Azenosertib Clinical Update

Dose Selection, Monotherapy and Chemotherapy Combinations Efficacy and Safety and Ongoing Development

June 2023

Nasdaq: ZNTL

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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.

Today's Agenda

1. Review of Azenosertib Monotherapy Trial Results: Declaration of New Azenosertib Monotherapy Dose
2. Currently Accruing Trials in Ovarian Cancer and USC
3. Review of Azenosertib + Chemotherapy in Platinum-Resistant Ovarian Cancer (Presented Yesterday: ASCO Abstract 5513)
4. Proposed Phase 3 Chemotherapy Combination Trial
5. Q&A

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Joining the Call Today

Kimberly Blackwell, MD
Chief Executive Officer
Zentalis Pharmaceuticals

Carrie Brownstein, MD
Chief Medical Officer
Zentalis Pharmaceuticals

Funda Meric-Bernstam, MD
Chair of the Department of Investigational Cancer Therapeutics -- the Phase 1 Program at The University of Texas MD Anderson Cancer Center; Member, Zentalis Scientific. Advisory Board

Zentalis' Clinical Transformation Has Yielded Significant Progress

Purpose

- To develop **first in class** and **best in class** therapies against known cancer targets

Azenosertib meets all the criteria

- High potential, **validated target** in difficult-to-treat tumors
- WEE1 inhibitor designed to have **superior selectivity** and pharmacologic properties
- **Monotherapy activity** and favorable safety profile
- 400+ patients dosed to date

People

- Management team with **deep oncology experience**
- **Respected** scientific and clinical advisors
- Established partnerships with **Pfizer, GSK**

Promising Programs: BCL-2i and Degrader

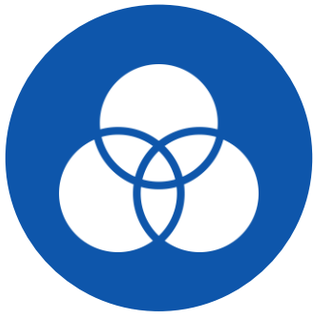
- **Multiple opportunities** in hematologic malignancies
- 100+ patients dosed to date

Positioned to Execute and Deliver

Today's Call - Two Large Phase 1 Data Sets: Four Critical Take Home Messages Around Azenosertib

Monotherapy Dose Optimization Has Been Successful:

- **Confirmed ORR of 36.8% in heavily pre-treated platinum-resistant ovarian cancer and USC**
- **Improved tolerability** over other WEE-1 Inhibitor and highly comparable to Antibody Drug Conjugates



Combination With Single Agent Chemotherapy Improves Response Rates And Durability Over Chemotherapy Alone In Platinum-resistant/Refractory Ovarian Cancer:

- 50% ORR, 5.6 month DOR and a 7.4 month mPFS with paclitaxel
- 36% ORR, 11.4 month DOR and a 10.4 month mPFS with carboplatin

Comprehensive and Ongoing Development Strategy In Ovarian Cancer and USC:

- Phase 2 Monotherapy in USC (all patients)
- Phase 2 Monotherapy in platinum-resistant ovarian cancer
- Phase 1/2 Monotherapy or in combination/alternating with niraparib PARPi-resistant PROC
- Proposed Phase 3 Study in Cyclin E1+ platinum sensitive ovarian cancer
  - Chemotherapy + azenosertib followed by azenosertib monotherapy maintenance compared to doublet chemotherapy followed by placebo

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USC, Uterine Serous Carcinoma; ORR, Confirmed Objective Response Rate; DOR, Duration of Response; mPFS, Median Progression Free Survival.

AZENOSERTIB NEW INTERMITTENT MONOTHERAPY DOSE

Azenosertib Intermittent Monotherapy Dose Substantially Improves Antitumor Activity and Tolerability

Monotherapy Dose Selection: 400 mg intermittent (5 days on, 2 days off a week; 5:2)

Compared to prior dosing regimen (300 mg continuous), intermittent dosing led to:

- More than a **doubling of exposures**
- A near **doubling of response** in both USC and HGSOC
  - Confirmed ORR of 36.8% in the patient population*
- Maintains or improves **safety and tolerability**

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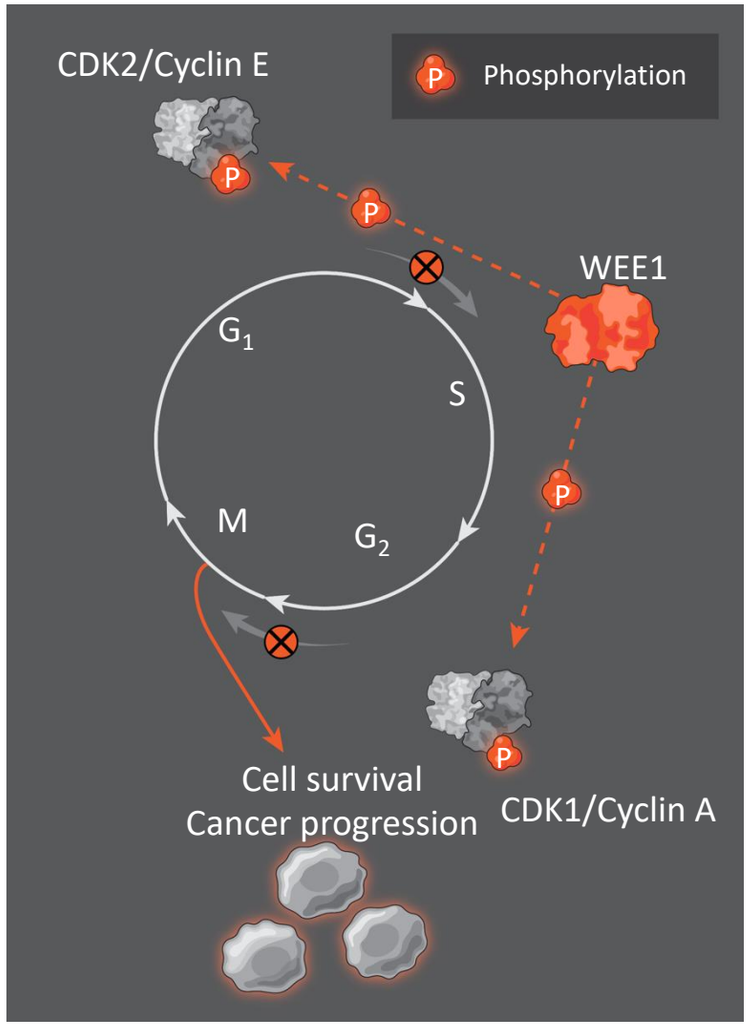
*Response evaluable: have baseline measurable disease by RECIST 1.1, at least one post baseline scan, and received at least one dose of drug;
Abbreviations: 5:2, 5-days of treatment followed by 2-days off treatment; USC, Uterine Serous Carcinoma;
HGSOC, High Grade Serous Ovarian Cancer; ORR, objective response rate

Azenosertib Targets WEE1, a Critical Protein for Cancer Cell Survival

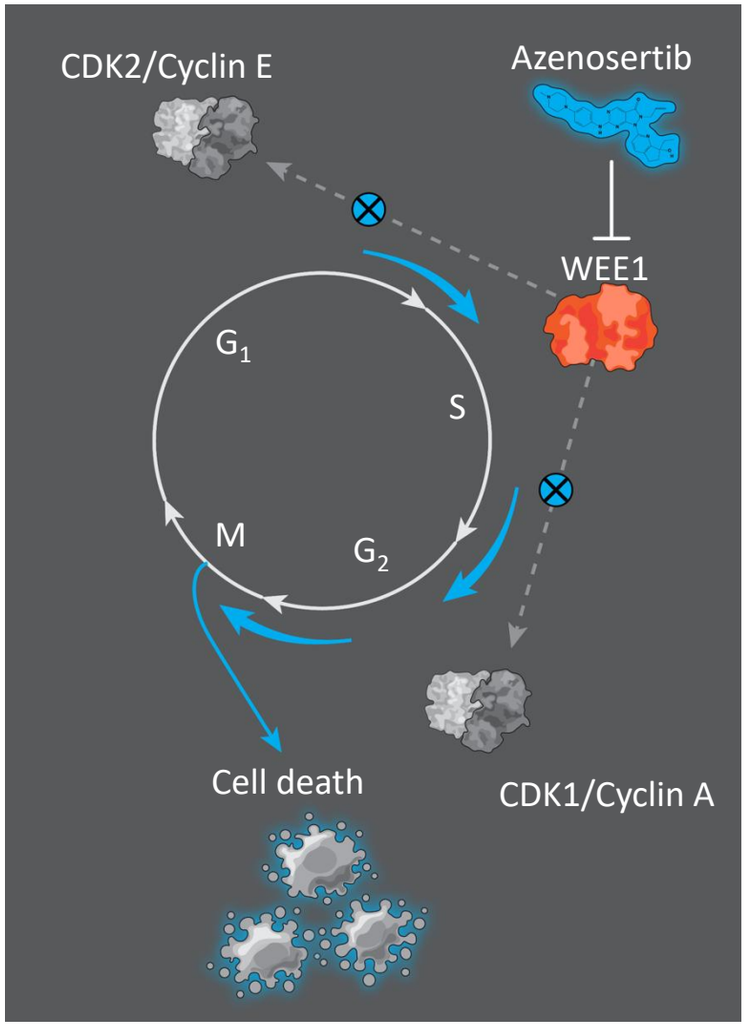
WEE1 activity in untreated cancer cell



- WEE1 phosphorylates CDK/Cyclin complexes to engage cell cycle checkpoints, allowing DNA repair to occur
- Azenosertib inhibits WEE1:
  - Leads to dephosphorylation of CDK 1 and 2, activating the cdk/cyclin complexes
  - 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



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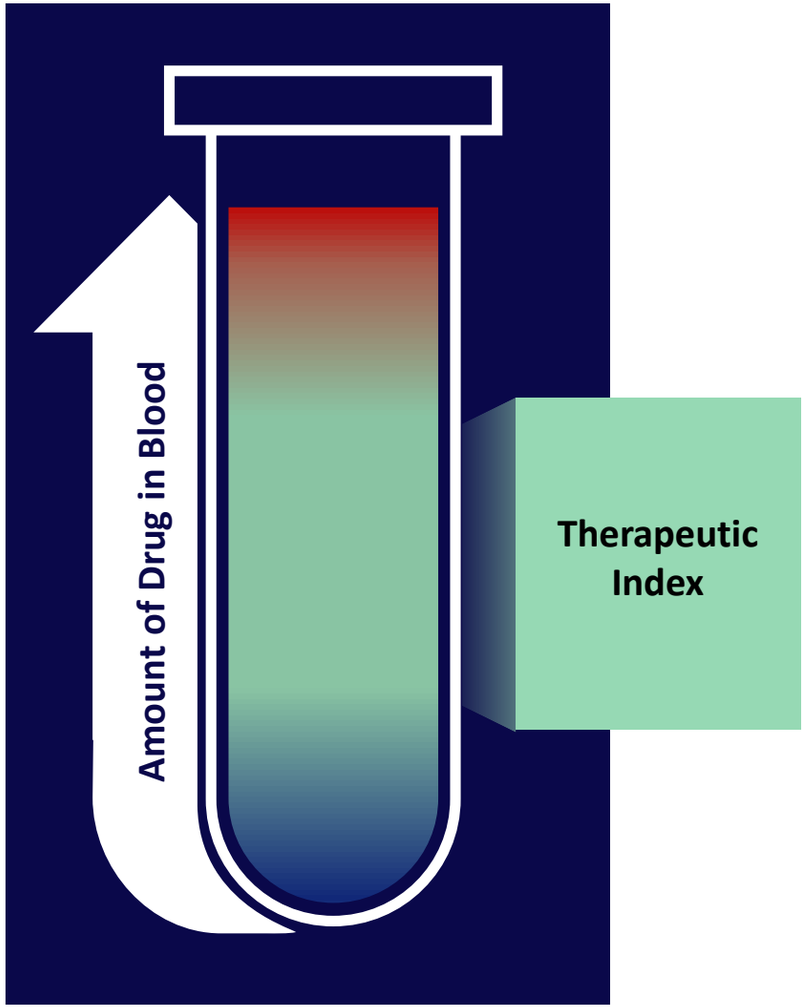
Luserna di Rora, et al. 2020. J Hem Onc. 13:126. Elbaek et al. 2022. Cell Reports. 38:110261. Abbreviations: MOA, mechanism of action

