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Cyclin E1 is a Predictive Biomarker of Azenosertib Benefit in Platinum-Resistant Ovarian Cancer (PROC): Outcomes From Part 1b of the DENALI Study (GOG-3066)

Fiona Simpkins[1], Alexandra Leary[2], Lyndsay Willmott[3], Bradley J. Monk[4], Jean-Sébastien Frenel[5], David C. Starks[6], Meena Okera[7], Angeles Alvarez Secord[8], David M. O'Malley[9], Lainie Martin[1], Kaissa Ouali[2], Martin K. Oehler[10], Jeffrey C. Goh[11], Brian M. Slomovitz[12], Peter C. Lim[13], Catherine M. Shannon[14], Robert Neff[15], Doris Kim[16], Hailun Li[16], Danielle Jandial[16], Floor J. Backes[9]

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

Financial Disclosures for Fiona Simpkins

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

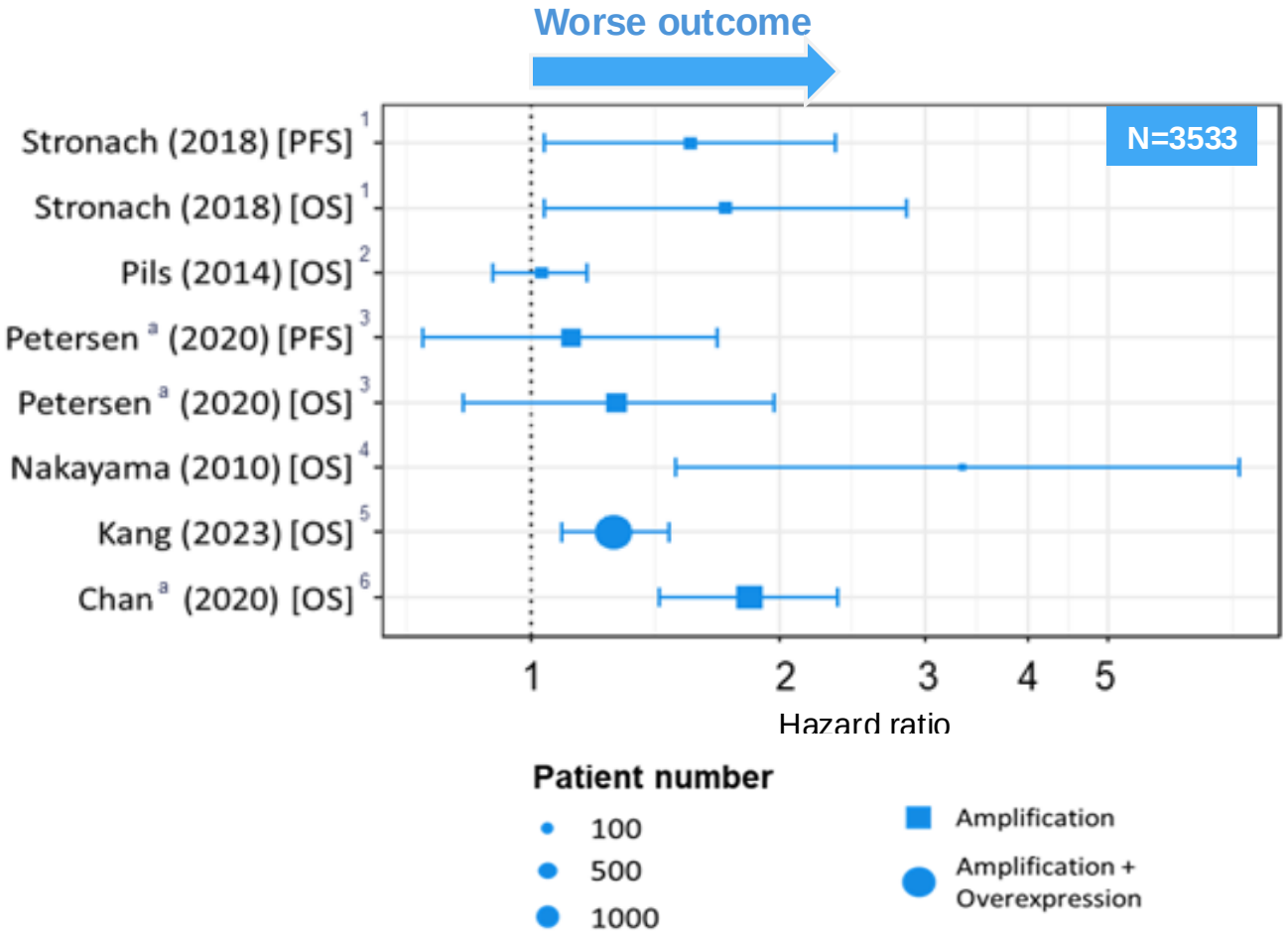
- **Consulting/Advisory Role**: AstraZeneca; GlaxoSmithKline; Zentalis, Repare Therapeutics, FoRx Therapeutics
- **Research Funding to Institution**: AstraZeneca; AstraZeneca/MedImmune; Instil Bio; Repare Therapeutics, Sierra Oncology

