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CORPORATE PRESENTATION

March 2023

Forward-Looking Statements and Disclaimer

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All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding potential for our product candidates to be first-in-class and/or best-in-class; potential for accelerated approval paths; potential for our product candidates to be developed as monotherapies and in combination; potential for azenosertib (ZN-c3) to address large populations with significant unmet need; our development approach for our product candidates, including azenosertib and ZN-d5; plans for and potential benefits of dose optimization, and the anticipated timing of updates on dosing optimization, including timing of declaring a monotherapy RP2D for azenosertib; timing of providing updates on azenosertib program timelines and potential paths to registration; timing of preclinical and clinical program updates; the potential unmet need in a particular indication and/or patient population; potential for combinations including our product candidates and the potential benefits thereof; the target profiles and potential benefits of our product candidates and their mechanisms of action, including as a monotherapy and/or in combination; our belief that we have strengthened our clinical development plans, including for azenosertib; clinical and regulatory progress of our product candidates, including the estimated timing of IND-enabling studies, enrollment, initiation of clinical trials and data announcements; the market opportunities for and market potential of our product candidates; timing of providing preclinical rationale for our Cyclin E1 enrichment strategy for azenosertib; timing of advancement of our preclinical programs, including BCL-xL and protein degrader programs; our anticipated milestones, as well as statements that include the words "design," "estimate," "expect," "may," "milestone," "opportunity," "plan," "potential," "strategy," "to come," "will" and similar statements of a future or forward-looking nature. 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Other risks and uncertainties include those identified under the caption "Risk Factors" in our most recently filed periodic reports on Forms 10-K and 10-Q and subsequent filings with the U.S. Securities and Exchange Commission in the future could cause actual results to differ materially from those indicated by the forward-looking statements made in this presentation. Any such forward-looking statements represent management's estimates as of the date of this presentation. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. While we may elect to update these forward-looking statements at some point in the future, we assume no obligation to update or revise any forward-looking statements except to the extent required by applicable law. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. 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Zentalis' product candidates are investigational drugs and have not yet been approved by the U.S. Food and Drug Administration or any other regulatory authority.

Company Overview

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

- Potential accelerated approval paths for monotherapy in multiple biomarker enriched populations
- Enriched patient populations including Uterine Serous Carcinoma (USC), Cyclin E1 driven and post-PARP progression
- Investigating highly synergistic concurrent combinations, including BRAF/MEK inhibitors in BRAF mutant mCRC and PARP inhibitors in high grade serous ovarian cancer
- Fast Track designation granted in USC

BCL-2 inhibitor ZN-d5: broad applicability as anti-apoptotic target; potential as monotherapy and in combination, including with azenosertib

BCL-xL heterobifunctional degrader for liquid and solid tumors (preclinical)

Additional discovery programs against validated cancer targets

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

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Advancing Focused Pipeline with Multiple Clinical Opportunities

COMPOUND	INDICATION	DEVELOPMENT APPROACH	PRECLINICAL	EARLY CLINICAL DEVELOPMENT	LATE CLINICAL DEVELOPMENT	STATUS / EXPECTED MILESTONES
Azenosertib (ZN-c3) Wee1 Inhibitor	Uterine Serous Carcinoma	Monotherapy				FDA Fast Track Designation
	Solid Tumors	Monotherapy				Update on azenosertib dosing 1H 2023 including RP2D
	Cyclin E1 Driven Ovarian Cancer	Monotherapy				Enrolling; preclinical update to come in 1H 2023
	PARP Resistant Ovarian Cancer	Monotherapy alternating with niraparib or concurrent with niraparib		gsk		Enrolling; opened alternating cohort in 4Q 2022
	Ovarian Cancer	+ Multiple Chemotherapy Backbones				Enrolling; Phase 1 dose escalation results in 2H 2023
	Osteosarcoma	+ gemcitabine				Presented data CTOS Conf Nov 2022
	BRAF Mutant Colorectal Cancer	+ encorafenib and cetuximab		Pfizer		Initiated enrollment in Q1 2023
	Pancreatic Cancer	+ gemcitabine				Dana Farber Cancer Institute, funded by SU2C/Lustgarten
ZN-d5 BCL-2 Inhibitor	AL Amyloidosis	Monotherapy				Provide interim clinical data and declare RP2D for monotherapy
	NHL	Monotherapy				Continues to enroll
	AML	+ azenosertib				Provide preliminary data from clinical trial
BCL-xL Degrader	Solid Tumors and Heme Malignancies					Declared development candidate; IND enabling activities initiated

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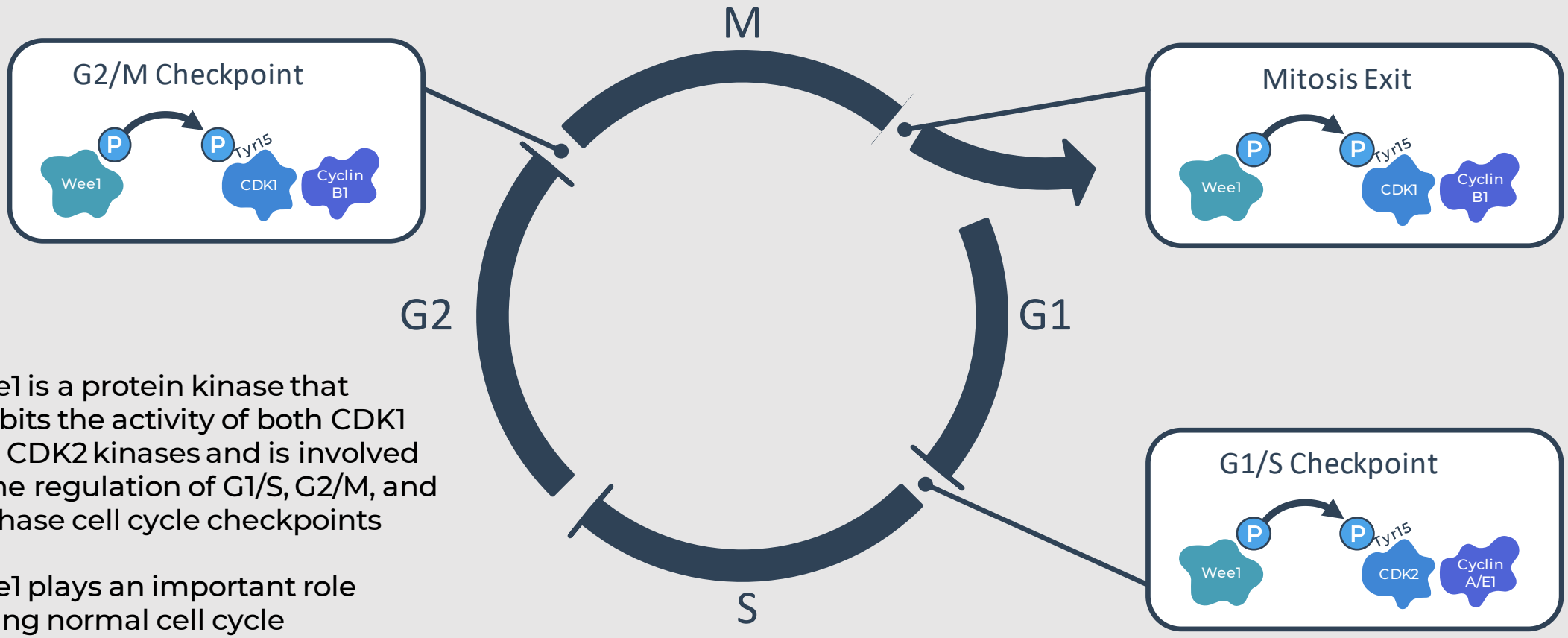
Azenosertib (ZN-c3)

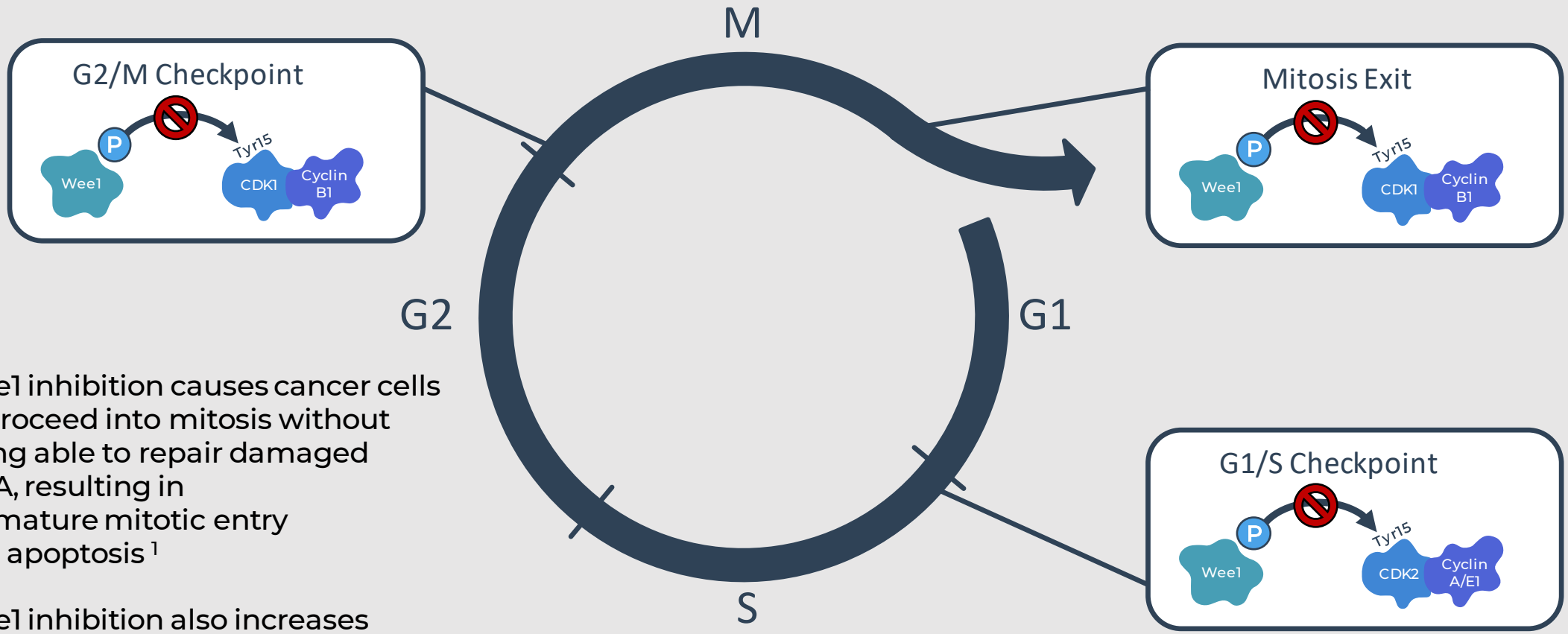
Wee1 Inhibitor

Wee1: A Critical Cell Cycle Regulation Target



- Wee1 is a protein kinase that inhibits the activity of both CDK1 and CDK2 kinases and is involved in the regulation of G1/S, G2/M, and M phase cell cycle checkpoints
- Wee1 plays an important role during normal cell cycle progression but also in response to DNA damage and interacts with DNA damage response (DDR) pathways

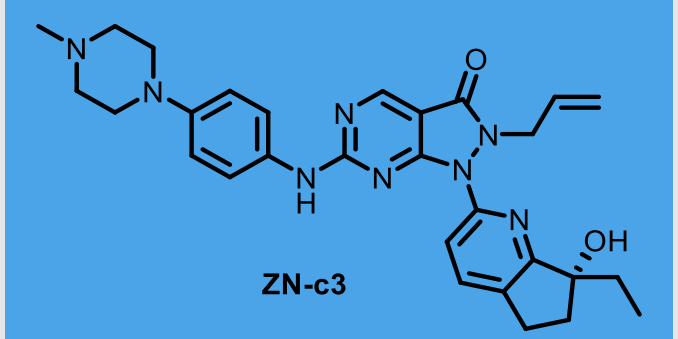
Wee1 Inhibition by Azenosertib Forces Cancer Cells to Proceed into Mitosis



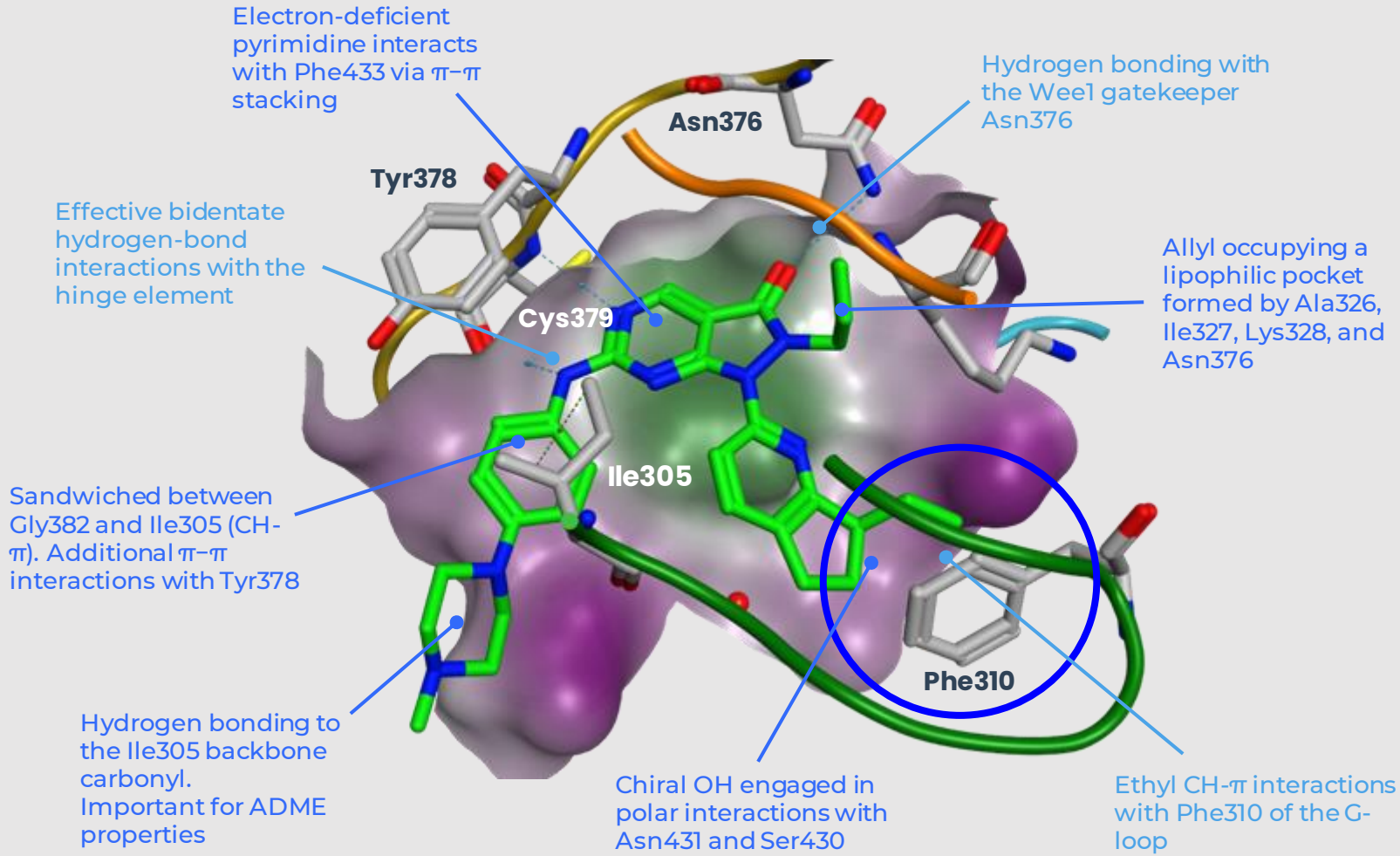
- Wee1 inhibition causes cancer cells to proceed into mitosis without being able to repair damaged DNA, resulting in premature mitotic entry and apoptosis [1]
- Wee1 inhibition also increases replication stress by inducing aberrant firing of replication origins and depletion of nucleotide pools [1]

