

# A Phase 1b dose-escalation study of ZN-c3, a Wee1 inhibitor, in combination with chemotherapy (CT) in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer

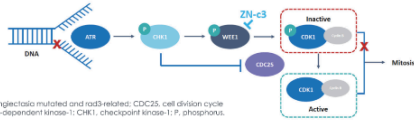
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## INTRODUCTION

- ZN-c3 is a novel, selective, and orally bioavailable Wee1 inhibitor that has demonstrated significant antitumor activity in vitro and in vivo models (Figure 1)

Figure 1. Mechanism of action of ZN-c3\*



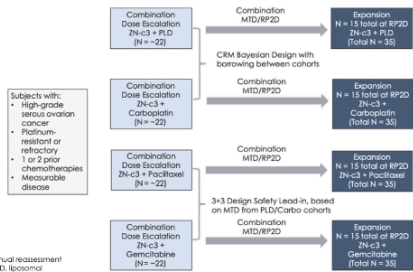
ATR, ataxia telangiectasia mutated and rad3-related; Cdc25, cell division cycle 25; Chk1, cyclin-dependent kinase-1; Chk2, checkpoint kinase-2; P, phosphorylation.

- Combining ZN-c3 with CT may inhibit repair of CT-induced DNA damage and provide therapeutic benefit in patients with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer

## MATERIALS AND METHODS

- This is an ongoing Phase 1b open-label, multicenter study evaluating the safety, tolerability, preliminary clinical activity, pharmacokinetics (PK), and pharmacodynamics of ZN-c3 in combination with standard chemotherapies (Figure 2)
- Study consists of 4 combination dose cohorts (Table 1)
- When the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) has been determined for a respective combination, approximately 15 subjects in total will be enrolled at the RP2D

Figure 2. Study design



## Endpoints

### Primary

- Incidence and severity of adverse events (AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0
- Incidence of dose-limiting toxicities (DLTs) in DLT-evaluable subjects during Cycle 1

### Secondary

- Estimates of clinical activity of ZN-c3 in combination with PLD, carboplatin, paclitaxel, or gemcitabine
- Plasma PK of ZN-c3
- Plasma PK of paclitaxel

## MATERIALS AND METHODS

### Subjects

- Inclusion and exclusion criteria are reported at clinicaltrials.gov (NCT04516447)

Table 1. Treatment

Treatment	Dose
<b>ZN-c3</b>	<ul style="list-style-type: none"> <li>• Taken orally (PO) and continuously once daily (QD) during each cycle</li> <li>• Starting dose of ZN-c3 was 200 mg QD with CT</li> </ul>
<b>PLD</b>	<ul style="list-style-type: none"> <li>• 40 mg/m<sup>2</sup> administered intravenously (IV) over 60 minutes every 4 weeks, on Day 1 of each 28-day cycle (± 3 days)</li> </ul>
<b>Carboplatin</b>	<ul style="list-style-type: none"> <li>• Target area under the concentration versus time curve (AUC) 5 mg·min administered IV over 15 minutes or longer every 3 weeks, administered on Day 1 of each 21-day cycle (± 3 days)</li> </ul>
<b>Paclitaxel</b>	<ul style="list-style-type: none"> <li>• Paclitaxel: 80 mg/m<sup>2</sup> administered IV over 60 minutes (± 10 minutes) on Days 1, 8, and 15 of each 28-day cycle</li> </ul>
<b>Gemcitabine</b>	<ul style="list-style-type: none"> <li>• 1000 mg/m<sup>2</sup> administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle</li> </ul>

## RESULTS

### Subjects

- As of the cutoff date of January 28, 2022, 56 treated subjects were evaluable for safety and 43 were response-evaluable
- Demographic and clinical characteristics of subjects enrolled are summarized in Table 2

Table 2. Characteristics of subjects enrolled

Characteristic*	ZN-c3 + PLD (n = 30)	ZN-c3 + Carboplatin (n = 17)	ZN-c3 + Paclitaxel (n = 9)	Total* (N = 56)
Median age, years (range)	55 (34-75)	61 (49-74)	67 (51-74)	58.5 (34-75)
Race, n (%)				
White	29 (97)	17 (100)	8 (89)	54 (96)
Asian	1 (3)	0	1 (11)	2 (4)
ECOG status, n (%)				
0	20 (67)	8 (47)	8 (89)	36 (64)
1	10 (33)	9 (53)	1 (11)	20 (36)
Prior lines of therapy, n (%)				
1	19 (63)	9 (53)	5 (56)	33 (59)
2	11 (37)	8 (47)	4 (44)	23 (41)
Prior bevacizumab	13 (43)	9 (53)	4 (44)	26 (46)
Prior PARP inhibitor	3 (10)	4 (24)	1 (11)	8 (14)
Prior therapy status, n (%)				
Resistant	24 (80)	15 (88)	9 (100)	48 (86)
Platinum refractory	6 (20)	2 (12)	0 (0)	8 (14)

\*No subjects have been enrolled in the gemcitabine cohort as of January 28, 2022. PARP, poly-ADP-ribose polymerase.

