zentalis®

Corporate Presentation

January 2026

Nasdaq: ZNTL

Forward Looking Statements and Disclaimer

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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 the potential for azenosertib (ZN-c3) to be first-in-class and best-in-class; the potential regulatory strategy, approach and pathway for azenosertib, including the potential for FDA accelerated approval of azenosertib in Cyclin E1-positive PROC and the potential for studies to be registrational or intended for registration; our development strategy and approach for azenosertib, including our strategy to focus on bringing azenosertib to patients with PROC who are Cyclin E1-positive and the potential for azenosertib to be a new treatment option for ovarian cancer patients; our planned strategy, vision and path forward; the market opportunity for azenosertib, including the opportunity in biomarker selected (Cyclin E1-positive) PROC patients and the potential size of the patient population; existing data being supportive of the go-forward azenosertib development strategy; the potential for the opportunity for azenosertib to be broad/expansive; the potential opportunities for azenosertib as a monotherapy and in combination in other indications and in other tumor types, including in earlier lines of ovarian cancer, breast, endometrial and bladder; the potential for Cyclin E1 to serve as a predictive biomarker for response to azenosertib; the opportunity to improve outcomes in the next stage of development, including via close monitoring; our projected cash runway; planned clinical trials for our product candidates, including the initiation of our ASPENOVA Phase 3 confirmatory trial of azenosertib in Cyclin E1-positive PROC; the potential of azenosertib to address a significant unmet need in patients with PROC who are Cyclin E1-positive; the potential benefits of azenosertib, including compared to available therapies and therapies in development (not head-to-head comparisons); the potential unmet need in a particular indication and/or patient population; the timing and content of our anticipated milestones, including DENALI Part 2a dose confirmation and the topline readout from DENALI Part 2 and its potential to support an accelerated approval; as well as statements that include the words such as “anticipate,” “beyond,” “continue,” “design,” “estimate,” “expect,” “forward,” “intent,” “milestone,” “ongoing,” “opportunity,” “path,” “plan,” “potential,” “predictive,” “projected,” “strategy,” "support," “vision,” “will” and similar statements of a future or forward-looking nature. 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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. Neither we nor our affiliates, advisors or representatives makes any representation as to the accuracy or completeness of that data or undertake to update such data after the date of this presentation.

Statements such as “not head-to-head,” “direct cross-study comparison not intended” and similar references indicate that no head-to-head clinical trial has been conducted evaluating azenosertib against the indicated therapies. Notable differences exist between the Company’s trial designs, conditions under study and subject characteristics as compared to the evaluated third party results and caution should be exercised when comparing data across these studies.

Azenosertib is an investigational drug and have not yet been approved by the U.S. Food and Drug Administration or any other regulatory authority.

Momentum Expected to Continue in 2026 for Azenosertib Development Program with Registration-Intent Studies

2025 Accomplishments

- Completed enrollment in DENALI Part 2a, designed to confirm dose for the registration-intended clinical trial
- Aligned with the FDA on randomized, confirmatory ASPENOVA Phase 3 clinical trial design
- Strong data across three clinical trials in platinum-resistant ovarian cancer (PROC) established a solid foundation for the lead indication in Cyclin E1-positive PROC
- Maintained a strong cash position supporting an estimated runway into late 2027 following strategic restructuring to focus pipeline and resources

Anticipated 2026 Milestones

- DENALI Part 2a dose confirmation expected in 1H 2026
- Confirmatory ASPENOVA Phase 3 trial initiation expected in 1H 2026
- DENALI Part 2 topline readout on track and expected by year-end 2026, which, if successful, has the potential to support an accelerated approval, subject to FDA review

$280.7M cash, cash equivalents and marketable securities as of September 30, 2025 expected to provide runway into late 2027

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Abbreviations: 5:2 schedule = 5 days once-daily administration of azenosertib, followed by 2 days without azenosertib

Extensive Data Support Azenosertib as Potential Best-in-Class, Orally Available, Non-Chemo Therapy for Patients with Cyclin E1-Positive Platinum-Resistant Ovarian Cancer (PROC)

>30% ORR, ~6 mos mDOR‡

in Cyclin E1-positive PROC patients at monotherapy dose of 400mg QD 5:2

- Cyclin E1 protein overexpression is a biomarker of poor prognosis and low benefit from standard-of-care (SOC) single-agent chemotherapy in PROC[1]
  - 4-13% ORR for SOC mono chemo in PROC reported in literature[2†]

350+ patients treated at active doses in monotherapy

200+ PROC patients treated at monotherapy 300mg and 400mg QD 5:2

Manageable safety profile*

Safety and tolerability at 300 and 400 mg QD 5:2 broadly comparable

‡ As of Jan. 13, 2025 data cutoff in DENALI Part 1b, mDOR subject to change; † Not a head-to-head comparison; *See integrated monotherapy safety data on slide 12

1. Kang EY, et al. *Cancer.* 2023;129:697-713
2. Eskander, R., et al. Overcoming the Challenges in Drug Development, Front Oncol. 2023 Oct 17; 13:1258228

Abbreviations: ORR = objective response rate; mDOR = median duration of response; 5:2 schedule = 5 days once-daily administration of azenosertib, followed by 2 days without azenosertib

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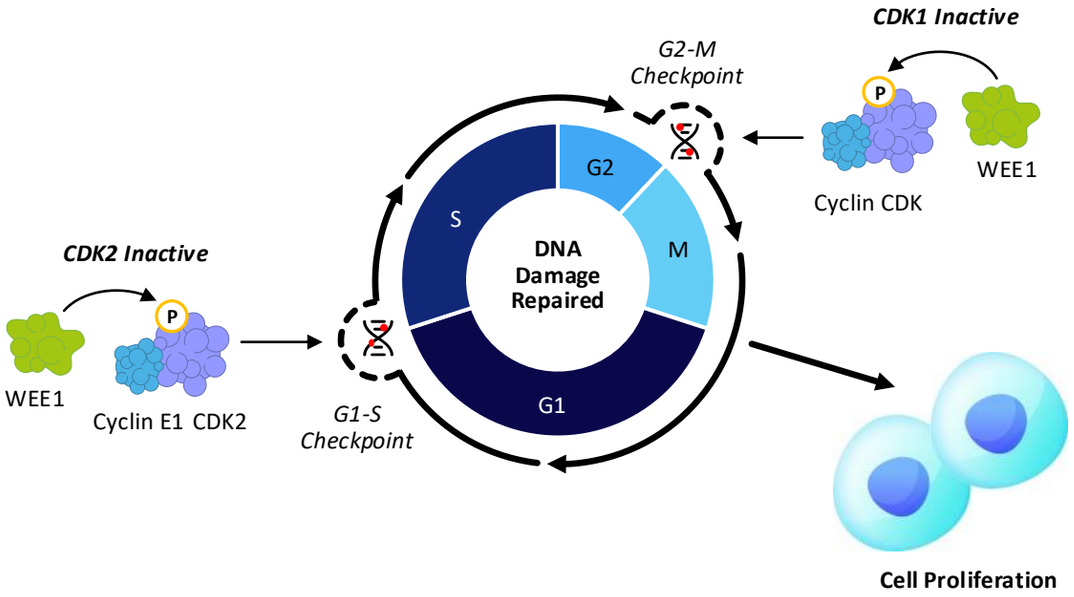
Cyclin E1 Overexpression Sensitizes Cancer Cells to Azenosertib

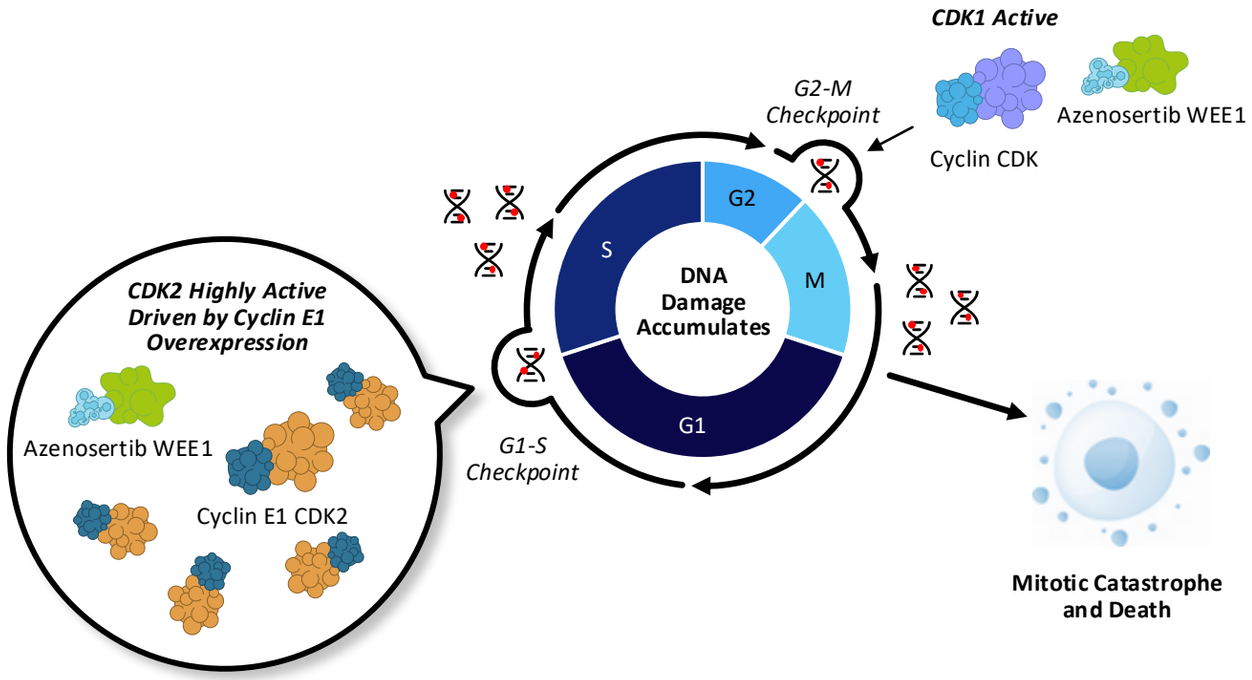
Normal Cell Cycle Regulation

- CDKs and their cyclin binding partners promote progression through the cell cycle
- Following DNA damage, WEE1 kinase inactivates Cyclin/CDK complexes at both G1-S and G2-M checkpoints to halt the cell cycle and allow for repair
- Upon DNA repair, cells progress through the cell cycle and proliferate