1. Kok, *et al.* Overexpression of Cyclin E1 or Cdc25A leads to replication stress, mitotic aberrancies, and increased sensitivity to replication checkpoint inhibitors. *Oncogenesis* 9, 88 (2020)

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



azenosertib 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



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

Azenosertib: Significant Market Opportunity Across a Broad Range of Solid and Liquid Tumors

Indication	Incidence Estimates (US+EU)	Development Approach
Ovarian Cancer	46,700 [1]	Strategic commitment to patients with multiple ongoing studies in monotherapy and combination settings
High Grade Serous Ovarian Cancer (HGSOC) (75% of Ovarian Cancer)	35,000 [2]	Ongoing study combining azenosertib with common chemotherapy backbones in platinum resistant populations. Additional ongoing study examining PARP inhibition in PARP resistant populations with GSK
Cyclin E1 Driven Ovarian Cancer (~25% of HGSOC)	8,800 [3]	Ongoing biomarker study with monotherapy regimen exploring high cyclin E1 protein expression and CCNE1 gene amplification
Other Cyclin E1 Driven Solid Tumors	80,000+ [3]	Potential follow-on opportunities including prostate, lung, breast, etc.
Uterine Serous Carcinoma	10,100 [4]	Fast track designation monotherapy program
Colorectal (BRAF mutant)	36,300 [5]	Initiated enrollment of azenosertib + BEACON regimen in Q1 2023 as part of Pfizer development partnership
Osteosarcoma	4,300 [6]	Azenosertib + gemcitabine combination. Initial data readout at 2022 CTOS Conference
Pancreatic Cancer	108,000 [7]	Azenosertib + gemcitabine combination. Potential to demonstrate POC via investigator sponsored trial at Dana Farber.
AML	25,600 [8]	Combine azenosertib with ZN-d5, BCL-2 inhibitor

1. Cancer of the Ovary - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/ovary.html for US and ECIS - European Cancer Information System for EU (applying EU27 female population to incidence cited) 2. Ovarian Cancer Research Alliance. Retrieved November 4, 2022. https://ocrahope.org/2021. 3. Chen et al. Mol Cell Proteomics. 2019 Aug 9:18(8 suppl 1):S15-S25 and TCGA dataset 4. Trastuzumab for Rare Form of Endometrial Cancer. (2020, August 13). National Cancer Institute. https://www.cancer.gov/news-events/cancer-currents-blog/2020/endometrial-cancer-usc-her2-trastuzumab (US only). 5. Cancer of the Colon and Rectum - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/colorect.html and ECIS - European Cancer Information System and applying estimated BRAF V600E proportion. 6. Cancer of the Bones and Joints - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/bones.html and Annals of Oncology, VOLUME 32, ISSUE 12, P1520-1536, DECEMBER 01, 2021 7. Cancer of the Pancreas - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/pancreas.html and ECIS - European Cancer Information System 8. Acute Myeloid Leukemia - Cancer Stat Facts. (n.d.). SEER. Retrieved November 2, 2022, from https://seer.cancer.gov/statfacts/html/amyl.html and Acute Myeloid Leukaemia: Mapping the Policy Response to an Acute Cancer in France, Germany, Italy, Spain, and the UK. (2019). The Economist Intelligence Unit.

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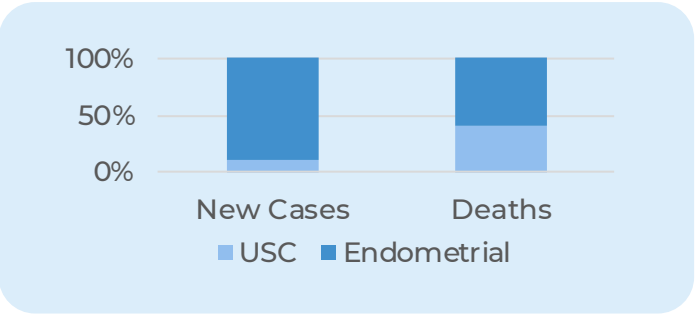
Azenosertib (ZN-c3)

Uterine Serous Carcinoma

Unmet Need in Uterine Serous Carcinoma is Significant

UNMET NEED

- USC is an aggressive form of endometrial cancer that accounts for 10-15% of all endometrial cancers [1]
- The 5-year survival for late-stage is approx. 41% compared to 75% in women with the most common form of endometrial cancer [2]
- USC is responsible for ~40% of endometrial cancer deaths [3]



UNIQUE BIOLOGY

- USC is molecularly distinct from endometrial cancer with frequent alterations in p53 (90%), CCNE1 (25%) and HER2 (25%) [4]
- High amounts of oncogene-driven replicative stress
- Wee-1 is a validated target in USC with reported ORR of 29.4% and a PFS6 rate of 47.1% with adavosertib [5]

COMPETITIVE LANDSCAPE

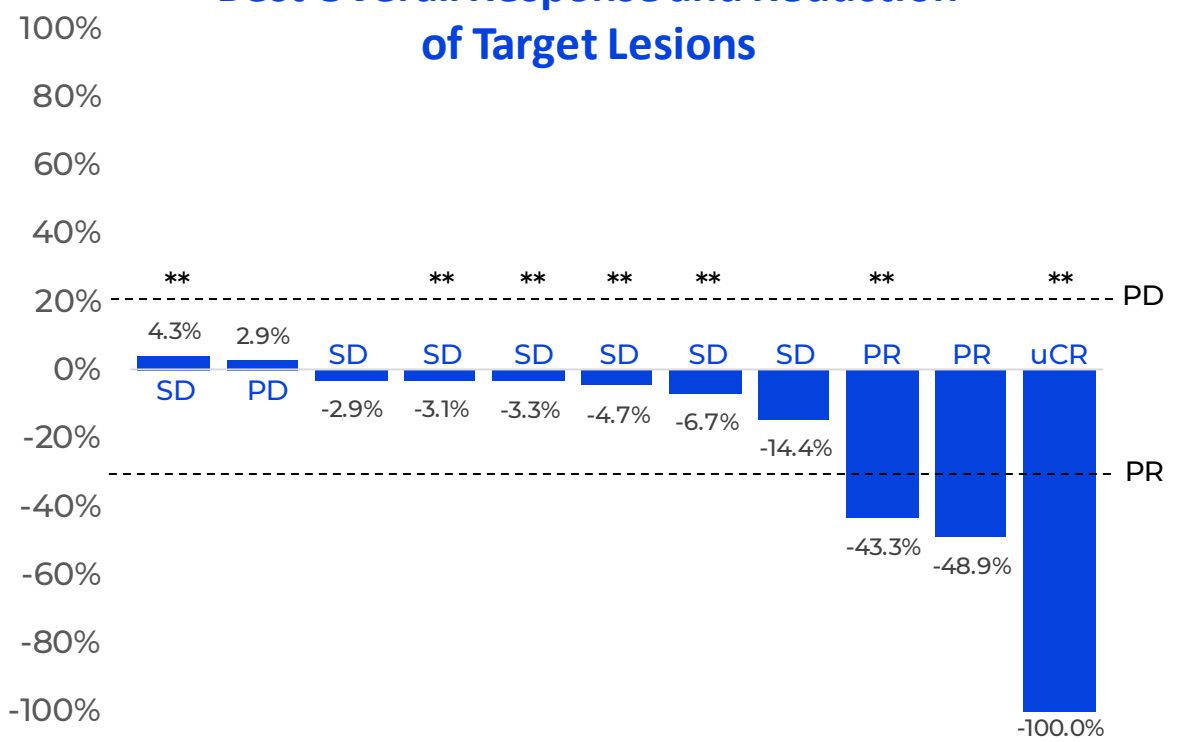
- Current standards of care for USC:
  - First line: Platinum based chemotherapy
  - Second line: Pembro + Lenvatinib
  - Third Line: No specific recommendations, single-agent chemotherapy (4-9%) and some limited use of bevacizumab [6]
- There is a high need for a therapeutic option in later line patients after prior platinum containing chemotherapy and pembrolizumab + lenvatinib treatment
- Azenosertib is potentially a first-in-class treatment option for USC

Azenosertib's emerging efficacy and tolerability profile show promise in addressing unmet need in USC

1. https://www.cancer.gov/news-events/cancer-currents-blog/2020/endometrial-cancer-usc-her2-trastuzumab 2. Boruta DM II, Cancer 101:2214-2221, 2004. 3. McGunigal M. Int J Gynecol Cancer 27:85-92, 2017.
4. Cancer Genome Atlas Research Network, Kandoth C. Nature 497:67-73, 2013. 5. Liu J. J Clin Oncol 39, 14:1531-1539, 2021. 6. CancerMPact, Future Trends and Insights Endometrial cancer June 2021; data on file.

ZN-c3-001: Summary of Clinical Activity – Meaningful and Durable Responses Seen in USC

Best Overall Response	N = 11†; n (%)
Complete Response (unconfirmed)*	1 (9.1)
Partial Response (confirmed)	2 (18.2)
Stable Disease	7 (63.6)
≥ 12 weeks	4 (36.3)
< 12 weeks	3 (27.3)
Progressive Disease	1 (9.1)
Overall Response Rate (95% CI = 6.0%, 61.0%)	3 (27.3)
DCR (CR + PR + SD) (95% CI = 58.7%, 99.8%)	10 (90.9)
Median Duration of Response	5.6 months
mPFS	4.2 months

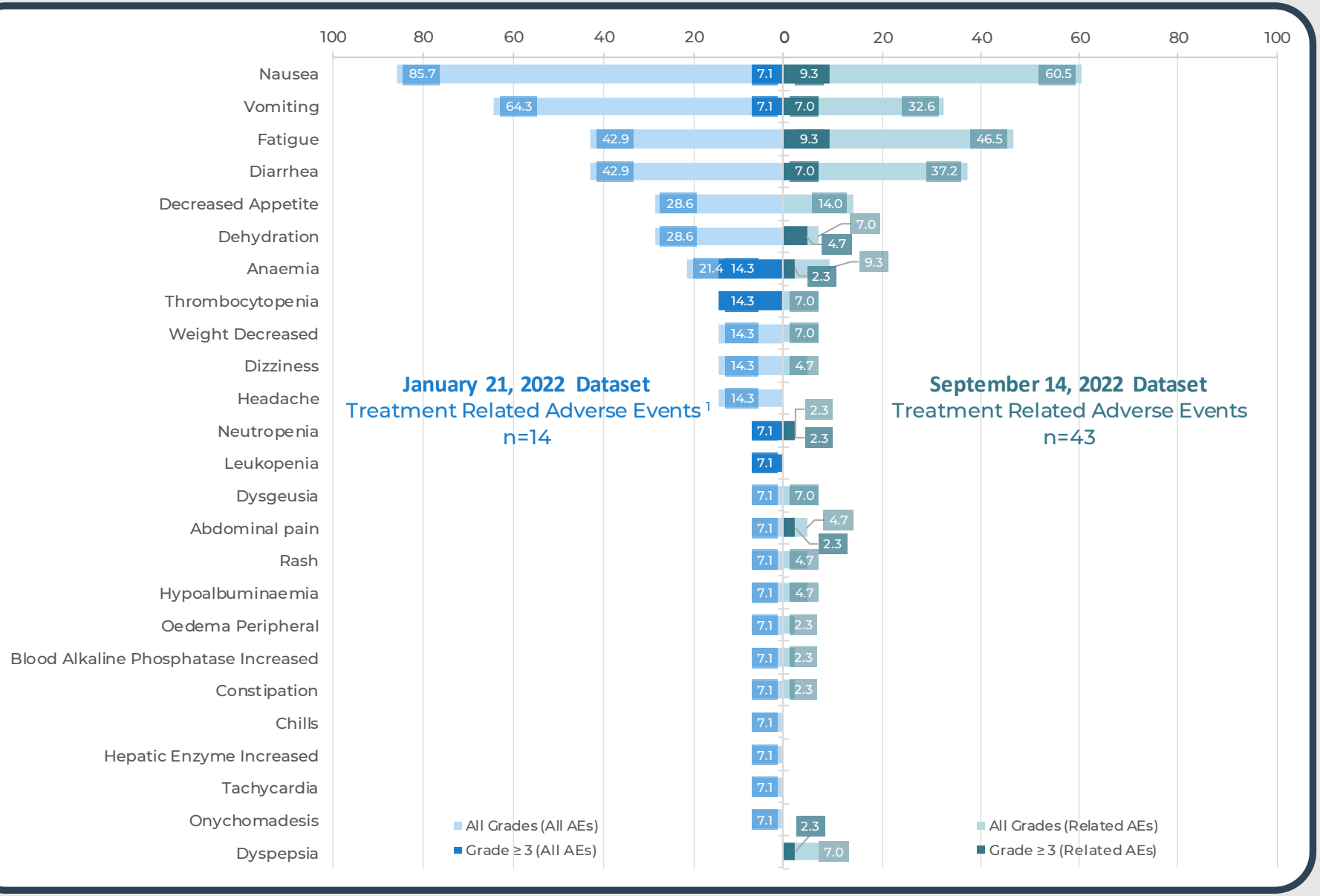


Meric-Bernstam et al. Presentation at American Association for Cancer Research 2022 Meeting. Safety and clinical activity of single-agent azenosertib, an oral Wee1 inhibitor, in a Phase 1 trial in subjects with recurrent or advanced uterine serous carcinoma (USC). Data cutoff January 21, 2022.

