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Creating Differentiated Therapies to Improve the Lives of Cancer Patients

Mid-Year Update
June 2021

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Data of Fulvestrant, RAD1901, Abemaciclib, Alpelisib, AZD1775, Venetoclax and Osimertinib presented in this presentation is based on evaluation of comparable proxy chemical compounds purchased from commercial sources rather than the pharmaceutical company commercializing or developing, as applicable, the compound.

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Mid-Year Update: Executive Summary

- Since AACR 2021, ZN-c3 has generated new clinical responses, further depth of responses, increased durability and improved hematological tolerability; representing one of the most promising clinical advances in DNA Damage Response (DDR) and synthetic lethality to date
- With broad utility across multiple large indications in both monotherapy and in combination, ZN-c3 is potentially both a first-in-class and best-in-class WEE1 inhibitor
- Following a recent EOP1 meeting with FDA, Zentalis initiated a registrational trial for ZN-c3 in USC, and will also start a novel biomarker-enabled trial by EOY - both trials have potential accelerated approval pathways
- ZN-c5's favorable tolerability data suggests potential for superiority amongst the oral SERDs, rivaling leading competition
- Clinical development plans for ZN-d5 (BCL-2) and ZN-e4 (EGFR) on track, expanding clinical and commercial opportunities with potential combinations

Zentalis is accelerating shareholder value accretion with the start of a registrational study with intent of an additional such trial by year end; both have potential for accelerated approvals

ZN-c3

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ZN-c3 WEE1 Inhibitor - Executive Summary

Since AACR 2021, ZN-c3 has generated new clinical responses, further depth of responses, increased durability and improved hematological tolerability; representing one of the most promising clinical advances in DNA Damage Response (DDR) and synthetic lethality to date

With broad utility across multiple large indications in both monotherapy and in combination, ZN-c3 is potentially both a first-in-class and best-in-class WEE1 inhibitor

Following a recent EOP1 meeting with FDA, Zentalis initiated a registrational trial for ZN-c3 in USC, and will also start a novel biomarker-enabled trial by EOY - both trials have potential accelerated approval pathways

- **Data presented at AACR 2021 continues to mature with both USC uPRs now confirmed PRs, and an additional uPR in a newly reported USC patient**
- **Further depth of tumor response and extended durability (8+ months) from exceptional responder observed**
- **Predictive biomarker may enable ZN-c3 to address tumor-agnostic indications**
- **Even lower overall severe hematological adverse event rates, with more patients enrolled on ZN-c3 since AACR 2021**
- **Two key designations (orphan drug and rare pediatric disease) received from FDA for ZN-c3 in combination with chemotherapy for osteosarcoma**
- **Two investigator-initiated trials (IIT) in GBM and TNBC with immunotherapy planned, in two very high unmet need indications**

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ZN-c3: Clinical Development Plan

Ongoing and Planned Clinical Programs

Phase 1

Solid Tumors: Monotherapy Dose Escalation and Expansion
Initial data presented at AACR 2021

Ovarian Cancer
Chemo Combination Ph 1b Study
Initiated 4Q 2020

Osteosarcoma
ZN-c3 + gemcitabine Ph 1/2 Study
Expected Initiation 3Q 2021

Ovarian Cancer
ZN-c3 + niraparib Ph 1/2 Study
Expected Initiation 4Q 2021

Phase 2

Uterine Serous Carcinoma
Monotherapy Ph 2 Study
Initiated

Predictive Biomarker Ph 2 Study
Expected Initiation 4Q 2021

Additional Clinical Studies

Monotherapy Study

Combination Study

Registrational trial with potential accelerated approval

Overview

- Initial Phase 1 monotherapy dose escalation and expansion data (1)
  - ZN-c3 was well-tolerated as a single agent
  - RP2D for ZN-c3 determined
  - ZN-c3 showed Exceptional Responses in heavily pre-treated subjects with advanced solid tumors
- Corresponding studies with Zentera in Greater China
- Two key designations now received from FDA for osteosarcoma for ZN-c3 combo with chemotherapy:
  - Orphan designation
  - Rare pediatric disease designation

(1) Reported at AACR 2021

ZN-c3: Expanding Indications through Investigator Initiated Studies

- New IITs to start:

  – Glioblastoma Multiforme: Preclinical study completed. Clinical study to commence in 2021

  – Triple Negative Breast Cancer: Combination with anti-PDL1 and chemotherapy. Clinical study to commence in 2022.

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ZN-c3 has the Potential to be Both First-in-Class and Best-in-Class

- **Key attributes to ZN-c3's Proof of Concept (POC) success:**
  1. Target biology known and validated
  2. Clinical results shown with monotherapy

- **ZN-c3's POC includes:**
  A. Determination of RP2D
  B. Evidence of relevant clinical activity in target populations
  C. Data on tolerability
  D. Strategy based on potential accelerated approvals in US

- **ZN-c3's POC has potential to lead to:**
  I. Multiple, large commercial opportunities as monotherapy and in combination

ZN-c3 has potential to be both first-in-class and best-in-class WEE1 inhibitor with broad market indications and path(s) to potential accelerated approval in US

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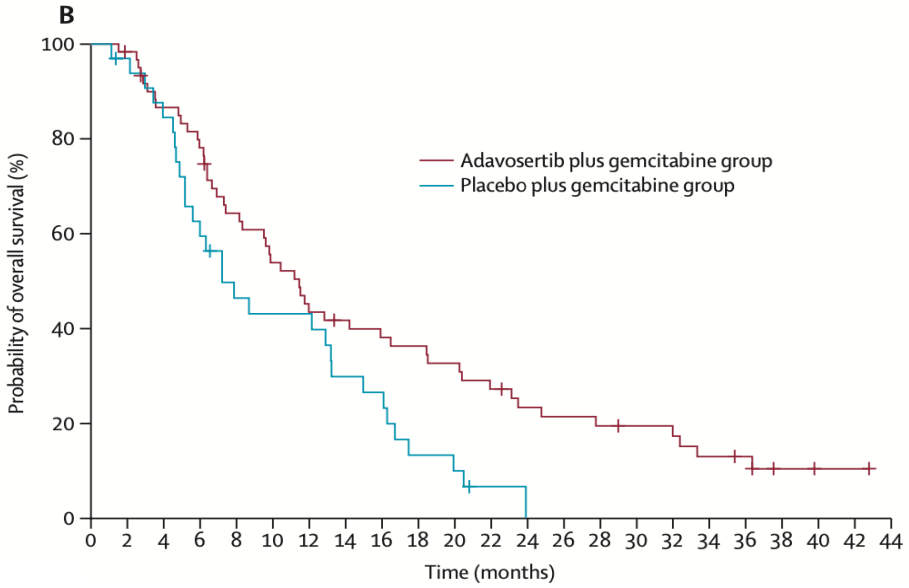
1. Target Biology Known and Validated

Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial

Stephanie Lheureux, Mihaela C Cristea, Jeffrey P Bruce, Swati Garg*, Michael Cabanero*, Gina Mantia-Smaldone, Alexander B Olawaiye, Susan L Ellard, Johanne I Weberpals, Andrea E Wahner Hendrickson, Gini F Fleming, Stephen Welch, Neesha C Dhani, Tracy Stockley, Prisni Rath, Katherine Karakasis, Gemma N Jones, Suzanne Jenkins, Jaime Rodriguez-Canales, Michael Tracy, Qian Tan, Valerie Bowering, Smitha Udagani, Lisa Wang, Charles A Kunos, Eric Chen, Trevor J Pugh, Amit M Oza*



similar results (p=0·007). Median overall survival at the time of data cutoff for the final analysis was 11·4 months (95% CI 8·2–16·5) in the adavosertib plus gemcitabine group versus 7·2 months (5·2–13·2) in the placebo plus gemcitabine group (HR 0·56 [95% CI 0·35–0·91]; log-rank p=0·017; figure 2). The proportion of

- **Publication in Lancet, Jan 23, 2021**
- **The inhibition of WEE1 has already been shown in a randomized double-blind, placebo-controlled study to exhibit a statistically significant overall survival advantage**
- **Rare for oncology drugs to show a survival advantage prior to approval**
- **Highly likely for a drug target to be approved if it shows a meaningful survival advantage (the "gold" standard)**

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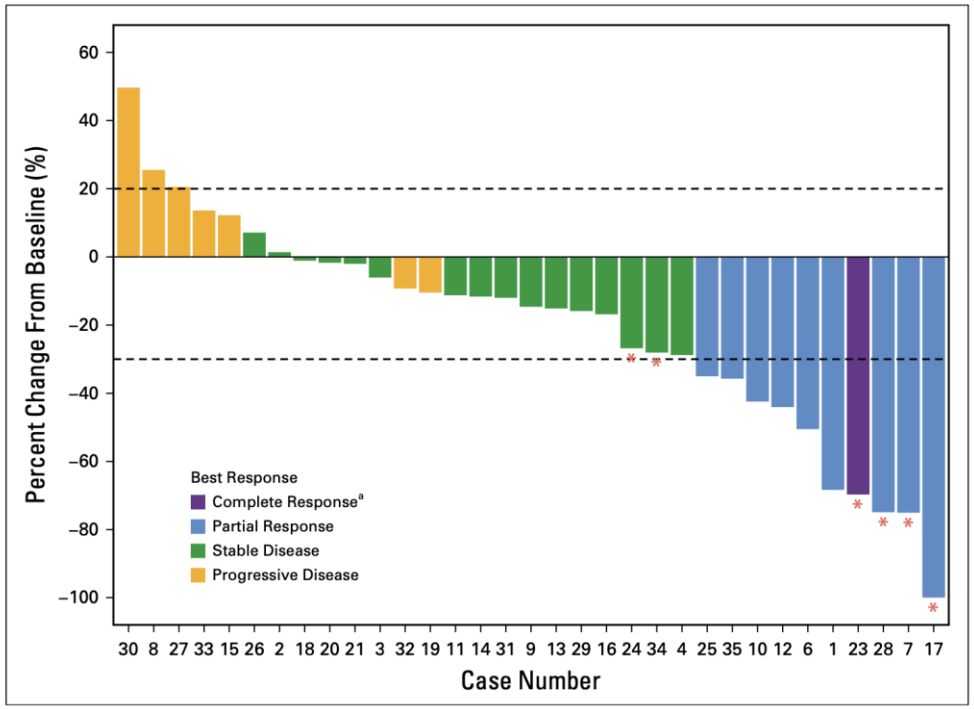
1. Target Biology Known and Validated

Phase II Study of the WEE1 Inhibitor Adavosertib in Recurrent Uterine Serous Carcinoma

Joyce F. Liu, MD, MPH[1]; Niya Xiong, MS[2]; Susana M. Campos, MD[1]; Alexi A. Wright, MD, MPH[1]; Carolyn Krasner, MD[1]; Susan Schumer, MD[1]; Neil Horowitz, MD[3]; Jennifer Veneris, MD, PhD[1]; Nabihah Tayob, PhD[2]; Stephanie Morrissey, RN, BSN[1]; Gabriela West, BA[1]; Roxanne Quinn, BA[1]; Ursula A. Matulonis, MD[1]; and Panagiotis A. Konstantinopoulos, MD, PhD[1]



RESULTS In 34 evaluable patients, 10 total responses (one confirmed complete response, eight confirmed partial responses, and one unconfirmed partial response) were observed with adavosertib monotherapy, for an ORR of 29.4% (95% CI, 15.1 to 47.5). Sixteen patients were progression-free at 6 months, for a PFS6 rate of 47.1% (95% CI, 29.8 to 64.9). Median PFS was 6.1 months, and median duration of response was 9.0 months.

