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Safety and clinical activity of single-agent ZN-c3, an oral Wee1 inhibitor, in a Phase 1 trial in subjects with recurrent or advanced uterine serous carcinoma (USC)

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Disclosure Information

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I have the following relevant financial relationships to disclose:

Consultant for: AbbVie, Aduro Bio-Tech Inc., Alkermes, AstraZeneca, DebioPharm, eFFECTOR Therapeutics, F. Hoffman-La Roche Ltd., Genentech Inc. IBM Watson, Infinity Pharmaceuticals, Jackson Laboratory, Kolon Life Science, Lengo Therapeutics, OrigiMed, PACT Pharma, Parexel International, Pfizer Inc., Sumsung Bioepis, Seattle Genetics Inc., Tallac Therapeutics, Tyra Biosciences, Xencor, Zymeworks, Black Diamond, Biovica, Eisai, Immunomedics, Inflection Biosciences, Karyopharm Therapeutics, Loxo Oncology, Mersana Therapeutics, OnCusp Therapeutics, Puma Biotechnology Inc., Silverback Therapeutics, Spectrum Pharmaceuticals, Zentalis

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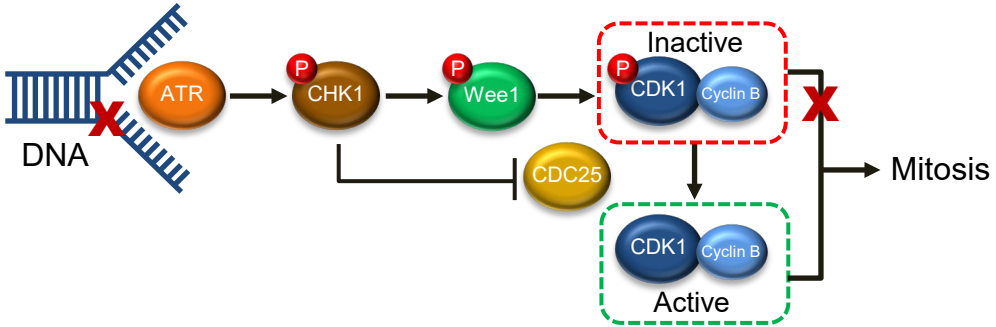
ZN-c3 Mechanism of Action

- ZN-c3 is a selective and orally bioavailable small molecule Wee1 inhibitor.[1]
- Wee1 is a crucial component of the G2/M cell cycle checkpoint that prevents cells from entering mitosis and allow repair of DNA damage before cell cycle progression.[2-4]

Figure 1[5]



- Wee1 inhibition causes cancer cells to proceed to mitosis without repairing DNA damage, resulting in premature mitotic entry and apoptosis.[6,7]
- ZN-c3 has demonstrated significant growth inhibition and induced apoptosis in vitro in multiple cell lines and antitumor activity in vivo in human xenograft tumor models.[1]

1. Huang PH, et al. J Med Chem. 2021 Sep 9;64(17):13004-13024. **2**. di Rora AGL, et al. *J Hematol Oncol*. 2020;13(1):126. **3**. Esposito F, et al. *Int J Mol Sci*. 202;22(19):10689. **4**. Mahajan K, Mahajn NP. *Trends Genet*. 2013;29(7):394-402. **5**. Matheson C, et al. *Trends Pharmacol Sci*. 2016;37(10):872-881. **6**. Duan Y, et al. *Oncol Lett*. 2018;16(4):5473-5481. **7**. Bukhari AB, et al. *Front Oncol*. 2022:12:8288684.