* Best overall response for this subject is PR. † N=11 subjects with measurable disease and at least 1 post-baseline tumor assessment. At time of data cutoff 2 SDs were ongoing on study
DCR=disease control rate; uCR=unconfirmed complete response.

Azenosertib Continues to Show Favorable Tolerability Profile in Monotherapy USC Setting

Patients with Adverse Events (%)



1. Presented at AACR 2022 by F. Meric-Bernstam

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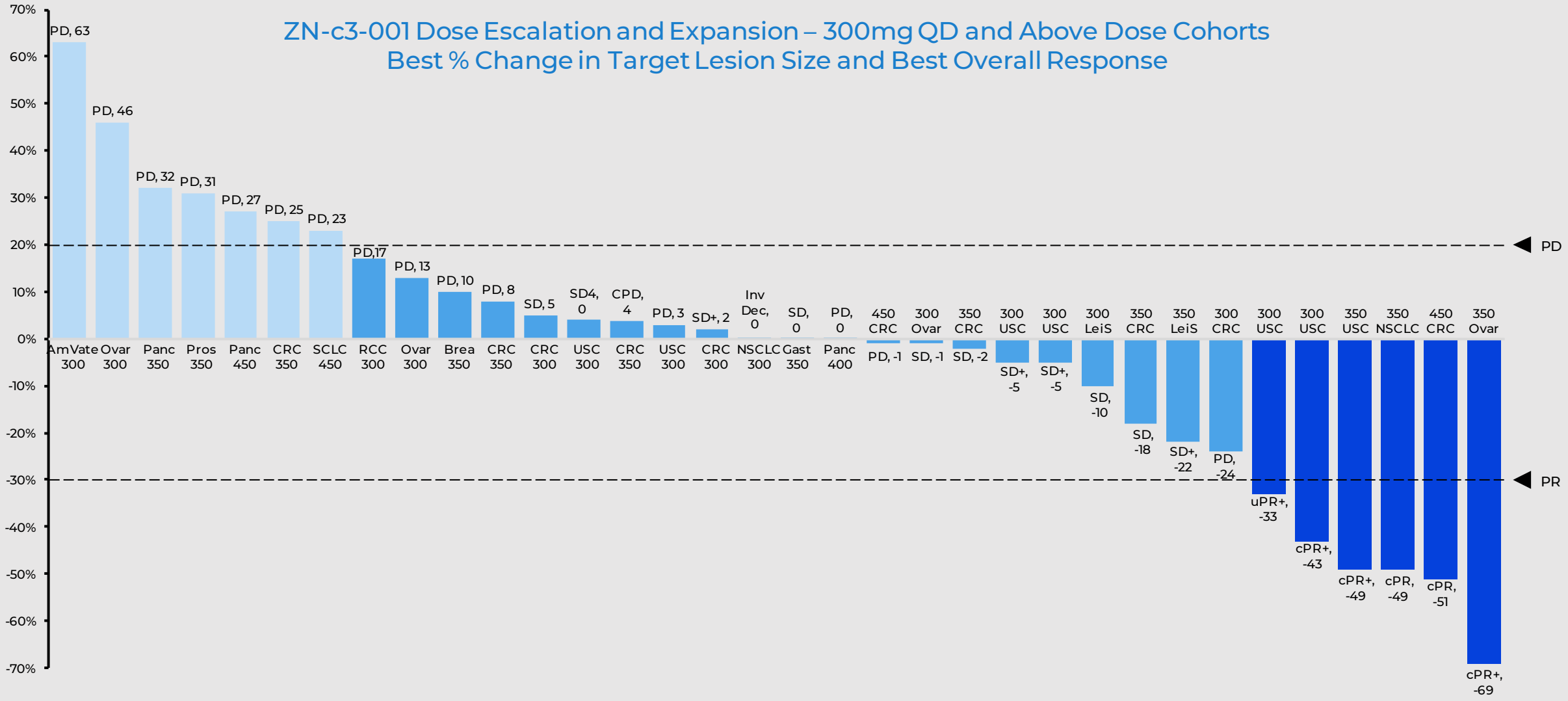
Azenosertib (ZN-c3)

Dose Optimization

Azenosertib: Multiple PRs Across Tumor Types as Monotherapy

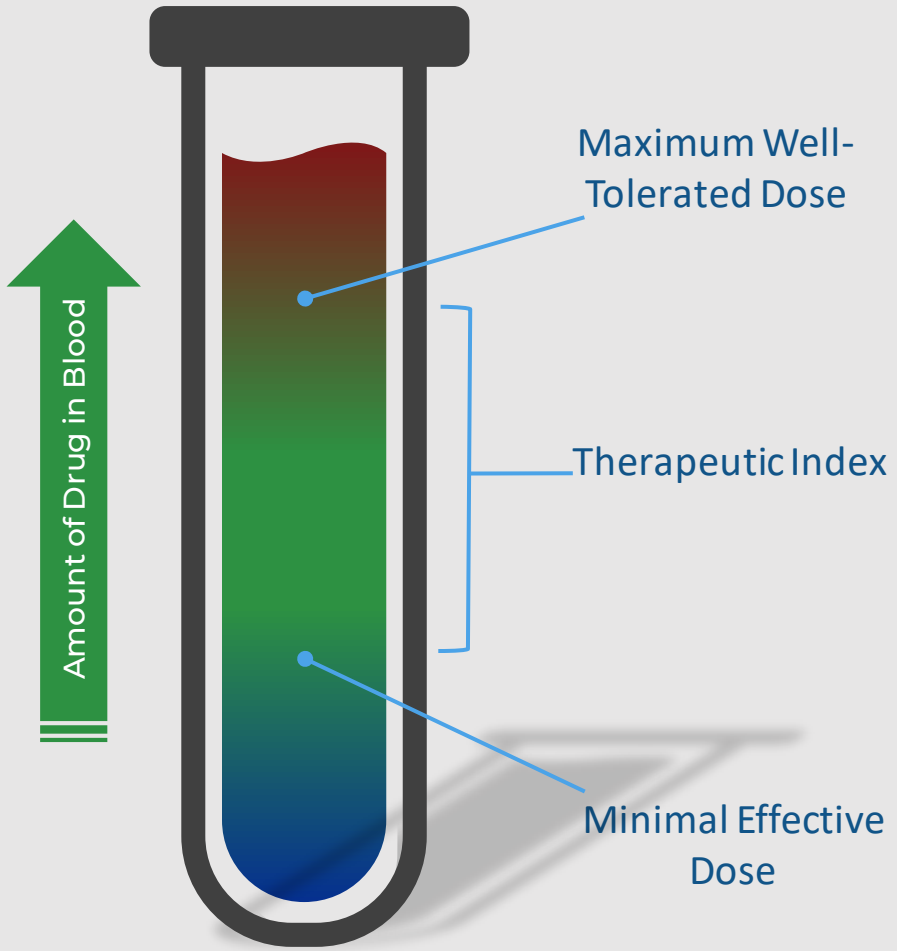


Waterfall as of 05/15/2021; 3 subjects with no treatment scans (CRC, USC, Pancreas), and experienced clinical progressive disease (CPD) + denotes treatment ongoing.
Newly reported uPR in USC is included. ORR based on radiographic responses. Both uPRs reported at AACR 2021 as of 03/15/2021 in USC were confirmed.

Optimizing the Therapeutic Index of Azenosertib

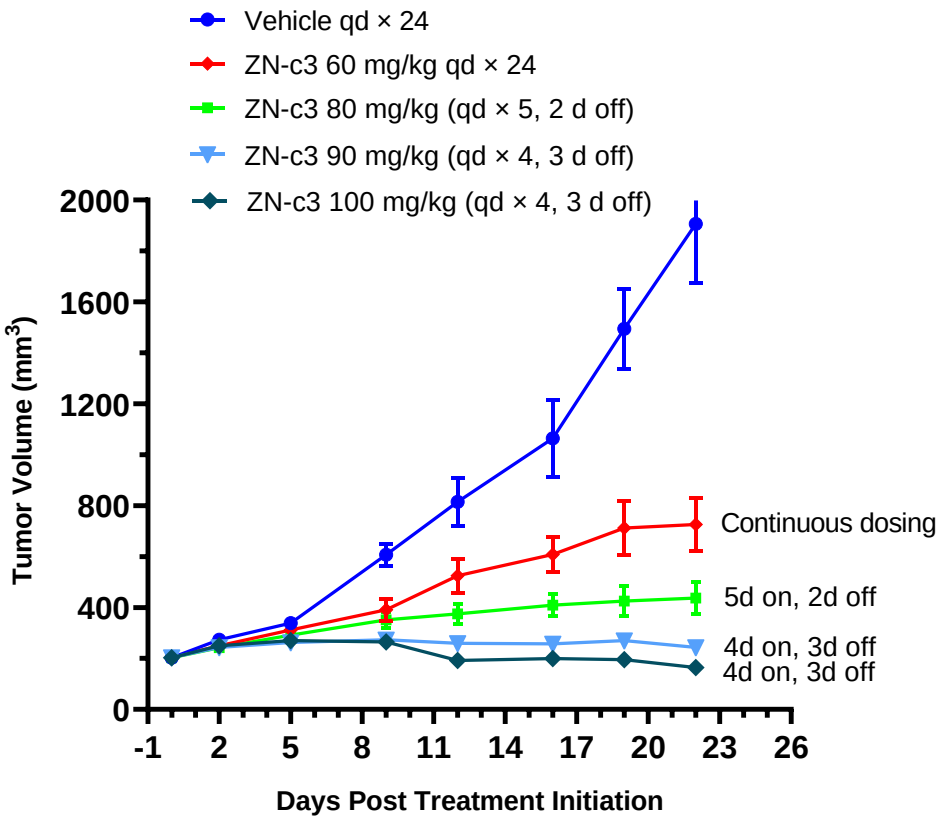
- Only set dose of azenosertib has been in USC (004 trial) at 300mg QD continuous daily dosing
  - Monotherapy activity demonstrated
  - Well tolerated safety profile
- From 300mg QD dosing, we will examine pushing the therapeutic index for monotherapy dosing across three trials as this represents the fastest path to regulatory approval considerations and meaningful clinical evidence
- Our experience to date (>200 patients) is that exposure and maintenance of exposure drives efficacy (both response and duration of response)
- Alternative dosing to date (>60 patients):
  - Less dose interruptions and modifications

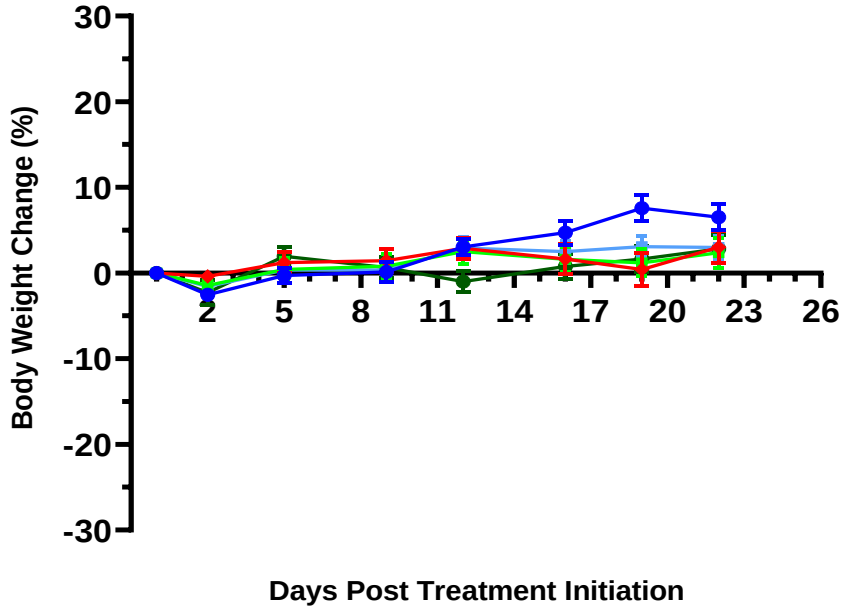
Dosing update planned 1H 2023



Azenosertib: Intermittent Dosing Increases Efficacy and Maintains Tolerability in Ovarian Cancer Models

OVCAR3 Model

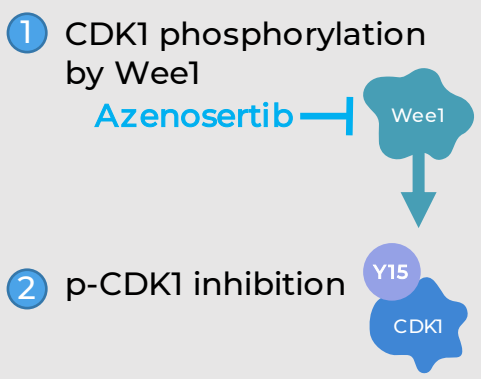




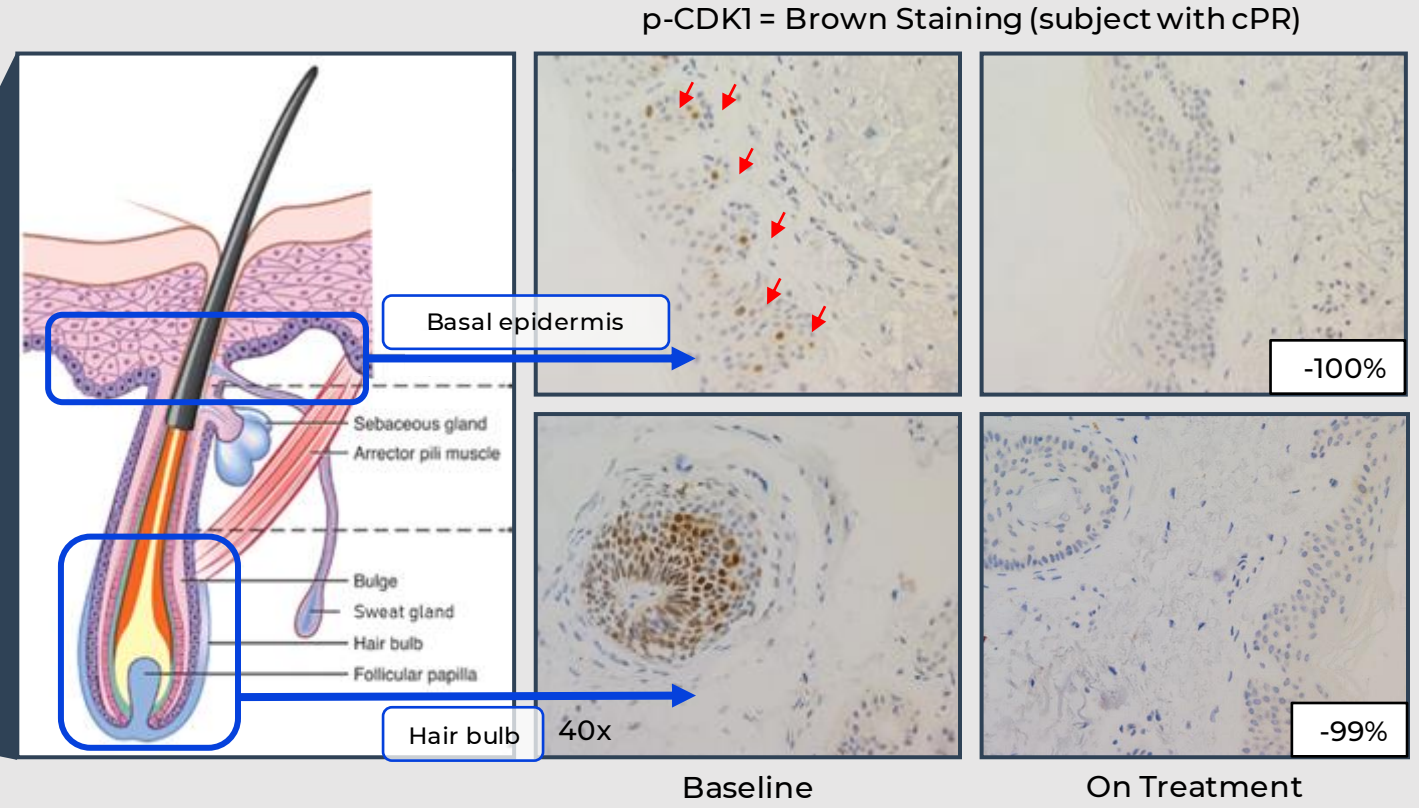
Decreases in p-CDK1 Show Target Engagement for Wee1 Inhibition