ACCME, Accreditation Council for Continuing Medical Education

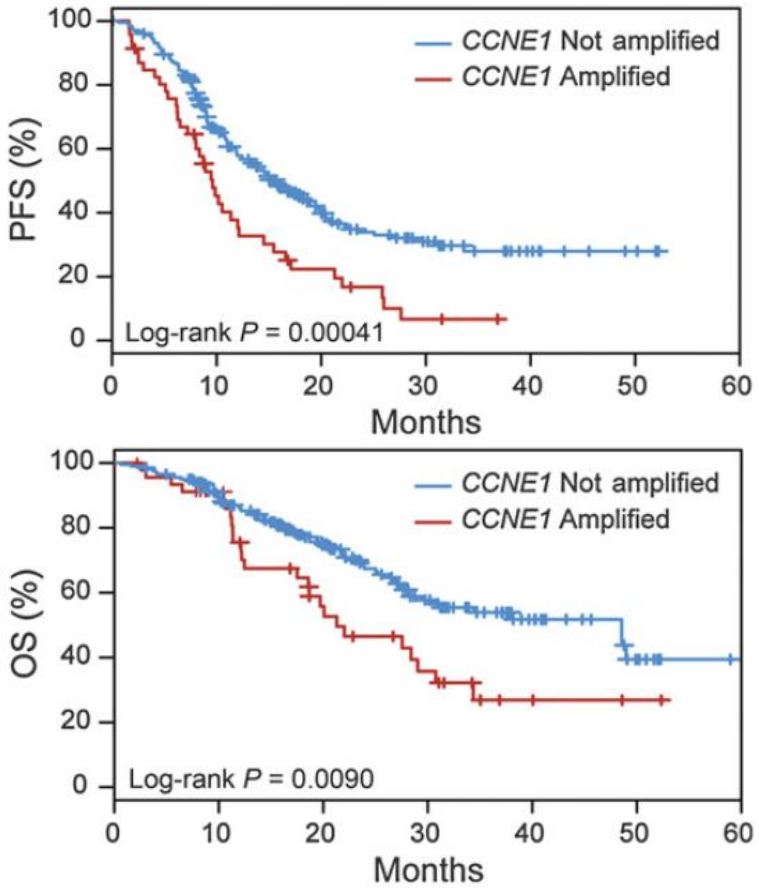
Unlabeled/Investigational Uses

I will be discussing the unlabeled or investigational use of Azenosertib, a WEE1 inhibitor, from Zentalis Pharmaceuticals

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.