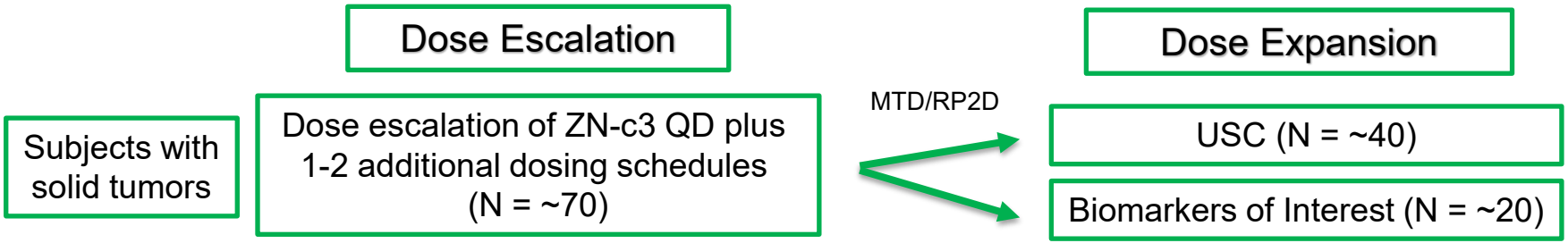
Uterine Serous Carcinoma

- Endometrial cancer is the most common gynecologic cancer in the United States[1]
- USC is an aggressive histologic type of endometrial cancer, accounting for 10% endometrial cancers but up to 40% of endometrial cancer deaths[2]
- Treatment options for USC include carboplatin and paclitaxel, with the addition of trastuzumab in ERBB2-amplified tumors,[3,4] as well as the recently approved regimen of pembrolizumab and lenvatinib[5,6]
- USC is molecularly characterized by frequent cell cycle alterations, and high levels of replication related stress[7]
- Recently, Liu et al. demonstrated clinical activity of Wee1 inhibitor adavosertib (AZD1775) in USC with an ORR of 29.4% and PFS of 6.1 months[7]

1. Siegel RL, Miller KD, Jemal A. *CA Cancer J Clin*. 2020;70(1):7-30. **2.** McGunigal M, et al. *Int J Gynecol Cancer*. 2017;27(1):85-92. **3**. Fader A, et al. *J Clin Oncol*. 2018;36:2044-2051. **4**. Fader AN, et al. *Clin Cancer Res*. 2020;26:3928-3935. **5**. Makker V, et al. *Lancet Oncol.* 2019;20(5):711-718. **6**. Makker V, et al. *J Clin Oncol.*2020;38(26):2981-2992. **7**. Liu JF, et al. J Clin Oncol. 2021;39(14):1531-1539.

PFS, progression-free survival; ORR, objective response rate; USC, uterine serous carcinoma.

ZN-c3-001 Study Schema and Endpoints



- As of January 21, 2022, a total of 80 subjects were enrolled across all tumor types with doses ranging from 25 mg to 450 mg QD
- ZN-c3 given at 2 dose levels in USC: 300 mg QD and 200 mg QD (just started) continuous dosing in 21-day cycle
- Study endpoints include:
  - Safety and tolerability of ZN-c3, determination of MTD based on a CRM model, and RP2D
  - Efficacy according to RECIST v 1.1: ORR, DOR, PFS, CBR
  - Investigate the plasma PK of ZN-c3
  - Evaluation of exploratory biomarkers

CBR, clinical benefit rate; DOR, duration of response; MTD, maximum tolerated dose; ORR, objective response rate; PO, oral; QD, once daily; PK, pharmacokinetics; PFS, progression-free survival; RP2D, recommended Phase 2 dose; RECIST, Response Evaluation Criteria In Solid Tumors; USC, uterine serous carcinoma.

Key Eligibility Criteria: USC Cohort

- Histologically confirmed recurrent or persistent USC
  - At least 10% serous component for mixed histology tumors
  - Carcinosarcomas excluded
- Measurable disease per RECIST version 1.1
- Prior lines
  - At least one prior platinum-based chemotherapy for advanced or metastatic USC
  - Chemotherapy administered with RT as radiosensitizer does not count as a systemic regimen
  - Subjects with known MSI/MMR status must have had prior therapy with PD-1/PD-L1 inhibitor either alone or in combination or not be a candidate for such therapy
  - No prior therapy with a Wee1 inhibitor
  - No overall line limit
- ECOG PS ≤ 2

ECOG PS, Eastern Cooperative Oncology Group performance status; MSI, Microsatellite Instability; MMR, Mismatch Repair; PD-1, Programmed Death-1; PD-L1, Programmed Death Ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors; RT, radiotherapy; USC, uterine serous carcinoma.

Patient Characteristics: USC Cohort

Baseline Characteristic	N = 14
Age in years, median (range)	65 (55-72)
Race, n (%)	
White	8 (57.1)
Black or African American	5 (35.7)
Asian	1 (7.1)
ECOG Performance Status, n (%)	
0	2 (14.3)
1	12 (85.7)
Stage at initial diagnosis, n (%)	
I	1 (7.1)
II	1 (7.1)
III	4 (28.6)
IV	8 (57.1)
Prior lines of systemic therapy for advanced/metastatic disease, median (range)	2 (1-5)
Number of prior lines for advanced/metastatic disease, n (%)	
1	5 (35.7)
2	4 (28.6)
3	2 (14.3)
4	2 (14.3)
≥ 5	1 (7.1)
Prior pembrolizumab + lenvatinib for advanced/metastatic disease, n (%)	8 (57.1)

- For USC, there were 14 subjects who received ZN-c3 at doses ≥ 300 mg QD
- Median duration of treatment was 12.4 weeks (range, 2-36 weeks)

ECOG, Eastern Cooperative Oncology Group; QD, once daily; USC, uterine serous carcinoma.