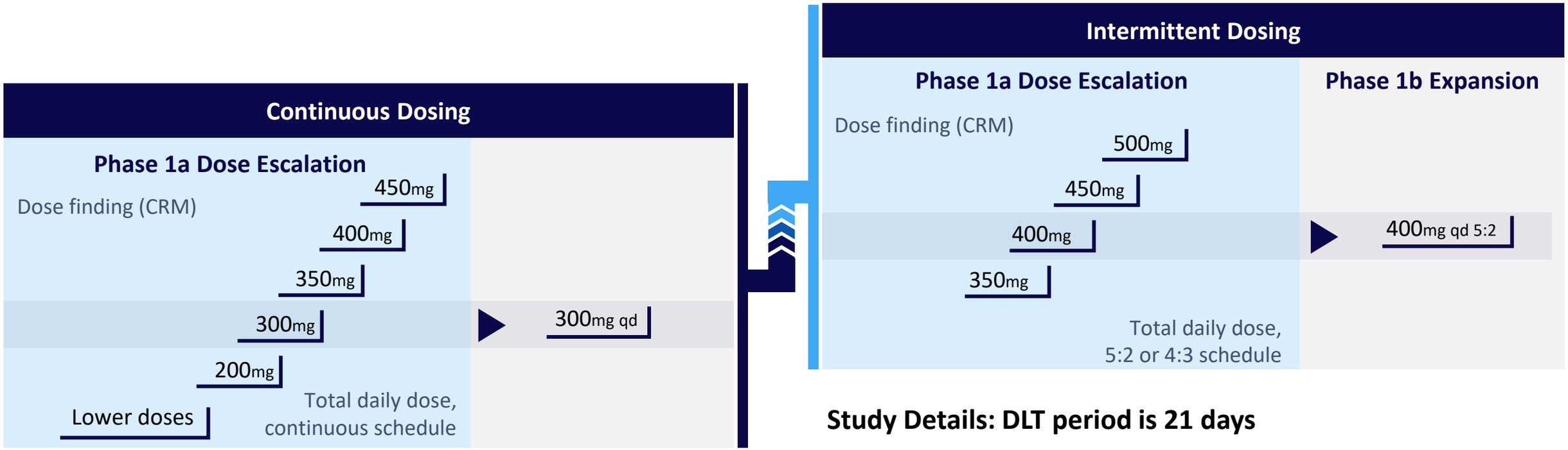
Finding The Optimal Dose of Azenosertib

300 mg continuous dose demonstrated favorable safety profile and antitumor activity, but preclinical models and clinical data suggested that intermittent dosing would allow for:

- Increased exposures at steady state
- Maintained or improved tolerability



Zentalis 001 Study: From First In Human 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

Zentalis 001: Heavily Pretreated Patients With Advanced Solid Tumors

	Continuous N = 74	Intermittent N = 53	Total N = 127
Age			
Median	67	64	65
Range (Min-Max)	(41 - 81)	(35 - 83)	(35 – 83)
Measurable Disease (N, %)	70 (94.6)	53 (100)	123 (96.9)
ECOG PS (N, %)			
ECOG 0	20 (27.0)	18 (34.0)	38 (29.9)
ECOG 1	53 (71.6)	35 (66.0)	88 (69.3)
ECOG 2	1 (1.4)	-	1 (0.8)
Prior Lines of treatment			
Mean (range)	4.33 (1-18)	4.71 (1-10)	4.37 (1-18)
Prior Therapies (N, %)			
Prior PARPi	9 (12.2)	13 (24.5)	22 (17.3)
Prior experimental agent	30 (40.5)	19 (35.8)	49 (38.6)
Prior VEGF-inhibitor	42 (56.8)	31 (58.5)	73 (57.5)
Prior anti-PD1/PDL1	35 (47.3)	18 (34.0)	53 (41.7)

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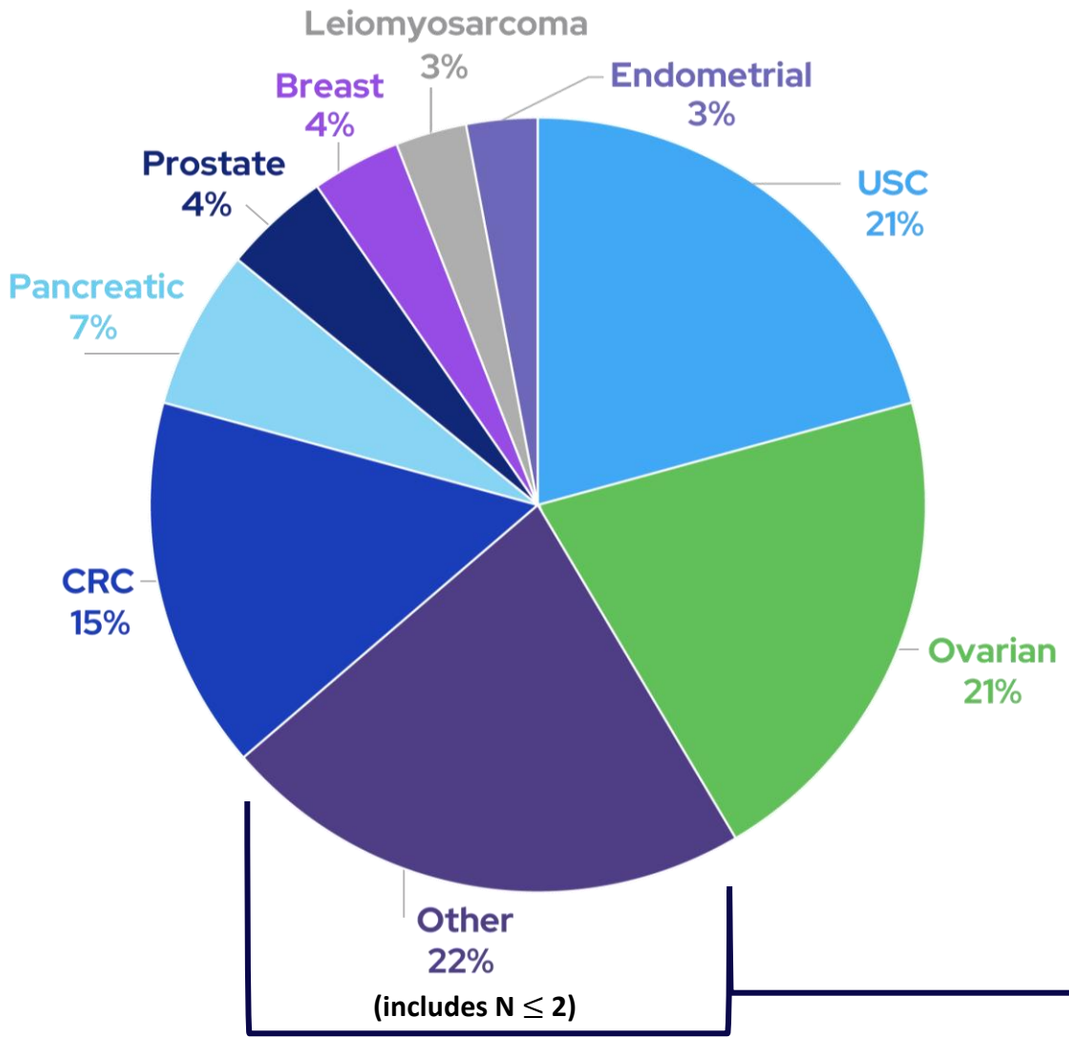
Patients who received ≥300 mg; Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PARPi, poly-ADP ribose polymerase inhibitor; VEGF, vascular endothelial growth factor; PD1/PDL1, programmed cell death protein 1/programmed death ligand 1

Data cut-off: April 24, 2023

Zentalis 001: Multiple Tumor Types, No Biomarker Stratification N=127



- Clear Cell RCC
- NSCLC
- Gastric Cancer
- Head and Neck SCC
- Anal SCC
- Melanoma
- SCLC
- Uterine stromal sarcoma
- Small cell ovarian
- Carcinosarcoma
- Adenoid cystic carcinoma
- Appendiceal

No biomarker, biopsy or prior therapy requirements for enrollment

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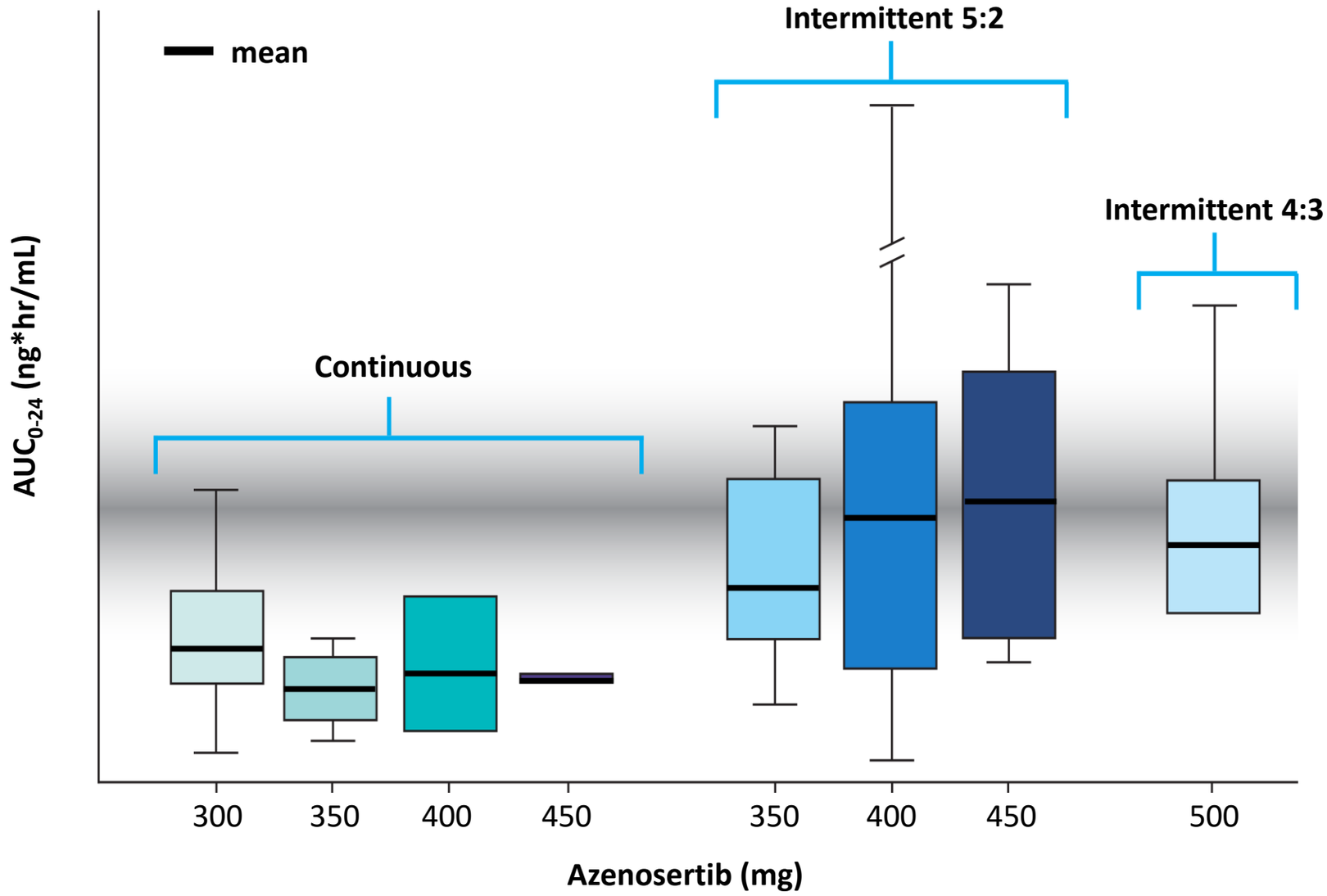
Patients who received ≥300 mg; Abbreviations: USC, uterine serous carcinoma; CRC, colorectal cancer; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; SCLC, small cell lung cancer