Targeting WEE1 with Azenosertib Exploits Critical Cell Cycle Checkpoints that Cyclin E1 Overexpressing Cells Require for Survival

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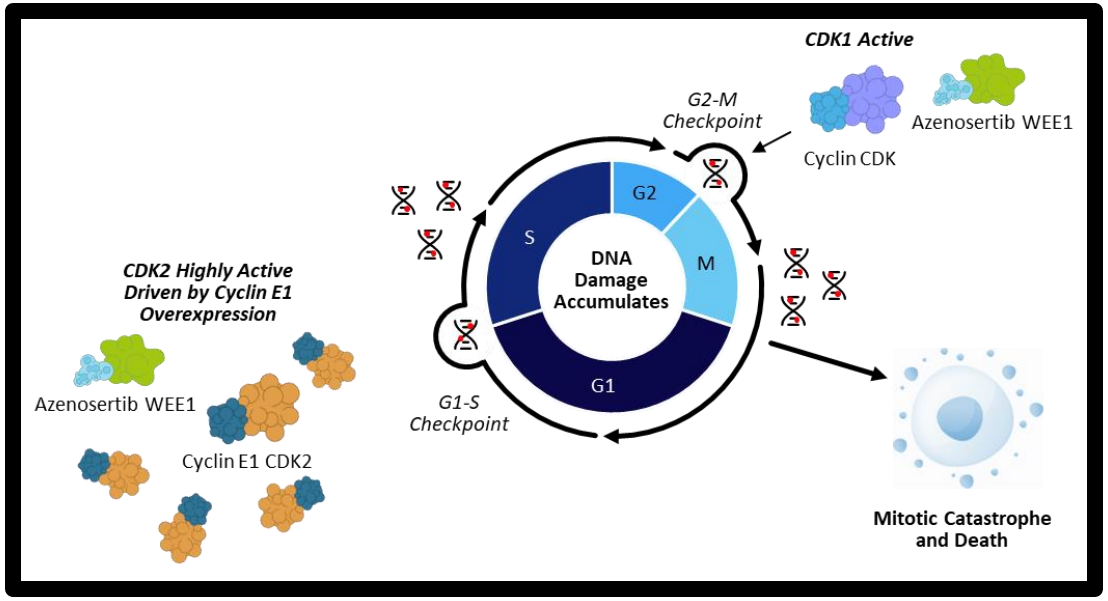
- Cyclin E1 protein overexpression results in cells moving prematurely from G1 to S, there by increasing reliance on the G2-M checkpoint to allow DNA repair[1,2]
- WEE1 is a master regulator of the cell cycle acting as a brake at G1-S and G2-M to allow DNA repair[3]
- Targeting WEE1 with azenosertib ultimately leads to mitotic catastrophe[4]



CDK, cyclin-dependent kinase; G1-S, Gap 1-Synthesis; G2-M, Gap 2-Mitosis; HGSOC, high-grade serous ovarian cancer.

1. Vriend LE, et al. *Biochim Biophys Acta.* 2013; 1836(2):227-335. **2.** Esposito F, et al. *Int J Mol Sci.* 2021;22(19):10689. 3. Gorski JW, et al. Diagnostics (Basel). 2020;10(5):279. **4.** Kim D, et al. *NPJ Precis Oncol.* 2025;9(3).

DENALI (GOG-3066): Phase 2, Open-Label, Multicenter Study of Azenosertib in PROC (Part 1 and 2)

Part 1b: Study design

Enrollment complete

Key eligibility criteria

- ✓ PROC
- ✓ 1-5 prior lines of therapy
- ✓ Prior bevacizumab
- ✓ **All comers** (irrespective Cyclin E1 status)

Enrollment (N=102)