- **Publication in JCO March 12, 2021**
- **A third party WEE1 inhibitor exhibited a 29% ORR in a Phase 2 study in very sick endometrial cancer patients with USC subtype (most of these women die within 5 years upon diagnosis)**
- **AZ has just started a registrational P2 study in USC with monotherapy dosing**

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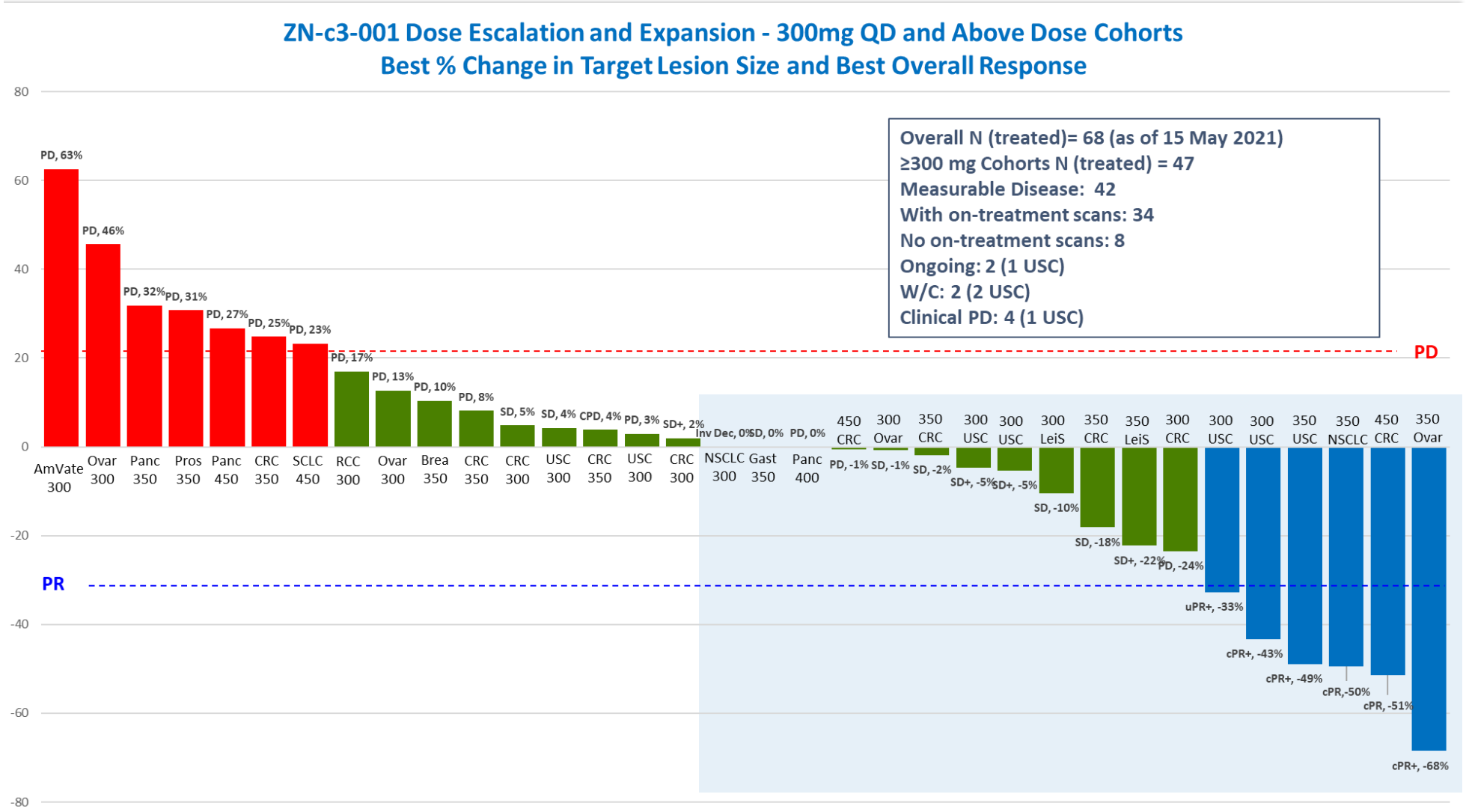
2. Evidence of Strong Clinical Activity Shown by ZN-c3



- **Clinically relevant responses seen in a refractory solid tumor untargeted all-comer population as monotherapy. Responses seen across four different tumor types signaling potential for broad oncology applicability**
- **We believe this is the first DDR drug (including ATM, ATR, CHK1/2, DNA-PK, or PARP) that has shown monotherapy responses in CRC and NSCLC pts (very difficult to treat)**
- **Currently 43% ORR (3/7) in USC pts[3]. AZD1775 observed a 29% ORR**
- **Exceptional responses seen were dramatic, unexpected and durable**

(1) 3 subjects with no treatment scans (CRC, USC, Pancreas), and experienced clinical progressive disease (CPD). + denotes treatment ongoing
(2) 3 confirmed Exceptional Responders PRs, including an additional confirmation of Exceptional Responder PR since AACR Presentation Press Release
(3) Waterfall as of 05/15/2021; both uPRs reported at AACR 2021 in USC are confirmed PRs. Newly reported uPR in USC is included. ORR based on radiographic responses.

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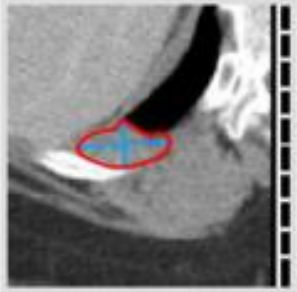
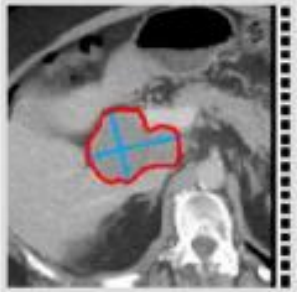
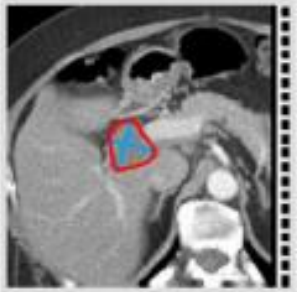
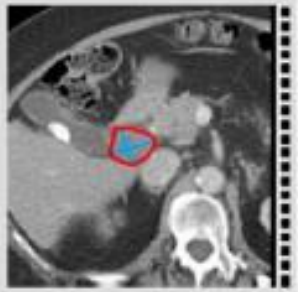
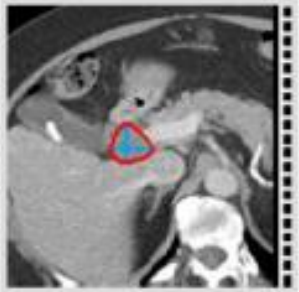
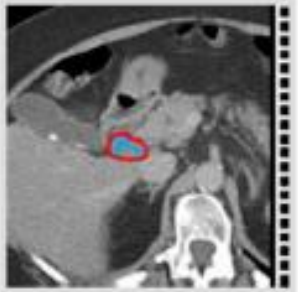
2. Exceptional Responder Clinical Update: Additional Scans Since AACR 2021 (Ovarian Cancer Exceptional Responder)

	Baseline (0 9/22/2020)	Follow-up 1 (11/24/2020)	Follow-up 2 (12/28/2020)	Follow-up 3 (03/01/2021)	Follow-up 4 (05/17/2021)
Target lesions					
T01 Pleura Pleura Size	 LA: 32.9 mm SA: 16.6 mm	Disappeared	Disappeared	Disappeared	Disappeared
T02 Peritoneum Peritoneum Size	 LA: 65.7 mm SA: 51.1 mm	 LA: 36.3 mm (-44.7% ΔP) SA: 34.0 mm (-33.5% ΔP)	 LA: 33.2 mm (-8.5% ΔP) SA: 27.2 mm (-20.0% ΔP)	 LA: 29.7 mm (-10.5% ΔP) SA: 27.6 mm (+1.5% ΔP)	 LA: 27.4 mm (-7.7% ΔP) SA: 18.9 mm (-31.5% ΔP)

All progress values are relative to their previous value (ΔP)

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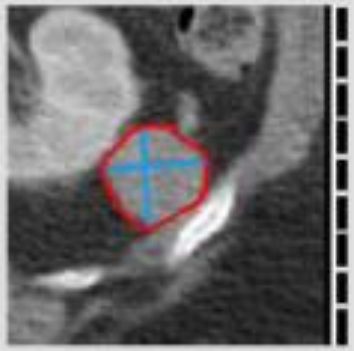
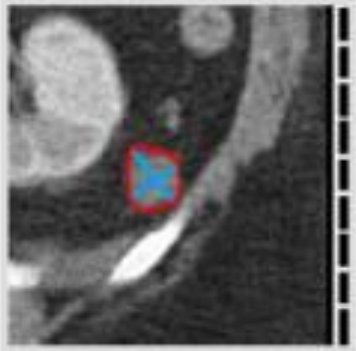
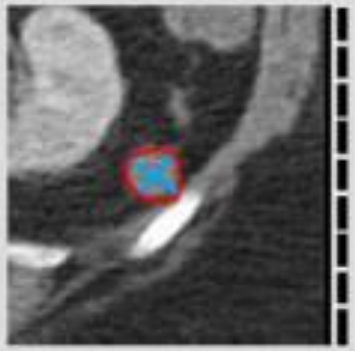
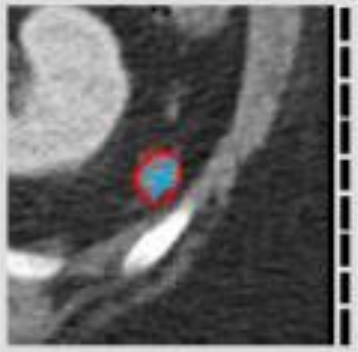
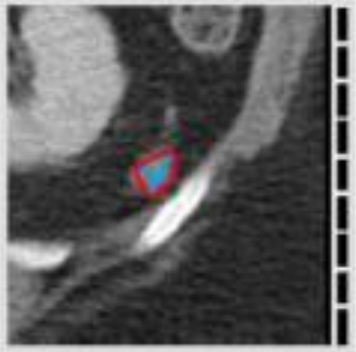
2. Exceptional Responder Clinical Update: Additional Scans Since AACR 2021 (Ovarian Cancer Exceptional Responder)

T03 Peritoneum
Peritoneum

Size

Baseline (0 9/22/2020)	Follow-up 1 (11/24/2020)	Follow-up 2 (12/28/2020)	Follow-up 3 (03/01/2021)	Follow-up 4 (05/17/2021)
				
LA: 28.2 mm SA: 26.7 mm	LA: 17.8 mm (-36.9% ΔP) SA: 14.9 mm (-44.2% ΔP)	LA: 16.3 mm (-8.4% ΔP) SA: 13.9 mm (-6.7% ΔP)	LA: 13.9 mm (-14.7% ΔP) SA: 11.0 mm (-20.9% ΔP)	LA: 12.7 mm (-8.6% ΔP) SA: 9.1 mm (-17.3% ΔP)

All progress values are relative to their previous value (ΔP)

