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R&D DAY

December 16, 2021

Forward-Looking Statements and Disclaimer

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This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. Neither we nor our affiliates, advisors or representatives makes any representation as to the accuracy or completeness of that data or undertake to update such data after the date of this presentation.

Company Overview

Lead Program: Wee1i (ZN-c3) potentially first- and best-in-class

- Monotherapy responses seen in 4 solid tumor types, with 3 Exceptional Responders and an additional 2 PRs confirmed in USC, 1 unconfirmed PR in USC thus far
- Potential accelerated approval paths for USC and biomarker-driven trials
- Fast Track designation granted in USC
- Orphan drug and rare pediatric disease designations granted in osteosarcoma

Oral SERD (ZN-c5) potentially best-in-class profile as monotherapy and in combination

Additional programs targeting fundamental cancer pathways: BCL-2 inhibitor (ZN-d5) & EGFR inhibitor (ZN-e4)

Investigating internal and third-party combination strategies

Integrated Discovery Engine: 4 FDA-cleared INDs within the first 5 years

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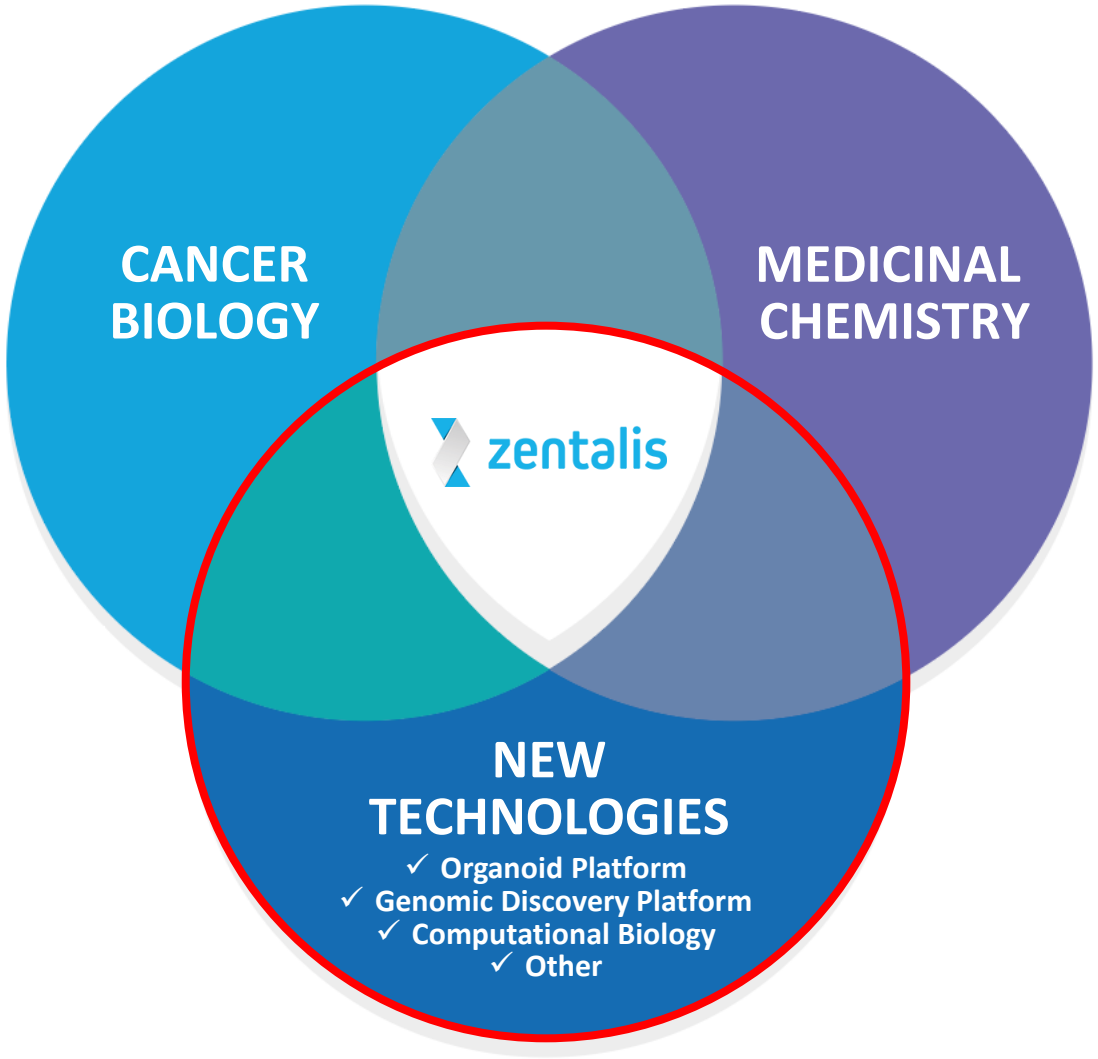
Integrated Discovery Engine

Highly Efficient 'Integrated Discovery Engine' Fueling Pipeline



1. **IDENTIFY** fundamental biological pathways of cancers
2. **ANALYZE** key compounds targeting these pathways and assess their limitations
3. **CREATE** proprietary NCEs designed to address observed limitations
4. **GENERATE** strong preclinical evidence to support potentially differentiated development profiles

Zentalis' Past, Present and Future

Past

PRE-CLINICAL SMALL MOLECULE DISCOVERY

- Small molecule chemistry and biology expertise delivering impactful oncology drugs
  - DDR: ZN-c3
  - Oral ER degraders: ZN-c5
  - Apoptosis: ZN-d5

Present

CLINICAL STAGE

- ZN-c3: Potential best-in-class DDR agent to address a wide range of solid tumor indications
- ZN-c5: Potential best-in-class oral SERD with excellent safety/tolerability profile
- ZN-d5: Promising oral agent targeting apoptosis for heme malignancies

Future

APPROVED DRUGS

MACHINE LEARNING

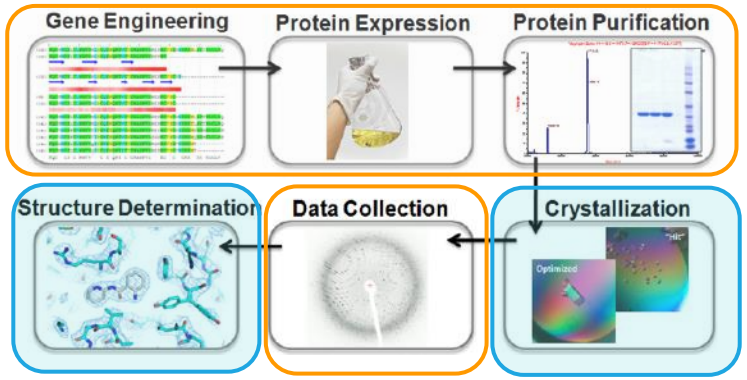
FUTURE PIPELINE PRODUCTS AND CLINICAL ASSETS

Integrated Discovery Engine

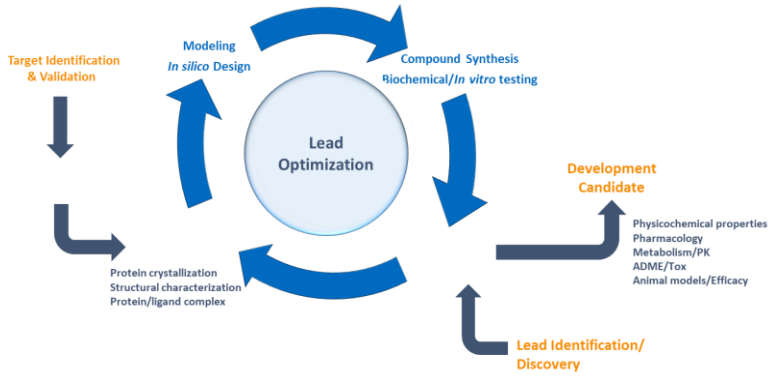
- **New drugs:** Determination of new targets and combination partners
- **Better clinical trials:** Novel patient selection; new combination partners and drug schedules; faster paths to global registration
- **Larger commercial markets:** New clinical indications

X-Ray Crystallography Platform Enables Structure-Based Drug Design and Accelerates Lead Optimization

Process

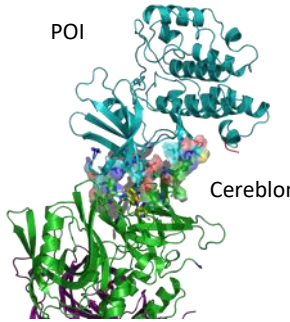


Iterative Structure-Based Design Cycle

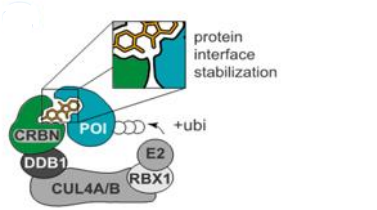


Targets of Interest

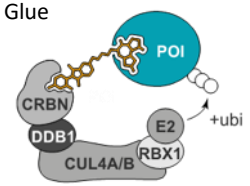
Degraders



Cereblon

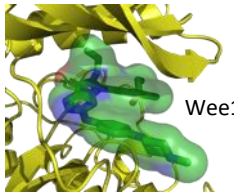


Molecular Glue



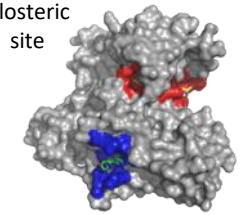
Heterobifunctional degrader

Active Site/Allosteric Inhibitors



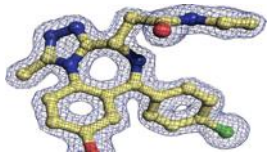
Wee1/ZN-c3

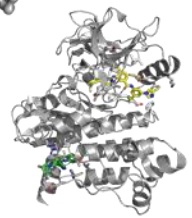
Allosteric site



Active Site/ Allosteric Inhibitors

Active site

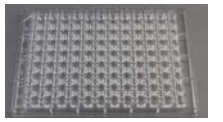




Infrastructure

- Integrated state-of-the-art instrumentation for HT protein crystallization and imaging

Submicroliter protein crystallization in 96-well format



RT and 4 °C plate incubation/automated imaging/crystal detection

www.formulatrix.com

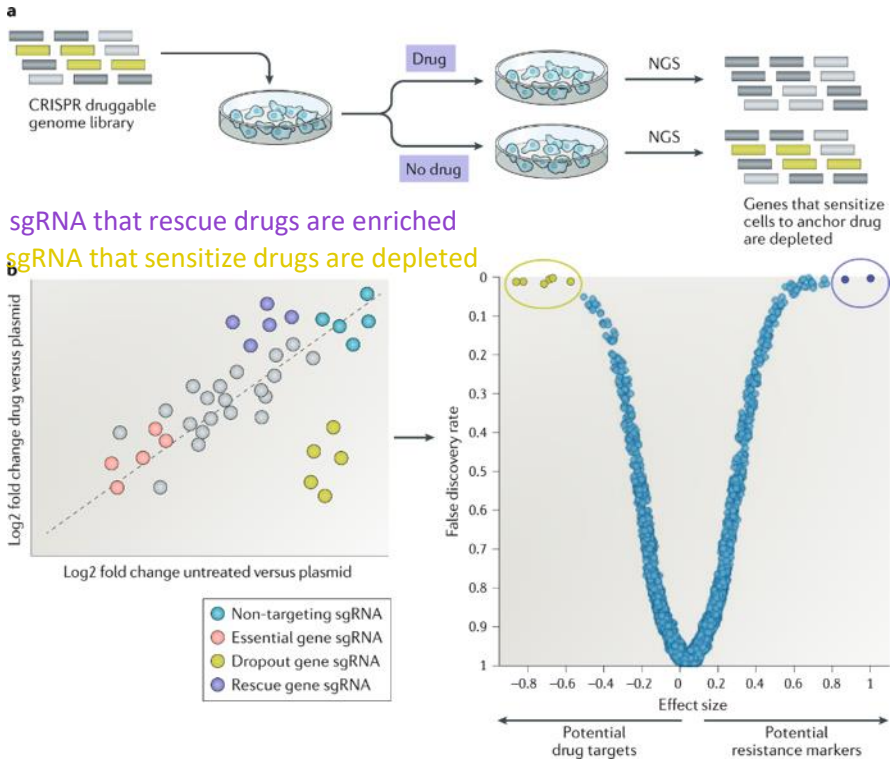
Synchrotron X-ray data collection through CRO

Figures from : https://slideplayer.com/slide/13076089/, https://www.protein-degradation.org/groups/winter/, https://www.lifesci.dundee.ac.uk/groups/alessio-ciulli/

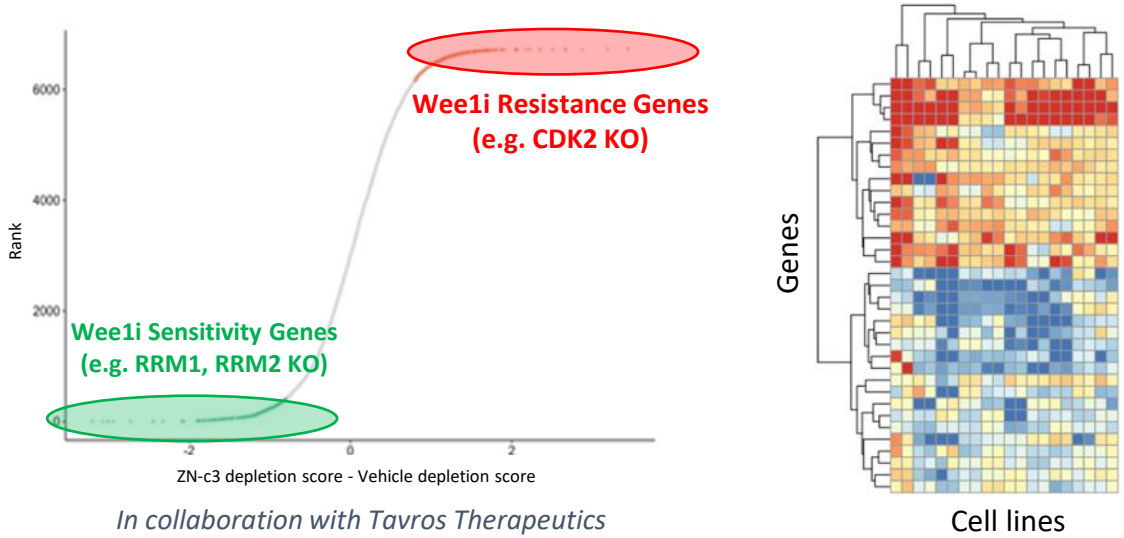
Genomic Discovery Platform: Identifying Gene Dependencies for Zentalis Drugs

Zentalis CRISPR-based Screens:

- Patient-Selection Biomarkers
- Potential Combinations
- New Targets



Huang A et al. Nat. Rev. Drug Dis. 19, 23-38 (2020)



In collaboration with Tavros Therapeutics

- Identification of genes conferring sensitivity and resistance to ZN-c3

Utilizing Machine Learning for Multi-Omics Prediction of ZN-c3 Sensitivity

aws docker amazon WorkSpaces DRAGEN nextflow

aws jupyter scikit learn

Bench & Bed to Data → **Machine Learning** → **Data to Knowledge**

Multi-Omics and Integration

CRISPR Screens | Organoids | Cell Lines

Genetic Dependencies

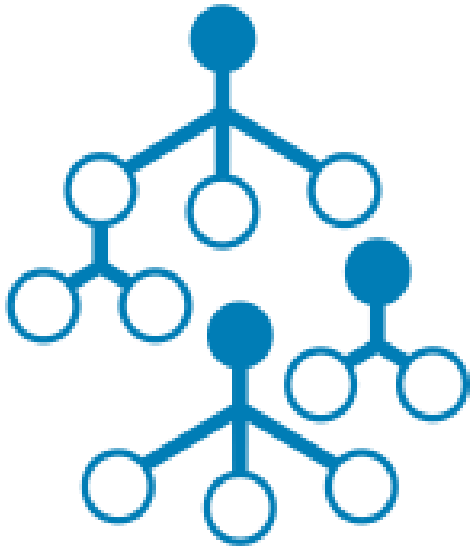
Genomics, Transcriptomics, Proliferation, Apoptosis

Mouse CDX/PDX | Patient Response | Public Data

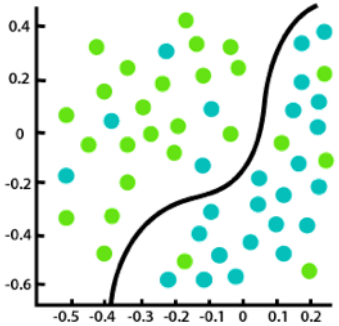
Baseline Expression, Mutations, Pathways Efficacy

Tissue and Blood Genetic Markers

PubMed depmap



Patient Classification



Predictions:

Histological Indication
Companion Dx
Drug Combination

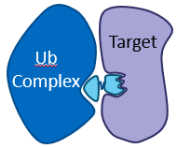
Drug Schedule
Resistance Mechanism

Expanding Zentalis' Discovery Capabilities

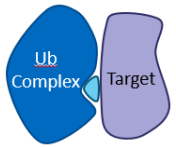
Enhanced Chemical Space: Targeted Protein Degradation Toolbox

- Extend reach to "undruggable" proteins
- Increase target and tissue selectivity

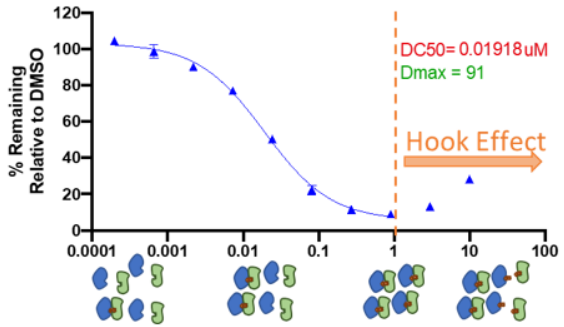
Heterobifunctional Degraders



Molecular Glues



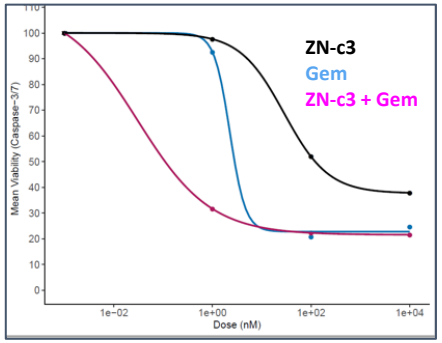
Protein Degraders



Using Organoids to Better Model Human Tumors

- Organoids derived directly from patient tumor biopsy
- Organoids expanded, phenotyped, cryopreserved and amenable to drug screening

Define patient-selection hypothesis and identify potential combinations



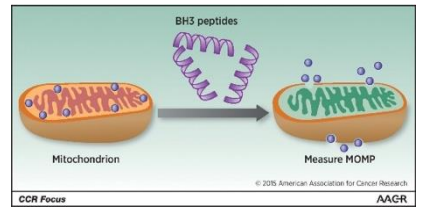
ZN-c3 + gemcitabine in ovarian organoid *

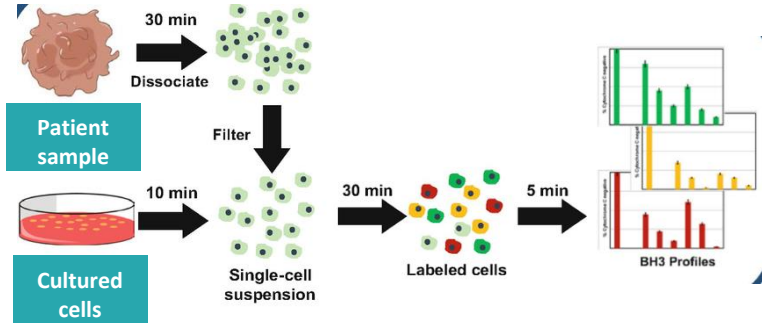
**Collaboration with Tempus*

TEMPUS

Determining Sensitivity via BH3 Profiling

- Functional assay measuring:
  - propensity for apoptosis
  - dependence on antiapoptotic proteins
- Measures changes due to mitochondrial outer membrane permeabilization (MOMP)



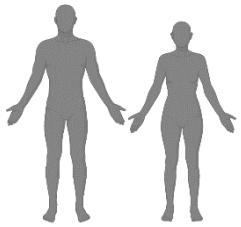


Adapted from Fraser C et al., BCL-2 Family Proteins (2018)

Starting with the Patient for the Benefit of the Patient: Utilizing the Integrated Discovery Engine to Generate Best-In-Class Drugs

Patients

Pathways



Genomic features

1

IDENTIFY

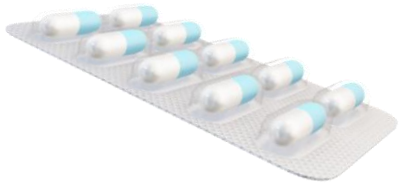
ANALYZE

2

CREATE

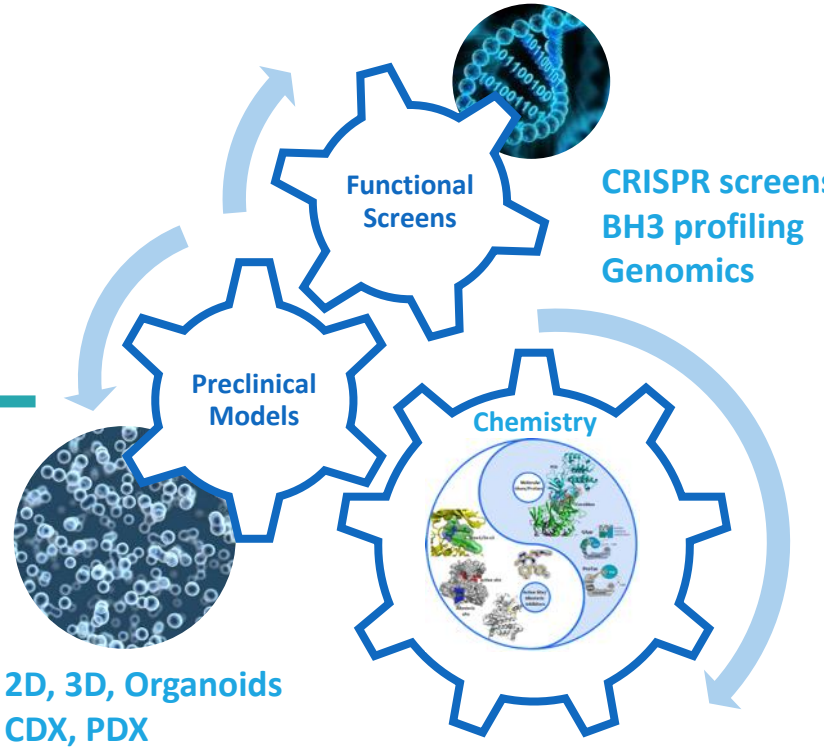
3

GENERATE



Zentalis Drugs

Zentalis Discovery Engine



CRISPR screens
BH3 profiling
Genomics

2D, 3D, Organoids
CDX, PDX

Enzymatic and allosteric inhibitors
Heterobifunctional Degraders and Molecular Glues
Crystallography and SBDD

Image reproduced from: https://blog.f1000.com/2017/02/01/f1000prime-f1000prime-faculty-launch-bioinformatics-biomedical-informatics-computational-biology/

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ZN-c3

Wee1 Inhibitor

ZN-c3: Oral Wee1 Inhibitor for Solid Tumors

1

IDENTIFY:
Wee1

- Highly attractive DNA damage response target
- Active across multiple tumor types with potential for combination
- **Opportunity: no approved Wee1 inhibitor;** only a few in development e.g., AstraZeneca's adavosertib (AZD1775)

2

ANALYZE:
Adavosertib

- Promising efficacy across tumor types (ovarian and pancreatic cancer)
- Potentially limited by **narrow therapeutic window and toxicity profile**

3

CREATE:
ZN-c3

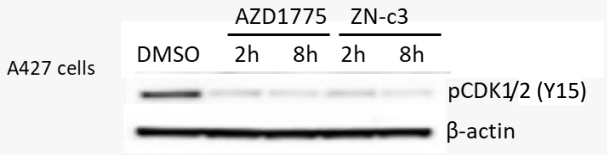
- Designed to have improved:
  - Potency
  - Solubility
  - Selectivity
  - PK properties
- **Goal: broader therapeutic window**
- Potential to have broad applicability as monotherapy and in combination

