Preliminary Data from a Phase 1 Dose Escalation Study of ZN-c3 Plus Gemcitabine in Relapsed/Refractory Osteosarcoma (NCT04833582)

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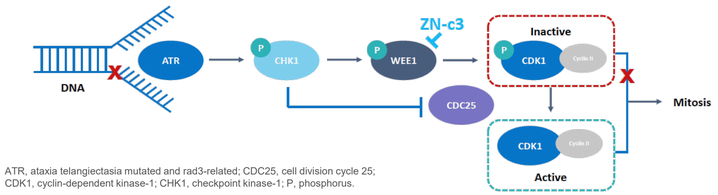
BACKGROUND

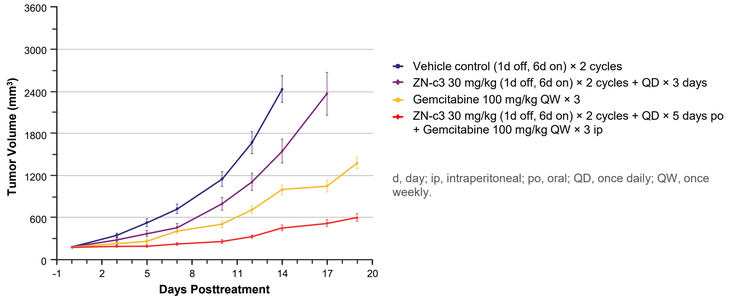
- Osteosarcoma (OS) is the most common primary bone malignancy with 5-year survival rates of 65% to 70% for localized disease and <30% for de novo metastatic or recurrent disease.[1-4]
- Wee1 kinase helps regulate DNA damage repair at the G2-M checkpoint. In the presence of DNA damage, Wee1 kinase is 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] and pharmacologic inhibition of Wee1 kinase produces cell death in both OS cell lines and patient-derived xenograft models.[7,8]
- ZN-c3 is a novel selective inhibitor of Wee1; (**Figure 1**)[9,10] and has demonstrated significant antitumor activity both alone and in combination with doxorubicin, paclitaxel, and carboplatin in several solid tumors including in combination with gemcitabine in OS models (SJSA-1) (**Figure 2**).[11]
- ZN-c3 has also demonstrated single-agent activity in phase 1 dose-escalation studies in solid tumors.[11]
- ZN-c3 is being evaluated in an extensive solid tumor program both as a single agent and in combination with chemotherapies (NCT04516447) and targeted therapies, including niraparib (NCT05198804) and encorafenib/cetuximab.

Figure 1. Mechanism of action of ZN-c3[10]



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

Figure 2. Suppression of tumor growth with ZN-c3 plus gemcitabine[11]



d, day; ip, intraperitoneal; po, oral; QD, once daily; QW, once weekly.

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ACKNOWLEDGEMENTS

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METHODS

Phase 1 single-arm, open-label, multicenter, dose escalation study **(Figure 3).**

Figure 3. Study design

Key Eligibility Criteria:

- Age ≥12 years
- Relapsed or metastatic OS, failed SOC, and no known curative therapy (or not tolerated)
- Measurable disease per RECIST v1.1
- Adequate hematological and organ function
- ECOG PS ≤2 (Lansky ≥ 50%)
- No prior treatment with a Wee1 inhibitor

Primary objective:

- Safety, tolerability, MTD and RP2D of ZN-c3 in combination with gemcitabine

Additional objectives:

- Preliminary antitumor activity

Dose Escalation
• 3+3 design • 3-6 subjects/cohort

	Gemcitabine	ZN-c3
DL 1	1000 mg/m²	300 mg QD
DL 0	1000 mg/m²	200 mg QD
DL -1	800 mg/m²	150 mg QD
DL -2	800 mg/m²	150 mg 5/2

Dose expansion

DL, dose level; IV intravenous.

Treatment:
Gemcitabine: IV Days 1 and 8 of each 21-day cycle
ZN-c3: orally with a meal in 21-day cycles

DL, dose level; ECOG; Eastern cooperative Oncology Group; IV intravenous; MTD, maximum tolerated dose; PS, performance status; QD, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumours 1.1; RP2D, recommended phase 2 dose; SOC, standard of care.

Figure 4: Subject Flow

Screening (28 days) → Cycle 1 (21 days) DLT observation → Treatment until PD, AE, withdrawal of consent, investigator decision Disease assessment Q6W → Safety F/U (30 days after last dose) → Disease assessment F/U → Survival F/U (Q12W)

AE, adverse event; F/U, follow-up.

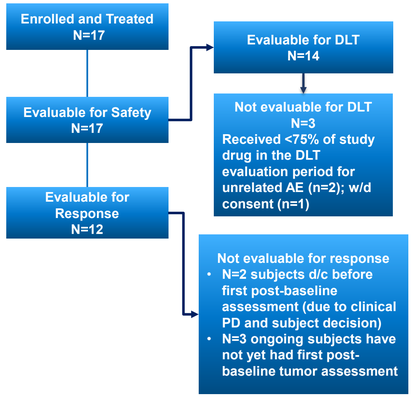
RESULTS

SUBJECTS: ENROLLMENT AND DISPOSITION

17 subjects enrolled and treated:

- 17 evaluable for safety (received at least 1 dose of study drug starting prior to data cutoff of October 24, 2022).
- 14 evaluable for DLT (completed the DLT period and received ≥75% of the planned dose or discontinued due to AE prior to completing).
- 12 evaluable for response (had baseline and at least 1 postbaseline tumor assessment) (**Figure 5**).
- 9 subjects d/c treatment: PD (n=6); AE (n=2); subject decision (n=1).
- 3 subjects died during study (all due to PD).

