562TiP: A Phase 1b dose-escalation study of ZN-c3, a WEE1 inhibitor, in combination with chemotherapy in patients with platinum-resistant or -refractory ovarian, peritoneal, or fallopian tube cancer

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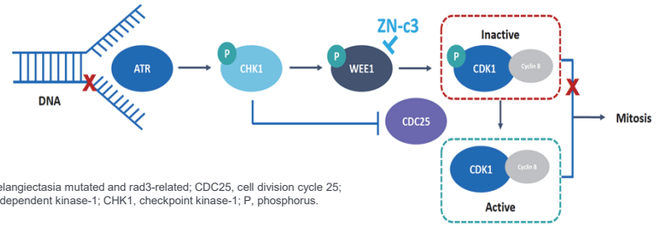
Introduction

- Wee1-like kinase (WEE1) is a tyrosine kinase that regulates entry into mitosis at the G2 to M-phase transition and has a role in inhibition of unscheduled DNA replication in S-phase.[1]
- WEE1 is frequently expressed in ovarian serous carcinoma effusions, and its expression is significantly higher following exposure to chemotherapy.[1] Inhibition of WEE1 in combination with chemotherapy has been shown to be effective in ovarian cancer.[2]
- ZN-c3 is a novel selective inhibitor of WEE1 (**Figure 1**), which is being evaluated in a Phase 1b trial in patients with refractory gynecologic tumors.

Figure 1. Mechanism of Action for ZN-c33



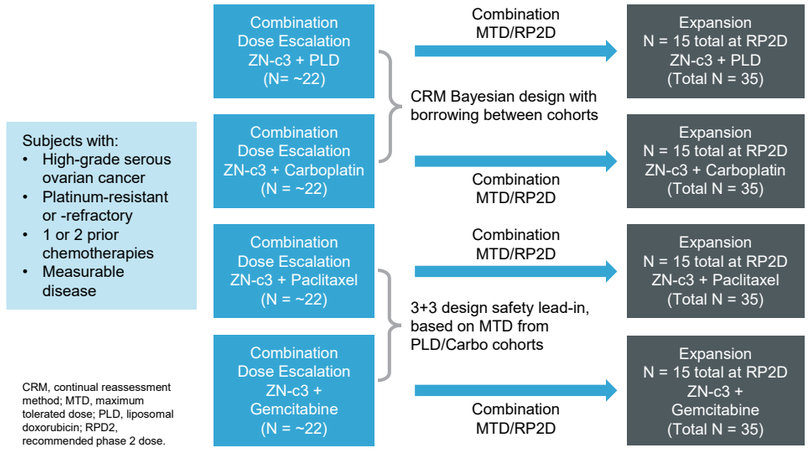
ATR, ataxia telangiectasia mutated and rad3-related; CDC25, cell division cycle 25; CDK1, cyclin-dependent kinase-1; CHK1, checkpoint kinase-1; P, phosphorus.

Methods

Study Design

The study design is provided in **Figure 2**.

Figure 2. Study Design



CRM, continual reassessment method; MTD, maximum tolerated dose; PLD, liposomal doxorubicin; RPD2, recommended phase 2 dose.

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Methods (continued)

Study Design (cont'd)

- This is a Phase 1b, open-label, multicenter study evaluating the safety, tolerability, preliminary clinical activity, pharmacokinetics (PK), and pharmacodynamics (PD) of ZN-c3.
- This study consists of 4 cohorts:
  - Combination Dose Escalation of ZN-c3 and pegylated liposomal doxorubicin (PLD)
  - Combination Dose Escalation of ZN-c3 and carboplatin
  - Combination Dose Escalation of ZN-c3 and paclitaxel
  - Combination Dose Escalation of ZN-c3 and gemcitabine
- When the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) has been determined for a respective combination, approximately 15 subjects will be enrolled at the RP2D.