4

GENERATE:
Preclinical Evidence

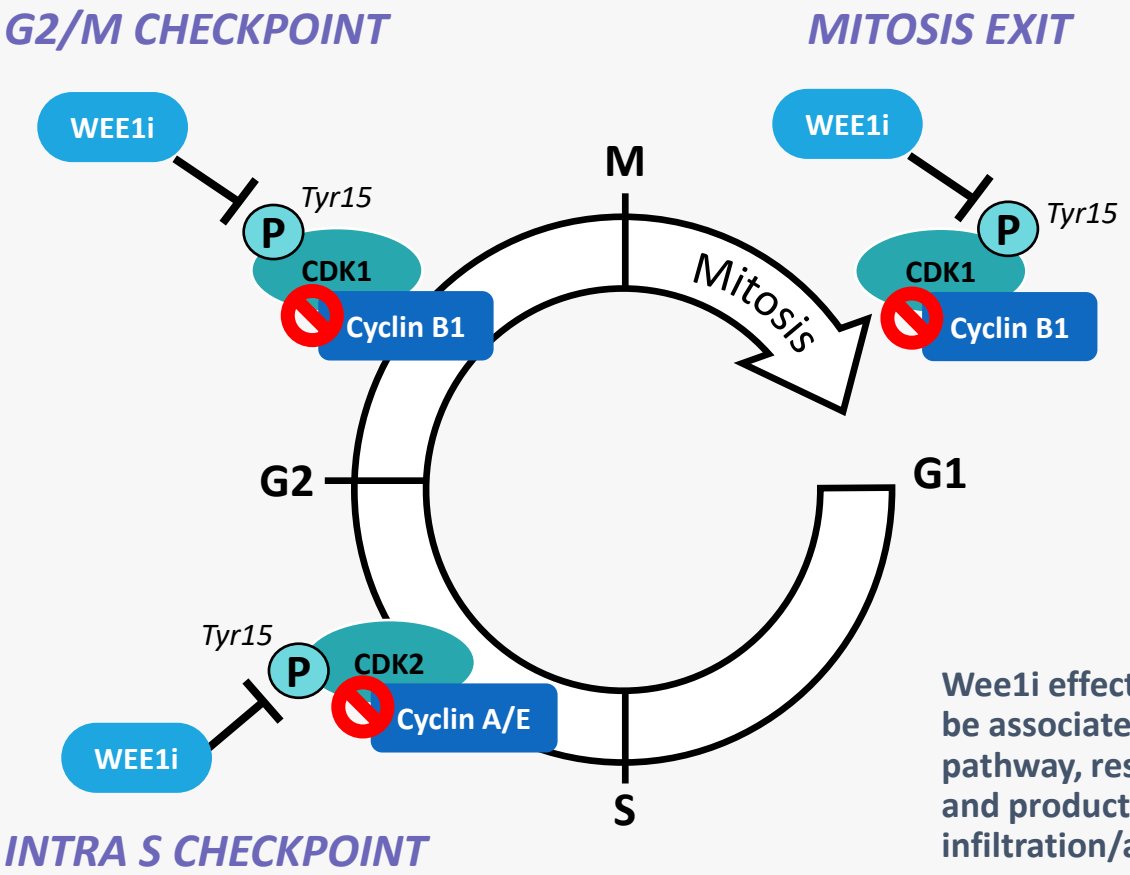
- 117x higher tumor concentration compared to adavosertib
- Greater selectivity for Wee1 compared to adavosertib
- Induced prolonged tumor growth delay in human NSCLC tumor xenograft model

Wee1 Inhibition: Clinically Proven DDR Target for Cancer



ZN-c3 inhibits CDK1/2 phosphorylation

Wee1 inhibition causes cancer cells to proceed to mitosis without repairing DNA damage, resulting in premature mitotic entry and apoptosis



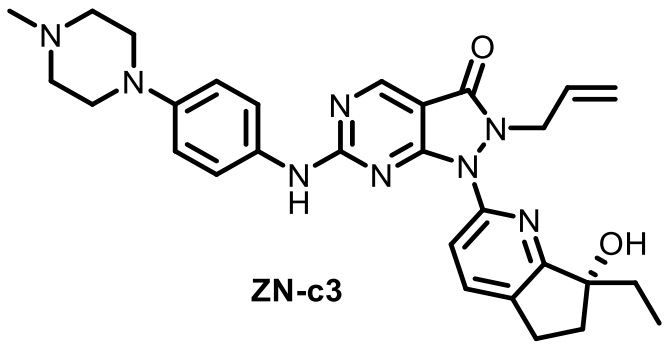
Inhibition of Wee1 may cause tumor cell death by:

- Aberrant origin firing causing exhaustion of the replication protein A1 (RPA1)[1]
- Degradation of ribonucleotide reductase subunit leading to exhaustion of dNTP pools[2]

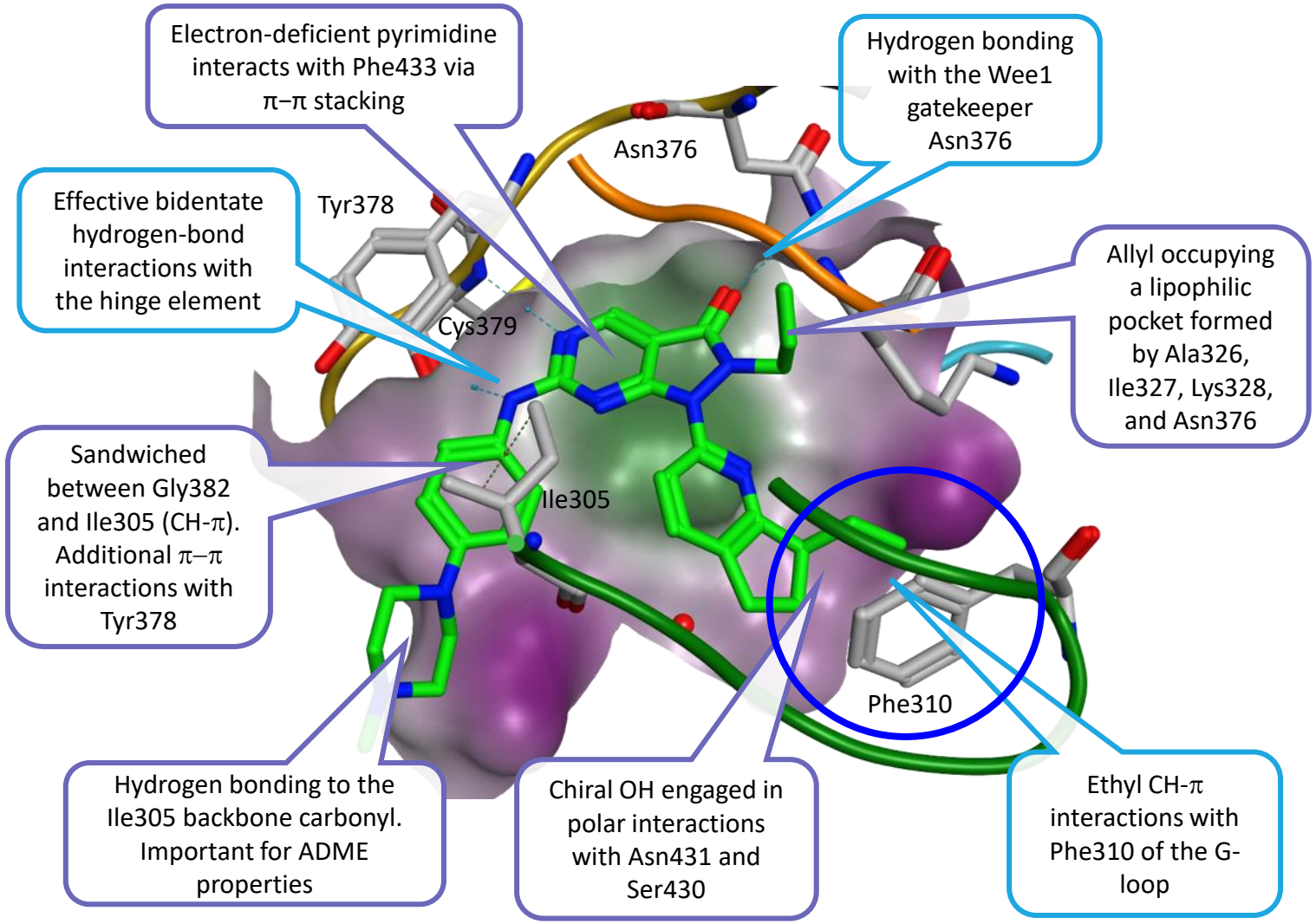
Wee1i effects on cell cycle and DNA damage may be associated with activation of cGAS/STING pathway, resulting in Type I interferon response and production of cytokines driving immune cell infiltration/activation into tumor[3-5]

(1) Di Rora AGL et al. J Hematol Oncol. 2020 Sep 21;13(1):126
(2) Pfister SX et al. Cancer Cell. 2015 Nov 9; 28(5): 557–568
(3) Keenan et al. Clin Canc Res. (2021)
(4) Hai J et al. Clin Cancer Res. 2020 Jul 1;26(13):3431-3442
(5) Guo e et al. J. Exp. Med. 2021 Vol. 219 No. 1

Structure-Based Drug Design (SBDD) Led to the Discovery of a Highly Potent and Selective Wee1 Inhibitor ZN-c3 with Improved ADME Properties(1)



ZN-c3 potency and ADME	
Wee1 IC_{50}	3.8 nM
H23 IC_{50}	103 nM
A427 IC_{50}	75 nM
Log *D*	2.4
*h*PPB	66%
*h*Hep	<18 mL/min/kg
solubility	> 2000 µM
CYP3A4	7 µM
hERG	> 30 µM



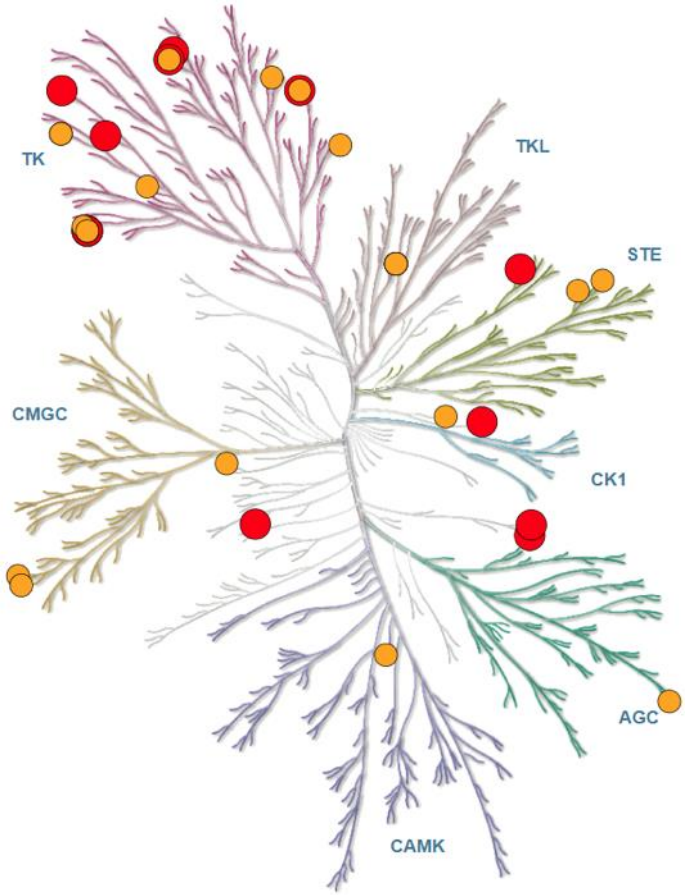
(1) Huang, PQ; *et al.* J. Med. Chem. **2021**, *64*, 13004-13024

ZN-c3: Differentiated Selectivity Profile(1)

Adavosertib

% Inhibition (@ 1µM)

- 90+ 13 kinases
- 75-89 24 kinases



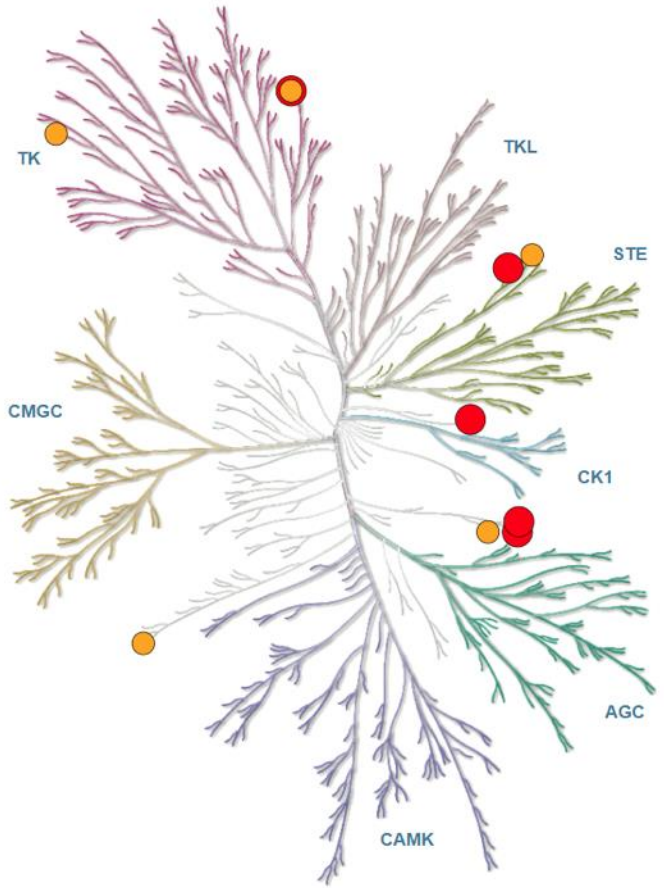
ASSAY	adavosertib	ZN-c3
WEE1	106	102
PLK2	101	96
MAP3K19 (YSK4)	92	95
EGFR (ErbB1) d747-74	90	93
PLK3	91	92
EGFR (ErbB1) d746-75	78	79
PLK1	70	79
NEK1	73	76
MAP3K3 (MEKK3)	66	76
LCK	87	75
DDR2 T654M	83	72
STK33	83	72
SYK	66	69
GAK	93	68
YES1	92	68
HIPK2	62	67
CDK4/cyclin D1	60	67
PKMYT1	86	65
RET S891A	43	64
NEK4	25	64
FLT3 D835Y	83	62
HIPK4	44	62
FES (FPS)	47	61
ABL1 G250E	85	59
EGFR (ErbB1) L858R	53	59
JAK3	81	58
MAP3K2 (MEKK2)	32	56
MUSK	101	55
FGR	91	55
EGFR (ErbB1) L861Q	53	54
DDR2 N456S	96	53
CDK4/cyclin D3	68	52
BMX	63	52
EIF2AK2 (PKR)	51	51
FYN	64	50
EGFR (ErbB1)	54	50
PEAK1	81	48
SNF1LK2	71	48
MAP4K5 (KHS1)	78	47
FRK (PTK5)	75	44
JAK2	63	44
JAK2 JH1 JH2 V617F	48	43
ABL1 Q252H	94	42
ABL1 M351T	90	42
SRC N1	88	42
ABL1 Y253F	85	41
ERBB4 (HER4)	26	41
ABL1 H396P	92	40
EPHB1	44	40
ABL2 (Arg)	82	39
NIM1K	43	39
CDK6/cyclin D1	65	38
JAK2 JH1 JH2	58	37
TYRO3 (RSE)	46	37
ABL1	84	36
SRC	74	36

>470 kinases

ZN-c3

% Inhibition (@ 1µM)

- 90+ 5 kinases
- 75-89 5 kinases



(1) Illustrations reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

ZN-c3: Cornerstone of Multiple Treatments

- Adavosertib has shown promising clinical activity; however, it is limited by toxicities
- ZN-c3 has superior kinase selectivity and has shown clinical activity across multiple indications(1)
- ZN-c3 is well tolerated, allowing for QD dosing at 300 mg (RP2D) with minimal heme related toxicities (1)
- Pre-clinical data showed activity in many indications and in several combinations (next slides)

Existing Clinical Trials

Indication	Treatment
USC*	ZN-c3 monotherapy
Solid Tumors	ZN-c3 monotherapy
Ovarian	ZN-c3 and chemotherapy
Osteosarcoma*	ZN-c3 and gemcitabine

Recently-Initiated Clinical Trials

Indication	Treatment
Predictive Biomarker*	ZN-c3 monotherapy
Ovarian	ZN-c3 and niraparib (PARPi)
Multiple Indications By Zentera	Multiple studies initiated in China

Additional Clinical Programs to be Announced Today

* Potentially registrational trial

(1) AACR 2021 presentation and/or corporate deck

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ZN-c3: Uterine Cancer

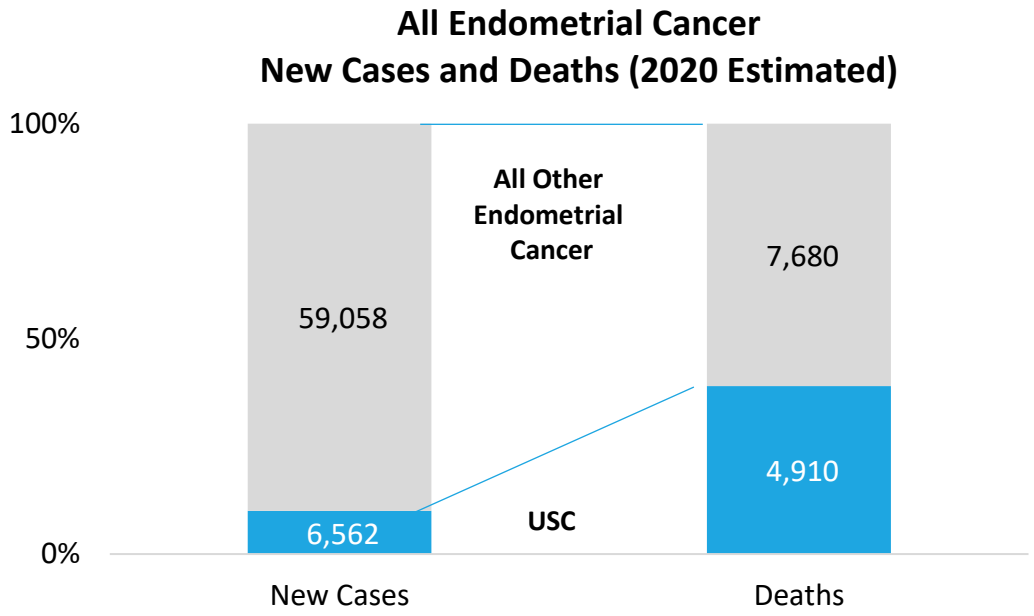
ZN-c3 Uterine Serous Carcinoma Indication Overview

Overview of Uterine Serous Carcinoma (USC)

- Type II endometrial cancer
- Not hormonally mediated
- Approximately 70% of USC present with Stage III or IV disease at diagnosis
- Poor survival rates; only 30-50%, even if confined to uterus
- Recurrence rates are 29-80% post-surgery
- ~6k new cases and ~4.5k deaths in U.S. per year
- Current standard of care: comprehensive surgery, adjuvant chemotherapy and adjuvant vaginal cuff brachytherapy

USC Represents High Unmet Medical Need

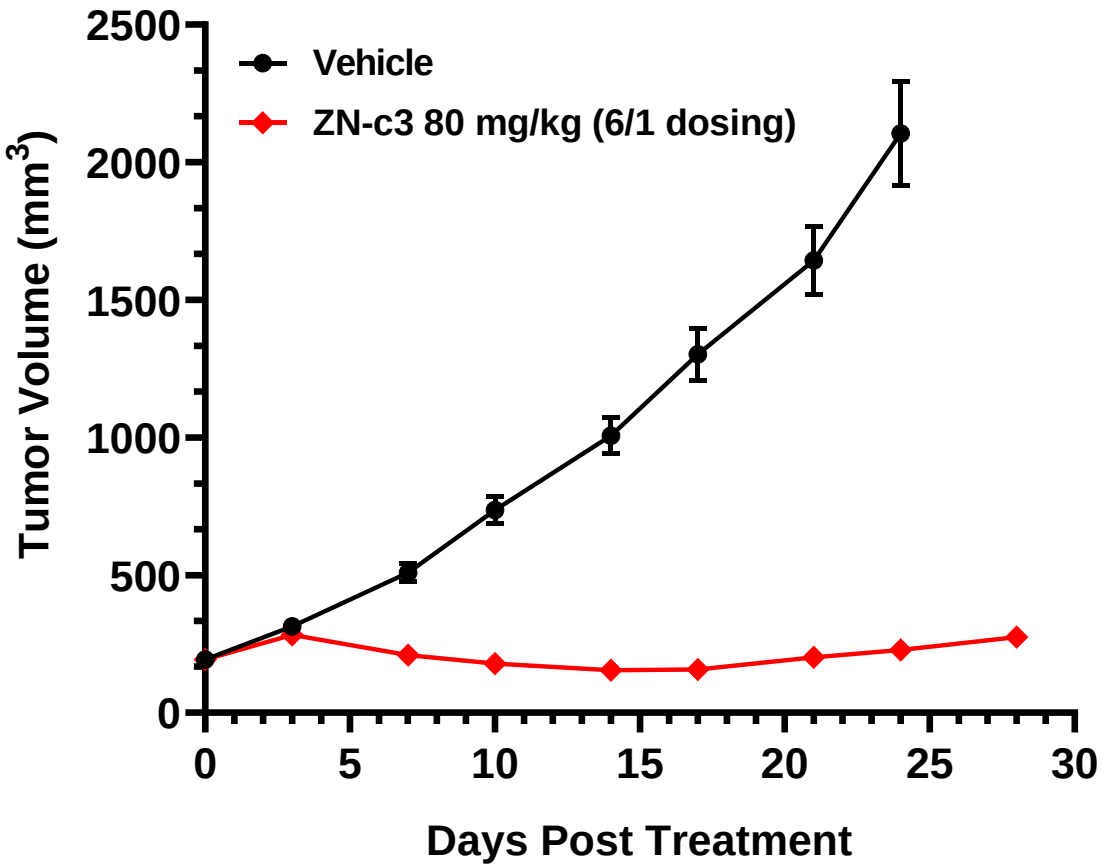
Comprises 10% of Endometrial Cancers with Highest Mortality



Source: Gynecologic Oncology 115 (2009) 142-153, David Boruta et al.; National Cancer Institute, SEER 2020 Data

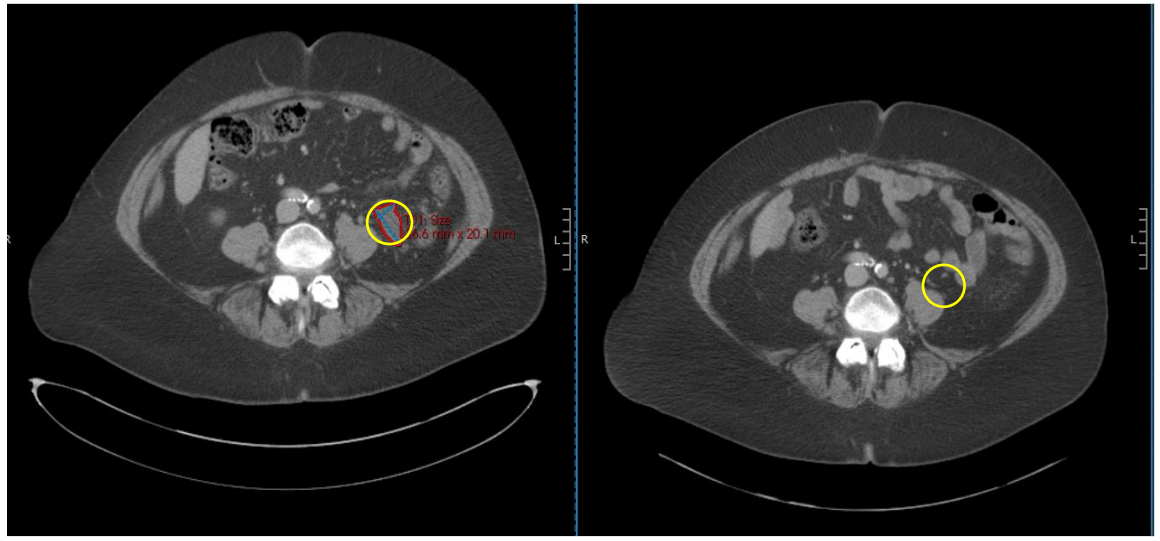
Opportunity for ZN-c3 Treatment in USC

SK-UT-1 Tumor Model



Zentalis Initiated a Phase 2 Monotherapy USC Trial in 3Q 2021

- Three USC patients had PR as best response (2 confirmed PRs, one unconfirmed PR) in Zentalis' ongoing Phase 1 study(1)
- USC is particularly amenable to Wee1 inhibition due to high frequency of TP53 mutation (>90%)(2)
  - Addressable patient population ~15,000(3)



(1) Data cut-off, May 14th 2021.
(2) Li, et al. JCO (2021).
(3) Gynecologic Oncology 115 (2009) 142-153, David Boruta et al.; National Cancer Institute, SEER 2020 Data. North America, Western Europe, and Japan.