Confirmation of Wee1 Target Engagement in Surrogate Tissue [1]

1. CDK1 phosphorylation (p-CDK1) is mediated by Wee1
2. Inhibition of Wee1 will lead to inhibition of p-CDK1
3. Skin biopsies were performed at baseline and on treatment to verify p-CDK1 levels and level of target engagement of Wee1

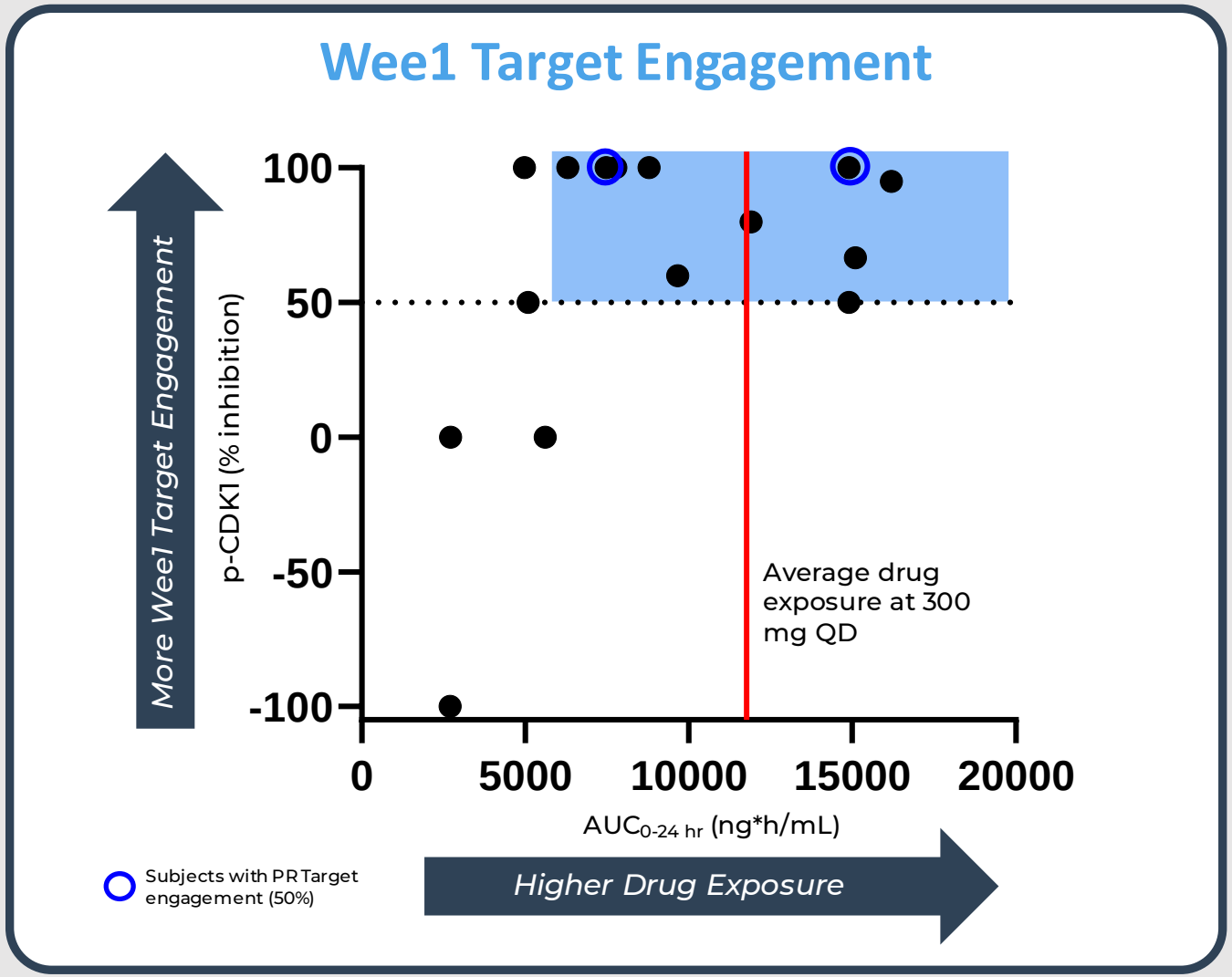


Decreases in p-CDK1 at Baseline vs on Treatment



1. Chalasani, P; *et al*. 526P Pharmacodynamic evidence for WEE1 target engagement in surrogate and tumor tissues from a phase I study of the WEE1 inhibitor ZN-c3. Annals of Onc. **2021**, 526P

Azenosertib: PK/PD Correlation Shows Active Target Engagement



- Inhibition of p-CDK1 demonstrated Wee1 target engagement
- Increase in dose / drug exposure directly related to Wee1 target engagement
- ≥300 mg QD showed highest AUC, with excellent target engagement and p-CDK1 levels decreased at least by 50%

1. Chalasani, P; *et al*. 526P Pharmacodynamic evidence for WEE1 target engagement in surrogate and tumor tissues from a phase I study of the WEE1 inhibitor ZN-c3. Annals of Onc. **2021**, 526P

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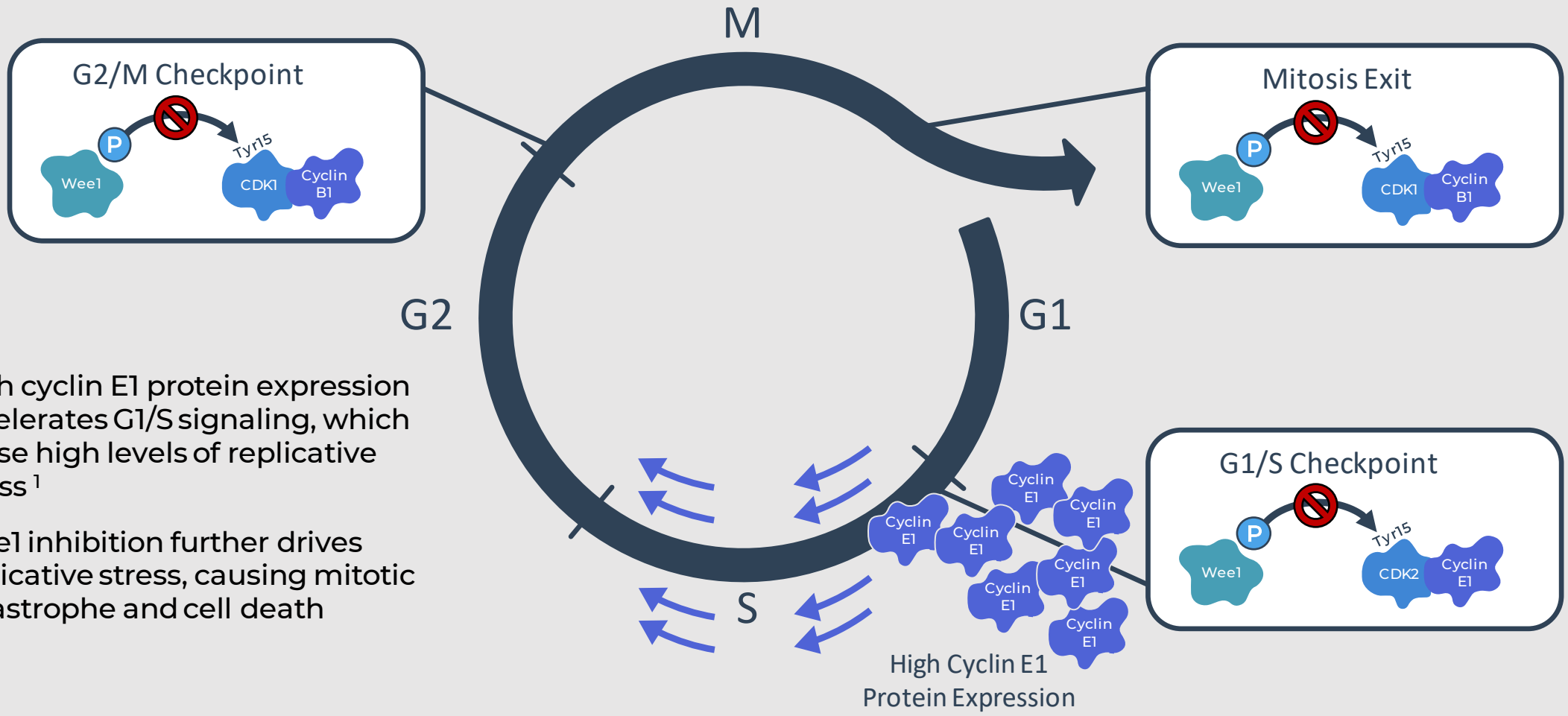
Azenosertib (ZN-c3)

Biomarker Approach: Cyclin E1 Driven Cancers

High Cyclin E1 Expressing Cancer Cells are Highly Sensitive to Wee1 Inhibition

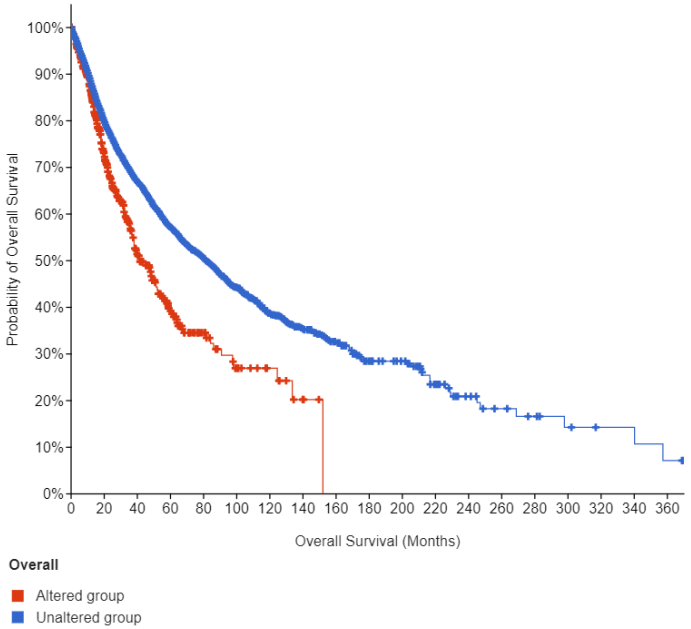


- High cyclin E1 protein expression accelerates G1/S signaling, which cause high levels of replicative stress [1]
- Wee1 inhibition further drives replicative stress, causing mitotic catastrophe and cell death

1. Kok, *et al*. Overexpression of Cyclin E1 or Cdc25A leads to replication stress, mitotic aberrancies, and increased sensitivity to replication checkpoint inhibitors. *Oncogenesis* 9, 88 (2020)

CCNE1 Gene Amplification is Associated with Poor Prognosis and Chemotherapy Response Across Tumor Types

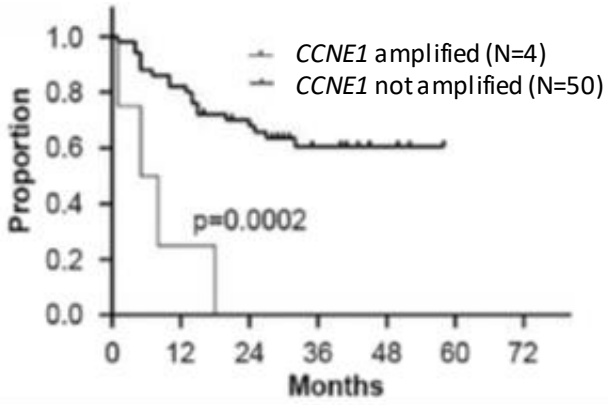
TCGA Pan Cancer Atlas [1]



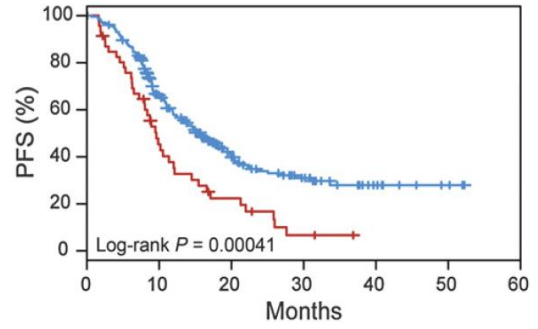
CCNE1 amplified (N=410)
CCNE1 not amplified (N=10,305)

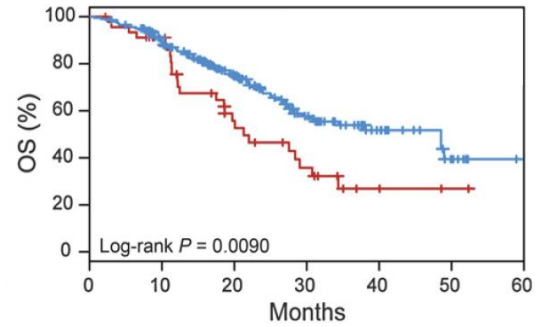
Log-rank test p-value=1.06 10^{-13}

Triple Negative Breast Cancer (TNBC) [2]