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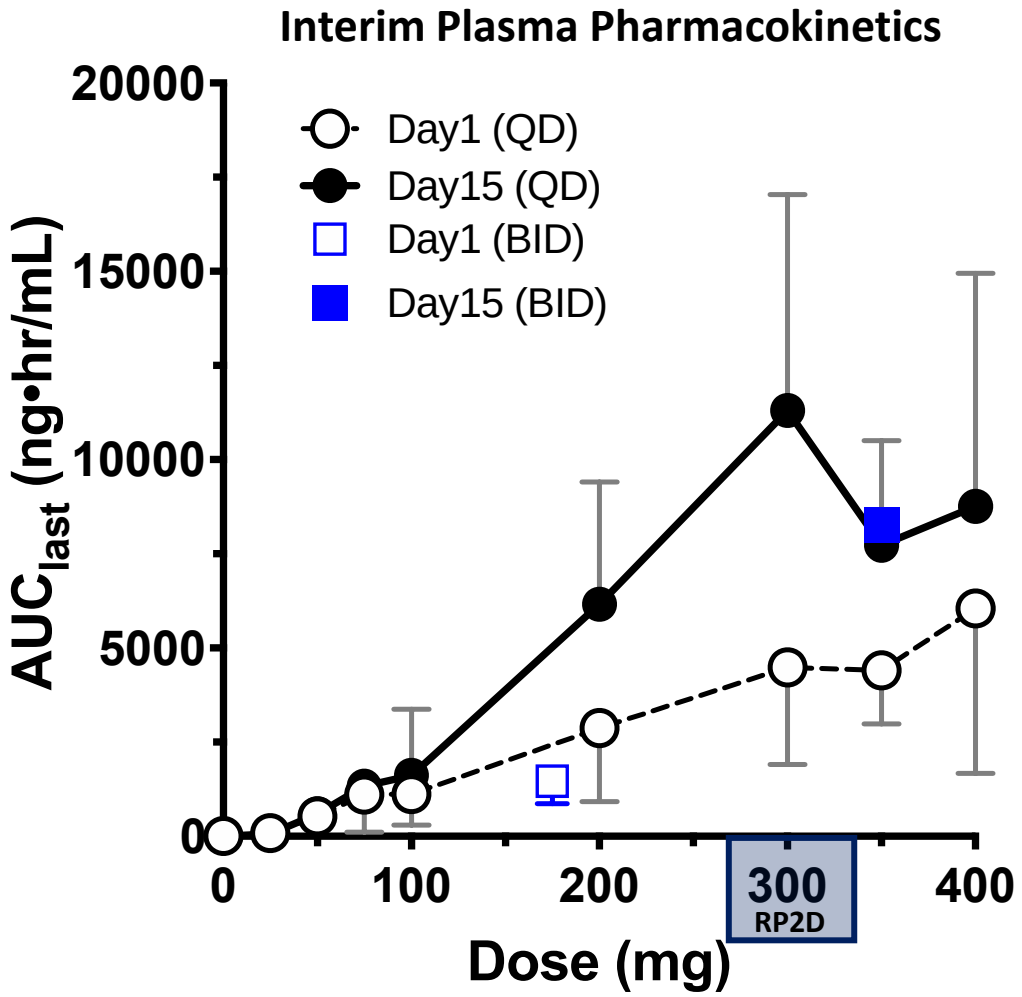
A. RP2D Selected



- Greater than dose proportional exposure up to 450 mg (not plotted)
- 1.87 to 2.50-fold accumulation at 200-350 mg dose
- No additional increase of exposure occurs beyond Day 15 (up to Cycle 6)
- 300 mg dose chosen as RP2D because it exhibited the highest mean AUC between 25-400 mg
- 300 mg dose was well-tolerated without dose reductions in majority of patients

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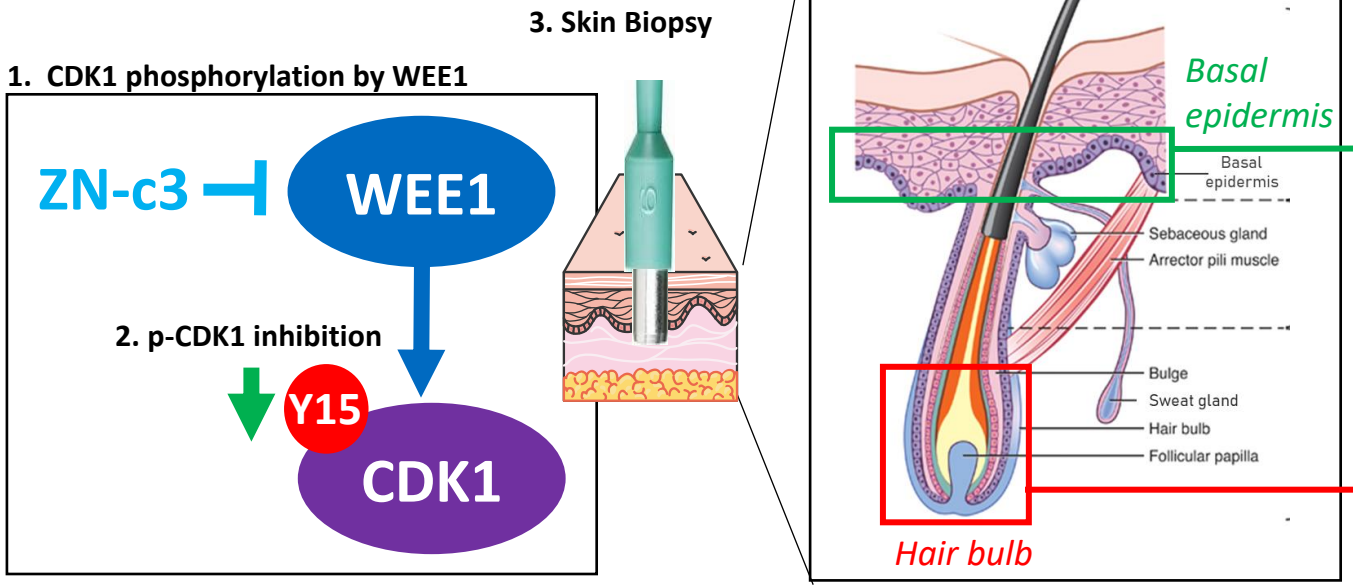
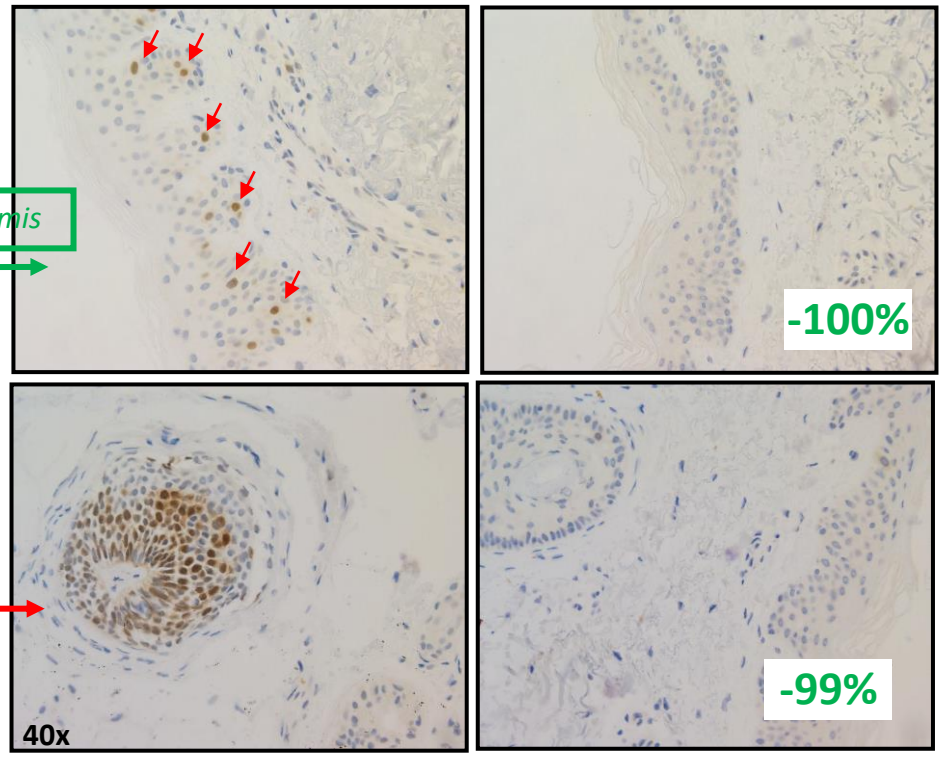
A. RP2D Selected (Cont.)

Confirmation of WEE1i Target Engagement in Surrogate Tissue

1. CDK1 phosphorylation (p-CDK1) is mediated by WEE1
2. Inhibition of WEE1 therefore will lead to inhibition of p-CDK1
3. Skin biopsies were performed at baseline (C1D1) and on-treatment (C1D15) to verify p-CDK1 levels, and hence level of target engagement of WEE1





Source: Drawing adapted from Servier Medical Art

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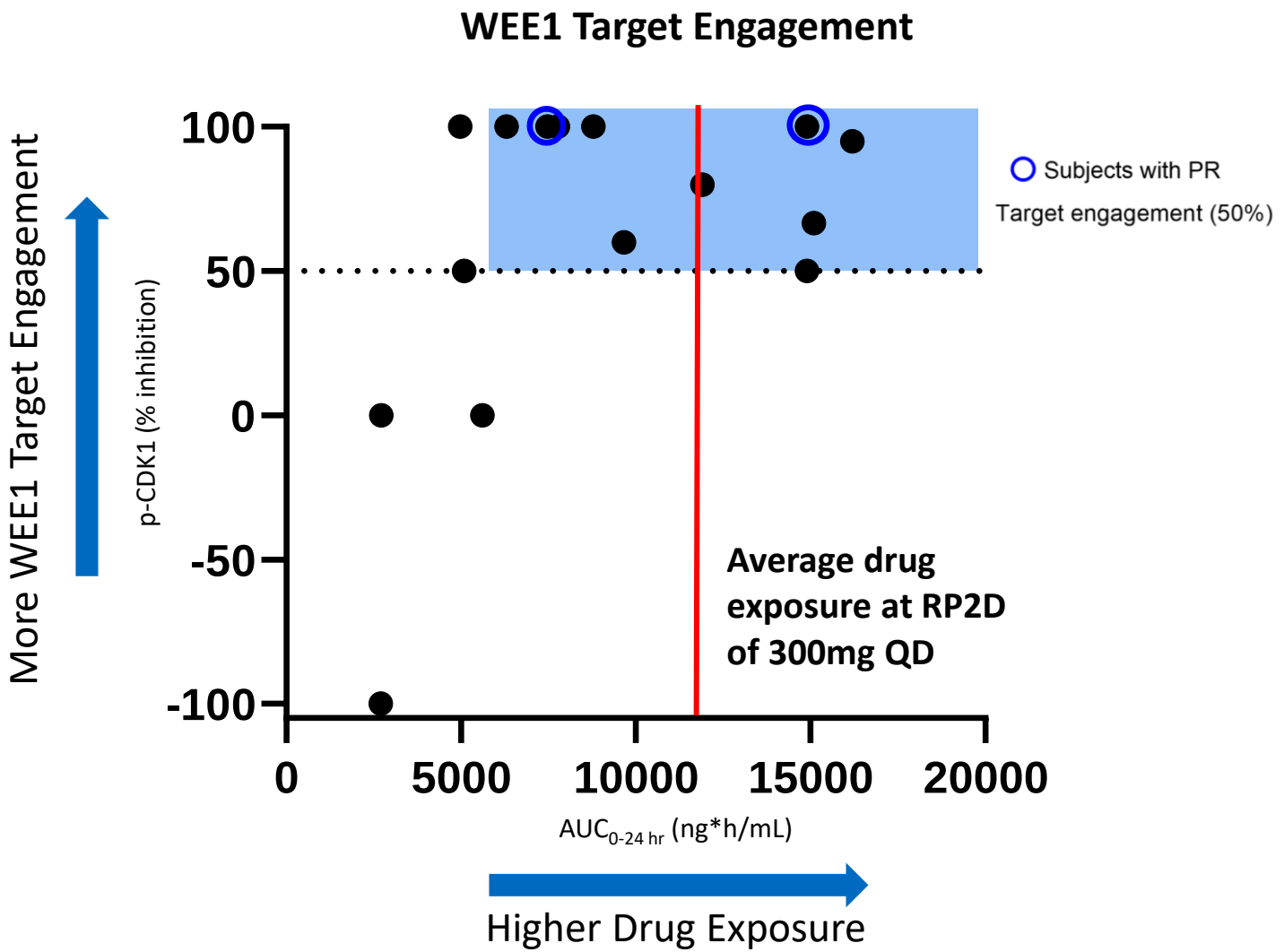
A. RP2D Selected (Cont.)