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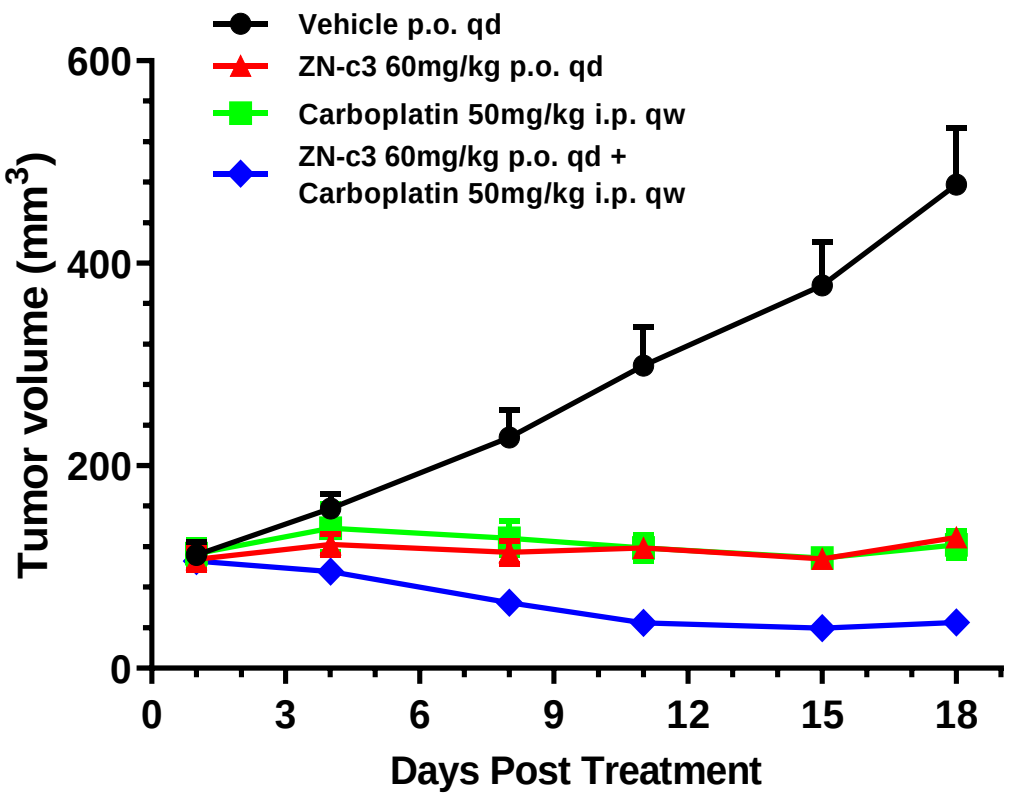
ZN-c3: Ovarian Cancer

ZN-c3 Combined with Chemotherapy is Active in a Preclinical Ovarian Cancer Model

Ovarian Cancer Model TOV21G

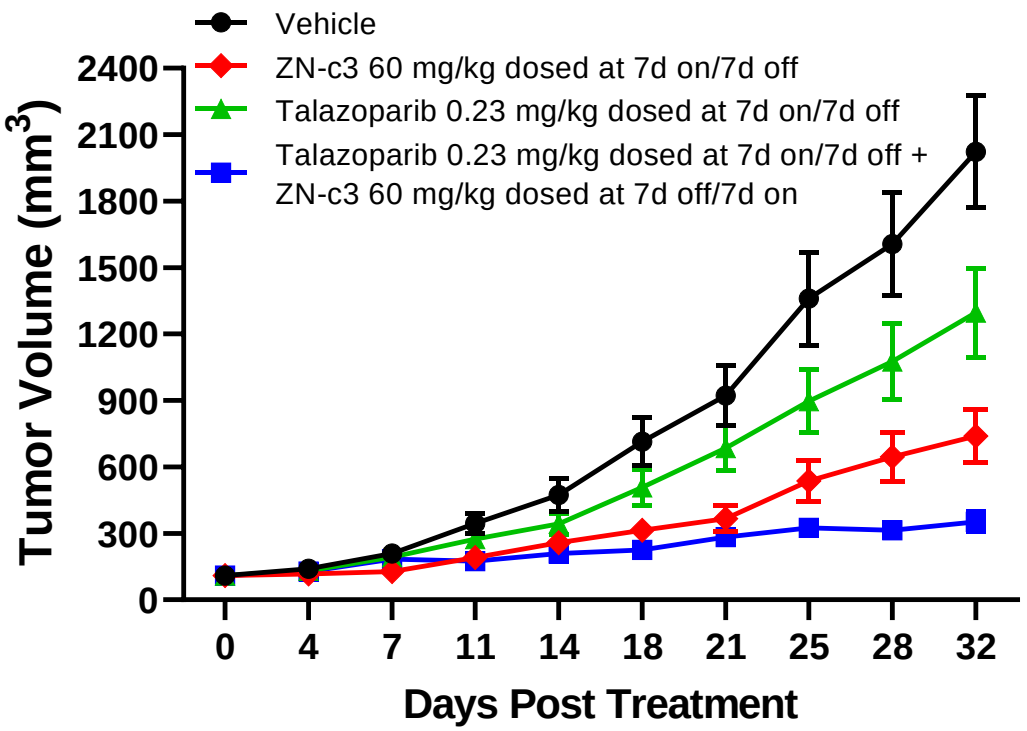


- ZN-c3 in combination with carboplatin shows better activity than single agent alone in an ovarian pre-clinical model
- ZN-c3 clinical study ongoing in combination with several chemotherapy agents
- Majority of epithelial ovarian cancer patients will relapse, with 25% platinum-resistant, experiencing disease recurrence within 6 months of 1L therapy, and having a poor prognosis(1)
- Potential addressable patient population of ~14,000(2)

(1) Leijen et al. JCO (2016)
(2) Informa Pharma Intelligence. Ovarian Cancer November 2020; Platinum resistant/refractory. North America, Western Europe, and Japan.

ZN-c3 + PARP Inhibition is Active in a Preclinical Ovarian Tumor Model

OVCAR3 Tumor Model (sequential dosing)



- Increased expression of Wee1 promotes de-sensitization of PARP inhibitors(1)
- Combination of Wee1 and PARP inhibition has been shown to induce replication stress, DNA damage and abrogation of the G2 DNA damage checkpoint, leading to significant tumor growth inhibition in pre-clinical models(2)
- A partial clinical benefit (PR) was observed in 2 of 6 BRCA1/2-mutated patients treated with a Wee1 inhibitor(3)
- Nearly all patients treated with PARP inhibitors relapse(4), making the ZN-c3/PARPi combination addressable patient population ~18,000(5)
- PARP class expected to generate $7bn in global revenue by 2025(5)(6)

(1) Garcia, TB eta al. Mol Cancer Ther. 2017 Oct;16(10):2058-2068
(2) Fan, Y et al. Cancer Cell. 2019 Jun 10;35(6):851-867
(3) Do, K et al. J Clin Oncol. 2015 Oct 20;33(30):3409-15
(4) McMullen et al. Cancers (2020)
(5) Informa Pharma Intelligence. Ovarian Cancer November 2020; estimated PARP treated patients. North America, Western Europe, and Japan.
(6) Sales for Lynparza, Rubraca, and Zejula.

ZN-c3 + PARPi Ovarian Study Schema

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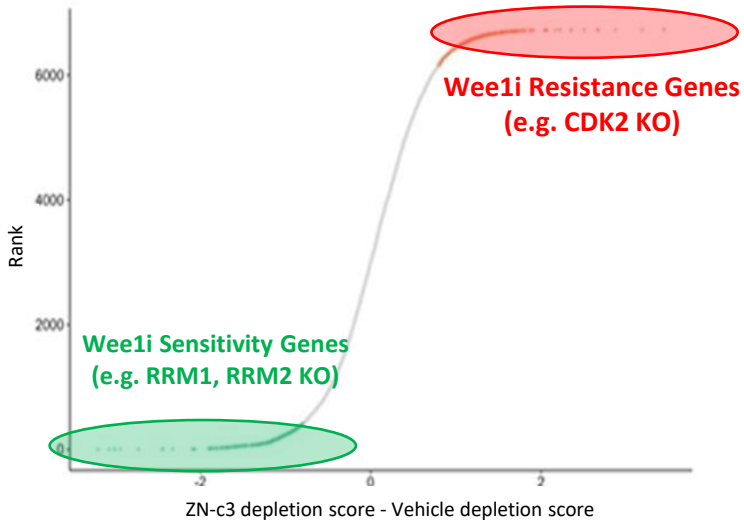
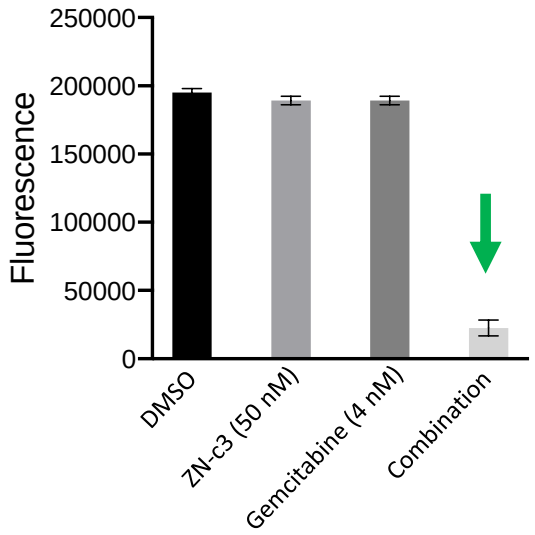
ZN-c3: Osteosarcoma

Opportunity for ZN-c3 in Combination with Gemcitabine

CRISPR screen



ZN-c3 + Gemcitabine in A427 Cells

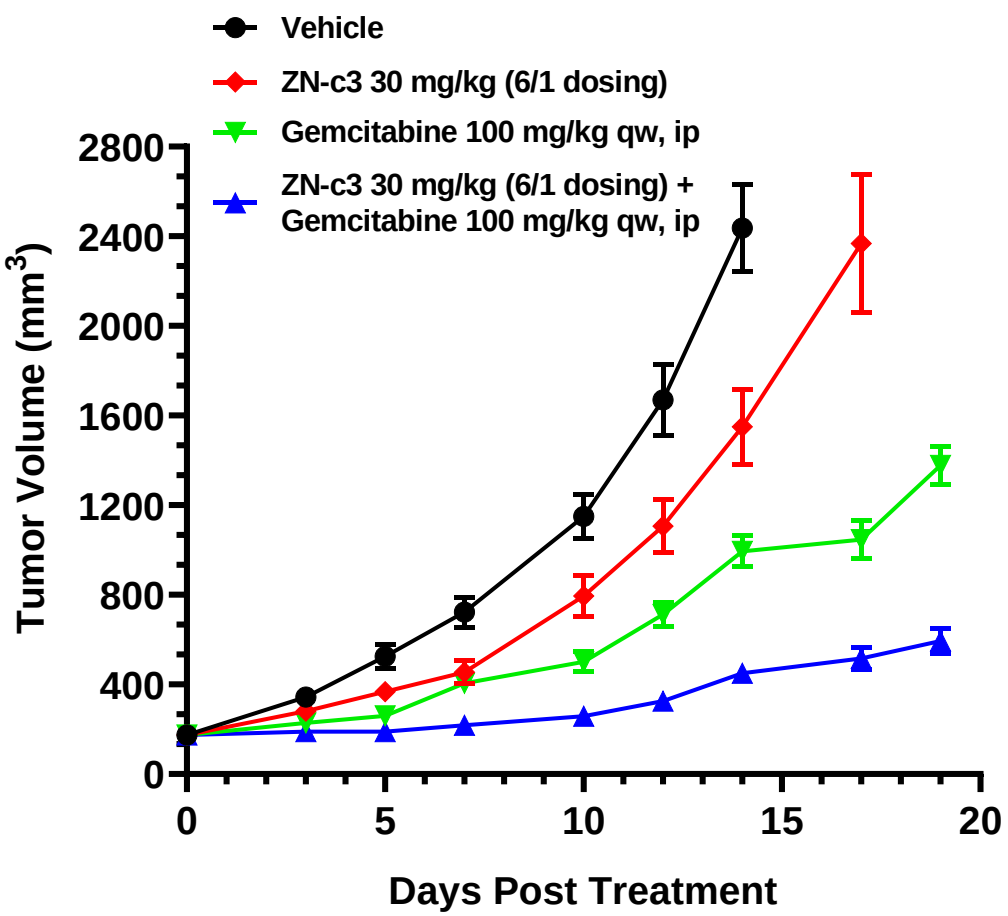


- Gemcitabine inhibits RRM1, a gene shown to be synthetically lethal with inhibition of Wee1 in our CRISPR screen(1)
- ZN-c3 + gemcitabine shows synergy in inhibiting viability of A427 cells(1)
- Wee1 inhibition + gemcitabine has also been shown to be active in a patient-derived xenograft mouse model *in vivo*(2)

(1) Data generated in collaboration with Tavros Therapeutics.
(2) Kreahling JM, Foroutan P, Reed D, et al. Plos One 2013;8(3):e57523

ZN-c3 in Combination with Gemcitabine Shows Strong Activity in an Osteosarcoma Cancer Model

Osteosarcoma Cancer Model SJSA-1



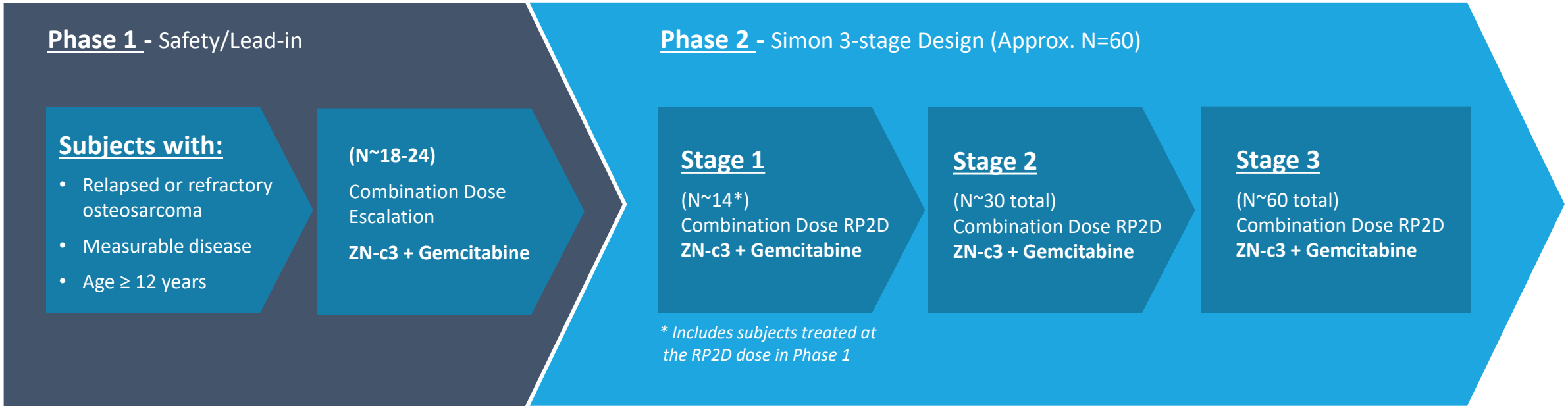
Clinical Unmet Need in Osteosarcoma

- Approximately 1,000 new cases in the US(1)
- Up to 90% have sequence mutations or structural variants in TP53 and are often enriched in relapsed or refractory cases, portending resistance to chemotherapy(2)
- No significant advances over the last 10 plus years(3)
- Overall survival rate for patients with metastatic or recurrent disease is <20%(4)

Phase 1/2 Initiated in 3Q 2021

(1) American Cancer Society. Last accessed on April 7th, 2020
(2) Tang et al. J *Orthop Res.* 2019;37(3):789–98
(3) Misaghi A et al. *Sicot-j*. 2018;4:12
(4) Harrison DJ et al. *Expert Rev Anticanc.* 2018;18:1, 39-50

ZN-c3 Osteosarcoma Study Schema



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ZN-c3: Promising Future Clinical Indications

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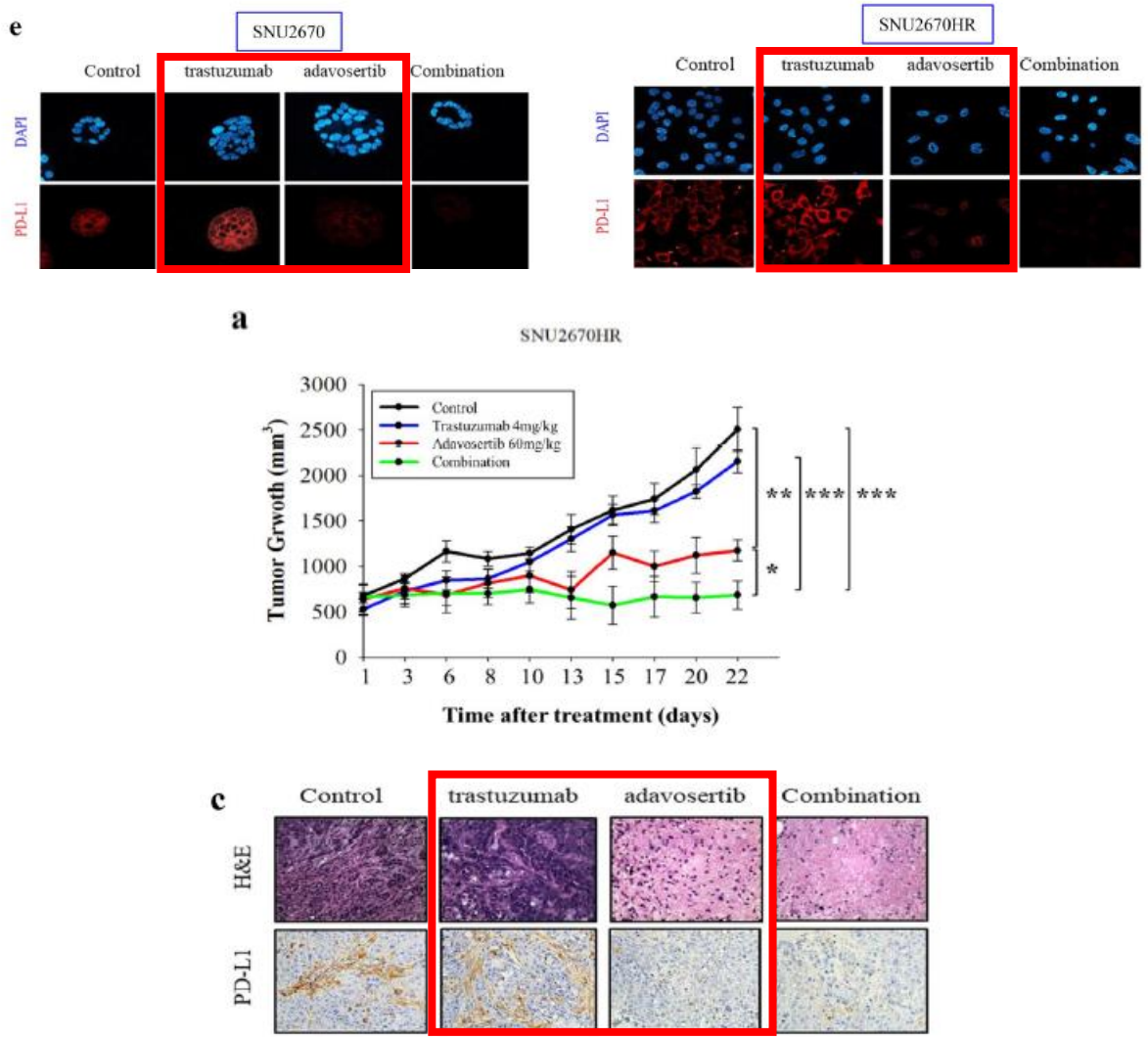
ZN-c3: Breast Cancer

Wee1 Inhibition Downregulates PD-L1 Expression and Reverses Trastuzumab Resistance

- Cell intrinsic PD-L1 stimulates DDR pathways such as Wee1 axis[1] and may antagonize activity of DDR inhibitors
- Inhibiting tumor cell-intrinsic PD-L1 may be synthetically lethal with DDR inhibitors[1]
- Wee1 inhibition has been shown to downregulate PD-L1 in HER-2+ gastric cancer cell lines[2] and reversed resistance to trastuzumab

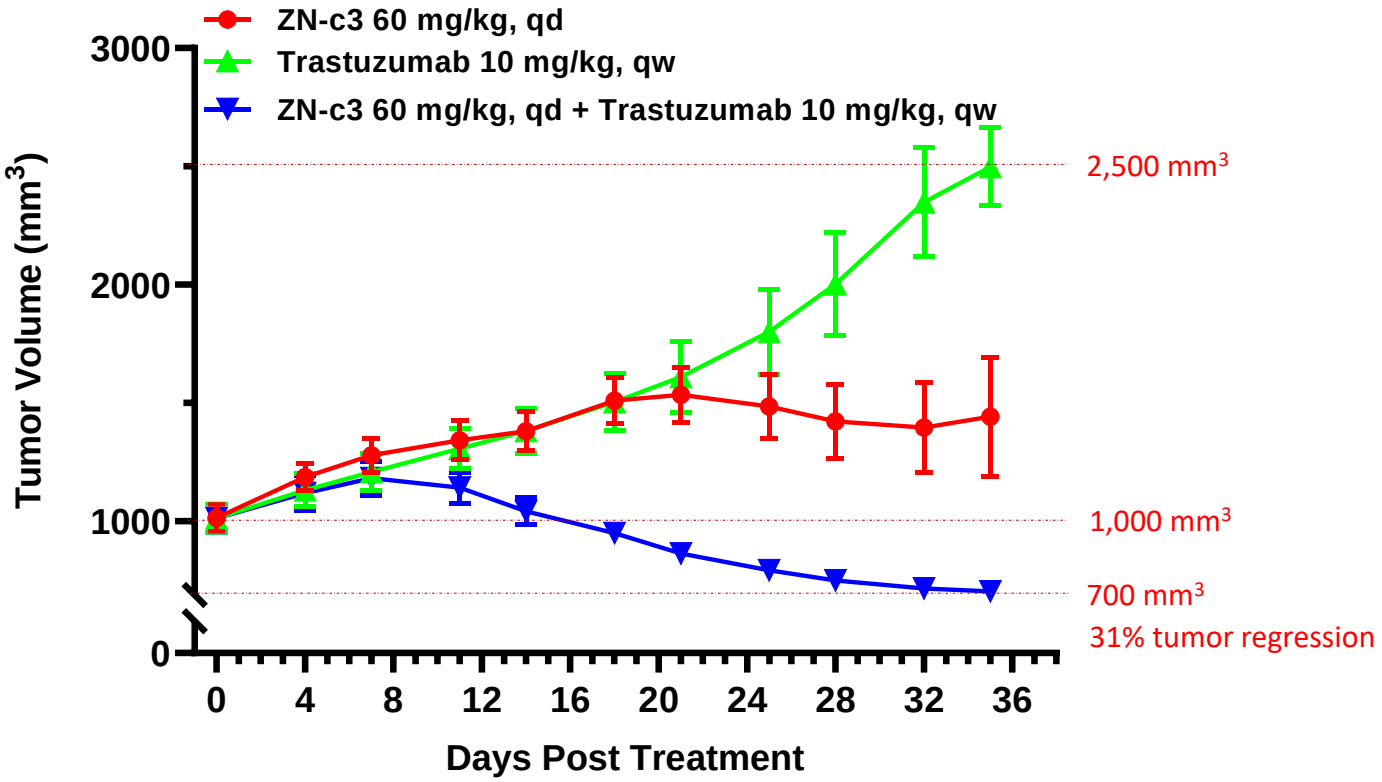
Wee1 inhibition downregulates expression of PD-L1[2]



(1) Kornepati AVR et al. SITC 2021, Abst #900
(2) Jin M-H et al. Gastric Cancer. 2021 Sep;24(5):1003-1020

ZN-c3 + Trastuzumab is Active in HER-2+ BC CDX Model from a Patient Resistant to Trastuzumab(1)

ZN-c3 + Trastuzumab regresses large tumors in the JIMT-1 model



- Trastuzumab is the standard of care in HER2+ breast cancer
- Estimated prevalence of HER2+ breast cancer in North America, Western Europe, and Japan is 400,000(2)
- Progressive disease after 1L trastuzumab often occurs after 12 months in the metastatic setting(3)
- Approximately 15% of adjuvant trastuzumab patients will relapse, suggesting an addressable patient population of 60,000(3)

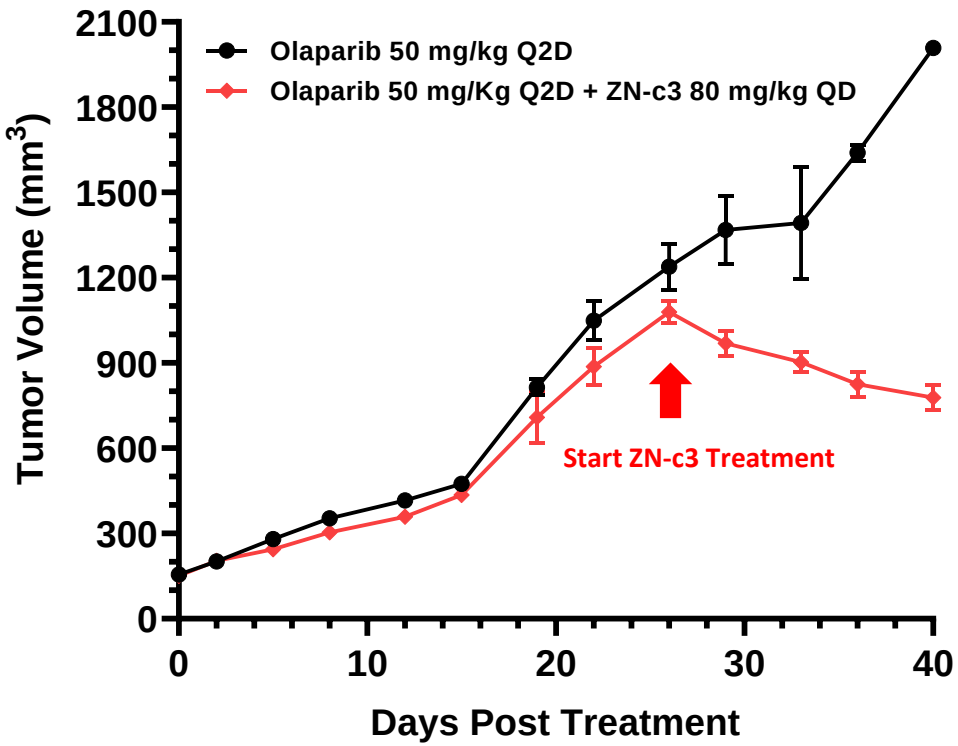
(1) Tanner M et al. Mol Cancer Ther. 2004 Dec;3(12):1585-92
(2) Informa Pharma Intelligence. HER2+ BC March 2021; All stages.
(3) Olson & Mullins. J Clin Trials (2013)