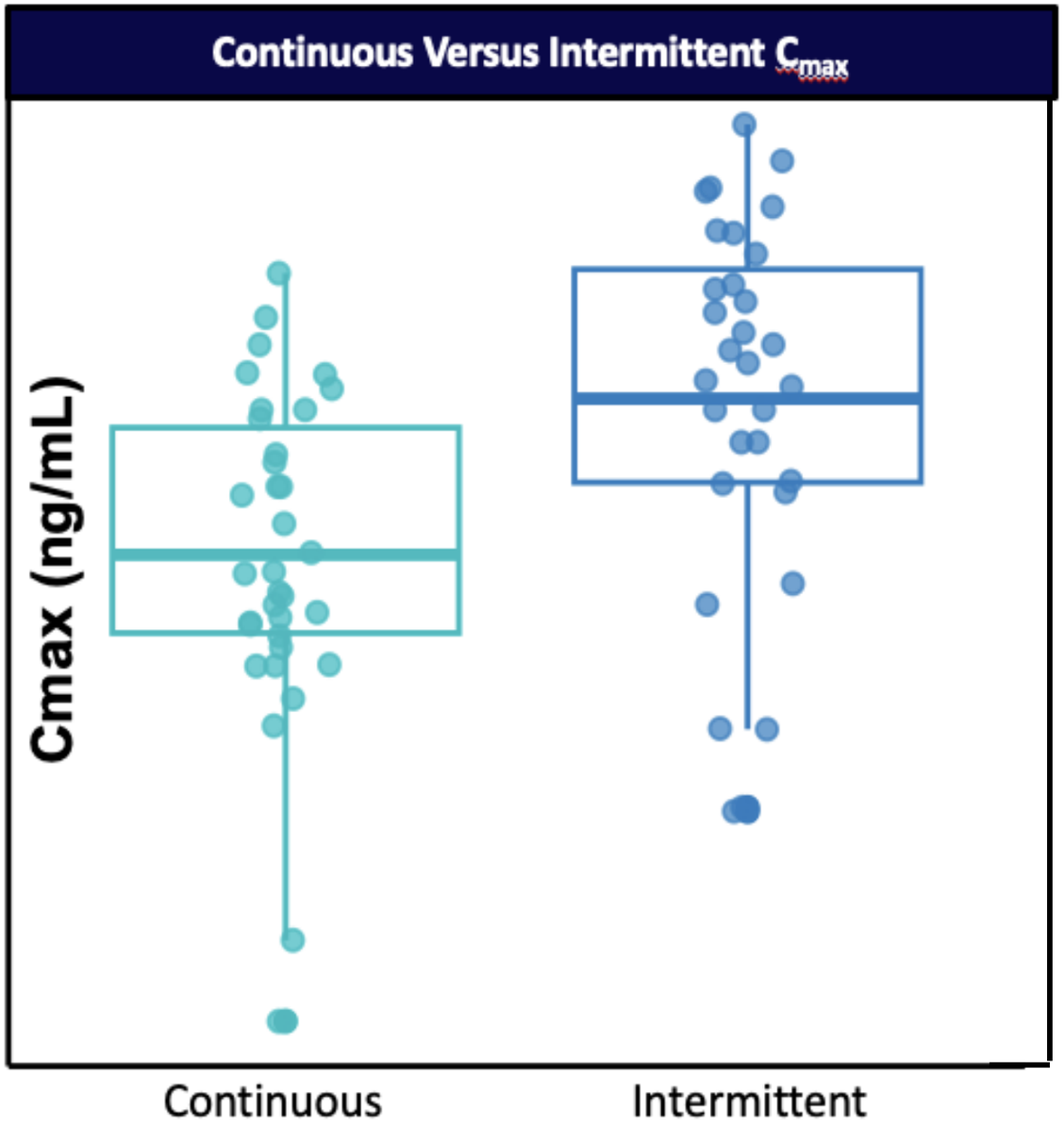
Intermittent Dosing Resulted In A Significant Increase In Steady State Exposure (AUC_{0-24})



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

Patients who received ≥300 mg; Collected at Day 12 after 3 consecutive days of dosing
Abbreviations: 5:2, 5-days of treatment followed by 2-days off treatment; AUC, area under the curve

Intermittent Dosing Achieves Higher Maximal Concentration (C_{max}) Levels



Patients who received ≥300 mg;
Collected at Day 12 after 3 consecutive days of dosing

AZENOSERTIB MONOTHERAPY EFFICACY IN OVARIAN AND UTERINE SEROUS CARCINOMA

Zentalis 001: Patients With Uterine Serous Carcinoma And Ovarian Cancer After Multiple Prior Therapies

51 Patients Enrolled with Uterine Serous Carcinoma or High-Grade Serous Ovarian Cancer

- Continuous and Intermittent dosing schedules
- Heavily Pretreated Group of Patients:

	USC N = 26	HGSOC N = 25
Prior Lines of treatment		
Mean (Range)	3.4 (1-9)	5.3 (1-18)
Platinum Resistant	26 (100%)	25 (100%)
Prior Therapies		
Prior PARPi	2 (7.7)	17 (68.0)
Prior experimental agent	5 (19.2)	7 (28.0)
Prior VEGF-inhibitor	19 (73.1)	21 (84.0)
Prior anti-PD1/PDL1	19 (73.1)	5 (20.0)

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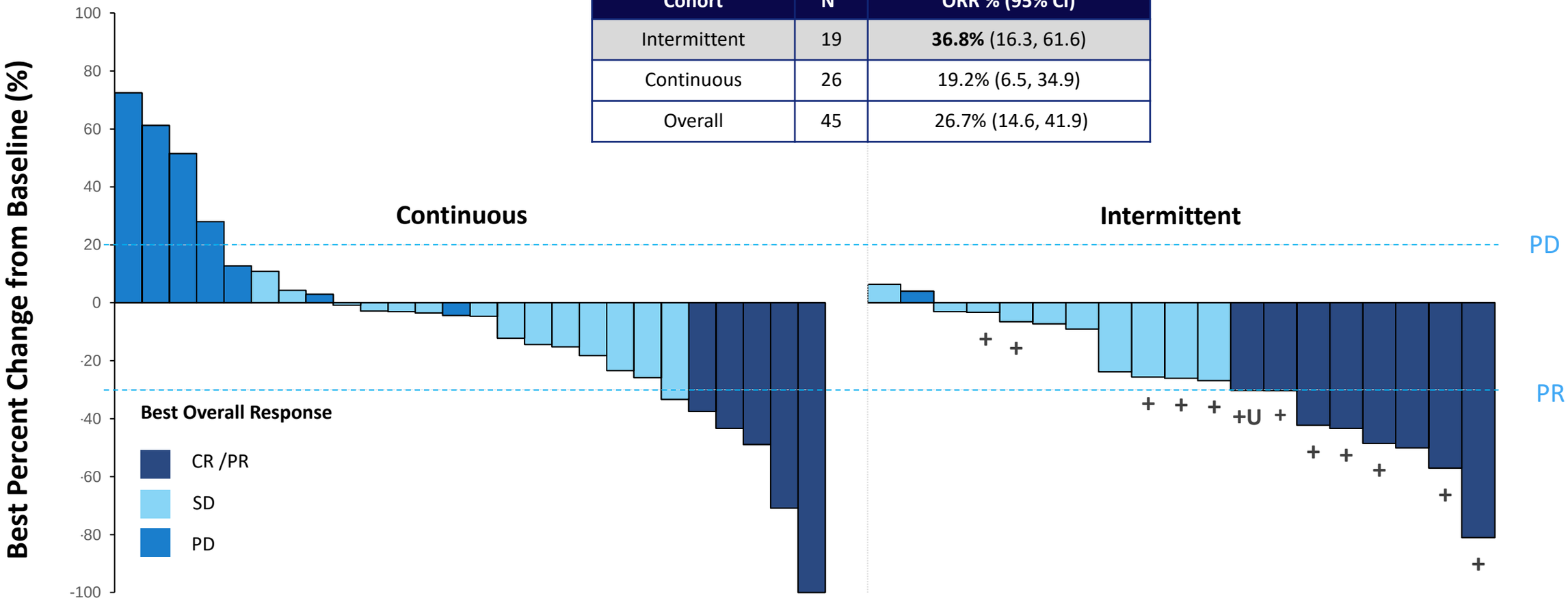
Patients who received ≥300 mg; Abbreviations: USC, uterine serous carcinoma; HGSOC, high-grade serous ovarian cancer
PARPi, poly-ADP ribose polymerase inhibitor; VEGF, vascular endothelial growth factor; PD1/PDL1, programmed cell death receptor 1/programmed death ligand 1

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, 34.9)
Overall	45	26.7% (14.6, 41.9)

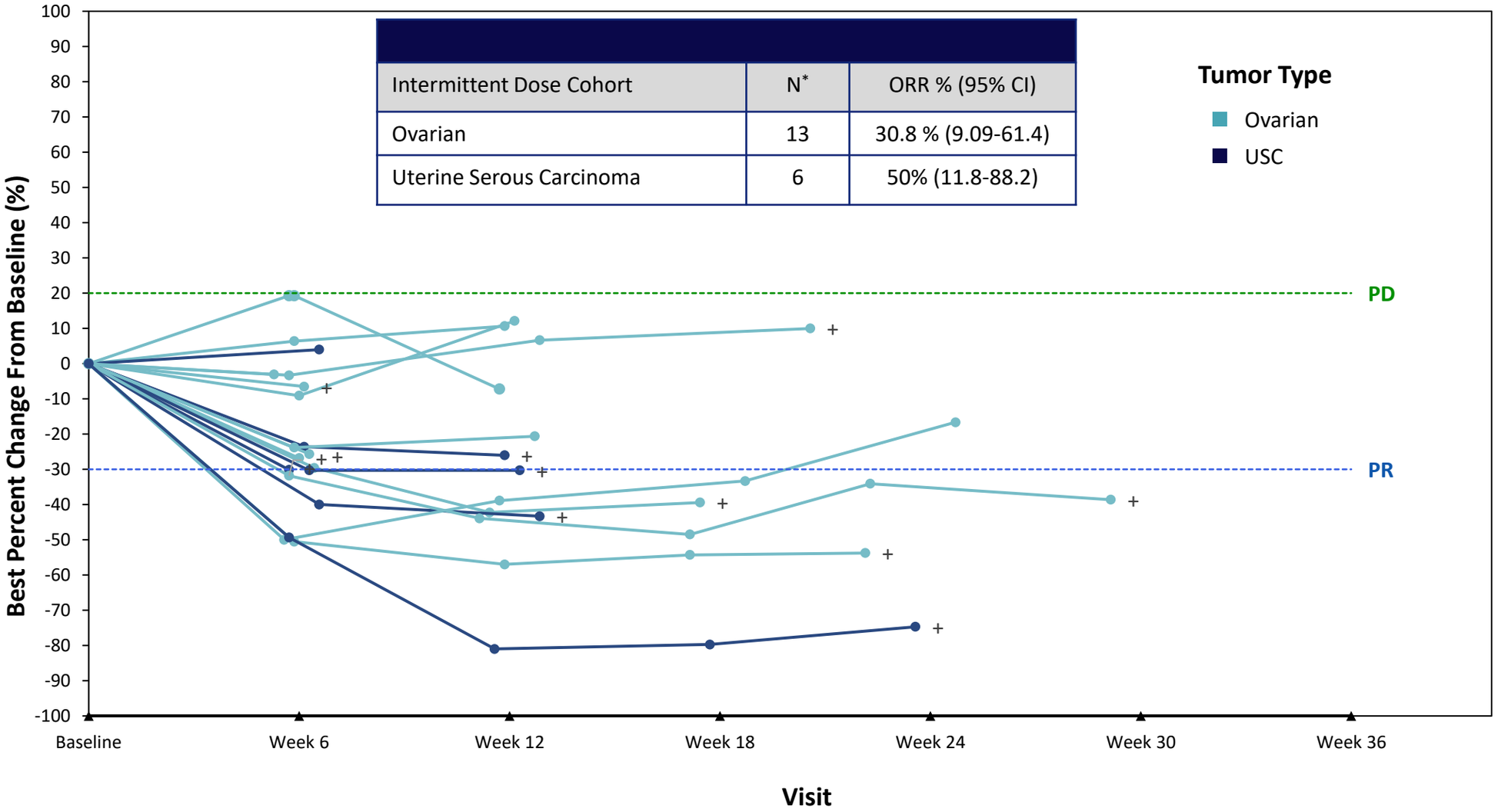


*Response evaluable: have baseline measurable disease by RECIST 1.1, at least one post baseline scan, and received at least one dose of drug
Patients who received ≥300 mg. Abbreviations: USC, uterine serous carcinoma; CR, complete response; PR, partial response;
SD, stable disease; PD, progressive disease;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

