April 2020 and is now the standard of care

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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).

Abbreviations: mCRC, metastatic colorectal cancer; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; ORR, objective response rate; DOR, duration of response; DCR, disease control rate; PFS, progression free survival; TTP, time to progression; OS, overall survival

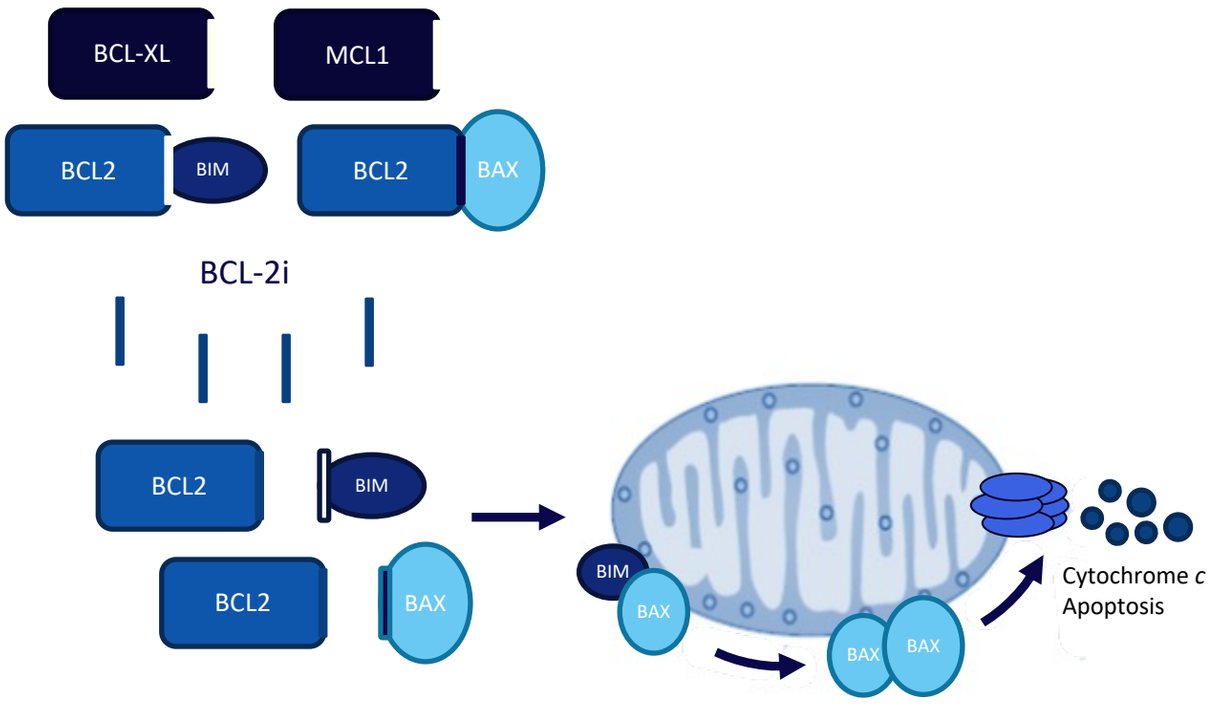
ZN-d5

BCL-2 Inhibitor with Potential Best-in-Class Profile

BCL-2: A Clinically Validated Oncology Target

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

Mechanism of Action of BCL-2 Inhibitors [1]



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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

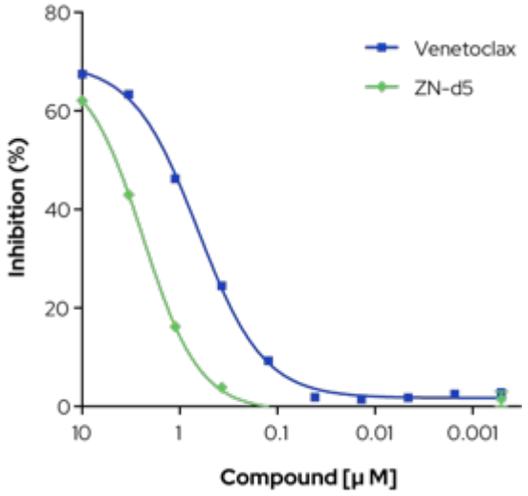
ZN-d5 has 10x Improved Selectivity for BCL-2 vs BCL-xL and Binds With Higher Affinity to BCL-2 Mutants than Venetoclax