All AEs and Treatment-Related AEs for ZN-c3 at 300 mg (≥3 events) all tumors

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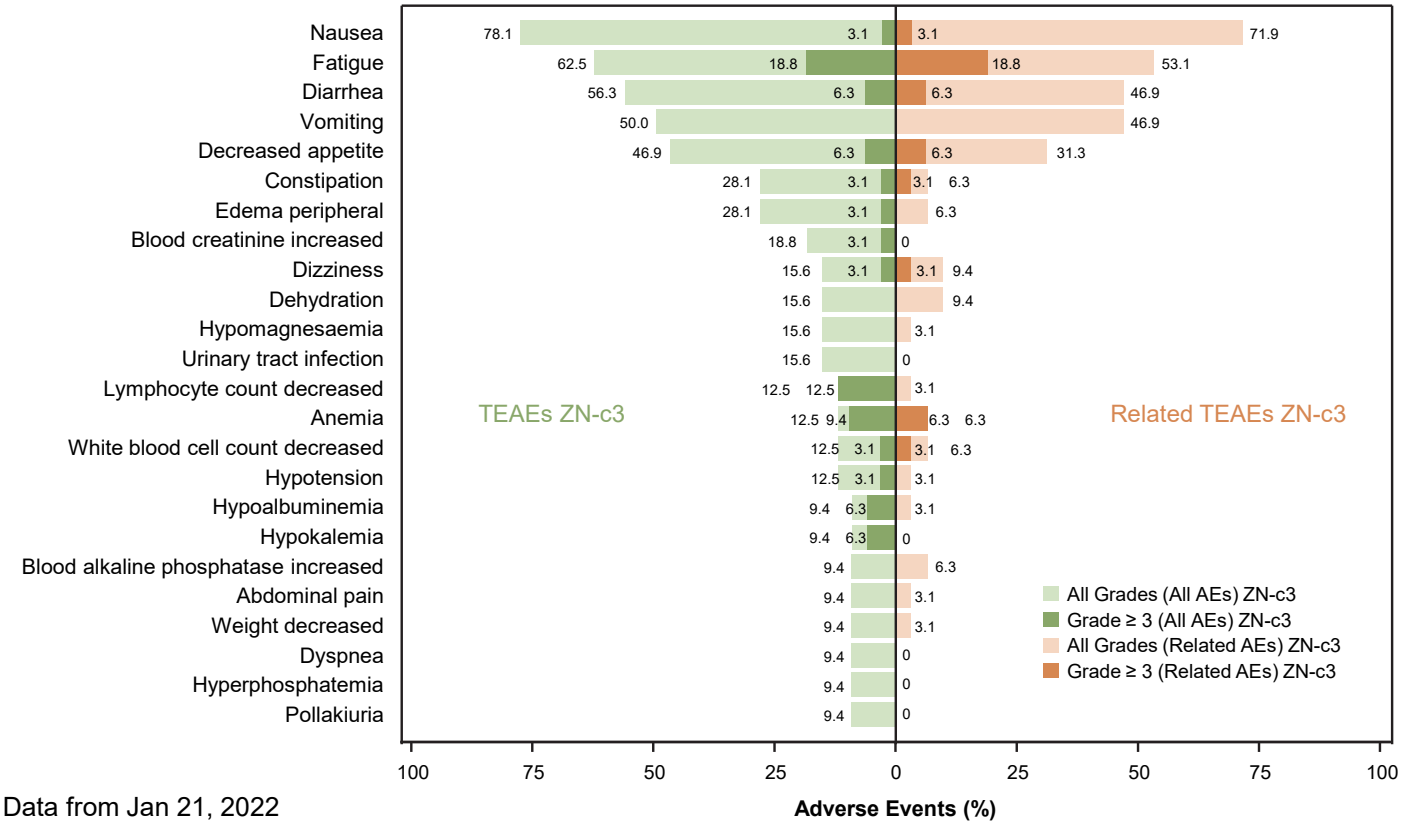