- **Inhibition of p-CDK1 demonstrated WEE1 target engagement**

  Increase in dose / drug exposure directly related to WEE1 target engagement

- **RP2D showed an AUC with excellent target engagement with p-CDK1 levels decreased at least by 50%**
- **In short, <u>RP2D showed highest AUC with excellent Pharmacodynamic data directly supportive of 300 mg QD</u>**

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B. Strong Comparative Efficacy Data of ZN-c3 vs AZD1775

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase I Study of Single-Agent AZD1775 (MK-1775), a Wee1 Kinase Inhibitor, in Patients With Refractory Solid Tumors

Khanh Do, Deborah Wilsker, Jiuping Ji, Jennifer Zlott, Tomoko Freshwater, Robert J. Kinders, Jerry Collins, Alice P. Chen, James H. Doroshow, and Shivaani Kummar

See accompanying article on page 3485

Khanh Do, Jennifer Zlott, Jerry Collins, Alice P. Chen, James H. Doroshow, and Shivaani Kummar, National Cancer Institute, Bethesda, MD; Deborah Wilsker, Jiuping Ji, and Robert J. Kinders, Leidos Biomedical Research, Frederick National Laboratory for Cancer Research, Frederick, MD; and Tomoko Freshwater, Merck Research Laboratories-Oncology, Boston, MA.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Presented at the 50th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, May 30-June 3, 2014.

A B S T R A C T

Purpose
Wee1 tyrosine kinase phosphorylates and inactivates cyclin-dependent kinase (Cdk) 1/2 in response to DNA damage. AZD1775 is a first-in-class inhibitor of Wee1 kinase with single-agent antitumor activity in preclinical models. We conducted a phase I study of single-agent AZD1775 in adult patients with refractory solid tumors to determine its maximum-tolerated dose (MTD), pharmacokinetics, and modulation of phosphorylated Tyr15-Cdk (pY15-Cdk) and phosphorylated histone H2AX (γH2AX) levels in paired tumor biopsies.

Patients and Methods
AZD1775 was administered orally twice per day over 2.5 days per week for up to 2 weeks per 21-day cycle (3 + 3 design). At the MTD, paired tumor biopsies were obtained at baseline and after the fifth dose to determine pY15-Cdk and γH2AX levels. Six patients with *BRCA*-mutant solid tumors were also enrolled at the MTD.

Results
Twenty-five patients were enrolled. The MTD was established as 225 mg twice per day orally over 2.5 days per week for 2 weeks per 21-day cycle. Confirmed partial responses were observed in two patients carrying *BRCA* mutations: one with head and neck cancer and one with ovarian cancer. Common toxicities were myelosuppression and diarrhea. Dose-limiting toxicities were supraventricular tachyarrhythmia and myelosuppression. Accumulation of drug ($t_{1/2}$ approximately 11 hours) was observed. Reduction in pY15-Cdk levels (two of five paired biopsies) and increases in γH2AX levels (three of five paired biopsies) were demonstrated.

Conclusion
This is the first report of AZD1775 single-agent activity in patients carrying *BRCA* mutations. Proof-of-mechanism was demonstrated by target modulation and DNA damage response in paired tumor biopsies.

- **Early study published in JCO Oct 20, 2015, enabling comparison head-to-head with ZN-c3's monotherapy refractory solid tumor study**
- **Due to tolerability issues for AZD1775 as monotherapy, MTD was established as 225 mg BID for 5 days per 21-day cycle vs ZN-c3's 300 mg QD continuous dosing**
- **ZN-c3 delivered 6.3 grams vs 2.25 grams per 21 days cycle for AZD1775 with better tolerability (~3x more drug with ZN-c3 at its RP2D)**
- **Zentalis has seen responses in four different tumor types including NSCLC, CRC, ovarian, and endometrial to date. AZ has not observed responses in CRC or NSCLC**
- **AZD1775's two PRs in USC were seen in BRCA mutant patients; ZN-c3 responses were seen in BRCA wildtype patients**

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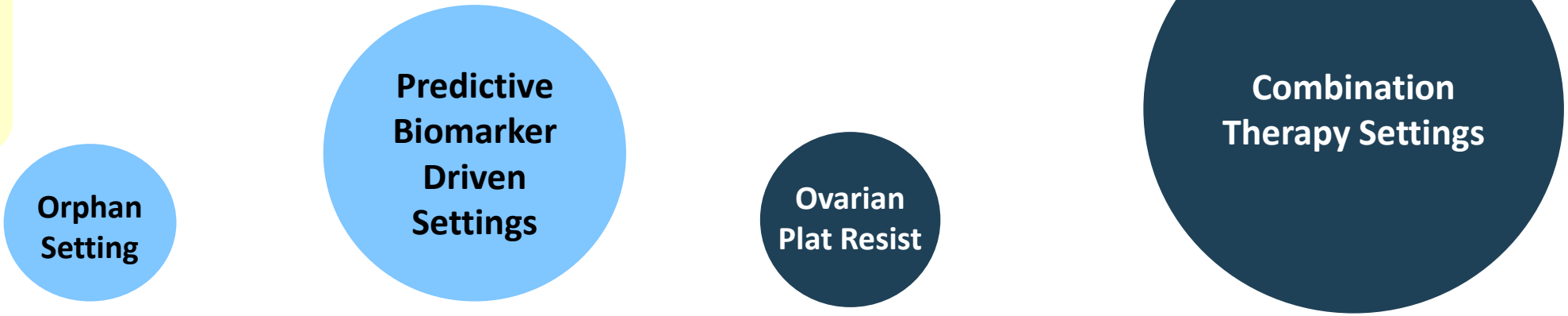
B. Compelling Data for ZN-c3 vs AZD1775 (Cont.)

Comparative Data for ZN-c3 vs AZD1775

Additional uPR in USC newly reported June 3, 2021



Drug Setting	Single Agent	Single Agent	Combinations with ZN-c3	Combinations
Representative Indication(s)	Uterine Serous Carcinoma	Biomarker Identified "Exceptional Responders" Across Tumor Types	Ovarian Plat Resistant	PARP Combo Chemo Combos Immunotherapy Combo Proprietary Combos
ZN-c3	ORR 43% (3/7)[1]	ORR 100% (3/3)	Expecting Initial Data 2022	Clinical Studies Initiated in PARP and Chemo combos Clinical Studies Planned in I/O Combos
AZD1775	ORR 29% (6/21)[2]	AZ Does Not Possess Biomarker	Demonstrated Survival Benefit[3]	Conducted 49 Clinical Trials with WEE1 Positive ORRs in PARP Combos[4] Positive ORRs in Chemo Combos[4]

(1) Non-head-to-head comparison. Results of a head-to-head comparison may differ significantly from those set forth herein. In addition, because our Phase 1 clinical trial for ZN-c3 and the Adavosertib clinical trials were separate trials, differences between the results of the trials may not be statistically or clinically meaningful. Data as of 05/15/2021; both uPRs reported at AACR 2021 in USC are confirmed PRs. Newly reported uPR in USC is included in ORR. ORR based on radiographic responses.

(2) Liu JF et al. *J Clin Oncol.* 2021 Mar 11:JCO2003167

(2) Lheureux S., Lancet (2021). Addition of a WEE1 to Gemcitabine shows a statistically significant improvement in mOS over Gemcitabine with placebo (HR=0.56, P=0.017)

(3) J Clin Oncol. 2019;37:2643-2650; Clin Cancer Res 26:4767-4776, 2020; J Clin Oncol. 2016;34:4354-4361

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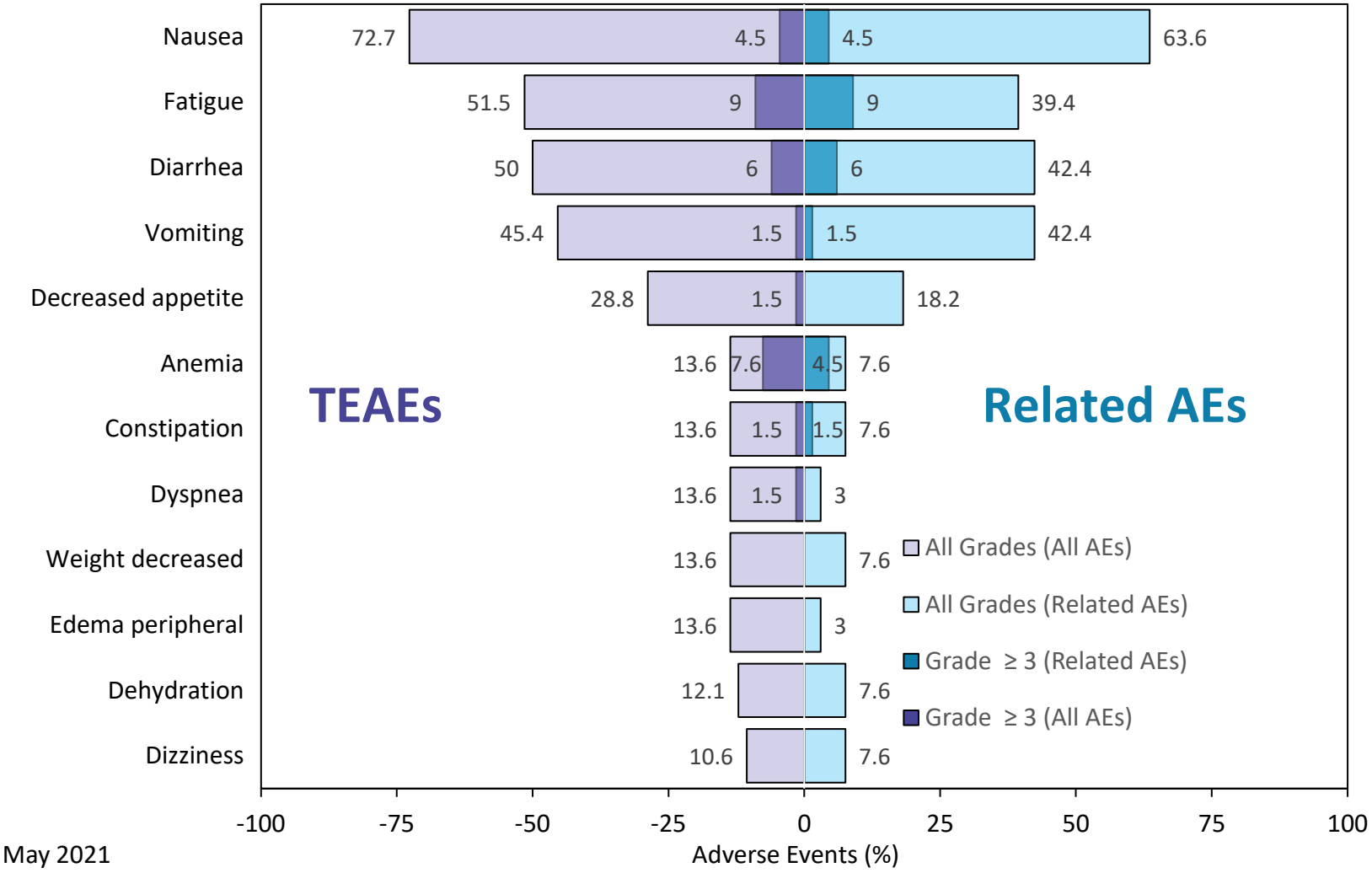
C. Tolerability Profile of ZN-c3