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

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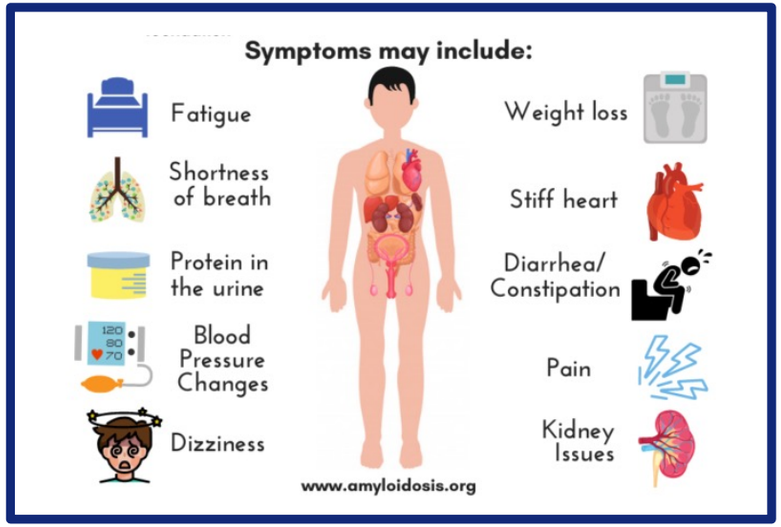
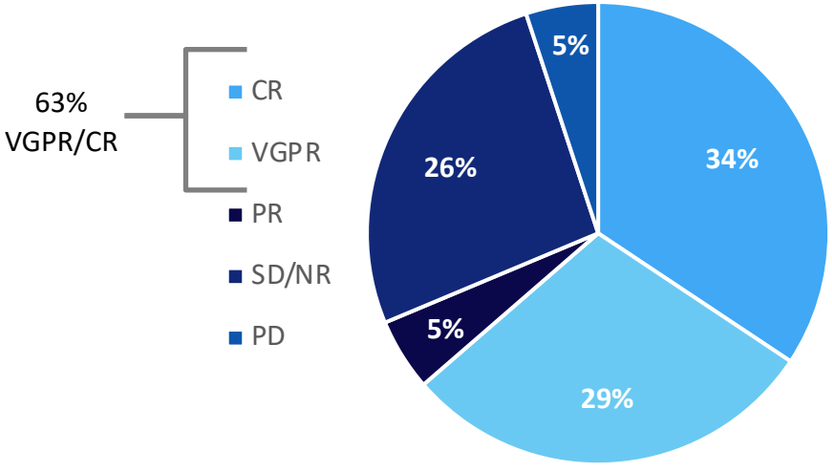
*Venetoclax data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound

ZN-d5 in AL (Primary) Amyloidosis

AL Amyloidosis study is currently enrolling patients

- 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

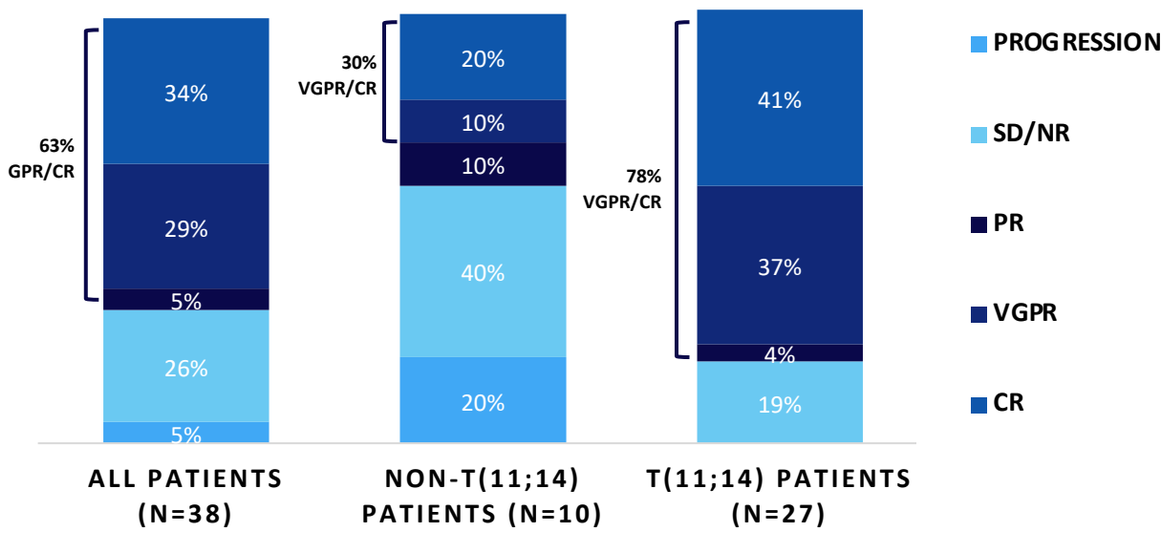




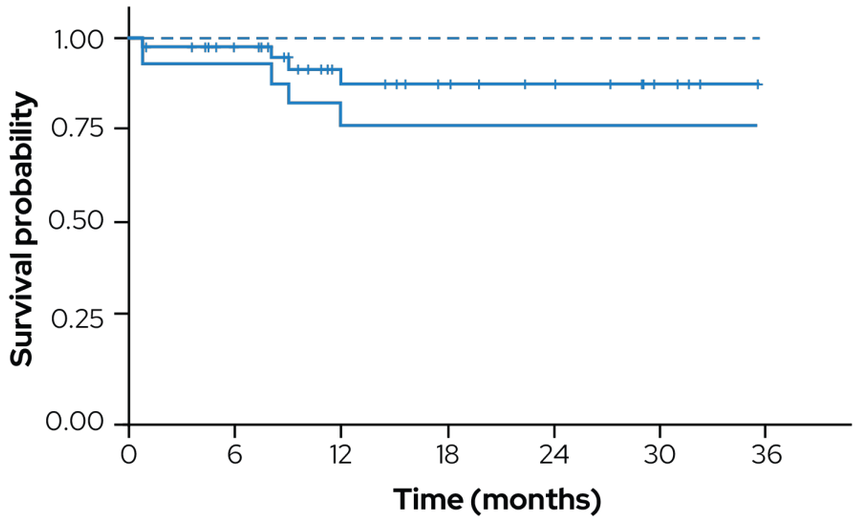
1. Zhang et al. Clin Lymphoma Myeloma Leuk. 2019;19(suppl 10):e339 2. Kyle et al, Mayo Clin Proc. 2019;94:465-471 3. Premkumar et al, Blood Cancer J 2021;11:10; hematologic response rate in 38 evaluable patients.

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

Best Response in Evaluable Patients



OS for All Patients



- 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

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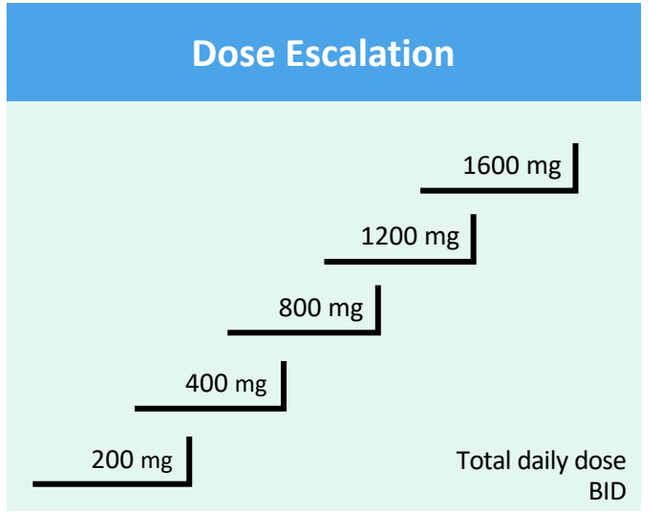
1. Premkumar et al, Blood Cancer J 2021;11:10; hematologic response rate in 38 evaluable patients.