Cancer Cell and Azenosertib

- Cyclin E1 overexpression increases CDK2 activity and accelerates G1-S transition, rendering cells more dependent on the DNA repair at the G2-M checkpoint
- Inhibition of WEE1 activates CDKs, accelerates G1-S and G2-M transitions, and increases DNA damage to intolerable levels, resulting in mitotic catastrophe and cell death



P *Phosphorylation, causing inactivation of Cyclin1/2*

DNA damage

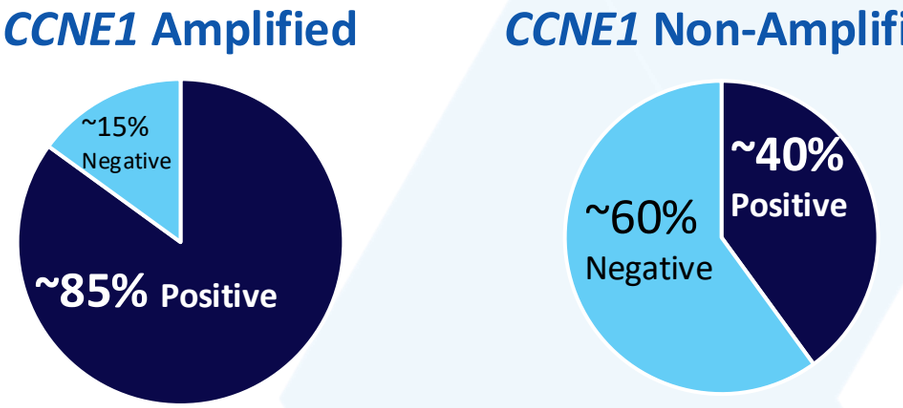
Multiple Drivers of Cyclin E1 Protein Overexpression

Companion diagnostic ready for use in registration-intent studies to identify Cyclin E1-Positive patients, ~50% of PROC patient population†

Cyclin E1 overexpression driven by different mechanisms[1], including:

- ***CCNE1*** **gene amplification**
- **Increased gene transcription**
- **Reduced protein degradation**

Cyclin E1-Positivity more than doubles the eligible patient population beyond *CCNE1* gene amplified:



Predicted Cyclin E1 IHC*

All PROC patients, regardless of* CCNE1 *amplification status, should be screened for Cyclin E1 overexpression

1. Kim, D., et al. Cyclin E1/CDK2 activation defines a key vulnerability to WEE1 kinase inhibition in gynecological cancers, npj Precis. Onc. 9, 3 (2025). https://doi.org/10.1038/s41698-024-00787-4

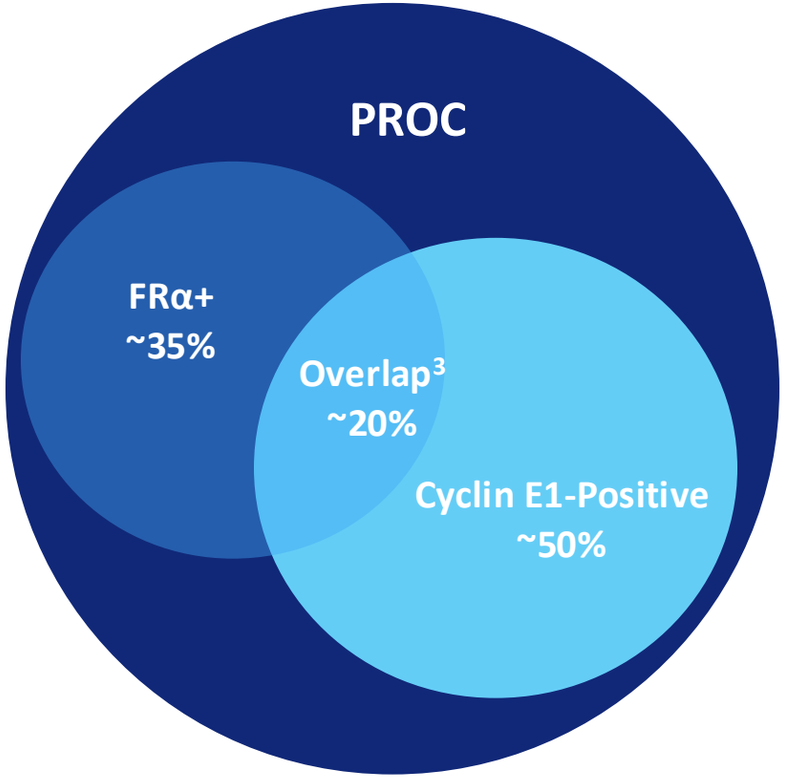
* Cyclin E1 IHC+ based on Zentalis proprietary IHC cutoff and Cyclin E1 IHC assay developed from the existing clinical data

† Cyclin E1 IHC+% based on literature and the unbiased CCNE1 amp & Cyclin E1 overlapping data generated from Zentalis clinical trial samples

IHC - immunohistochemistry

Significant Market Opportunity in High Unmet Need Cyclin E1-Positive PROC

- **No approved treatment option** specifically for this biomarker selected PROC population
- **~21,500** Cyclin E1-Positive PROC patients* (~50% of PROC population)
- Elahere (mirvetuximab soravtansine) approved for biomarker selected FRα+ PROC population; total sales in 1H 2025 were $338 million[1]
  - Underscores demand for biomarker-directed therapies for PROC patients
- Additional opportunities in earlier lines of ovarian cancer and other tumor types with Cyclin E1 protein overexpression, including breast, endometrial, bladder[2]



* Based on 2024 annual estimates in US and EU4 (France, Germany, Italy, Spain) + UK

1. Abbvie Q2 2025 Earnings: https://news.abbvie.com/2025-07-31-AbbVie-Reports-Second-Quarter-2025-Financial-Results
2. NAKAYAMA, K. et al. Int. J. Oncol. 48, 506–516 (2015); Aziz, D. et al. J. Pathol.: Clin. Res. 8, 355–370 (2022); Lotan, Y. et al. Eur Urol 64, 465–471 (2013).
3. Based on internal data

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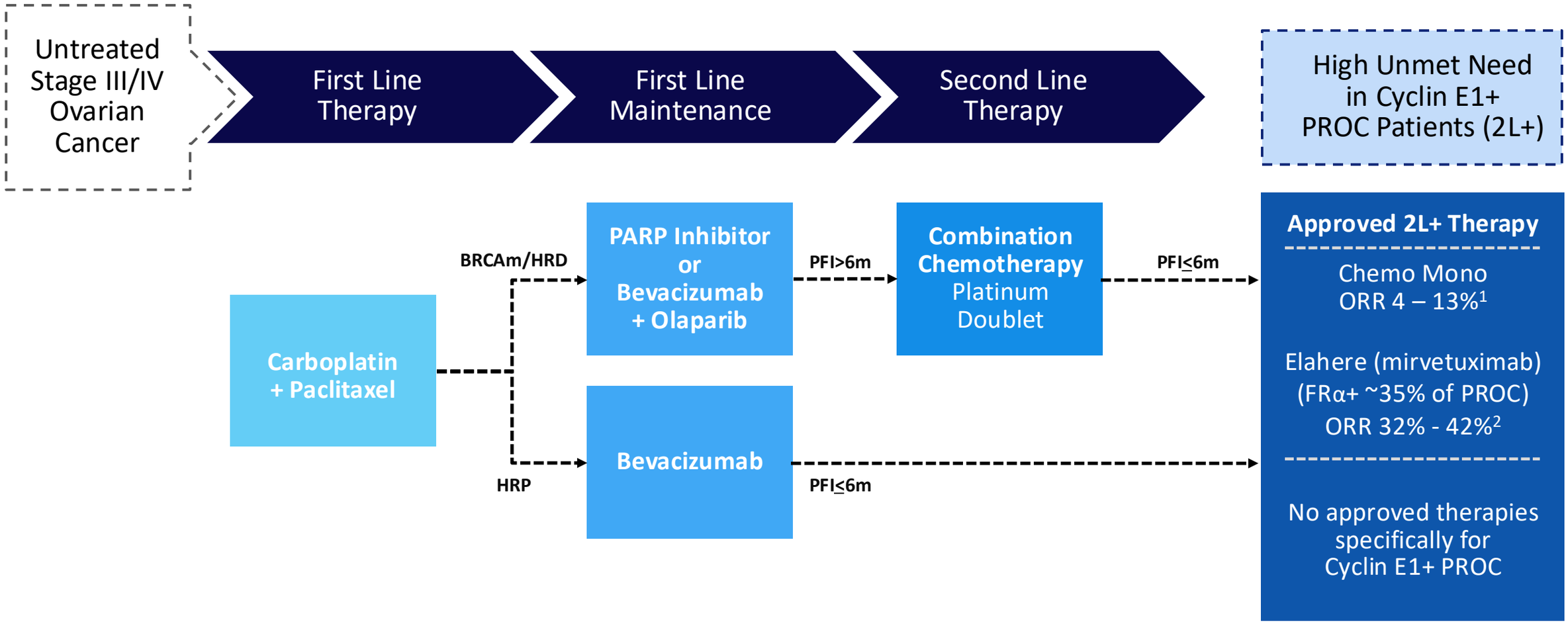
Platinum Resistant Ovarian Cancer: High Unmet Need Provides Opportunity for Azenosertib Monotherapy



PROC, platinum-resistant ovarian cancer; FRα, Folate Receptor alpha

1 Eskander, R., et al. Overcoming the Challenges in Drug Development, Front Oncol. 2023 Oct 17; 13:1258228; 2 Clinical Trial SORAYA ORR 32%, MIRASOL ORR 42%

Standard of Care Single-Agent Chemotherapy has Low Efficacy in PROC

New Options with Greater Efficacy Needed

Study	Study Population	Chemotherapy Arm	ORR, %	mPFS, mo	mOS, mo
JAVELIN Ovarian 200[1] (n=190)	≤3 priors, 75% PROC and 25% Platinum refractory (28% prior bev)	PLD	4	3.5	15.7
FORWARD I re-read[2] (n=61)	PROC 1–3 priors high FRα (33% prior bev)	Paclitaxel or PLD or topotecan	6	3.2	12
CORAIL[3] (n=199)	PROC ≤3 priors (46% prior bev)	PLD or topotecan	12	3.6	11
NINJA[4] (n=159)	PROC 77% >2 prior	Gemcitabine or PLD	13	3.8	12.1
AURELIA[5] (n=182)	PROC ≤2 priors; 25% platinum refractory (8% prior bev)	Paclitaxel or PLD or topotecan	13	3.4	13.3

Direct cross-study comparison of results from independently conducted clinical trials is not intended on this slide.

bev, bevacizumab; FRα, folate receptor alpha; mo, months; ORR, objective response rate; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant ovarian cancer.