As of 14 May 2021

- **AEs (≥10%) for all dose levels (25 mg QD to 450 mg QD)**
- **In N=66, most AEs were of Grade 1/2 nature with GI symptoms**
- **Grade 1/2 GI symptoms particularly nausea managed well with antiemetic use; GI symptoms abated after first cycle**
- **Majority of patients tolerated RP2D without dosing change**
- **Grade 3/4 AEs were of single percentage point nature**

Promising tolerability data suggest the potential for a wide therapeutic window

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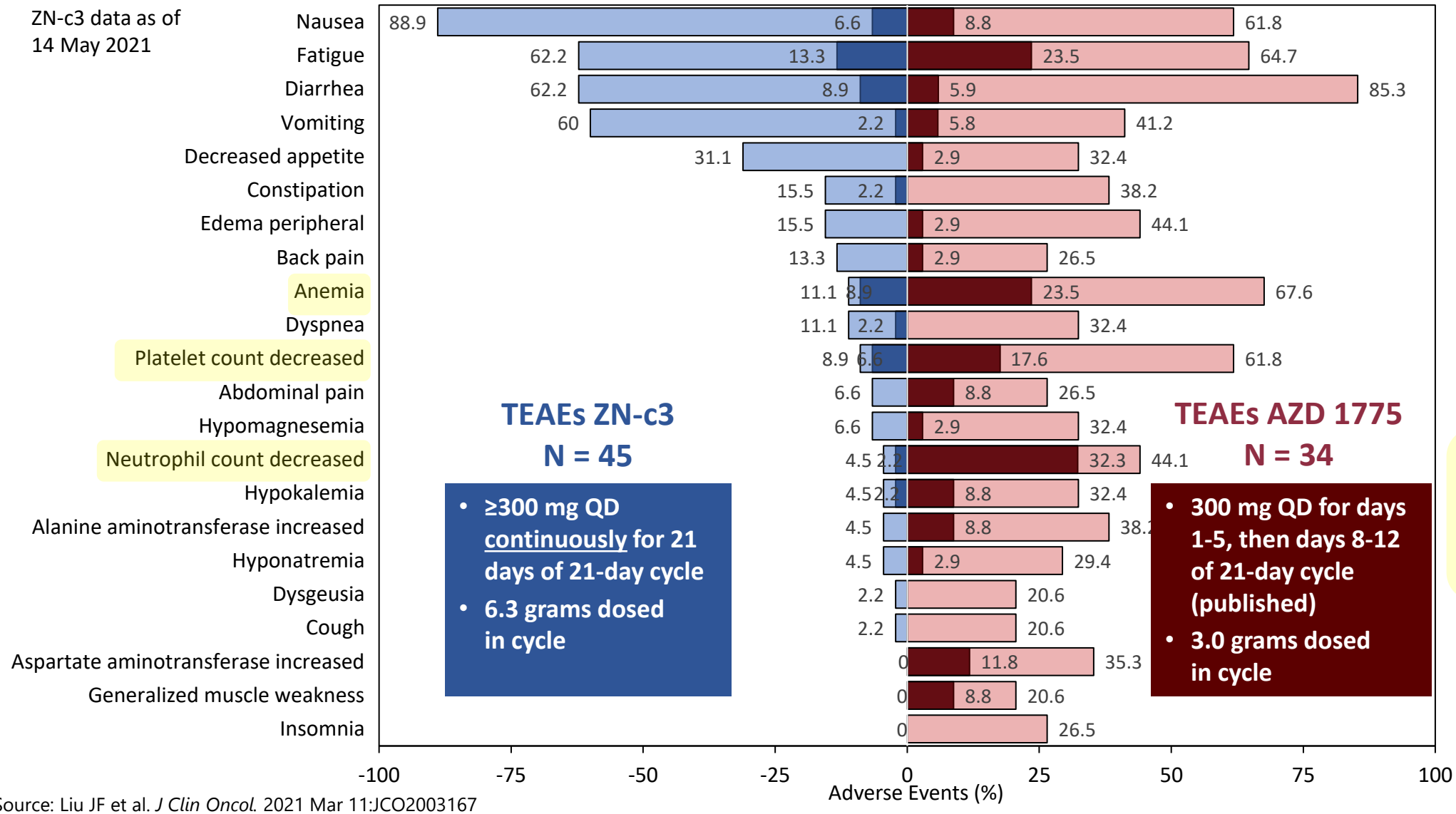
C. Safety/Tolerability vs AZD1775 (1)

ZN-c3 data as of
14 May 2021



- **Due to the tolerability issues of AZD1775 the drug was dosed intermittently while ZN-c3 was dosed continuously**
- **Despite having a 2x higher dose intensity (6.3g vs 3g), ZN-c3 safety and tolerability were favorable**

Source: Liu JF et al. *J Clin Oncol.* 2021 Mar 11:JCO2003167

(1) Non-head-to-head comparison. Results of a head-to-head comparison may differ significantly from those set forth herein. In addition, because our Phase 1 clinical trial for ZN-c3 and the Adavosertib clinical trials were separate trials, differences between the results of the trials may not be statistically or clinically meaningful

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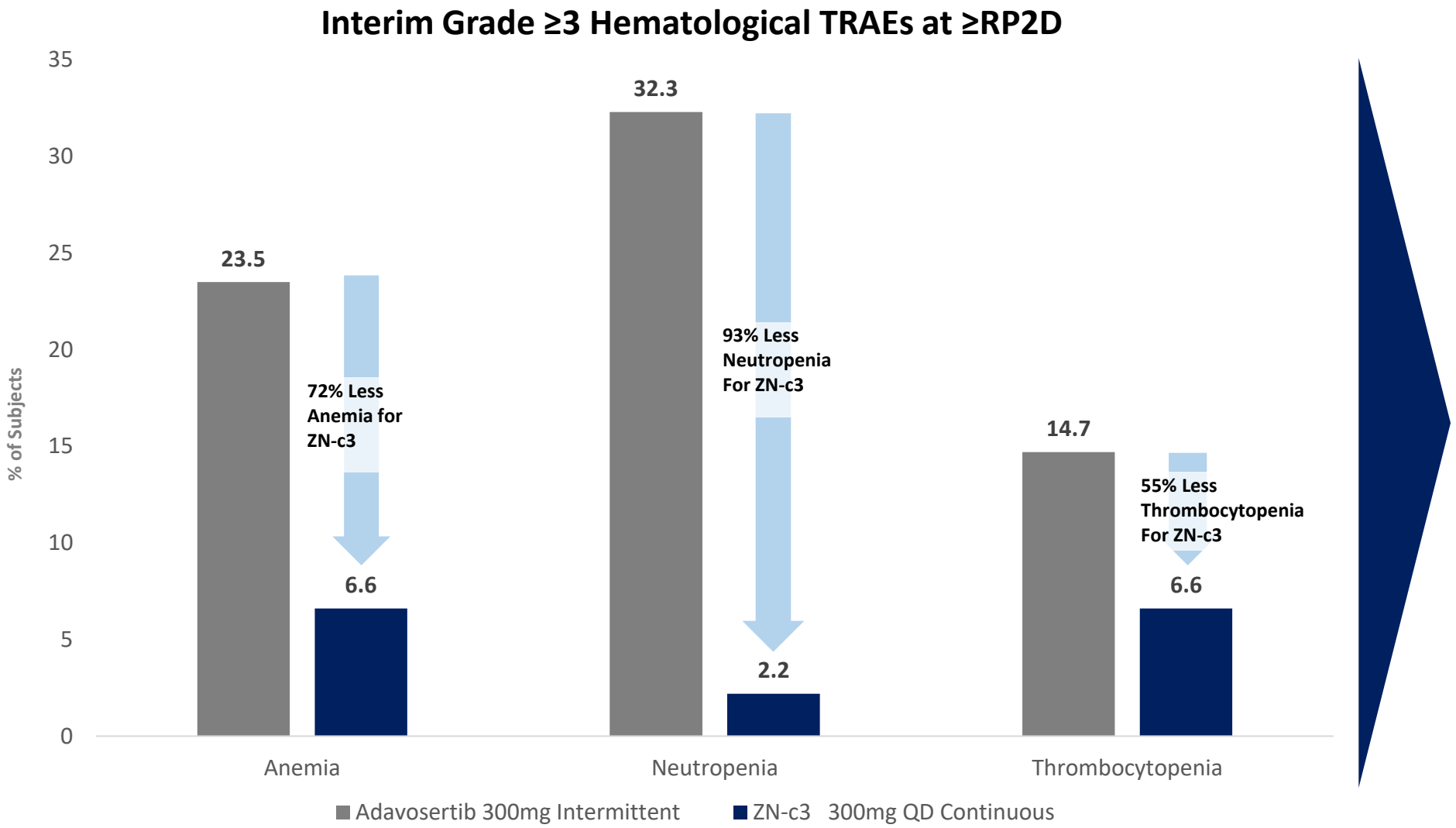
C. Safety/Tolerability vs AZD1775 (Cont.)



- **Even lower overall severe hematological AE rate over AZD1775 even with 11 more ZN-c3 patients enrolled since AACR 2021**
- **Despite continuous dosing delivering twice the drug load, ZN-c3 induced markedly less hematological toxicity than AZD1775 did in its clinical trials**
- **Better tolerability also unlocks the potential for wide ranging drug combinations providing potential for both increased efficacy and commercial potential**

Source: Liu JF et al. J Clin Oncol. 2021 Mar 11:JCO2003167

(1) Non-head-to-head comparison. Results of a head-to-head comparison may differ significantly from those set forth herein. In addition, because our Phase 1 clinical trial for ZN-c3 and the Adavosertib clinical trials were separate trials, differences between the results of the trials may not be statistically or clinically meaningful

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D. Path to Potential Accelerated Approvals

- Conducted EOP1 Mtg with FDA re: study ZN-c3-004, a monotherapy trial planned with registrational intent in women with recurrent or persistent USC
  - **Proposed study for ZN-c3-004 designed with registrational intent for potential accelerated approval**
- In 2H 2021, Zentalis expects to approach FDA with a biomarker-driven, tumor-agnostic monotherapy clinical trial design with registrational intent
- FDA has now granted two key designations for ZN-c3's use in combination with chemotherapy in osteosarcoma
  - **Orphan Drug Designation**
  - **Rare Pediatric Disease Designation**

I. Commercial Opportunity

	Near-Term Monotherapy Registrational Paths		Near-Term Combo Registrational Path	Future Combo Registrational Path
	Orphan Setting	Predictive Biomarker Driven Settings	Ovarian Plat Resist	Combination Therapy Settings
Drug Setting	**Single Agent ZN-c3**	**Single Agent ZN-c3**	**Combinations with ZN-c3**	**Combinations with ZN-c3**
Representative Indication(s)	**Uterine Serous Carcinoma**	**Biomarker Identified "Exceptional Responders" Across Tumor Types**	**Ovarian Platinum Resistant**	**PARP Combo (e.g., Ovarian) Chemo Combo (e.g., CRC, NSCLC or GBM) Immunotherapy Combos (e.g., TNBC or CRC)**
Addressable Patient Populations[1]	**~11,500[(2)]**	**~55,000[(3)]**	**~13,000**	**Very Large**

(1) North America, Western Europe and Japan
(2) Gynecologic Oncology 115 (2009) 142-153, David Boruta et al.; National Cancer Institute, SEER 2020 Data
(3) Observed predictive biomarker frequency data across solid tumor types; predictive biomarker not disclosed

