Abstract Number: CT148

# 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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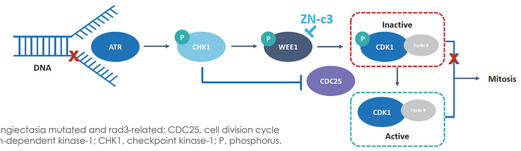
## INTRODUCTION

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

**Figure 1. Mechanism of action of ZN-c3[2]**



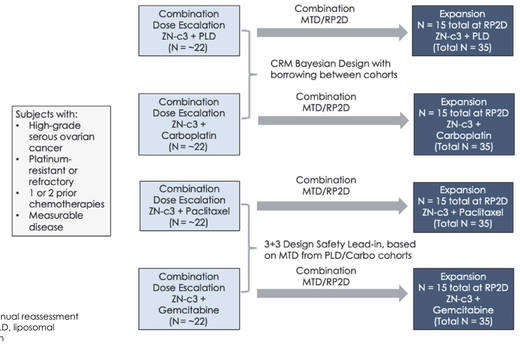

ATR, ataxia telangiectasia mutated and rad3-related; CDC25, cell division cycle 25; CDK1, cyclin-dependent kinase-1; CHK1, checkpoint kinase-1; P, phosphorus.

- 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**




CRM, continual reassessment method; PLD, liposomal doxorubicin

### 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 |
|---|---|
| **ZN-c3** | • Taken orally (PO) and continuously once daily (QD) during each cycle<br>• Starting dose of ZN-c3 was 200 mg QD with CT |
| **PLD** | • 40 mg/m² administered intravenously (IV) over 60 minutes every 4 weeks, on Day 1 of each 28-day cycle (± 3 days) |
| **Carboplatin** | • Target area under the concentration versus time curve (AUC) 5 mg/mL · min administered IV over 15 minutes or longer every 3 weeks, administered on Day 1 of each 21-day cycle (± 3 days) |
| **Paclitaxel** | • Paclitaxel: 80 mg/m² administered IV over 60 minutes (± 10 minutes) on Days 1, 8, and 15 of each 28-day cycle |
| **Gemcitabine** | • 1000 mg/m² administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle |

## 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) | 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) |
| Hypoalbuminemia | 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

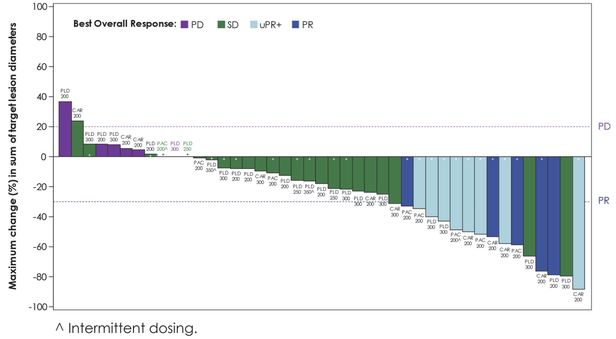
- Responses to treatment in response-evaluable subjects (N = 43) are summarized in **Table 5**. Waterfall plots for evaluable subjects overall, and in each of the 3 chemotherapy cohorts, are provided in **Figures 3** and **4.**

**Table 5. Treatment responses (RECIST v1.1)**

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

Measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1
Of evaluable subjects, ORR is percentage with PR/uPR; and DCR is percentage with ORR + 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.

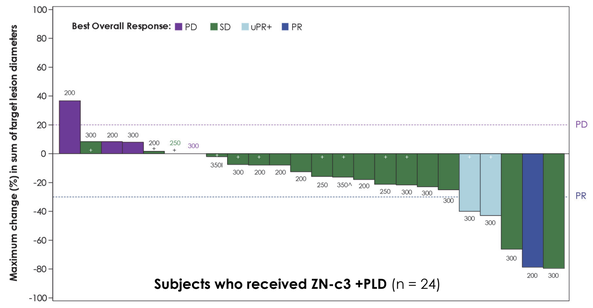
**Figure 3. Clinical activity for subjects who received ZN-c3 + CT: Best overall response (RECIST v1.1) [N = 43]**

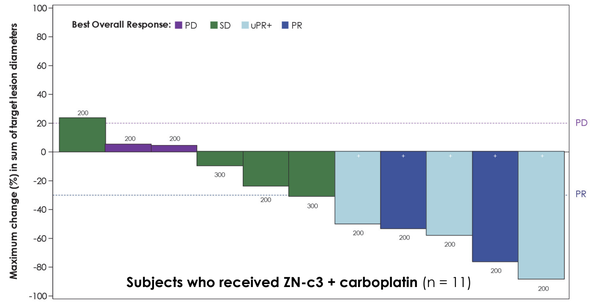


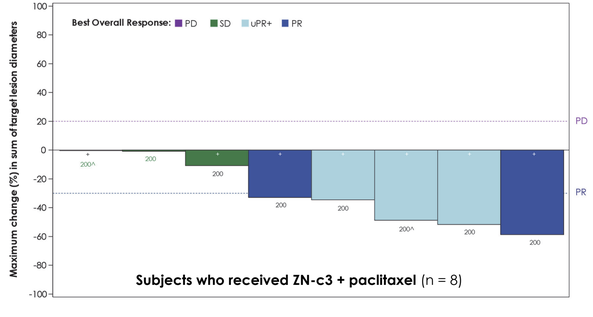

^ Intermittent dosing.
+ Indicates treatment is ongoing for this subject.
The number on each bar is the starting dose (mg) of ZN-c3 for that subject.
CAR, carboplatin; PAC, paclitaxel; PLD, liposomal doxorubicin.

## 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.