Carboplatin-treated Ovarian Cancer [3]



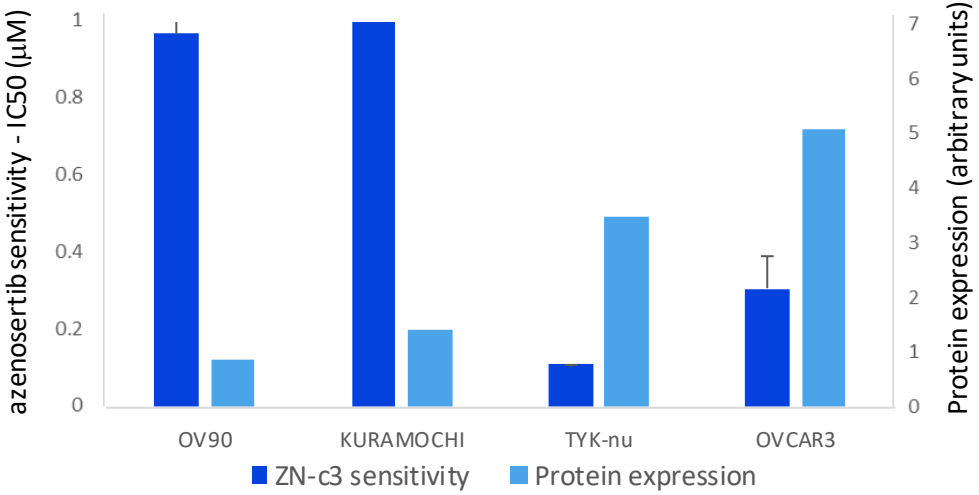


CCNE1 amplified (N=47)
CCNE1 not amplified (N=201)

1. Liu, J. et al., Cell, 2018, 173, 400-416; (figure generated using cBioPortal.org, see Cerami et al. Cancer Discovery. 2012 2; 401 and Gao et al. Sci. Signal. , 2013, 6, pl1).
2. Huang, X. et al., Frontiers in Oncology, 2020, 10, Article 583314, 1-16
3. Stronach, E., et al., Molecular Cancer Research, 2018, 1103-1111.

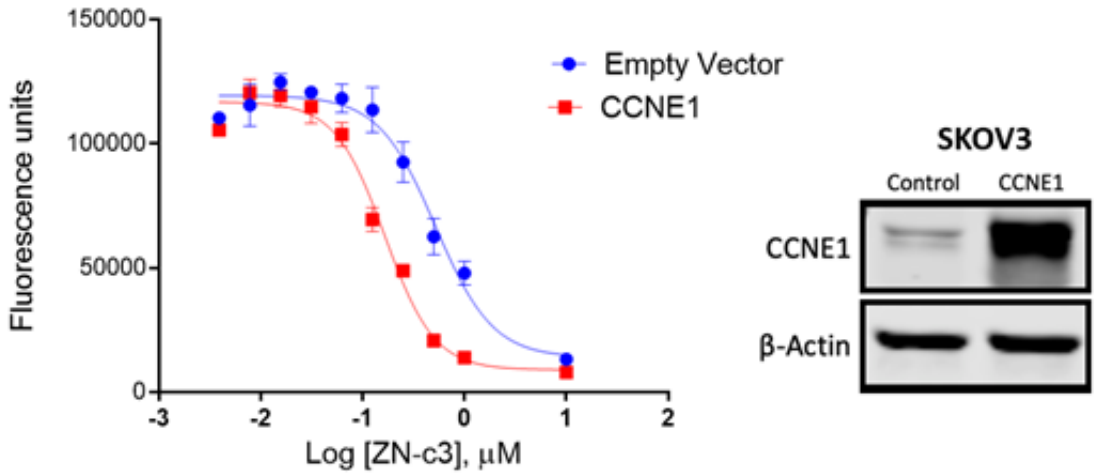
High Cyclin E1 Protein Expression is Associated with Increased Sensitivity to Azenosertib in Ovarian Cell Lines

Azenosertib Sensitivity and Cyclin E1 Protein Expression [1]



- Ovarian cell lines with high Cyclin E1 protein expression are more sensitive to azenosertib
- High Cyclin E1 protein expression sensitizes the low-sensitive cell line SKOV-3 to azenosertib

Azenosertib Sensitivity in SKOV3 High Expressing Cyclin E1 [2]

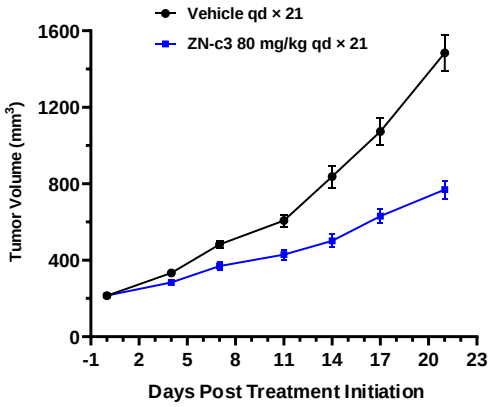


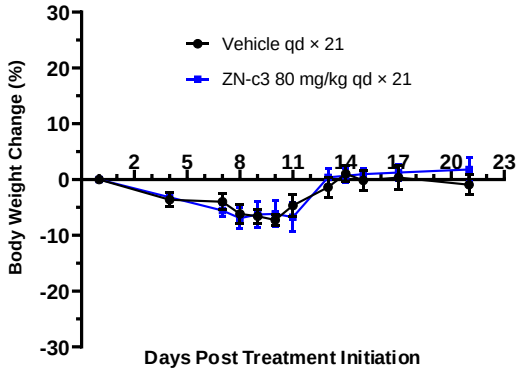
1. Azenosertib sensitivity is assessed by CellTiter Glo after 96 hours of culture. Data represent an average of at least 2 independent studies. Protein expression was assessed by Western Blot and is representative of 2 independent experiments.
2. Cyclin E1 was over-expressed in SKOV3 by lentivirus transduction followed by puromycin selection. Empty vector control was generated simultaneously.

CCNE1 Gene Amplification is Associated with Poor Prognosis and Chemotherapy Response Across Tumor Types

SKOV3
CCNE1 not amplified, TP53 mut

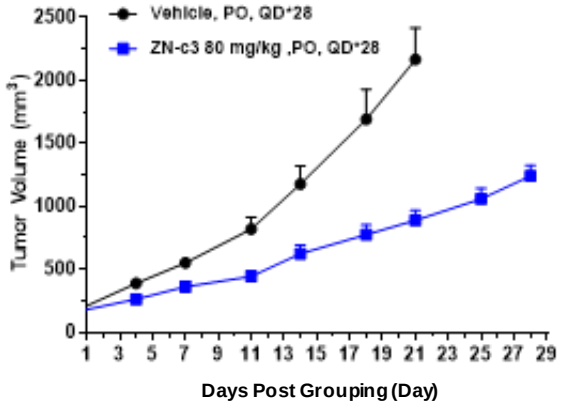
$TGI_{(80\ mpk,\ Day\ 28)}$ = 51.5%

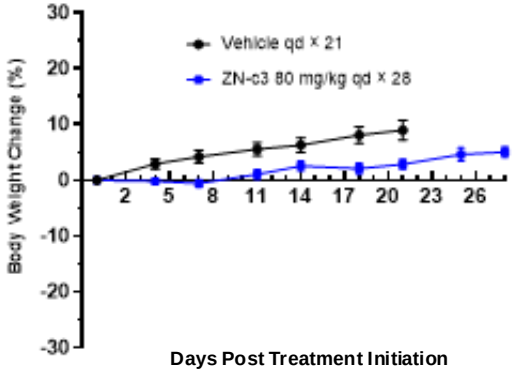




HCC1806 CDX
CCNE1 amp (CN=7), TP53 mut

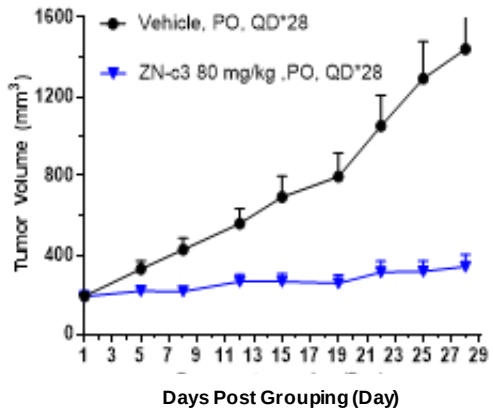
$TGI_{(80\ mpk,\ Day\ 28)}$ = 63.5%

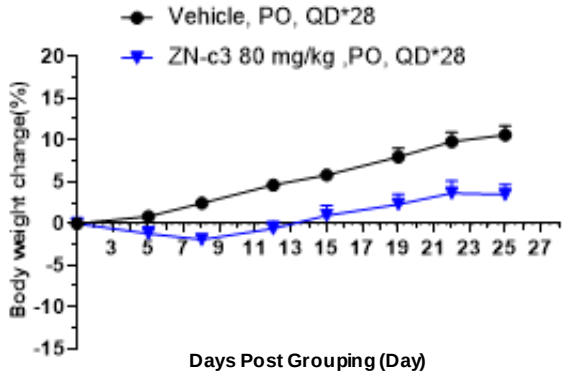




OVCAR3 CDX
CCNE1 amp (CN=14)

$TGI_{(80\ mpk,\ Day\ 28)}$ = 88%





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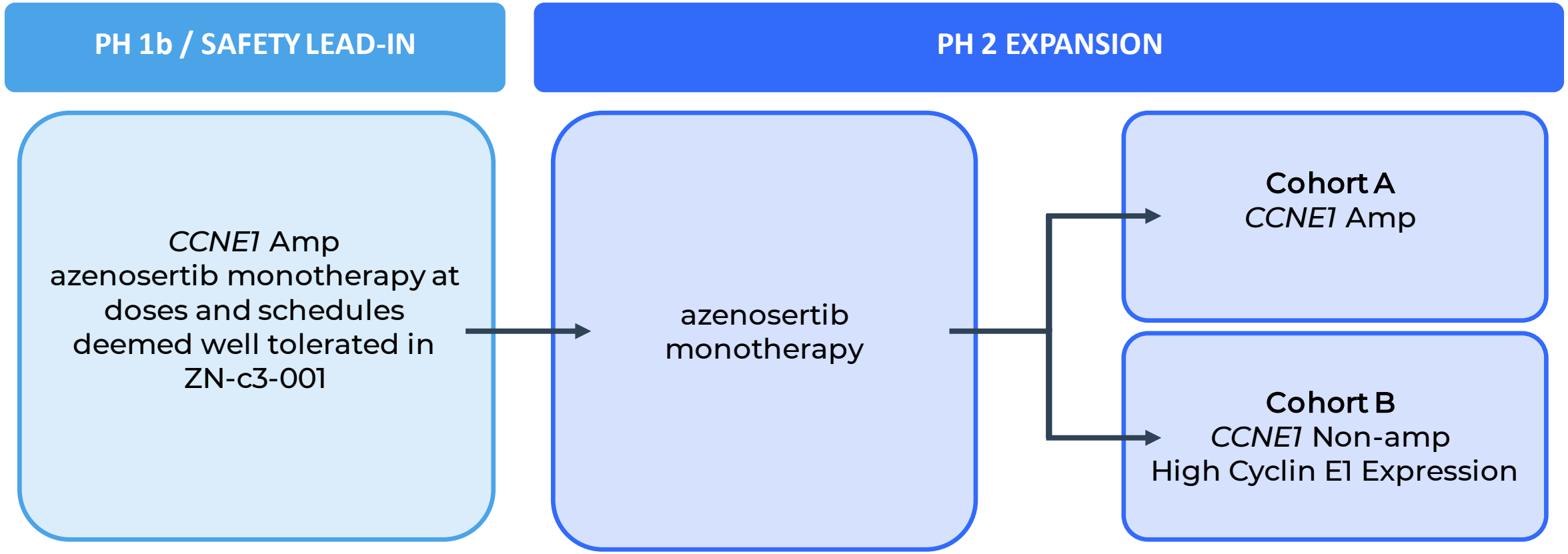
Moving Forward with Cyclin E1 patient enrichment in HGSOC: Revised ZN-c3-005 Study Design



Platinum-resistant HGSOC 1-3 prior lines (prior bevacizumab required)

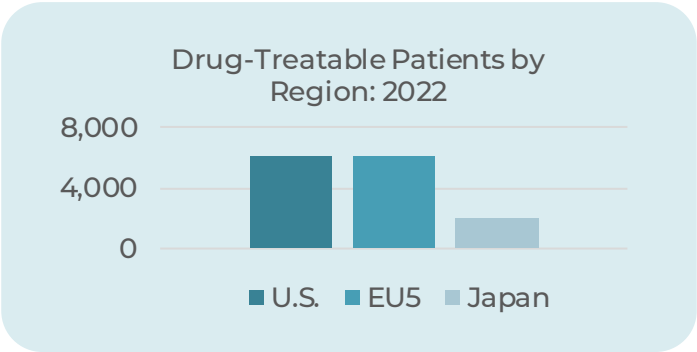
Platinum-Resistant/Refractory Ovarian Cancer Remains an Unmet Need

UNMET NEED

- Platinum-resistant and -refractory ovarian cancer represents a high unmet need
- It is associated with a poor prognosis and limited treatment options
  - ORR of 11.8% with standard of care [1] for platinum-resistant patients
- Improvement in efficacy with acceptable safety profile would make a meaningful difference for patients

PATIENT POPULATION

- In 2022, the total number of drug-treatable second line platinum-resistant ovarian cancer patients is estimated to be >14,000 in the United States, EU5 and Japan [2]



COMPETITIVE LANDSCAPE

- Current standard of care for second line platinum-resistant ovarian patients is single-agent chemotherapy ± bevacizumab [3]
- Ongoing pivotal trials focus on novel MOAs, including ADCs, and combinations with either PARPi or chemotherapy [3]
- Azenosertib is potentially a first-in-class treatment option that works synergistically with other anticancer therapies

Azenosertib's efficacy and tolerability profile are well-positioned for the platinum-resistant/refractory ovarian population

1. Pujade-Lauraine et al. J Clin Oncol 2014; 32:1302-1308; AURELIA study
2. Decision Resources Group; data on file.
3. CancerMPact Treatment Architecture Ovarian cancer July 2021; data on file.

