

Azenosertib in Platinum-Resistant Ovarian Cancer (PROC): Overall Survival Analysis From Part 1b of the DENALI Study (GOG-3066)

Fiona Simpkins¹, Alexandra Leary², Lyndsay Willmott³, Bradley J. Monk⁴, Jean-Sébastien Frenel⁵, David C. Starks⁶, Meena Okera⁷, Angeles Alvarez Secord⁸, David M. O'Malley⁹, Lainie Martin¹⁰, Kaissa Ouali², Martin K. Oehler¹⁰, Jeffrey C. Goh¹¹, Brian M. Slomovitz¹², Peter C. Lim¹³, Catherine M. Shannon¹⁴, Robert Neff¹⁵, Hailun Li¹⁶, C. Matthias Wilk¹⁶, Floor J. Backes⁹

¹Penn Medicine Abramson Cancer Center, Philadelphia, PA, USA; ²Gustave Roussy Cancer Center, Villejuif Cedex, France; ³Arizona Center for Cancer Care, Phoenix, AZ, USA; ⁴Florida Cancer Specialists & Research Institute, West Palm Beach, FL, USA; ⁵Institut de Cancérologie de l'Ouest, Saint-Herblain, France; ⁶Avera Cancer Institute, Sioux Falls, SD, USA; ⁷Cancer Research SA, Adelaide, SA, Australia; ⁸Duke Cancer Institute of Duke University Health System, Durham, NC, USA; ⁹The Ohio State Wexner Medical Center and The James CCC, Columbus, OH, USA; ¹⁰Royal Adelaide Hospital, Adelaide, SA, Australia; ¹¹ICON Cancer Centre, Chermiside, QLD, Australia; ¹²Mount Sinai Medical Center, Miami Beach, FL, USA; ¹³Center of Hope at Renown Regional Medical Center, Reno, NV, USA; ¹⁴Mater Cancer Care Centre, South Brisbane, Australia; ¹⁵TriHealth Cancer Institute, Cincinnati, OH; ¹⁶Zentalis Pharmaceuticals, Inc. San Diego, CA, USA

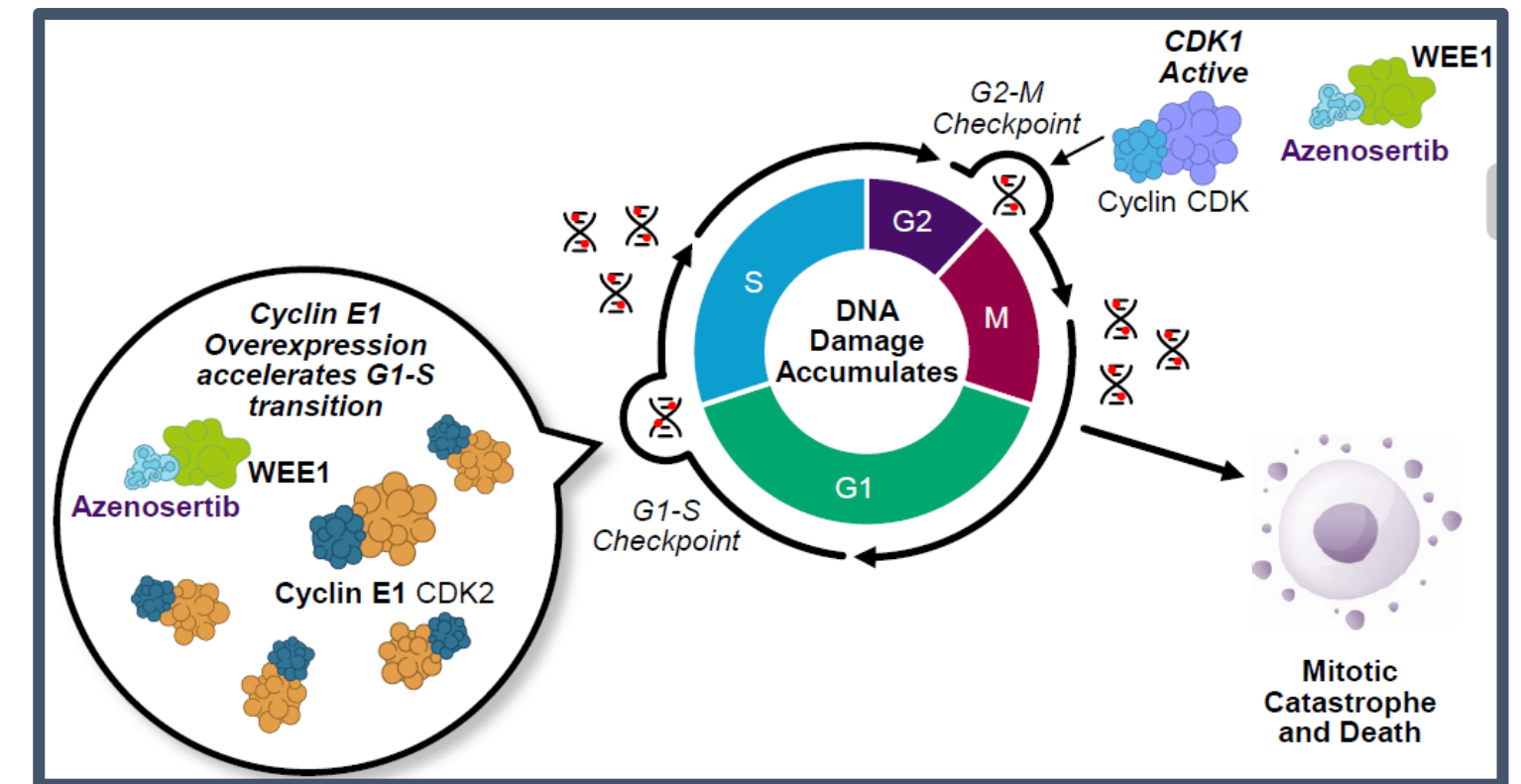
Financial Disclosures for Fiona Simpkins

