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Azenosertib Ovarian Cancer Clinical Discussion

November 10, 2023

Nasdaq: ZNTL

Joining the Call Today

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Azenosertib Ovarian Cancer Discussion

1 **Positive Updated Phase 1 Data**

Strong Monotherapy Efficacy and Safety/Tolerability in Platinum Resistant Ovarian and Uterine Serous Cancers

2 **Ongoing Phase 2 Trials in Platinum Resistant Ovarian Cancer**

Data readouts in 2024 and 2025

3 **Blockbuster Opportunity in Platinum Sensitive 1L Ovarian Cancer**

High Unmet Need HRP Population

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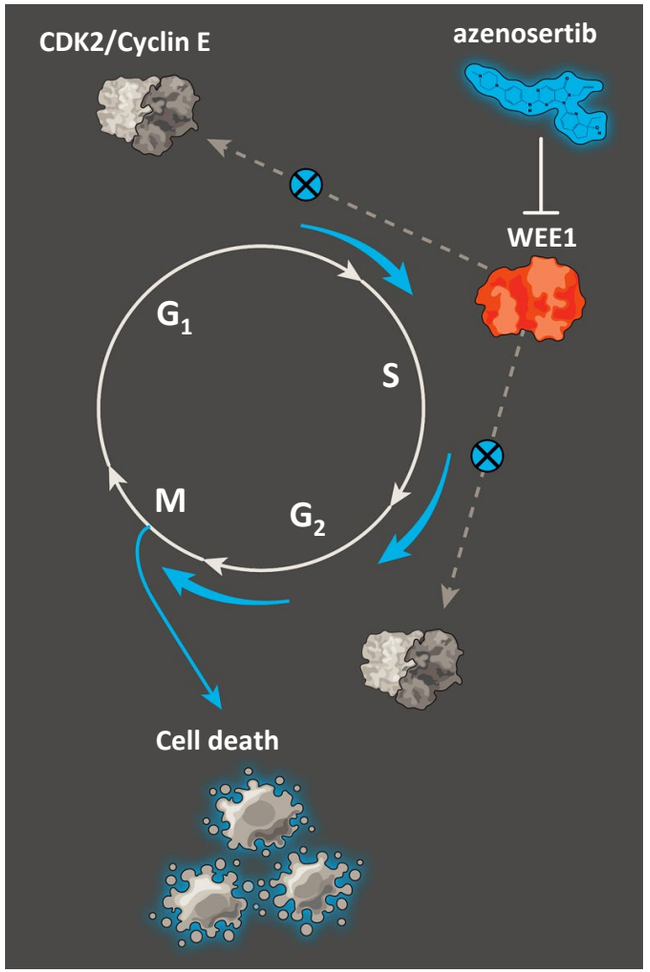
HRP, homologous-recombination repair proficient

Azenosertib's Mechanism of Action Causes Accumulation of DNA Damage Leading to Cancer Cell Death

- Azenosertib **dephosphorylates CDK1 and CDK2** which abrogates G1-S and G2-M cell cycle checkpoints, accelerating cell cycling[1]
- **Acceleration of cell cycling** does not allow for adequate DNA repair[1,2]
- **DNA damage** increases and accumulates[1,2]
- Cancer cell undergoes **mitotic catastrophe**[1,2]

Clinically active as a single agent in tumors with high genomic instability, such as ovarian and uterine serous carcinoma



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1 Ghelli Luserna di Rorà A, et al. J Hematol Oncol 2020;13:126; 2 Elbæk CR, et al. Cell Rep 2022

Azenosertib Monotherapy Updated Results

Monotherapy Anti-tumor Activity in Gynecologic Malignancies with Favorable Safety and Tolerability Profile

Longer Follow Up Improves Duration of Benefit

Strong Safety and Tolerability of Azenosertib Monotherapy

CORPORATE CALL
June 6, 2023

- **37% Objective Response Rate** using intermittent dosing in ovarian and USC patients
- Established monotherapy **RP2D** of 400 mg 5:2
- **Doubled steady state drug exposure** compared to continuous dosing

UPDATED DATA
Nov 6, 2023

- **Median follow up has increased by nearly 5 months and mPFS has increased to 6.5 months**
- **Maintained excellent safety and tolerability with intermittent dosing**

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Abbreviations: USC, uterine serous carcinoma; RP2D: recommended Phase 2 dose; 5:2 refers to administration schedule of five days on therapy and two days off; mPFS, median progression-free survival