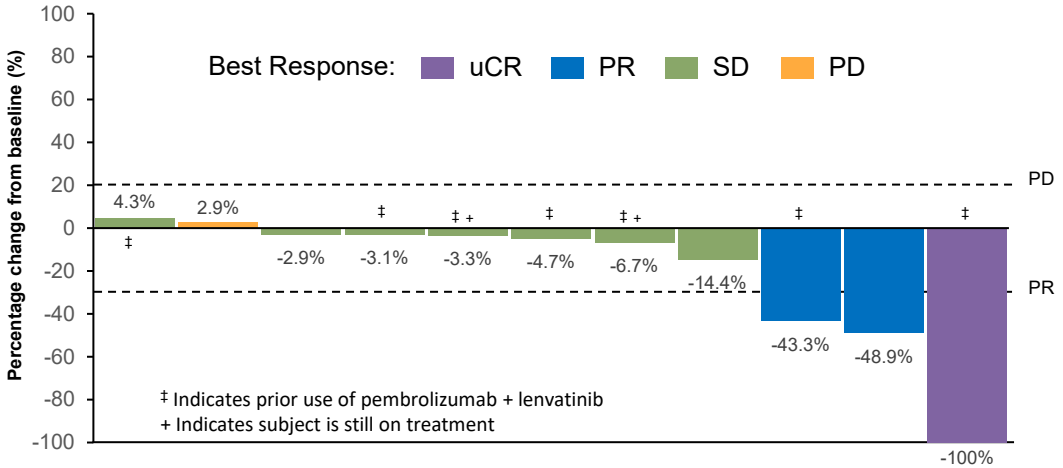
Data from Jan 21, 2022
N = 32

Dose modifications

Dose reductions, n (%)	
None	23 (71.9)
1	5 (15.6)
2	4 (12.5)
Dose interruptions, n (%)	
Yes	13 (40.6)
No	19 (59.4)
Dose discontinuations due to AEs, n (%)	3 (9.4)
Relative Dose Intensity	
Median	100%
Mean	88.3%

Clinical Activity: Response Rate

Best Overall Response	N = 11† n (%)
Complete Response (unconfirmed)*	1 (9.1)
Partial Response (confirmed)	2 (18.2)
Stable Disease	7 (63.6)
≥ 12 weeks	4 (36.3)
< 12 weeks	3 (27.3)
Progressive Disease	1 (9.1)
Objective Response Rate (95% CI = 6.0%, 61.0%)	3 (27.3)
DCR (CR + PR + SD) (95% CI = 58.7%, 99.8%)	10 (90.9)
mPFS	4.2 months



†Subjects with measurable disease and at least 1 post-baseline tumor assessment
*The BOR for this subject is cPR

BOR, best overall response; cPR, confirmed partial response; DCR, disease control rate; mPFS, median progression free survival; PD, progressive disease; PR, partial response; SD, stable disease; uCR, unconfirmed complete response.