- Consulting/Advisory Role: AstraZeneca, FoRx Therapeutics, GlaxoSmithKline, Repare Therapeutics, Zentalis Pharmaceuticals
- Research Funding to Institution: AstraZeneca, AstraZeneca/MedImmune, Instil Bio, Repare Therapeutics, Sierra Oncology

WEE1 Inhibition Has Strong Scientific Rationale for Cyclin E1-positive Platinum-resistant Ovarian Cancer (PROC)

- Although platinum-based chemotherapy remains the standard of care in ovarian cancer, platinum resistance often ultimately develops¹
- *CCNE1* amplified (~20%) and cyclin E1 overexpressing ovarian cancers (~50%) have poor outcomes
- Cyclin E1 protein overexpression results in cells moving prematurely from G1 to S, thereby increasing reliance on the G2-M checkpoint to allow DNA repair^{1,2}
- WEE1 is a master regulator of the cell cycle acting as a brake at G1-S and G2-M to allow DNA repair³
- Targeting WEE1 with azenosertib, an investigational, novel, selective, oral WEE1 tyrosine kinase inhibitor, ultimately leads to mitotic catastrophe⁴

Azenosertib and Cancer Cell



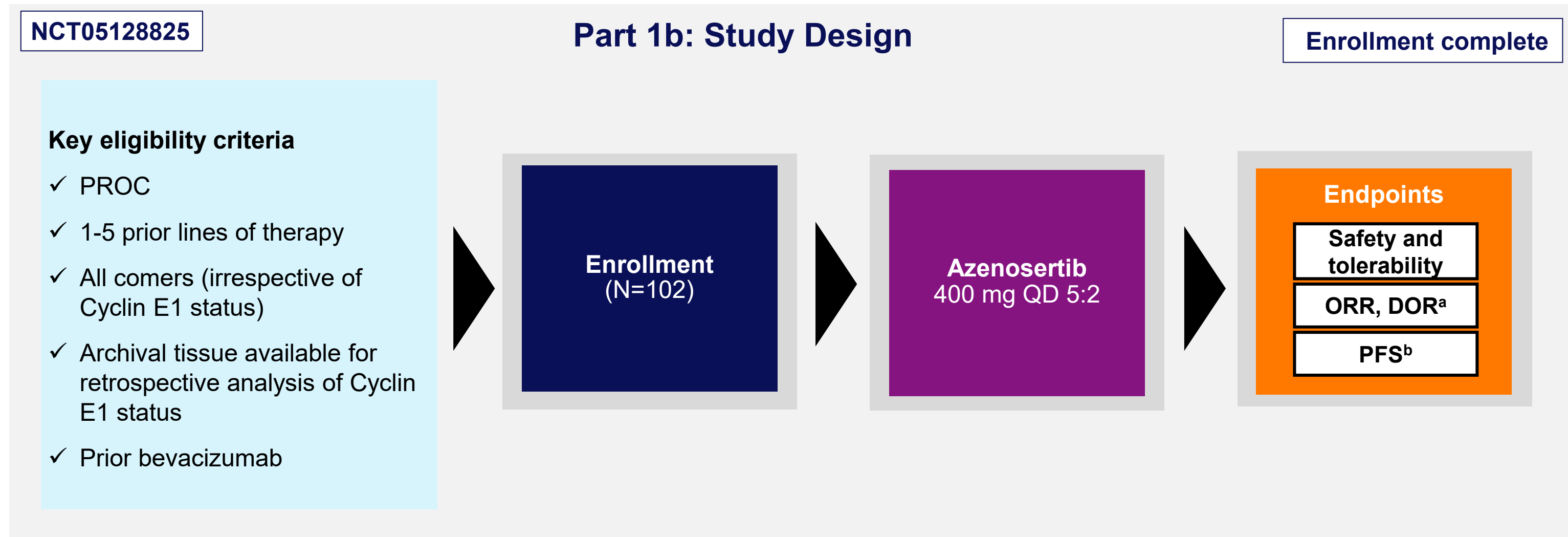
Fiona Simpkins, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

