Abstract #58117

Results From the Phase 1 Dose Escalation and Dose Expansion Study of Azenosertib, a WEE1 Inhibitor, in Patients With Advanced Solid Tumors

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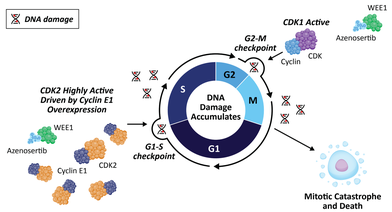
*Formerly employed by Zentalis

BACKGROUND

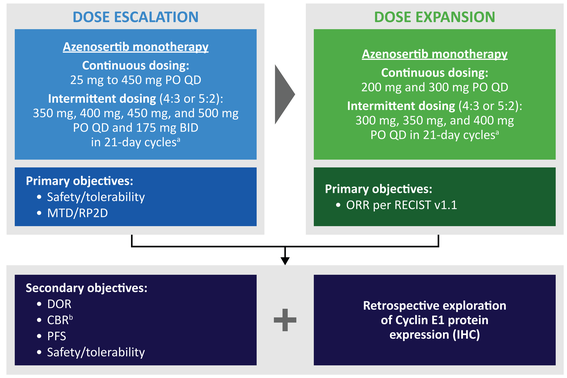
- WEE1 is a tyrosine kinase with a key role in several stages of the cell cycle, including the G1-S and G2-M checkpoints through negative regulation of both CDK1/2, preventing replication of cells with damaged DNA[1,2]
- WEE1 inhibition results in unscheduled mitosis without adequate DNA repair and eventual cancer cell death[1,3] and is a promising target in patients with solid tumors with increased levels of Cyclin E1 protein
  - Increased levels of Cyclin E1 protein accelerates the G1-S transition, resulting in replication stress and rendering cells even more sensitive to WEE1 inhibition[4]
- In the gynecologic malignancies space, both platinum-resistant ovarian cancer (PROC) and uterine serous carcinoma (USC) represent areas of substantial unmet need with urgently needed novel effective targeted therapies to improve outcomes in the advanced setting[5,6]
- Azenosertib is a potential best-in-class, small molecule, highly selective oral WEE1 kinase inhibitor[7] (**Figure 1**)
- **This first-in-human phase 1 dose-escalation and dose-expansion study evaluated safety, tolerability, and efficacy of azenosertib monotherapy in heavily pretreated patients with advanced/metastatic solid tumors including PROC and USC**

Figure 1. Mechanism of action of azenosertib



METHODS

Figure 2. Study design of ZN-c3-001



[a]±3 days with food. [b]Complete response + partial response + stable disease ≥16 weeks.

- ZN-c3-001 is the first-in-human, open-label, multicenter Phase 1 study of azenosertib monotherapy in solid tumors consisting of (**Figure 2**):
  - Dose escalation:
    - 25 mg to 450 mg PO QD, continuous dosing or 350 mg to 500 mg PO QD (including 175 mg BID), intermittent dosing (4:3 or 5:2)
  - Dose expansion:
    - 200 mg and 300 mg PO QD, continuous dosing or 300 mg to 400 mg PO QD, intermittent dosing (4:3 or 5:2)
- The study was conducted in patients with advanced/metastatic solid tumors, with focus on PROC and USC

CONCLUSIONS

- WEE1 inhibitor azenosertib demonstrated a manageable safety profile at total daily doses (300 mg to 500 mg), with continuous or intermittent (4:3 or 5:2) dosing
- Promising antitumor activity was observed in Cyclin E1 positive PROC and USC tumors, supporting further assessment of azenosertib in these patient populations
- The DENALI Part 2 study (NCT05128825) is currently evaluating azenosertib in patients with Cyclin E1 positive PROC[8]

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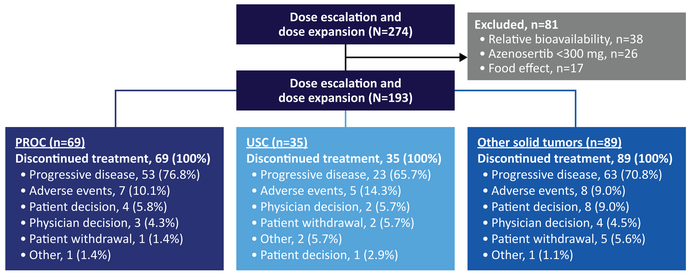
RESULTS

Figure 3. Patient disposition



Data cutoff: July 15, 2025.