ZN-c3-002: Summary of Clinical Activity

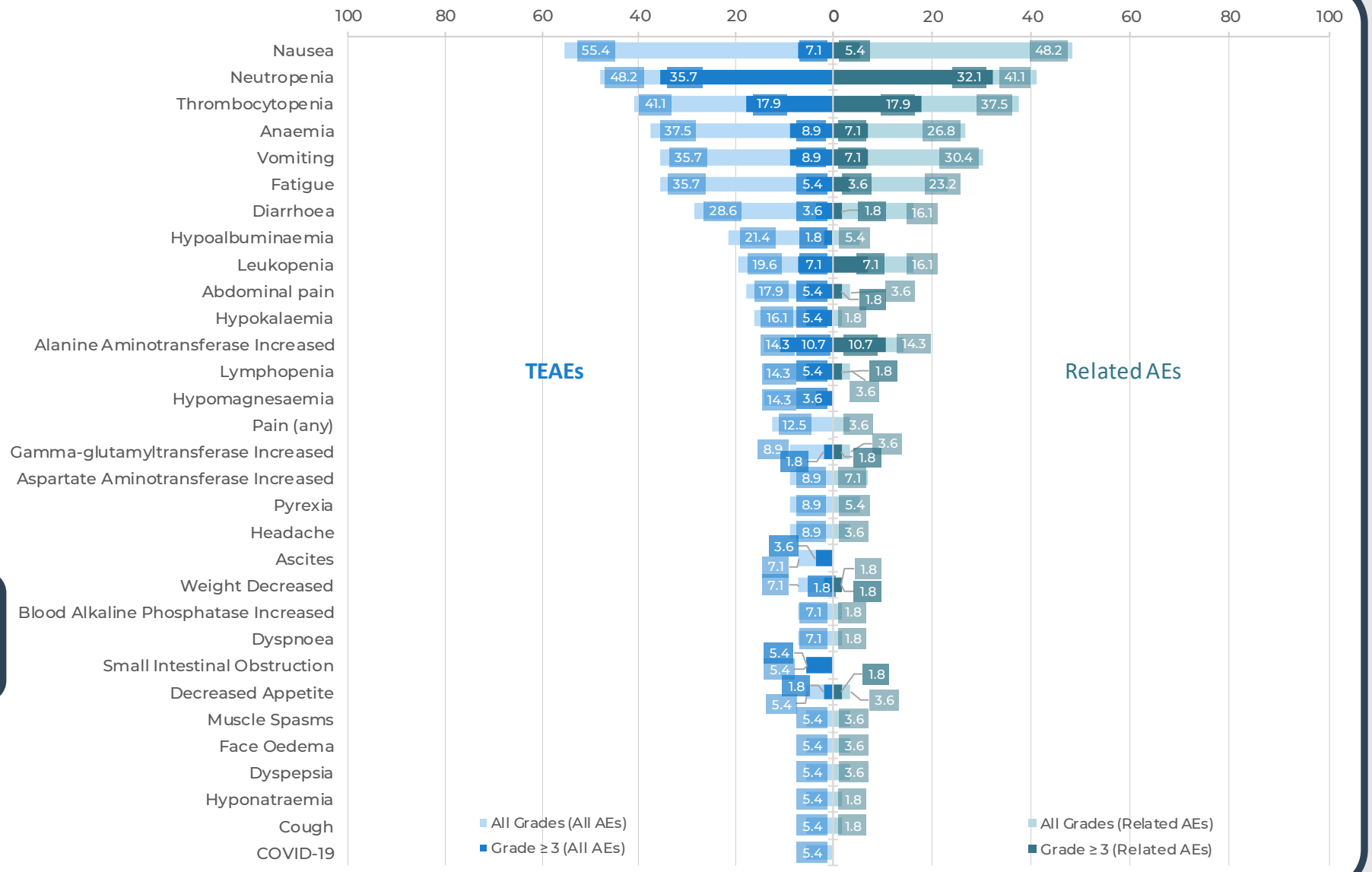
Summary of Clinical Activity (All Cohorts)							
Group	N	Evaluable* (n)	PR/uPR (n)	SD (n)	PD (n)	DCR (%)	ORR (%)
Azenosertib + Paclitaxel	9	8	5	3	–	100	62.5
Azenosertib + Carboplatin	17	11	5	4	2	81.8	45.5
Azenosertib + PLD	30	24	3	17	4	83.3	12.5
Total	56	43	13	24	6	86.0	30.2

Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1
* Patients with measurable disease and at least one post-baseline scan
Of evaluable subjects, ORR is percentage with PR/uPR; DCR = disease control rate, percentage of ORR + SD; uPR = unconfirmed partial response
Data cutoff January 28, 2022

Pasic, et al. Poster Presented at American Association for Cancer Research Annual Meeting (2022): Abstract CT148: A phase 1b dose-escalation study of ZN-c3, a WEE1 inhibitor, in combination with chemotherapy (CT) in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer.

ZN-c3-002: TEAEs ≥5% for All Patients (N=56)

Adverse Events



January 28, 2022 data cutoff.

Pasic, et al. Poster Presented at American Association for Cancer Research Annual Meeting (2022): Abstract CT148: A phase 1b dose-escalation study of ZN-c3, a WEE1 inhibitor, in combination with chemotherapy (CT) in subjects with platinum-resistant or refractory ovarian, peritoneal, or fallopian tube cancer

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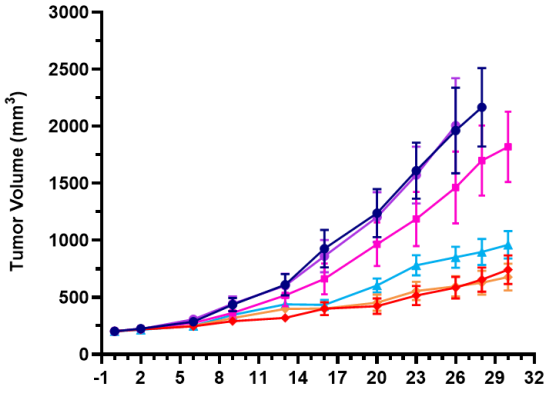
Azenosertib (ZN-c3)

PARP-Refractory Ovarian Cancer

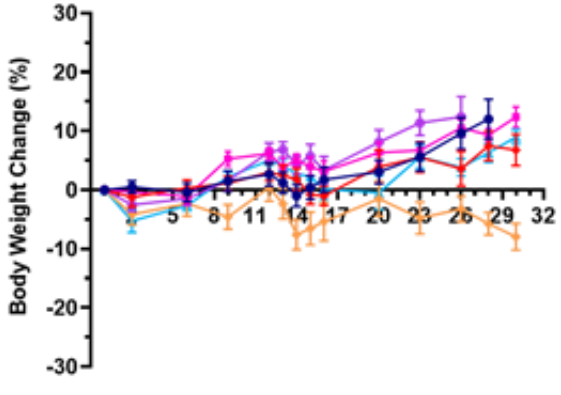
Azenosertib + PARP Inhibitor Combinations are Active in both Ovarian CDX and TNBC PDX Models

OVCAR3 Model

TGI

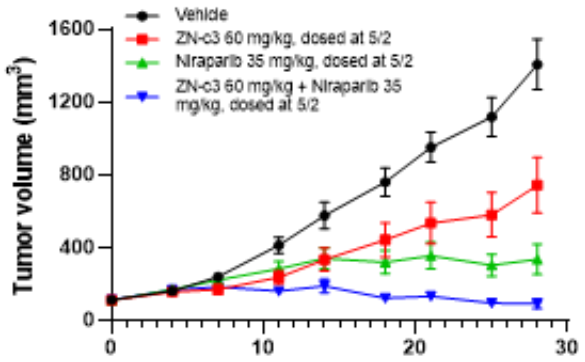


Body Weight

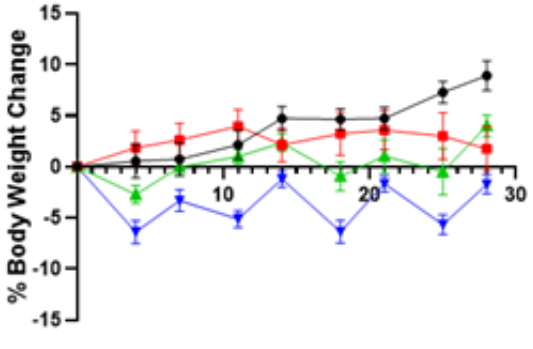


TNBC Model

TGI



Body Weight



- Combination of PARP and Wee1 inhibitors in TNBC results in synergistic cell killing in preclinical models with either BRCA1 mutations or high levels of cyclin E1 [1]
- The combination of azenosertib and niraparib shows efficacy in both ovarian and TNBC in vivo models
- Preclinically, sequential administration of PARP and azenosertib is efficacious but is better tolerated than concurrent based on body weight loss
- Wee1 inhibition may broaden the application range of PARP inhibitors in ovarian cancer and TNBC, consistent with results from the EFFORT [2] and STAR trials [3]

1. Chen X Cancers (Basel). 2021 Apr 1;13(7):1656 2. Westin, S.; J Clinical Oncology, 39, N15 (Supplement). 2021, 5505. 3. Yap T. Eur J Cancer. Vol 174 (Supplement 1), S7: 2022.

ZN-c3-006: Phase 1/2 Study of Azenosertib In Combination with Niraparib in Patients with PARP-Resistant Ovarian Cancer

KEY ELIGIBILITY

Key Eligibility:

- Recurrent high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancer (serous, clear cell or endometrioid).
- Prior therapy: 1 – 5 prior lines for advanced/metastatic disease
- Disease progression while taking a PARPi as maintenance treatment (minimum of 3 months of treatment required).

Primary Endpoint

- Determine MTD/RP2D and optimal administration schedule

PHASE 1: SAFETY LEAD-IN

3+3 dose escalation design

azenosertib + niraparib administered concurrently

azenosertib + niraparib administered in an alternating schedule

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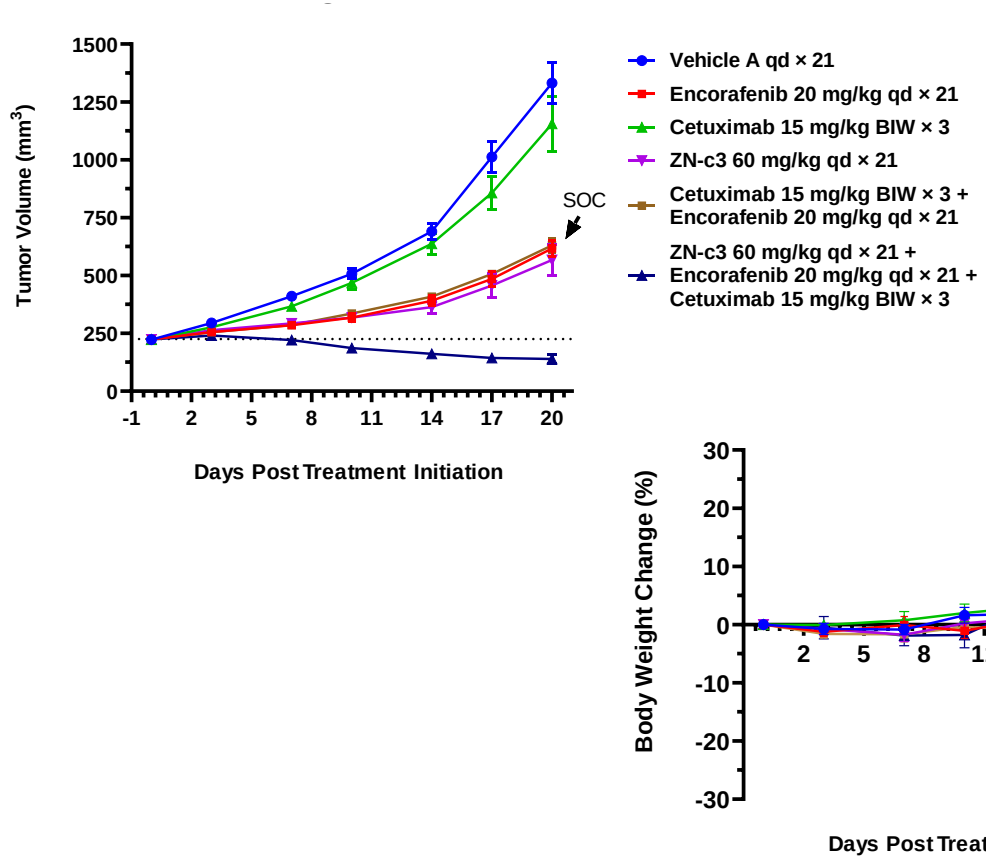
Azenosertib (ZN-c3)

BRAF Metastatic Colorectal Cancer

Preclinical Data Supports the Combination of Azenosertib with Encorafenib and Cetuximab: BEACON REGIMEN



- Oncogene-induced replication stress in mutationally driven cancers such as BRAF mutant colorectal cancer leads to DNA damage and genomic instability
- Oncogene activation disrupts replication regulation leading to slow and stalled replication forks and other defects and leads to DNA damage
- Dependency of cancers with replication stress on Wee1 signaling provides a mechanistic basis for synergy with EGFR/BRAF inhibition
- Addition of azenosertib to the BEACON regimen is well tolerated and provides superior efficacy in an *in vivo* model of BRAF mutant CRC

BRAF mCRC Study in Collaboration with Pfizer

Large Patient Population…

- Up to 21% of mCRC patients have BRAF mutations (~15,000 patients per year, U.S.) with over 90% V600E[1]
- Testing for BRAF mutations is routine, providing opportunity to identify patients

With Significant Unmet Need

- Median OS in BRAF mutant CRC patients <1 year, vs. BRAF WT >2 years[2]
- While targeted BRAF inhibition (e.g., vemurafenib) has been successful in melanoma with response rates >80%, this strategy has failed in CRC (OR ~5%) due to innate resistance[3]
- Encorafenib in combination with cetuximab (BEACON) was approved for BRAF V600E mCRC in April 2020 and is now the standard of care

Phase 1/2, Open-Label, Multi-center Study Of Azenosertib In Adults With Metastatic Colorectal Cancer

Pfizer

PHASE 1: DOSE FINDING

- Patients with mCRC and documented BRAFV600E mutation
- Disease progression after 1 or 2 previous regimens for metastatic disease
- Prior therapy may include BRAF and/or EGFR directed therapy (e.g. may have progressed after BEACON regimen)

→ Encorafenib + Cetuximab + Escalating Dose Levels of azenosertib →

PHASE 2: DOSE EXPANSION

N: Up to 80 patients

- Phase 1 Endpoints: Safety, tolerability, MTD, RP2D
- Phase 2 Endpoint(s): ORR; DOR, DCR, PFS, TTP

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1 Sorbye H, Dragomir A, Sundström M, et al. High BRAF Mutation Frequency and Marked Survival Differences in Subgroups According to KRAS/BRAF Mutation Status and Tumor Tissue Availability in a Prospective Population-Based Metastatic Colorectal Cancer Cohort. PLoS One. 2015;10(6):e0131046. 2 Corcoran et al. Combined BRAF and MEK Inhibition With Dabrafenib and Trametinib in BRAF V600–Mutant Colorectal Cancer. J Clin Oncol (2015) Dec 1; 33(34): 4023-4031
3 Kopetz et al. Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer. NEJM (2019) 381: 1632-1643 Zentalis maintains full economic ownership and control of azenosertib, apart from Greater China rights (Zentara).