CDK, cyclin-dependent kinase; G1-S, Gap 1-synthesis; G2-M, Gap 2-mitosis; PROC, platinum-resistant ovarian cancer; OS, overall survival.

1. Richardson DL, et al. *JAMA Oncol.* 2023;9(6):851–859. doi:10.1001/jamaoncol.2023.0197. 2. Stronach EA, et al. *Mol Cancer Res.* 2018;16:1103-1111. 3. Pils D, et al. *Eur J Cancer.* 2014;50:99-110. 4. Peterson S, et al. *Gynecol Oncol.* 2020;157:405-410. 5. Nakayama N, et al. *Cancer.* 2010;116:2621-2634. 6. Kang EY, et al. *Cancer.* 2023;129:697-713. 7. Chan AM, et al. *J Pathol Clin Res.* 2020;6:252-262.

DENALI (GOG-3066) Part 1b – Azenosertib Monotherapy in PROC, a Phase 2, Multipart, Open-Label, Multicenter Study



Here, we present overall survival (OS) interim data from DENALI Part 1b

Fiona Simpkins, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

^aPer RECIST v1.1 by IRC and investigator every 6 weeks until disease progression, death from any cause (ORR: up to 12 months; DOR: up to 60 months). ^bPer RECIST v1.1 by IRC and investigator every 6 weeks until disease progression, death from any cause up to 12 months. 5:2, 5 days on, 2 days off; DOR, duration of response; IRC, Independent Review Committee; ORR, objective response rate; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

Patient Demographics and Baseline Characteristics in DENALI (GOG-3066) Part 1b

Characteristics ^a (All treated patients, 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 ^c , n (%)	
0	49 (48)
1	52 (51)
Prior lines of treatment	
Median (range)	3 (1-5)
1–2, n (%)	35 (34)
3–4, n (%)	57 (56)
5, n (%)	10 (10)