- Primary reason for treatment discontinuation in each cohort was progressive disease (**Figure 3**)

Table 1. Baseline demographics and clinical characteristics in the PROC, USC, and other solid tumors cohorts in dose escalation and expansion, continuous or intermittent dosing ≥300 mg (FAS[a])

Characteristic	PROC (n=69)	USC (n=35)	Other solid tumors[b] (n=89)	Total (N=193)
Median age (range), years	66 (48-83)	66 (53-78)	64 (26-81)	65 (26-83)
Female, n (%)	69 (100)	35 (100)	54 (60.7)	158 (81.9)
Race, n (%)				
White	54 (78.3)	23 (65.7)	70 (78.7)	147 (76.2)
Black/African American	7 (10.1)	8 (22.9)	5 (5.6)	20 (10.4)
Asian	2 (2.9)	3 (8.6)	1 (1.1)	6 (3.1)
Other	5 (7.2)	1 (2.9)	13 (14.6)[c]	19 (9.8)
Ethnicity, n (%)				
Hispanic/Latino	9 (13.0)	5 (14.3)	16 (18.0)	30 (15.5)
Not Hispanic/Latino	54 (78.3)	28 (80.0)	65 (73.0)	147 (76.2)
Not reported/unknown	6 (8.7)	2 (5.7)	8 (9.0)	16 (8.3)
ECOG PS, n (%)			*n=88*	*n=192*
0	19 (27.5)	8 (22.9)	32 (36.0)	59 (30.6)
1	50 (72.5)	26 (74.3)	54 (60.7)	130 (67.4)
2	0	1 (2.9)	2 (2.2)	3 (1.6)
Median number of prior LoTs (range)	5 (1-19)	3 (0-12)	4 (0-11)	4 (0-19)
1-3, n (%)	22 (31.9)	22 (62.9)	32 (36.0)	76 (39.4)
≥4, n (%)	47 (68.1)	12 (34.3)	54 (60.7)	113 (58.5)
Prior therapies, n (%)				
Prior PARP inhibitor[d]	46 (66.7)	3 (8.6)	5 (5.6)	54 (28.0)
Prior VEGF inhibitor[e]	61 (88.4)	27 (77.1)	39 (43.8)	127 (65.8)
Prior anti–PD-1/PD-L1[f]	12 (17.4)	27 (77.1)	35 (39.3)	74 (38.3)
Cyclin E1 protein expression by IHC, n (%)				
Positive	26 (37.7)	15 (42.9)	9 (10.1)	50 (25.9)
Negative	29 (42.0)	11 (31.4)	25 (28.1)	65 (33.7)
Not evaluable	14 (20.3)	9 (25.7)	55 (61.8)	78 (40.4)

Data cutoff: July 15, 2025. [a]FAS includes all enrolled patients who received at least one dose of any study drug. [b]Anus, appendix, biliary tract, bladder, breast, cecum, cervix, colon, duodenum, endometrium, esophagus, kidney, lung, other, ovary, pancreas, peritoneum, prostate, rectum, stomach, uterus, vulva/vagina, including one patient who had unknown ECOG status. [c]One patient American Indian/Alaska Native. [d]PARP inhibitor includes olaparib, rucaparib, niraparib, talazoparib, veliparib. [e]VEGF inhibitor includes bevacizumab, axitinib, lenvatinib, pazopanib, ramucirumab, sunitinib, cediranib. [f]PD-1/PD-L1 includes pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, cemiplimab, dostarlimab, retifanlimab, spartalizumab.

