A Phase 1/2 Dose Escalation and Dose Expansion Study of ZN-c3 in Combination with Gemcitabine in Adult and Pediatric Subjects with Relapsed or Refractory Osteosarcoma

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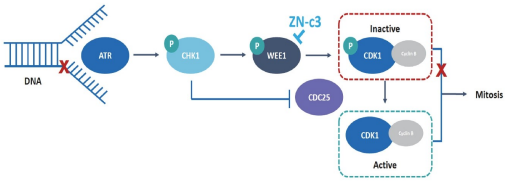
Background

- Osteosarcoma (OS) is the most common primary bone malignancy with 5-year survival rates of 65-70% for localized disease and <30% for de novo metastatic disease or recurrent disease.[1-4]
- Wee1 kinase helps regulate DNA damage repair at the G2-M checkpoint. In the presence of DNA damage, Wee1 kinase is activated, arresting cells in the G2 phase and preventing entry into the M phase. Inhibiting Wee1 kinase abrogates the G2-M checkpoint, forcing cancer cells to undergo unscheduled mitosis even in the presence of DNA damage, leading to mitotic catastrophe.[5]
- Wee1 kinase is upregulated in OS.[6] Additionally, up to 90% of OS tumors have alterations in p53, a critical protein in the regulation of the G1-S checkpoint.[7,8] With a dysfunctional G1-S checkpoint, cancer cells may further rely on G2-M checkpoint to repair DNA damage.[9]
- Prior studies have demonstrated that pharmacologic inhibition of Wee1 kinase produced cell death in OS cell lines and patient-derived xenografts.[9,10]
- ZN-c3 is a novel selective inhibitor of Wee1 (**Figure 1**),[11] and the objective of this phase 1/2 dose escalation and dose expansion study was to evaluate the clinical activity and safety, pharmacodynamics (PD), and pharmacokinetics (PK) of ZN-c3 in combination with gemcitabine in relapsed or refractory osteosarcoma.

Figure 1. Mechanism of Action for ZN-c3[11]



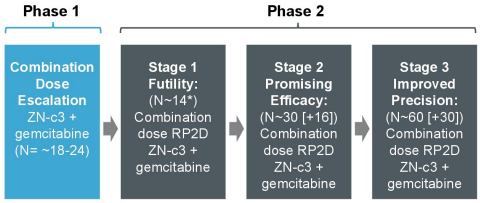
ATR, ataxia telangiectasia mutated and rad3-related; CDC25, cell division cycle 25; CDK1, cyclin-dependent kinase-1; CHK1, checkpoint kinase-1; P, phosphorus.

Methods

Study Design

- Phase 1/2 single-arm, open-label multicenter study (**Figure 2**).

Figure 2. Study Design



* Includes subjects treated with RP2D in Phase 1
RP2D, recommended Phase 2 dose.

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Methods (continued)

Study Design (cont'd)

Phase 1

- The starting dose of ZN-c3 is 200 mg once daily continuous dosing in combination with gemcitabine and will not exceed the determined recommended phase 2 dose (RP2D) for ZN-c3 monotherapy from the clinical study ZN-c3-001 (NCT04158336).
- When the maximum tolerated dose (MTD)/RP2D for ZN-c3 combination therapy with gemcitabine has been preliminarily determined, ≥6-12 additional subjects will be enrolled at a dose lower than the preliminary MTD/RP2D for ZN-c3 combination therapy with gemcitabine to better evaluate the clinical pharmacology and exposure-response relationship; concurrently, the Phase 2 part of the study will be initiated.

Phase 2

- It will enroll ~60 subjects and will consist of 3 stages: futility, promising clinical activity, and improved precision for clinical activity. The sample size and advancement criteria for the first 2 stages will follow a Simon optimal two-stage design, and the third stage, targeting precision to differentiate event-free survival (EFS) at 18 weeks, is based on historical data.