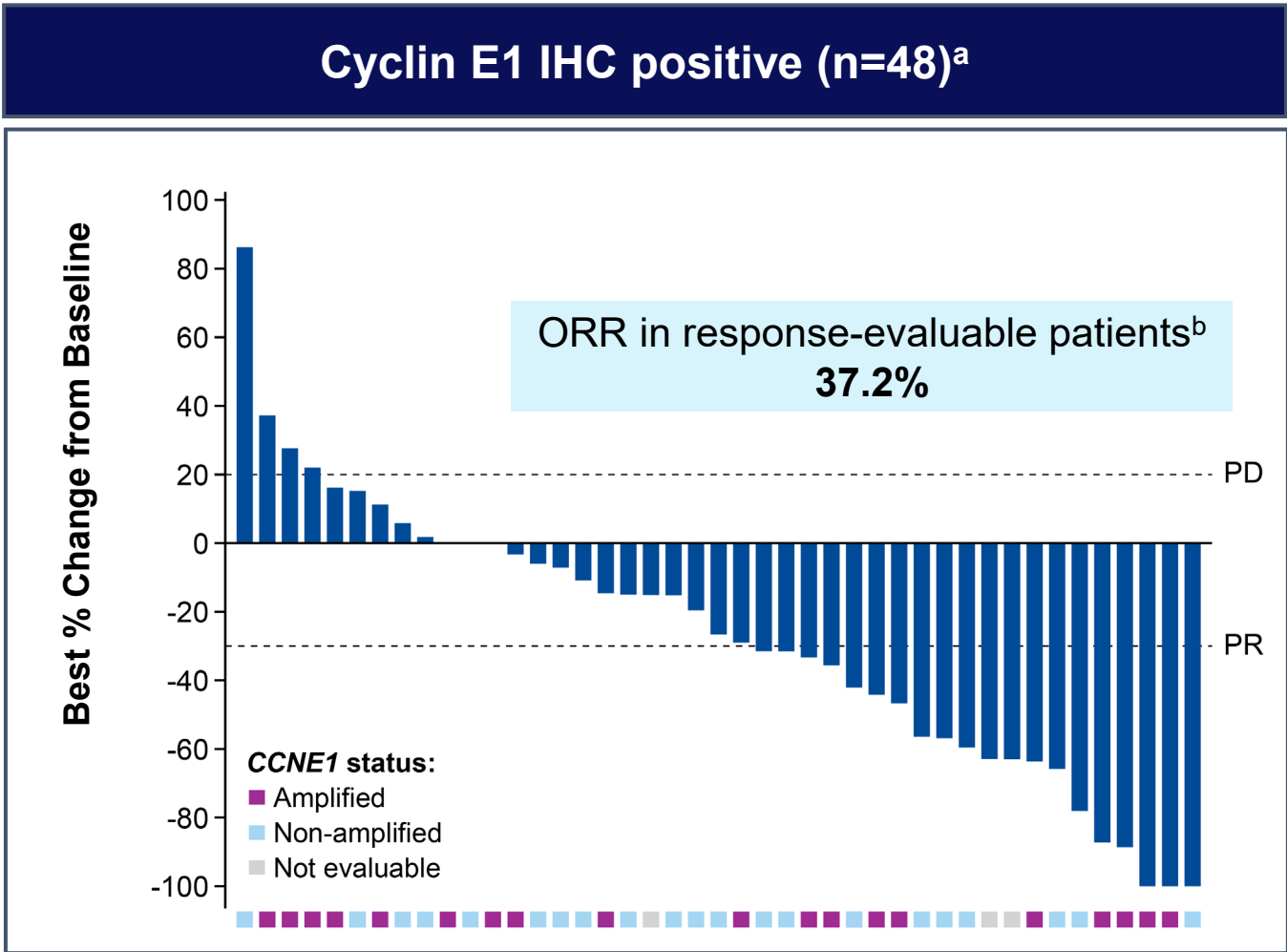
Characteristics ^a (All treated patient, N=102)	
Prior therapy, n (%)	
Taxane	99 (97)
Bevacizumab	93 (91)
PARPi	56 (55)
Mirvetuximab	15 (15)
CCNE1 amplification, ^d	
Evaluable, n	88
Amplified, n (%)	27 (31)
Cyclin E1 status	
Evaluable, n	94
IHC positive ^e , n (%)	48 (51)