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

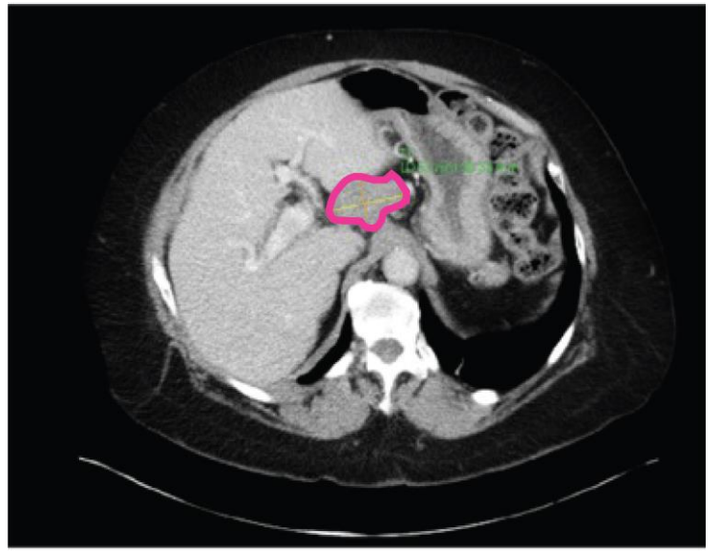
Azenosertib Patient Profile: Durable cPR In Cyclin E Amplified Platinum Resistant Ovarian Cancer

73-year-old female w/ HGSOC
CCNE1amp (Foundation)

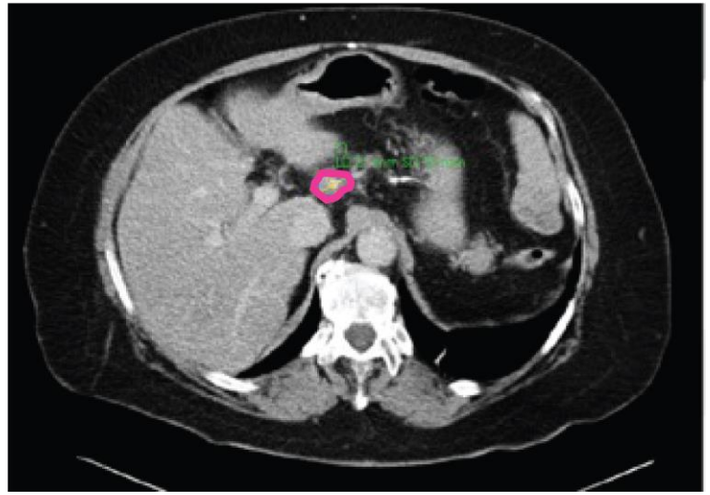
Prior lines of therapy:

1. Avelumab **(SD)**
2. Doxorubicin Liposomal **(PD)**
3. Topotecan/bevacizumab **(PD)**
4. Cyclophosphamide/bevacizumab **(unknown)**
5. XMT1536 (NaPi2b ADC) **(PR)**
6. APG115 (MDM2 inh) / Pembrolizumab **(SD)**
7. ABBV-155 (CD275 ADC) **(PD)**
8. NC318 (Siglec-15 mAB) **(SD)**
9. SM08502 (CLK inhibitor) **(PD)**
10. NBMBMX (HDAC8 inh) **(SD)**

Response	**cPR (-71%)**
Treatment Length	**11** months
Current Status	**Off** treatment



Baseline



12 weeks

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Abbreviations: cPR, confirmed partial response; HGSOC, high-grade serous ovarian cancer; SD, stable disease; PD, progressive disease; PR, partial response.

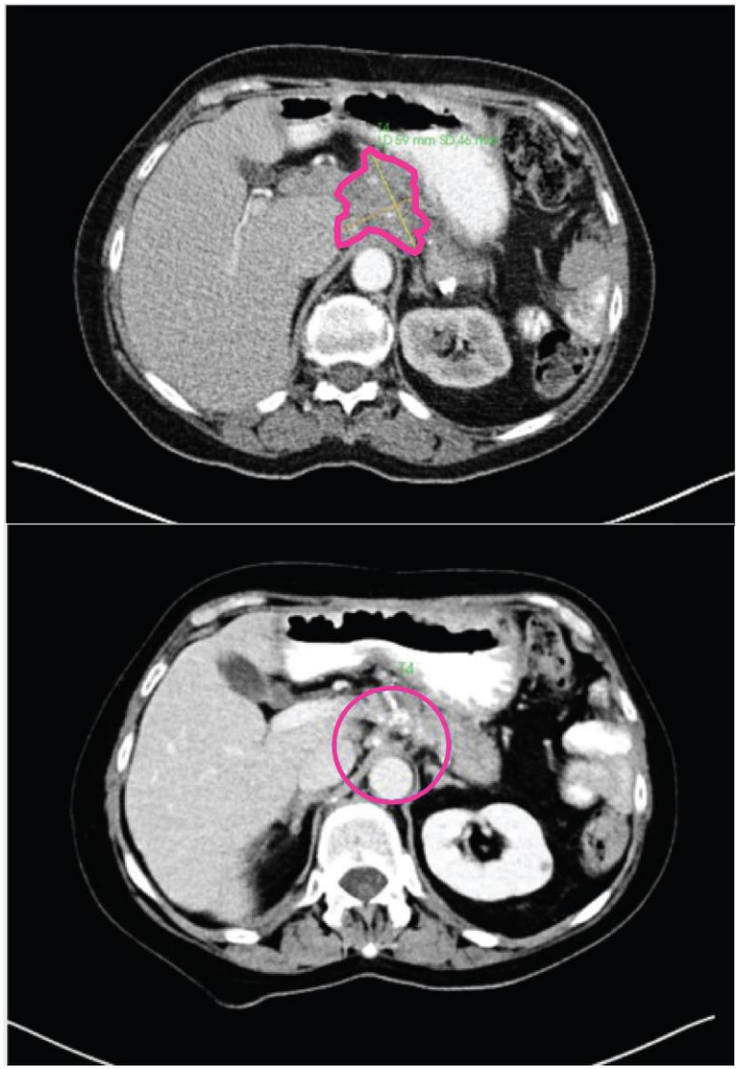
Azenosertib Patient Profile: Durable cPR In HRD+ PARPi Platinum Resistant Ovarian Cancer

64-year-old female
HGSOC; BRCA1m (Foundation)

Prior lines of therapy

1. Carbo/taxol/abraxane/bev/Olaparib **(PD)**
2. Pembrolizumab **(PD)**
3. NaPi2b targeting-ADC (XMT-1536) **(PD)**
4. Carbo/gem/bevacizumab **(PD)**
5. Pegylated doxorubicin **(PD)**
6. Topotecan **(PD)**
7. PABP-1 RNP (ATRC-101) **(PD)**

Response	Treatment Length	Current Status
cPR (-48%)	**5** months	**On** treatment



Baseline

Target Lesion No Longer Visualized

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Abbreviations: cPR, confirmed partial response HGSOC, high-grade serous ovarian cancer; HRD+, homologous recombination repair deficiency; PARPi, poly-ADP ribose polymerase inhibitor; high-grade serous ovarian cancer; BRCA1m, BRCA1 mutant; PD, progressive disease

AZENOSERTIB MONOTHERAPY SAFETY IN PATIENTS FROM ZENTALIS 001

Intermittent Dosing Maintains Safety And Improves Tolerability Over Continuous Dosing

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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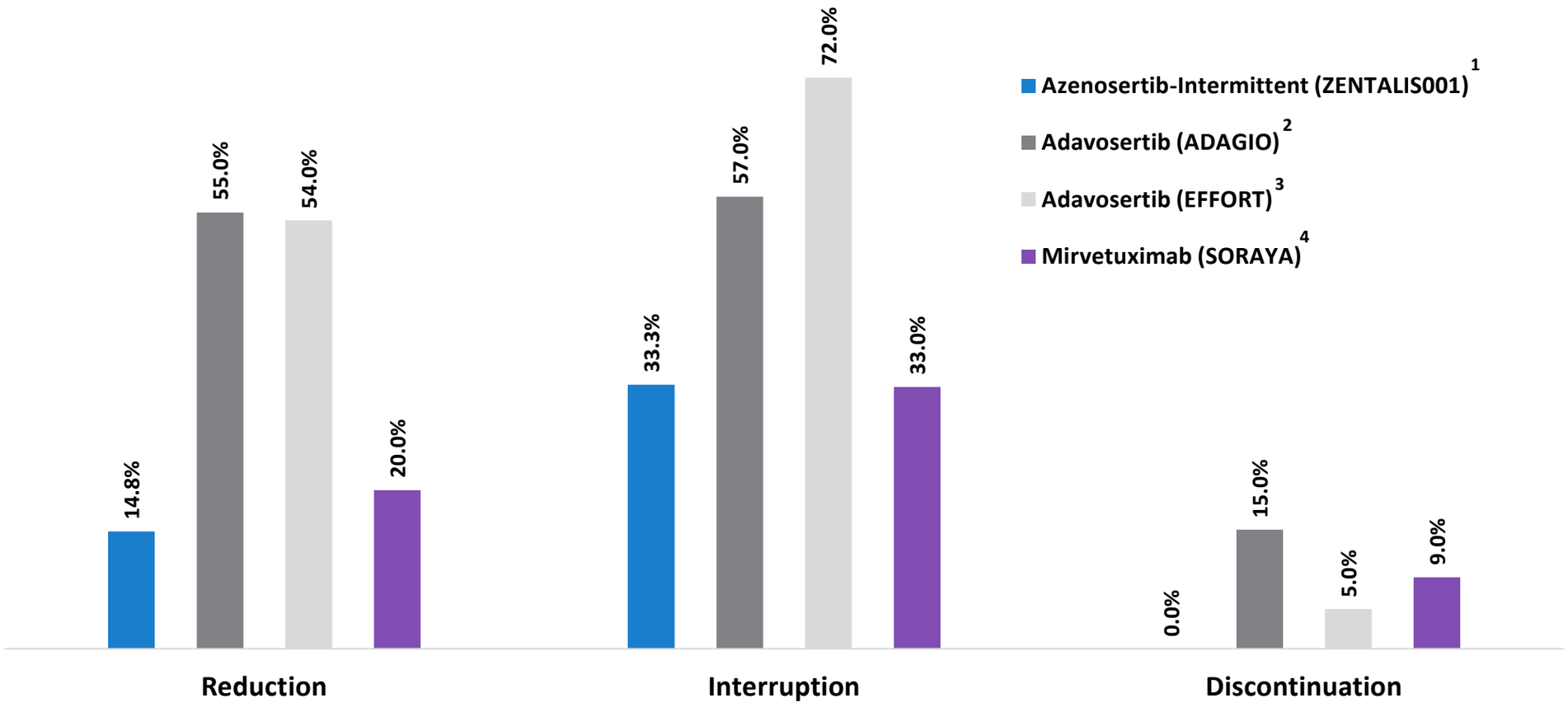
Azenosertib At Intermittent Schedules Reduces Dose Modifications And Serious Adverse Events

	Continuous N = 67	Intermittent N = 27	Total* N =94
Treatment Related AEs leading to, N (%):			
Dose reduction	19 (28.4)	4 (14.8)	23 (24.5)
Dose interruption	17 (25.4)	9 (33.3)	26 (27.7)
Discontinuation	4 (6.0)	-	4 (4.3)
Death	-	-	-
Treatment Related SAEs	5 (7.5)	-	5 (5.3)

*Safety Evaluable Population: Received at least one dose of drug; Continuous 300, 350, 400; Intermittent 350 5:2 and 400 5:2
Abbreviations: SAEs, serious adverse events

Azenosertib: Tolerability* Compared To Adavosertib and Mirvetuximab



*Attributable to Treatment Related AEs. Not direct head-to-head comparisons.

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

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Data cut-off: April 24, 2023

AZENOSERTIB MONOTHERAPY ONGOING STUDIES IN USC AND OVARIAN CANCER

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:

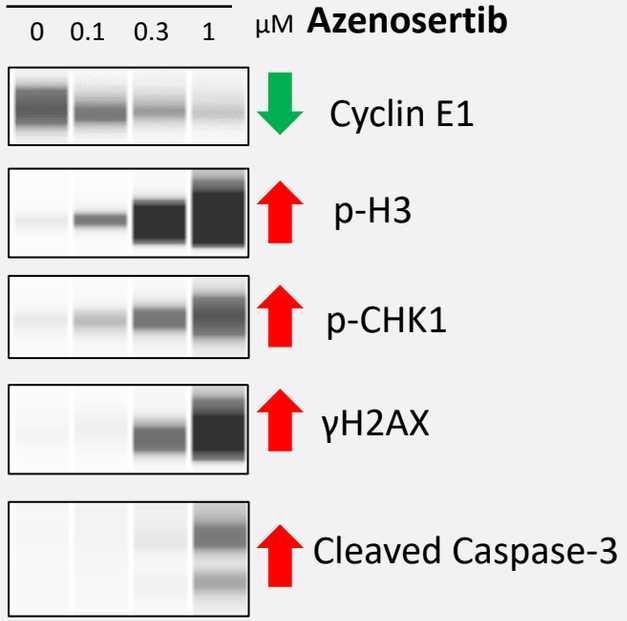
Cyclin E1+ Tumors

- 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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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.

