

Azenosertib in Combination With Bevacizumab as Maintenance Therapy in Patients With Advanced Ovarian Cancer: Part 2 of a Phase 1b study (MUIR/Zn-c3-002)

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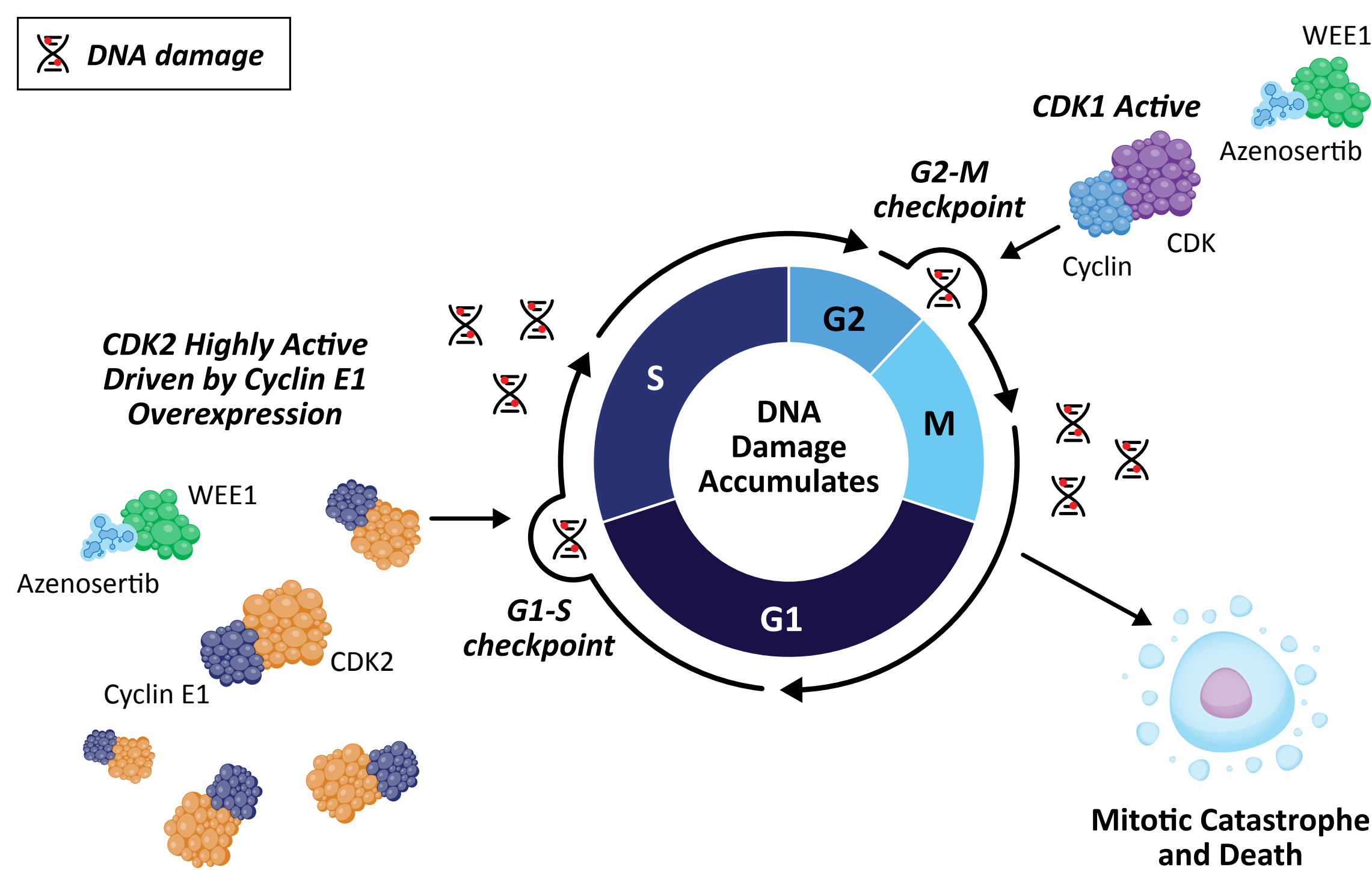
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INTRODUCTION/BACKGROUND

