



Cyclin E1–Positive Protein Status Is a Predictive Biomarker of Azenosertib Benefit in Platinum-Resistant Ovarian Cancer: Part 2 of the DENALI Study (GOG-3066)

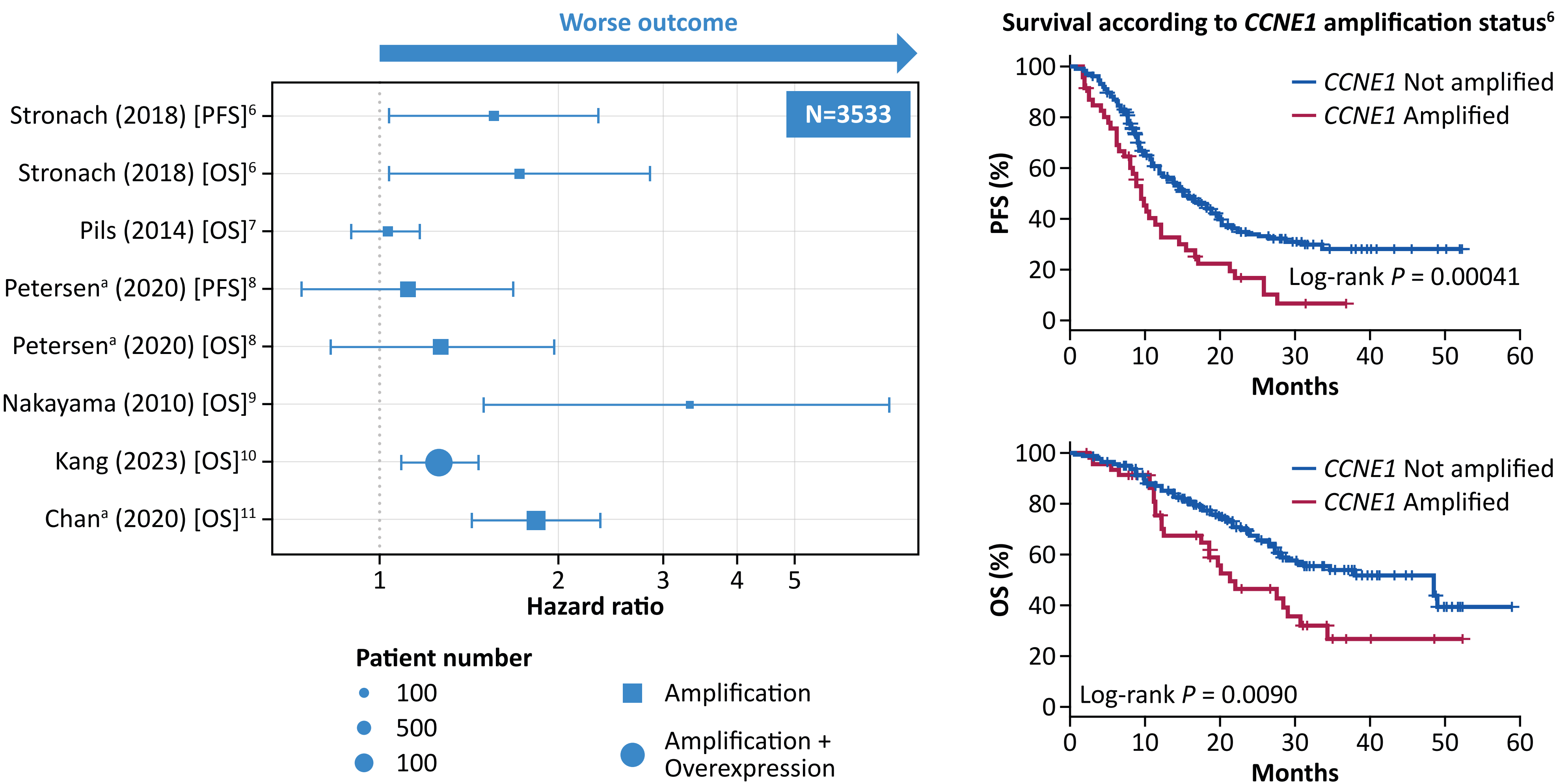
Alexandra Leary¹, Lyndsay Willmott², Bradley J. Monk³, Jean-Sébastien Frenel⁴, David C. Starks⁵, Meena Okera⁶, Angeles Alvarez Secord⁷, David M. O’Malley⁸, Lainie Martin⁹, Kaissa Ouali¹⁰, Martin K. Oehler¹¹, Jeffrey C. Goh¹², Brian M. Slomovitz¹³, Peter C. Lim¹⁴, Catherine M. Shannon¹⁵, Robert Neff⁸, Floor J. Backes⁸, Divya Rajendran¹⁶, Heekyung Chung¹⁶, Doris Kim¹⁶, Hailun Li¹⁶, Danielle Jandial¹⁶, Fiona Simpkins¹⁷