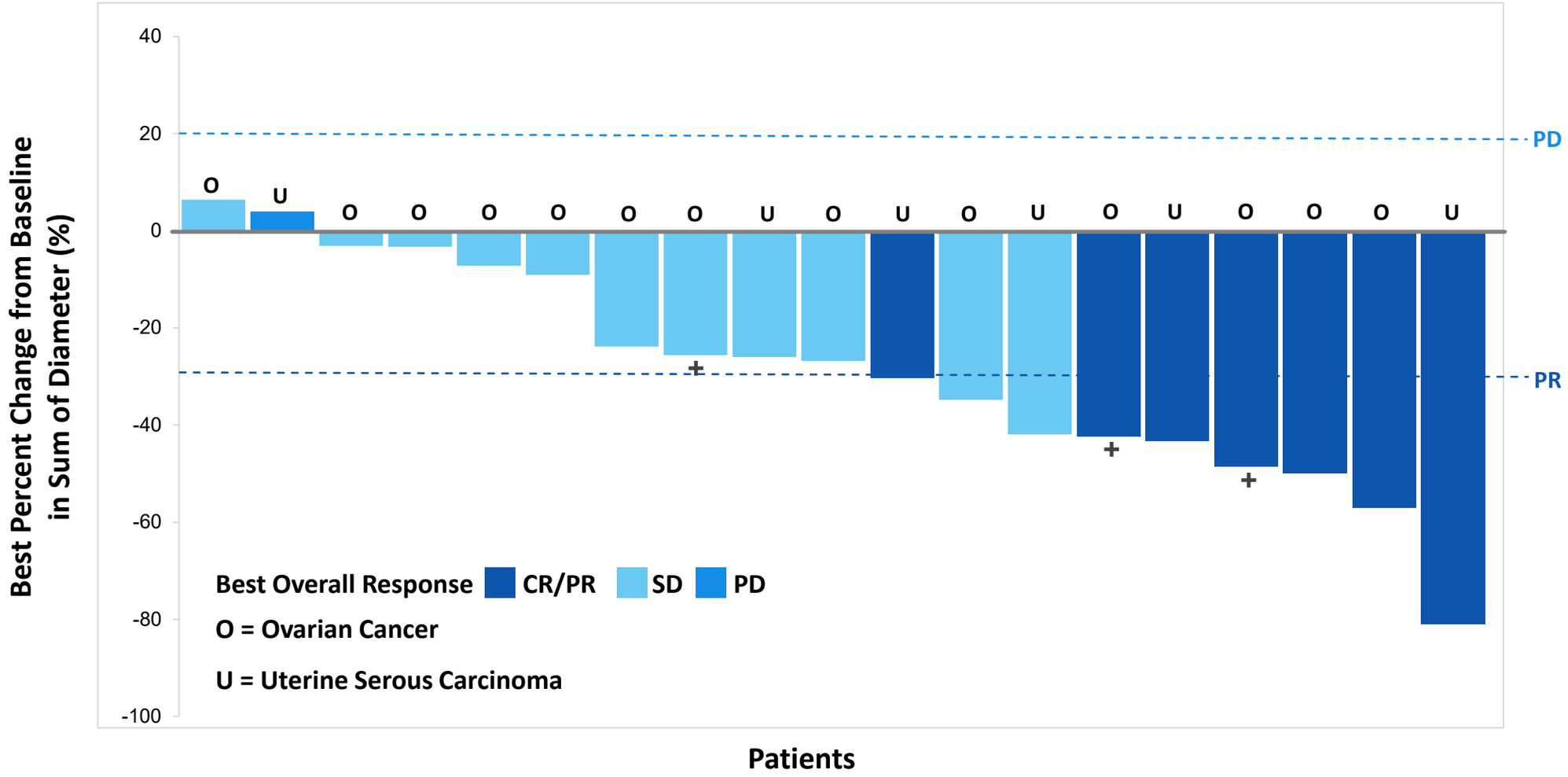
Intermittent Monotherapy Patient Population Was Heavily Pretreated and Treatment Refractory

	USC	HGSOC
	N=6	N=13
Prior Lines of Treatment		
Median (Range)	3.5 (1-6)	6 (2-11)
Platinum Resistant* (N, %)	5 (83.3)	5 (38.5)
Platinum Refractory** (N, %)	NA	8 (61.5)
Prior Therapies (N, %)		
Prior PARP Inhibitor	1 (16.7)	10 (76.9)
Prior Experimental Agents	0 (0.0)	5 (38.5)
Prior VEGF Inhibitor	5 (83.3)	11 (84.6)
Prior Anti-PD-1/PD-L1	6 (100)	1 (7.7)

USC and HGSOC subjects who received at least one dose of azenosertib with intermittent dosing schedule, have baseline measurable disease by RECIST 1.1, and at least one post-baseline scan.
*Platinum Resistant: For USC patients, received prior platinum therapy. For HGSOC patients, progression within 90-180 days of prior dose of a platinum-based regimen in any line of therapy.
**Platinum Refractory: Progression within 90 days of prior dose of a platinum-based regimen in any line. Progression date based on progression date if available or start date of next therapy.
Abbreviations: USC, uterine serous carcinoma; HGSOC, high grade serous ovarian cancer; PARP, poly-ADP ribose polymerase; VEGF, vascular endothelial growth factor; PD-1/PD-L1, programmed cell death protein 1/programmed death ligand 1.