Figure 5. Subject disposition



AE, adverse event; d/c, discontinued; DLT, dose-limiting toxicity; PD, progressive disease; w/d withdrawn.

DEMOGRAPHICS

Men (n=10); median age of 27 yrs (range [15-76]). The median number of prior lines of systemic therapy was 3 (range [1-7]).

RESULTS

SAFETY: Table 1. Treatment-related AEs (occurring in ≥10% of total subjects)

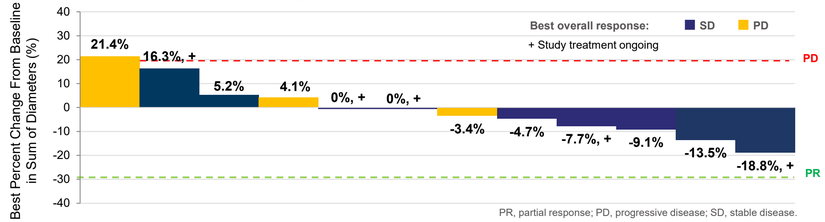
Adverse Events	ZN-c3 200 mg QD + Gem 1000 mg/m² (N=9), n (%)		ZN-c3 150 mg QD + Gem 800 mg/m² (N=5), n (%)		ZN-c3 150 mg Intermittent (5/2) + Gem 800 mg/m² (N=3), n (%)		Total (N=17), n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any event	8 (88.9)	6 (66.7)	5 (100)	3 (60.0)	1 (33.3)	0	14 (82.4)	9 (52.9)
Pyrexia	3 (33.3)	0	0	0	1 (33.3)	0	4 (23.5)	0
Platelet count decreased/thrombocytopenia	6 (66.7)	4 (44.4)	2 (40.0)	2 (40.0)	0	0	8 (47.1)	6 (35.3)
Fatigue	4 (44.4)	1 (11.1)	1 (20.0)	0	0	0	5 (29.4)	1 (5.9)
Nausea	4 (44.4)	0	1 (20.0)	0	0	0	5 (29.4)	0
Rash	3 (33.3)	1 (11.1)	2 (40.0)	0	0	0	5 (29.4)	1 (5.9)
Diarrhea	2 (22.2)	0	2 (40.0)	1 (20.0)	0	0	4 (23.5)	1 (5.9)
Vomiting	4 (44.4)	0	0	0	0	0	4 (23.5)	0
ALT increased	3 (33.3)	0	0	0	0	0	3 (17.6)	0
Anemia	1 (11.1)	1 (11.1)	2 (40.0)	1 (20.0)	0	0	3 (17.6)	2 (11.8)
AST increased	3 (33.3)	1 (11.1)	0	0	0	0	3 (17.6)	1 (5.9)
Dyspnea	3 (33.3)	2 (22.2)	0	0	0	0	3 (17.6)	2 (11.8)
Constipation	2 (22.2)	0	0	0	0	0	2 (11.8)	1 (5.9)
Headache	2 (22.2)	0	0	0	0	0	2 (11.8)	0
Neutropenia	2 (22.2)	2 (22.2)	1 (20.0)	1 (20.0)	0	0	3 (17.6)	3 (17.6)
White blood cell decreased	1 (11.1)	1 (11.1)	1 (20.0)	0	0	0	2 (11.8)	1 (5.9)
Conjunctival hemorrhage	0	0	1 (20.0)	0	0	0	1 (5.9)	0
Decreased appetite	0	0	1 (20.0)	1 (20.0)	0	0	1 (5.9)	1 (5.9)
Hypocalcemia	0	0	1 (20.0)	0	0	0	1 (5.9)	0
Lymphopenia	0	0	1 (20.0)	1 (20.0)	0	0	1 (5.9)	1 (5.9)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Gem, gemcitabine; QD, once daily.

PRELIMINARY ANTITUMOR ACTIVITY

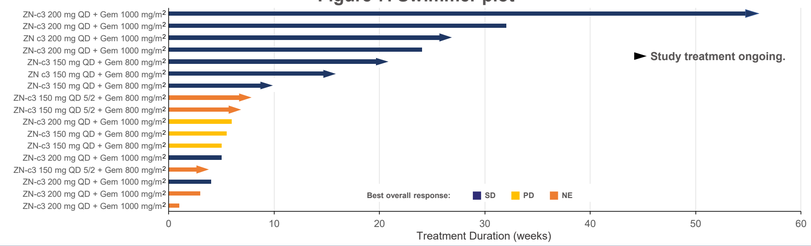
- 9 of 12 subjects (75%) evaluable for efficacy achieved best overall response of stable disease (SD) (**Figure 6**).
- 4 subjects out of the 12 evaluable for event-free survival (EFS) at 18 weeks demonstrated SD at the 18-week tumor assessment; corresponding to 33% EFS at 18 weeks. Swimmer plot is shown in **Figure 7.**

Figure 6. Best overall responses



PR, partial response; PD, progressive disease; SD, stable disease.

Figure 7. Swimmer plot



CONCLUSION

- The preliminary data from this phase 1 dose escalation study of ZN-c3 + gemcitabine demonstrate a manageable safety profile with encouraging clinical activity in a heavily pretreated population of subjects with relapsed and/or metastatic OS.
- Preliminary antitumor activity (EFS at 18 weeks of ~33%) is encouraging given the historically poor outcomes for patients with relapsed/refractory OS (historical EFS at 18 weeks ~12%).
- The phase 1 portion of the study continues, and enrollment is ongoing.