Patients

Inclusion Criteria

- Females ≥18 years with Eastern Cooperative Oncology Group performance status ≤2
- Histologically or cytologically confirmed high-grade serous epithelial ovarian carcinoma, fallopian tube carcinoma, or peritoneal carcinoma
- Received 1 or 2 prior therapeutic regimens/lines of therapy in the metastatic setting. At least 1 regimen must have contained cisplatin or carboplatin
- Disease must be platinum resistant (platinum refractory is permitted); platinum-free interval <6 months
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Adequate hematologic and organ function
- Willingness to release archival tissue for research
- Left ventricular ejection fraction ≥50% (only for subjects treated with PLD)

Exclusion Criteria

- Histology of abdominal adenocarcinoma of unknown origin, or diagnosis of a borderline ovarian tumor
- Active (uncontrolled, metastatic) second malignancies or requiring therapy
- A serious illness or medical condition
- Recent interventions, including major surgery within 28 days, radiation therapy within 21 days, or autologous or allogeneic stem cell transplantation within 3 months
- Receipt of drugs known as moderate to strong inducers of CYP3A4 within 2 weeks

Treatment

Treatment dosing is provided in **Table 1**.

Table 1. Treatment

Treatment	Dose
ZN-c3	• Taken orally and continuously once daily (QD) in 21-day treatment cycles (± 3 days) when combined with carboplatin or gemcitabine and in 28-day cycles (± 3 days) when combined with PLD or paclitaxel • Starting dose for continuous dosing with PLD or carboplatin is 200 mg QD • Starting dose in combination with paclitaxel or gemcitabine in the safety lead-in period will be at least 1 dose level below the highest well-tolerated dose in either of the carboplatin or PLD combination cohorts
PLD	• 40 mg/m^2 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 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/m^2 administered IV over 60 minutes (±10 minutes) on Days 1, 8, and 15 of each 28-day cycle
Gemcitabine	• 1000 mg/m^2 administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle

Endpoints

The study endpoints are provided in **Table 2**.

Table 2. Study Endpoints

Primary
• Incidence and severity of adverse events (AEs), graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 • Incidence and severity of dose-limiting toxicities (DLTs) in DLT-evaluable subjects during Cycle 1
Secondary
• Clinical activity as defined by the revised RECIST v1.1: objective response rate and duration of response • Progression-free survival according to the Gynecologic Cancer Intergroup (GCIG) criteria • Time to progression of cancer antigen 125 • Plasma PK parameters of ZN-c3 (and its potential metabolites as applicable) • Plasma PK parameters of paclitaxel (and its potential metabolites as applicable)
Exploratory
• Description of the biological activity of WEE1 inhibition in pre-dose versus post-dose tumor tissue and hair follicle samples of the following parameters including, but not limited to, γH2AX, phosphorylated cyclin-dependent kinase 1 (phospho-CDK1), and Ki-67 • Determination including, but not limited to, cyclin E expression • Determination of molecular determinants of sensitivity to ZN-c3 including, but not limited to, the following: mutational status; mismatch repair (MMR) deficiencies; other DNA damage repair (DDR); gene mutations, insertions, deletions, copy number variations, and structural variants; indices of genetic instability; or gene (expression) signatures in tumor tissue or cell-free DNA (cfDNA)

Current Enrollment Status

As of August 20th, 2021, 29 subjects have been enrolled across 6 cohorts; treatment is ongoing in 21 subjects.

Conclusions

- ZN-c3 + chemotherapy represents a promising approach to treatment in women with gynecologic malignancies because it targets a tyrosine kinase known to be involved in these cancers.
- Enrollment in the study is ongoing.

References

1. Slipicevic A, et al. *Gynecol Oncol.* 2014;135(1):118-124; **2.** Leijen S, et al. *J Clin Oncol.* 2016;34(36): 4354-4361; **3.** Matheson CJ, et al. *Trends Pharmacol Sci.* 2016;37(10):872-881.

Disclosure

Dr Fu: none.