Monotherapy Azenosertib Results in a 37% Confirmed Response Rate

In Both Platinum Resistant Ovarian Cancer and Uterine Serous Carcinoma

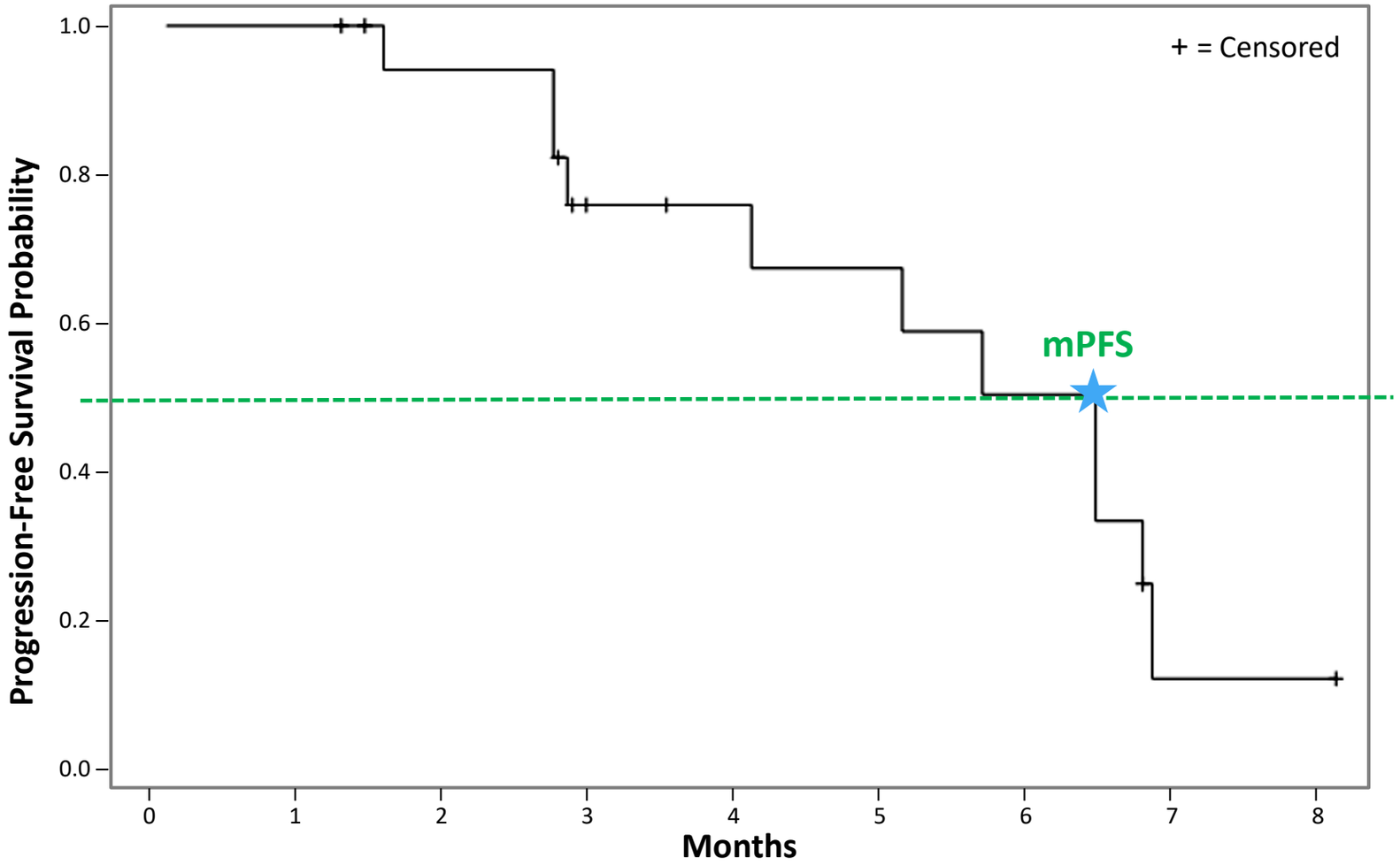


ORR = 36.8%

Subjects who received at least one dose of azenosertib with intermittent dosing schedule, have baseline measurable disease by RECIST 1.1, and at least one post-baseline scan.
Abbreviations: +, patients remain on therapy at the time of data cut-off; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate

Data cut-off: October 25, 2023

Monotherapy Azenosertib Has Meaningful and Durable Benefit to Platinum Resistant Ovarian Cancer/USC Patients



At Risk	19	19	16	10	9	8	6	1	1

mPFS (95% CI):
6.5 months (2.79, 6.87)