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ZN-c5

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ZN-c5 Executive Summary

- New interim clinical data from Phase 1/2 monotherapy studies suggest ZN-c5 has the potential to be best-in-class with favorable safety/tolerability data in mono and combo settings
- New interim clinical data rival other oral SERD efficacy data; awaiting completion of study before final selection of RP2D (likely to be 50 mg QD)
- Combination studies with palbociclib and abemaciclib continue on track

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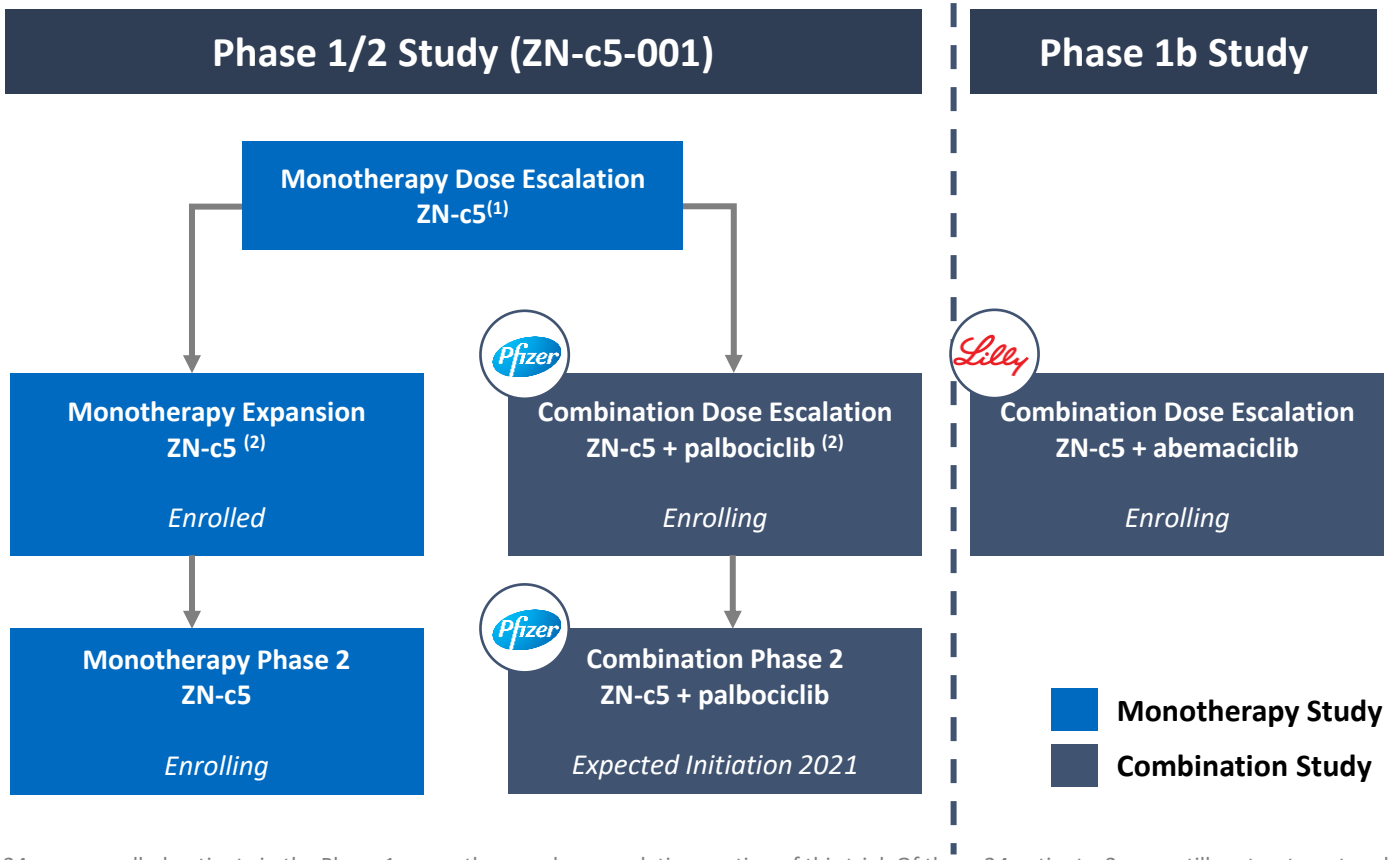
ZN-c5: Clinical Development Plan

Ongoing Clinical Programs



Other studies

- Window of Opportunity study initiated in 2020 to analyze tumor ER degradation (enrollment completed, 35 patients)
- Food effect study (18 subjects) completed, CSR in preparation
  - Results showed ZN-c5 could be administered with or without food
- Multiple dose cohorts may be chosen in monotherapy Phase 2 study

(1) As of May 11, 2021, n=24 were enrolled patients in the Phase 1, monotherapy dose escalation portion of this trial. Of these 24 patients, 3 were still on treatment and 21 discontinued due to disease progression (n = 20), and physician decision (n = 1).

(2) As of May 11, 2021, 32 patients were enrolled in the Phase 1, monotherapy expansion portion of this trial. Of these 32 patients, 12 were still on treatment and 20 discontinued due to disease progression (n = 18), adverse event (n = 1, hypersensitivity) and physician decision (n = 1). As of May 11, 2021, we have enrolled 41 patients in the Phase 1, combination dose escalation portion of this trial. Of these 41 patients, 23 were still on treatment and 18 discontinued due to disease progression (n = 14), patient decision (n = 2), intercurrent illness (n = 1, endometrial cancer) and physician decision (n = 1).

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ZN-c5-001: First-in-Human Study - Design & Endpoints

Design		Primary Endpoint
• Monotherapy Dose escalation (3+3 design)	→	Maximum tolerated dose/Recommended Phase 2 Dose
• Monotherapy Expansion	→	Safety and tolerability
• Monotherapy Phase 2	→	Clinical Benefit Rate (CBR)
• Combination with Palbociclib Dose escalation (3+3)	→	Maximum tolerated dose/Recommended Phase 2 Dose
• Combination with Palbociclib Phase 2	→	Clinical Benefit Rate (CBR)

Key Secondary Endpoints

- Safety and tolerability
- Pharmacokinetics
- Anti-tumor activity (RECIST): objective response rate, CBR, duration of response, progression-free survival, overall survival
- Pharmacodynamic and prognostic biomarkers

Dosing

- Administered orally, doses from 25 to 300 mg/day, dose once (QD) or twice (BID) a day

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ZN-c5-001: Key Inclusion Criteria

- ER+/HER2-negative advanced breast cancer
- ECOG PS 0 – 2
- Females postmenopausal or pre/peri-menopausal
- Evaluable or measurable disease by RECIST v1.1

Protocol Portion	N Prior therapies allowed for advanced/met disease	
	Endocrine-based therapies	Chemotherapies
Phase 1 Monotherapy Dose Escalation	unlimited	0 – 2
Phase 1 Combination Dose Escalation	unlimited	0 – 1
Phase 1 Monotherapy Expansion	0 – 2	0 – 1
Phase 2 Monotherapy	1 – 2	0
Phase 2 Combination	0 – 1	0 – 1

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ZN-c5-001: Baseline Demographics - ZN-c5 Monotherapy

Patient Characteristics	ZN-c5 Monotherapy N = 56
Median age, years (range)	58.5 (38 – 89)
ECOG status, n (%) 0 1 2	 30 (55%) 25 (45%) 0
N (range) prior lines of therapy (adv/mt) N (range) endocrine-based N (range) chemotherapy N prior CDK4/6i N prior fulvestrant N Prior PI3Ki	2 (0 – 9) 2 (0 – 6) 0 (0 – 3) 38 (68%) 26 (46%) 4 (7%)
Measurable disease, n (%) N Visceral disease	40 (71%) 28 (50%)

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New Clinical Data: ZN-c5-001 Monotherapy Efficacy Summary by Dose

Interim Monotherapy Efficacy Results

Data cut-off 11 May 2021

Dose (mg)	Likely RP2D 50	75	100	150	300	Overall
N (enrolled)	16	3	3	21	13	56
CBR	2/5 (40%)	0/3 (0%)	1/3 (33%)	4/21 (19%)	7/13 (54%)	14/42 (33%)
ORR*	0/14	0/2	0/3	1/13 (8%)	1/8 (13%)	2/40 (5%)

* Patients with measurable disease

- **Interim clinical data for ZN-c5 consistent with data from third party studies of other oral SERD competitors**
- **Last cohort in ZN-c5's monotherapy studies is the 50 mg dose, with a large number of patients on study**
- **RP2D selection to finalize after completion of study, with the 50 mg QD dose as likely RP2D**

Awaiting Large Number of Patients on 50 mg to Complete Study

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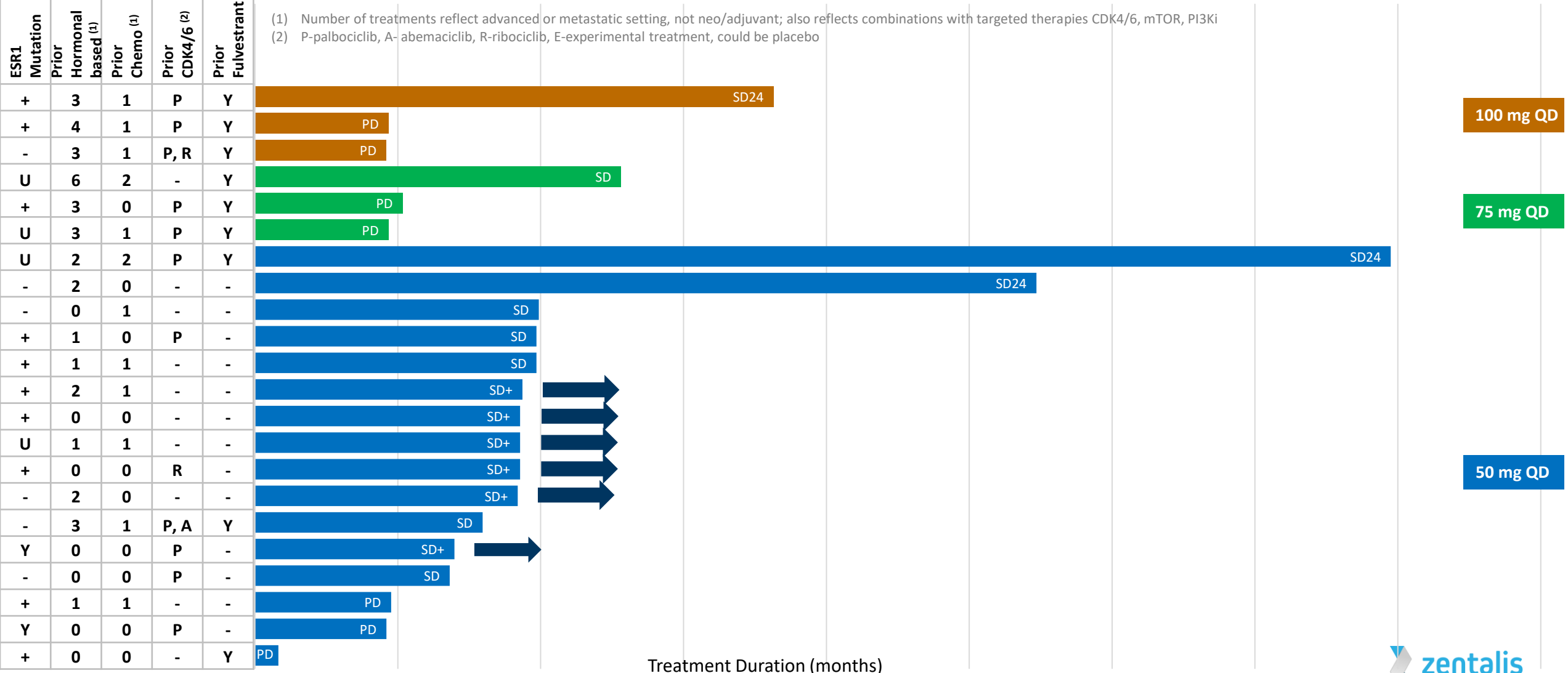
New Interim Clinical Data: ZN-c5-001 Monotherapy 50-100 mg