1. Pujade Lauraine E et al. *Lancet Oncol.* 2021;22(7):1034-1046, 2. Moore KN et al. ESMO 2019, 3. Gaillard SL et al. ESMO 2018, 4. Omatsu K ESMO 2020, 5. Pujade-Lauraine E et al. *J Clin Oncol*. 2014;32(13):1302–1308.

Integrated Data and Potential Path to Registration in PROC

Integrated Safety Analysis in All Patients Total Daily Dose ≥300mg (N=356)

Monotherapy Safety Profiles in 001, MAMMOTH, DENALI

Treatment Related AEs*, N (%)	All Grade	Grade 3+
Gastrointestinal		
Decreased appetite	93 (26.1)	6 (1.7)
Diarrhea	181 (50.8)	26 (7.3)
Nausea	218 (61.2)	13 (3.7)
Vomiting	63 (17.7)	5 (1.4)
Dehydration	33 (9.3)	2 (0.6)
Hematologic		
Anemia	113 (31.7)	42 (11.8)
Thrombocytopenia	108 (30.3)	39 (11.0)
Neutropenia	57 (16.0)	44 (12.4)
Febrile Neutropenia	6 (1.7)	6 (1.7)
Pancytopenia	2 (0.6)	2 (0.6)
Fatigue	191 (53.7)	44 (12.4)
Sepsis	4 (1.1)	4 (1.1)

* TRAEs listed here represent adverse events of special interest and adverse events of clinical significance for azenosertib and this class of molecules

Treatment Related AEs, N (%)	
TRAE leading to dose reduction	145 (40.7)
TRAE leading to dose interruption	163 (45.8)
TRAE leading to discontinuation	38 (10.7)
TRAE leading to death	4 (1.1)
Treatment related SAE	52 (14.6)

- Well characterized, manageable safety profile in relatively large sample size
- All Grade 5 TRAEs previously reported

Neutropenia: Neutropenia, neutrophil count decreased, neutrophil percentage decreased; Thrombocytopenia: platelet count decreased and thrombocytopenia; Anemia: haematocrit decreased, haemoglobin decreased, RBC count decreased

Abbreviations: AE, adverse event; TRAE, treatment related adverse event. SAE, serious adverse event.

Data Cutoff Dec 2 2024 Active database; subject to further change

Safety and Tolerability at 300 and 400 mg 5:2 Broadly Comparable

Monotherapy Safety Profiles in PROC Patients 300 mg & 400mg QD 5:2

Treatment-related AEs*, N (%)	300mg (N=38)		400mg (N=165)	
	All Grade	Grade 3+	All Grade	Grade 3+
Gastrointestinal				
Decreased appetite	8 (21.1%)	1 (2.6%)	40 (24.2%)	2 (1.2%)
Diarrhea	18 (47.4%)	1 (2.6%)	86 (52.1%)	12 (7.3%)
Nausea	23 (60.5%)	0	101 (61.2%)	6 (3.6%)
Vomiting	3 (7.9%)	0	17 (10.3%)	3 (1.8%)
Dehydration	1 (2.6%)	0	14 (8.5%)	1 (0.6%)
Fatigue	14 (36.8%)	2 (5.3%)	90 (54.5%)	20 (12.1%)
Sepsis	0	0	4 (2.4%)	4 (2.4%)
Hematologic				
Anemia	13 (34.2%)	3 (7.9%)	53 (32.1%)	20 (12.1%)
Thrombocytopenia	13 (34.2%)	2 (5.3%)	36 (21.8%)	8 (4.8%)
Neutropenia	4 (10.5%)	3 (7.9%)	30 (18.2%)	21 (12.7%)
Febrile Neutropenia	0	0	4 (2.4%)	4 (2.4%)

Treatment-related AEs, N (%)	300mg (N=38)	400mg (N=165)
Treatment-Related SAE	6 (15.8%)	31 (18.8%)
TRAE leading to dose reduction	13 (34.2%)	69 (41.8%)
TRAE leading to dose interruption	16 (42.1%)	89 (53.9%)
TRAE leading to discontinuation	5 (13.2%)	26 (15.8%)
TRAE leading to death	0	3 (1.8%)

- While numerically different, broadly comparable safety profiles at 300mg and 400mg 5:2
- Low frequency of previously reported G5 TRAEs, G3+ febrile neutropenia and sepsis observed at 400mg 5:2

* TRAEs listed here represent adverse events of special interest and adverse events of clinical significance for azenosertib and this class of molecules

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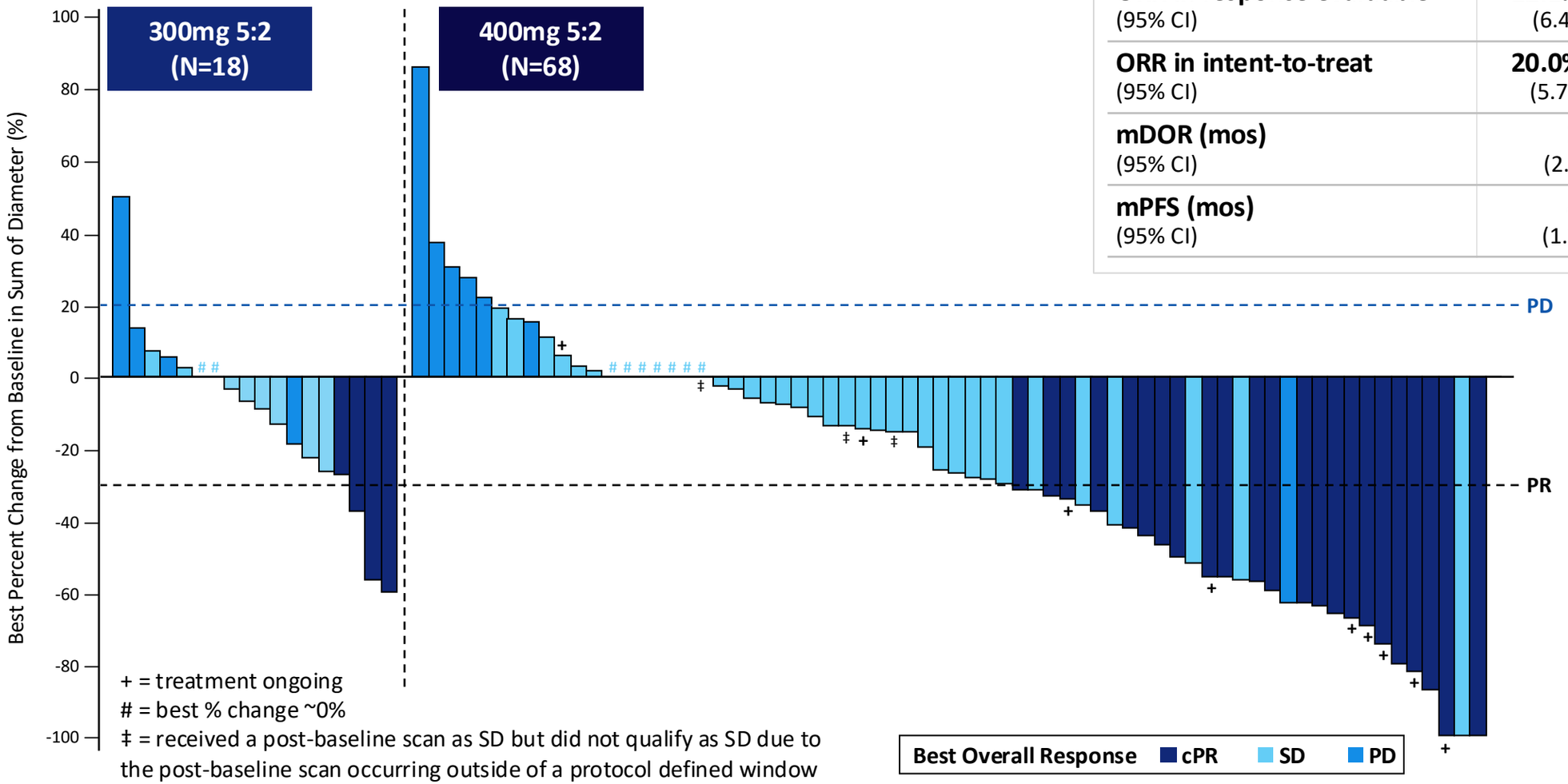
Neutropenia: Neutropenia, neutrophil count decreased, neutrophil percentage decreased; Thrombocytopenia: platelet count decreased and thrombocytopenia; Anemia: hematocrit decreased, hemoglobin decreased, RBC count decreased
Abbreviations: AE, adverse event; TRAE, treatment related adverse event. SAE, serious adverse event.

Data Cutoff Dec 2 2024
Active database; subject to further change

400mg 5:2 Shows Meaningful Response Rates >30% and mDOR >5 mos

PROC, Cyclin E1+	300 mg 5:2	400 mg 5:2
ORR in response evaluable* (95% CI)	**22.2%** (4/18) (6.4 - 47.6)	**33.8%** (23/68) (22.8 - 46.3)
ORR in intent-to-treat (95% CI)	**20.0%** (4/20) (5.7 – 43.7)	**31.5%** (23/73) (21.1 – 43.4)
mDOR (mos) (95% CI)	**3.9** (2.8, NE)	**5.5** (3.5, 6.3)
mPFS (mos) (95% CI)	**4.1** (1.3, 6.6)	**4.4** (2.8, 6.8)



*Includes patients who received at least one post-treatment scan
Abbreviations: CI, confidence interval; cPR, confirmed partial response; mDOR, median duration of response; PD, progressive disease; SD, stable disease; NE, not estimable due to small number of subjects and events.