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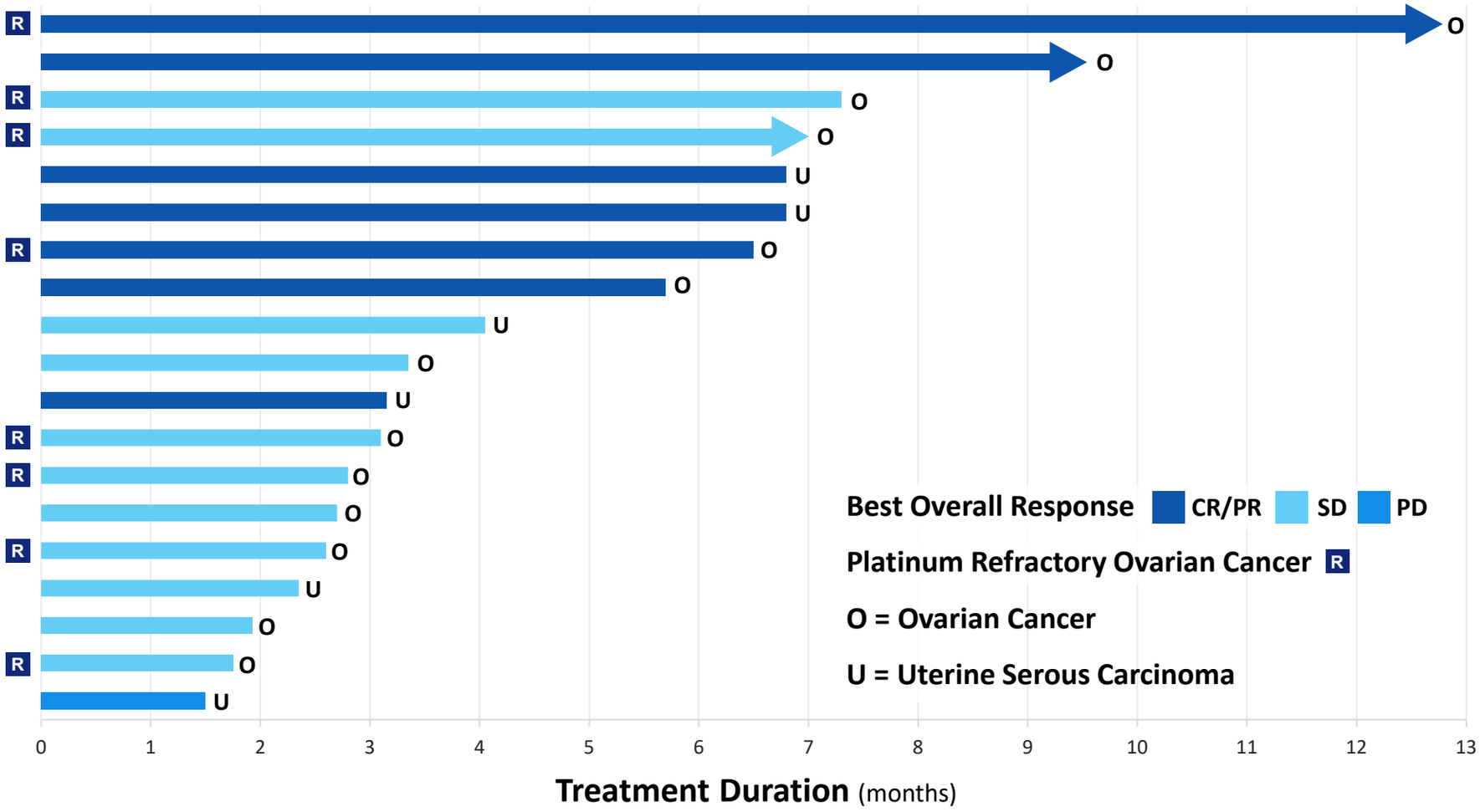
* Subjects who received at least one dose of azenosertib with intermittent dosing schedule, have baseline measurable disease by RECIST 1.1, and at least one post-baseline scan.
Abbreviations: USC, uterine serous carcinoma; mPFS, median progression-free survival

Monotherapy Azenosertib Has Meaningful and Durable Benefit to Platinum Resistant Ovarian Cancer/USC Patients



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* Subjects who received at least one dose of azenosertib with intermittent dosing schedule, have baseline measurable disease by RECIST 1.1, and at least one post-baseline scan.
Abbreviations: PROC, platinum resistant ovarian cancer; USC, uterine serous carcinoma; mPFS, median progression-free survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Platinum Refractory: Progression within 90 days of last dose of a platinum-based regimen in any line.

Azenosertib Monotherapy Continues to Demonstrate Excellent Safety Profile with Additional Patients Across Tumor Types*

Treatment Related AEs, n (%)