Treatment Duration (months) and Response by Dose as of 11 May 2021

ESR1 Mutation	Prior Hormonal based (1)	Prior Chemo (1)	Prior CDK4/6 (2)	Prior Fulvestrant
+	3	1	P	Y
+	4	1	P	Y
-	3	1	P, R	Y
U	6	2	-	Y
+	3	0	P	Y
U	3	1	P	Y
U	2	2	P	Y
-	2	0	-	-
-	0	1	-	-
+	1	0	P	-
+	1	1	-	-
+	2	1	-	-
+	0	0	-	-
U	1	1	-	-
+	0	0	R	-
-	2	0	-	-
-	3	1	P, A	Y
Y	0	0	P	-
-	0	0	P	-
+	1	1	-	-
Y	0	0	P	-
+	0	0	-	Y

(1) Number of treatments reflect advanced or metastatic setting, not neo/adjuvant; also reflects combinations with targeted therapies CDK4/6, mTOR, PI3Ki
(2) P-palbociclib, A- abemaciclib, R-ribociclib, E-experimental treatment, could be placebo



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New Interim Clinical Data: ZN-c5-001 Monotherapy 150-300 mg

Treatment Duration (months) and Response by Dose as of 11 May 2021

ESR1 m	(1)Prior Hormonal	(1)Prior Chemo	(2)Prior CDK4/6	Prior Fulvestrant	
U	5	1	P	Y	SD24+
-	2	1	-	-	SD24+
+	2	1	P	-	SD24
+	1	1	P	-	PR+
-	2	0	-	-	SD24
-	1	0	P	-	SD
U	2	0	P	Y	SD
-	1	0	P	-	SD
+	2	0	P	Y	PD
-	0	1	-	-	NE
-	0	0	-	-	SD24+
+	3	1	P	Y	SD24+
-	1	0	-	-	SD
-	1	0	P	-	PR+
U	1	0	-	Y	SD24+
-	1	0	R	-	SD24+
-	2	1	P	-	SD24
+	2	0	P	Y	SD
-	0	0	-	-	SD
+	2	1	P	Y	SD
-	1	0	P	Y	SD
-	2	0	P, R(E)	Y	SD
-	2	0	P	Y	SD
-	1	0	P	-	PD
-	1	1	P	Y	SD
-	1	0	P	-	PD
-	2	0	P, R*	Y	PD
-	1	0	P	-	PD
-	1	0	P	Y	SD
+	2	1	P	Y	SD+
-	1	1	P	Y	SD
-	1	0	P	-	SD
+	3	2	R, R*	Y	SD
-	3	0	P	Y	SD

(1) Number of treatments reflect advanced or metastatic setting, not neo/adjuvant; also reflects combinations with targeted therapies CDK4/6, mTOR, PI3Ki

(2) P-palbociclib, A- abemaciclib, R-ribociclib, E-experimental treatment, could be placebo

300 mg QD

150 mg BID

150 mg QD

75 mg BID

Treatment Duration (months)

0.00 2.00 4.00 6.00 8.00 10.00 12.00 14.00 16.00 18.00

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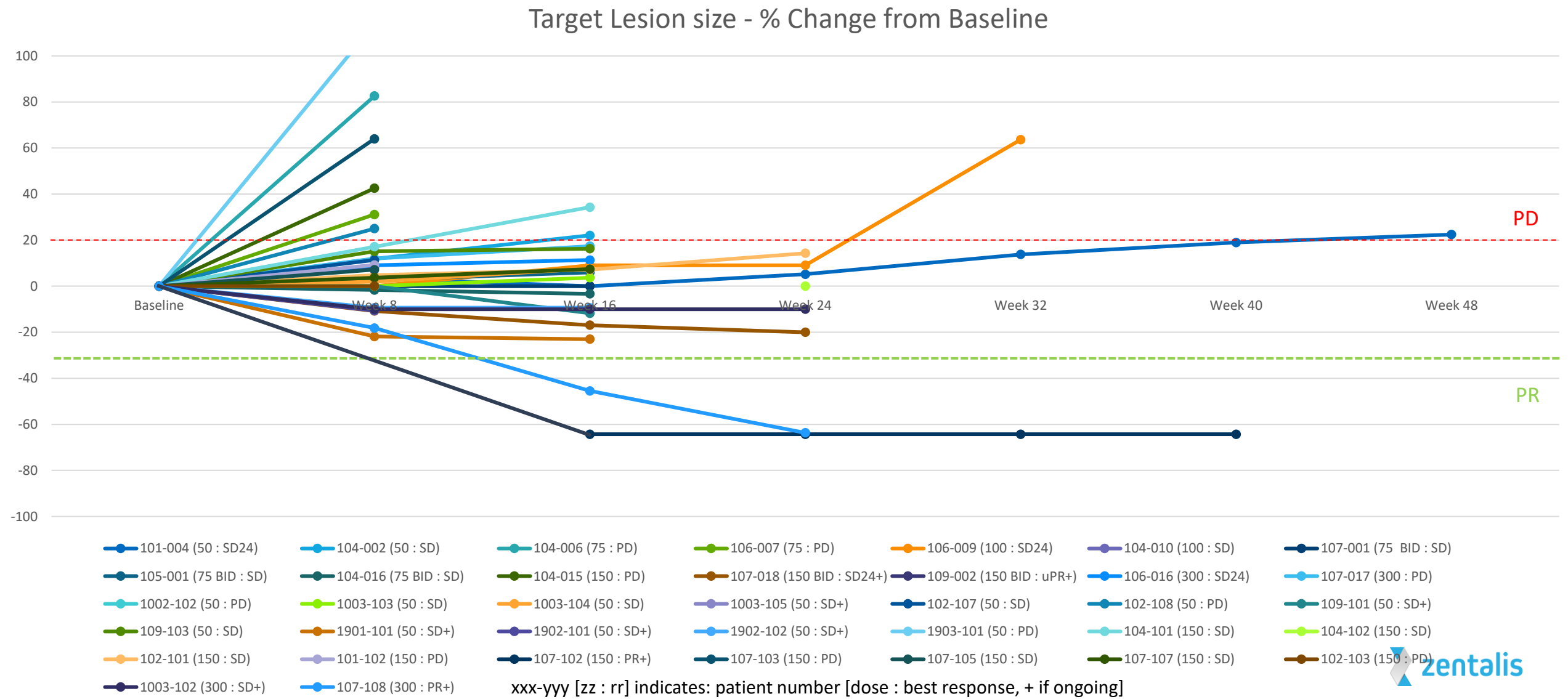
New Interim Clinical Data: ZN-c5-001 Monotherapy

Subjects with Measurable Disease as of 11 May 2021



xxx-yyy [zz : rr] indicates: patient number [dose : best response, + if ongoing]

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New Interim Clinical Data: ZN-c5 Plasma PK Parameters in Combo Arms

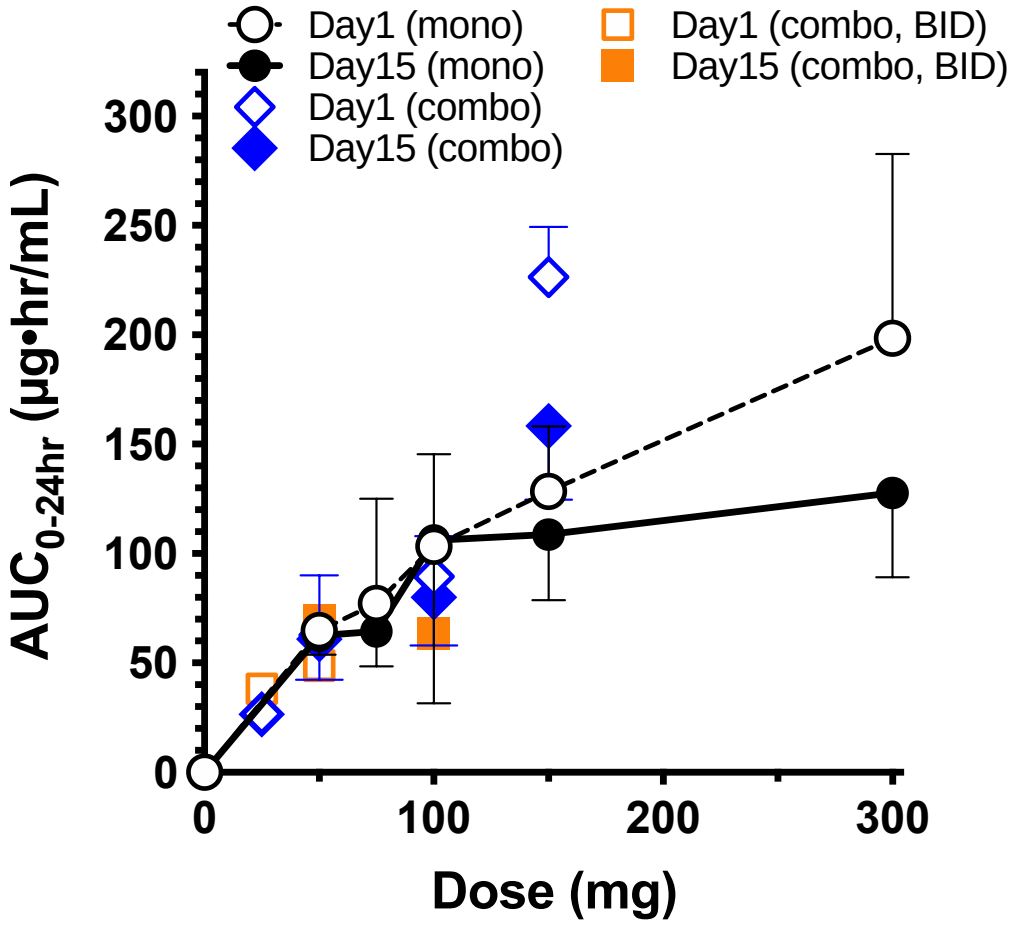
25 – 150 mg ZN-c5 + 125 mg Palbociclib (*preliminary*) as of 1 May 2021

ZN-c5 Dose (mg)		ZN-c5 on Day 1			ZN-c5 on Day 15			ZN-c5 Accum by AUC
		C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng*h/mL)	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-}24hr}$ (ng*h/mL	
25 (n=3/2)	Mean	2,230	2	26,800	2,360	2	26,500	1.2
	SD	*447*	*2-2*	*7,040*	*(2,230, 2,490)*	*2,2*	*28,000, 25,100)*	*(1.2, 1.2)*
50 (n=6)	Mean	5,140	1.5	62,700	5,390	1.5	60,800	1.1
	SD	*1,080*	*1-24*	*27,100*	*1,380*	*1-4*	*18,400*	*0.36*
100 (n=8)	Mean	6,960	2	89,600	6,640	2	80,000	0.90
	SD	*1,290*	*1-8*	*18,500*	*1,050*	*2-8*	*22,000*	*0.19*
150 (n=3)	Mean	18,500	2	226,000	13,300	2	158,000	0.71
	SD	*4,370*	*1-8*	*22,700*	*3,370*	*1-2*	*33,800*	*0.23*
25BID (n=3)	Mean	3,280	2	$AUC_{0\text{-}inf}$ 38,200	4,730	1	69,500*	1.0**
	SD	*121*	*1-2*	*5,930*	*2,300*	*1-2*	*37,100*	
50BID (n=2)	Mean	5,030 *(3990, 6070)*	2 *(2, 2)*	$AUC_{0\text{-}inf}$ 48,900	4,430 *(3,900, 4,950)*	1.5 *(1, 2)*	63,400* *(48,400, 78,200)*	0.94**