Summary of Clinical Activity

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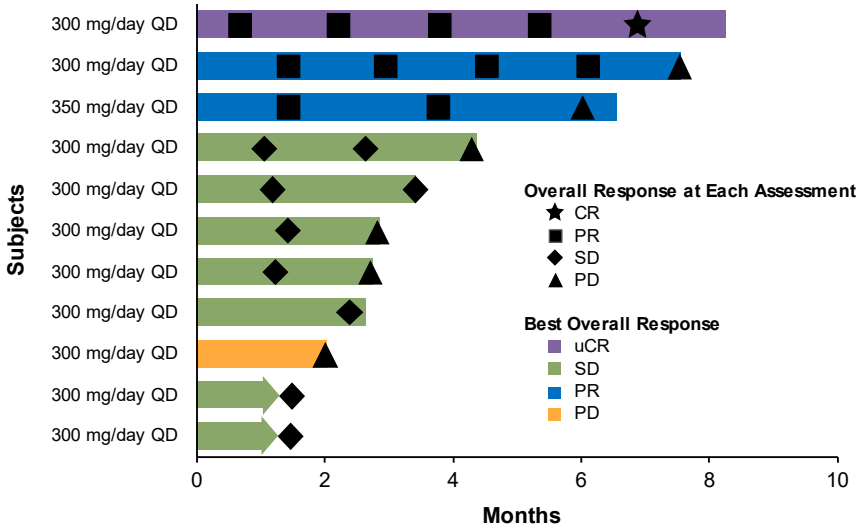
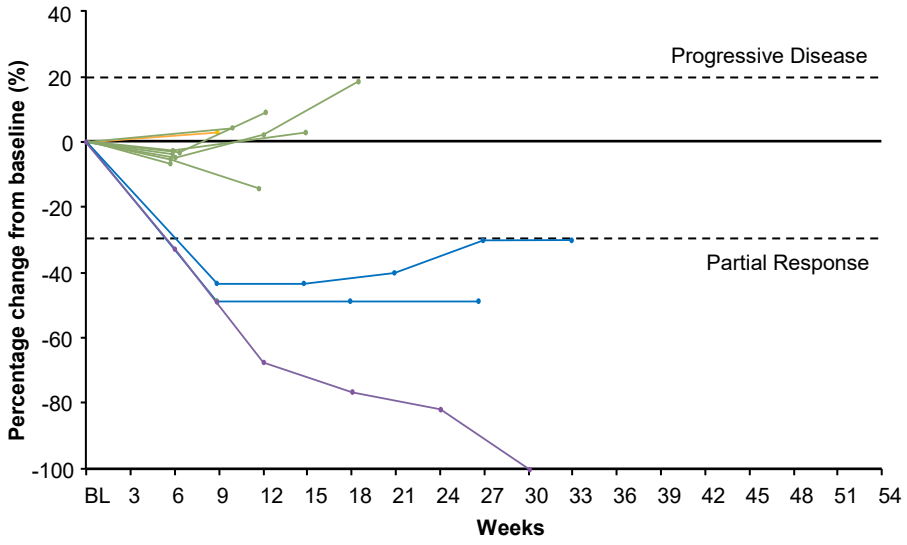




Median duration of response for 3 responders: 5.55 months (95% CI, 4.11 - not available)

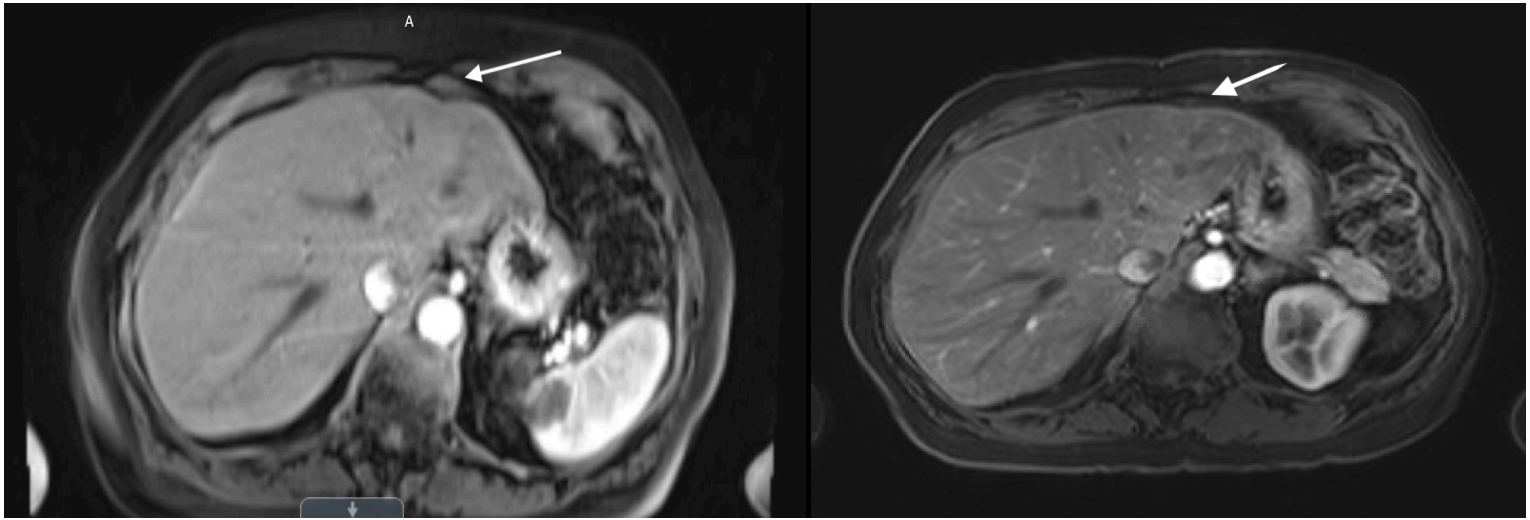
CI, confidence interval; cPR, confirmed partial response; CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; uCR, unconfirmed complete response.