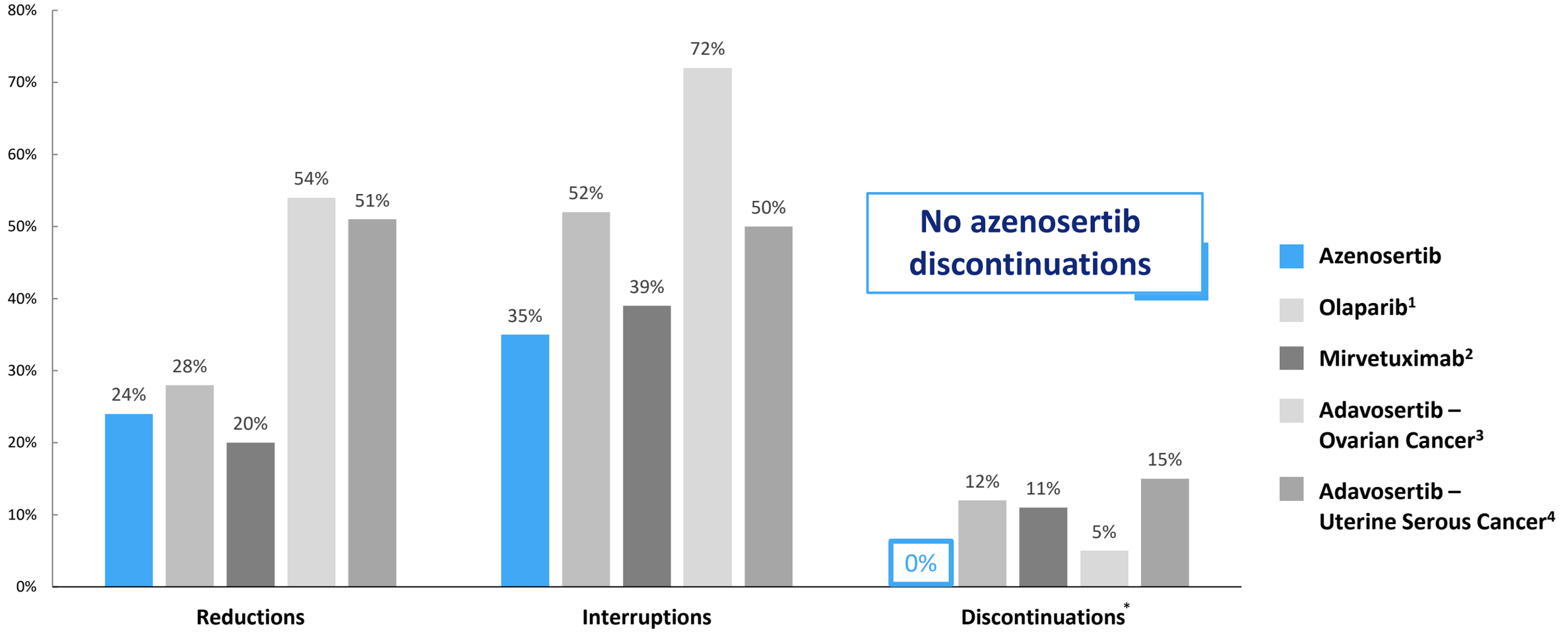
	ALL GRADES	GRADE 3/4
Gastrointestinal		
Nausea	20 (43.5)	2 (4.3)
Diarrhea	22 (47.8)	4 (8.7)
Vomiting	8 (17.4)	1 (2.2)
Decreased appetite	4 (8.7)	1 (2.2)
Dehydration	5 (10.9)	0

	ALL GRADES	GRADE 3/4
Fatigue		
	18 (39.1)	5 (10.9)
Hematologic		
Anemia	11 (23.9)	5 (10.9)
Thrombocytopenia	9 (19.6)	4 (8.7)
Neutropenia	9 (19.6)	7 (15.2)

No cases of febrile neutropenia or sepsis

*Safety Evaluable Population (All tumor types; n=46) as of Sept 27, 2023 versus n=27 reported on June 6, 2023 corporate call: Received at least one dose of drug; Intermittent 350 5:2 and 400 5:2; Treatment Related AEs > 10% for entire trial and treatment related AEs of interest. Abbreviations: AE, adverse event; 5:2, 5-days of treatment followed by 2-days off treatment

Azenosertib is Well Tolerated with Similar or Better Tolerability Compared to Other Gynecologic Malignancy Therapies



Safety Evaluable Population (All tumor types; n=46): Received at least one dose of drug; Intermittent 350 5:2 and 400 5:2; Not head-to-head comparisons; *Discontinuations due to treatment related adverse events

1 Poveda A, et al. Lancet Oncol 2021;22:620-631; 2 Moore K, et al. J Clin Oncol 2023;41:abstr LBA5507; 3 Westin S, et al. J Clin Oncol 2021 39:15_suppl, 5505;
4 Liu JF, et al. Society of Gynecologic Oncology Annual Meeting on Women's Cancer; March 25-28; Tampa, Florida. Abstract 219

Monotherapy Conclusions

Data Supports Ongoing **Azenosertib** Monotherapy Potentially Registrational Studies in Ovarian Cancer and Uterine Serous Carcinoma

MONOTHERAPY EFFICACY

37% confirmed ORR

IMPROVED mPFS of 6.5 MONTHS

With longer follow-up

EXCELLENT TOLERABILITY & SAFETY

Consistent or better than other available agents

DEFINITIVE DATA

Supports differentiation from other clinical WEE1 inhibitors

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Abbreviations: ORR, objective response rate; mPFS, median progression-free survival; Comparisons to other agents are not head-to-head.