### Safety

Table 3. DLTs as of January 28, 2022 (N = 56). The evaluation of the RP2D is ongoing for all combinations

ZN-c3 Dose	CT	DLT Category (per protocol)	DLT Criteria (per protocol)	Additional Information
200mg QD	PLD	Hematologic Toxicity	Grade ≥ 3 Febrile Neutropenia	G3 Febrile Neutropenia
300mg QD	PLD	Non-Hematologic Toxicity	Grade ≥ 3	G3 Fatigue
300mg QD	PLD	Hematologic Toxicity	Any AE leading to a ZN-c3 Cycle 1 dose intensity of < 75%	G4 Neutropenia
200mg QD	Carboplatin	Hematologic Toxicity	Grade 4 Thrombocytopenia	-
200mg QD	Carboplatin	Hematologic Toxicity	Any AE leading to a ZN-c3 Cycle 1 dose intensity of < 75%	G3 Thrombocytopenia
300mg QD	Carboplatin	Hematologic Toxicity	Grade 4 Thrombocytopenia	-
300mg QD	Carboplatin	Hematologic Toxicity	Inability to initiate D1 of C2 within 14 days of schedule if due to any AE	G3 Thrombocytopenia G3 Neutropenia
200mg QD	Paclitaxel	Non-Hematologic Toxicity	Grade ≥ 3	G3 ALT Increased
200mg QD	Paclitaxel	Non-Hematologic Toxicity	Inability to initiate D1 of C2 within 14 days of schedule if due to any AE	G3 ALT Increased

## REFERENCES

1. Huang PQ, et al. *J Med Chem.* 2021;64(17):13004-13024.
2. Matheson CJ, et al. *Trends Pharmacol Sci.* 2016;37(10):872-881.

## RESULTS

### Safety

- Clinical and hematologic treatment-emergent adverse events (TEAEs) are summarized in Table 4.

Table 4. Treatment-emergent adverse events

Adverse events occurring in ≥ 10% of subjects	ZN-c3 + PLD (n = 30), n (%)		ZN-c3 + Carboplatin (n = 17), n (%)		ZN-c3 + Paclitaxel (n = 9), n (%)		Total (N = 56), n (%)	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
Nausea	18 (60.0)	3 (10.0)	10 (58.8)	1 (5.9)	3 (33.3)	0 (0.0)	31 (55.4)	4 (7.1)
Neutropenia	18 (60.0)	13 (43.3)	4 (23.5)	5 (55.6)	3 (33.3)	27 (48.2)	20 (35.7)	
Thrombocytopenia	7 (23.3)	1 (3.3)	12 (70.6)	8 (47.1)	4 (44.4)	1 (11.1)	23 (41.1)	10 (17.9)
Anemia	8 (26.7)	2 (6.7)	8 (47.1)	2 (11.8)	5 (55.6)	1 (11.1)	21 (37.5)	5 (8.9)
Fatigue	8 (26.7)	2 (6.7)	7 (41.2)	0 (0.0)	5 (55.6)	1 (11.1)	20 (35.7)	3 (5.4)
Vomiting	12 (40.0)	3 (10.0)	6 (35.3)	0 (0.0)	2 (22.2)	2 (22.2)	20 (35.7)	5 (8.9)
Diarrhea	10 (33.3)	1 (3.3)	3 (17.6)	0 (0.0)	3 (33.3)	1 (11.1)	16 (28.6)	2 (3.6)
Hypalbuminemia	7 (23.3)	1 (3.3)	2 (11.8)	0 (0.0)	3 (33.3)	0 (0.0)	12 (21.4)	1 (1.8)
Leukopenia	9 (30.0)	4 (13.3)	1 (5.9)	0 (0.0)	1 (11.1)	0 (0.0)	11 (19.6)	4 (7.1)
Abdominal pain	5 (16.7)	2 (6.7)	4 (23.5)	1 (5.9)	1 (11.1)	0 (0.0)	10 (17.9)	3 (5.4)
Hypokalemia	3 (10.0)	0 (0.0)	4 (23.5)	1 (5.9)	2 (22.2)	2 (22.2)	9 (16.1)	3 (5.4)
Alanine aminotransferase increased	1 (3.3)	0 (0.0)	4 (23.5)	3 (17.6)	3 (33.3)	3 (33.3)	8 (14.3)	6 (10.7)
Hypomagnesemia	3 (10.0)	0 (0.0)	3 (17.6)	1 (5.9)	2 (22.2)	1 (11.1)	8 (14.3)	2 (3.6)
Lymphocyte count decreased	6 (20.0)	3 (10.0)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (14.3)	3 (5.4)
Pain (any)	3 (10.0)	0 (0.0)	4 (23.5)	0 (0.0)	0 (0.0)	0 (0.0)	7 (12.5)	0 (0.0)