Fiona Simpkins, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

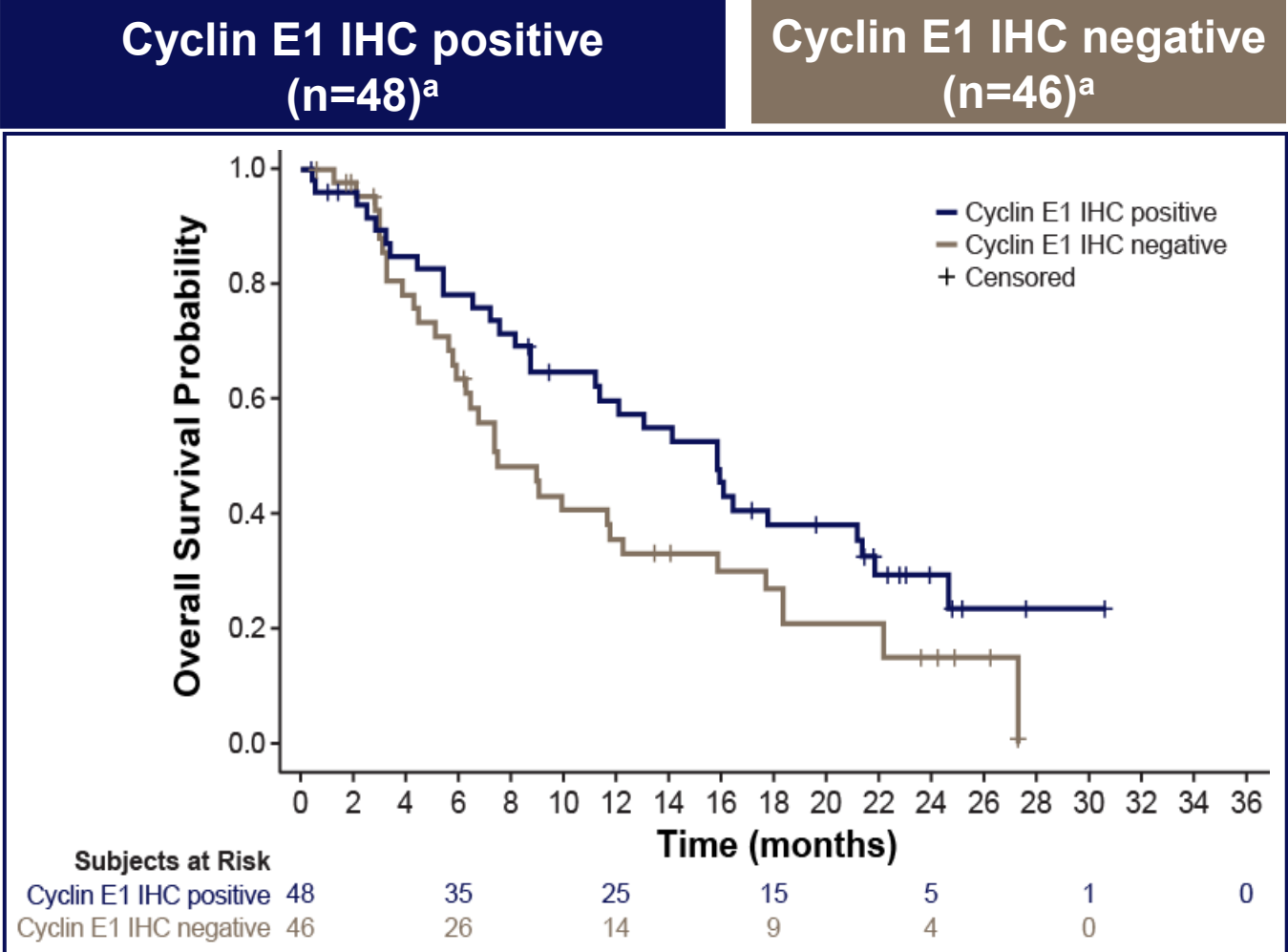
Data cutoff: May 22, 2026. ^aFull Analysis Set: all treated patients. Biomarker dataset: all treated patients with evaluable tissue and Cyclin E1 IHC status. ^bHispanic. ^cOne patient had ECOG PS 2. ^dCCNE1 amplification defined as copy number ratio ≥3 with genomic ploidy correction as per Foundation Medicine. ^eIHC positive based on Sponsor’s proprietary cutoff. ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; PARPi, poly(ADP-ribose) polymerase inhibitor.

Cyclin E1 Positivity by IHC Predicts Clinical Response and Is Associated With Improved Outcomes With Azenosertib Treatment



Data cutoff: May 22, 2026.

	Cyclin E1 IHC positive (n=48)
ORR, % (n/N; 95% CI)	33.3 (16/48; 20.4–48.4)
ORR in response-evaluable patients ^b , % (n/N; 95% CI)	37.2 (16/43; 23.0–53.3)
Median DOR, months (95% CI)	5.5 (4.5–15.9)
Median PFS, months (95% CI)	4.1 (2.8–6.8) ^c



Data cutoff: May 22, 2026.

	Cyclin E1 IHC positive (n=48)	Cyclin E1 IHC negative (n=46)
Median OS, months (95% CI)	15.9 (8.7–21.2)	7.5 (5.8–12.3)
Events, n (%)	31 (65)	34 (74)