Data Cutoff
Dec 2 2024
Active database; subject to further change

Higher Response Rates and Longer PFS with Fewer Prior Lines of Therapy

Subgroup Analysis by Prior Line of Therapy
Cyclin E1+ PROC patients treated at 400mg QD 5:2 in 001, MAMMOTH and DENALI

	Overall	1-3 PLoT	4+ PLoT
ORR in response evaluable* (95% CI)	**33.8%** (23/68) (22.8 – 46.3)	**40.0%** (16/40) (24.9 – 56.7)	**25.0%** (7/28) (10.7 – 44.9)
ORR in intent-to-treat (95% CI)	**31.5%** (23/73) (21.1 – 43.4)	**36.4%** (16/44) (22.4 – 52.2)	**24.1%** (7/29) (10.3 – 43.5)
mDOR (mos) (95% CI)	**5.5** (3.5 – 6.3)	**5.5** (3.5 – 6.3)	**NE** (2.7 – NE)
mPFS (mos) (95% CI)	**4.4** (2.8 – 6.8)	**5.4** (2.8 – 6.8)	**4.1** (2.6 – 8.5)

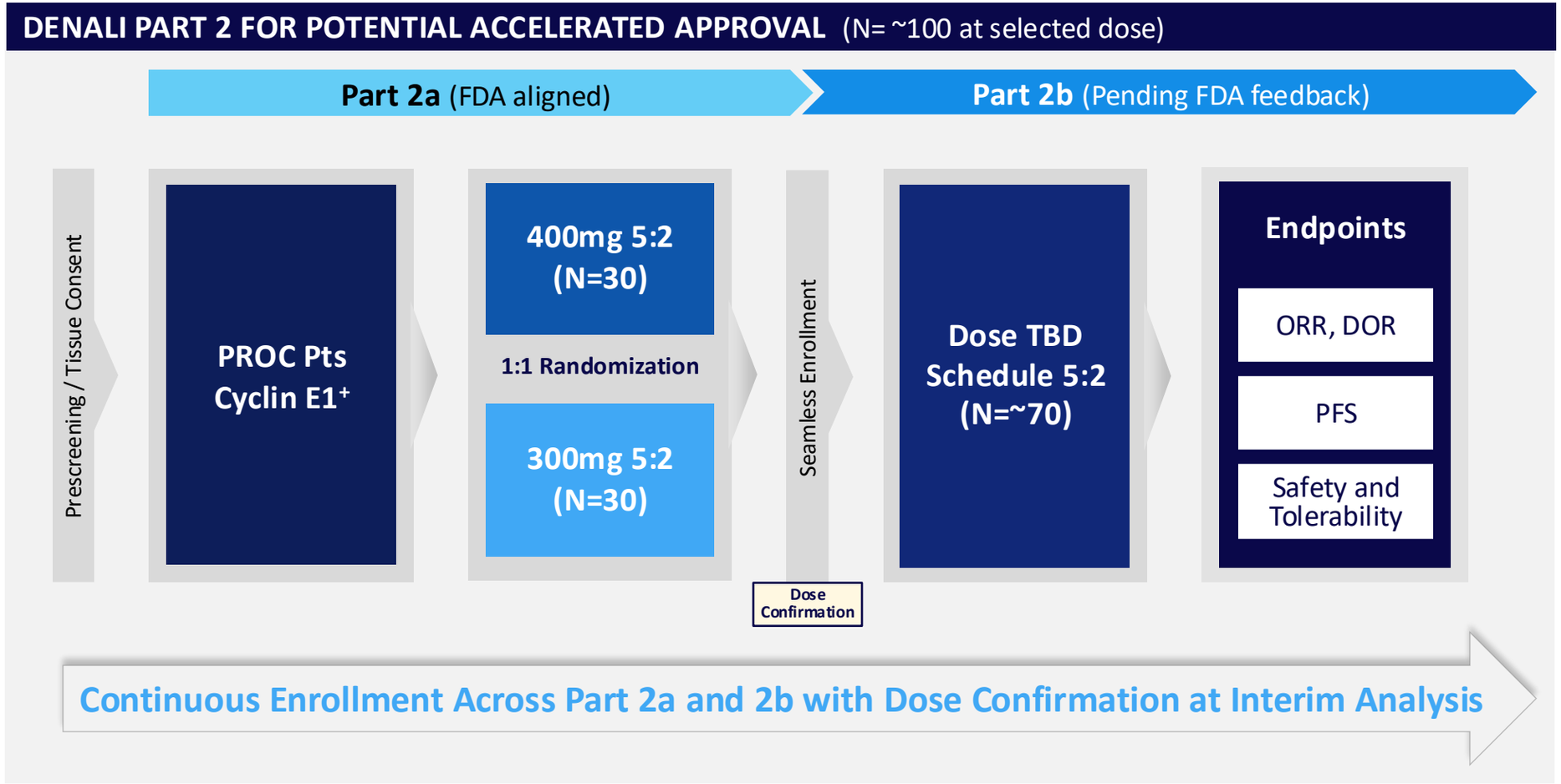
*Includes patients who received at least one post-treatment scan
Abbreviations: CI, confidence interval; mDOR, median duration of response; mPFS, median progression free survival; NE, not estimable due to small number of subjects and events; PLoT, prior line of therapy

Data Cutoff
Dec 2 2024
Active database; subject to further change

DENALI – Phase 2 Registration-Intent Study for Accelerated Approval of Azenosertib Monotherapy in Cyclin E1+ PROC Patients

Key Eligibility

- ✓ **Platinum-resistant ovarian cancer**
- ✓ **1-3 prior lines of therapy**
- ✓ **Prior MIRV if high FRα, up to 4 prior lines allowed**
- ✓ **Cyclin E1+ by proprietary IHC cutoff criteria**



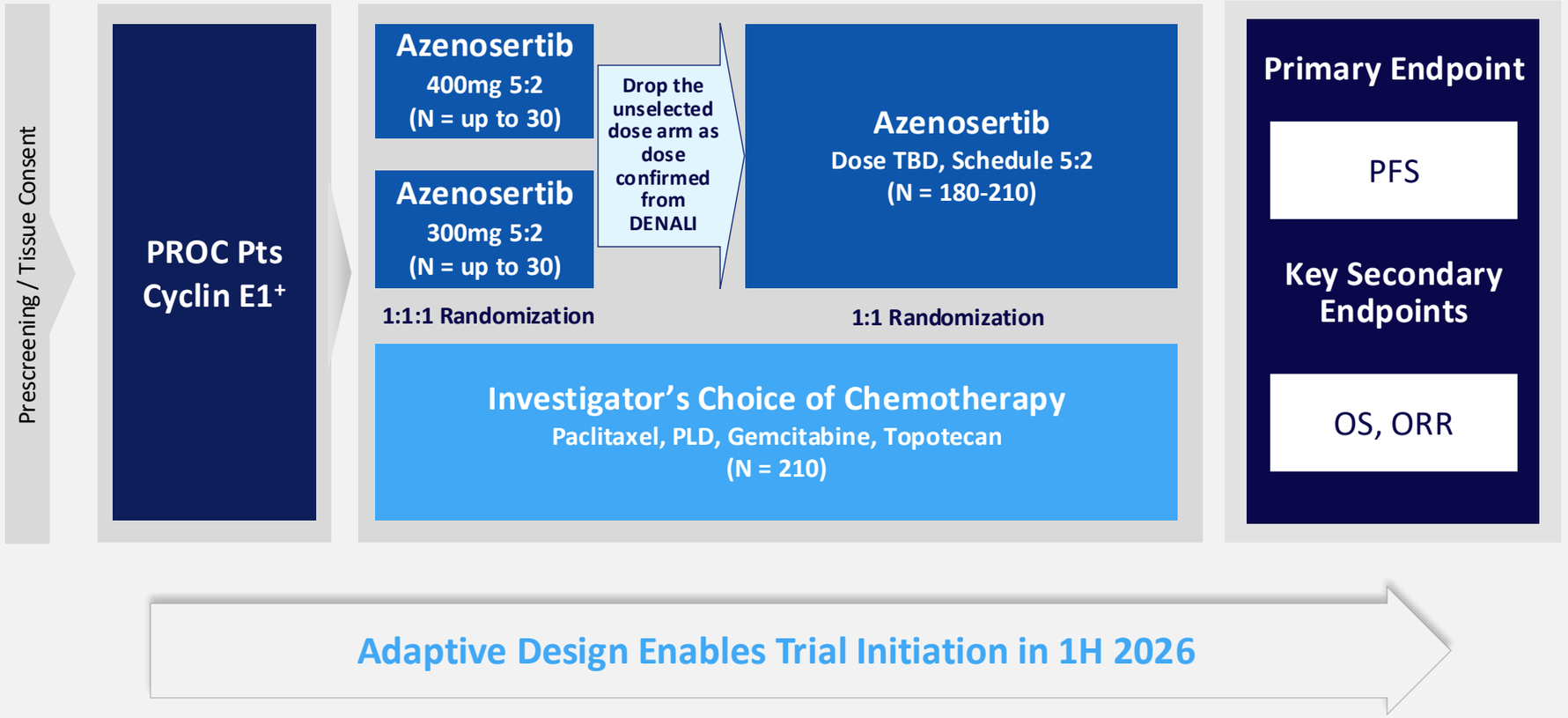
*Abbreviations: 5:2 schedule = 5 days once-daily administration of azenosertib, followed by 2 days without azenosertib; IHC= immunohistochemistry; MIRV=mirvetuximab soravtansine; PROC=platinum resistant ovarian cancer; DOR=duration of response; ORR=overall response rate; PFS=progression free survival.