Azenosertib 400 mg QD 5:2

Endpoints

- **Safety and tolerability**
- **ORR, DOR[a]**
- **PFS[b]**

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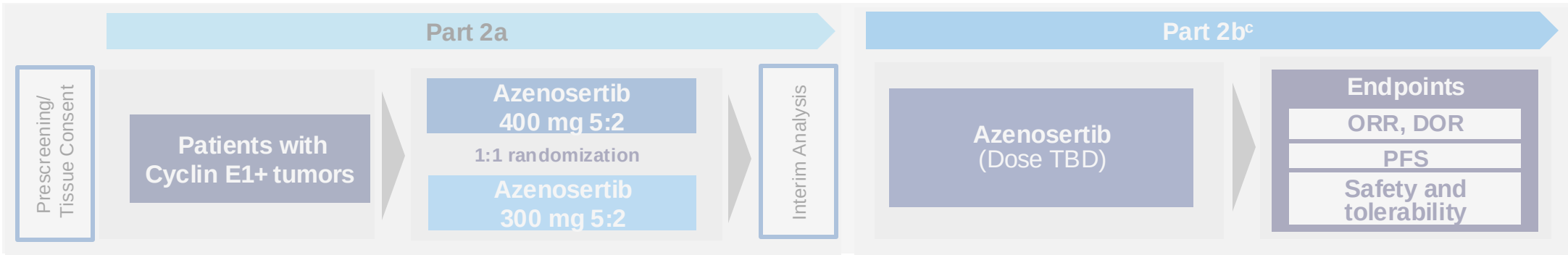

[a]Per RECIST v1.1 by ICR and investigator every 6 weeks until disease progression, death from any cause (ORR: up to 12 months; DOR: up to 60 months). [b]Per RECIST v1.1 by ICR and investigator every 6 weeks until disease progression, death from any cause up to 12 months. [c]Subject to FDA feedback. 