- A total of 274 patients were enrolled in the study, of which 81 (relative bioavailability [n=38]; azenosertib total daily dose <300 mg [n=26], and food effect [n=17]) were excluded (**Figure 3**)
- As of July 15, 2025, 193 patients (PROC, n=69; USC, n=35; other solid tumors, n=89) received a total daily dose (300 mg to 500 mg) of azenosertib, continuously or intermittently (5:2 or 4:3)
- Across all cohorts, median age was 65 years (range, 26-83) and 98% of patients had ECOG PS ≤1 (**Table 1**)
  - Patients were heavily pretreated with a median number of prior lines of therapy of 5 (PROC), 3 (USC), and 4 (other solid tumors)
  - 61 (88%) patients with PROC, 27 (77%) patients with USC, and 39 (44%) patients with other solid tumors had received a prior VEGF inhibitor
  - 46 (67%) of patients in the PROC cohort had received a PARP inhibitor
  - 27 (77%) patients in the USC cohort and 35 (39%) patients in the other solid tumors cohort had received prior anti–PD-1/PD-L1 therapy, respectively
- A total of 55 (PROC cohort) and 26 (USC cohort) specimens were collected and retrospectively evaluated across all dosing cohorts for Cyclin E1 protein expression by IHC
  - 26 (47%) in the PROC cohort, and 15 (58%) in the USC cohort were Cyclin E1 positive per Sponsor's proprietary clinical assay and cutoff

Table 2. TRAEs in the PROC, USC, and other solid tumors cohorts in dose escalation and expansion, continuous or intermittent dosing ≥300 mg

TRAEs[a] by preferred term, n (%)	PROC (n=69)		USC (n=35)		Other solid tumors (n=89)		Total (N=193)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	63 (91.3)	31 (44.9)	34 (97.1)	15 (42.9)	81 (91.0)	37 (41.6)	178 (92.2)	83 (43.0)
Gastrointestinal								
Nausea	40 (58.0)	2 (2.9)	27 (77.1)	2 (5.7)	50 (56.2)	4 (4.5)	117 (60.6)	8 (4.1)
Diarrhea	40 (50.8)	6 (8.7)	18 (51.4)	1 (2.9)	43 (48.3)	8 (9.0)	101 (52.3)	15 (7.8)
Decreased appetite	18 (26.1)	1 (1.4)	12 (34.3)	1 (2.9)	23 (25.8)	1 (1.1)	53 (27.5)	3 (1.6)
Constipation	12 (17.4)	0	7 (20.0)	0	9 (10.1)	1 (1.1)	28 (14.5)	1 (0.5)
Vomiting	10 (14.5)	0	12 (34.3)	1 (2.9)	28 (31.5)	1 (1.1)	50 (25.9)	2 (1.0)
Hematologic								
Anemia[b]	24 (34.8)	7 (10.1)	15 (42.9)	7 (20.0)	19 (21.3)	9 (10.1)	58 (30.1)	23 (11.9)
Thrombocytopenia[c]	20 (29.0)	5 (7.2)	12 (34.3)	8 (22.9)	19 (21.3)	8 (9.0)	51 (26.4)	21 (10.9)
Leukopenia[d]	13 (18.8)	6 (8.7)	7 (20.0)	4 (11.4)	14 (15.7)	6 (6.7)	34 (17.6)	16 (8.3)
Neutropenia[e]	15 (21.7)	12 (17.4)	7 (20.0)	6 (17.1)	8 (9.0)	8 (9.0)	30 (15.5)	26 (13.5)
Other								
Fatigue	43 (62.3)	8 (11.6)	23 (65.7)	7 (20.0)	48 (53.9)	11 (12.4)	114 (59.1)	26 (13.5)
Dehydration	7 (10.1)	1 (1.4)	7 (20.0)	0	8 (9.0)	0	22 (11.4)	1 (0.5)

Data cutoff: July 15, 2025. Safety analysis set includes patients who received at least one dose of azenosertib. [a]TRAEs presented are those occurring in ≥15% of patients for any grade. [b]Anemia includes preferred terms of anemia, hematocrit decreased, hemoglobin decreased, and red blood cell count decreased. [c]Thrombocytopenia includes preferred terms of platelet count decreased and thrombocytopenia. [d]Leukopenia includes preferred terms of leukopenia and white blood cell count decreased. [e]Neutropenia includes preferred terms of neutropenia, neutrophil count decreased, and neutrophil percentage decreased.