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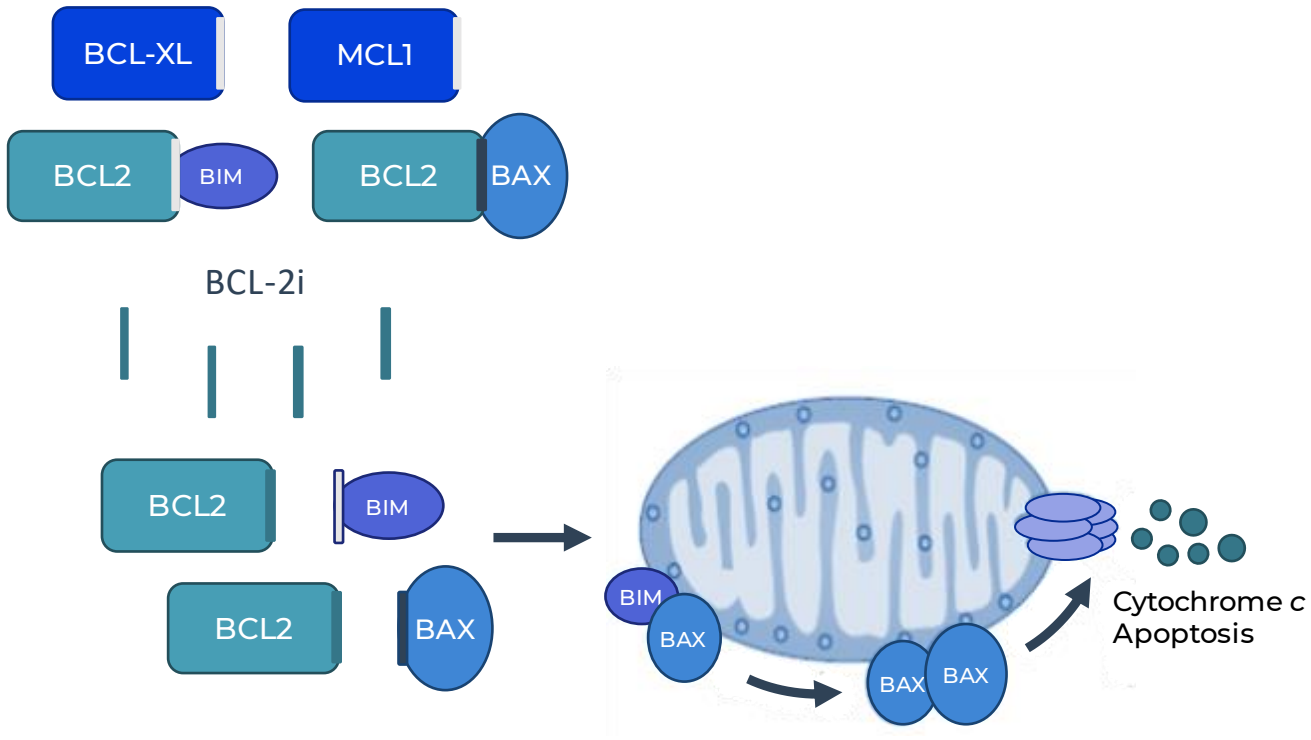
ZN-d5

BCL-2 Inhibitor

BCL-2: A Clinically Validated Oncology Target

- BCL-2 is an anti-apoptotic protein involved in tumor survival and chemo resistance [1]
- The intrinsic apoptotic pathway is controlled by the BCL-2 protein family on the mitochondrial outer membrane [2, 3]
- BCL-2 inhibitors may restore the normal apoptosis process, making it an important target for cancer treatments

Mechanism of Action of BCL-2 Inhibitors [1]



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

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

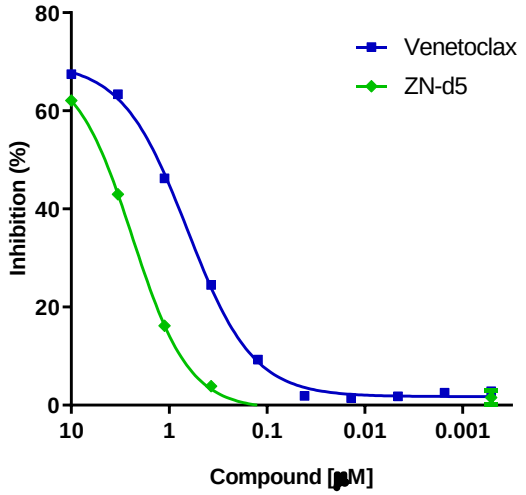
ZN-d5 has 10x Improved Selectivity for BCL-2 vs BCL-xL and Binds With Higher Affinity to BCL-2 Mutants than Venetoclax

Compound ID	Affinity (Kd, nM)			IC_{50} (nM) BCL-2 Type			
	BCL-2	BCL-xL	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} (mM)
Venetoclax	0.6
ZN-d5	2.4

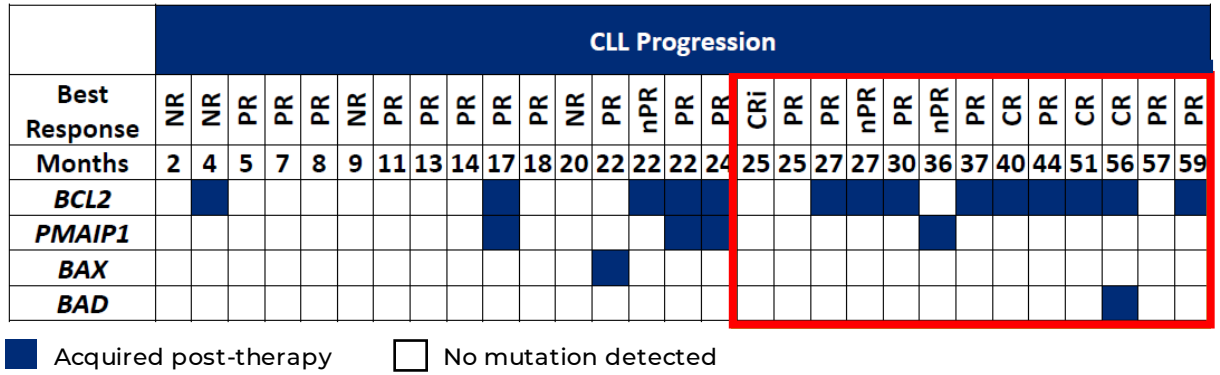
ZN-d5 shows activity in preclinical models of ALL, NHL and AML

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

ZN-d5: May Bind with Higher Affinity to BCL-2 Mutants than Venetoclax

Mutations in BCL-2 May be Driving Sub-Clonal Pockets of Resistance to Venetoclax in CLL

CLL Progression on Venetoclax



55% (16/29) patients acquired mutations in BCL-2 family members

- 41% (14/29) with mutations in BCL-2
- 21% (6/29) with mutations in PMAIP1 (NOXA), BAX or BAD

Majority (9/14) were detected with BCL-2 mutations after 24 months on venetoclax

- 55% (16/29) of patients with CLL progression

Compound ID	IC_{50} (nM) BCL-2 Type			
	WT	G101V	F104L	D103Y
Venetoclax	1.3	7.3	8.4	18.3
ZN-d5	1.4	3.7	1.4	5.0

Note: Competition assay for displacing BAK peptide bound to BCL-2

Source: Chyla, B. ASH Presentation (2019)
Venetoclax data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound.

ZN-d5 Clinical Development Plan

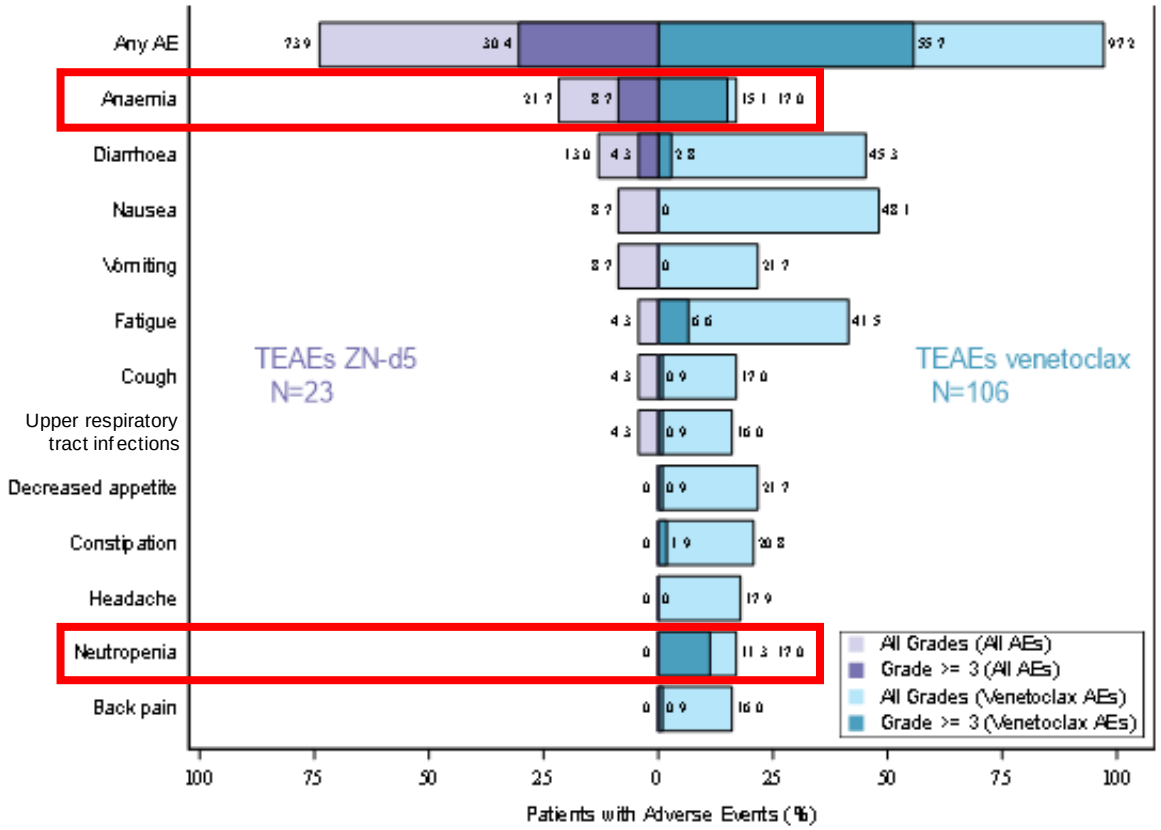
- Improved *in vitro* potency and has 10x improved selectivity for BCL-2 vs BCL-xL compared to venetoclax
- Observed to bind with higher affinity to BCL-2 mutants than venetoclax in *in vitro* assay
  - Mutations in BCL-2 may be driving sub-clonal pockets of resistance to venetoclax
- Preclinical combination data of ZN-d5 + azenosertib (ZN-c3) utilizing novel biology showed synergistic and additive activity across multiple indications in both solid and liquid tumors, often at subtherapeutic doses

Ongoing and Planned Clinical Programs		
Indication	Treatment	Trial Updates
Non-Hodgkin's Lymphoma	ZN-d5	Continues to enroll
AL Amyloidosis	ZN-d5	Continues to enroll
AML	ZN-d5 & azenosertib	Trial initiated in 4Q 2022

ZN-d5: Favorable Early Comparison to Venetoclax in NHL

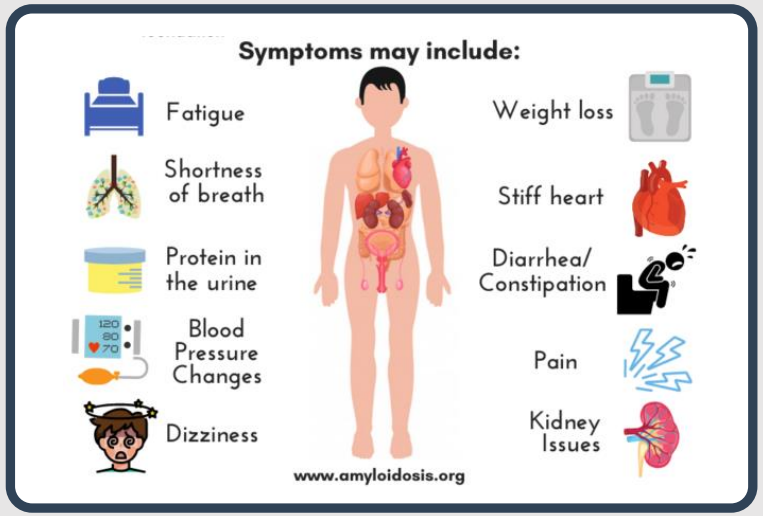
- ZN-d5 100-1200mg, empty stomach
- Venetoclax 200-1200mg with food
- Early toxicity profile in NHL favorable vs. published venetoclax data [1]
  - Fewer AEs of any Grade, Grade ≥3
  - No TLS observed
  - Venetoclax AEs not dose-dependent

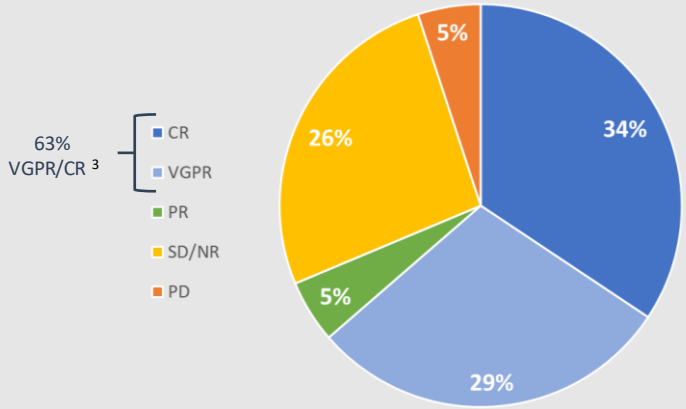
Adverse Event	Any Grade			
	All Doses (N = 106)	≤ 400 mg (n = 22)	600 to 900 mg (n = 33)	1,200 mg (n = 51)
Emergent*				
Any event	103 (97)	21 (96)	33 (100)	49 (96)
Nausea	51 (48)	9 (41)	15 (45)	27 (53)
Diarrhea	48 (45)	7 (32)	14 (42)	27 (53)
Fatigue	44 (42)	10 (45)	9 (27)	25 (49)
Decreased appetite	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. Not a head-to-head study