5:2, 5 days on, 2 days off; DOR, duration of response; ICR, independent committee review; ORR, objective response rate; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TBD, to be determined. ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05128825

DENALI (GOG-3066) 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)

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.

DENALI (GOG-3066) Part 1b: Cyclin E1+ by IHC is a Biomarker Predicting Response to Azenosertib

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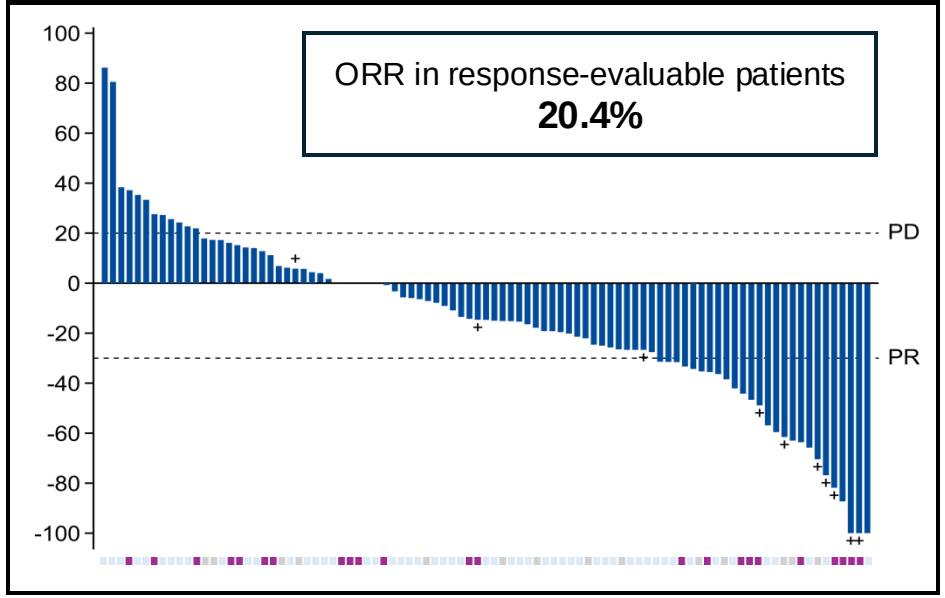
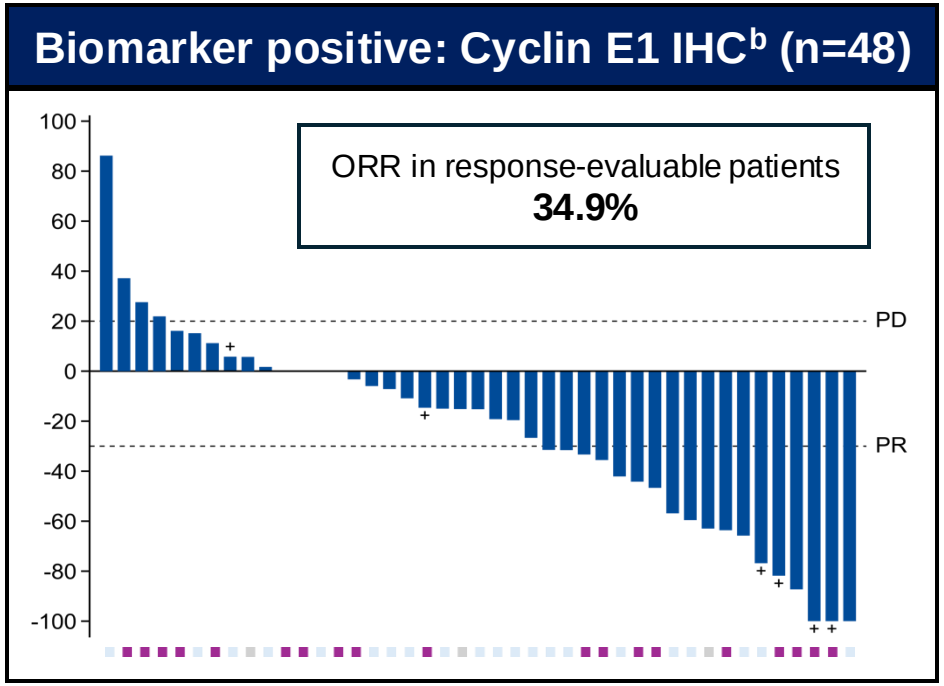
All treated patients[a] (N=102)