¹Gustave Roussy Cancer Center, Villejuif, France; ²Arizona Center for Cancer Care, Phoenix, AZ; ³GOG Foundation, Florida Cancer Specialists and Research Institute, West Palm Beach, FL; ⁴Institut de Cancérologie de L’Ouest, Saint-Herblain, Nantes, France; ⁵Avera Cancer Institute, Sioux Falls, SD; ⁶Cancer Research SA, Adelaide, SA, Australia; ⁷Duke Cancer Institute, Durham, NC; ⁸The Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus, OH; ⁹Penn Medicine Abramson Cancer Center, Philadelphia, PA; ¹⁰Gustave Roussy, DITEP, Villejuif, France; ¹¹University of Adelaide, Royal Adelaide Hospital, Adelaide, SA, Australia; ¹²ICON Research, South Brisbane & Queensland University of Technology, Brisbane, QLD, Australia; ¹³Mount Sinai Medical Center, Miami Beach, FL; ¹⁴Center of Hope at Renown Regional Medical Center, Reno, NV; ¹⁵Mater Cancer Care Centre, South Brisbane, Australia; ¹⁶Zentalis Pharmaceuticals, San Diego, CA; ¹⁷University of Pennsylvania School of Medicine, Philadelphia, PA

BACKGROUND

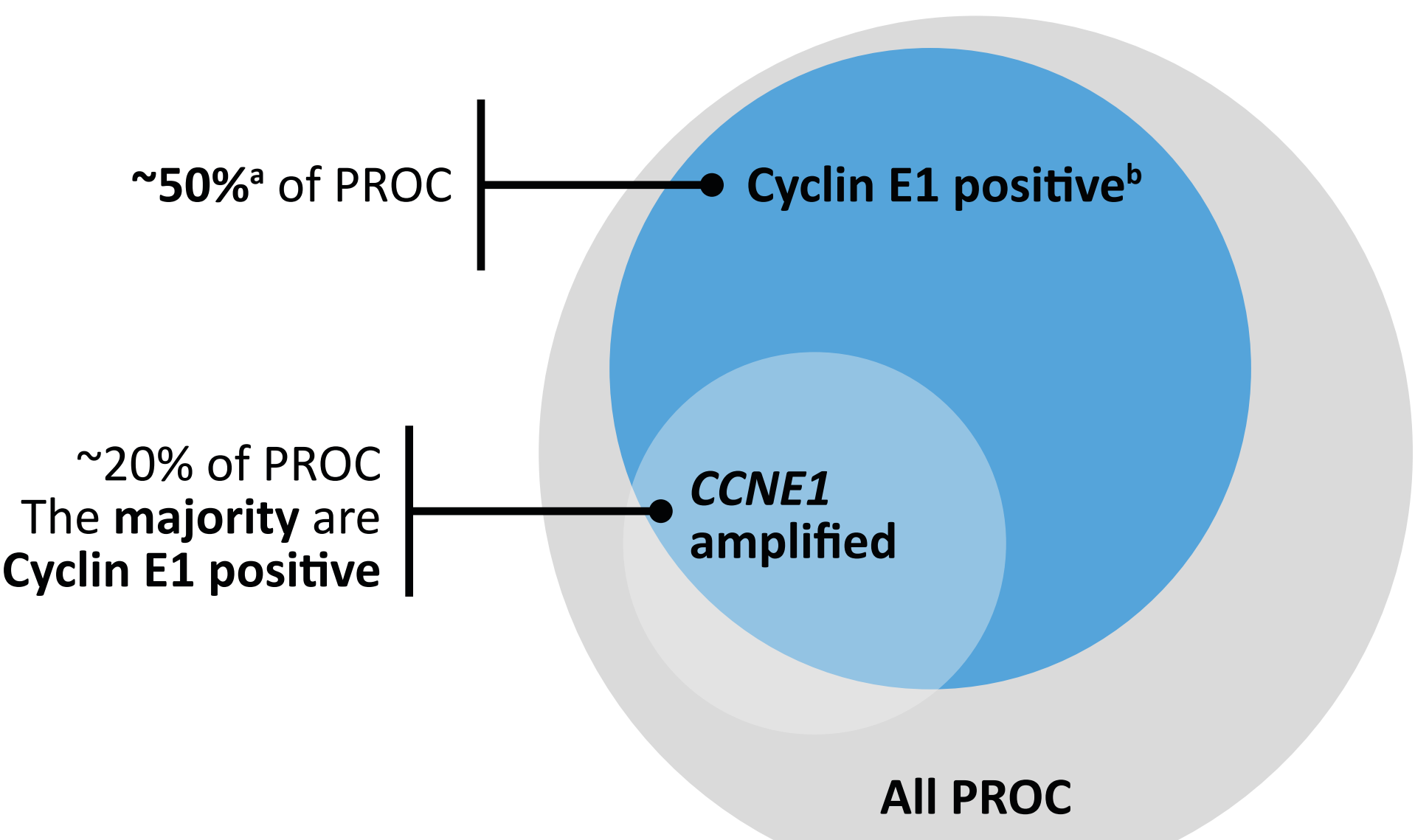
- Cyclin E1–positive protein expression comprises a significant portion of patients with platinum-resistant ovarian cancer (PROC) and has been associated with poor prognosis in patients with ovarian cancer (**Figure 1**)
- Currently, there are no approved therapies specifically for Cyclin E1–positive-PROC, presenting a significant unmet need
- WEE1 is a master regulator of the cell cycle acting as a brake at G1-S and G2-M to allow DNA repair¹