Inclusion Criteria

- Age ≥12 years old at the time of informed consent
- Body weight ≥40 kg
- Histologically documented relapsed or metastatic osteosarcoma
- Gemcitabine confirmed as an appropriate treatment approach
- Any number of prior therapies and prior treatment with gemcitabine allowed
- Measurable disease according to RECIST Guideline version 1.1 criteria
- Eastern Cooperative Oncology Group Performance (PS) ≤2 for subjects ≥16 years of age or Lansky PS ≥50 for subjects <16 years of age
- Adequate hematologic and organ function
- Ability and willingness to take oral medication
- Willingness to release archival tissue for research purposes or to undergo a tumor tissue biopsy prior to dosing on Cycle 1 Day 1 if ≥18 years old

Exclusion Criteria

- Major surgery <28 days, any chemotherapy <21 days or 5 half-lives (whichever is shorter), prior radiotherapy <14 days, any investigational drug therapy <28 days or 5 half-lives (whichever is shorter) from Cycle 1 Day 1
- Unresolved toxicity of Grade >1 attributed to any prior therapies
- Prior therapy with a Wee1 inhibitor.
- Known hypersensitivity to gemcitabine or its excipients.
- Known hypersensitivity to any drugs similar to ZN-c3 in class
- Active (uncontrolled, metastatic) second malignancies or requiring therapy

Table 1. Treatment

Treatment	Phase 1	Phase 2
ZN-c3*	• Subjects will take ZN-c3 in 21-day cycles (± 3 days) • Dose levels will be 100, 200, or 300 mg • The MTD is defined as the highest dose level with ≤1 DLT in a cohort of 6 subjects. The RP2D may be lower but not higher than the MTD	• Subjects will receive the RP2D determined in phase 1 in 21-day cycles (± 3 days), under fasted conditions
Gemcitabine	• 1000 mg/m^2 administered IV over 30 minutes on Days 1 and 8 of each 21-day cycle	

* Two intermediate doses of ZN-c3 may be considered, e.g., 150 mg or 250 mg.
DLT, dose-limiting toxicity.

Table 2. Study Endpoints

Phase 1	Phase 2
Primary	
• Incidence and severity of DLTs in DLT-evaluable subjects during Cycle 1 of Phase 1	• EFS at 18 weeks
Phase 2	
Secondary	

• Clinical activity according to RECIST Guideline v1.1 and clinical criteria:
  • EFS
  • OS (median and at 12 months)
• Incidence and severity of adverse events (AEs) graded according to NCI common terminology criteria for AEs (CTCAE), version 5.0
• Plasma PK parameters of ZN-c3 (and its potential metabolites as applicable), including but not limited to maximum concentration (C_{max}), time to maximum concentration (T_{max}), and area under the concentration-time curve over the dosing interval (AUC_{0-24h})	

Exploratory	
• Subject-reported incidence and severity of AEs • Change from baseline in self-reported global health status and quality of life • ZN-c3 concentrations in tumor tissue (and its potential metabolites as applicable) • Description of the biological activity of Wee1 inhibition in pre- versus post-dose tumor tissue and hair follicle samples, by the following parameters, including, but not limited to phosphorylated cyclin-dependent kinase 1 (phospho-CDK1), γH2AX, and Ki-67 • Determination of molecular determinants of sensitivity to ZN-c3, including, but not limited to, the following: mutational status, mismatch repair deficiencies, other DNA damage repair gene mutations, insertions, deletions, copy number variations, structural variants, or indices of genetic instability, or gene (expression) signatures in either tumor tissue or cell-free DNA • Objective response rate as defined by the revised RECIST Guideline v1.1	

Current Enrollment Status

As of May 10th, 2022, 9 subjects have been enrolled in the Phase 1 portion of the study. Enrollment in the study is ongoing.

Conclusions

- ZN-c3 + chemotherapy represents a promising approach to treatment of patients with OS since it targets Wee1 which is often upregulated in this cancer.