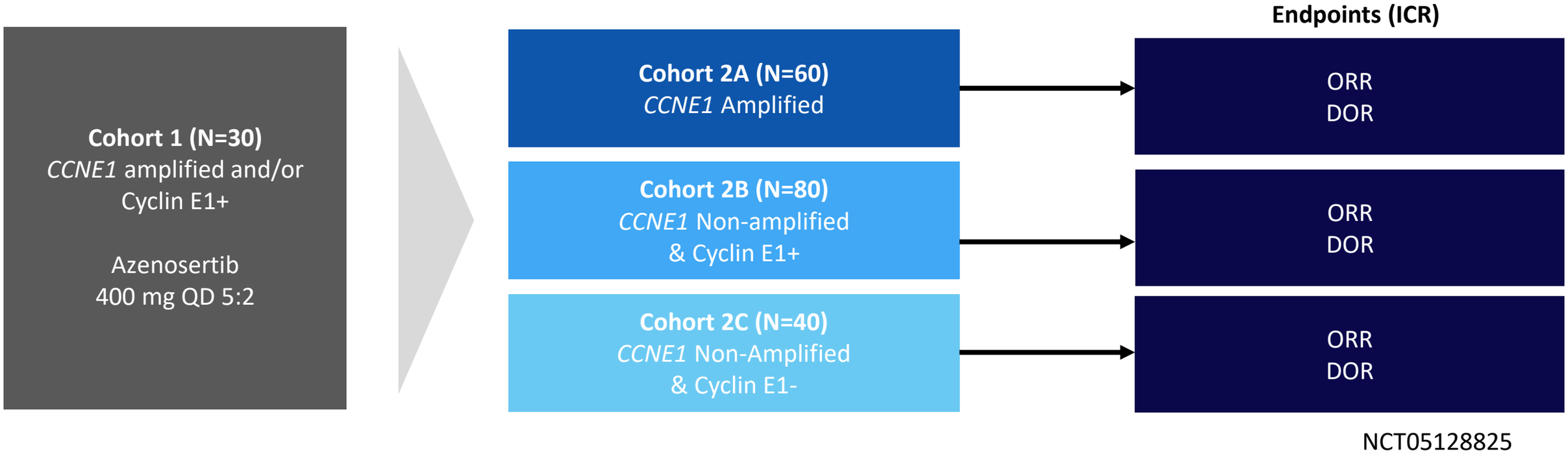
NCT04814108

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

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

CURRENTLY ACCRUING

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; Cyclin E1 IHC+ and/or CCNE1 amplified.



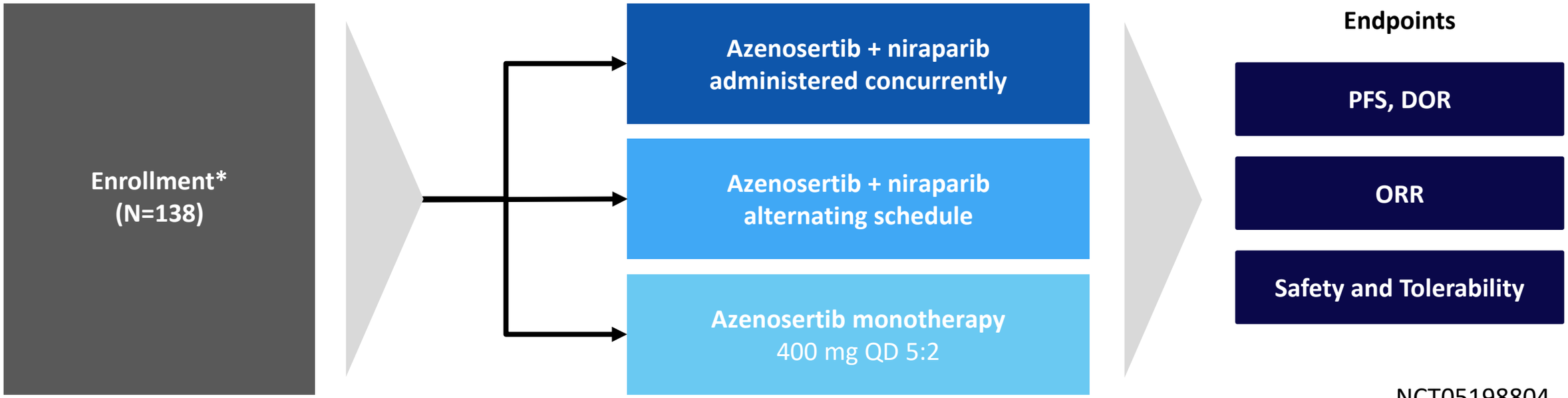
NCT05128825

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 is Highly Active Agent in Ovarian Cancer and USC and has Favorable Safety Profile

- Recommended Phase 2 dose of 400 mg at 5:2 schedule selected based on clinical safety and efficacy

36.8% Confirmed Response Rate in Ovarian and Uterine Serous Carcinomas with intermittent dosing*

Majority of patients remain on intermittent treatment

- Update on monotherapy efficacy data, and clinical trial timelines in 2H23

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*Response evaluable patients (having received at least one scan)
USC, Uterine Serous Carcinoma

AZENOSERTIB CHEMOTHERAPY COMBINATIONS

Abstract #5513
Poster Bd #208

2023 ASCO® ANNUAL MEETING

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)

Joyce Liu[1], Siqing Fu[2], Gary Richardson[3], Zivko Vranjes[4], Tarek Meniawy[5], Catherine Shannon[6], Erika P. Hamilton[7], Stephanie Blank[8], Cara Mathews[9], Jasmina Alidzanovic[10], Rossitza Krasteva[11], Qing Shi[13], Olivier Harismendy[13], Mieke Ptaszynski[14], Shannon N. Westin[2], Funda Meric-Bernstam[2], Premal H.Thaker[15]

[1]Dana Farber Cancer Institute, Boston, MA [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Cabrini Hospital, Malvern, Australia; [4]University Clinical Center of Republic of Srpska, Bosnia and Herzegovina; [5]Linear Cancer Research, University of Western Australia, Perth, Australia; [6]Mater Hospital, Brisbane, Australia; [7]Tennessee Oncology, Sarah Cannon Research Institute, Nashville, TN; [8]Icahn School of Medicine at Mount Sinai, New York City, NY; [9]Women & Infants Hospital of Rhode Island, Providence, RI; [10]University Clinical Center Tuzla, Bosnia and Herzegovina; [11]Uni Hospital, Panagyurishte, Bulgaria; [13]Zentalis Pharmaceuticals, New York, NY; [14]Formerly Zentalis Pharmaceuticals, New York, NY; [15]Siteman Cancer Center, Washington University, St Louis, MO

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Azenosertib Is Active With Favorable Tolerability Profile in Combination with Chemotherapy

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
  - cORR of 34%; cDOR of 8.3 months; mPFS of 9.0 months (response evaluable=94)
- Cyclin E1 status predicts benefit of azenosertib addition to chemotherapy
  - Suggests azenosertib restores chemotherapy sensitivity in heavily pre-treated platinum- resistant ovarian cancer

*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

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;

Patient Characteristics*

Characteristic		Azenosertib + Paclitaxel (N=26)	Azenosertib + Carboplatin (N=36)	Azenosertib + Gemcitabine (N=18)	Azenosertib + PLD (N=35)	Total (N=115)
Age, years	Median (Range)	61.5 (45-83)	61.0 (48-77)	62.5 (47-77)	56.0 (34-75)	61.0 (34-83)
Race and Ethnicity, N (%)	White	24 (92.3)	34 (94.4)	16 (88.9)	34 (97.1)	108 (93.9)
	Black or African-American	0	0	0	0	0
	Asian	1 (3.8)	1 (2.8)	1 (5.6)	1 (2.9)	4 (3.5)
	Other / NR	1 (3.8)	1 (2.8)	1 (5.6)	0	3 (2.6)
	Hispanic (Yes/No/NR)	1/25/0 (3.8/96.2/0)	0/34/2 (0/94.4/5.6)	1/17/0 (5.6/94.4/0)	1/33/1 (2.9/94.3/2.9)	3/109/3 (2.6/94.8/2.6)
ECOG Performance Status, N (%)	0	21 (80.8)	21 (58.3)	12 (66.7)	24 (68.6)	78 (67.8)
	1	5 (19.2)	15 (41.7)	6 (33.3)	11 (31.4)	37 (32.2)
Geographic Region, N (%)	US	6 (23.1)	10 (27.8)	10 (55.6)	5 (14.3)	31 (27.0)
	Europe	10 (38.5)	10 (27.8)	6 (33.3)	27 (77.1)	53 (46.1)
	Australia	9 (34.6)	15 (41.7)	1 (5.6)	3 (8.6)	28 (24.3)
	Korea	1 (3.8)	1 (2.8)	1 (5.6)	0	3 (2.6)
Platinum Status	Refractory, n (%)	5 (19.2)	9 (25.0)	3 (16.7)	7 (20.0)	24 (20.9)
Prior Lines of Therapy	1-2, n (%)	22 (84.6)	30 (83.3)	18 (100)	33 (94.3)	103 (89.6)
	3-4, n (%)	4 (15.4)	6 (16.7)	-	2 (5.7)	12 (10.4)
Prior PARP Inhibitor	n (%)	8 (30.8)	10 (27.8)	5 (27.8)	5 (14.3)	28 (24.3)
Prior Bevacizumab	n (%)	8 (30.8)	18 (50.0)	6 (33.3)	15 (42.9)	47 (40.9)

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*Safety Evaluable Population: Received at least one dose of drug.

Abbreviations: PLD, pegylated liposomal doxorubicin; NR, not reported; ECOG, Eastern Cooperative Oncology Group

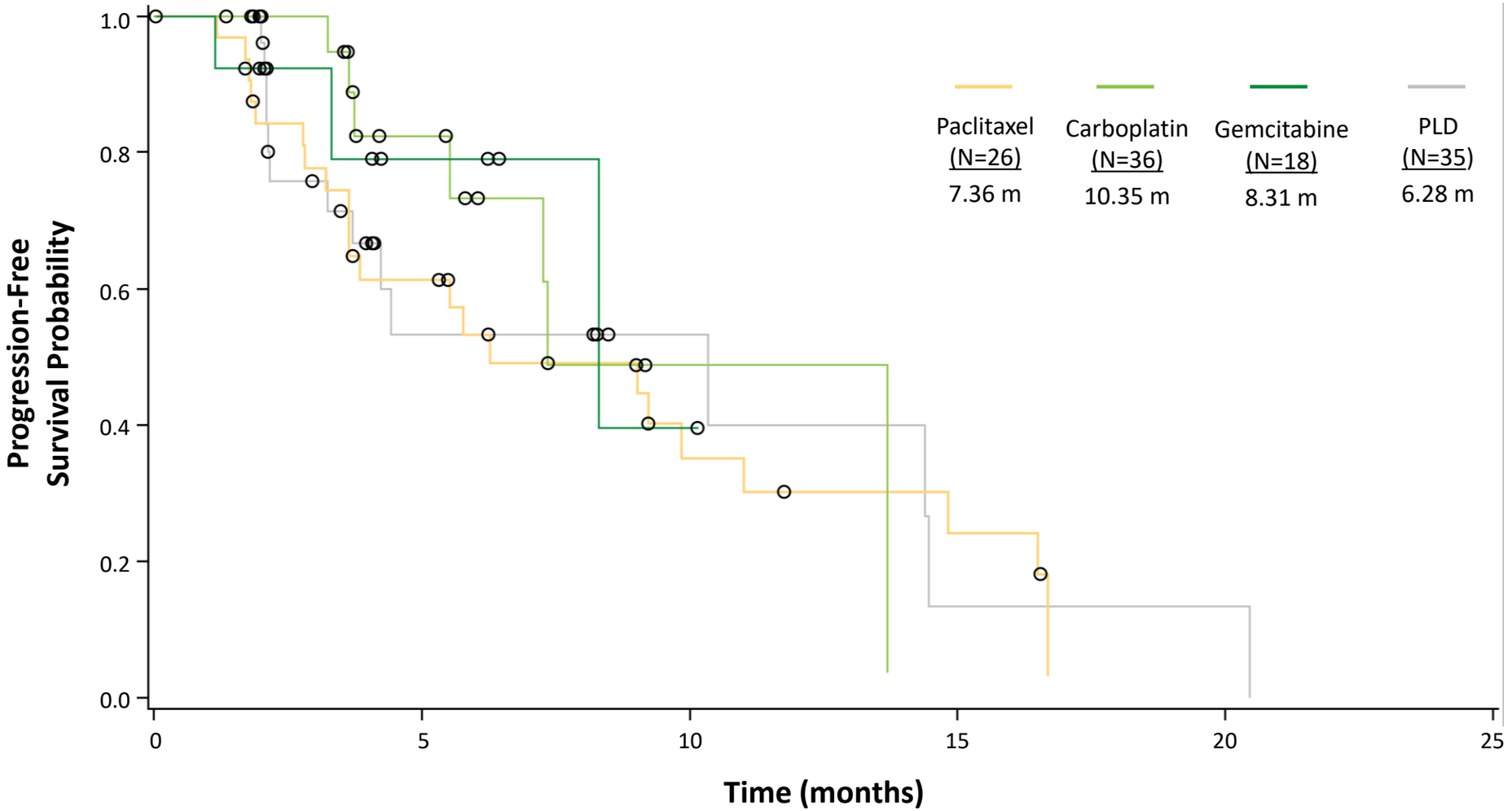
Data cut-off: April 10, 2023

High Response of Azenosertib 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