Phase 2 Trials of Azenosertib

Potential Paths to Registration in Platinum Resistant Ovarian Cancer and Uterine Serous Carcinoma

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

Untreated Stage III/IV Ovarian Cancer

First Line Therapy

Carboplatin + Paclitaxel

BRCAm/HRD

HRP

First Line Maintenance

PARP Inhibitor or Bevacizumab + Olaparib

Bevacizumab

PFI>6m

PFI≤6m

Second Line Therapy

Combination Chemotherapy

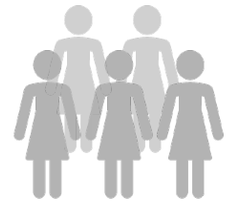
Platinum Doublet

PFI≤6m

Unmet Need

Platinum Resistant

Single Agent Chemotherapy or Mirvetuximab (~35% pts)[2]



42,981 Treatable Patients[1] US/EU5

1 Figures represent Company estimates of U.S. and EU5 patients with conditions covered by the Company's targeted indications; Source: IQVIA, DRG Clarivate;
2 Matulonis U. JCO 2023 41:13:2436-2445; Abbreviations: BRCAm, BRCA mutant; HRD, homologous-recombination repair deficient; HRP, homologous-recombination repair proficient; PFI, platinum-free interval

DENALI (ZN-c3-005): Prospective Evaluation of *CCNE1* Amplification and Cyclin E1+ in Platinum Resistant High-Grade Serous Ovarian Cancer

CURRENTLY ACCRUING

Key Eligibility: 1-5 prior lines of therapy in Cohort 1 (1-4 prior lines in Cohort 2); Mandatory Sufficient Tissue; Can not be Platinum Refractory (DFI < 3month from last platinum based therapy)

Cohort 1 (N=30)
No Biomarker Eligibility Requirements

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

ORR
DOR

Topline data 1H 2025

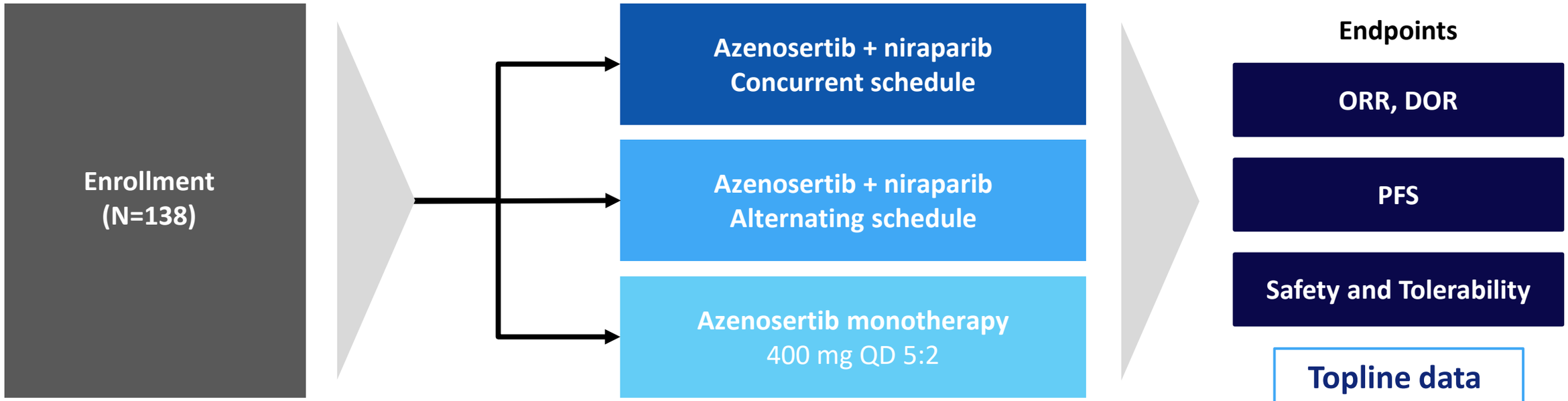
Abbreviations: QD, once daily; 5:2, 5-days of treatment followed by 2-days off treatment; ORR, objective response rate; DOR, Duration of Response; 1H, first half

NCT05128825

MAMMOTH (ZN-c3-006): Phase 1/2 Study of Azenosertib in Combination with Niraparib or Alternating with Niraparib or as a Monotherapy in Patients with PARP-Resistant High-Grade Epithelial Ovarian Cancer