ZN-c3 is Active in a PARPi Resistant TNBC Tumor Model

MDA-MB-436 cells were made resistant to PARPi

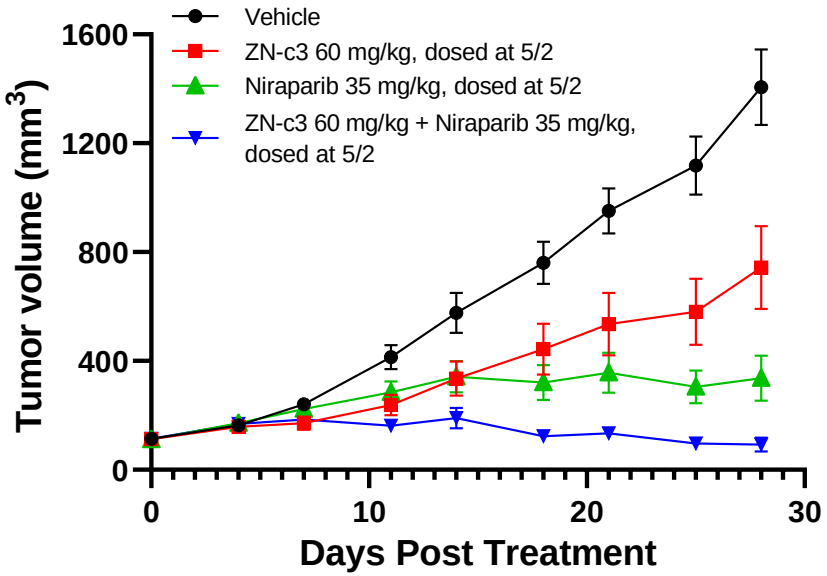
Compound	MDA-MB-436 (IC_{50}, nM)		
	Wild Type	Olaparib^R	Niraparib^R
ZN-c3	**282**	**174**	**185**
Niraparib	103	7731	8648
Olaparib	95	> 10000	> 10000
AZD6738 (ATRi)	3668	1842	1770
AZD0156 (ATMi)	4979	1986	2076
AZD7648 (DNA-PKi)	> 10000	> 10000	> 10000
MK8776 (CHK1i)	> 10000	5969	ND

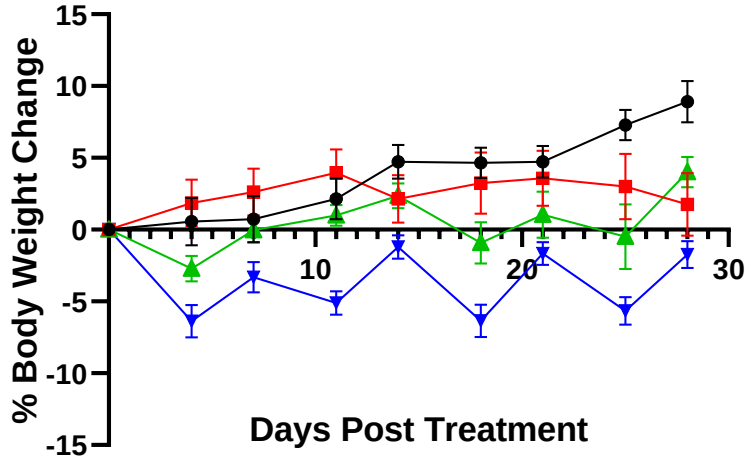
MDA-MB-436 OlaparibR TNBC model



- MDA-MB-436 cells (TNBC) were treated with PARP inhibitors *in vitro* until the cells become resistant
- ZN-c3 was equally active in wild type and resistant cells (Olaparib^R and Niraparib^R)
- ZN-c3 is active in this model *in vivo*

ZN-c3 + PARP Inhibitor Combination Induces Regressions and is Well Tolerated in a TNBC PDX Tumor Model





- Patients with TNBC have worse prognosis than patients with other breast cancer subtypes
- Cyclin E–high tumors have enhanced sensitivity to Wee1 inhibition(1)
- Combination of PARP and Wee1 inhibitors in TNBC:
  - Results in synergistic cell killing in pre-clinical models with either BRCA1 mutations or high levels of cyclin E(2)
  - Has shown to induce replication stress, DNA damage and abrogation of the G2 DNA damage check point leading to significant tumor growth inhibition in pre-clinical models(3)
- Wee1 inhibition may broaden the application range of PARP inhibitors in TNBC
- Up to 20% of TNBC patients harbor BRCA1/2 mutations(4), suggesting an addressable patient population of ~45,000 from a total prevalence of 225,000(5)

(1) Chen X et al Clin Cancer Res. 2018 Dec 15;24(24):6594-6610
(2) Chen X Cancers (Basel). 2021 Apr 1;13(7):1656
(3) Fan, Y et al. Cancer Cell. 2019 Jun 10;35(6):851-867
(4) Yin et al. Breast Cancer Res (2020)
(5) Informa Pharma Intelligence. TNBC BC December 2020; North America, Western Europe, Japan

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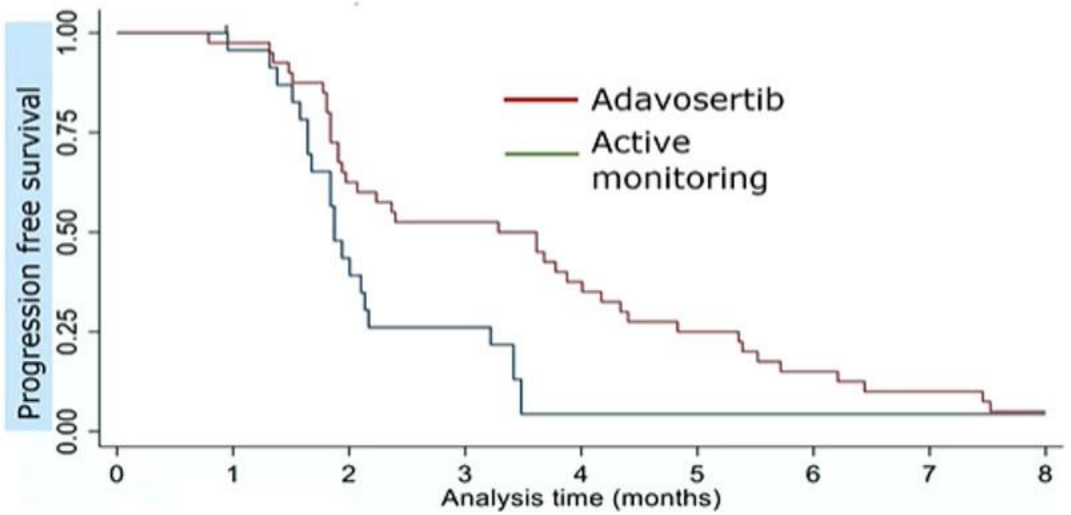
ZN-c3: Colorectal Cancer

Inhibition of Wee1 Is Effective in TP53 and RAS Mutant Metastatic Colorectal Cancer

Primary Analysis: Progression Free Survival from Point of Randomization into FOCUS 4-C[(1)]



Events/ N	Median PFS (mths)
40/40	3.61
22/24	1.87

HR = 0.35 (0.18 – 0.68),
p = 0.0022

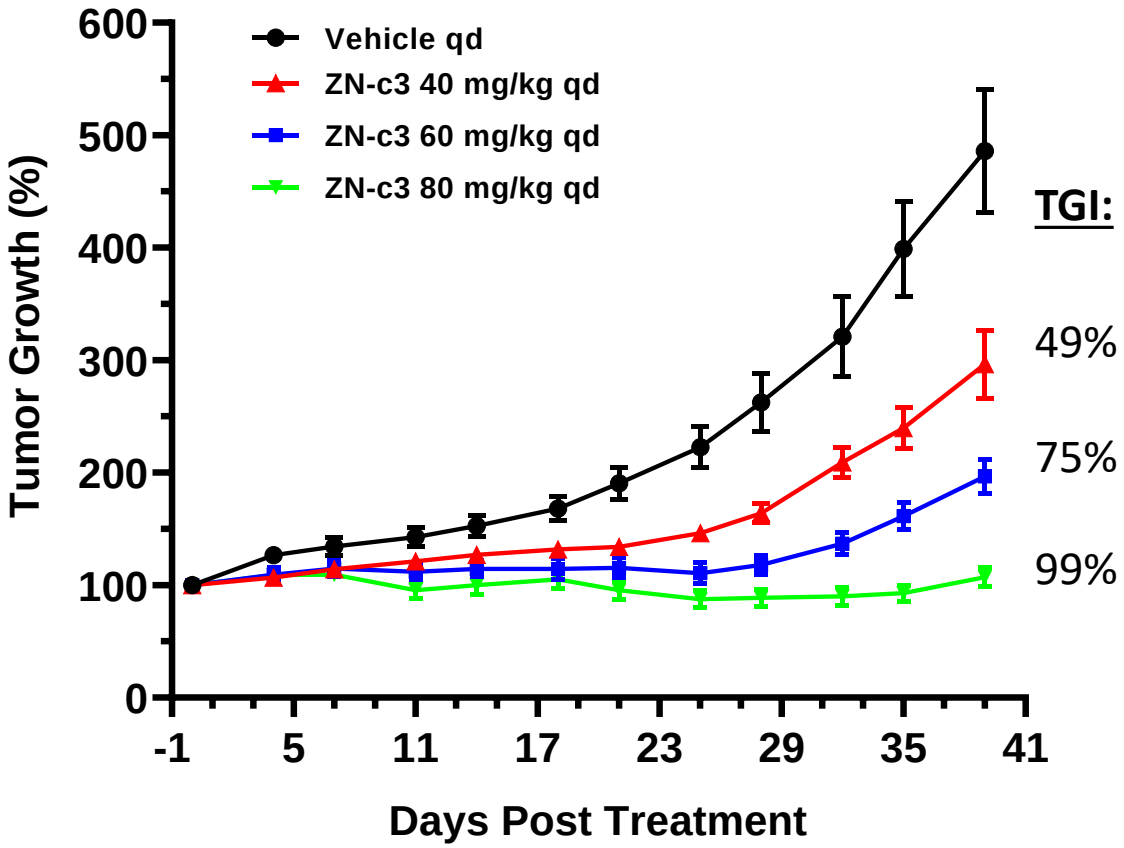
Treatment Arm	Numbers at risk (failures)								
	0	1	2	3	4	5	6	7	8
AM	24 (1)	22 (12)	10 (4)	6 (5)	1 (0)	1 (0)	1 (0)	1 (0)	1 (0)
Adavosertib	40 (1)	39 (14)	25 (4)	21 (6)	15 (5)	10 (4)	6 (2)	4 (2)	2 (0)

2021 ESMO congress

(1) Seligmann JF et al. J Clin Oncol. 2021 Sep 18

ZN-c3 is Active in a KRAS/TP53 Mutant Preclinical Colorectal Cancer Model

SW1116 CRC xenograft model

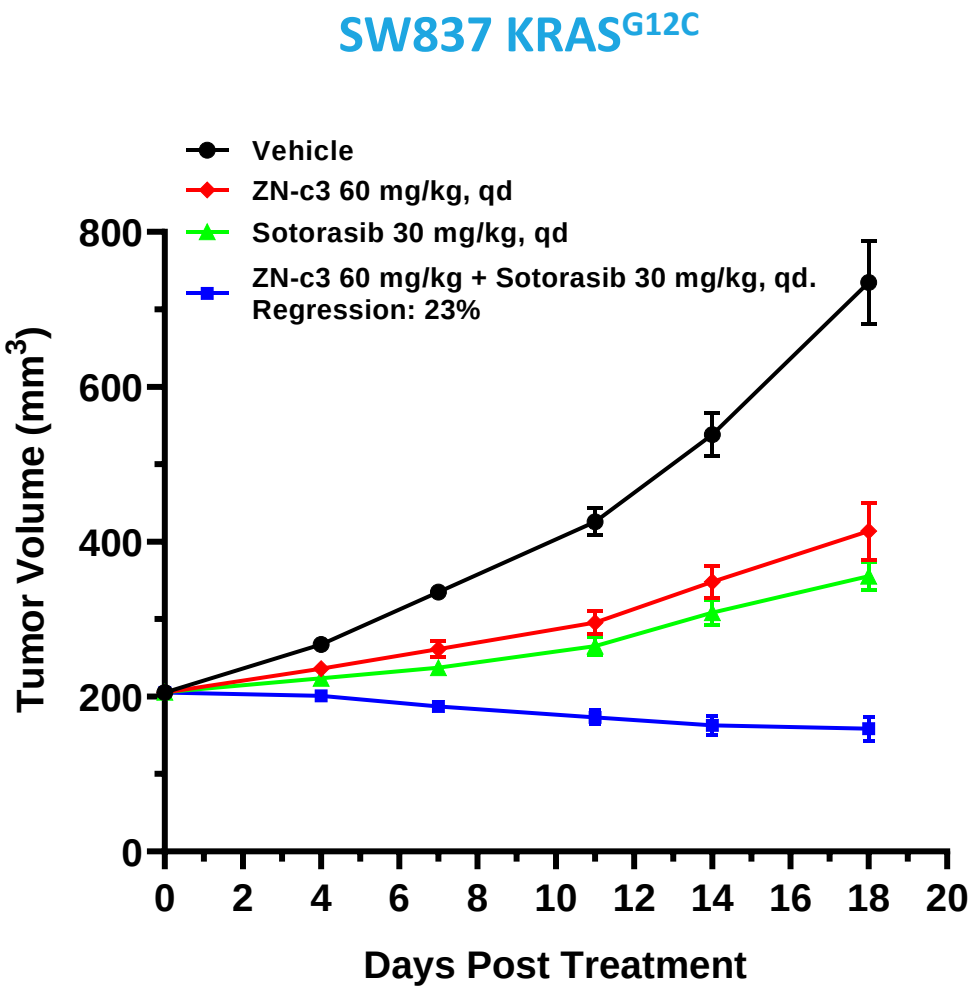


TP53 mutant (VUS), KRAS^{G12A}

- Oncogenic mutations such as those in KRAS, drive cell cycle progression leading to replication stress. Loss of TP53 function leads to dependence on the G2/M check point governed by Wee1 to repair DNA damage[(1)(2)]
- Multiple opportunities for combining ZN-c3 with different agents: 5-FU, irinotecan, anti-PD-1 and others
- Mutant CRC sub-populations represent a large prevalent market opportunity:
  - TP53/KRAS mutant population in the US alone is ~500,000 patients[(3)(4)]

(1) Matheson CJ et al Trends Pharmacol Sci. 2016 Oct;37(10):872-881
(2) Murcia L et al. Cell Rep 28: 119-131.e4, 2019
(3) American Cancer Society Facts & Figures 2020
(4) Based on flowchart of patients from Seligmann JF et al. J Clin Oncol. 2021 Sep 18

ZN-c3 in Combination with Sotorasib(1) Induces Regressions in a KRAS/TP53 Mutant Preclinical Colorectal Cancer Model



- Wee1 inhibition has been shown to improved PFS compared with active monitoring in patients with KRAS/TP53 mutated CRC (FOCUS4C trial)(2)
- These data support combining ZN-c3 with KRASG12C inhibitors in this population

(1) Sotorasib (AMG510, KRAS G12C inhibitor)
(2) Seligmann JF et al. J Clin Oncol. 2021 Sep 18

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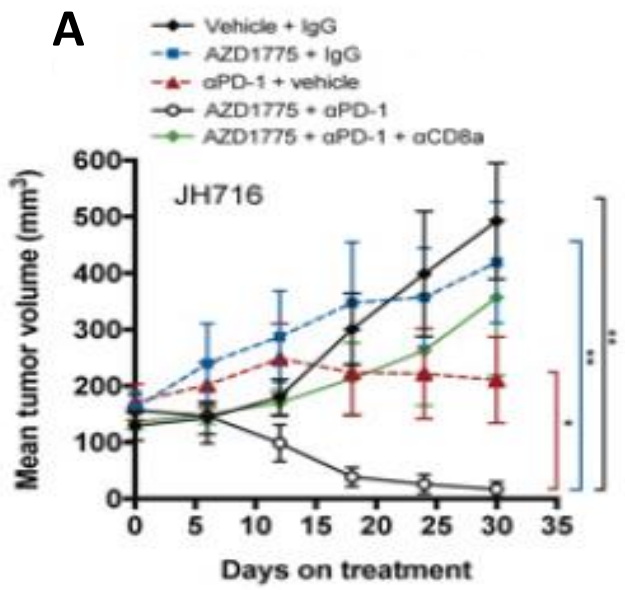
ZN-c3: I/O Potential

Wee1 Combined with Anti-PD1 Therapy has Better Anti-Tumor Activity than Single Agent Alone in Preclinical Models

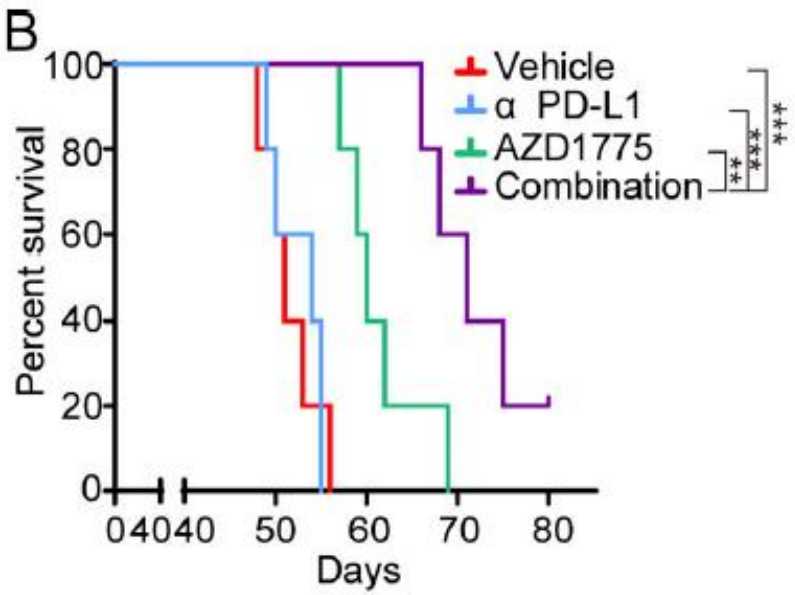
Wee1i Induces IFN Signaling and Immune Activation

Generation of genetically engineered mouse lung organoid models for squamous cell lung cancers allows for the study of combinatorial immunotherapy(1)



Mean tumor volume of subcutaneous JH716 (n=5–7/group) implants in mice treated with vehicle, AZD1775, anti–PD-1, or the combination when tumor burden reached approximately 150mm^3

Wee1 inhibition induces anti-tumor immunity by activating ERV and the dsRNA pathway(2)

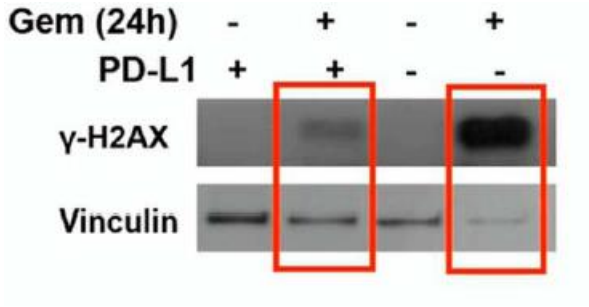


Kaplan–Meier survival curves of C57BL/6 mice with ID8 tumors treated as described

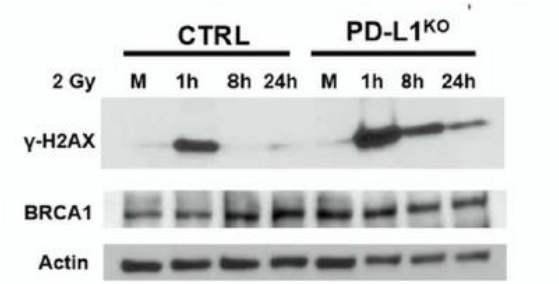
(1) Hai J et al. Clin Cancer Res. 2020 Jul 1;26(13):3431-3442
(2) Guo E et al. J. Exp. Med. 2021 Vol. 219 No. 1

Depletion of Tumor Cell–Intrinsic PD-L1 induces Synthetic Lethality with Inhibitors of the DNA Damage Response[1]

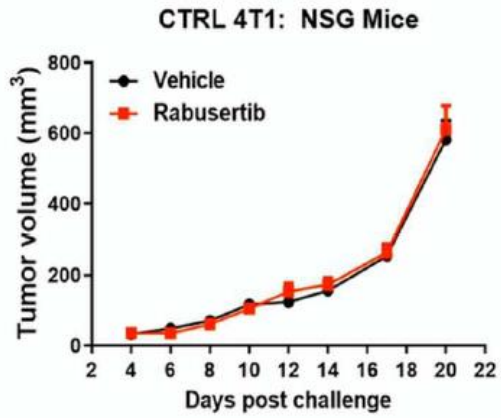
Tumor PD-L1 antagonizes DNA damage caused by gemcitabine[1]

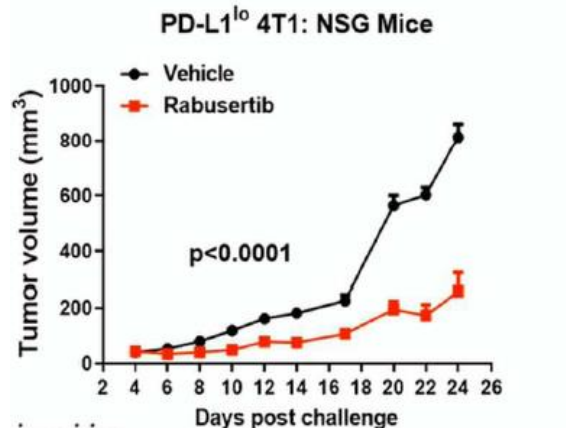


Tumor PD-L1 promotes Homologous recombination DNA repair [1]

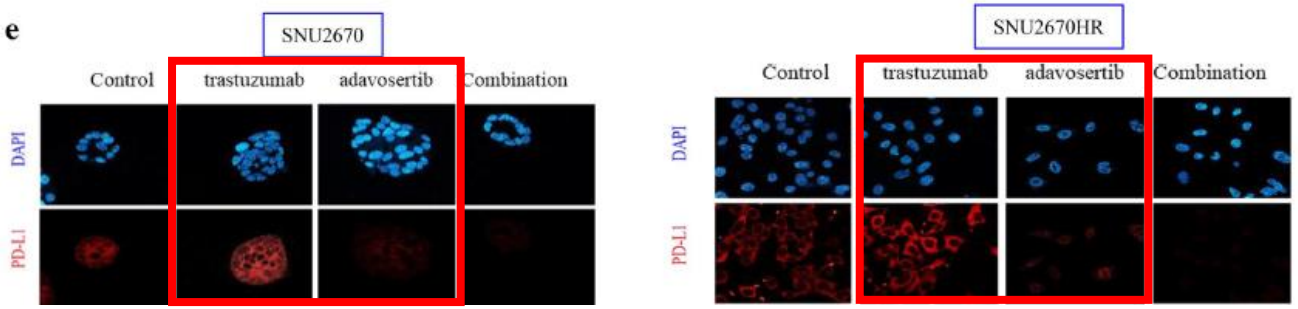


Tumor PD-L1 promotes resistance to Chk1 inhibitor *in vivo*[1]





Wee1 inhibition has been shown to downregulate PD-L1 in HER-2+ gastric cancer cell lines[2]

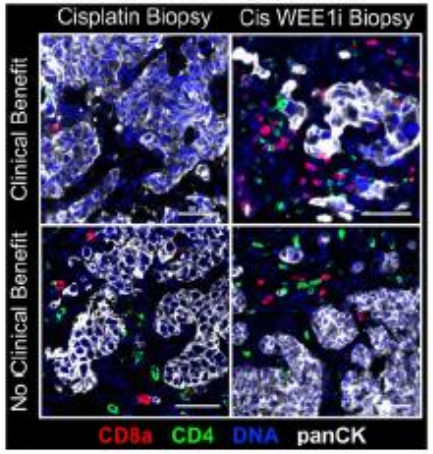


Wee1 inhibition may deplete tumor PD-L1 avoiding resistance as seen for CHK1i

(1) Abstract #900. Kornepati AVR et al. SITC 2021
(2) Jin M-H et al. Gastric Cancer. 2021 Sep;24(5):1003-1020

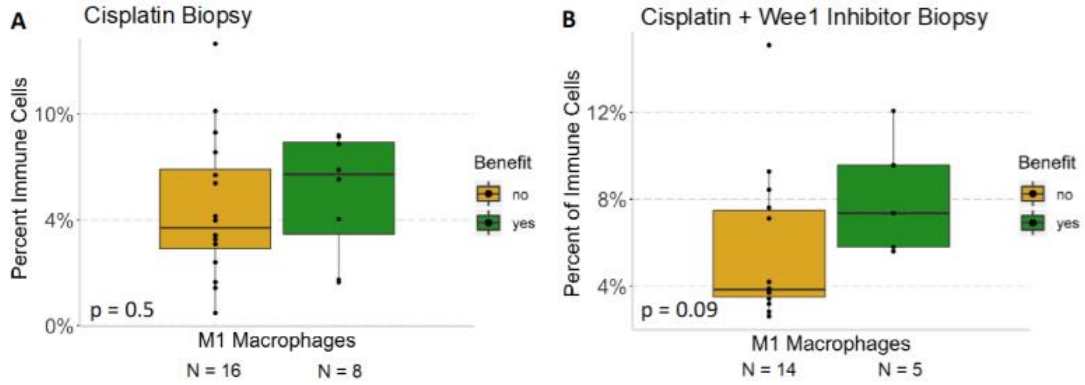
Combination of Wee1i and Cisplatin Favorably Alters the Tumor Microenvironment

T Cells



Intra-tumoral $CD3^+CD4^+$ and $CD3^+CD8^+$ T cell infiltration increased more in patients with a partial response or stable disease versus those with progressive disease(1)

M1 Macrophages



Anti-tumor M1 macrophages also trended higher in post-Wee1 inhibitor biopsies from patients with clinical benefit (Wilcoxon P = 0.09)(1)

Wee1 inhibition may be associated with activation of cGAS/STING pathway, which can result in Type I interferon response and immune stimulation

(1) Keenan et al. Clin Canc Res. (2021)