Kaplan-Meier Curves of Progression-Free Survival: Durable Responses



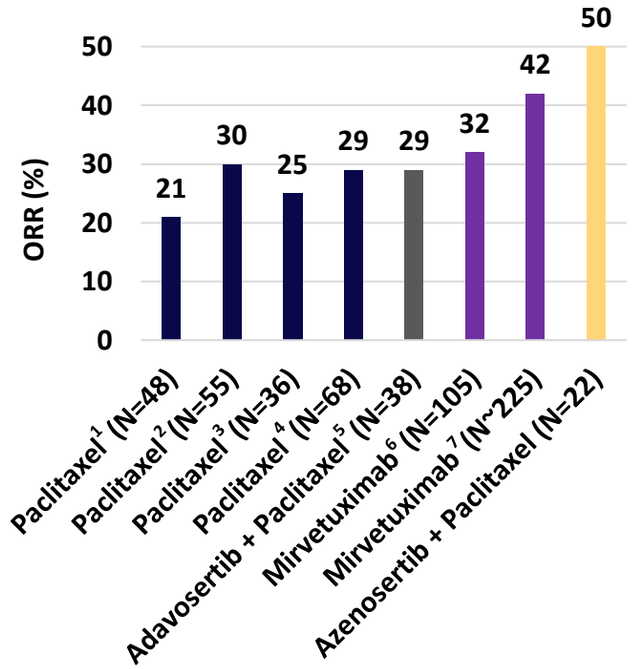
Patients at risk

26	11	1	0		Paclitaxel
36	8	4	1	1	Carboplatin
18	4	1	0		Gemcitabine
35	18	7	4	0	PLD

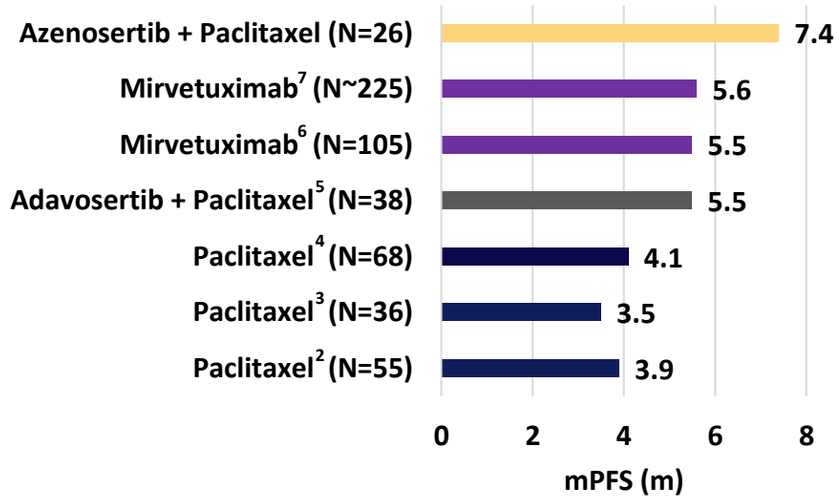
Abbreviations: PLD, pegylated liposomal doxorubicin; PFS, progression free survival; m, months.

The Activity of Azenosertib + Paclitaxel is Robust and Durable Compared to Historical Reports of Single Agent Paclitaxel, Adavosertib + Paclitaxel and Mirvetuximab in Platinum-Resistant Ovarian Cancer

Objective Response Rate (ORR)



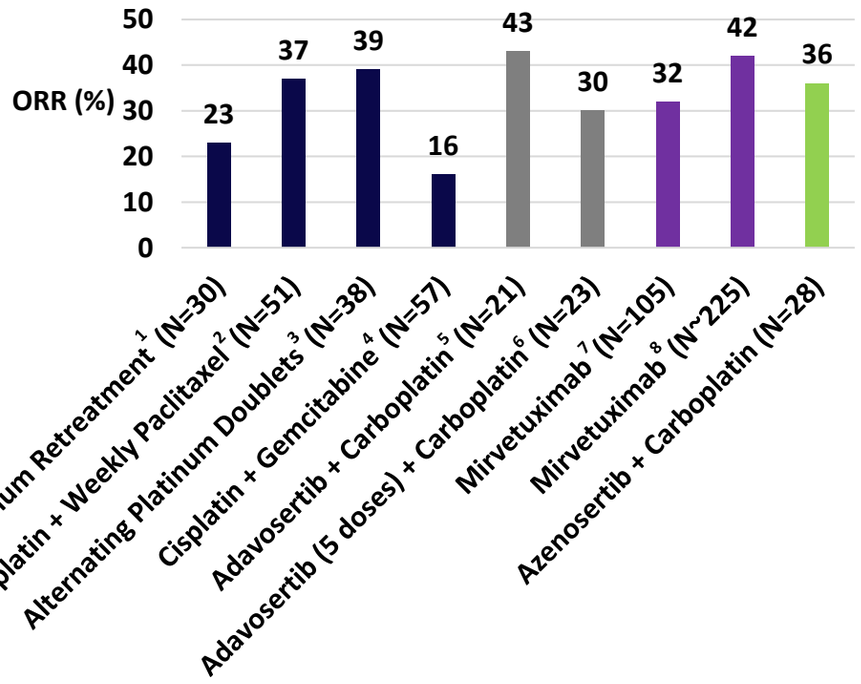
Median Progression Free Survival (mPFS)



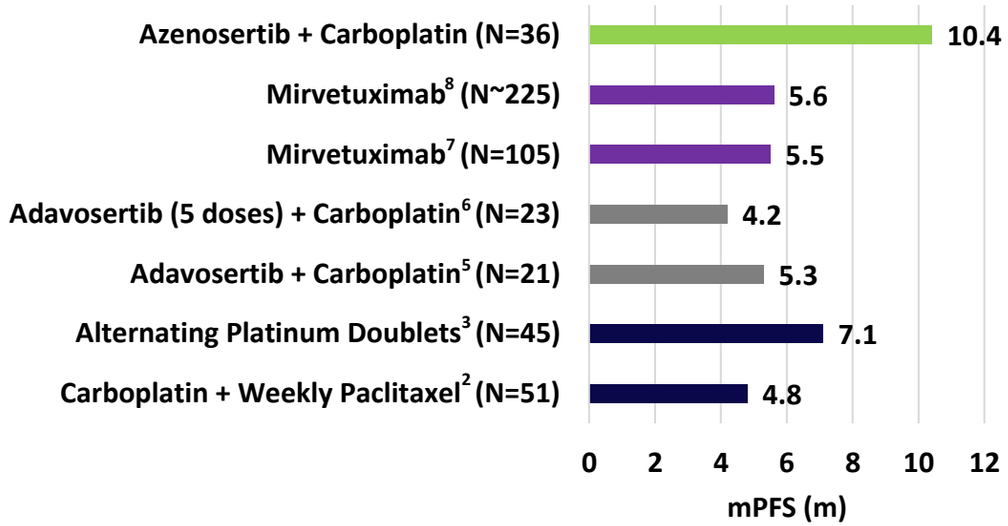
References: 1. Markman et al. Gynecol Oncol 2006;101:436-40. 2. AURELIA: Avastin USPI 3. MITO11: Pignata et al. Lancet Oncol 2015;16:561-68. 4. OCTOPUS: Banerjee et al. ESMO 2019. 5. GYN49: Moore et al. Clin Cancer Res 2022;28:36-44. 6. SORAYA: Matulonis et al. J Clin Oncol 2023;41:2436-45. 7. MIRASOL: Immunogen Press Release May 3, 2023.
Abbreviations: ORR, objective response rate; mPFS, median progression free survival; m, months. Not direct head-to-head comparisons.

The Activity of Azenosertib + Carboplatin is Robust and Durable Compared to Historical Reports of Single Agent Paclitaxel, Adavosertib + Paclitaxel and Mirvetuximab in Platinum-Resistant Ovarian Cancer

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. Not direct head-to-head comparisons.