### Efficacy

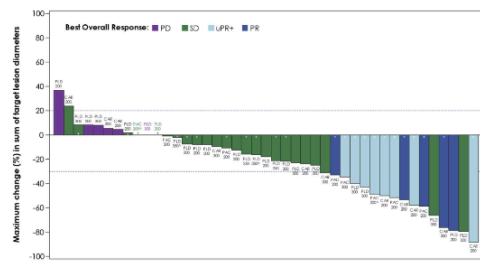
- Responses to treatment in response-evaluable subjects (N = 43) are summarized in Table 5. Waterfall plots for evaluable subjects overall, and in each of the 3 chemotherapy cohorts, are provided in Figures 3 and 4.

Table 5. Treatment responses (RECIST v1.1)

Group	N	Evaluable (n)	PR/UPR (%)	SD/SD+ (n)	PD (n)	DCR (%)	ORR (%)
<b>Total</b>	56	43	13	24	6	86.0	30.2
<b>PLD + ZN-c3</b>	30	24	3	17	4	83.3	12.5
<b>Carboplatin + ZN-c3</b>	17	11	5	4	2	81.8	45.5
<b>Paclitaxel + ZN-c3</b>	9	8	5	3	-	100	62.5

Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1  
 CR: complete response; CRR: percentage with CR; ORR: percentage with CR + SD/SD+  
 + indicates treatment is ongoing for this subject  
 DCR: disease control rate; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease; UPR: unconfirmed partial response.

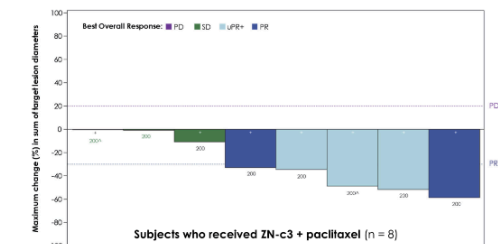
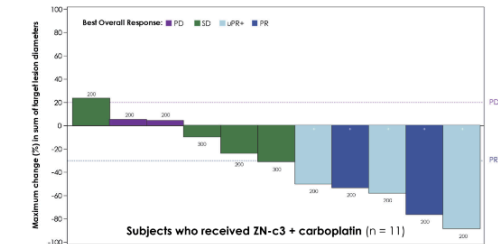
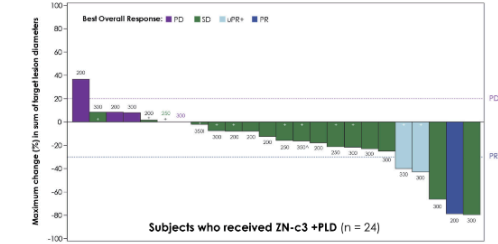
Figure 3. Clinical activity for subjects who received ZN-c3 + CT: Best overall response (RECIST v1.1) [N = 43]



^ Intermittent dosing, + indicates treatment is ongoing for this subject. The number on each bar is the starting dose (mg) of ZN-c3 for that subject. CAR, carboplatin; PAC, paclitaxel; PLD, liposomal doxorubicin.

## RESULTS

Figure 4. Clinical activity for subjects who received ZN-c3 + CT: best overall response (RECIST v1.1) by chemotherapy cohort



## CONCLUSIONS

ZN-c3, combined with CT, appears to be well tolerated and is demonstrating clinical activity in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer. The study is ongoing.

## ACKNOWLEDGEMENTS

We thank the patients, their families, and the study investigators participating in this ongoing study.