- Azenosertib is a potential best-in-class, small molecule, highly selective oral WEE1 kinase inhibitor (**Figure 2**)
- Cyclin E1 protein overexpression has been shown to directly correlate with an increased reliance on the G2-M checkpoint in the cell cycle^{2,3} and is a predictive biomarker of azenosertib sensitivity in preclinical models of ovarian cancer⁴
 - Targeting WEE1 with azenosertib removes the brake at G1-S and G2-M ultimately leading to mitotic catastrophe⁴
- Azenosertib monotherapy (400 mg) administered on an intermittent schedule (5 days on, 2 days off [5:2]) demonstrated clinically meaningful response rates (objective response rate 35%) and duration of response (median, 6.3 months) in heavily pretreated patients with Cyclin E1–positive PROC in DENALI Part 1b⁵
- In addition, azenosertib has shown to have a manageable safety profile with a low rate of serious treatment-related adverse events⁵
- These promising results indicate that Cyclin E1 protein expression is a clinically relevant biomarker associated with response to azenosertib monotherapy, warranting further investigation with azenosertib in patients with Cyclin E1–positive PROC
- The objective of DENALI Part 2 to evaluate the efficacy and safety of azenosertib in Cyclin E1–positive PROC patients prospectively screened and identified on sponsor’s central immunohistochemistry assay**

Figure 1A. Patients with ovarian cancer with Cyclin E1 protein overexpression and/or CCNE1 amplification have worse outcomes