Table 3. Dose modifications and serious TRAEs in the PROC, USC, and other solid tumors cohorts in dose escalation and expansion, continuous or intermittent dosing ≥300 mg

TRAEs, n (%)	PROC (n=69)	USC (n=35)	Other Solid Tumors (n=89)	Total (N=193)
TRAEs leading to:				
Dose reduction	28 (40.6)	20 (57.1)	30 (33.7)	78 (40.4)
Treatment interruption	30 (43.5)	18 (51.4)	28 (31.5)	76 (39.4)
Treatment discontinuation	4 (5.8)	3 (8.6)	3 (3.4)	10 (5.2)
Death	0	1 (2.9)	0	1 (0.5)
Any serious TRAEs	8 (11.6)	6 (17.1)	5 (5.6)	19 (9.8)

Data cutoff: July 15, 2025.

- Across cohorts, the most common TRAEs were nausea (61%), fatigue (59%), and diarrhea (52%) (**Table 2**)
- The most frequent grade ≥3 TRAEs were fatigue and neutropenia (13% each), anemia (12%), and thrombocytopenia (11%) (**Table 2**); all were clinically manageable
- TRAEs led to dose reduction in 78 patients (40%), treatment interruption in 76 patients (39%), treatment discontinuation in 10 patients (5%), and one death (cause unknown at 175 mg BID 5:2) (**Table 3**)
- Approximately 10% of all patients experienced serious TRAEs (**Table 3**)

Table 4. Efficacy overview in the PROC, USC, and other solid tumors cohorts in dose escalation and expansion, continuous and intermittent dosing ≥300 mg

Tumor type	PROC (n=69)				USC (n=35)				Other solid tumors (n=89)			
Dose schedule	Intermittent		Continuous		Intermittent		Continuous		Intermittent		Continuous	
Cyclin E1 IHC status	All comers	Cyclin E1 positive	All comers	Cyclin E1 positive	All comers	Cyclin E1 positive	All comers	Cyclin E1 positive	All comers	Cyclin E1 positive	All comers	Cyclin E1 positive
Number of patients	58	23	11	3	19	11	16	4	43	4	46	5
ORR, % (n/n) [95% CI]	20.7% (12/58) [11.2-33.4]	34.8% (8/23) [16.4-57.3]	18.2% (2/11) [2.3-51.8]	33.3% (1/3) [0.8-90.6]	26.3% (5/19) [9.2-51.2]	36.4% (4/11) [10.9-69.2]	18.8% (3/16) [4.1-45.7]	25.0% (1/4) [0.6-80.6]	2.3% (1/43) [0.1-12.3]	0% (0/4) [0.0-60.2]	4.3% (2/46) [0.5-14.8]	0% (0/5) [0.0-52.2]
Median DOR, months [95% CI]	5.1 (3.0-6.9)	5.5 (2.8-NE)	7.1 (4.2-NE)	4.2 (NE-NE)	5.5 (5.4-NE)	5.5 (5.4-NE)	5.6 (4.1-NE)	6.9 (NE-NE)	4.3 (NE-NE)	NA	3.3 (3.0-NE)	NA

- In patients with PROC who received azenosertib intermittently, ORR was 35% (8/23) in patients with Cyclin E1 positive tumors vs 21% (12/58) in all comers (median DOR, Cyclin E1 positive: 5.5 months [range, 2.8-NE]; all comers: 5.1 months [range, 3.0-6.9]) (**Table 4**)
- In patients with USC who received azenosertib intermittently, ORR was 36% (4/11) in patients with Cyclin E1 positive tumors vs 26% (5/19) all comers (median DOR, Cyclin E1 positive: 5.5 months [range, 5.4-NE]; all comers: 5,5 months [range, 5.4-NE]) (**Table 4**)

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Additional Information

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

Abbreviations

4:3, 4 days on, 3 days off; 5:2, 5 days on, 2 days off; BID, twice daily; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FAS, full analysis set; G1-S, Gap 1-Synthesis; G2-M, Gap 2-Mitosis; IHC, immunohistochemistry; LoT, line of therapy; MTD, maximum tolerated dose; NA, not applicable; NE, not evaluable; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PD-1/PD-L1, programmed cell death protein-1/programmed death-ligand 1; PFS, progression-free survival; PO, orally; PR, partial response; PROC, platinum-resistant ovarian cancer; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; SD, stable disease; USC, uterine serous carcinoma; TRAE, treatment-related adverse event; VEGF, vascular endothelial growth factor.