ASPENOVA – Phase 3 Registration-Intent, Confirmatory Study for Full Approval of Azenosertib Monotherapy in Cyclin E1+ PROC Patients

Key Eligibility

- ✓ Platinum-resistant ovarian cancer
- ✓ 1-3 prior lines of therapy
- ✓ Prior MIRV if high FRα, up to 4 prior lines allowed
- ✓ Cyclin E1+ by proprietary IHC cutoff criteria

ASPENOVA RANDOMIZED TRIAL INTENDED FOR FULL APPROVAL (FDA Aligned, N= 420-450)



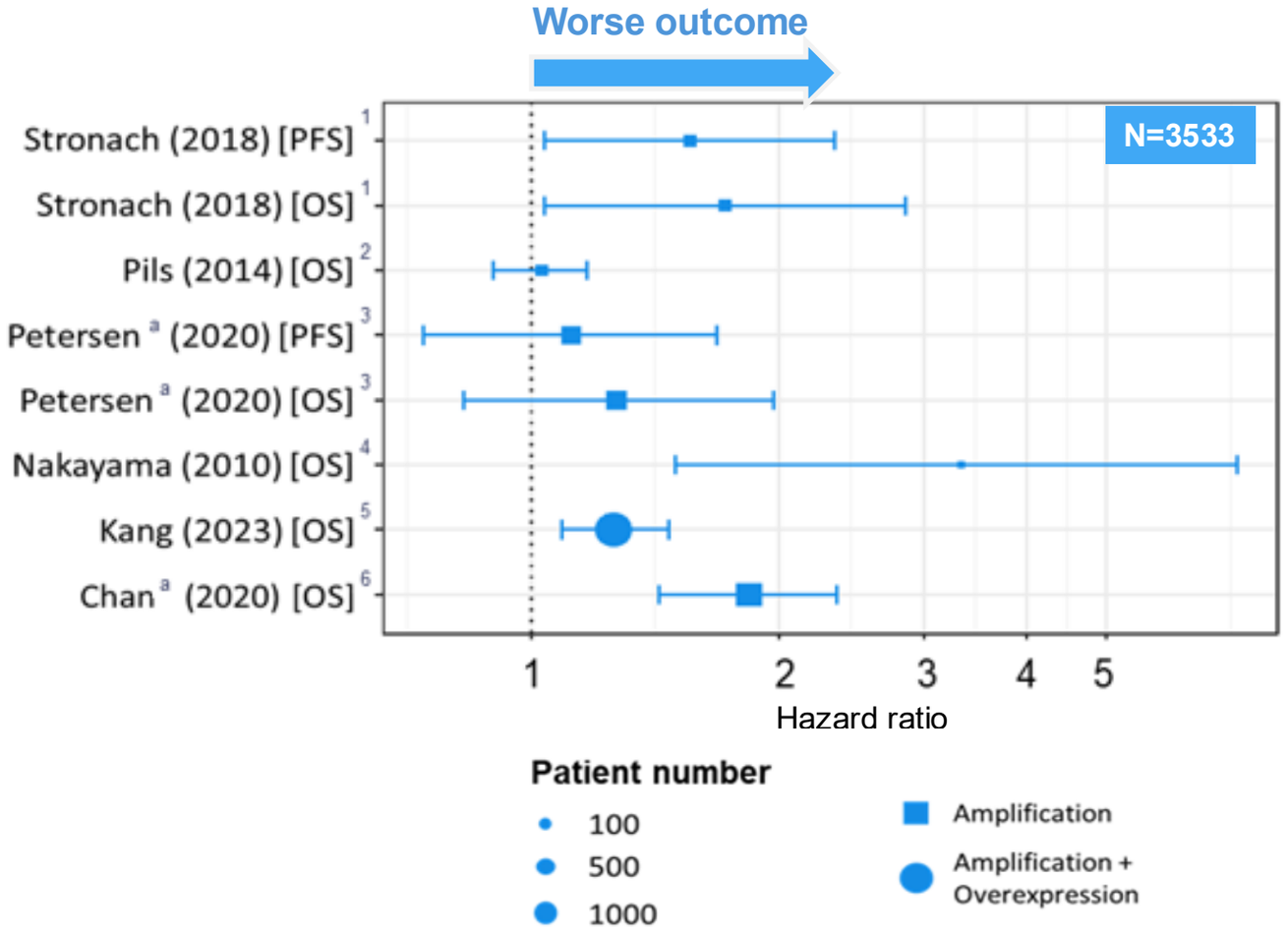
Abbreviations: 5:2 schedule = 5 days once-daily administration of azenosertib, followed by 2 days without azenosertib; IHC= immunohistochemistry; MIRV=mirvetuximab soravtansine; PROC=platinum resistant ovarian cancer; PLD=pegylated liposomal doxorubicin; OS=overall survival; ORR=overall response rate; PFS=progression free survival

DENALI Part 1b (ZN-c3-005)

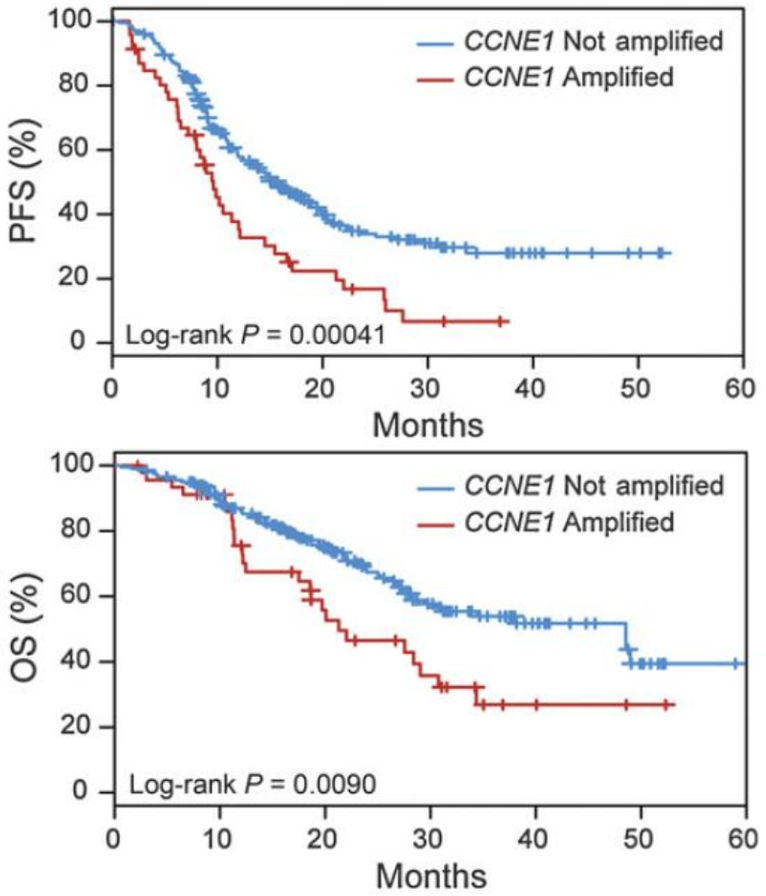
NCT05198804

Updated data at SGO 2025, Data cutoff January 13, 2025

Ovarian Cancer Patients With Cyclin E1 Overexpression and/or *CCNE1* Amplified Ovarian Cancers Have Worse Outcomes



Survival according to *CCNE1* amplification status[1]



[a]Timing of tissue collection was not disclosed. OS, overall survival; PFS, progression-free survival. **1.** Stronach EA, et al. *Mol Cancer Res.* 2018;16:1103-1111. **2.** Pils D, et al. *Eur J Cancer.* 2014;50:99-110. **3.** Peterson S, et al. *Gynecol Oncol.* 2020;157:405-410. **4.** Nakayama N, et al. *Cancer.* 2010;116:2621-2634. **5.** Kang EY, et al. *Cancer.* 2023;129:697-713. **6.** Chan AM, et al. *J Pathol Clin Res.* 2020;6:252-262.

DENALI Part 1b Evaluated 400mg 5:2 QD and Confirmed Cyclin E1 Biomarker

Study Design

Key Eligibility

- ✓ Platinum-resistant ovarian cancer
- ✓ 1-5 prior lines of therapy
- ✓ Tissue mandatory for biomarker assessment

Enrollment
(N=102)

Azenosertib monotherapy
400 mg QD 5:2

Endpoints

- ORR, DOR
- PFS
- Safety and Tolerability

Status Part 1b Enrollment Complete

Abbreviations: QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival

DENALI Part 1b: Patient Baseline Characteristics

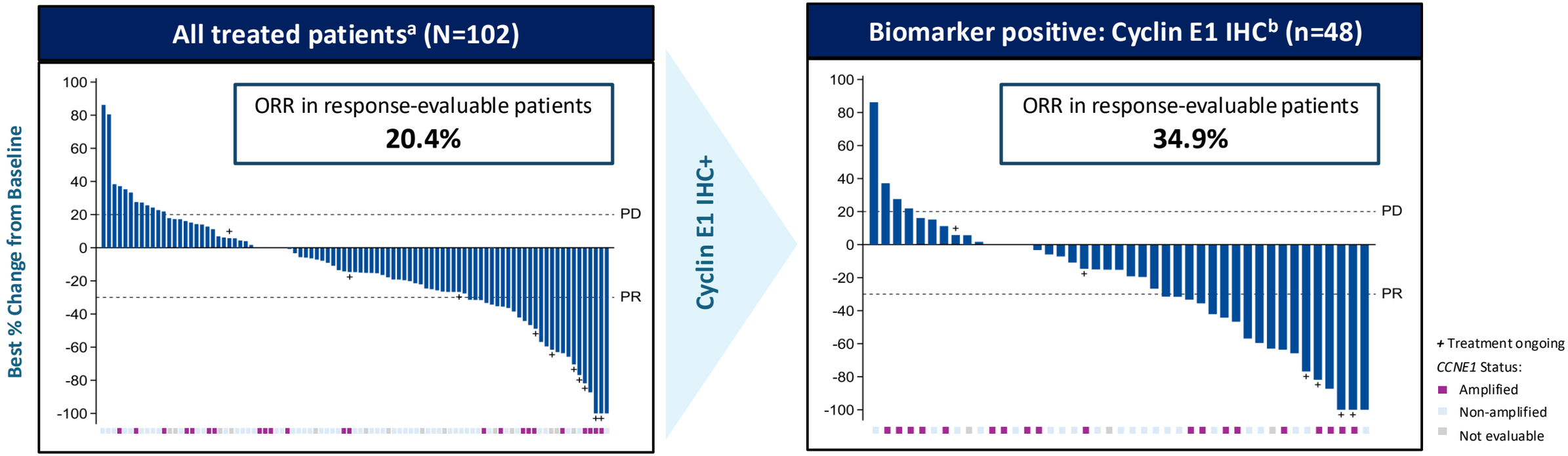
Characteristics[a] (N=102)	
Median age (range), years	66 (34-82)
Race, n (%)	
White	70 (69)
Black/African American	6 (6)
Asian	3 (3)
Other[b]	1 (1)
Not reported	22 (22)
ECOG PS, n (%)	
0	53 (52)
1	49 (48)
Prior lines of treatment	
Median (range)	3 (1-5)
1-2, n (%)	35 (34)
3-4, n (%)	57 (56)
5, n (%)	10 (10)

Characteristics[a] (N=102)	
Prior therapy, n (%)	
Bevacizumab	93 (91)
PARPi	57 (56)
Mirvetuximab	15 (15)
***CCNE1* amplification,[c]**	
Evaluable, n	88
Amplified, n (%)	27 (31)
Cyclin E1 status by IHC	
Evaluable, n	94
IHC+, n (%)	48 (51)

- **Heavily pre-treated population: >65% with 3+ lines of therapy**
- **~50% of patients identified with Cyclin E1 overexpression per Zentalis IHC assay**

Data cutoff date: January 13, 2025. [a]Full analysis set: all treated patients. Biomarker dataset: all treated patients with evaluable tissue and Cyclin E1 IHC status. [b]Hispanic. [c]85% (23/27) of patients with *CCNE1*-amplified tumors were also Cyclin E1+ by IHC. Amp, amplified; *CCNE1* amplification defined as Copy Number ratio ≥3 with genomic ploidy correction as per Foundation Medicine. ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; PARPi, poly(ADP-ribose) polymerase inhibitor.