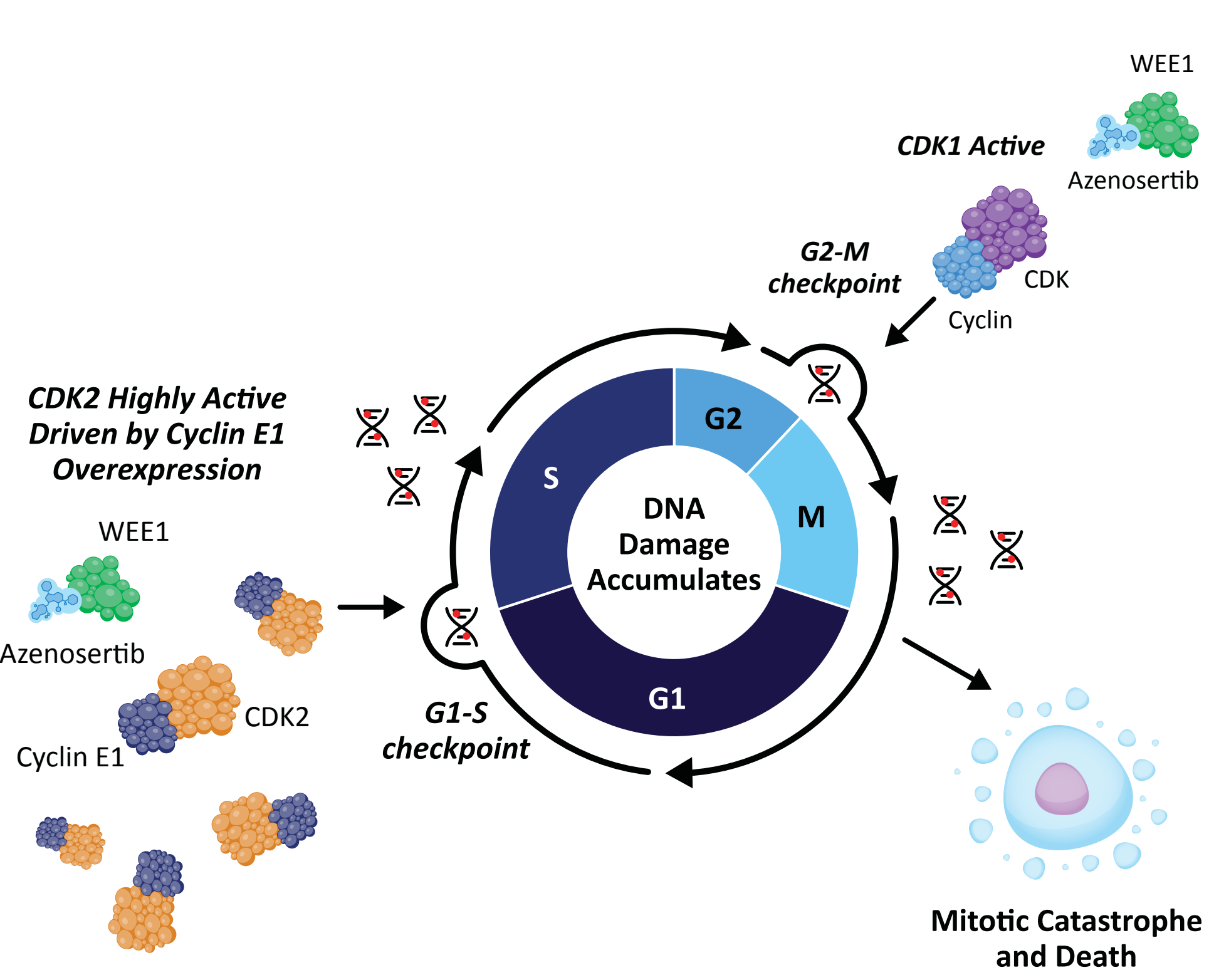
^a Timing of tissue collection was not disclosed.

Figure 1B. Cyclin E1 positive tumors comprise a significant portion of the PROC population including a vast majority that are CCNE1 amplified.