Cyclin E1 IHC+

Biomarker positive: Cyclin E1 IHC[b] (n=48)

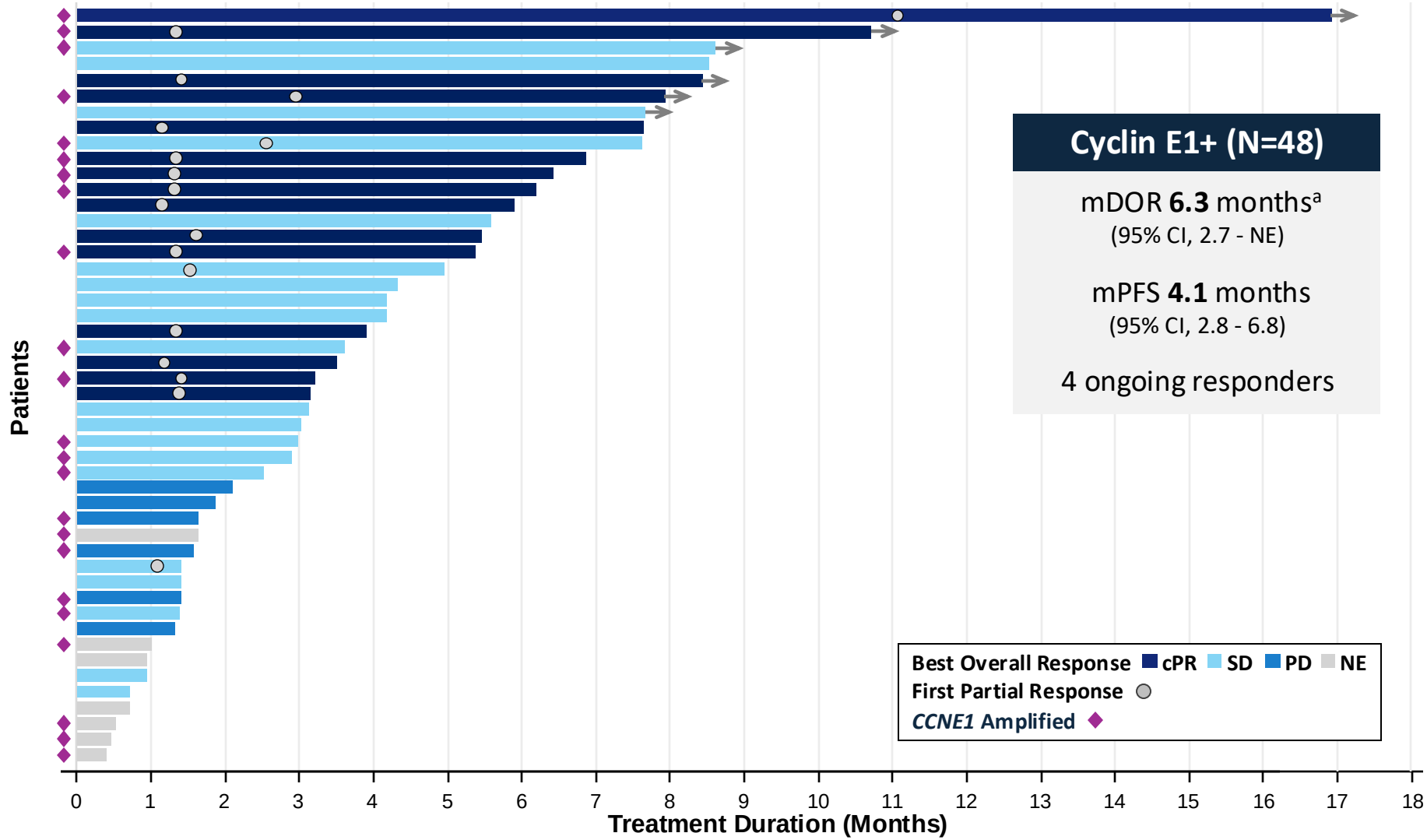


	All treated patients (N=102)
ORR in response-evaluable[c] patients, % (n/N; 95% CI)	**20.4** (19/93; 12.8-30.1)
ORR, ITT[a] % (n/N; 95% CI)	**18.6** (19/102; 11.6-27.6)

	Cyclin E1 IHC+ (n=48)
ORR in response-evaluable[c] patients, % (n/N; 95% CI)	**34.9** (15/43; 21.0-50.9)
ORR, ITT[a] % (n/N; 95% CI)	**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.