Cyclin E1+ by IHC is a Biomarker Predicting Response to Azenosertib



	All treated patients (N=102)	Cyclin E1 IHC+ (n=48)
ORR in response-evaluable[c] patients, % (n/N; 95% CI)	**20.4** (19/93; 12.8-30.1)	**34.9** (15/43; 21.0-50.9)
ORR, ITT[a] % (n/N; 95% CI)	**18.6** (19/102; 11.6-27.6)	**31.3** (15/48; 18.7-46.3)

Data cutoff date: Jan 13, 2025. [a]Intent to treat/Full analysis set: all treated patients. [b]Biomarker dataset: all treated patients with evaluable tissue and Cyclin E1 IHC status. [c]Includes patients who received at least one post-treatment scan.
Amp, amplified; IHC, immunohistochemistry; ITT, Intent to treat population; ORR, objective response rate; PD, progressive disease; PR, partial response.

DENALI Part 1b: Duration of Response in Cyclin E1 IHC+ Ovarian Cancer

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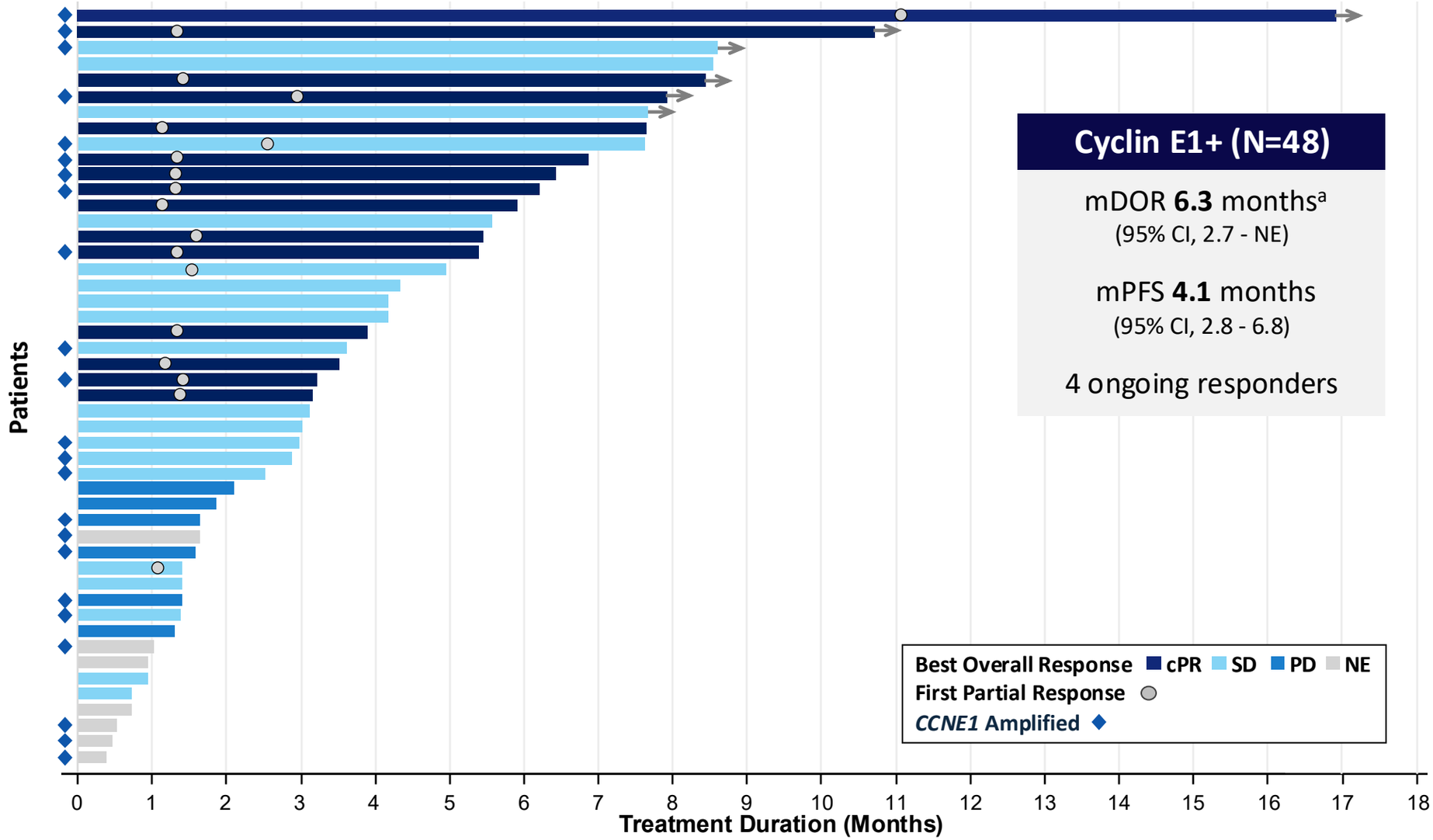


Cyclin E1+ (N=48)

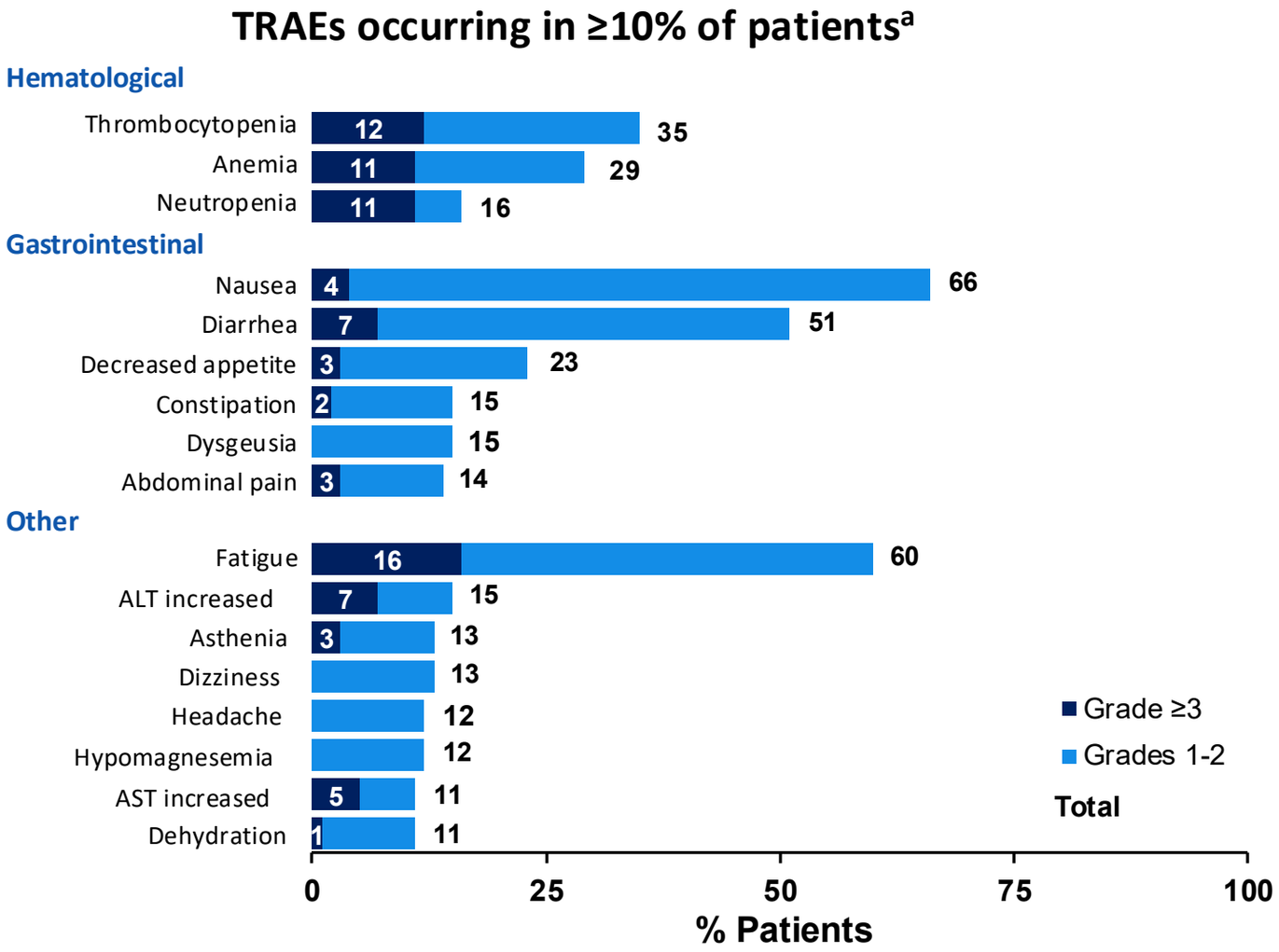
mDOR **6.3** months[a]
(95% CI, 2.7 - NE)

mPFS **4.1** months
(95% CI, 2.8 - 6.8)

4 ongoing responders

[a]mDOR is subject to change, there are 4 ongoing responders as of the January 13, 2025 data cutoff. IHC, immunohistochemistry; cPR, confirmed partial response; SD, stable disease; PD, progressive disease; mDOR, median duration of response; mPFS, median progression free survival; NE, not evaluable

DENALI Part 1b: Safety and Tolerability Summary



TRAEs, n (%)	
Leading to dose reduction	44 (43.1)
Leading to dose interruption	59 (57.8)
Leading to discontinuation	22 (21.6)
Leading to death	2 (2.0)[b]
Serious TRAEs	22 (21.6)