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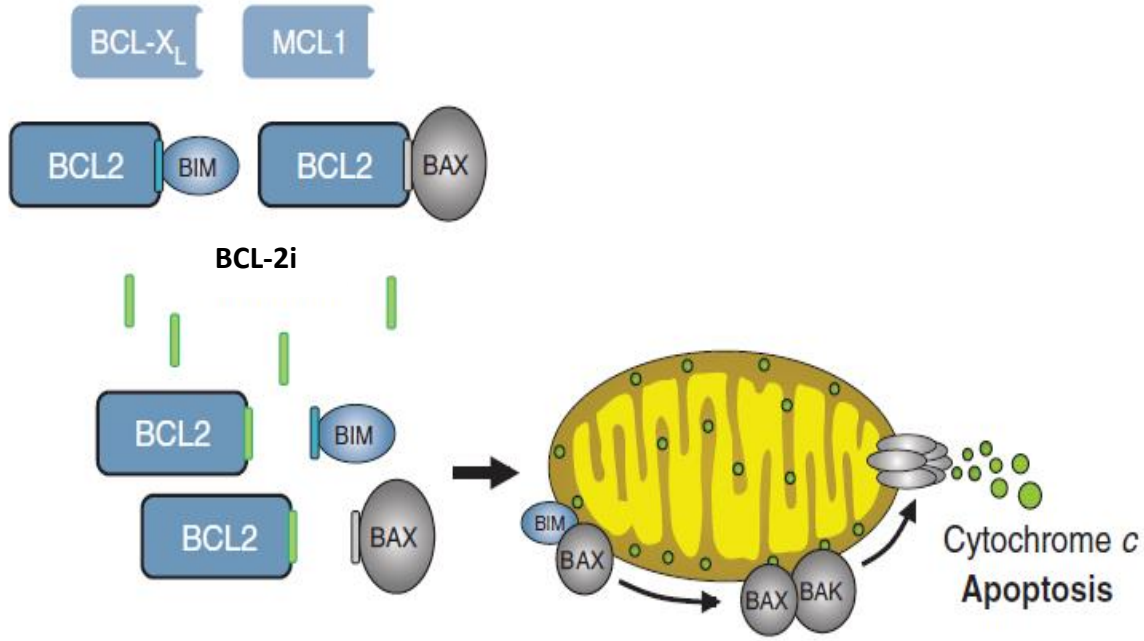
ZN-d5

BCL-2 Inhibitor

BCL-2: A Clinically Validated Oncology Target

- Execution of the intrinsic apoptotic pathway is controlled by the BCL-2 family of proteins at the level of the mitochondrial outer membrane[1][2]
- BCL-2 is an antiapoptotic protein involved in tumor survival and chemo resistance that binds to and sequester the apoptosis effectors, as well as the apoptosis "sensitizers" preventing the initiation of the intrinsic apoptotic pathway[3]
- Venetoclax, a BCL-2 inhibitor, has been granted approval for CLL, small lymphocytic lymphoma (SLL) and subtypes of AML. Venetoclax has also shown clinical benefit in clinical trials in NHL and Multiple Myeloma, and in a few solid tumors as a monotherapy and/or in combination[3]

Mechanism of action of BCL-2 inhibitors[4]



(1) Bhola PD and Letai A. Mol Cell. 2016;61(5):695-704
(2) Konopleva M and Letai A. Blood. 2018 Sep 6;132(10):1007-1012
(3) Diepstraten ST et al. Nat Rev Cancer. 2021 Oct 18
(4) Konopleva M et al. Cancer Discov. 2016 Oct;6(10):1106-1117

ZN-d5: Oral BCL-2 Inhibitor for Hematologic Malignancies

1 IDENTIFY: BCL-2

- Broad applicability as anti-apoptotic target
- Difficult target given intracellular location
- Potential for use in combination
- **Venetoclax: only approved BCL-2 inhibitor**
- Small number of agents in development

2 ANALYZE: Venetoclax

- Demonstrated clinical efficacy in hematologic malignancies
- Approvals in CLL/SLL and AML
- Addresses side effects of previous BCL-2 inhibitors
- **Thrombocytopenia still observed in 29% of patients, attributed to BCL-xL inhibition**

3 CREATE: ZN-d5

- Designed to optimize:
  - Potency
  - Selectivity
  - PK properties

4 GENERATE: Preclinical Evidence

- Improved *in vitro* potency and has 10x improved selectivity for BCL-2 vs BCL-xL compared to venetoclax
- Observed to bind with higher affinity to BCL-2 mutants than venetoclax in *in vitro* assay
  - Mutations in BCL-2 may be driving sub-clonal pockets of resistance to venetoclax
- Strong anti-tumor activity consistent with venetoclax in leukemia model

ZN-d5: A Potent BCL-2 Inhibitor with Improved Selectivity for BCL-2

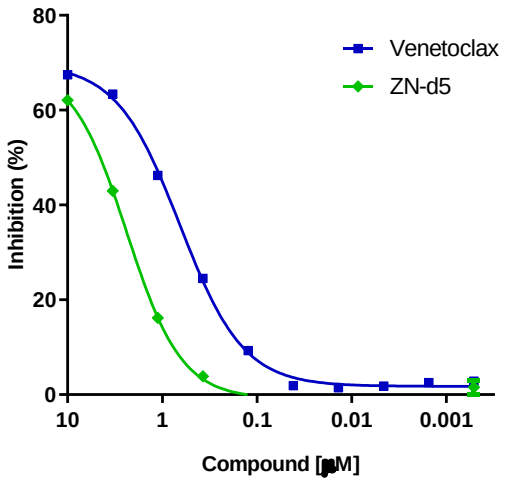
ZN-d5 has >14x Improved Selectivity for BCL-2 vs BCL-x_L and Binds With Higher Affinity to BCL-2 Mutants than Venetoclax

Compound ID	Affinity (Kd, nM)			IC_{50} (nM) BCL-2 Type			
	BCL-2	BCL-x_L	MCL-1	WT	G101V	F104L	D103Y
Venetoclax	0.41	28	>30000	1.3	7.3	8.4	18.3
ZN-d5	0.29	190	>30000	1.4	3.7	1.4	5.0

ZN-d5 Exhibits Potent *In Vitro* Activity Across Multiple Tumor Cell Lines

Compound ID	CTG IC_{50} (nM)							
	ALL	MCL		DLBCL		AML		
	RS4;11	Mino-1	Granta-519	DOHH-2	Toledo	HL-60	Molm-13	MV4-11
Venetoclax	2.9	1.1	161	43	191	26	18	3.8
ZN-d5	5.1	0.1	89	50	92	21	39	5.1

ZN-d5: Less Human Platelet Toxicity Compared to Venetoclax in an *In Vitro* Assay



Compound ID	CTG (24 h) IC_{50} (μM)
Venetoclax	0.6
ZN-d5	2.4

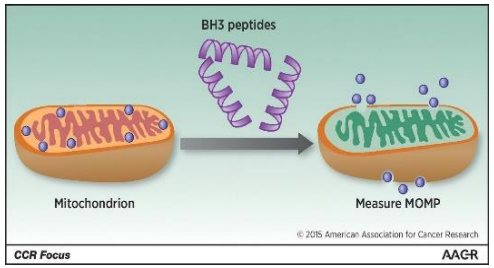
ZN-d5 shows activity in preclinical models of ALL, NHL and AML

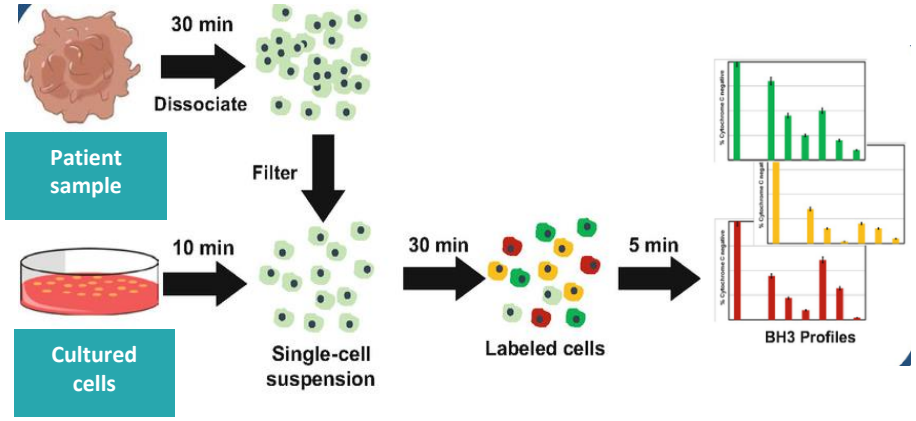
BH3 Profiling for Patient Selection / Stratification

BH3 profiling enables determination of sensitivity to BH3 mimetics

- Zentalis has licensed BH3 profiling technology(1) from Dana-Farber Cancer Institute
- BH3 profiling has been used in several clinical trials to determine sensitivity to BH3 mimetics such as BCL-2 inhibitors(1-4)

- Functional assay to assess the propensity of cells to undergo apoptosis ('apoptotic priming'), and the relative dependence on different antiapoptotic proteins
- Measures changes due to mitochondrial outer membrane permeabilization (MOMP)





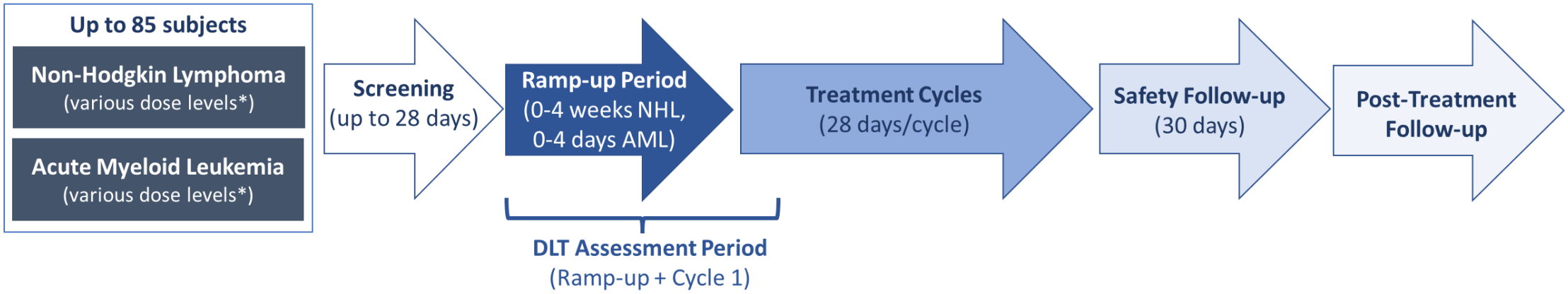
Adapted from Fraser C et al., BCL-2 Family Proteins, 2018

(1) Letai A et al. Cancer Lett. 2013 May 28; 332(2): 202–205
(2) Konopleva M et al. Cancer Discov. 2016 Oct;6(10):1106-1117
(3) Anderson MA et al. Blood. 2016;127(25):3215-3224
(4) Kapoor I et al. Cell Death Dis. 2020;11(11):1-11

ZN-d5: Clinical Update

ZN-d5-001 is a first-in-human dose escalation study of ZN-d5 in relapsed/refractory NHL and AML

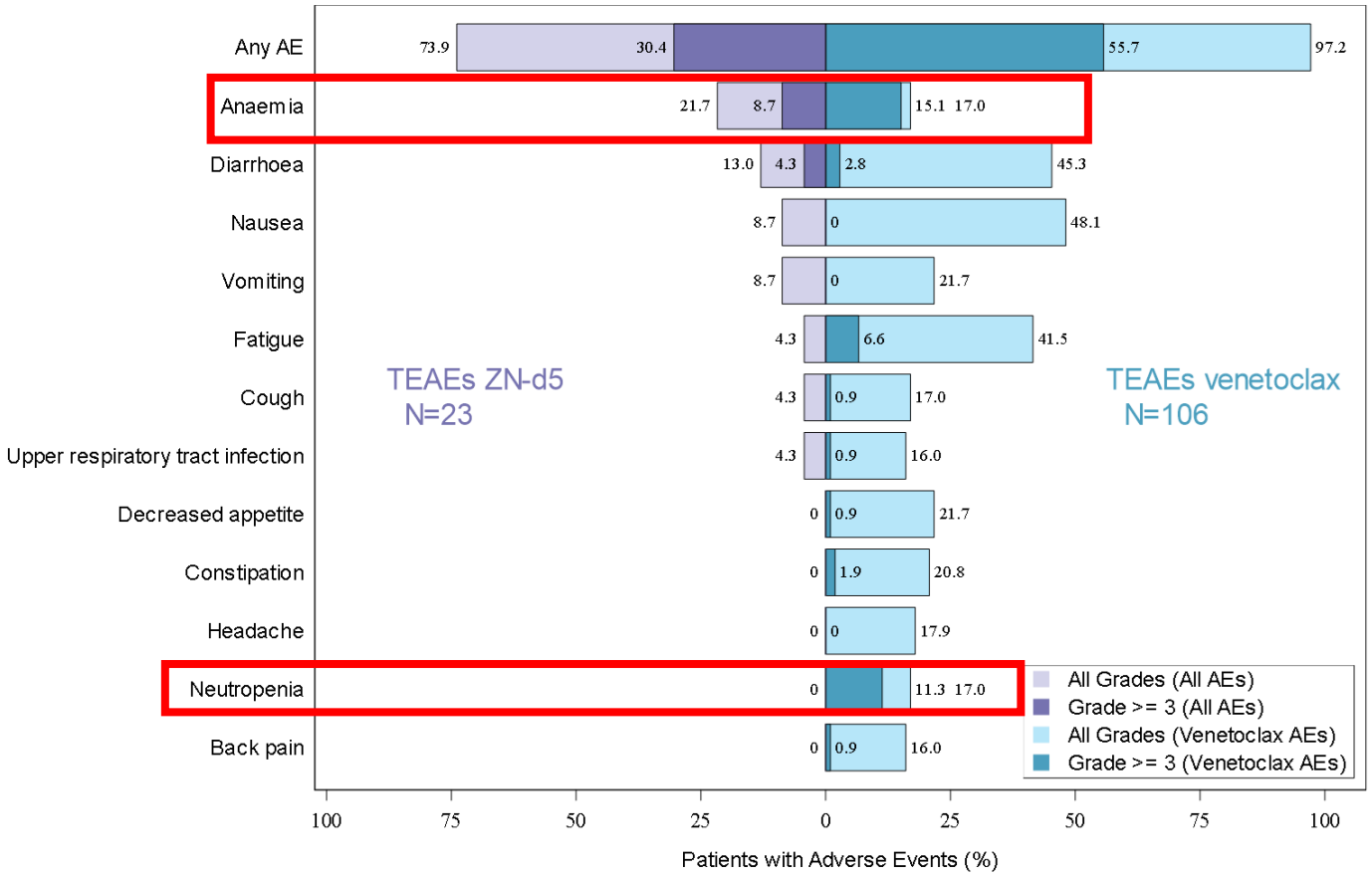
- NHL recruitment opened in October 2020 and AML in June 2021
- As of November 3: 27 treated (23 NHL including 13 DLBCL)
- Escalated doses through 1200 mg daily in the fasting state currently and will transition to the fed state in 2022



ZN-d5: Favorable Early Comparison to Venetoclax in NHL

- ZN-d5 100-1200 mg, empty stomach
- Venetoclax 200-1200 mg with food
- Early toxicity profile in NHL favorable vs. published venetoclax data(1)
  - Fewer AEs of any Grade, Grade ≥3
  - No TLS observed
  - Venetoclax AEs not dose-dependent

Adverse Event	Any Grade			
	All Doses (N = 106)	≤ 400 mg (n = 22)	600 to 900 mg (n = 33)	1,200 mg (n = 51)
Emergent*				
Any event	103 (97)	21 (96)	33 (100)	49 (96)
Nausea	51 (48)	9 (41)	15 (45)	27 (53)
Diarrhea	48 (45)	7 (32)	14 (42)	27 (53)
Fatigue	44 (42)	10 (45)	9 (27)	25 (49)
Decreased appetite	23 (22)	4 (18)	4 (12)	15 (29)
Vomiting	23 (22)	5 (23)	6 (18)	12 (24)
Constipation	22 (21)	6 (27)	7 (21)	9 (18)
Headache	19 (18)	2 (9)	7 (21)	10 (20)
Anemia	18 (17)	7 (32)	6 (18)	5 (10)
Cough	18 (17)	7 (32)	6 (18)	5 (10)
Neutropenia	18 (17)	4 (18)	8 (24)	6 (12)
Back pain	17 (16)	3 (14)	6 (18)	8 (16)
Upper RTI	17 (16)	5 (23)	8 (24)	4 (8)



(1) Davids et al, J Clin Oncol 2017;35:826-833; emergent AEs reported in ≥15% of subjects. ZN-d5 results as of 03 Nov 2021 data cutoff.

ZN-d5: Preliminary Cross-Trial Data Comparison to Venetoclax

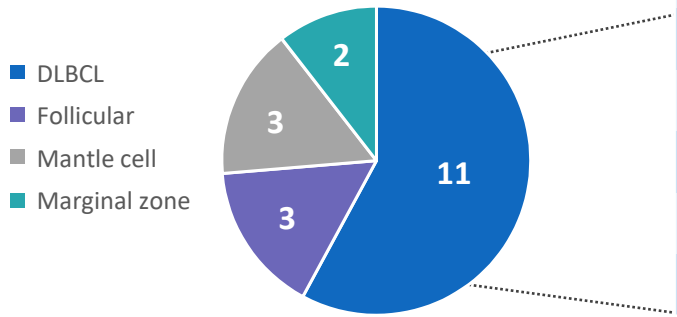
Pharmacology Data Comparison

	ZN-d5	Venetoclax
Dosing state	empty stomach	with food
Mean AUC (µg·hr/mL) @ 400 mg	8.7	32.8 [2]
Unbound drug fraction (%)[1]	0.12	0.06

- Higher AUCs expected for ZN-d5 when dosing commences with food in 2022

Clinical Data Comparison

ZN-d5 All Evaluable Subjects [3]



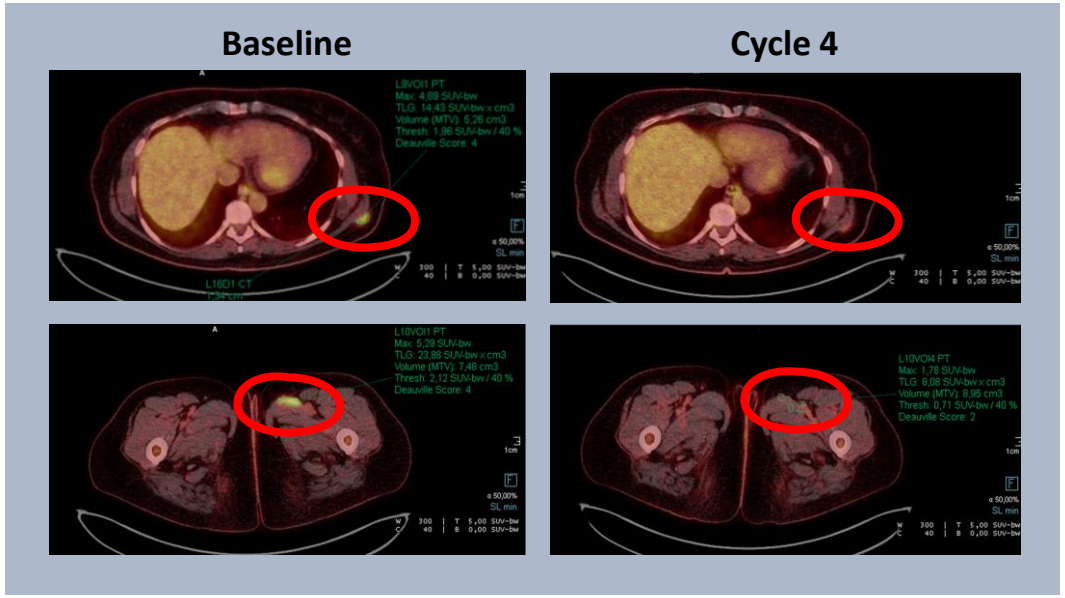
		ZN-d5	Venetoclax
DLBCL	n	11	34
	ORR	2 (18%)	6 (18%)
	CR	1 (9%)	4 (12%)
	cPR	1 (9%)	2 (6%)
	SD	2 (18%)	8 (24%)
	PD	7 (64%)	19 (56%)

Caveat: Small number of evaluable NHL subjects for cross-study comparison

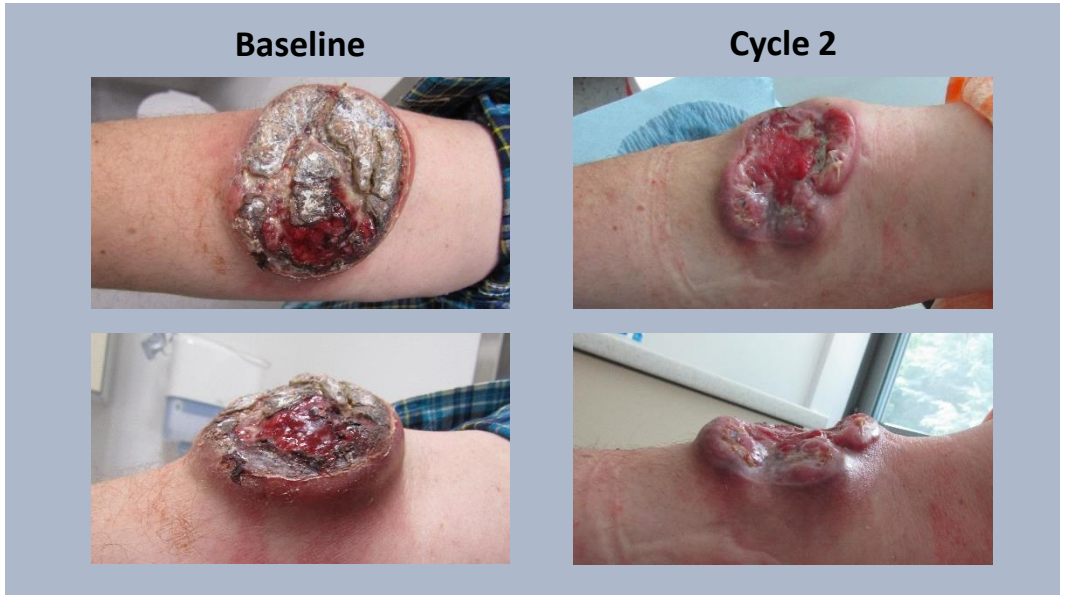
- Clinical activity (18% ORR, 36% DCR) in DLBCL is promising at this early stage and on par with venetoclax activity
- An additional unconfirmed PR in follicular lymphoma at 800 mg ZN-d5 (w/o food) observed after Nov 3, 2021 data cut

(1) Human plasma protein binding comparison was run multiple times in 10% plasma and calculated to 100% plasma.
(2) Salem et al. J Clin Pharmacol 2017;57:484-492
(3) N=19 response-evaluable NHL subjects dosed with ZN-d5

ZN-d5: Efficacy Snapshots

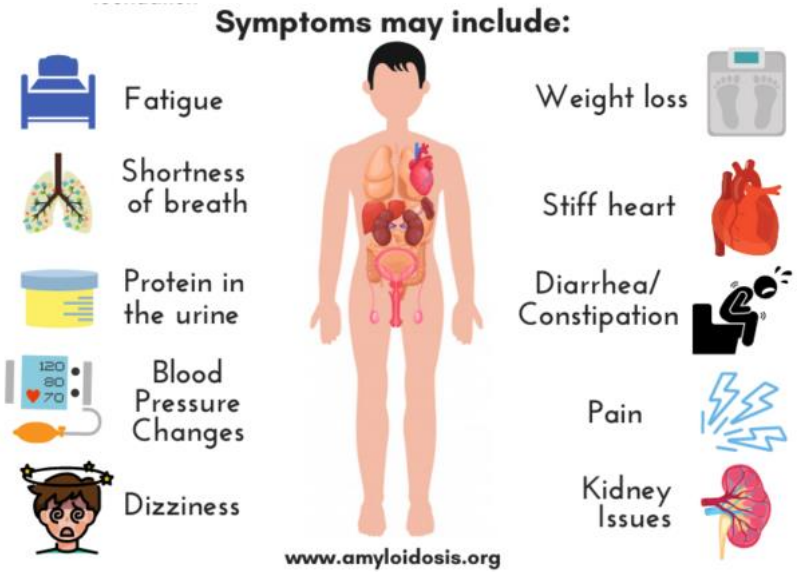


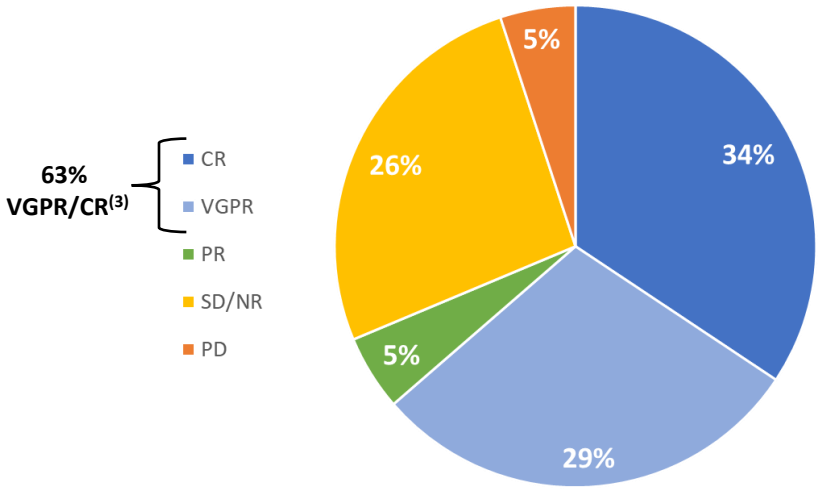
- 61 yo female with DLBCL
  - Stage IV disease, diagnosed 2014
  - 3 prior lines of therapy including R-CHOP and stem cell transplant
- ZN-d5 400 mg QD (fasting)
- CR by investigator assessment. Duration of response 8.5+ months (last scan October 2021)



- 60 yo male with DLBCL
  - Stage IV disease, diagnosed 2008
  - 4 prior lines of therapy including R-CHOP and stem cell transplant
- ZN-d5 800 mg QD (fasting)
- Cutaneous lesion had substantial response; nodal disease progressed

ZN-d5 in AL (Primary) Amyloidosis





- AL Amyloidosis: Deposition of immunoglobulin light chains
  - Clonal plasma cell population secretes misfolding light chain
  - Progressive systemic amyloid accumulation causes widespread organ damage
  - **High morbidity and mortality**
- Orphan disease
  - Estimated worldwide prevalence is 75,000(1)
  - About 4k new cases/year in the US(2)
- Not a cancer, but treated like one
  - Agents active in multiple myeloma used in first-line and relapsed/refractory settings
  - Daratumumab only approved therapy, for first-line use with CyBorD
- **Relapsed/refractory setting is a high unmet medical need**
- BCL-2 is a validated target for plasma cell diseases
  - Venetoclax is active in multiple myeloma; small case series have shown venetoclax activity in AL amyloidosis(3)
  - ZN-d5 is active in multiple myeloma models

(1) Zhang et al. Clin Lymphoma Myeloma Leuk. 2019;19(suppl 10):e339
(2) Kyle et al, Mayo Clin Proc. 2019;94:465-471
(3) Premkumar et al, Blood Cancer J 2021;11:10; hematologic response rate in 38 evaluable patients.