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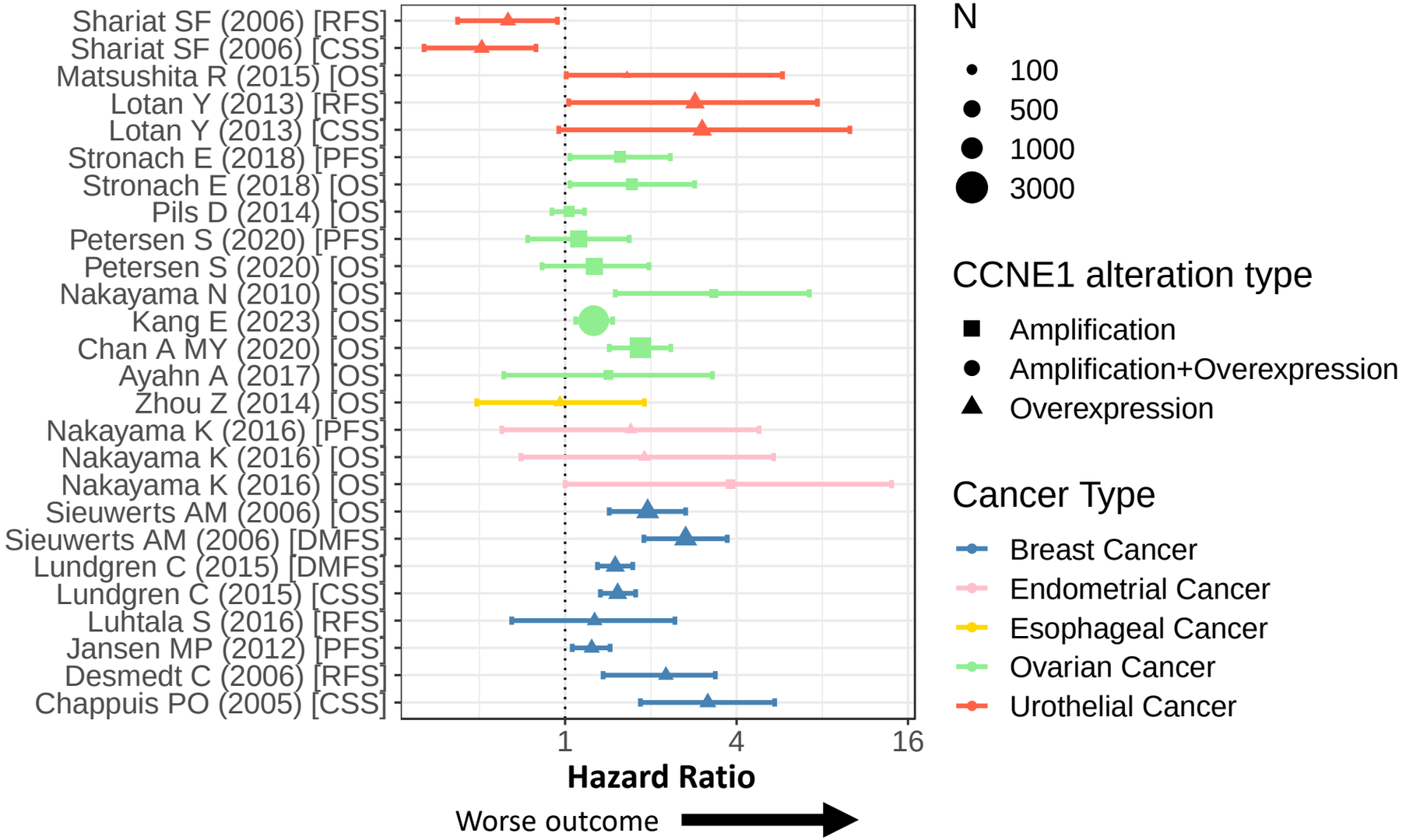
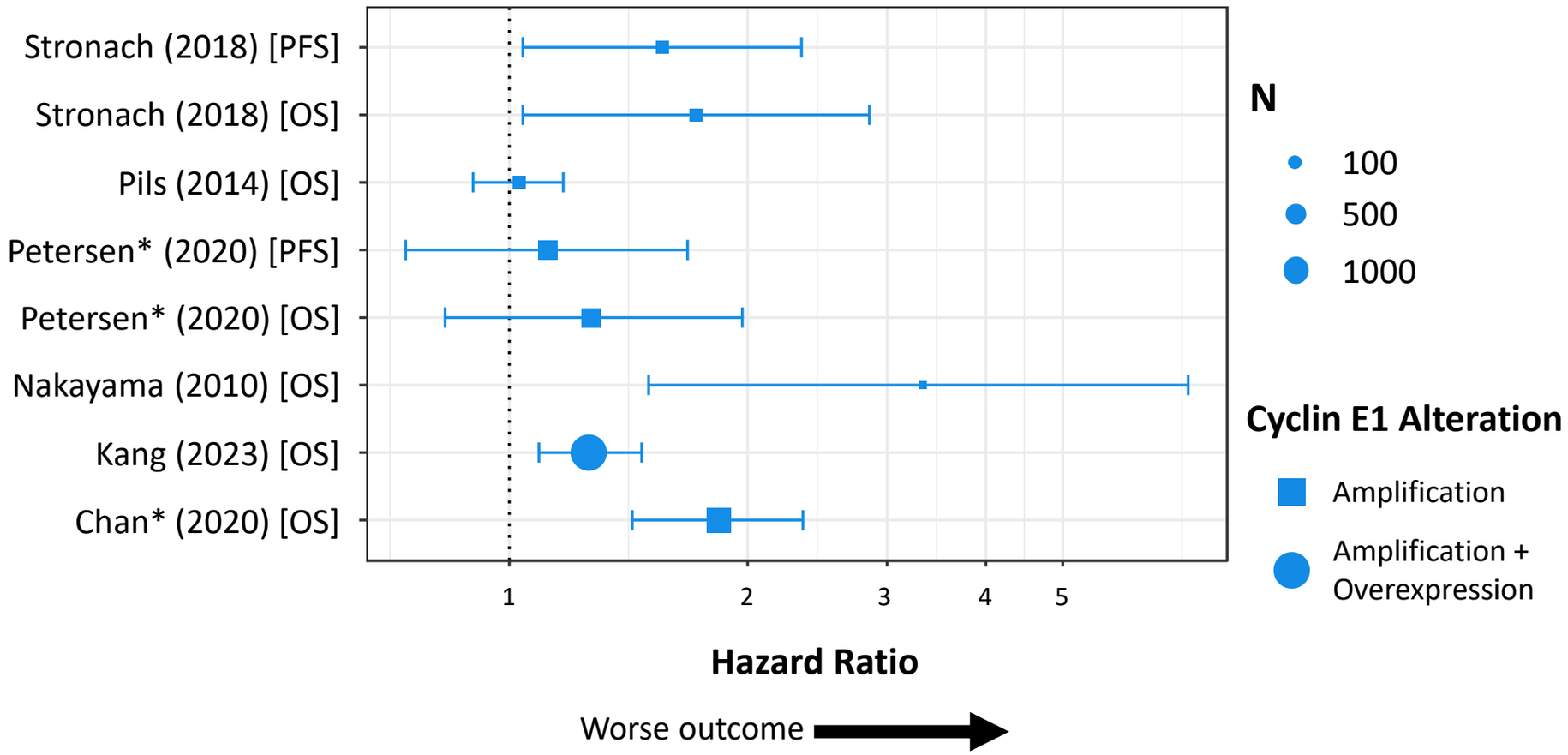
Data cut-off: April 10, 2023

Patients With Cyclin E1+ Tumors Consistently Have Worse Outcomes On Chemotherapy



Abbreviations: RFS, recurrence free survival, CSS; cancer specific survival, OS; overall survival; PFS, Progression free survival; DMFS; distant metastasis free survival,

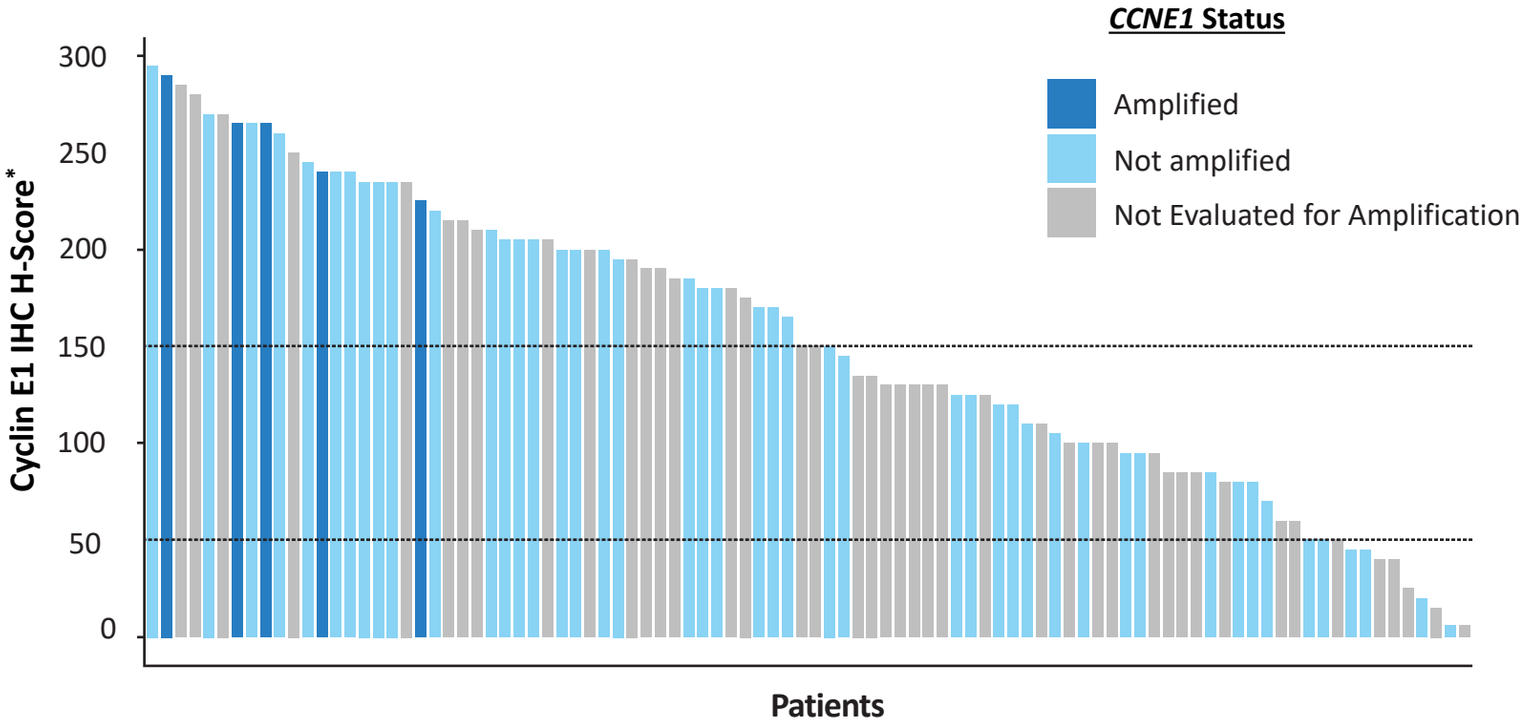
Ovarian Cancer Patients with *CCNE1* Amplified and/or Cyclin E1 + Cancers have a Worse Outcome Following Platinum-Based Chemotherapy Treatment Independent of Platinum-Sensitivity Status



- 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

*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%).**

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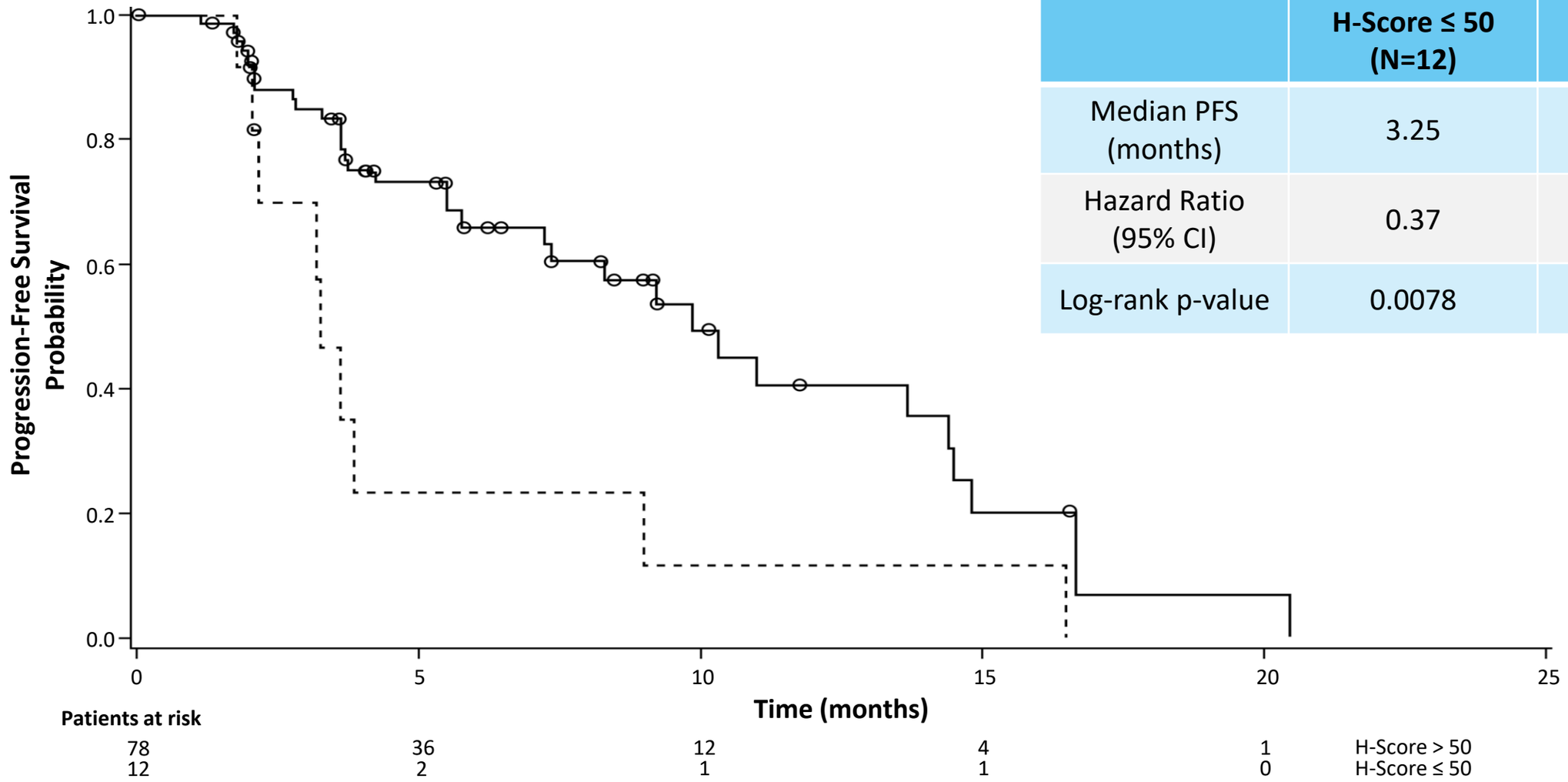
*H-scores calculated by multiplying the percentage of cells (0 to 100%) with intensity of Cyclin E1 expression (0 to 3); IHC: Immunohistochemistry

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

Progression Free Survival is Significantly Improved in Cyclin E1+, Cohort compared to Cyclin E1- 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 subjects are treated subjects with baseline measurable disease per RECIST version 1.1 and at least one post-baseline assessment.
Abbreviations: IHC, immunohistochemistry ; CI, confidence interval

Treatment-related Adverse Events: All Doses Moving Forward Involve Intermittent Dosing

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)