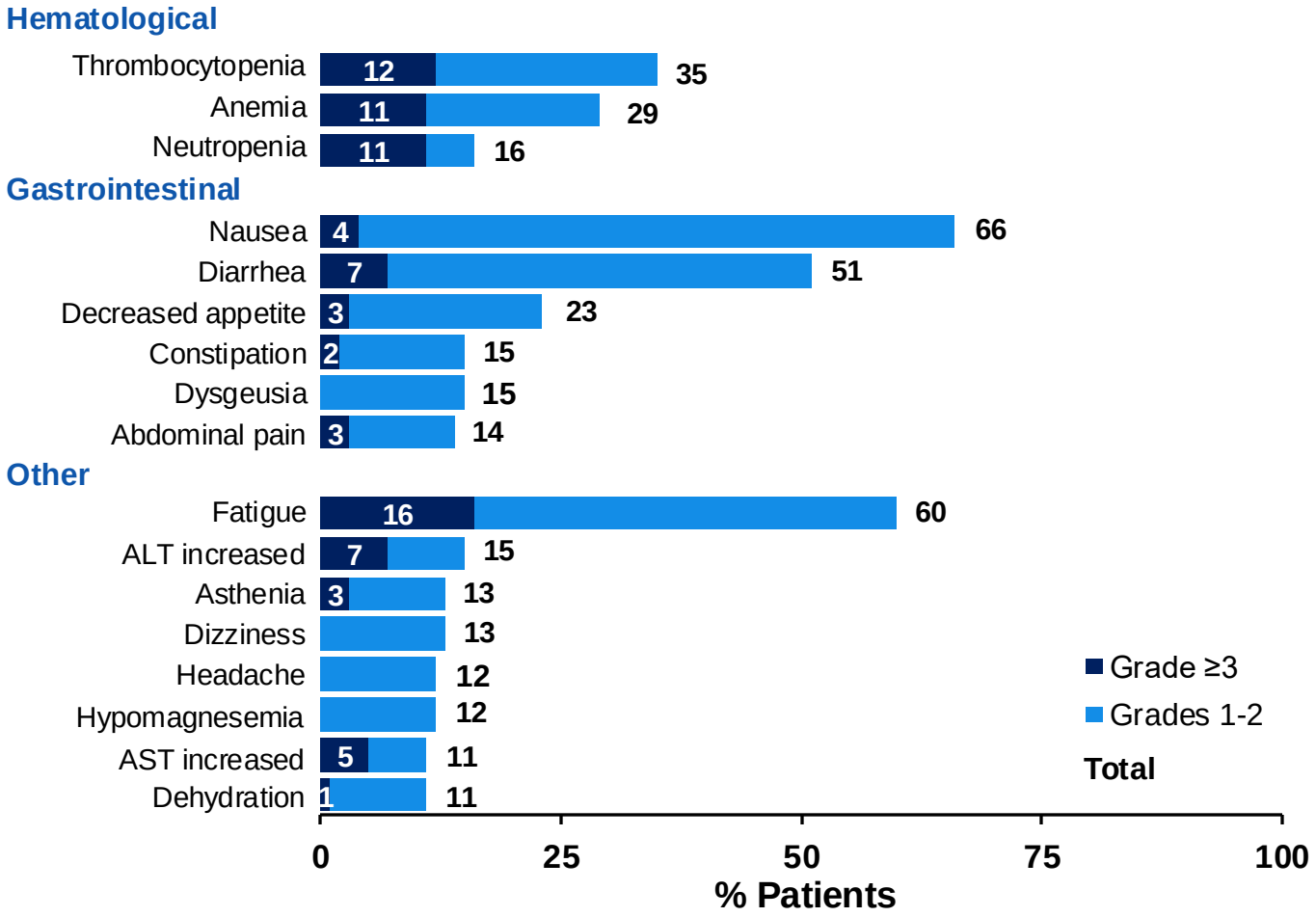
DENALI (GOG-3066) Part 1b: Duration of Response in Cyclin E1 IHC+ Ovarian Cancer



[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 (GOG-3066) Part 1b: Safety and Tolerability Summary

TRAEs occurring in ≥10% of patients[a]