Study of ZN-d5 in AL Amyloidosis

Based on the unmet medical need, **Zentalis will initiate a potentially registrational global clinical study of ZN-d5 in relapsed/refractory AL amyloidosis in 1Q 2022**

Key Inclusion Criteria

AL amyloidosis, r/r to 1-3 prior lines of therapy; dFLC ≥20 mg/L; history of cardiac, renal, hepatic and/or neurologic involvement; ECOG PS ≤2; adequate hematologic and organ function

Part A

Bayesian optimal interval dose escalation

Objectives: safety, efficacy, phase 2 dose

n = 15-30

Part B

Two-stage Bayesian optimal phase 2 design

Stage 1
(n = 80)

Stage 2
(n = 40)

Objectives: efficacy (hematologic response rate) and safety

Study Initiation 1Q 2022

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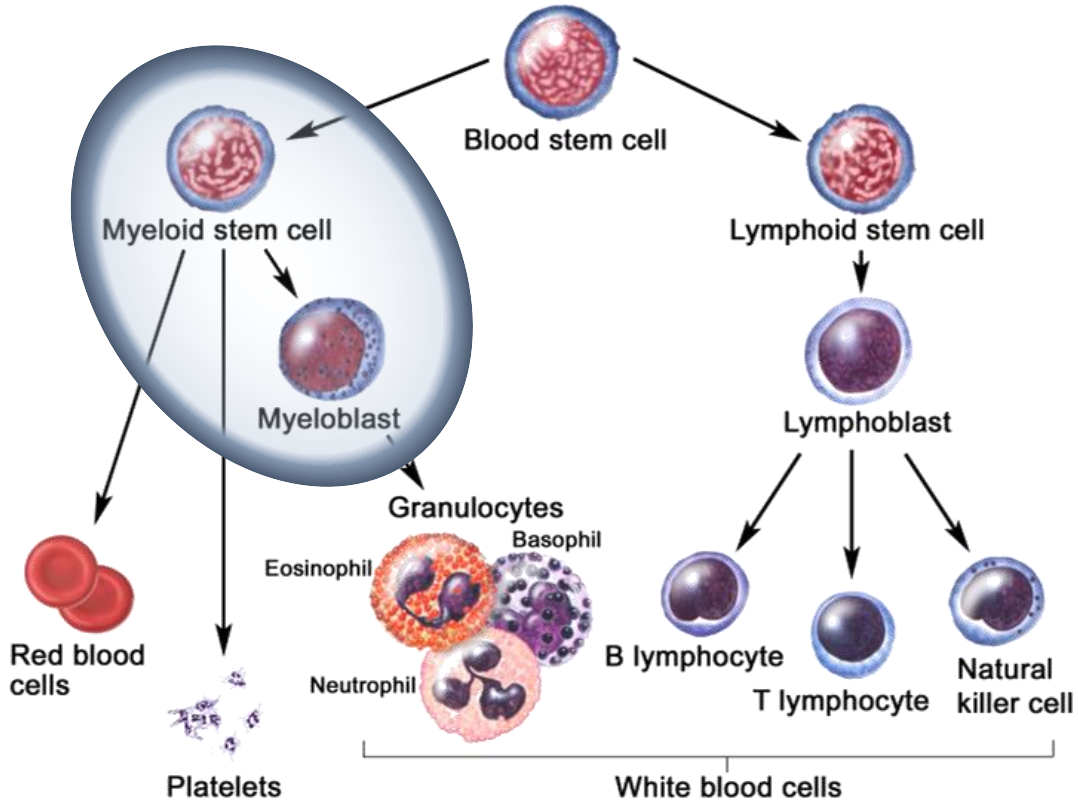
ZN-d5 + ZN-c3: Acute Myeloid Leukemia (AML)

Acute Myeloid Leukemia (AML) is an Aggressive Heme Malignancy

- AML is an aggressive malignancy of myeloid precursor cells with suppression of normal hematopoiesis & resulting pancytopenias
- Incidence/mortality in US is 20k/10k per year; <30% 5-year survival
- R/R AML and AML in patients not eligible for standard induction chemotherapy is a significant unmet need
- Preclinical data demonstrate combination is effective
- Venetoclax + low-dose Ara-C or HMAs is approved for newly diagnosed AML in patients ≥75 yrs, or who cannot tolerate intensive induction chemotherapy
- TP53 is a poor prognostic and negative predictive biomarker
  - TP53 mutations confer poor prognosis in AML (1)
  - Efficacy (CR/CRi, DoR, OS) of V+LDAC or HMA is inferior in TP53 mutated AML(2)
- **TP53 mutations likely associated with sensitivity to Wee1 inhibition** (3)

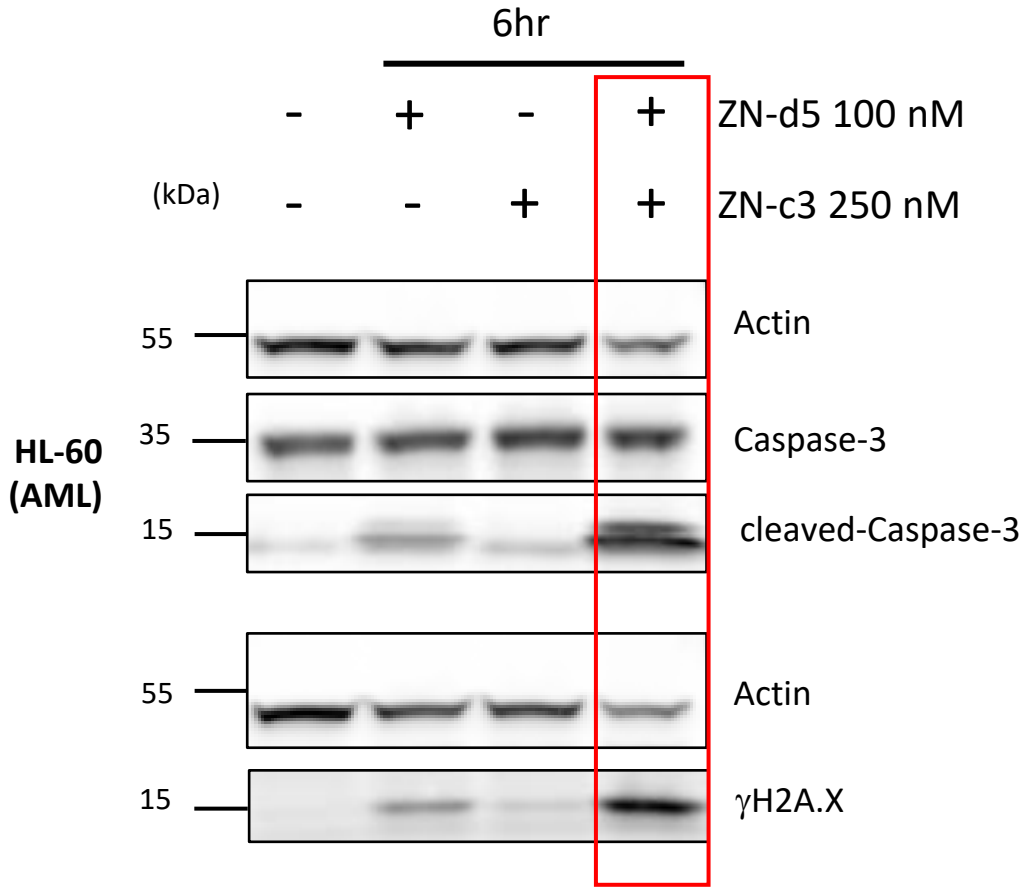


(1) Kadia 2016; Kuykendal 2018; Molica 2021
(2) Wei 2019, 2020; DiNardo 2018, 2019, 2020; Aldoss 2021; Samra 2020; Sillar 2019
(3) Diab 2019; Pappano 2014; Clausse 2016; Ku 2017

A Novel Therapeutic Modality Combining BCL-2 and Wee1 Inhibitors

***In vitro* screens show that ZN-d5 plus ZN-c3 is active in several tumor types, including AML. This combination represents a novel MOA:**

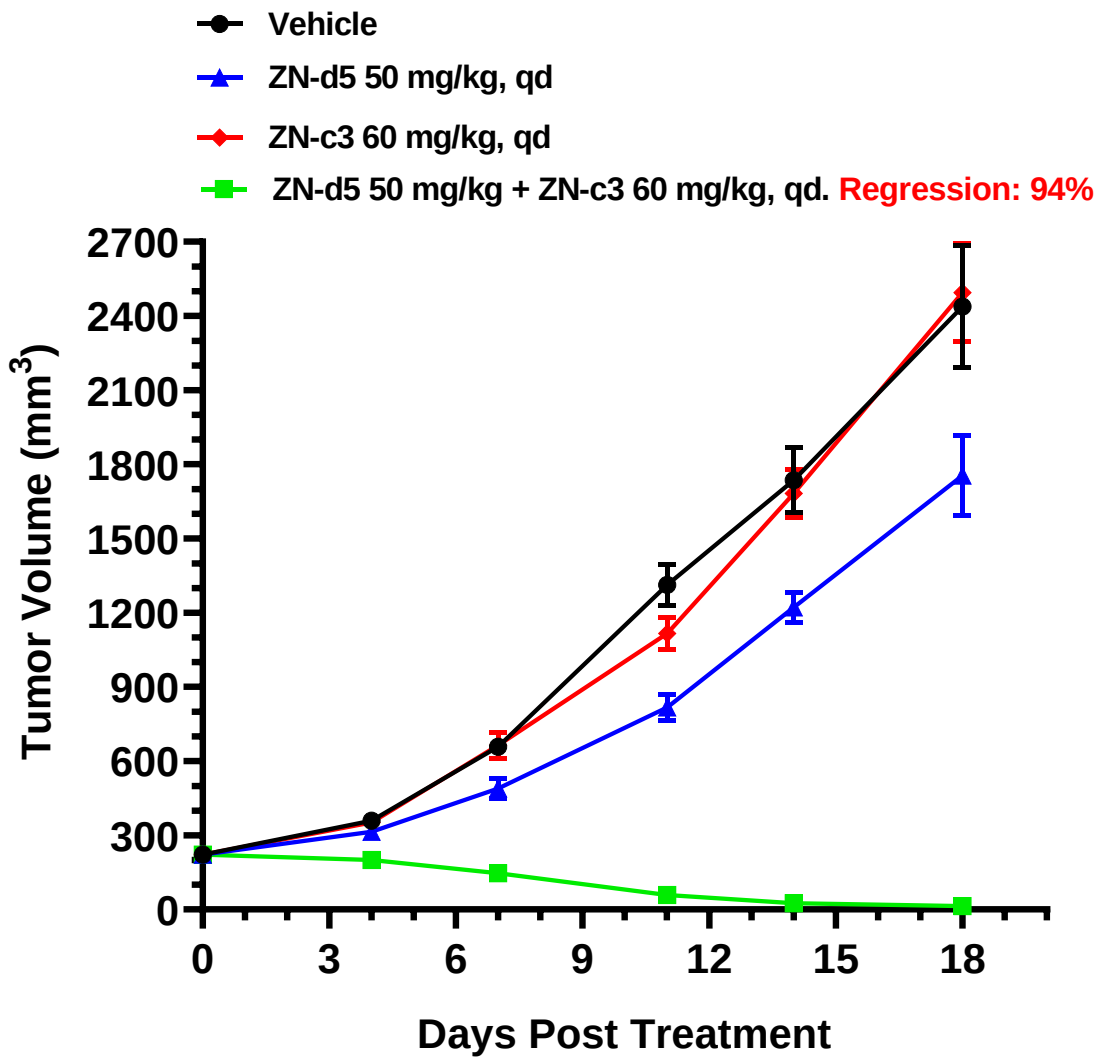
- **ZN-d5 induces DNA damage at subtherapeutic doses** (increase in γH2AX)
- ZN-c3 combined with ZN-d5 **enhances the levels of DNA damage and apoptosis** (cleaved caspase-3)
- The effects are seen at low doses of ZN-d5 that cause minimal cell death by apoptosis



IC_{50} in HL-60: ZN-d5 = 125 nM; ZN-c3 = 1,000 nM

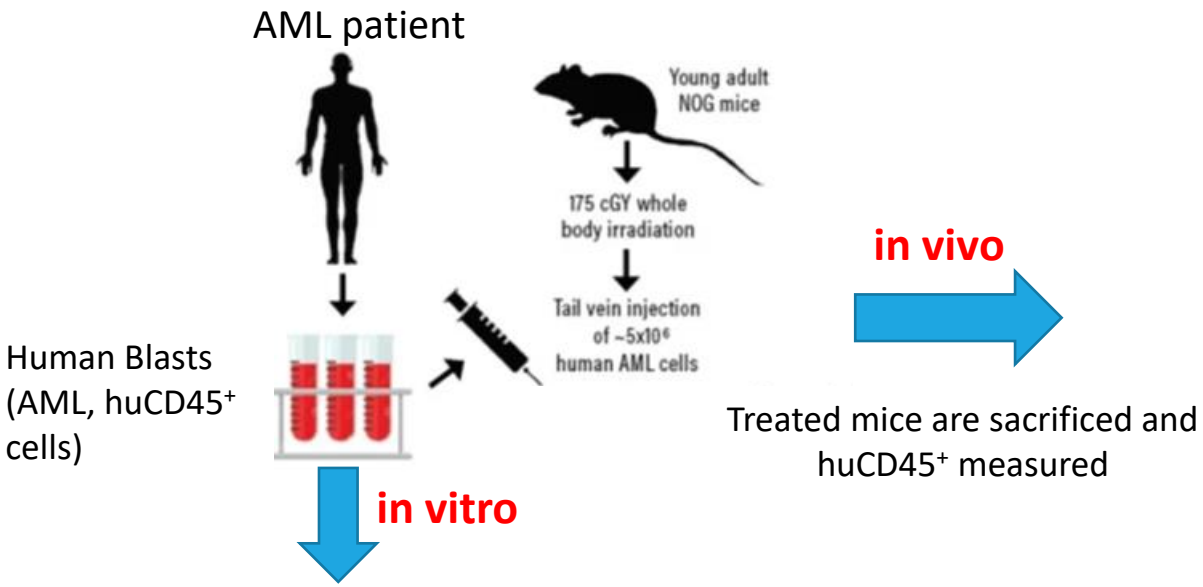
The Combination of BCL-2 and Wee1 Inhibitors Results in Synergism in Several Tumor Models Including AML

HL-60 AML model



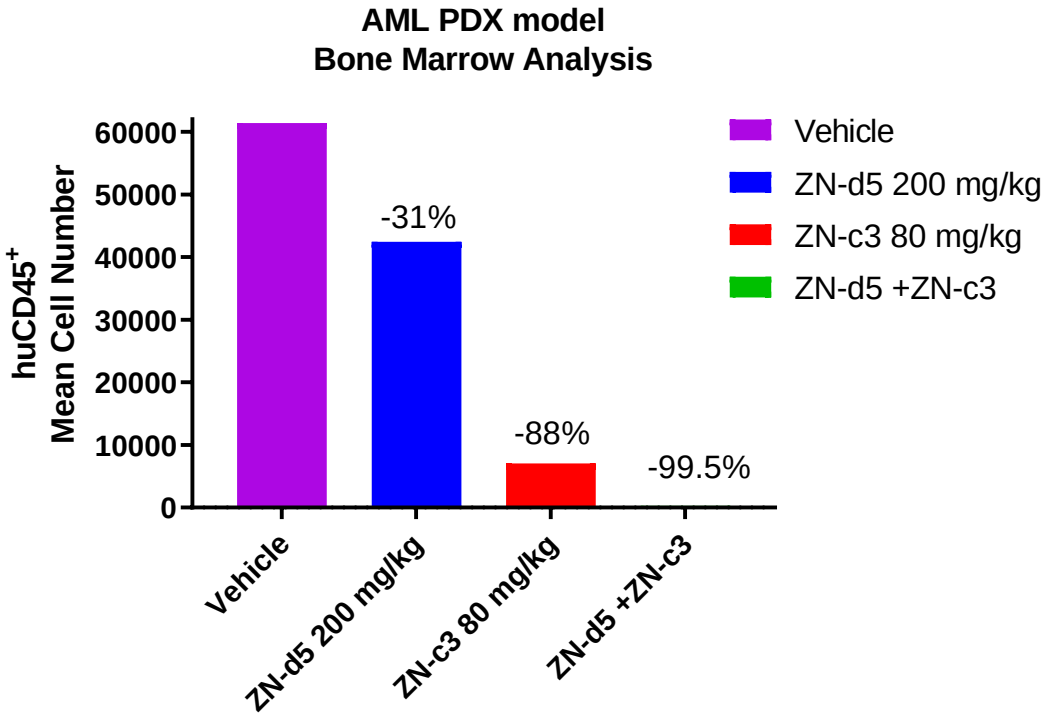
- The combination of ZN-d5 and ZN-c3 represents a novel therapeutic approach
- Significant enhancement of activity than single agent in several indications, including AML
- Combination regimen was well-tolerated in mice
- **Zentalis is the only company known to have both inhibitors in clinical development**

ZN-d5 Combined with ZN-c3 is Active in Patient-Derived AML Samples



Clinical				In vitro (ZN-d5+ZN-c3)	
Patient	Blasts % (before treatment)	Post- Collection Treatment	Blasts % (After Treatment)	ZN-d5/ZN-c3 Treatment (nM)	Blasts % (After Treatment)
3930	93.4	Vidaza/Venetoclax	Residual AML (33% blast) (~2 months post-treatment)	120/500	4.6
3977	62.1	Vidaza/Venetoclax	Residual AML (68% blast) (~2 months post-treatment)	65/100	0
3978	41.1	Gilteritinib/Venetoclax	Residual AML (32% blast) (~1 month post-treatment)	65/500	3.6

- The combination of ZN-d5+ ZN-c3 is active *in vitro* in **3/3 samples from patients who progressed on venetoclax**
- The combination of ZN-d5 + ZN-c3 is active *in vitro* in 29 patient's derived AML samples independently of TP53 mutation



n= 6 or 10, qd x 17 treatment

ZN-d5 + ZN-c3 shows promising activity in samples from AML patients progressing on venetoclax

A Phase 1/2 Trial of ZN-d5 and ZN-c3 in AML

Based on the encouraging preclinical results and the clinical rationale, **Zentalis is initiating a clinical trial of ZN-d5 and ZN-c3 in AML**

- Approximately 100 subjects (40 in phase 1, 60 in phase 2 expansion cohorts)
- Phase 1: Safety of combined BCL-2 and Wee1 inhibition
- Phase 2: Clinical activity

Key Inclusion Criteria
AML (primary, secondary, treatment-associated); ECOC PS ≤2; adequate organ function

Phase 1

Bayesian optimal interval dose escalation

Objectives: safety, efficacy, phase 2 dose for ZN-d5 + ZN-c3

n = up to 40

Phase 2
Expansion cohorts A, B and C

Expansion Cohort A	Expansion Cohort B	Expansion Cohort C
(n = 20) AML, r/r to ≥1 prior lines, venetoclax-naive	(n = 20) AML, r/r to ≥1 prior lines including venetoclax	(n = 20) AML, treatment naive, ineligible for induction chemo, TP53 mutation

Objectives: efficacy and safety

Study Initiation 1H 2022

Large ZN-d5 + ZN-c3 Commercial Opportunity in AML

Despite recent approvals, the unmet medical need in AML remains for patients who are:

Unfit for intensive chemotherapy

- Venetoclax + azacitidine is the standard of care in this setting
- Venetoclax projected to generate >$4bn in sales globally by 2026(1)
- Approximately 8,000 (40%(2)) of newly diagnosed patients in the US are not eligible for intensive chemotherapy

TP53-mutant

- TP53 mutations confer poor prognosis in AML(3)
- Approximately 13%(4) of AML patients have mutated TP53, implying an addressable patient population in the US of ~9,000(5)

Relapsed/refractory

- Despite venetoclax improving remission rates in the first-line setting in combination with low-dose cytarabine and hypomethylating agents, approximately 25-30% are refractory and many patients will relapse over time(6)

(1) EvaluatePharma.
(2) Informa Market Intelligence. AML Disease Analysis. Feb 2021.
(3) Kadia 2016; Kuykendal 2018; Molica 2021
(4) Welch JS. Patters of mutations in TP53 mutated AML. Best Pract Res Clin Haematol (2018)
(5) Cancer.org; SEER database (2018); US AML prevalence of ~68,000.
(6) Aldoss et al Ther Adv Hematol. 2021

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ZN-c5

Oral SERD

ZN-c5: Oral SERD Candidate for ER+/HER2- Breast Cancer

1

IDENTIFY:
SERD

- Clinically validated approach
- Potential use as backbone therapy
- **Fulvestrant: only FDA-approved SERD**
- **Opportunity to combine with ZN-c3 in CDK4/6 inhibitor-resistant population**

2

ANALYZE:
Fulvestrant

- Fulvestrant limitations:
  - 2 painful monthly intramuscular injections (insoluble)
  - Capped efficacy at approved dose
  - Low convenience and high resource utilization

3

CREATE:
ZN-c5

- Designed to have improved:
  - High potency and selectivity
  - Improved solubility
  - Compelling PK (long half life)
  - Favorable safety and tolerability
  - No agonist activity
- **Goal: safely establish increased drug exposure to enhance efficacy**

4

GENERATE:
Preclinical Evidence

- Dose proportional responses and meaningful tumor shrinkage in combination with CDK4/6 inhibitor
- Anti-tumor activity in ESR1 models as monotherapy and in combination with CDK4/6 inhibitors
- No agonist activity in uterus
- Bone protective activity in mouse model of osteoporosis

ZN-c5: SABCS Update 2021

San Antonio Breast Cancer Symposium - December 7-10, 2021

Abstract #300
Program Number: P1-17-02

ZN-c5, an oral selective estrogen receptor degrader (SERD), in women with advanced estrogen receptor-positive (ER+)/ human epidermal growth factor receptor 2 negative (HER2-) breast cancer

Kevin Kalinsky[1], Vandana Abramson[2], Pavani Chalasani[3], Hannah M. Linden[4], Jasmina Alidzanovic[5], Rachel M. Layman[6], Zivko Vranjes[7], Julie R. Nangia[8], Katherine D. Crew[1], Zoran Andric[9], Marijana Milovic-Kovacevic[10], Jasna Trifunovic[11], Jose Suarez[12], Matt Suster[12], Mieke Ptaszynski[12], Joanne Mortimer[13]

[1] Columbia University Medical Center, New York , NY, USA; [2] Vanderbilt Medical Center, Nashville, TN, USA; [3] University of Arizona Cancer Center – Arizona Health Sciences Center, Tucson, AZ, USA; [4] University of Washington, Seattle, WA, USA; [5] University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina; [6] MD Anderson Cancer Center, Houston, TX, USA; [7] University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina; [8] Baylor College of Medicine – Baylor Clinic, Houston, TX, USA; [9] Clinical Hospital Centre Bezanijska Kosa, Belgrade, Serbia; [10] Institute for Oncology and Radiology of Serbia, Belgrade, Serbia; [11] Oncology Institute of Vojvodina, Sremska Kamenica, Serbia; [12] Zentalis Pharmaceuticals, New York, NY, USA; [13] City of Hope, Los Angeles, CA, USA