ZN-d5-003: Phase 1 Multicenter International Clinical Trial in R/R AL Amyloidosis

Key Eligibility: AL amyloidosis ; R/R to 1-3 prior lines of therapy; dFLC ≥20 mg/L; ECOG PS ≤2; Adequate hematologic and organ function

Part A: Bayesian Optimal Interval Dose Escalation



RP2D Combo

Part B: Dose Expansion

ZN-d5 Monotherapy at RP2D

Primary Objectives

Part A:
Safety
Recommended Phase 2 Dose

Part B:
Efficacy
(Hematologic Response Rate)

Study Details: DLT Period is 28 days

- Hematologic disease response assessments done every cycle for the first 6 months
- Protocol permits Backfill enrollment of additional patients at or below the highest previously cleared dose level

NCT05199337

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Abbreviations: R/R, refractory/resistant; AL, amyloid light chain; dFLC, difference between involved minus uninvolved serum free light chains; ECOG PS, Eastern Cooperative Oncology Group performance score; BID, twice daily; RP2D, recommended Phase 2 dose

BCL-xL Protein Degrader

Compelling Discovery Program

BCL-xL Degrader Background and Rationale

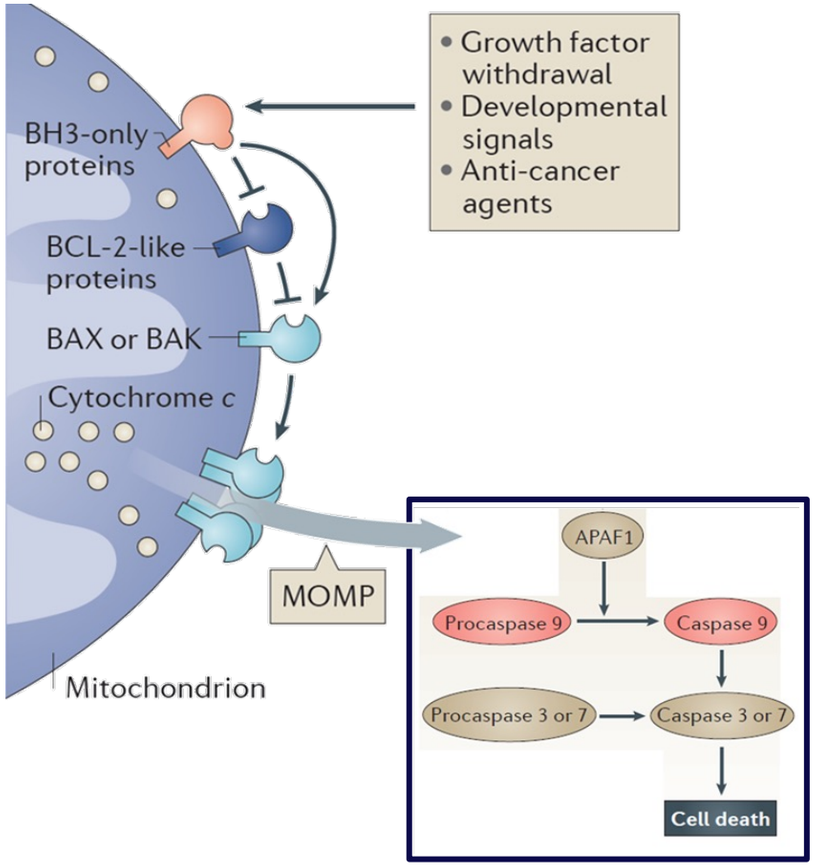
Declared development candidate and initial IND enabling activities

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.

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 non-functional or dysfunctional E3 ubiquitin ligase complex 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 the therapeutic index.