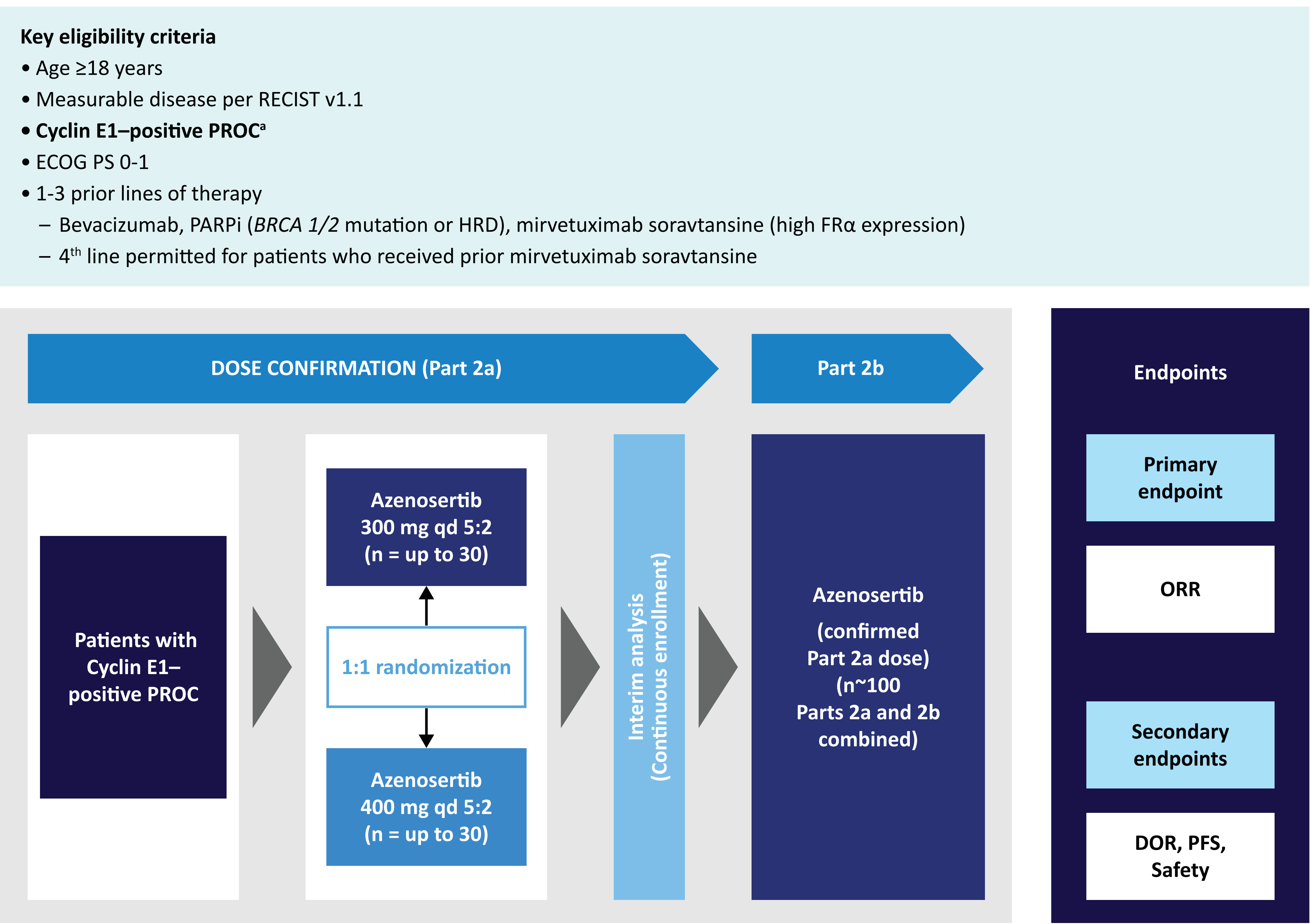
^aCyclin E1 IHC positive % based on literature (~20% CCNE1 amplification) and the unbiased CCNE1 amplification and Cyclin E1 overlapping data generated from Zentalis clinical trial samples. ^bCyclin E1 IHC positive based on Zentalis proprietary IHC cutoff and Cyclin E1 IHC assay developed from the existing clinical data.

Figure 2. Mechanism of action of azenosertib



METHODS

Figure 3. Study design of DENALI (GOG-3066) Part 2



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^a By IHC per sponsor’s central assay (prescreening can be performed during current therapy).

- DENALI (GOG-3066) is a phase 2, open-label, multicenter, 2-part (Part 1b and Part 2a/b) study assessing the safety and efficacy of azenosertib in patients with PROC, with the focus here being on Part 2a/b (**Figure 3**)
 - Part 1b enrolled all-comers (irrespective of Cyclin E1 protein expression status; 1-5 prior lines of therapy; N=102) with PROC who received azenosertib 400 mg 5:2⁵
 - **Part 2** (currently enrolling patients with Cyclin E1–positive PROC; with registration-intent for potential accelerated approval):
 - Part 2a: Dose confirmation with patients randomized 1:1 to receive 300 mg or 400 mg on a 5:2 schedule
 - Part 2b: Continuous enrollment at the confirmed dose from Part 2a with a target of ~100 patients
- An Independent Data Monitoring Committee has been chartered for this study

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Trial Status

Part 2 enrollment started in April 2025 and will be at more than 80 sites internationally

Acknowledgments

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Additional Information

For more information on this study, visit www.zentalis.com or contact publications@zentalis.com

Abbreviations

5:2, 5 days on, 2 days off; *BRCA 1/2*, breast cancer genes 1/2; CDK, cyclin-dependent kinase; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FRα, factor receptor alpha; G1-S, Gap 1-Synthesis; G2-M, Gap 2-Mitosis; HRD, homologous recombination deficiency; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; PS, performance status; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.