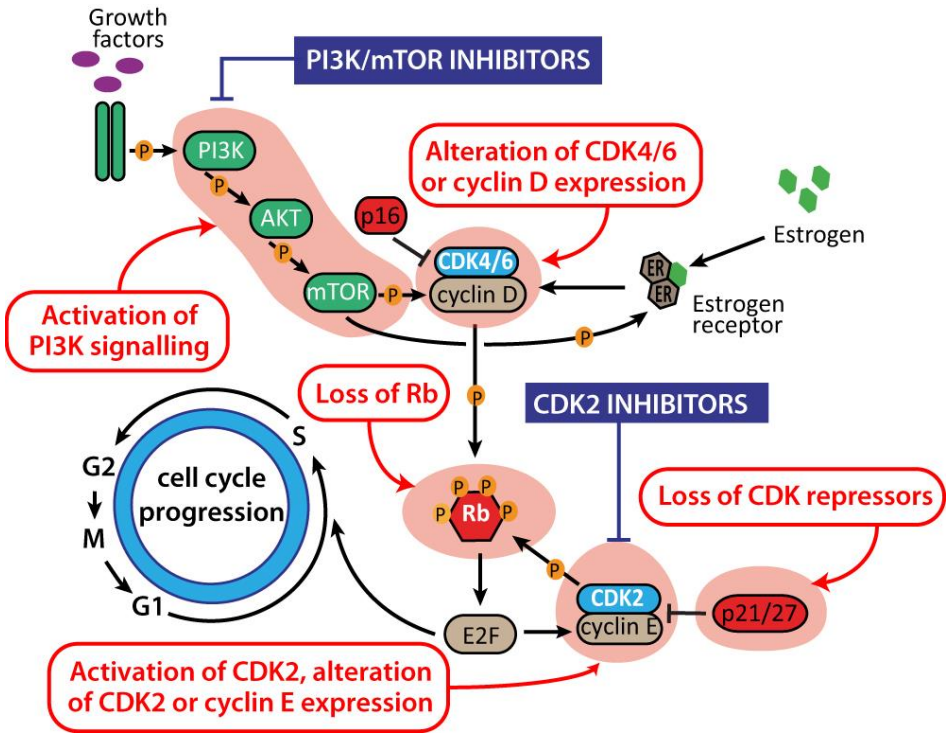
Efficacy Update

- ZN-c5 continues to show good clinical benefit (radiographic disease stabilizations and confirmed PRs)
- All patients at potential RP2D of 50 mg: CBR 44% (PR + SD ≥ 24 weeks), PFS 3.9 months
- **Patients at 50 mg without prior CDK4/6i: CBR 56%, PFS 8.3 months**
- Phase 2 part ongoing in this study, with ZN-c5 dosed at 50 mg QD and possibly at 25 mg QD

Safety Update

- No dose-limiting toxicities at any dose level
- AEs did not increase with dose
- No change in pattern of AEs since corporate mid-year update

Unmet Need for CDK4/6i-Resistant Patients

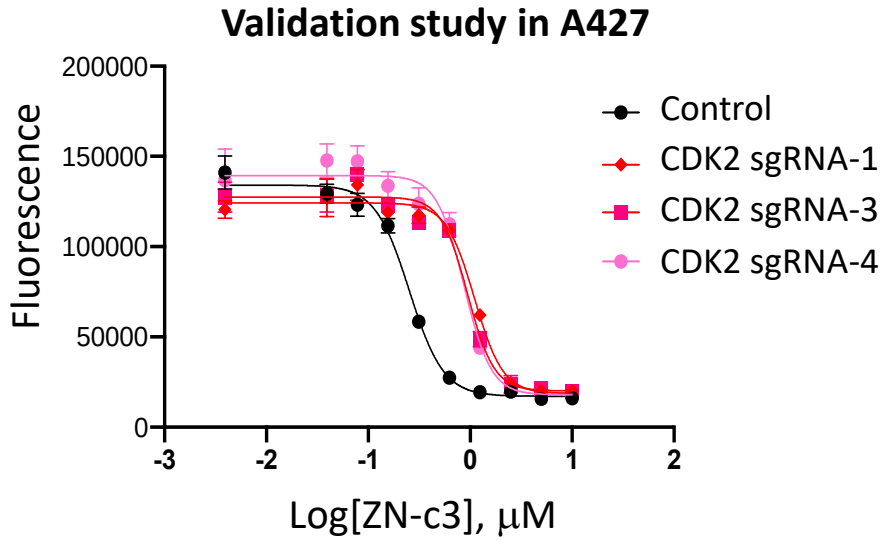


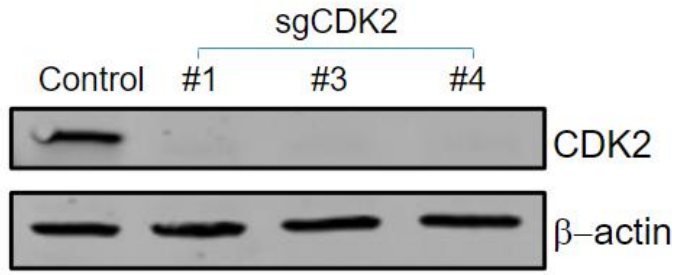
CDK4/6i resistance mechanisms[1,2]

- CCNE1 amplification / CDK2 activation
- Loss of Rb1
- CDK7 overexpression
- MDM2 overexpression
- Wee1 overexpression

Increased dependence on G2/M checkpoint

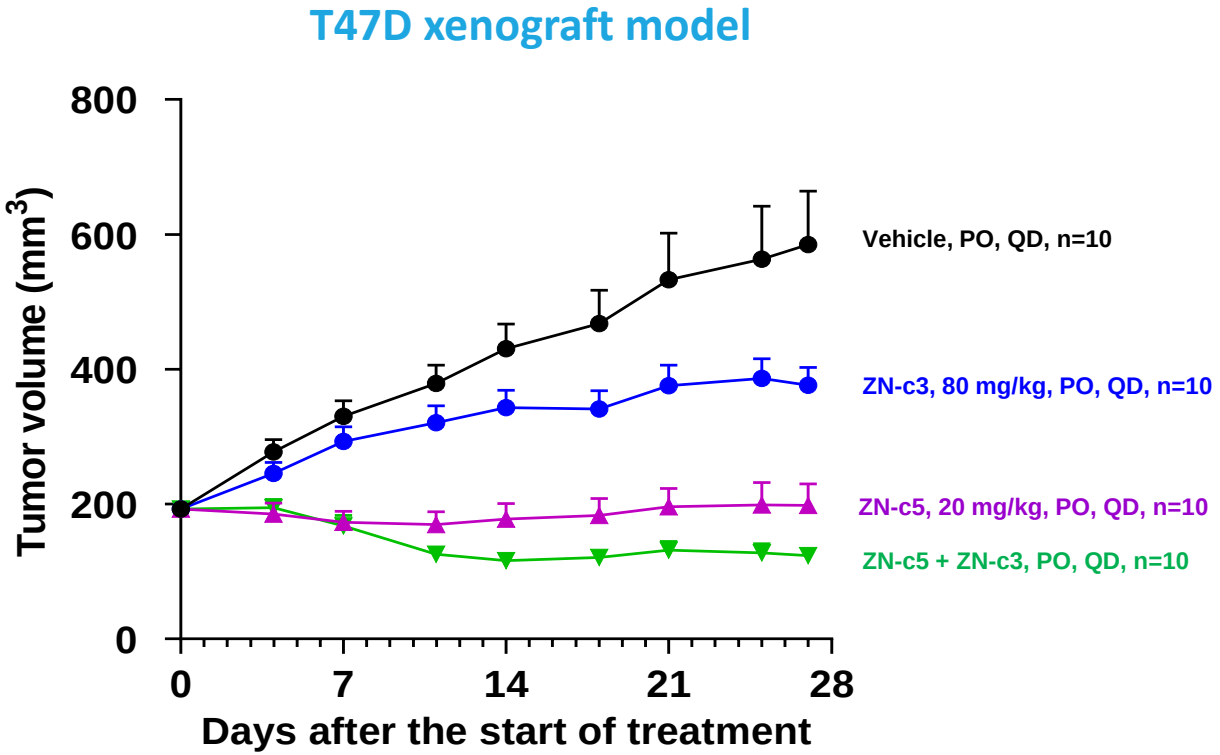
Internal CRISPR screen shows CDK2 is associated with increased sensitivity to ZN-c3





(1) Portman N. et al., Endocrine-Related Cancer (2019) 26, R15–R30
(2) McCartney A. et al. Front Oncol. (2019) Jul 23;9:666

Combining ZN-c5 with ZN-c3 in ER+/HER2- Breast Cancers R/R to CDK4/6i



* Currently assessing ZN-c3 + ZN-c5 in palbociclib-resistant ER+/HER2- Breast PDX models

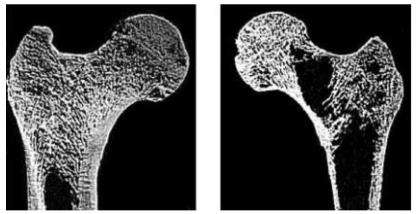
- ER+/HER2- is the largest breast cancer subtype with a prevalence >1,500,000(1)
- In the PALOMA-2 trial (palbociclib + letrozole), 30% of patients developed CDK4/6 inhibitor resistance within 2 years(2), leaving limited treatment options for such a large patient population
- Addressable patient population ~450,000

Study Initiation 2022

(1) Informa Pharma Intelligence. ER+/HER2- BC December 2020; All stages. North America, Western Europe, and Japan.
(2) Li et al. Front Pharmacol (2020)

ZN-c5 Safety Profile and Bone Protective Activity Supports Use in Adjuvant Settings

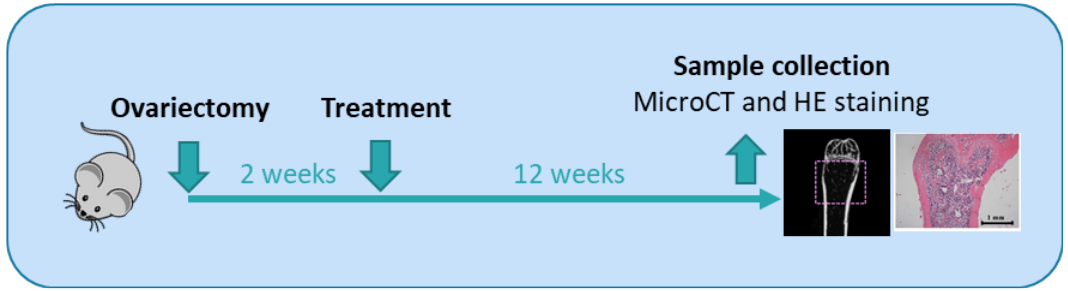
- Loss of estrogen associated with osteoporosis in post-menopausal women



ResearchGate / Thesis / Ehsan Basafa (2013)

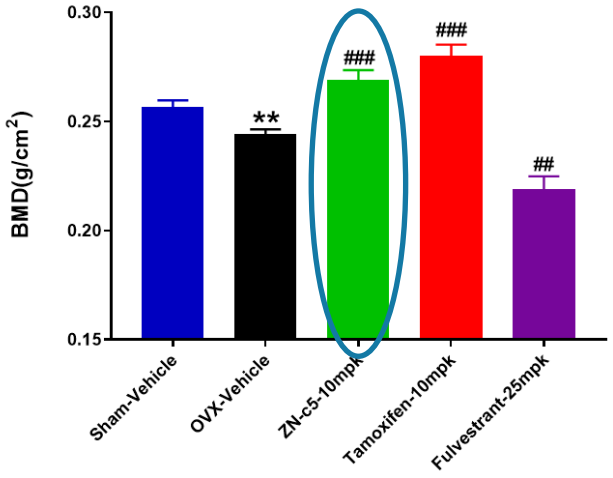
- Advanced breast cancer patients suffer from osteolytic bone metastasis
- Treatment with Fulvestrant is associated with osteolysis
- ZN-c5 opportunity:
  - **ZN-c5 combines anti-tumor effect with bone-protective effect**

Assessment of ZN-c5 on bone density in ovariectomized mice



Bone Mineral Density

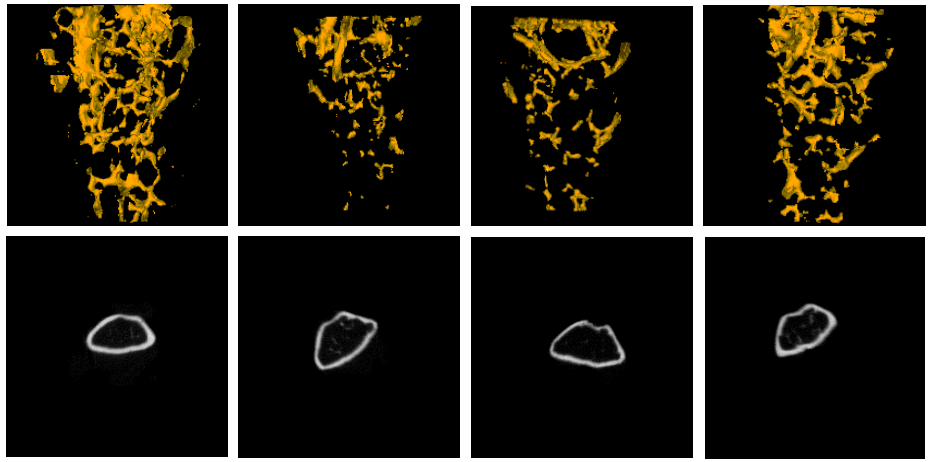
9 weeks; Femur



***p < 0.05, **p < 0.01, ***p < 0.001,* analyzed by unpaired t-test. All data are presented as mean ± SEM.
** Compared with sham-vehicle group; # Compared with OVX-vehicle group*

Micro-CT of Trabecular Bone

12 weeks; Femur



Sham Vehicle | OVX Vehicle | OVX Fulvestrant | OVX ZN-c5 10mpk

Note: Fulvestrant was dosed sc QW, ZN-c5 was dosed po QD

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ZN-e4

EGFR Inhibitor

ZN-e4: Third-Generation EGFR Inhibitor for NSCLC

1 IDENTIFY: EGFR

- Regulator of proliferation and survival in lung cancer
- Third generation inhibitors targeting T790M mutation have produced clinically meaningful benefits
- **Osimertinib: only approved third-generation EGFR inhibitor**
- Broad combination potential

2 ANALYZE: Osimertinib

- Addresses the T790M-mediated acquired resistance and improving efficacy
- ~60% of patients reported rashes
- **AZ5104, a major metabolite of osimertinib, may be responsible for these toxicities**

3 CREATE: ZN-e4

- Designed to achieve similar potency with:
  - Improved selectivity for mutant EGFR
  - No production of potent metabolite for wild-type EGFR
  - Better solubility
- **Actively evaluating potential combinations**

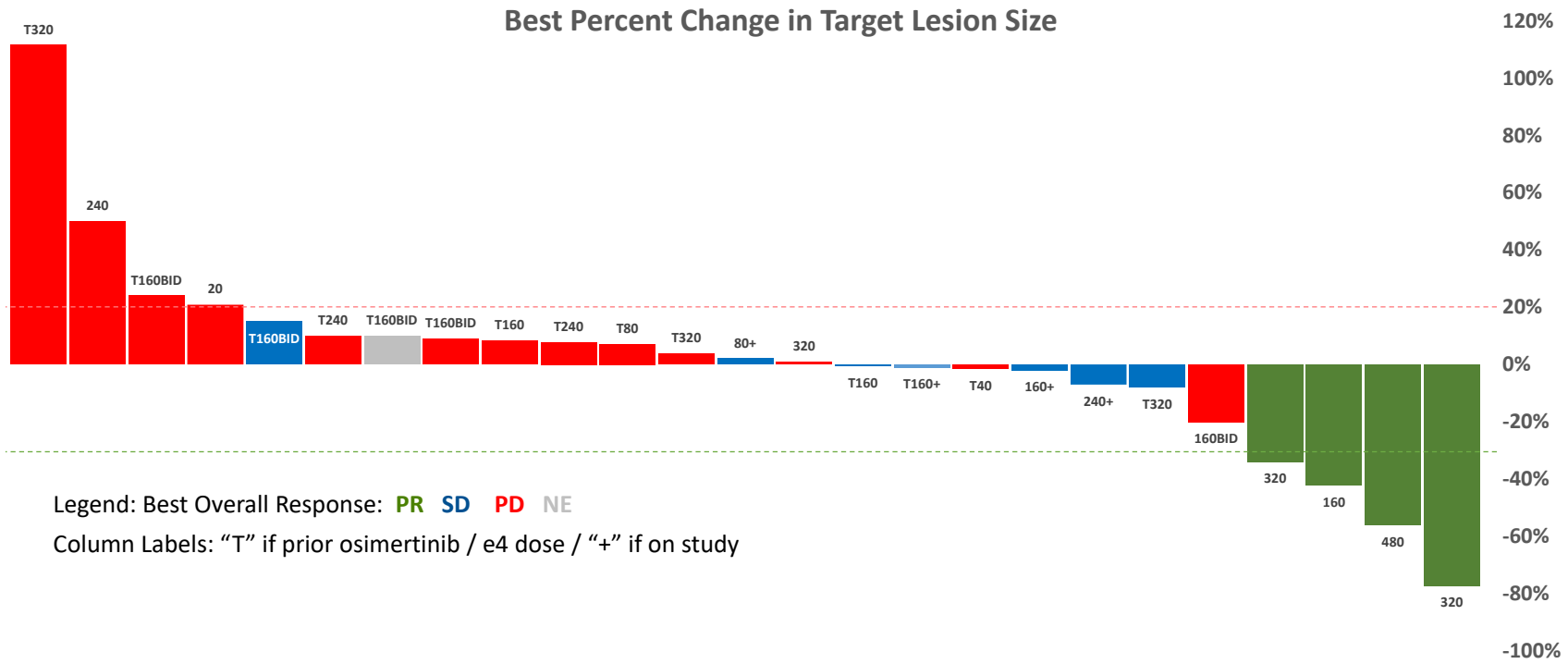
4 GENERATE: Preclinical Evidence

- Improved selectivity in comparison to osimertinib across single mutant, double mutant and wild-type cells
- Confirmed no potent metabolite for wild-type EGFR formed
- Favorable tolerability observed, similar weight loss to osimertinib at 5x efficacious dose

Source: Osimertinib data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound

ZN-e4: Clinical Data Update

- **ZN-e4 shows clear efficacy and excellent safety in osimertinib-naïve NSCLC**
  - N=32 subjects in total
  - Skin toxicity appears substantially better
  - ORR 36% (4/11) in relapsed, osimertinib-naïve subjects
    - All failed prior EGFRi and 1-2 lines of chemo
    - Only one subject with T790M positive
- Phase 2 dose will be 240 mg



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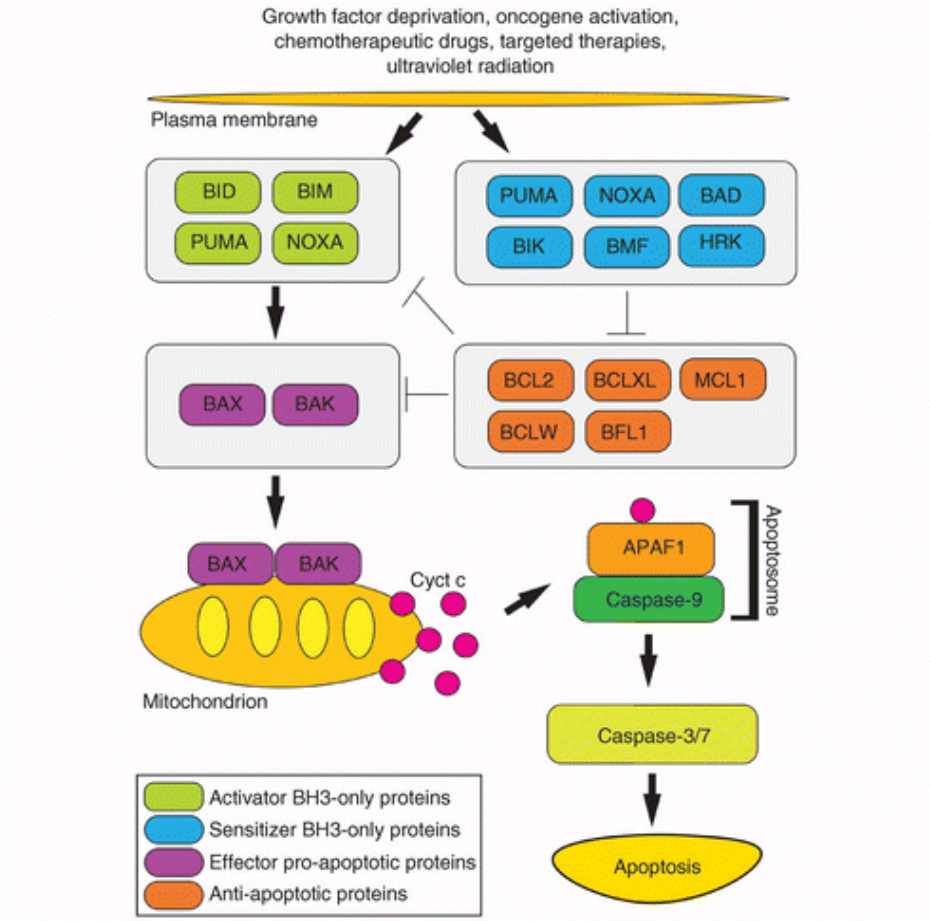
BCL-xL Heterobifunctional Degrader

BCL-xL is a Promising Oncology Target

- Execution of the intrinsic apoptotic pathway is controlled by the BCL-2 family of proteins at the level of the mitochondrial outer membrane[1][2]
- BCL-xL is an antiapoptotic protein involved in tumor survival and chemo resistance[3]
- BCL-xL is involved in venetoclax resistance[4]
- BCL2L1, the gene that encodes BCL-xL protein, is often amplified in solid tumors[5]
- Navitoclax, a dual BCL-2 / BCL-xL inhibitor, has shown clinical activity in hematopoietic malignancies but is dose limited because of thrombocytopenia driven by BCL-xL inhibition[6]

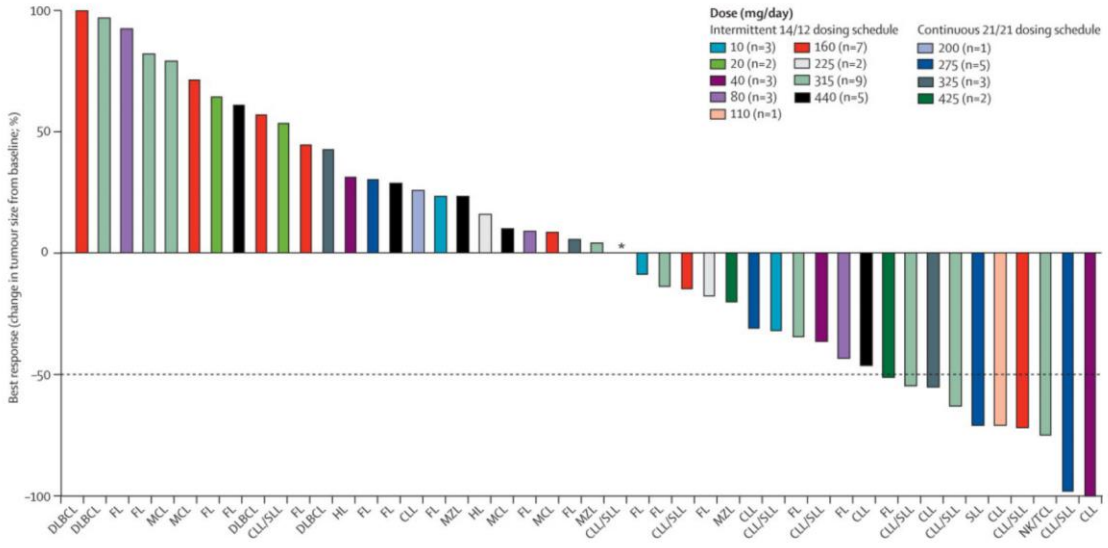
Mechanism of action [3]



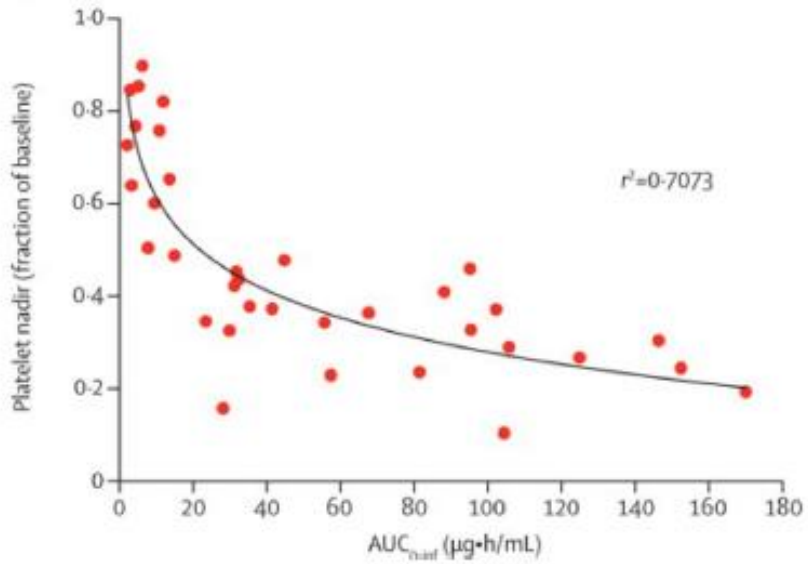
(1) Bhola PD and Letai A. Mol Cell. 2016;61(5):695-704
(2) Konopleva M and Letai A. Blood. 2018 Sep 6;132(10):1007-1012
(3) Rahman SFA et al., Future Oncology, 2020, 16(28)
(4) Yue et al., Cancer Cell Int., 2020, 20(254)
(5) cbioportal.org
(6) Wilson WY et al., Lancet Oncol., 2010; 11(12):1149-1159

BCL-xL: A Clinically Relevant Target with Associated Thrombocytopenia Liability

Anti-tumor effect of navitoclax in lymphoid malignancies



Effect of navitoclax on platelets



Events	Intermittent (14/21) schedule All patients (N=38)		Continuous (21/21) All patients (N=17)		Intermittent (14/21) schedule MTD 315 mg (N=9)		Intermittent (14/21) schedule MTD 325 mg (N=5)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Platelets	15 (39%)	**18 (47%)**	5 (29%)	**11 (65%)**	2 (22%)	**7 (78%)**	2 (40%)	**3 (60%)**

Source: Wilson WH et al., Lancet Oncol., 11(12):1149-1159 (2010)