Data cutoff date: January 13, 2025

[a]If a patient had multiple grades of the same adverse event, The worse grade was reported [b]One patient had sepsis, and 1 patient had pancytopenia.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

Registration-Intent DENALI Part 2 Topline Data Anticipated by YE2026

Azenosertib data support further development in Cyclin E1+ PROC in Part 2 of the ongoing DENALI study

Cyclin E1+ / overexpression by IHC represents ~ 50%[c] of PROC
- Cyclin E1+ IHC more than doubles the eligible patient population beyond CCNE1 amp

Azenosertib demonstrates ORR of ~35% in evaluable[a] patients with Cyclin E1+ PROC
- Median duration of response is 6.3 months[b]

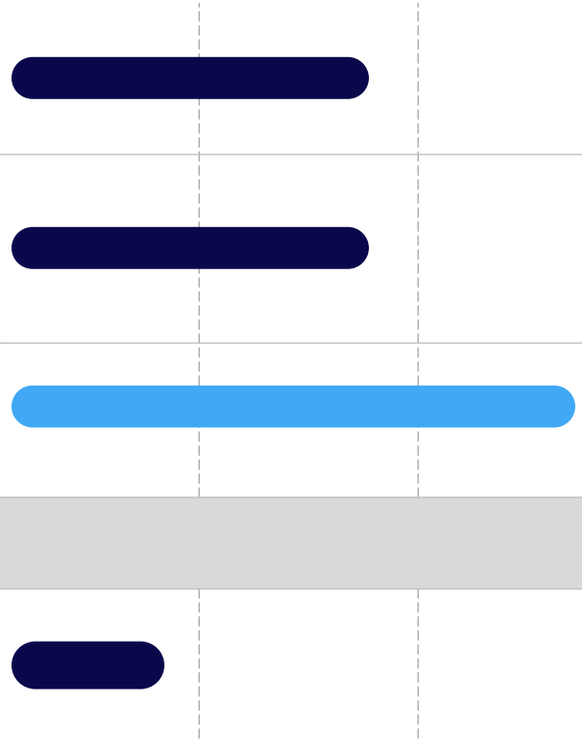
Cyclin E1 by IHC is a predictive biomarker for response to azenosertib

Manageable safety profile
- GI toxicity (nausea, diarrhea) and fatigue are the most common TRAEs; although less common, hematological toxicities require close monitoring during treatment with azenosertib

[a]Includes patients who received at least one post treatment scan as of the January 13, 2025 data cut off; [b]mDOR is subject to change, there are 4 ongoing responders as of the January 13, 2025 data cut off; [c] Cyclin E1 IHC+ based on Zentalis proprietary IHC cutoff and Cyclin E1 IHC assay developed from the existing clinical data; Cyclin E1 IHC+% based on literature (~20% CCNE1 amplification) and the unbiased CCNE1 amp & Cyclin E1 overlapping data generated from Zentalis clinical trial samples
GI, gastrointestinal; mDOR, median duration of response; PROC, platinum-resistant ovarian cancer; TRAE, treatment-related adverse event.

Azenosertib has the Potential to be a First-in-Class and Best-in-Class WEE1 Inhibitor for Patients with Ovarian Cancer and Other Tumor Types

TRIAL NAME	DEVELOPMENT APPROACH	PHASE 1	PHASE 2	PHASE 3	STUDY STATUS
Cyclin E1-Positive PROC Monotherapy (lead indication)					
DENALI	**DENALI Part 1b** Demonstrated Cyclin E1 protein overexpression as biomarker predicting response to azenosertib				Ongoing In Long-term Follow-up Only
	DENALI Part 2a + Part 2b Registration-intent Cyclin E1+ *FDA Fast Track Designation*				Top line Readout Expected YE 2026 Ongoing Study
ASPENOVA	**Azenosertib vs. SOC chemo** Randomized, confirmatory trial Cyclin E1+				Initiation Expected 1H 2026 Planned Study
Ovarian Cancer Combination Therapy					
MUIR*	**Azenosertib + multiple chemo backbones and bevacizumab**				Currently Enrolling Bevacizumab Combo Ongoing Study



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* Also known as ZN-c3-002

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APPENDIX

ZN-c3-001 Dose-Escalating Monotherapy Study in Solid Tumors

NCT04158336

First-in-Human Phase 1 Dose and Schedule Optimization in Solid Tumors: Therapeutic Window Established

Key Eligibility

- ✓ 1+ prior lines of therapy
- ✓ Solid tumor, PROC and USC enriched
- ✓ Tissue collected for biomarker analysis

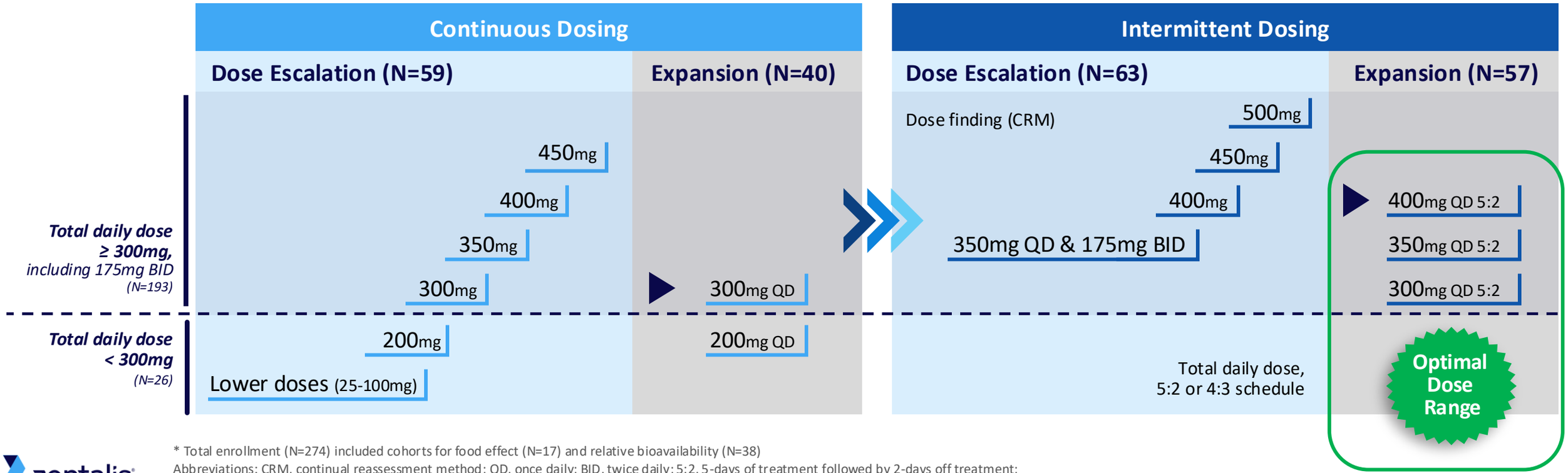
Total Enrollment

N=274 across all tumor types and dose*

N=193 at total daily dose ≥ 300mg; evaluated for safety and anti-tumor activity

Status

Fully Enrolled



* Total enrollment (N=274) included cohorts for food effect (N=17) and relative bioavailability (N=38)

Abbreviations: CRM, continual reassessment method; QD, once daily; BID, twice 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; PROC, platinum resistant ovarian cancer; USC, uterine serous carcinoma

Heavily Pre-Treated Patient Population with Multiple Tumor Types; Patients with PROC had a Median of Five Prior Lines of Therapy

Patient Demographics and Clinical Characteristics
Total Daily Dose ≥ 300 mg – Continuous and Intermittent (N=193)

	PROC N = 69	USC N = 35	Other Solid Tumors* N = 89
Age (years)			
Median	66	66	64
Range (Min-Max)	(48 – 83)	(53 – 78)	(26 – 81)
ECOG PS (n, %)			
ECOG 0	19 (28%)	8 (23%)	32 (36%)
ECOG 1	50 (72%)	26 (74%)	54 (61%)
ECOG 2	0	1 (3%)	2 (2%)
Prior Lines of Treatment			
Median (Range)	5 (1 - 19)	3 (0 - 12)	4 (0 - 11)
0	0	1 (3%)†	1 (3%)‡
1-3	22 (32%)	22 (63%)	34 (36%)
≥4	47 (68%)	12 (34%)	54 (61%)

	PROC N = 69	USC N = 35	Other Solid Tumors N = 89
Prior Therapies (n, %)			
PARPi	46 (67%)	3 (9%)	5 (6%)
VEGFi	60 (87%)	27 (77%)	39 (44%)
PD-1/PD-L1	12 (17%)	27 (77%)	35 (39%)
Cyclin E1 Status (n, %)			
Positive	26 (38%)	15 (43%)	9 (10%)
Negative	29 (42%)	11 (31%)	25 (28%)
Unknown	14 (20%)	9 (26%)	55 (62%)

*Anus, Appendix, Biliary tract, Bladder, Breast, Cecum, Cervix, Colon, Duodenum, Endometrium, Esophagus, Kidney, Lung, Other, Ovary, Pancreas, Peritoneum, Prostate, Rectum, Stomach, Uterus, Vulva/Vagina, including one patient who had unknown ECOG status; † patient had no prior therapy ; ‡ patient rolled over from the DDI study

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; PARPi, poly-ADP ribose polymerase inhibitor; VEGFi, vascular endothelial growth factor inhibitor; PD-1/PD-L1, programmed cell death protein 1/programmed death ligand 1.