Responder #1: Overall Summary

- 72-year-old, White female, stage IV USC, metastases to peritoneum and lymph node, ECOG PS 1
- 2 prior lines of therapy in the advanced/metastatic setting
- ZN-c3 starting dose: 350 mg QD in December 2020
  - The subject remained on the study drug for 199 days until radiologic disease progression
- CA-125 decreased from 36 U/mL at baseline to a minimum of 12 U/mL after ~3 months of treatment
- TP53 mutation
- Confirmed PR with 49% reduction overall

CA-125, cancer antigen 125; CISH, chromogenic in situ hybridization; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor 2; IHC, immunohistochemistry; MSS, microsatellite stability; pMMR, proficient mismatch repair; PR, partial response; QD, once daily; TP53, tumor protein 53; USC, uterine serous carcinoma.

Responder #1: Baseline and Follow-up Abdominal Imaging



Baseline: November 2020

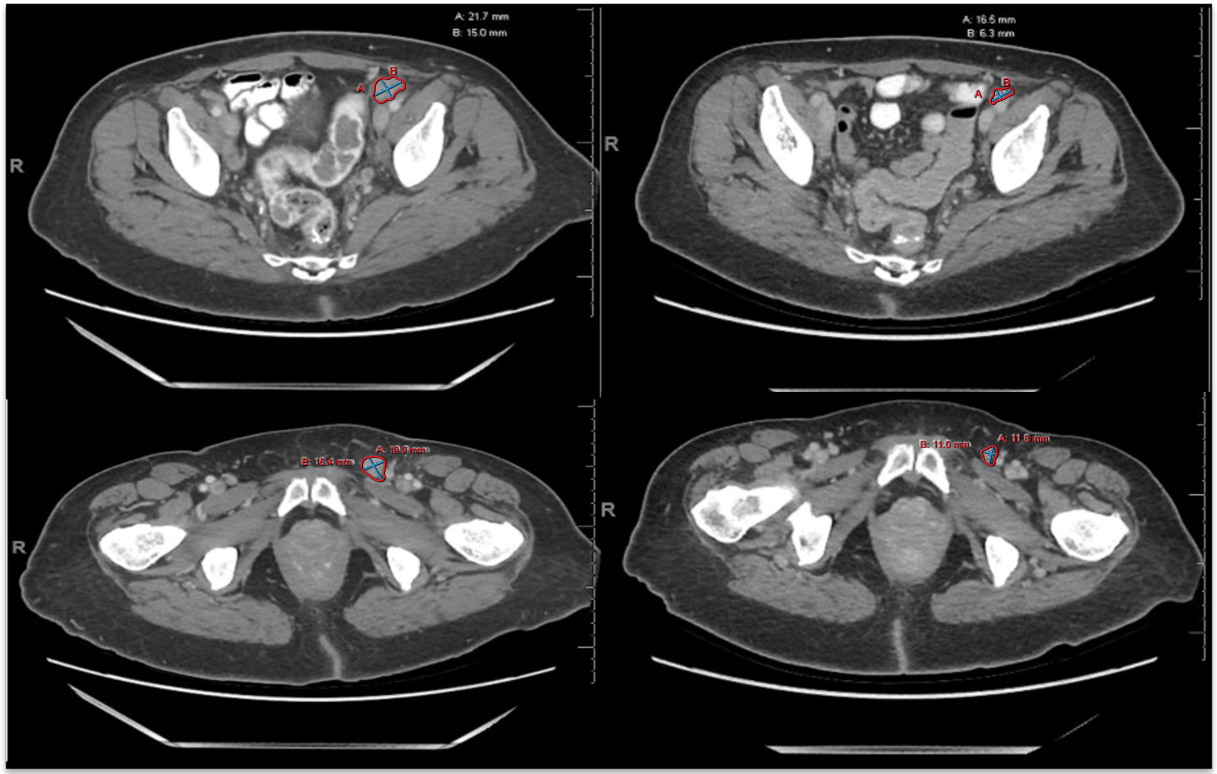
2nd restaging: April 2021

Responder #2: Overall Summary

- 69-year-old, African American female, Stage IV USC, metastases to lymph node and lung, ECOG PS 0
- 4 prior lines of therapy in the advanced/metastatic setting, including prior use of pembrolizumab plus lenvatinib
- ZN-c3 starting dose: 300 mg QD in January 2021
  - The subject remained on the study drug for 230 days until radiologic disease progression
- CA-125 decreased from 440 U/mL at baseline to <50 U/mL after 2 months of treatment
- TP53 mutation
- Confirmed PR with 43% reduction overall

CA-125, cancer antigen 125; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor; MMR, mismatch repair; MSI, microsatellite instability; PR, partial response; QD, once daily; TP53, tumor protein 53; USC, uterine serous carcinoma.