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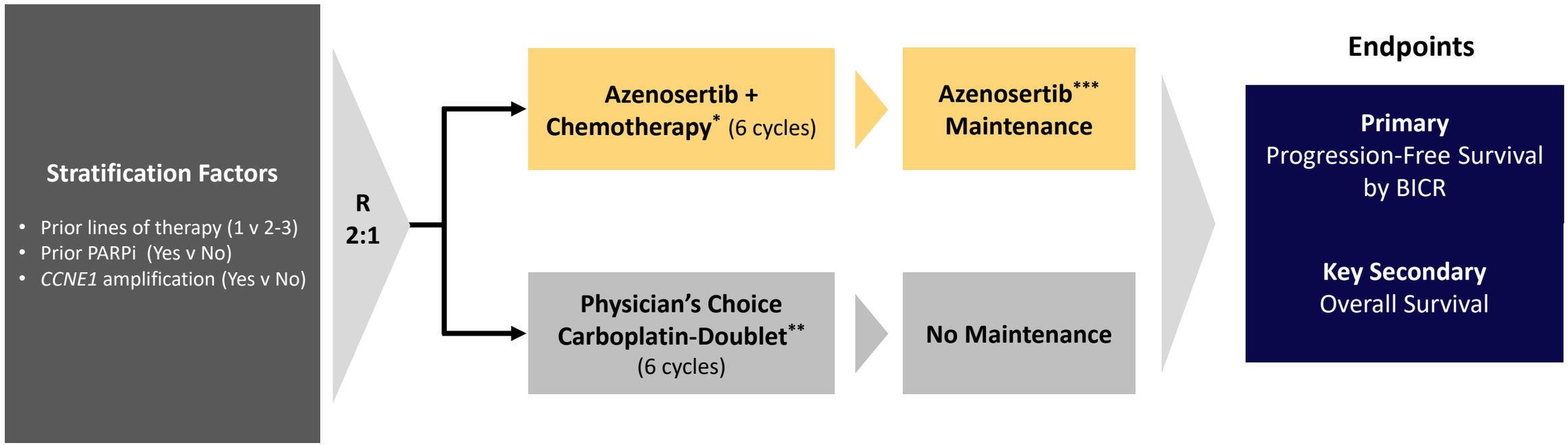
Abbreviations: C, Continuous azenosertib dosing; I, Intermittent azenosertib dosing; MTD, maximum tolerated dose; PLD, pegylated liposomal doxorubicin
*All doses were at or below the MTD
A MTD for Gemcitabine + Azenosertib has not been determined, further dose cohorts are ongoing. * Safety evaluable: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

Proposed Randomized Phase 3 Trial Design of Azenosertib + Chemotherapy in Recurrent Platinum-Sensitive Ovarian Cancer that is Cyclin E1+

Key Eligibility: High-Grade Serous Ovarian Cancer; ECOG performance status 0-1; ≥1L Prior Line of Platinum-based chemotherapy; Platinum-Sensitive (Platinum-free interval ≥ 6 months); Prior Bevacizumab & PARPi if eligible and per regional standard of care; Cyclin E1 + (either *CCNE1* amplified and/or Cyclin E1 IHC-Positive)



*Paclitaxel or Carboplatin
**Paclitaxel or Pegylated Liposomal Doxorubicin
***Azenosertib, 400 mg QD 5:2
Abbreviations: ECOG, Eastern Cooperative Oncology Group; 1L, 1 line; PARPi, poly-ADP ribose polymerase inhibitor; IHC, immunohistochemistry; BICR, blinded independent central review.

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Conclusions: Data Supports Dose and Advancement of Azenosertib-Chemotherapy Combination into Platinum-Sensitive Ovarian Cancer

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 chemotherapy 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

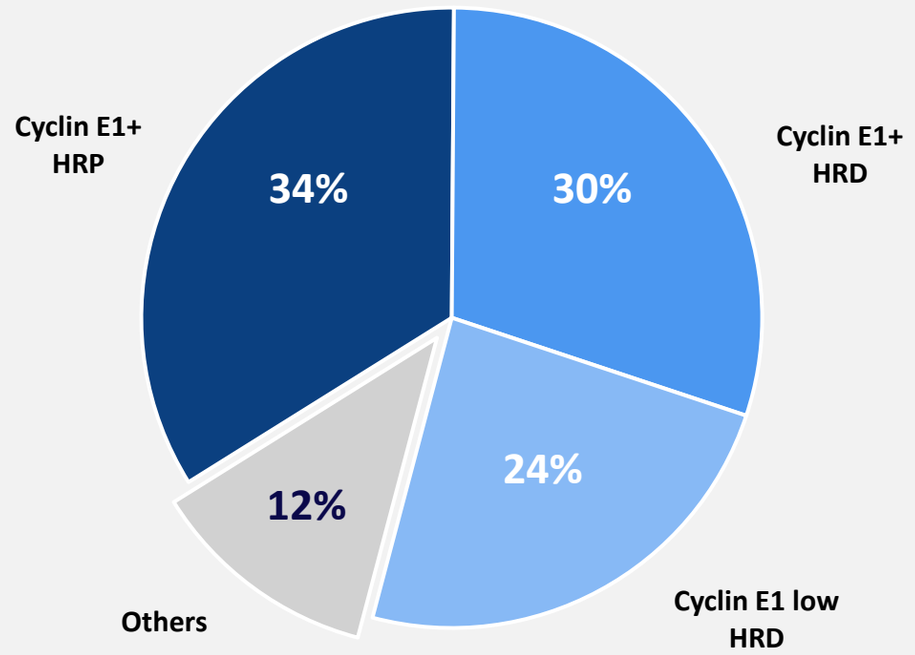
Potential to Transform Treatment Paradigm for Patients and Capture Significant Market Share in Ovarian Cancer

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 3A 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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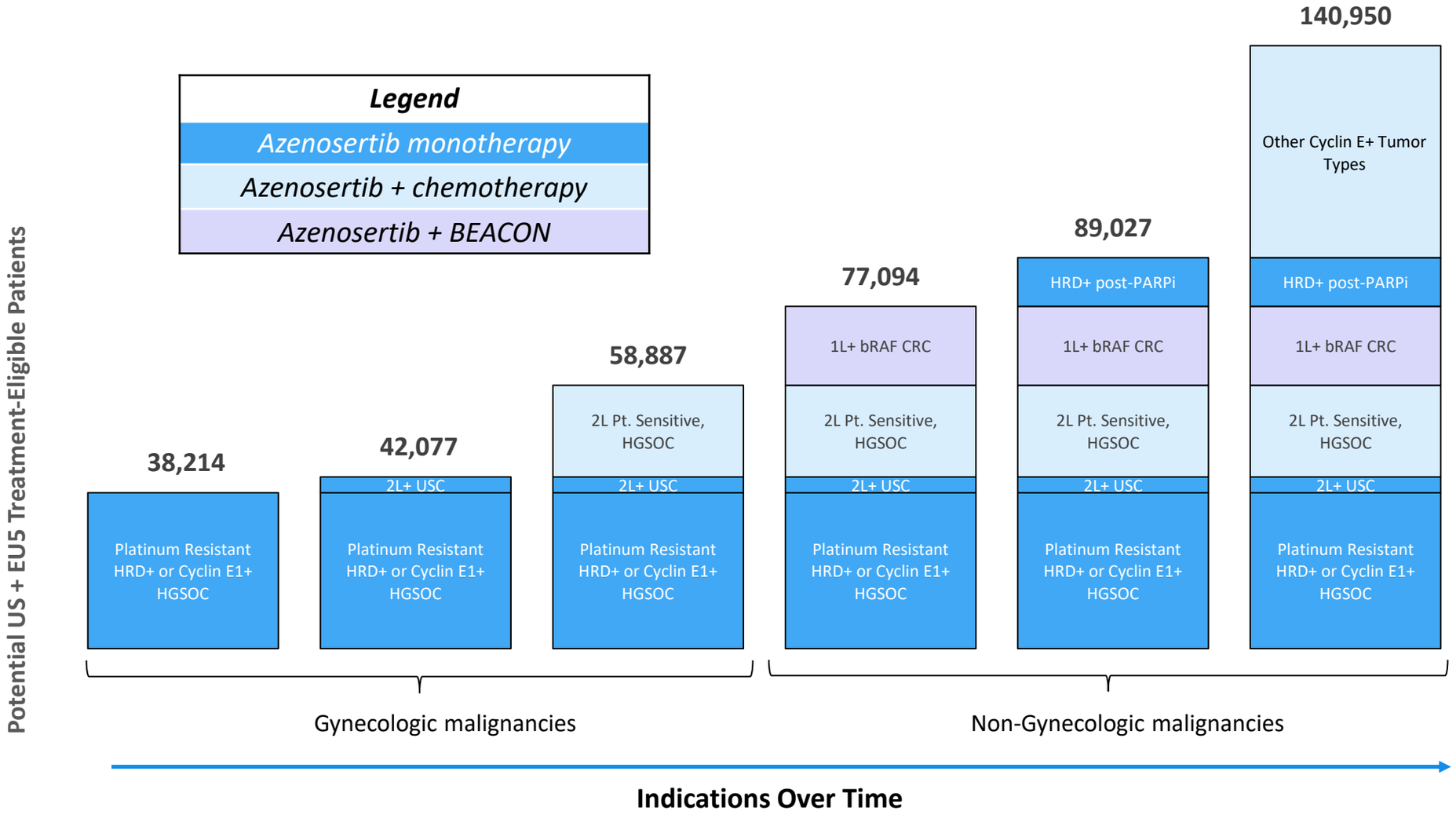
Addressable Patient Population More than Doubles as Franchise Expands to Non-Gynecological Malignancies



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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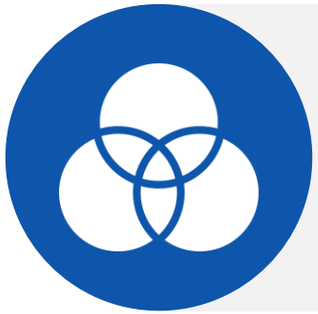
Today's Conclusions: Great Progress in Advancing Azenosertib's Potential to Transform Cancer Care

Azenosertib monotherapy RP2D dose: 400 mg intermittent (5 days on, 2 days off a week; 5:2)

- Increased exposures with intermittent dosing led to an ORR of 36.8% in Ovarian Cancer and USC
- Strong safety profile: no treatment-related discontinuations
- Majority of patients remain on therapy; update in 2H23



Solid efficacy with multiple chemotherapy combinations

- Significant improvements in ORR and mPFS over chemotherapy alone or chemotherapy + adavosertib
- Opportunity to use Cyclin E+ as biomarker to identify patients who would benefit from azenosertib addition to chemo

Comprehensive Clinical Strategy

- All lines of therapy for ovarian cancer, both as a monotherapy and in combination with chemotherapy
- Post-pembro (≥2 L) therapy for USC
- Clinical trial timelines to be updated in 2H23

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Abbreviations: RP2D, recommended Phase 2 dose; ORR, confirmed objective response rate; HGSOC, High Grade Serous Ovarian Cancer; USC, Uterine Serous Carcinoma of the Endometrium; 2H23, second half of 2023; mPFS, media progression free survival

Our Thanks And Deepest Appreciation To All Patients, Caregivers, Families, And Investigators

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Question & Answer Session

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Chief Executive Officer
Zentalis Pharmaceuticals

Carrie Brownstein, MD
Chief Medical Officer
Zentalis Pharmaceuticals

Funda Meric-Bernstam, MD
Chair of the Department of Investigational Cancer Therapeutics -- the Phase 1 Program at The University of Texas MD Anderson Cancer Center; Member, Zentalis Scientific. Advisory Board

Backup: Data Breakdown for ASCO Disclosures

N, ORR (%)	Azenosertib + Paclitaxel	Azenosertib + Carboplatin	Azenosertib + Gemcitabine	Azenosertib + PLD	Total
Efficacy Evaluable in Abstract*	9/18 (50.0)	9/27 (33.3)	2/14 (14.3)	5/35 (14.3)	25/94 (26.6)
Efficacy Evaluable ASCO Poster Data Cut**	11/26 (42.3)	10/29 (34.5)	5/18 (27.8)	6/35 (17.1)	32/104 (30.8)
Response Evaluable on ASCO Poster**	11/22 (50.0)	10/28 (35.7)	5/13 (38.5)	6/31 (19.4)	32/94 (34.0)

Definitions:

- **Efficacy evaluable:** received at least 1 dose of study drug, measurable disease at baseline
- **Response evaluable:** received at least one dose of study drug, measurable disease at baseline AND at least one follow-up scan

*Data Cut Off of January 17, 2023
**Data Cut Off of April 10, 2023
Reasons for 21 patients not being evaluable: No post-baseline scan yet (n=11); AE (n=4); Subject decision (n=4); Withdrawal of consent (n=1); Clinical progression (n=1)

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