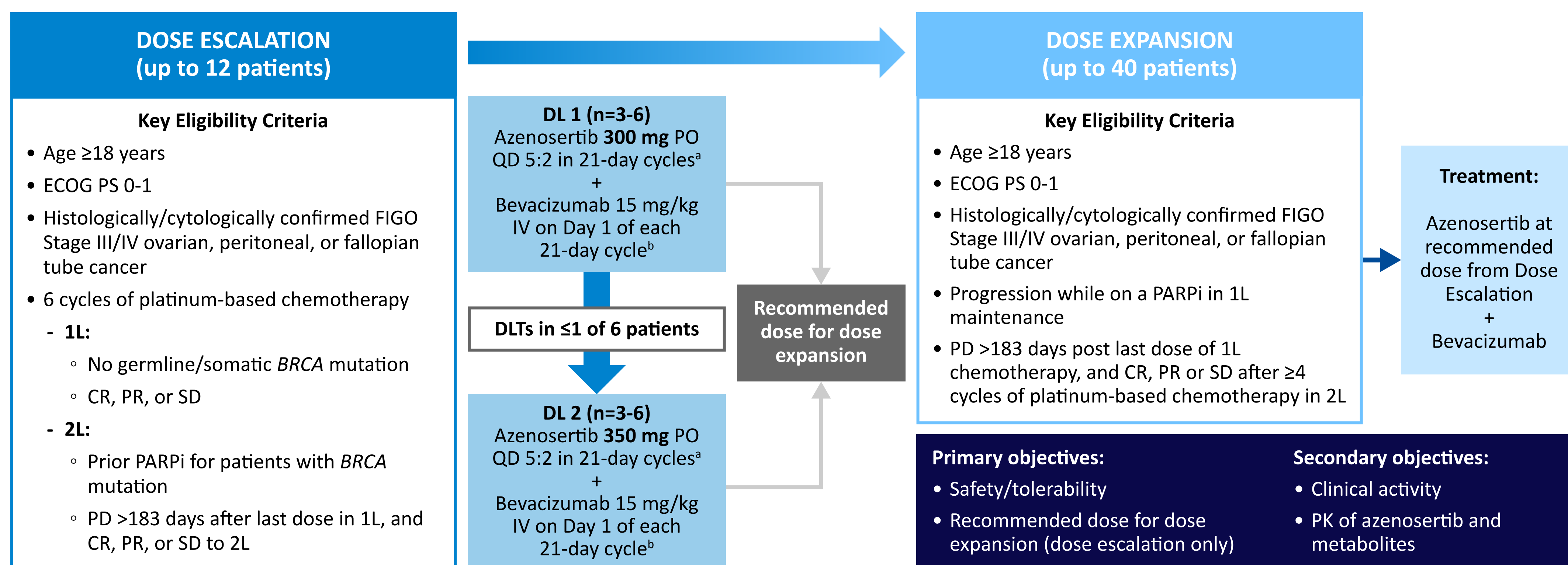
- Surgical debulking followed by adjuvant carboplatin-paclitaxel chemotherapy remains the standard approach for patients with Stage III/IV ovarian cancer (OC)
- Most patients ultimately experience relapsed disease within the first 5 years due to the advanced stage at diagnosis and face an unfavorable prognosis¹; effective novel targeted therapies are needed to address this substantial unmet need
- WEE1 tyrosine kinase is a key regulator of multiple checkpoints that prevents progression through the cell cycle, allowing time for DNA repair before cell division^{2,3}
- Inhibition of WEE1 tyrosine kinase results in unscheduled mitosis and eventually cancer cell death^{3,4}
- Azenosertib (Figure 1), a potential best-in-class, small molecule, highly selective oral WEE1 inhibitor demonstrated clinically meaningful activity in Cyclin E1 positive platinum-resistant, high-grade serous OC (HGSOC) in the DENALI Part 1b clinical trial (NCT05128825)⁵
- Maintenance therapy with a poly(ADP-ribose) polymerase inhibitor (PARPi) following 6 cycles of platinum-based chemotherapy is a standard of care for many patients with advanced HGSOC⁶, and has demonstrated significantly prolonged progression-free survival in patients with platinum-sensitive, recurrent OC⁷
 - Nearly half of patients relapse while on first-line maintenance with a PARPi⁸, and outcomes are poor with a time from first to second treatment of 6.1 months vs 11.4 months in patients who progressed after first-line maintenance⁶, representing a significant therapeutic challenge in this patient population
- Bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody approved for the maintenance of advanced OC following platinum-based chemotherapy^{9,10}
- Distinct mechanisms of action and limited overlapping toxicities provide a strong rationale for adding azenosertib to bevacizumab as maintenance therapy in HGSOC
- Combining azenosertib with anti-VEGF antibody was well tolerated and showed enhanced activity in PSOC preclinical models¹¹
- This combination regimen is currently being evaluated in the Zn-c3-002 study (MUIR; NCT04516447)

Figure 1. Mechanism of action of azenosertib



METHODOLOGY

Figure 2. Study Design of MUIR – Part 2



Duration of Patient Participation



^aUp to 24 months. ^bUp to 15 months.

- Zn-c3-002 (NCT04516447; MUIR) is an open-label, 2-part, Phase 1b study, evaluating preliminary efficacy, safety, and pharmacokinetics of azenosertib combination regimens in patients with OC
- In Part 1, patients receive azenosertib with investigator's choice of chemotherapy (pegylated liposomal doxorubicin, carboplatin, paclitaxel, or gemcitabine)
- In Part 2, patients receive azenosertib in combination with bevacizumab (Figure 2)
- Primary objectives:**
 - Safety/tolerability assessed by:
 - Incidence and severity of adverse events
 - Incidence of dose interruptions, reductions and discontinuations due to treatment-related adverse events
 - Recommended dose for dose expansion (dose escalation only)

- Secondary objectives:**
 - Clinical activity assessed by:
 - ORR, CBR, and DOR^a
 - PFS
 - Time to progression by CA-125 assessment
 - PK of azenosertib and metabolites
- Exploratory objectives:**
 - Association between sensitivity to azenosertib and molecular characteristics of tumor tissue and plasma including:
 - Cyclin E1 expression
 - Gene mutations, insertions, deletions, copy number variations, and structural variants
 - Gene expression signatures

^aFor patients who enter the study with measurable disease.

Trial Status

Dose escalation is ongoing; dose expansion will enroll in Europe, US, and Australia

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Additional Information

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

Abbreviations

1L, first line; 2L, second line; 5:2, 5 days on, 2 days off; BRCA, BRCA1/2 gene; CA-125, cancer antigen 125; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CR, complete response; DL, dose level; DLT, dose limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; FIGO, International Federation of Gynecology and Obstetrics; G1-S, GAP1-synthesis; G2-M, GAP2-mitosis; HGSOC, platinum-resistant high-grade serous ovarian cancer; IV, intravenous; OC, ovarian cancer; ORR, objective response rate; PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PO, oral; PR, partial response; QD, daily; SD, stable disease; VEGF, vascular endothelial growth factor.