*For BID, $AUC_{0\text{-}24hr}$ on Day 15 is calculated as 2 x $AUC_{0\text{-}12hr}$

**For BID, accumulation is calculated based in $AUC_{0\text{-}12hr}$

- **ZN-c5 exposure on Day 15 was approximately dose proportional between 25 and 150 mg QD (with somewhat lower exposure at 100 mg)**



- ZN-c5 PK at 50 & 100 mg is consistent with mono, at 150 mg – higher than in mono

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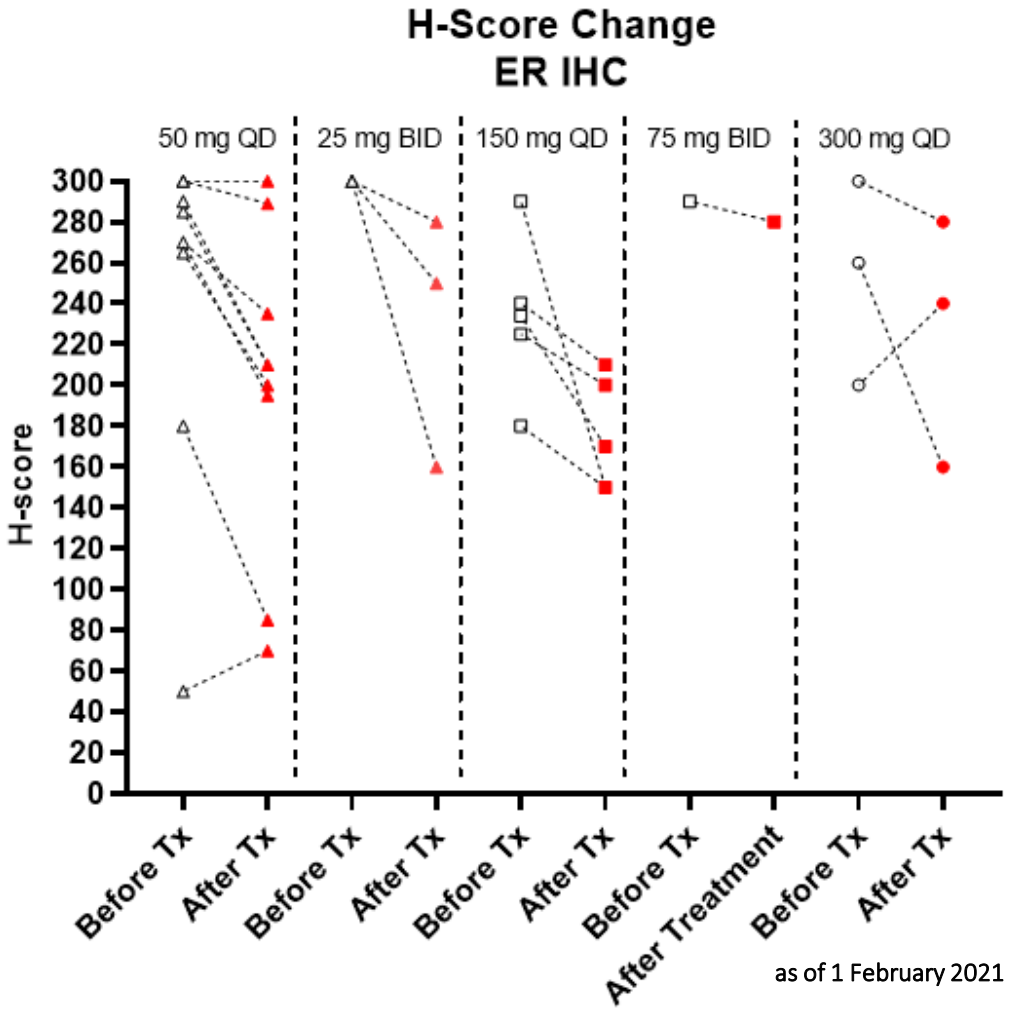
New Interim Clinical Data: ZN-c5 Window of Opportunity Initial Biomarker Study



	N	Mean	STD
All doses	**21**	**-17%**	**22%**
25 BID	3	-23%	21%
50 QD	9	-15%	26%
50 mg*	12	-17%	24%
150 mg*	6	-20%	16%
300 QD	3	-8%	29%

*total daily dose

Linear Regression %H-score change from baseline = intercept + slope*total daily dose

R-squared=0.013
intercept= 20% 95% CI (-37%, -3%) p-value=0.022
slope= 0 95% CI (-.1, .1) p-value=0.623

Initial Impressions of Interim Data:

- No dose correlation with ER degradation status
- High variability with assay and difficulty in cross comparing with other studies
- One pt at 300 mg dose with Grade 3/4 LFT increases resolved without incident after study end: patient with concomitant issues of fever, infection, acetaminophen use and steatosis
- Study continues to enroll; full study results to be published in future

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New Interim Clinical Data: ZN-c5 Monotherapy – Related AEs in ≥ 10%

TEAE's Related to ZN-c5

Data cut-off 11 MAY 2021

AEs in N	50 mg QD N = 16			75 mg QD N = 3			100 mg QD N = 3			75 mg BID N = 6			150 mg QD N = 15			150 mg BID N = 3			300 mg QD N = 10			Total N = 56			
Grade	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**All N (%)**
Any AE	6	2	0	1	0	0	0	0	0	2	2	0	5	4	0	1	1	1	5	2	1	20	11	2	33 (59%)
Hot Flushes										2			3						1	2		6	2	0	8 (14%)
Nausea	1									1			1	1			1		1	2		4	4	0	8 (14%)
Fatigue	1									1			2			1			1	1		6	1	0	7 (13%)

Diarrhea events: 2 out of 56 subjects (3.6%), only grade 1 or 2 events observed
Grade 3 events: n=1 hypersensitivity (300 mg qd); n=1 γGT increase (150 mg bid)

No observed bradycardia, no visual disturbances, no QTC, no dizziness

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New Interim Clinical Data: ZN-c5 Combination with Palbociclib – Related TEAEs ≥ 10%

Data cut-off 11 MAY 2021

TEAE's Related to ZN-c5

	25 mg QD N = 6				25 mg BID N = 5				50 mg QD N = 13				50 mg BID N = 2				100 mg QD N = 12				150 mg QD N = 3				Total N = 41			
Grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Any AE	1	1			2				4	3			1	1			3	1			2	1			13	7		
Hot Flush		1			1				1	1			1								1				4	2		
Arthralgia					1				2	1															3	1		

TEAE's Related to Palbociclib

	25 mg QD N = 6				25 mg BID N = 5				50 mg QD N = 13				50 mg BID N = 2				100 mg QD N = 12				150 mg QD N = 3				Total N = 41			
Grade	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Any AE		4	1	1	2	2			1	7	5		1	1			5	2	5				3		9	16	14	1
Neutrophil count decreased		4	1		1	1				7	3		1					2	5				3		2	14	12	
WBC count decreased	1	2	1		2	1			2	4	2		1				5	2	2			1	1		11	10	6	
Anemia	1	1			1				4	1							4				1	1			11	3		
Lymphocyte count decreased		1	1	1		1				2	2			1			2				1				3	5	3	1
Fatigue	1								3	2							3				1				8	2		
Platelet count decreased		2			1				2								3				1				7	2		
Nausea									2								2				1				5			
Hot Flush		1			1				1												1				3	1		
Arthralgia					1				2	1															3	1		

Grade 3 events: n=1 hypersensitivity (300 mg qd); n=1 γGT increase (150 mg bid)

ZN-c5 tolerability data suggest best-in-class of oral SERDs and ideal for combos

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ZN-d5

ZN-d5: Clinical Development Plan

Ongoing and Planned Clinical Programs

Phase 1	Phase 2 [2]
AML and Non-Hodgkin's Lymphoma: Monotherapy Dose Escalation [1] *Initiated 4Q 2020*	**Monotherapy Phase 2 Study** *Expected Initiation 1Q 2022*
Undisclosed Indication: Phase 1b Combination Study *Expected Initiation 1H 2022*	

(1) Enrollment of trial ongoing
(2) Trial designs will be based off data generated from Phase 1 trials

Monotherapy Study
Combination Study

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ZN-d5 Update

- ZN-d5 is a highly selective, oral BCL-2 inhibitor
  - In internal preclinical studies, ZN-d5 is 14x more selective for BCL-2 over BCL-xL than venetoclax, potentially yielding less thrombocytopenia
- Entered the clinic in October 2020 in a dose-escalation study in relapsed/ refractory non-Hodgkin's lymphoma (NHL) and acute myeloid leukemia (AML)
  - 14 subjects with NHL enrolled (diffuse large B cell, mantle cell, follicular and marginal zone lymphomas all represented)
  - Completed first 4 dosing cohorts without dose-limiting toxicities; 5th cohort ongoing
  - No unexpected safety findings; evidence of biological activity
  - Plan to open the study to AML this summer

ZN-e4

ZN-e4 Update

- ZN-e4 is a potent, third generation EGFR inhibitor
  - Lack of active metabolite binding to wild type EGFR provides potential for better tolerability than osimertinib
- First-in-human dose escalation study in EGFR-mutant non-small cell lung cancer is ongoing
  - Enrolled 26 subjects, both osimertinib-naïve and -experienced
  - Escalated from 20 mg through 480 mg, with clinical activity at doses >80 mg QD
  - Well-tolerated at all doses; rash AE observed in one subject and only grade 1 (1/26 subjects, 4%) as of March 25, 2021 data cutoff
  - Currently back-filling several dose cohorts to have robust PK and exposure-toxicity data to support Phase 2 dose selection

Milestones

Updated Key Milestones

Event	Expected Timing
ZN-c3 (WEE1 Inhibitor)	
Initiate Phase 2 monotherapy in uterine serous carcinoma	Completed
Initiate Phase 1/2 chemotherapy combo in osteosarcoma	3Q 2021
Initiate Phase 1/2 niraparib combo in ovarian cancer	4Q 2021
Initiate Phase 1/2 tumor agnostic, predictive biomarker study	4Q 2021
Initial readouts on Phase 1 USC expansion cohort and Phase 1b ovarian chemo combo	1H 2022
Initial readouts on Phase 2 USC trial and Phase 1/2 chemotherapy combo in osteosarcoma	2H 2022
ZN-c5 (Oral SERD)	
Phase 1 interim results from monotherapy dose expansion and escalation studies, Window of Opportunity study, palbo combo safety	Completed
Initiate Phase 2 monotherapy study	Completed
Phase 1b combination study topline results with palbociclib; Phase 1b combination study topline results with abemaciclib	1H 2022
ZN-d5 (BCL-2 Inhibitor)	
Initiate monotherapy Phase 2 trial	1Q 2022
Phase 1 initial results from dose escalation study in AML and Non-Hodgkin's Lymphoma	1H 2022
Initiate combination Phase 1b trial in undisclosed indication	1H 2022
ZN-e4 (EGFR Inhibitor)	
Phase 1 initial results from dose escalation study	4Q 2021
Evaluate potential for use in combinations for treatment of lung cancer	2021+
Integrated Discovery Engine	
R&D Day	4Q 2021
Zentera	
Submit ZN-c5, ZN-c3, ZN-d5 CTAs in China	Completed
Potential HK listing	2022

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