Responder #2: Baseline and Follow-up Peritoneum Imaging



Baseline: January 2021

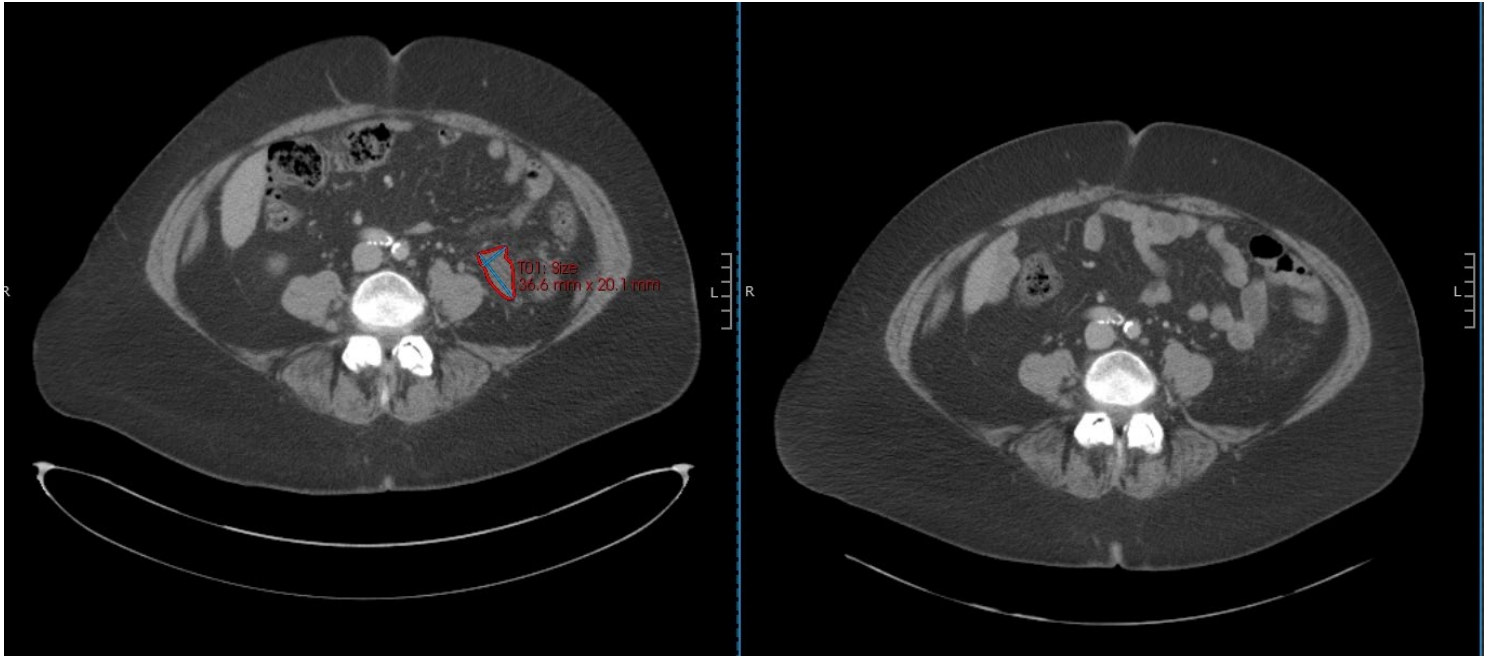
1st restaging: March 2021

Responder #3: Overall Summary

- 60-year-old, White female, Stage IV USC, metastases to peritoneum, ECOG PS 1
- 2 prior lines of therapy in the advanced/metastatic setting, including prior use of pembrolizumab plus lenvatinib
- ZN-c3 starting dose: 300 mg QD in April 2021
  - The subject remained on the study drug for 252 days until clinical disease progression
- CA-125 was not collected at baseline
- No TP53 mutation detected (liquid biopsy)
- Unconfirmed CR with 100% reduction overall

CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor 2; MSS, microsatellite stability; pMMR, proficient mismatch repair; QD, once daily; TP53, tumor protein 53; USC, uterine serous carcinoma.