Zentalis BCL-xL Heterobifunctional Degrader

1 IDENTIFY: BCL-xL

- Highly attractive BH3 mimetic
- Active across multiple tumor types with potential for combination
- Thrombocytopenia liability
- No approved BCL-xL inhibitors
- Potential combination with ZN-c3 or ZN-d5

2 ANALYZE: Navitoclax

- Dual BCL-2/BCL-xL inhibitor
- Demonstrated clinical efficacy in lymphoid malignancies
- **Thrombocytopenia, attributed to BCL-xL inhibition, is dose-limiting**

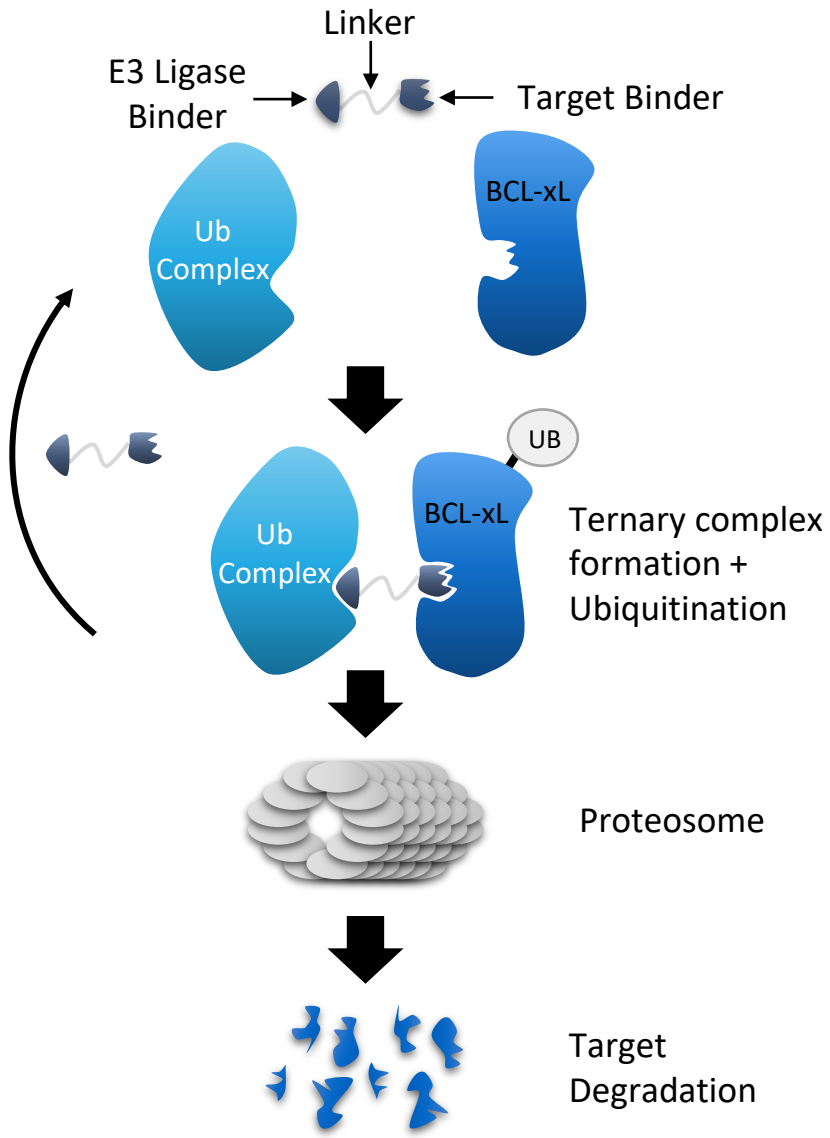
3 CREATE: BCL-xL Degrader

- **Goal: To create heterobifunctional degraders that degrade BCL-xL and avoid thrombocytopenia since platelets have reduced levels of E3 ligases**
- Potential to have broad applicability across heme and solid tumors, as monotherapy and in combination

4 GENERATE: Preclinical Evidence

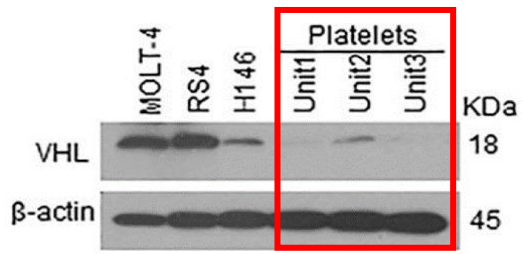
- Potent BCL-xL degradation in tumor cells
- Improved cellular potency over navitoclax
- *In vivo* efficacy
- No toxicity on platelets

A Heterobifunctional Degrader Offers a Path to Target BCL-xL While Avoiding Thrombocytopenia

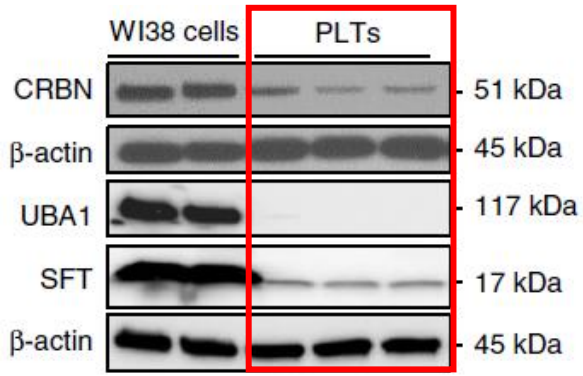


Protein degradation offers an alternative to inhibition by removing the protein from the cells through ubiquitination dependent proteolysis

- Heterobifunctional degraders link an E3 binder to a target binder
- Platelets express low levels of known E3 ligases



Khan et al. Nature Med 12, 1938-1947 (2019)

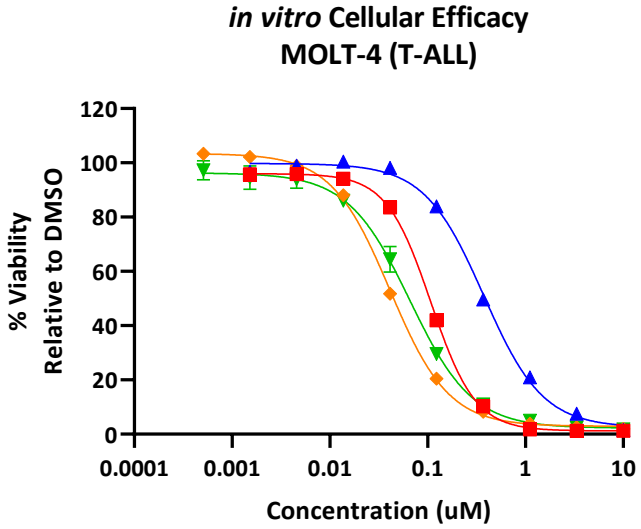


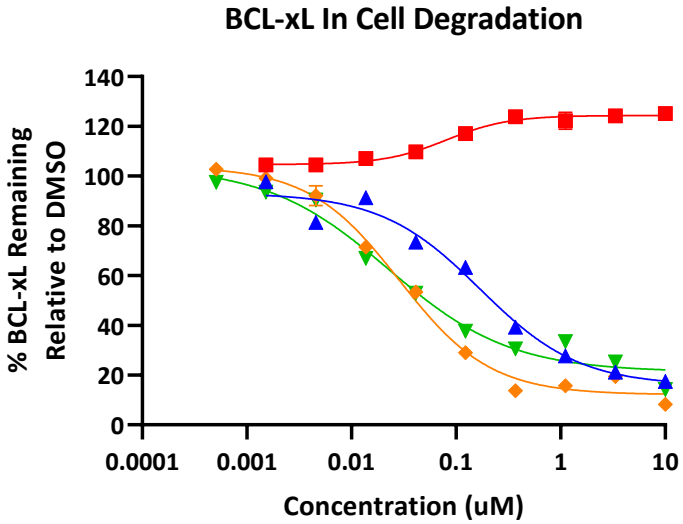
He et al. Nature Comm 11, (2020)

Therapeutic hypothesis:

- A BCL-xL heterobifunctional degrader would deplete BCL-xL from tumor cells while sparing platelets

Zentalis BCL-xL Heterobifunctional Degraders Induce Efficient Degradation in Cells



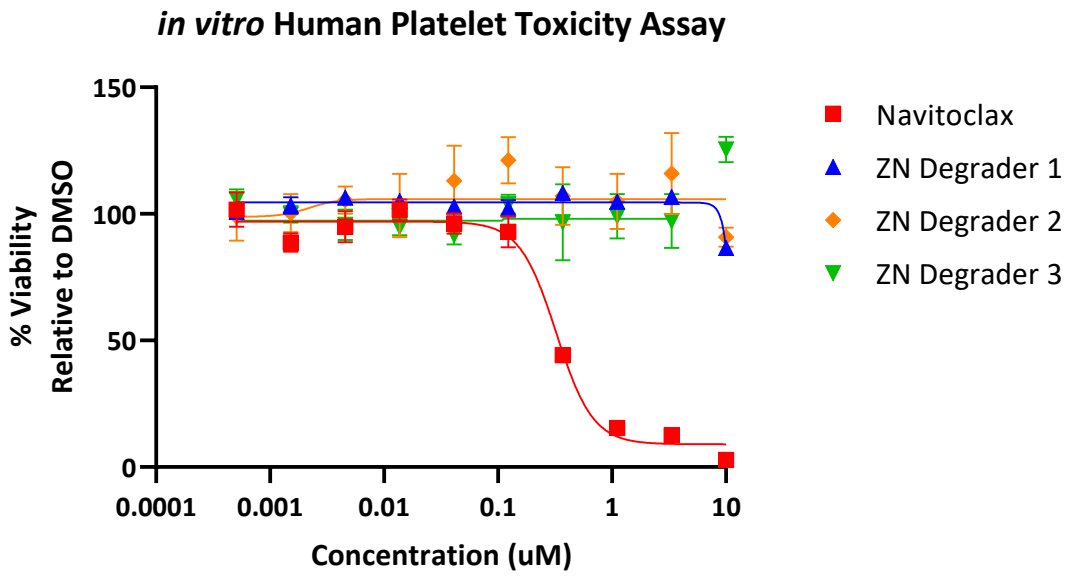


navitoclax ZN Degrader 1 ZN Degrader 2 ZN Degrader 3

compound	MOLT-4 viability		BCL-xL degradation	
	IC_{50} (nM)	Ymax (%)	DC_{50} (nM)	Dmax (%)
Navitoclax	98	98	>10,000	0
ZN Degrader 1	405	96	136	72
ZN Degrader 2	59	99	37	72
ZN Degrader 3	61	98	31	70

Average of ≥ 3 independent experiments

Zentalis BCL-xL Heterobifunctional Degraders Spare Platelets

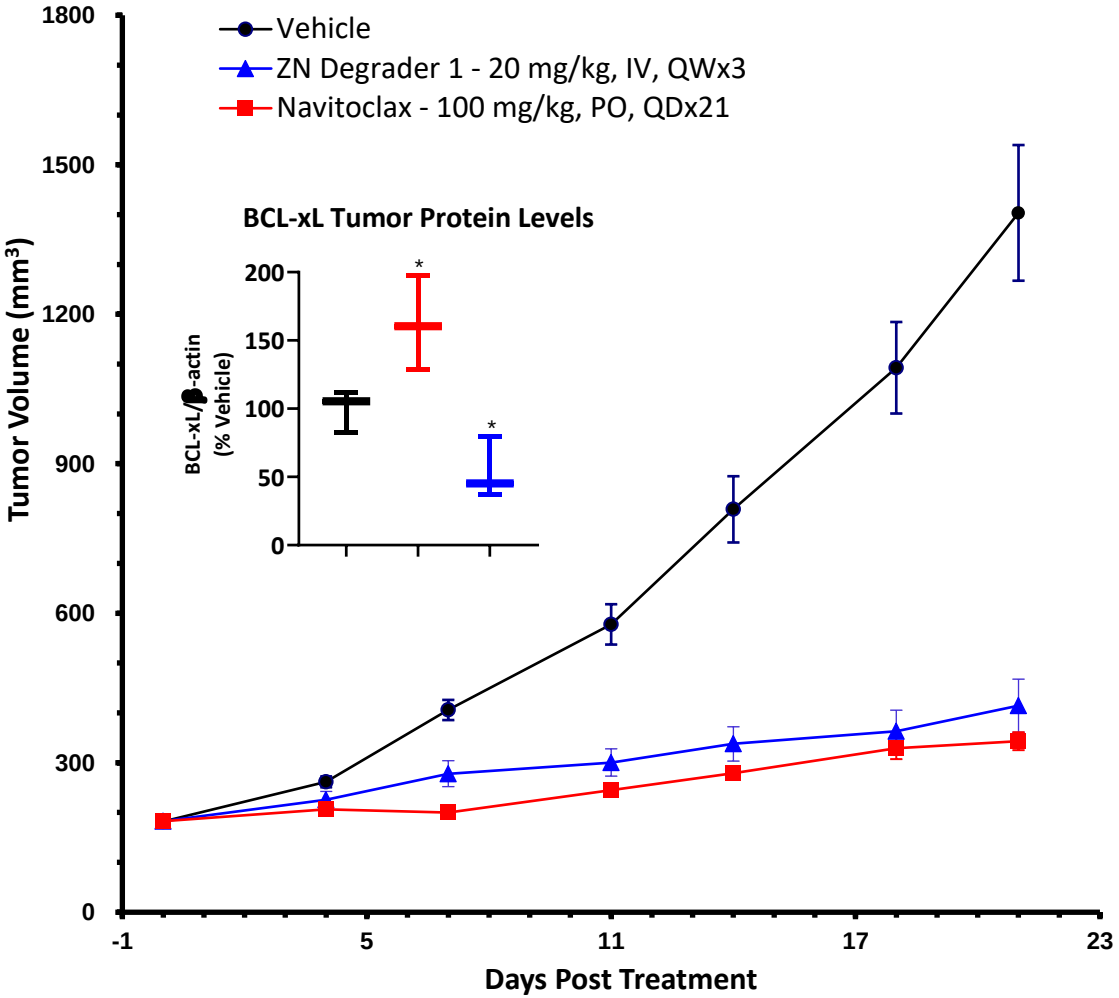


compound	platelet viability	
	IC_{50} (nM)	Ymax (%)
Navitoclax	372	95
ZN Degrader 1	>10,000	19
ZN Degrader 2	>10,000	9
ZN Degrader 3	>10,000	14

Average of ≥ 2 independent experiments

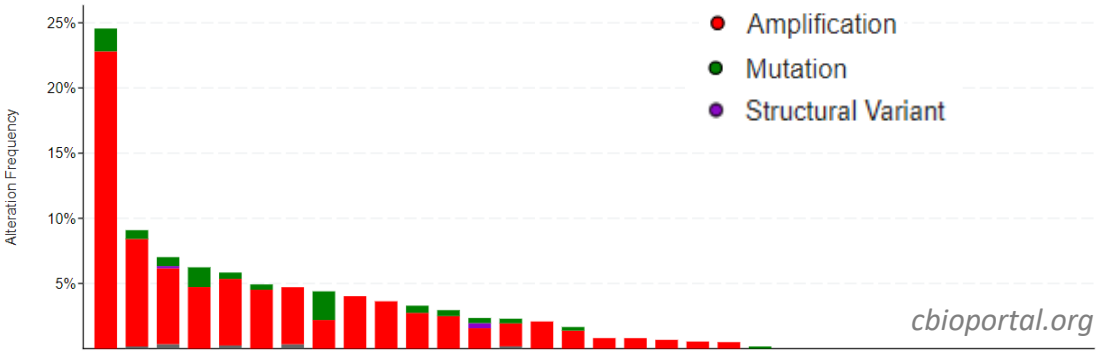
Zentalis BCL-xL Heterobifunctional Degrader Shows Comparable *in vivo* Efficacy to Navitoclax

MOLT-4 (T-ALL) tumor efficacy model



- Currently profiling more advanced compounds
- Promising potential combination with ZN-c3 and ZN-d5

Opportunity for hematopoietic malignancies and solid tumors



Solid tumors and hematological malignancies (TCGA)

Candidate Nomination Planned for 2022

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Summary

ZN-c3: Cornerstone of Multiple Treatments in Many Indications

- Potentially registrational trials underway
- Superior selectivity and tolerability profile supports combination therapies across multiple indications
- Efficacy observed in hematologic tumors in addition to solid tumors

ZN-c3 Development Program			
Indication	Treatment	Status	Addressable Patient Population(1)
USC*	ZN-c3 monotherapy	Enrolling	~12,000(2)
Solid Tumors	ZN-c3 monotherapy	Enrolling	N/A
Ovarian	ZN-c3 and chemotherapy	Enrolling	~14,000(3)
Osteosarcoma*	ZN-c3 and gemcitabine	Enrolling	~1,000(4) (US incidence)
Predictive Biomarker*	ZN-c3 monotherapy	Initiated Dec 2021	~55,000(5)
Ovarian	ZN-c3 and niraparib (PARPi)	Initiated Dec 2021	~18,000(6)
Breast (ER+/HER2-)	ZN-c5 (SERD) and ZN-c3	Initiate 2022	>1,500,000(7) (total); ~450,000 (CDK4/6i r/r)(8)
Breast (HER2+)	ZN-c3 and trastuzumab	-	~400,000(9) (total); ~60,000 (trastuzumab resistant)(10)
Colorectal	ZN-c3 monotherapy	-	>2,000,000(11) (total); ~500,000 (TP53/KRAS mutant)(12)
AML	ZN-d5 (BCL-2i) and ZN-c3	Initiate 1H 2022	~68,000(13) (US prevalence)

* Potentially registrational trial

(1) North America, Western Europe, and Japan prevalence unless otherwise stated.
(2) Gynecologic Oncology 115 (2009) 142-153, David Boruta et al.; National Cancer Institute, SEER 2020 Data.
(3) Informa Pharma Intelligence. Ovarian Cancer November 2020; Platinum resistant/refractory.
(4) Cancer.org; SEER database.
(5) Observed predictive biomarker frequency data across solid tumor types; biomarker not disclosed.
(6) Informa Pharma Intelligence. Ovarian Cancer November 2020; estimated PARP treated patients.
(7) Informa Pharma Intelligence. ER+/HER2- BC December 2020; All stages.
(8) Li et al. Mechanisms of CDK4/6 Inhibitor Resistance in Luminal Breast Cancer. Front Pharmacol (2020).
(9) Informa Pharma Intelligence. HER2+ BC March 2021; All stages.
(10) Olson & Mullins. When Standard Therapy Fails in Breast Cancer: Current and Future Options for HER2-Positive Disease. J Clin Trials (2013).
(11) Globocan 2020 https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9 Colorectum fact sheet.pdf
(12) American Cancer Society Facts & Figures 2020; Based on flowchart of patients from Seligmann JF et al. J Clin Oncol. 2021. US population.
(13) Cancer.org; SEER database (2018).

Disclosed today

R&D Day Summary

Integrated Discovery Engine

- Comprehensive new capabilities integrated:
  - X-ray crystallography and SBDD
  - Genomic discovery platform
  - Multi-omics and Machine Learning
  - New Degrader Platform
- BCL-xL heterobifunctional degrader program announced; candidate nomination in 2022

New Preclinical Data

- Strong ZN-c3 activity in uterine, ovarian and osteosarcoma models
- ZN-c3 induces tumor regression in trastuzumab resistant CDX, PARPi resistant TNBC PDX, and CRC models
- Strong supporting evidence for ZN-c3 with I/O
- Exciting ZN-d5 + ZN-c3 synergy in AML
- ZN-c5 is bone protective unlike fulvestrant

New Clinical Data

- ZN-d5 (BCL-2i) shows promising initial signs of efficacy with multiple responses and an excellent safety/tolerability profile
- ZN-c5 (SERD) with a 44% CBR in heavily pretreated patients at potential 50 mg RP2D (56% in CDK4/6i naïve); continued excellent safety/tolerability
- ZN-e4 (EGFRi) RP2D determined

Clinical Trial Updates

- ZN-c3 + PARPi ovarian cancer trial initiated
- ZN-c3 in biomarker driven trial initiated
- New ZN-c5 + ZN-c3 trial in CDK4/6i resistant breast cancer planned to start in 2022
- New potentially registrational ZN-d5 trial in amyloidosis to start in 1Q 2022
- New ZN-d5 + ZN-c3 trial in AML to start 1H 2022

Zentalis' Past, Present and Future

PRE-CLINICAL SMALL MOLECULE DISCOVERY

- Small molecule chemistry and biology expertise delivering impactful oncology drugs
  - DDR: ZN-c3
  - Oral ER degraders: ZN-c5
  - Apoptosis: ZN-d5

CLINICAL STAGE

- ZN-c3: Potential best-in-class DDR agent to address a wide range of solid tumor AND heme indications
- ZN-c5: Potential best-in-class oral SERD with excellent safety/tolerability profile
- ZN-d5: Promising oral agent targeting apoptosis for heme malignancies

APPROVED DRUGS

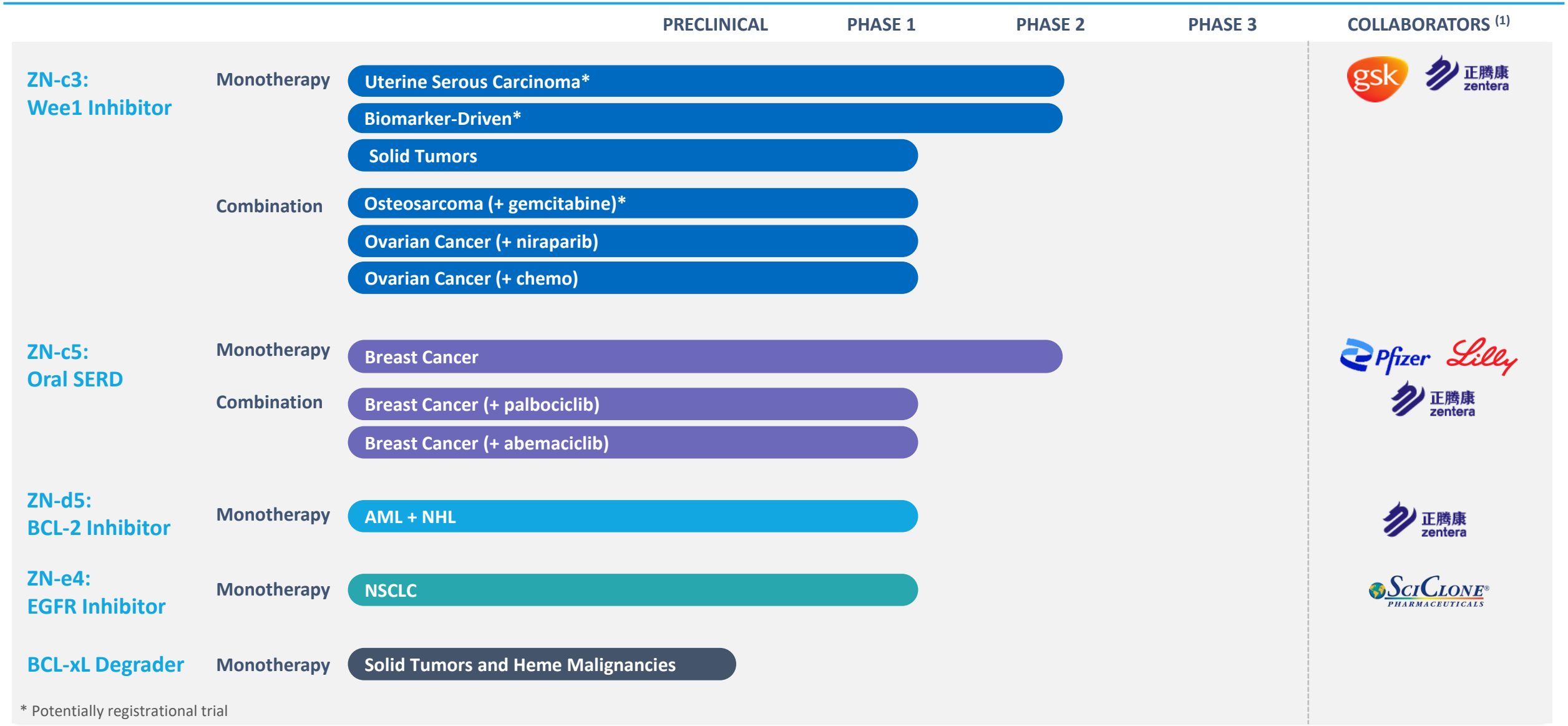
MACHINE LEARNING

FUTURE PIPELINE PRODUCTS AND CLINICAL ASSETS

Integrated Discovery Engine

- **New drugs:** Determination of new targets and combination partners
- **Better clinical trials:** Novel patient selection; new combination partners and drug schedules; faster paths to global registration
- **Larger commercial markets:** New clinical indications

Broad Oncology Pipeline Designed to Improve Patient Outcomes



* Potentially registrational trial

(1) Zentalis is currently evaluating ZN-c5 in combination with palbociclib (Ibrance®), as part of a clinical research collaboration with Pfizer, evaluating ZN-c5 in combination with abemaciclib (Verzenio®), as part of a clinical research collaboration with Lilly. Zentalis intends to evaluate ZN-c3 in combination with niraparib (ZEJULA®), as part of a clinical research collaboration with GlaxoSmithKline. Zentalis maintains full ownership of ZN-c5 and ZN-c3 in each such collaboration. SciClone has development and commercial rights to ZN-e4 in Greater China (including Macau and Hong Kong), South Korea, Taiwan and Vietnam. Zentera, our joint venture, has development and commercial rights to ZN-c5, ZN-c3 and ZN-d5 in select Asian countries (including China). Zentera received CTA acceptances in China for ZN-c3, ZN-c3 in combination, ZN-c5 and ZN-d5 and four clinical trials are ongoing.