Data Cutoff Dec 2 2024
Active database; subject to further change

Tolerable at Active Dose Levels Across Tumor Types

Safety Profile
Total Daily Dose ≥ 300 mg – Continuous and Intermittent (N=193)

Treatment Related AEs*, n (%)	All Grade	Grade 3+
Gastrointestinal		
Decreased appetite	52 (26.9%)	3 (1.6%)
Diarrhea	100 (51.8%)	15 (7.8%)
Nausea	117 (60.6%)	8 (4.1%)
Vomiting	49 (25.4%)	2 (1.0%)
Dehydration	22 (11.4%)	1 (0.5%)
Fatigue	113 (58.5)	26 (13.5%)
Hematologic		
Anemia	58 (30.1%)	22 (11.4%)
Thrombocytopenia	51 (26.4%)	21 (10.9%)
Neutropenia	29 (15.0%)	25 (13.0%)
Febrile Neutropenia	2 (1.0%)	2 (1.0%)

*TRAEs listed here represent adverse events of special interest and adverse events of clinical significance for azenosertib and this class of molecules

Treatment Related AEs, n (%)	
Treatment-Related SAE	19 (9.8%)
TRAE leading to dose reduction	76 (39.4%)
TRAE leading to dose interruption	78 (40.4%)
TRAE leading to discontinuation	10 (5.2%)
TRAE leading to death	1 (0.5%)

- **No gastrointestinal TRAE > G3 observed**
- **Low rate of G3+ TR hematological toxicities, the majority G3**
- **Low rate of TRAE leading to treatment discontinuation**
- **One G5 TRAE previously reported**

Neutropenia: Neutropenia, neutrophil count decreased, neutrophil percentage decreased; Thrombocytopenia: platelet count decreased and thrombocytopenia; Anemia: hematocrit decreased, hemoglobin decreased, RBC count decreased

Abbreviations: AE, adverse event; TRAE, treatment related adverse event. SAE, serious adverse event.

Data Cutoff Dec 2 2024 Active database; subject to further change

Azenosertib Demonstrated Encouraging ORR and DOR at ≥300mg Total Daily Dose, Intermittent in PROC

Clinical Activity Overview - Total Daily Doses ≥ 300 mg - Continuous and Intermittent (N=193)

Tumor Type	PROC				USC				Other Solid Tumors			
Dose Schedule	Intermittent		Continuous		Intermittent		Continuous		Intermittent		Continuous	
Cyclin E1 IHC Status	All	Cyclin E1+	All	Cyclin E1+	All	Cyclin E1+	All	Cyclin E1+	All	Cyclin E1+	All	Cyclin E1+
Number of Patients	58	23	11	3	19	11	16	4	43	4	46	5
ORR, (%), n (95% CI)	20.7%, (12/58) (11.2 - 33.4)	34.8%, (8/23) (16.4 - 57.3)	18.8% (2/11) (2.3 - 51.8)	33.3% (1/3) (0.8 - 90.6)	26.3% (5/19) (9.2 - 51.2)	36.4% (4/11) (10.9 - 69.2)	18.8% (3/16) (4.1 - 45.7)	25.0% (1/4) (0.6 - 80.6)	2.3% (1/4) (0.1 - 12.3)	0.0% (0/4) (0.0 - 60.2)	4.3% (2/46) (0.5 - 14.8)	0.0% (0/5) (0.0 - 52.2)
mDOR (mos) (95% CI)	5.1 (3.0, 5.9)	5.2 (2.8, 6.9)	7.1 (4.2, NE)	4.2 (NE, NE)	5.5 (5.4, NE)	5.5 (5.4, NE)	5.6 (4.1, NE)	6.9 (NE, NE)	4.3 (NE, NE)	NA	3.3 (3.0, NE)	NA

Greater anti-tumor activity seen with intermittent dosing schedule and Cyclin E1+ patients
Results direct focused development on doses of 300 and 400 mg at intermittent dosing schedule

[1] Not a head-to-head comparison
PROC, platinum-resistant ovarian cancer; USC, uterine serous carcinoma; ORR, objective response rate; mDOR, median duration of response; IHC, immunohistochemistry; NE, not evaluable

Data Cutoff
Dec 2 2024
Active database; subject to further change

Key Takeaways from 001

Meaningful therapeutic window identified providing a favorable risk-benefit profile in Cyclin E1^{+} PROC patients at total daily doses of 300 and 400mg QD 5:2

- **Azenosertib studied in a large patient population across multiple tumor types**
- **Platinum-resistant ovarian cancer (PROC) identified as an indication particularly susceptible to WEE1 inhibition**
- **Cyclin E1 identified as predictive biomarker for response to azenosertib**

MAMMOTH (ZN-c3-006)

NCT05198804

MAMMOTH: Two Clinically-active Monotherapy Doses Studied in Heavily Pre-treated, PARPi-resistant PROC Patient Population

Study Design

Key Eligibility

- ✓ 1-5 prior lines of therapy
- ✓ Platinum-resistant, progressed while receiving an approved PARP inhibitor
- ✓ Mandatory sufficient tissue for biomarker analysis

Enrollment
(N=117)

Azenosertib monotherapy
300 or 400 mg QD 5:2
(N=61)

Azenosertib + niraparib
Concurrent schedule
(N=28)

Azenosertib + niraparib
Alternating schedule
(N=28)

Endpoints

- **ORR, DOR**
- **PFS**
- **Safety and Tolerability**

Status Enrollment Complete

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Abbreviations: QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; ORR, objective response rate DOR, duration of response; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor

Heavily Pre-Treated PARPi-resistant PROC Population

Patient Demographics and Clinical Characteristics
Monotherapy Cohorts Only

	300 mg 5:2 (N=25)	400 mg 5:2 (N=36)
Age (years)		
Median	71.0	63.0
Range (Min-Max)	45 – 80	31 - 84
ECOG PS (n, %)		
ECOG 0	7 (28%)	16 (44%)
ECOG 1	18 (72%)	20 (56%)
Prior Lines of Treatment (n, %)		
1-3	15 (60%)	20 (56%)
≥4	10 (40%)	16 (44%)
PARP	25 (100%)	36 (100%)
Bevacizumab	24 (96%)	34 (94%)
Cyclin E1 Status (n, %)		
Positive	13 (52%)	16 (44%)
Negative	10 (40%)	15 (42%)
Unknown	2 (8%)	5 (14%)

Abbreviations: QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; ORR, objective response rate DOR, duration of response; PFS, progression-free survival, PROC, platinum-resistant ovarian cancer

Data Cutoff
Dec 2 2024
Active database; subject to further change

Well-characterized Safety and Tolerability in PROC Monotherapy Cohorts at 300mg QD and 400mg QD (5:2) Doses

Azenosertib Monotherapy 300 mg & 400mg QD (5:2)

Treatment-related AEs*, N (%)	300mg (N=25)		400mg (N=36)	
	All Grade	Grade 3+	All Grade	Grade 3+
Gastrointestinal				
Decreased appetite	7 (28.0%)	1 (4.0%)	11 (30.6%)	0
Diarrhea	13 (52.0%)	0	17 (47.2%)	4 (11.1%)
Nausea	15 (60.0%)	0	19 (52.8%)	1 (2.8%)
Vomiting	2 (8.0%)	0	4 (11.1%)	1 (2.8%)
Dehydration	0	0	0	0
Fatigue	6 (24.0%)	1 (4.0%)	11 (30.6%)	1 (2.8%)
Sepsis	0	0	1 (2.8%)	1 (2.8%)
Hematologic				
Anemia	10 (40.0%)	3 (12.0%)	14 (38.9%)	6 (16.7%)
Thrombocytopenia	8 (32.0%)	2 (8.0%)	13 (36.1%)	4 (11.1%)
Neutropenia	4 (12.0%)	3 (12.0%)	8 (22.2%)	5 (13.9%)
Febrile Neutropenia	0	0	1 (2.8%)	1 (2.8%)

* TRAEs listed here represent adverse events of special interest and adverse events of clinical significance for azenosertib and this class of molecules

Treatment-related AEs, N (%)	300mg (N=25)	400mg (N=36)
Treatment-Related SAE	4 (16.0%)	5 (13.9%)
TRAE leading to dose reduction	11 (44.0%)	15 (41.7%)
TRAE leading to dose interruption	11 (44.0%)	14 (38.9%)
TRAE leading to discontinuation	4 (16.0%)	2 (5.6%)
TRAE leading to death	0 (0.0%)	1 (2.8%)

- Similar rates of TR SAEs across doses
- Low rate of TR G3+ hematological toxicities with the majority being G3 events (only one G4 febrile neutropenia and one sepsis event)
- Low rate of TRAEs leading to treatment discontinuation
- One G5 TRAE previously reported

Neutropenia: Neutropenia, neutrophil count decreased, neutrophil percentage decreased; Thrombocytopenia: platelet count decreased and thrombocytopenia; Anemia: hematocrit decreased, hemoglobin decreased, RBC count decreased

Abbreviations: AE, adverse event; TRAE, treatment related adverse event. SAE, serious adverse event.

Data Cutoff Dec 2 2024 Active database; subject to further change

Azenosertib Demonstrated Clinically Meaningful Responses in PARPi-resistant Monotherapy Cohorts

Azenosertib Monotherapy 300 mg & 400mg QD (5:2)				
Dose and Schedule	**300mg 5:2**		**400mg 5:2**	
Cyclin E1 IHC Status	**All**	**Cyclin E1+**	**All**	**Cyclin E1+**
Number of Patients	**25**	**14**	**36**	**16**
ORR, (%), n (95% CI)	**20.0% (5/25) (6.8 - 40.7)**	**21.4% (3/14) (4.7 - 50.8)**	**22.2% (8/36) (10.1 - 39.2)**	**31.3% (5/16) (11.0 - 58.7)**
mDOR, months (95% CI)	**4.9 (2.8 - NE*)**	**4.9 (3.0 - NE*)**	**5.5 (2.7 - NE*)**	**4.2 (3.0 - NE*)**

400mg 5:2 shows numerically better ORR in Cyclin E1+ PROC patients compared to 300mg 5:2

*Not estimable due to small number of subjects and events

Abbreviations: PARPi, poly (ADP-ribose) polymerase inhibitor; IHC, immunohistochemistry; QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; ORR, objective response rate; CI, confidence interval; mDOR, median duration of response; NE, not evaluable

Data Cutoff Dec 2 2024
Active database; subject to further change

Key Takeaways from MAMMOTH Monotherapy Cohort

Learnings continue to support development of azenosertib in Cyclin E1+ PROC

- Consistent antitumor activity in PARPi-resistant patients
- Tolerability and toxicity consistent with 001 study and similar between the assessed doses
- 400mg QD 5:2 showed numerically higher response rates than 300mg QD 5:2

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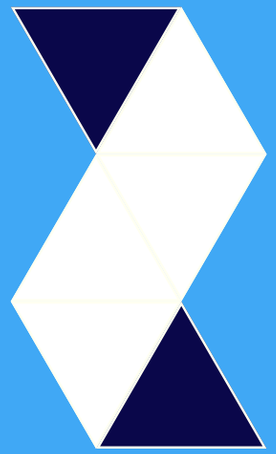
Abbreviations: QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; PROC, platinum-resistant ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor



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