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

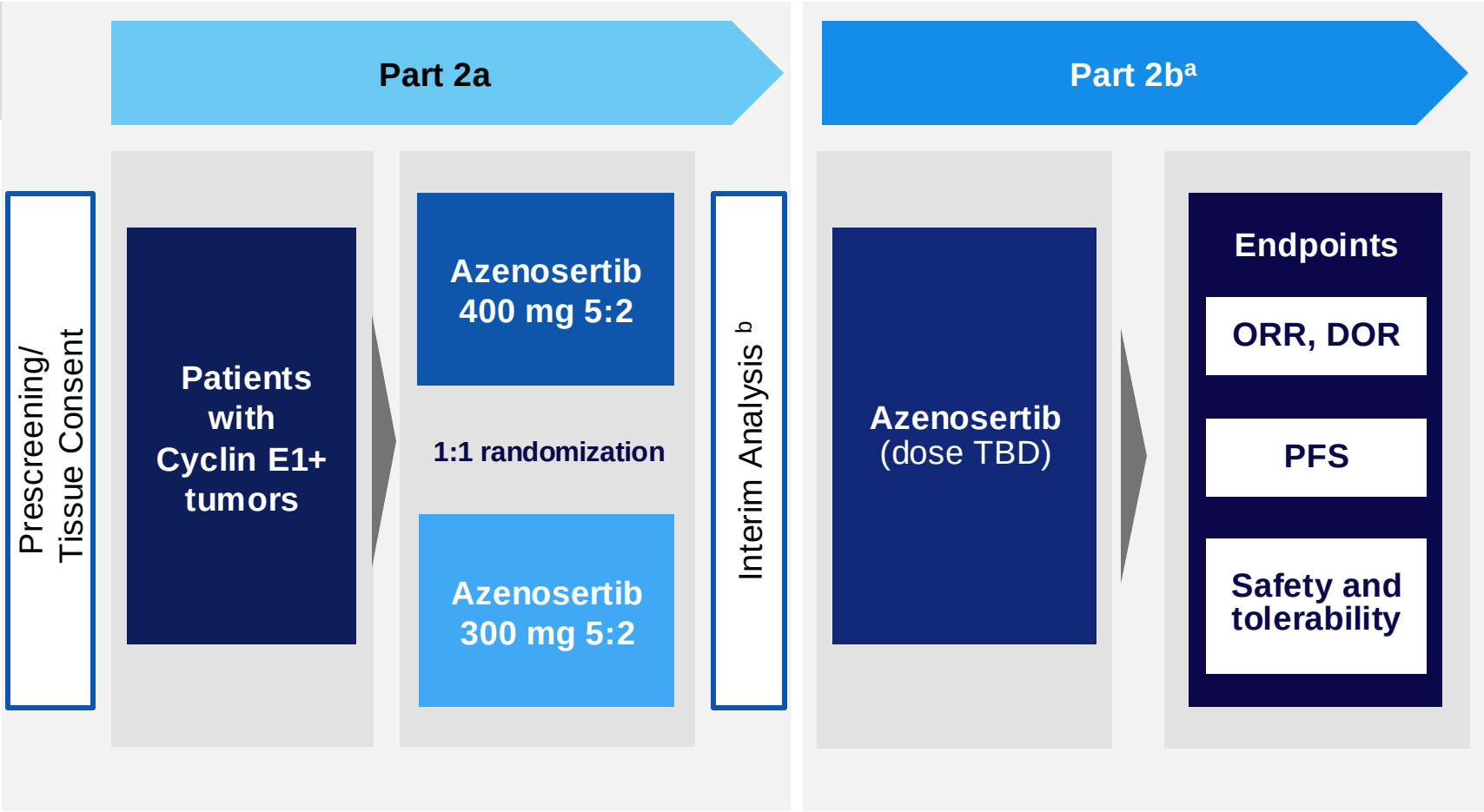
[a]If a patient had multiple grades of the same adverse event, The worse grade was reported [b]One patient had sepsis, and 1 patient had pancytopenia.

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

DENALI (GOG-3066): Phase 2, Open-Label, Multicenter Study Investigating Azenosertib in Cyclin E1+ PROC

Part 2
Key eligibility criteria

- ✓ PROC
- ✓ **Cyclin E1+ IHC**
- ✓ 1-3 prior lines of therapy
- ✓ 4 if prior mirvetuximab



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[a]Subject to FDA feedback. [b]Enrollment will continue through the interim analysis
5:2, 5 days on, 2 days off; DOR, duration of response; FRa, folate receptor alpha; ORR, objective response rate; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; TBD, to be determined.
ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05128825.

Conclusions

- Cyclin E1+ / overexpression by IHC represents ~ 50% 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+ HGSOC
  - Median duration of response is 6.3 months
- Cyclin E1 by IHC is a predictive biomarker for response to azenosertib
- GI toxicity (nausea, diarrhea) and fatigue are the most common TRAEs; although less common, hematological toxicities require close monitoring during treatment with azenosertib

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

[a]Includes patients who received at least one post treatment scan [b]mDOR is subject to change, there are 4 ongoing responders as of the January 13, 2025 data cut off
GI, gastrointestinal; HGSOC, high-grade serous ovarian cancer; mDOR, median duration of response; PROC, platinum-resistant ovarian cancer; TRAE, treatment-related adverse event.

Acknowledgements

Enrolling 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
- EDOG Institut de Cancérologie de l'Ouest – PPDS
- 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

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