Cyclin E1 positivity predicted longer OS with azenosertib

Fiona Simpkins, MD

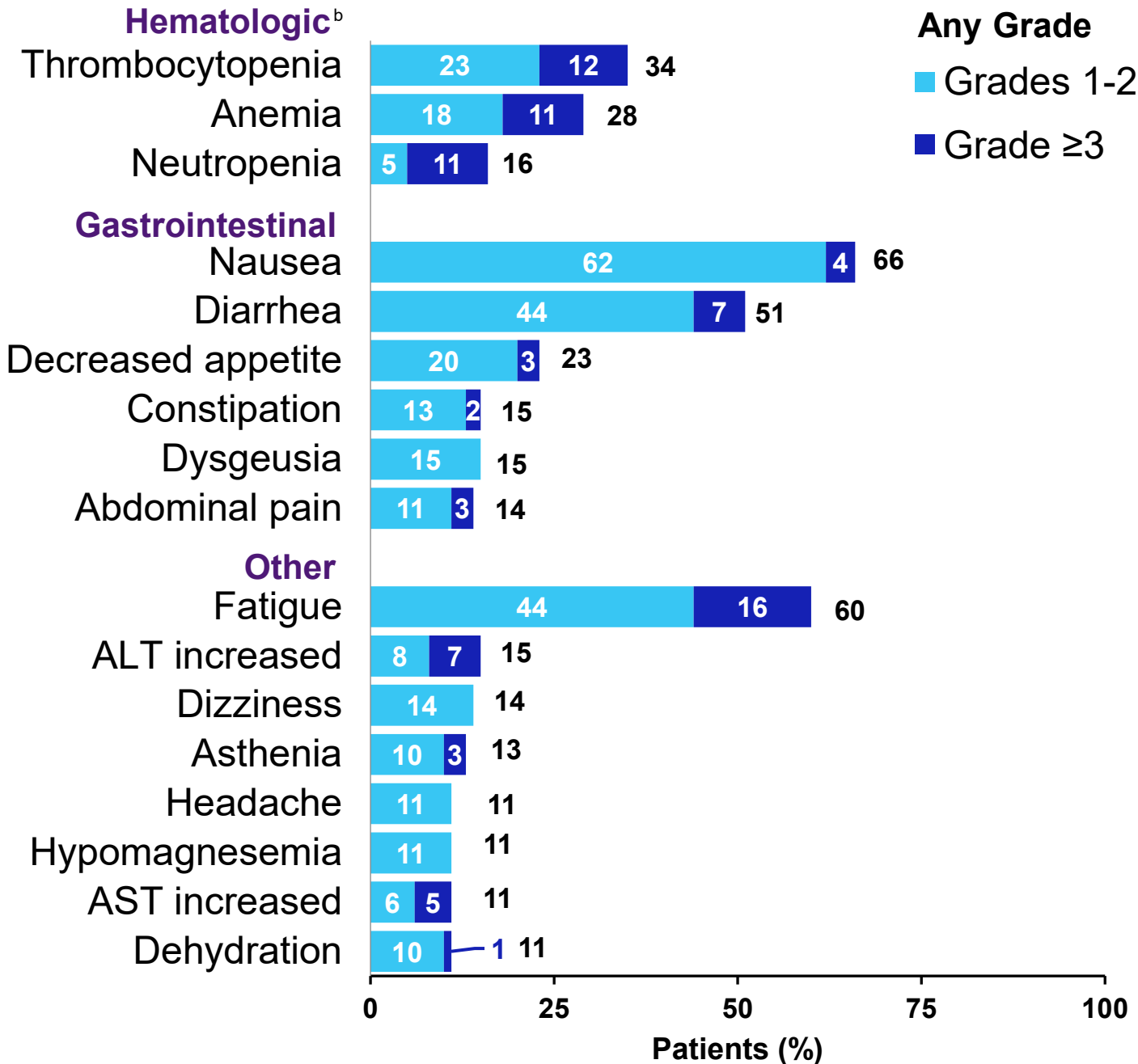
Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Data cutoff: May 22, 2026. ^aBiomarker dataset: all treated patients with evaluable tissue and Cyclin E1 IHC status. ^bIncludes patients who received at least one post-baseline scan. Horizontal lines at -30% and +20% are marked as 'PR' and 'PD', respectively, for illustrative purposes based on target lesion change. Overall response was assessed by the Investigator according to RECIST v1.1. ^cMedian PFS in DENALI Part 1b confounded by early withdrawal, which is now addressed by mitigation strategies in DENALI Part 2 and ASPENOVA.CR, complete response; DOR, duration of response; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Safety and Tolerability for All Patients

The Majority of Treatment-Related Adverse Events Are Low Grade

TRAEs reported in ≥10% of patients^a



TRAEs, n (%)	
Leading to dose reduction	44 (43.1)
Leading to dose interruption	58 (56.9)
Leading to discontinuation	20 (19.6)
Leading to death	2 (2.0) ^c
Serious	22 (21.6)

Exposure to Azenosertib	
Median relative dose intensity, % (range)	84.6 (20.0–101.6)

Since mitigation strategies have been implemented in Part 2a, TRAEs leading to discontinuation decreased by half to ~10%

Fiona Simpkins, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

Data cutoff: May 22, 2026. ^aIf a patient had multiple grades of the same adverse event, the worse grade was reported. ^bCombined preferred terms. ^cOne patient had sepsis and one patient had pancytopenia. ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event. *Company dose selection press release on Apr 9, 2026.