CURRENTLY ACCRUING

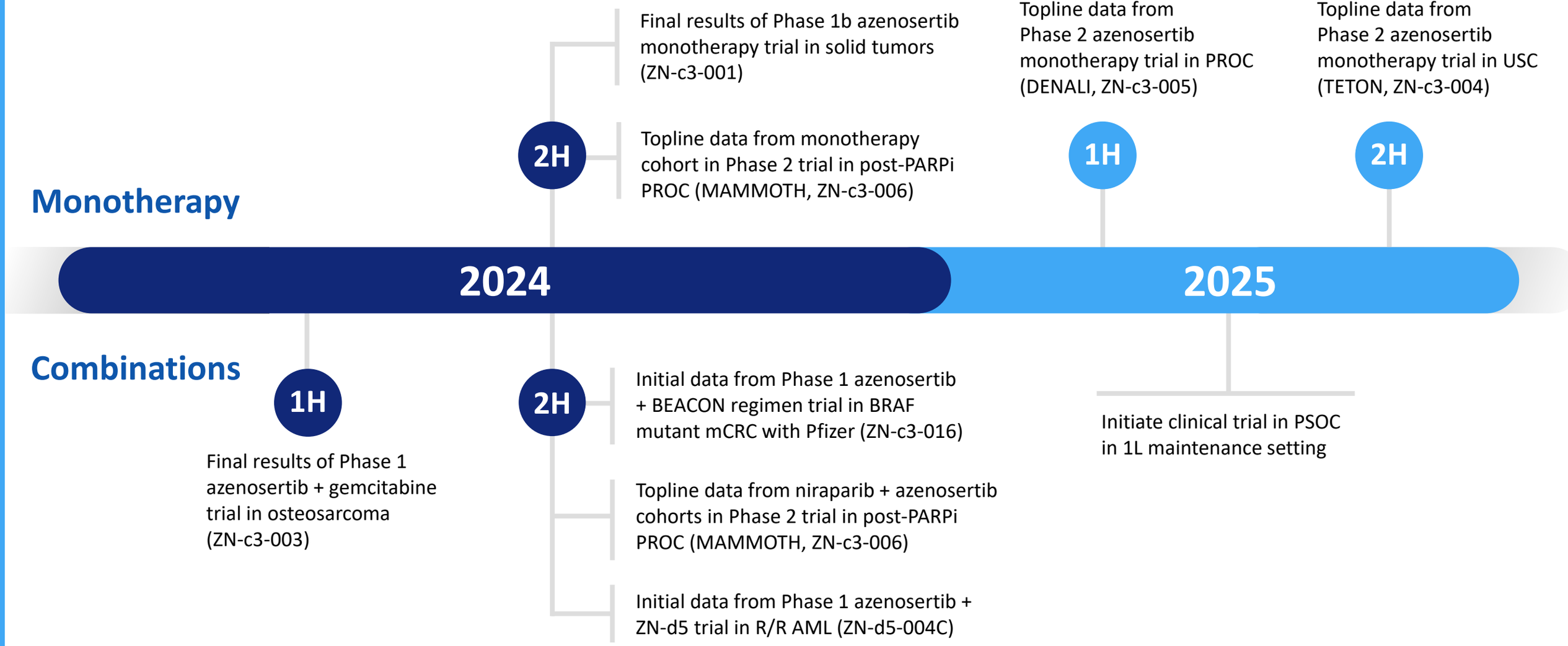
Key Eligibility: 1-5 prior lines of therapy; platinum-resistant, progressed while receiving an approved PARP inhibitor; Mandatory Sufficient Tissue; Can not be Platinum Refractory (DFI < 3 months from last platinum based therapy)



NCT05198804

Abbreviations: PARP, poly-ADP ribose polymerase; 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; 2H, second half

Upcoming Clinical Milestones



Abbreviations: 1H, first half; 2H second half; BRAF, V-Raf murine sarcoma viral oncogene homolog B; mCRC, metastatic colorectal cancer; PARPi, poly-ADP ribose polymerase inhibitor; R/R AML, relapsed or refractory acute myeloid leukemia; PROC, platinum resistant ovarian cancer; USC, uterine serous carcinoma; PSOC, platinum sensitive ovarian cancer; 1L, first line

Azenosertib in Platinum Sensitive Ovarian Cancer Revised Strategy

1L Maintenance Opportunity to Provide Prolonged Benefit for a Larger Number of Patients

Potential for Azenosertib to Impact the Greatest Number of Ovarian Cancer Patients in the 1L Maintenance Setting

2x as **many patients**

receive 1L maintenance treatment compared to 2L treatment[1]

Evolving labels and prescribing practice for PARPi **presents an opportunity**

for a new 1L maintenance oral therapy for patients with HRP/unknown tumors

40% of **1L maintenance patients**

are HRP[2] and not eligible to receive a PARPi

Azenosertib uniquely positioned for success in maintenance setting

Oral non-chemotherapy agent
Clear global regulatory pathways

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1 Figures represent Company estimates of U.S. and EU5 patients with conditions covered by the Company's targeted indications; Source: IQVIA, DRG Clarivate Kantar and DRG;
2 Ray-Coquard I., N Engl J Med 2019; December 2019 381:2416-2428; Abbreviations: 1L, first line treatment; 2L, second line treatment; HRP, homologous-recombination repair proficient; PARPi, poly-ADP ribose polymerase inhibitor

Opportunity for Azenosertib in First Line Maintenance in Homologous Repair Proficient (HRP) Platinum Sensitive Ovarian Cancer

Untreated Stage III/IV Ovarian Cancer

First Line Therapy

Carboplatin + Paclitaxel

BRCAm/HRD

HRP

First Line Maintenance

PARP Inhibitor or Bevacizumab + Olaparib

Bevacizumab

PFI>6m

Second Line Therapy

Combination Chemotherapy

Platinum Doublet

PFI≤6m

PFI≤6m

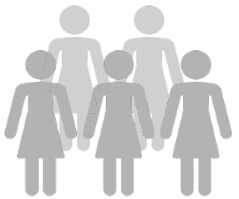
Platinum Resistant

Single Agent Chemotherapy or Mirvetuximab (~35% pts)[3]