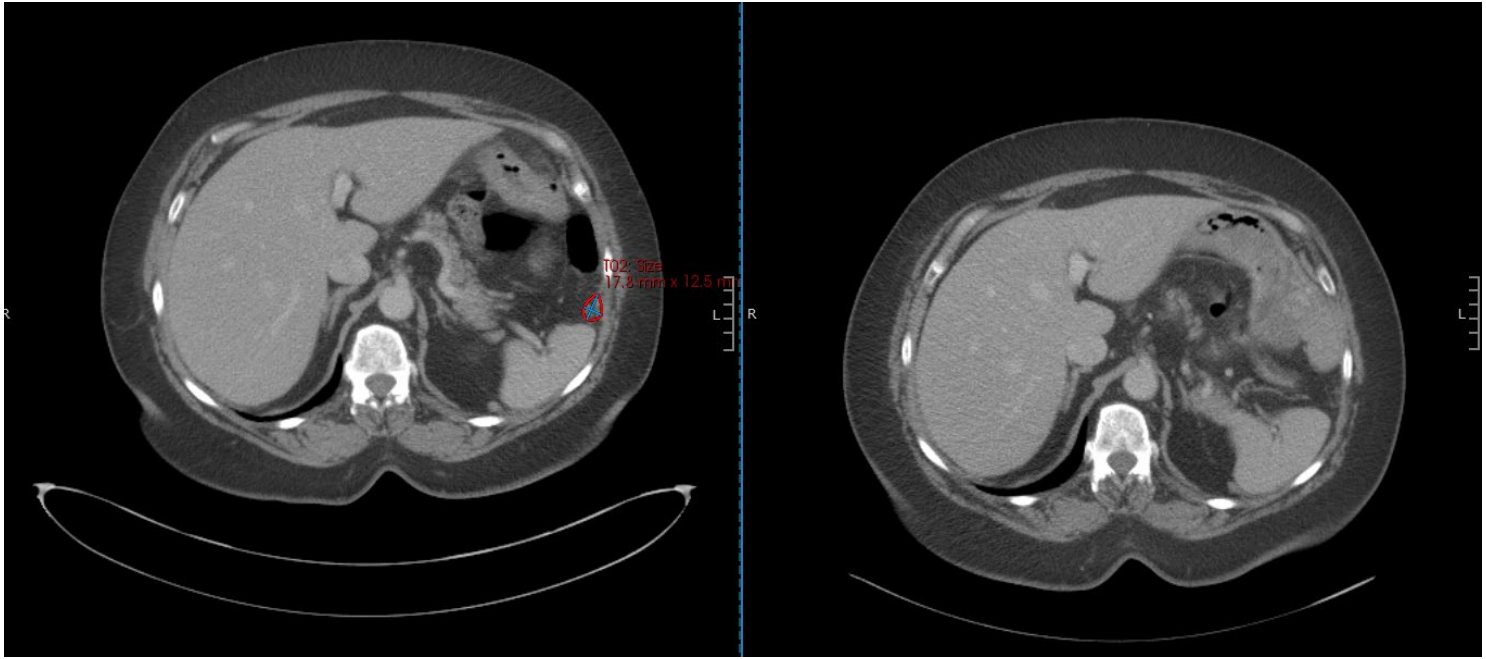
Responder #3: Baseline and Follow-up Peritoneum Imaging



Baseline: April 2021

5th restaging: November 2021

Responder #3: Baseline and Follow-up Peritoneum Imaging



Baseline: April 2021

5th restaging: November 2021

Conclusions

- The dose expansion study in USC subjects is still enrolling at both 200 mg and 300 mg QD dose levels
- Genomic data currently being analyzed
- ZN-c3 appears to be safe and well-tolerated as a single agent and demonstrated clinical activity in subjects with recurrent or advanced USC
  - Main AEs (upper GI toxicity) addressed with prophylactic antiemetic treatment
  - Low rate of myelosuppression at 300 mg QD continuous dosing
- Preliminary efficacy in USC is encouraging and will be confirmed in a dedicated phase 2 study (ZN-c3-004; NCT04814108) in this patient population

AE, adverse events; GI, gastrointestinal; QD, once daily; USC, uterine serous carcinoma.

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