Patient Selection

- Heme malignancies
- Solid tumors

Chemical Modality

Heterobifunctional degrader linking a BH3 binding moiety to an E3 binding moiety

Internal Combination Opportunities

Azenosertib (WEE1 inhibitor) and ZN-d5 (BCL-2 inhibitor)

Competitive Landscape

Multiple inhibitors and one degrader in the clinic (Ph1/2)

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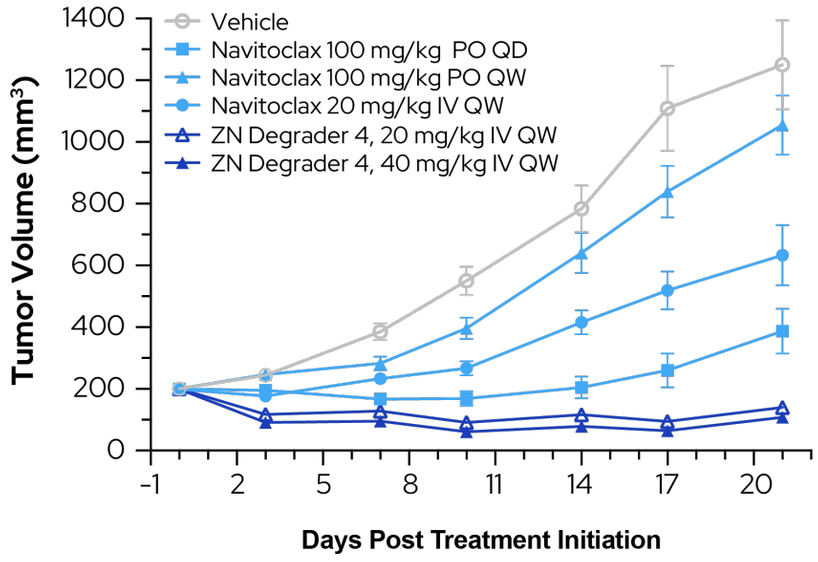
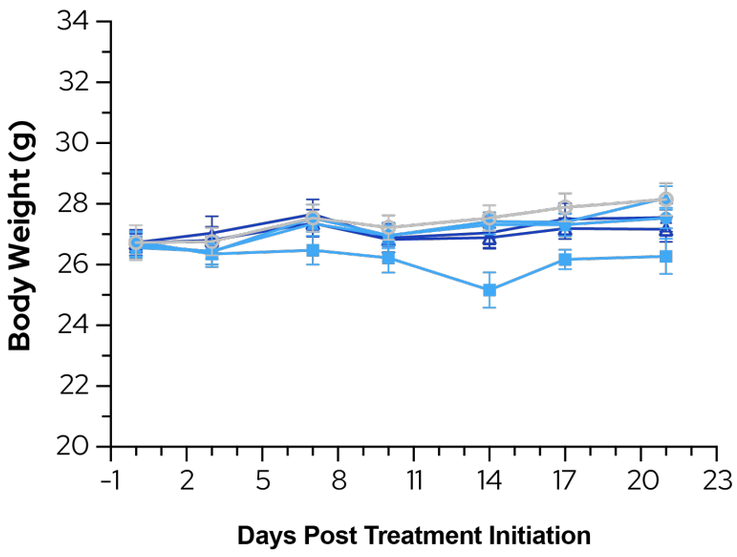
1. Bhola PD and Letai A. Mol Cell. 2016;61(5):695-704 2. Konopleva M and Letai A. Blood. 2018 Sep 6;132(10):1007-1012 3. Rahman SFA et al., Future Oncology, 2020, 16(28) 4. Yue et al., Cnacer Cell Int., 2020, 20(254)
5. cbioportal.org 6. Wilson WY et al., Lancet Oncol., 2010; 11(12):1149-1159 7. Khan 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 Degrader is More Efficacious than BCL-xL Inhibitor (Navitoclax) in MOLT4 (T-ALL) Model

MOLT4 tumor model (T-ALL)





- 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

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

2023 is a Catalyst Rich Year – Key Milestones

Azenosertib 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	Results from Phase 1b ovarian chemotherapy combination trial, including clinical translational data on Cyclin E1 amplification / overexpression
2H 2023	Update interim efficacy clinical data from monotherapy dose optimization in solid tumors
2H 2023	Update monotherapy program timelines and potential paths to registration
1Q 2024	Initiate randomized Phase 3 trial of azenosertib + chemotherapy in Cyclin E1+ platinum sensitive ovarian cancer

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

Discovery

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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