Azenosertib Demonstrated Meaningful Anti-tumor Activity and Tolerability as an Oral Investigational Monotherapy in Cyclin E1-positive PROC

- In heavily pre-treated patients with Cyclin E1-positive PROC, ORR with azenosertib was 37.2% in response-evaluable patients^a and median DOR was 5.5 months
 - Median OS (15.9 months) compares favorably to standard of care chemotherapy^{1-5,b}
 - Cyclin E1 positivity by IHC more than doubles the *CCNE1* amplification population
- Nausea, diarrhea and fatigue were the most common TRAEs and are clinically manageable; although less common, hematologic toxicities such as neutropenia, require monitoring

Azenosertib is currently being evaluated in the ongoing DENALI Part 2 registrational trial (NCT05128825) and ASPENOVA Phase 3 (NCT07546500) confirmatory study for Cyclin E1-positive PROC

Fiona Simpkins, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

^aIncludes patients who received at least one post-baseline scan. ^bCross-trial comparisons should be interpreted with caution because study designs, patient populations, and other factors may differ.

DOR, duration of response; ORR, objective response rate; OS, overall survival; PROC, platinum-resistant ovarian cancer; TRAE, treatment-related adverse event.

1. Pujade Lauraine E, et al. *Lancet Oncol.* 2021;22(7):1034-1046. 2. Moore KN, et al. *Ann Oncol.* 2021;32(6):757-765. 3. Gaillard SL et al. *Gynecologic Oncology.* 2021; 163:237-245. 4. Hamanishi J, et al. *J Clin Oncol.* 2021;39(33):3671-3681. 5. Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32(13):1302-1308.

Acknowledgements

We would like to extend our gratitude and thanks to the patients, families, and treatment teams associated with this study

Participating sites

- Alliance Cancer Specialists, PC – USOR – Wynnewood
- Arizona Oncology Associates, PC – HAL
- Avera Cancer Institute
- Baystate Medical Center
- Burnside War Memorial Hospital – The Brian Fricker Oncology Centre
- Cancer Research South Australia
- Carle Cancer Center
- Center of Hope
- Centre Antoine Lacassagne Centre Régional de Lutte Contre le Cancer
- Centre Oscar Lambret
- Centrum Badań Klinicznych JCI
- Community Cancer Center North
- Cox Medical Centers
- Dana-Farber Cancer Institute
- Duke Cancer Institute
- Institut de Cancérologie de l'Ouest
- Florida Cancer Specialists – EAST – SCRI – PPDS
- Icon Cancer Care Chermside
- Institut Gustave Roussy
- Lancaster General Hospital
- Mark H Zangmeister Center – SCRI – PPDS
- Maryland Oncology Hematology, P.A. (Rockville)
- Mater Hospital Brisbane
- Memorial Health University Medical Center
- Mercy Hospital St Louis
- Minnesota Oncology Hematology, PA – Maplewood
- Mitchell Cancer Institute
- Monument Health Rapid City Hospital
- Mount Sinai Medical Center
- Nebraska Methodist Hospital
- NorthShore University Health System
- Northwell Health Cancer Institute
- Norton Cancer Institute, Downtown
- Ohio State University Comprehensive Cancer Center
- Oncology Associates of Oregon
- Ridley Tree Cancer Center
- Rocky Mountain Cancer Centers
- Sarasota Memorial Healthcare System
- St. Louis Cancer Care LLP
- Texas Oncology (Tyler)
- Texas Oncology, PA – Austin
- TriHealth Cancer Institute
- UC San Diego Moores Cancer Center
- University Hospitals Case Medical Center
- University of Pennsylvania
- Utah Cancer Specialists (Salt Lake City)
- Virginia Oncology Associates (Norfolk) – USOR

Fiona Simpkins, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.



Thank you!