Unmet Need

~40% patients are HRP/not eligible for maintenance PARP[1]

Platinum Sensitive

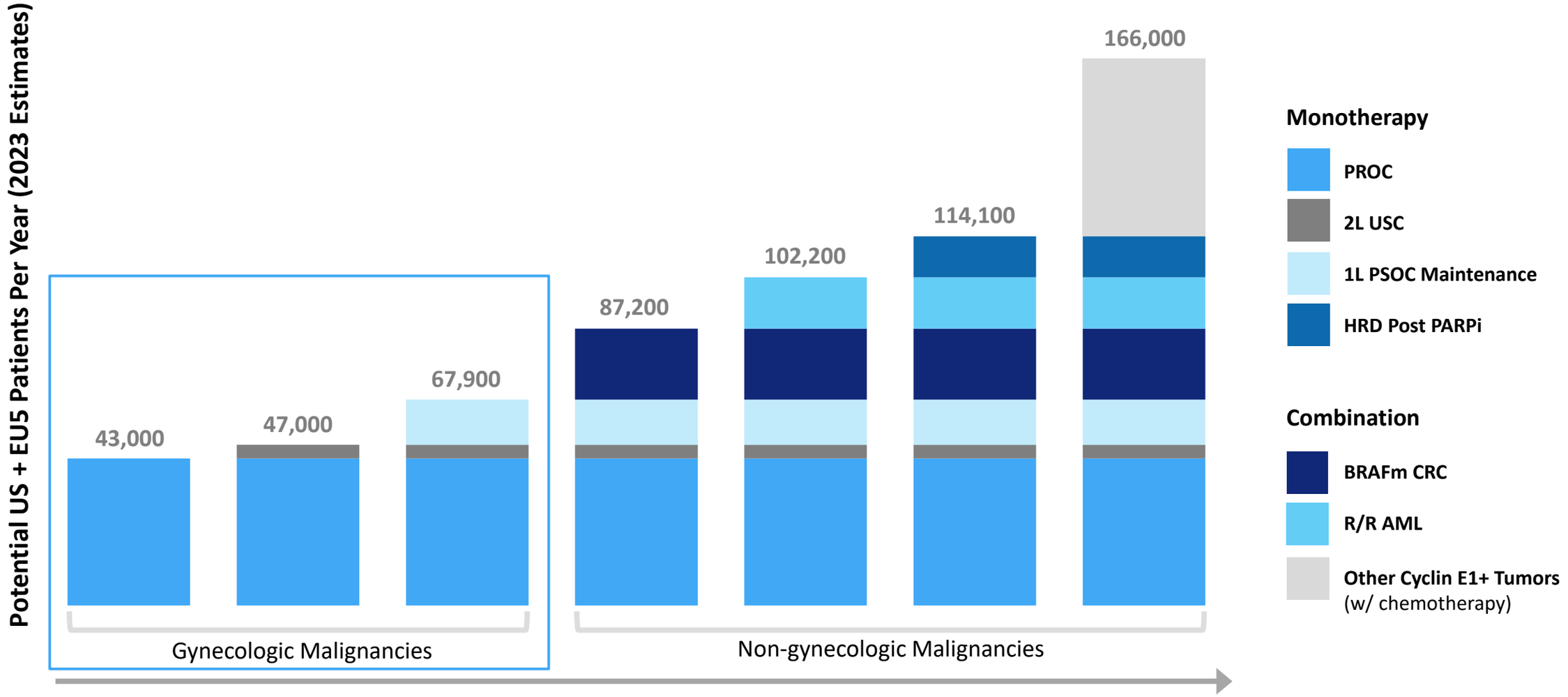


20,905

Treatable Patients[2] US/EU5

1 Ray-Coquard I. N Engl J Med 2019; December 2019 381:2416-2428; 2 Figures represent Company estimates of U.S. and EU5 patients with conditions covered by the Company's targeted indications; Source: IQVIA, DRG Clarivate;
3 Matulonis U. JCO 2023 41:13:2436-2445; Abbreviations: BRCAm, BRCA mutant; HRD, homologous-recombination repair deficient; HRP, homologous-recombination repair proficient; PFI, platinum-free interval

Azenosertib Treatable Patient Population More Than Doubles as Franchise Expands to Non-Gynecologic Malignancies



'Drug treatable' estimates from DRG Clarivate. For 'Other Cyclin E1+ tumors' used incidence reported by SEER and ECIS.
HRD Post PARPi tumor types: Prostate, Pancreas and Breast; Other Cyclin E1+ Tumor Types include bladder, stomach, esophageal, lung, and breast cancer
Abbreviations: PROC, platinum resistant ovarian cancer; 2L, second line USC, uterine serous carcinoma; PSOC, platinum sensitive ovarian cancer; HRD, homologous recombination repair deficient; PARPi, poly-ADP ribose polymerase inhibitor; BRAFm CRC, BRAF V600E mutant colorectal cancer; R/R AML, relapsed or refractory acute myeloid leukemia

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High Unmet Need HRP Population

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HRP, homologous-recombination repair proficient

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