European Society for Medical Oncology (ESMO)

Via Ginevra 4, CH-6900 Lugano

T. +41 (0)91 973 19 00

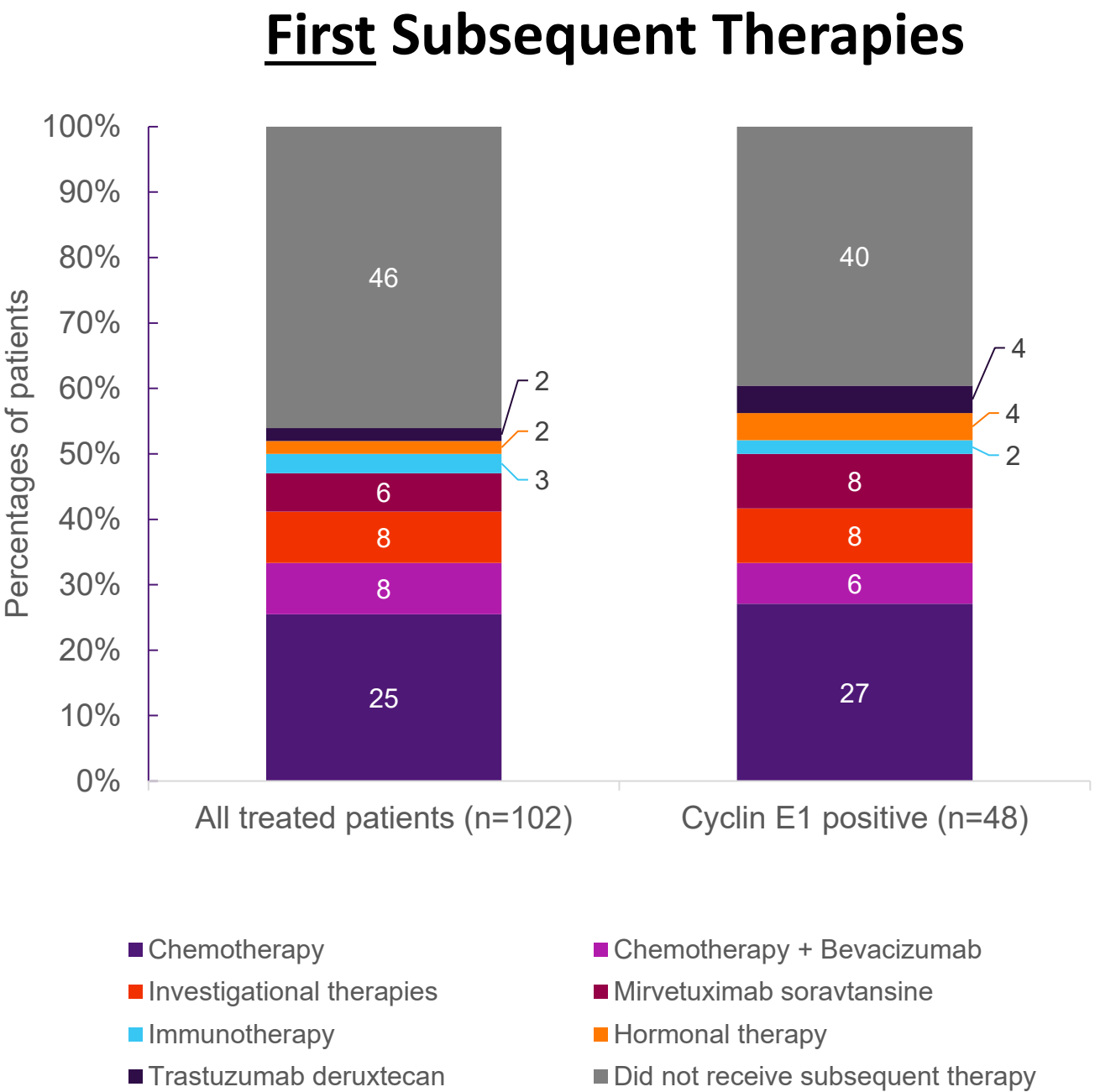
esmo@esmo.org

esmo.org



Supplement

First and All Subsequent Anti-Cancer Therapies for Patients With Cyclin E1-positive Tumors Are Similar to Those for All



All Subsequent Therapies

	All treated patients (n=102)	Cyclin E1 IHC positive (n=48)
Patients receiving subsequent therapies, n (%)	55 (53.9)	29 (60.4)
Including but not limited to:		
Bevacizumab	20 (19.6)	11 (22.9)
Paclitaxel	21 (20.6)	10 (20.8)
Investigational therapies	15 (14.7)	9 (18.8)
PLD or doxorubicin	14 (13.7)	8 (16.7)
Gemcitabine	18 (17.6)	7 (14.6)
Pembrolizumab	13 (12.7)	7 (14.6)
Cyclophosphamide	11 (10.8)	7 (14.6)
Carboplatin	8 (7.8)	5 (10.4)
Mirvetuximab soravtansine	6 (5.9)	4 (8.3)

Fiona Simpkins, MD

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.