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

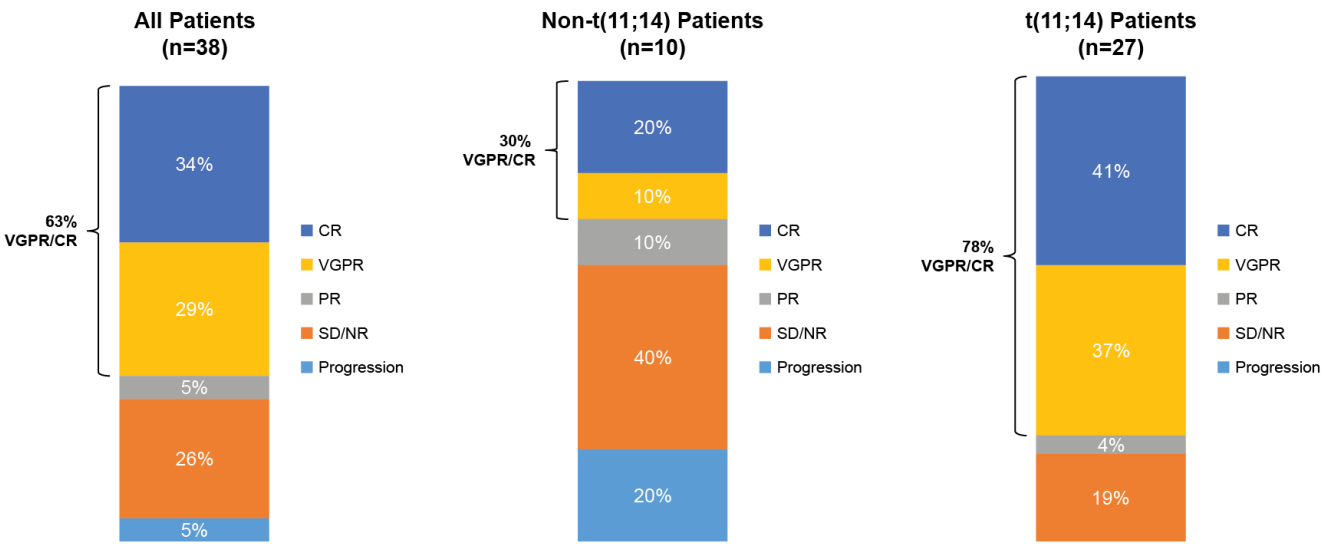
AL Amyloidosis study is currently enrolling patients

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.

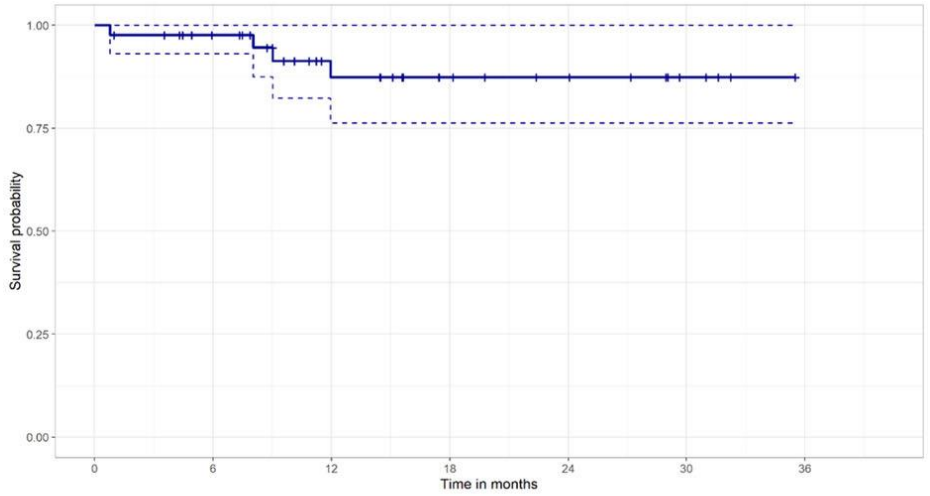
BCL-2 Inhibition has Shown Robust Clinical Activity in AL Amyloidosis

- Patients with the t(11;14) translocation have a worse prognosis than the general AL amyloidosis population [1]
- BCL-2 inhibition showed an improved response rate in the t(11;14) cohort with a trend towards better survival

Best Response in Evaluable Patients



OS for All Patients



1. Premkumar et al, Blood Cancer J 2021;11:10; hematologic response rate in 38 evaluable patients.

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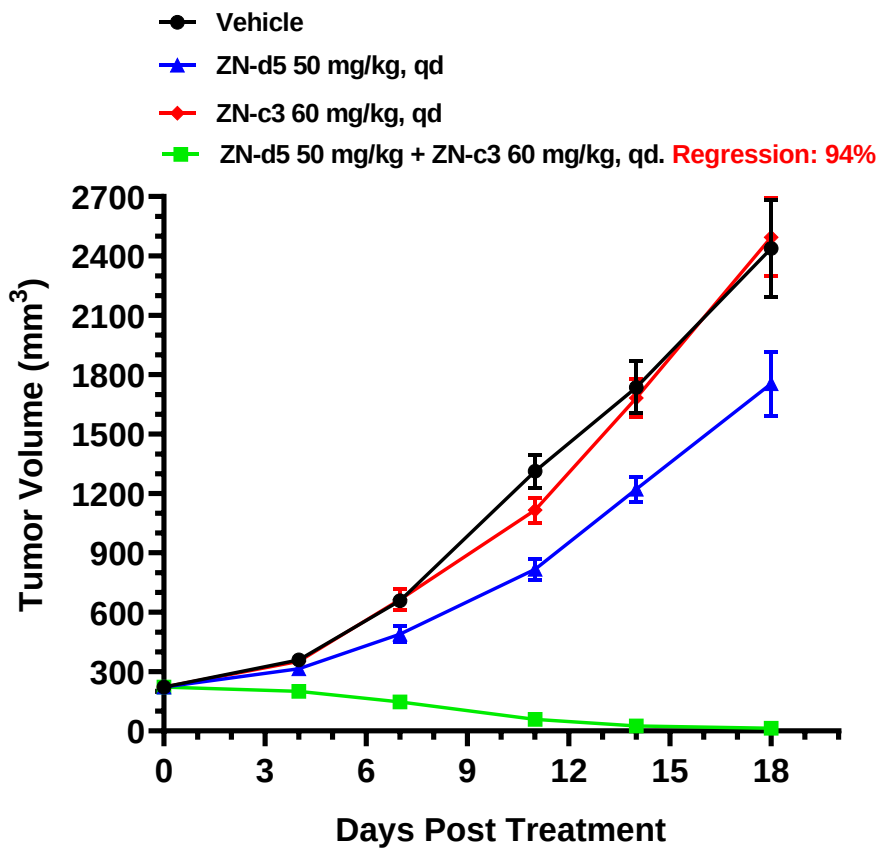
Potential Combination of Azenosertib (ZN-c3) and ZN-d5

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

HL-60 AML Model

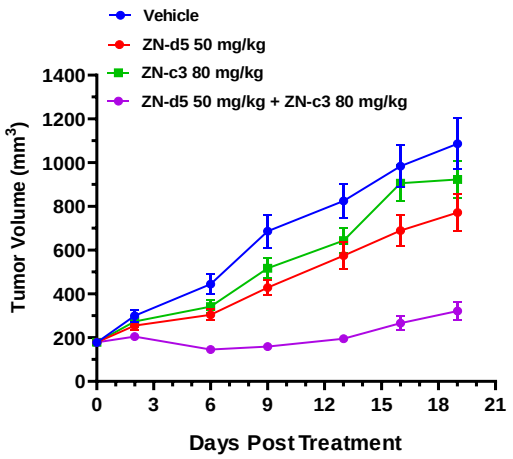


- ZN-d5 and azenosertib combination represents a novel therapeutic approach
- Significant enhancement of activity than single agent in several indications, including AML
- Combination regimen was well-tolerated in mice
- Zentalis is the only company known to have both inhibitors in clinical development

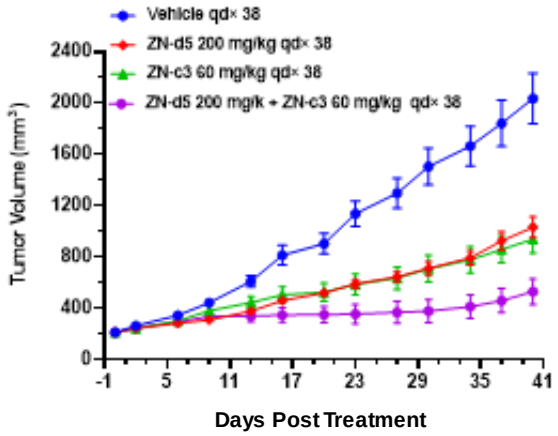
Presented at AACR 2022 by Izadi, H.; et. al. Cancer Res (2022) 82 (12_supplement): 2591.

Antitumor Activity in Solid Tumor Models with the ZN-d5 + Azenosertib Combination Represents Market Expansion Opportunities

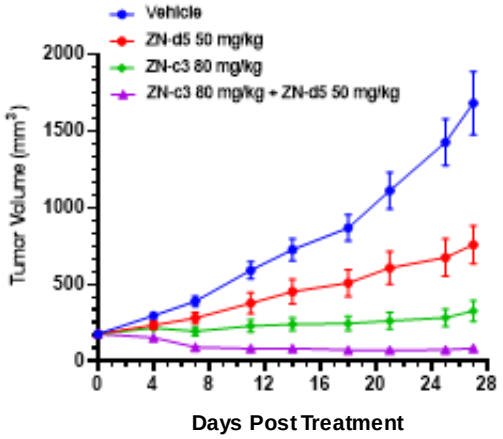
SCLC Model (DMS53)[1]



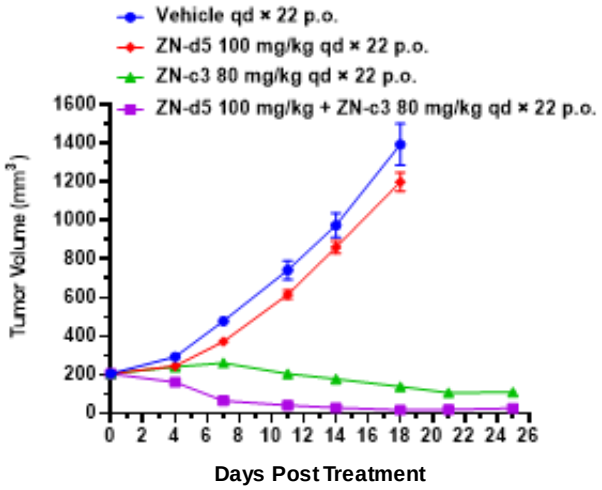
TNBC Model (MDA-MB-436)



NSCLC Model (H146)



Neuroendocrine Prostate Model (H660)



1. Izadi, H. et. al. Cancer Res (2022) 82 (12_Supplement): 2605.

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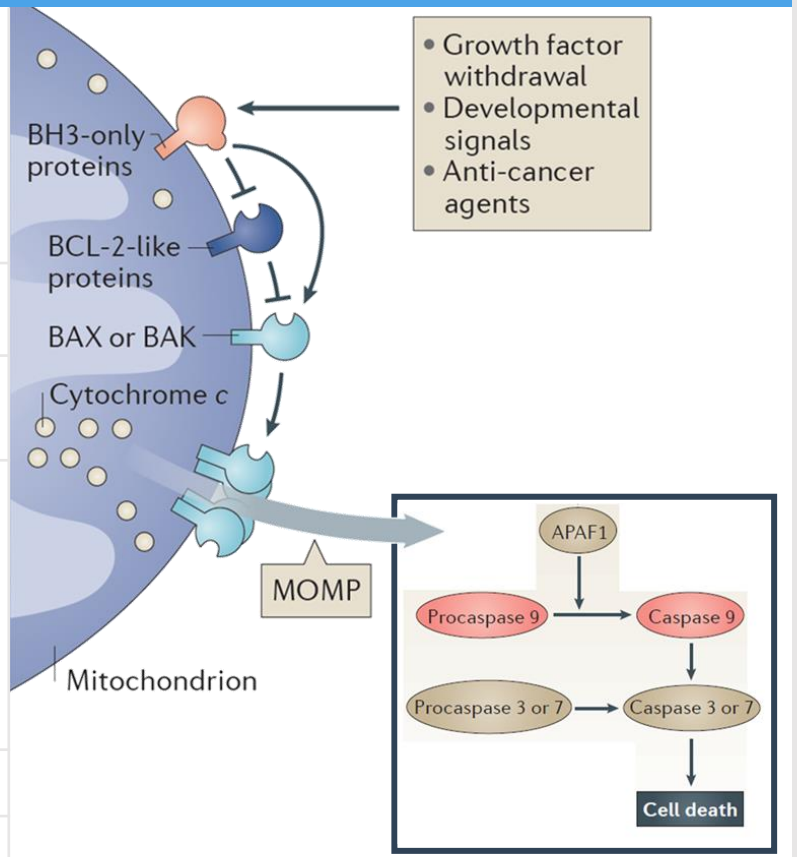
BCL-xL Protein Degrader

BCL-xL Degrader Background and Rationale

Background, Clinical Relevance, and Approach	
Therapeutic Hypothesis	• BCL-xL is a member of the anti-apoptotic BCL-2 proteins and is clinically validated. [1, 2] • Expression of BCL-xL contributes to therapeutic resistance mechanisms. [3, 4, 5] • Degrading BCL-xL will induce cell death and overcome resistance mechanisms in multiple cancer types, while reducing the possibility of on-target thrombocytopenia.
Patient Selection	• Heme malignancies. • Solid tumors.
Internal Combination Opportunities	• Azenosertib (ZN-c3; Wee1 inhibitor) and ZN-d5 (BCL-2 inhibitor)
Therapeutic Window	• BCL-xL is required for platelet viability and BCL-xL inhibitors (e.g. navitoclax) are dose limited in the clinic due to on-target thrombocytopenia. [6] • A degradation approach with a E3 ligase low expressed in platelets could help mitigate thrombocytopenia. [7, 8] • Efficacy may be achieved at lower doses and frequencies due to the catalytic MOA of degraders, further reducing the chance of thrombocytopenia and increasing TI.
Chemical Modality	• Heterobifunctional degrader linking BH3-binding moiety.
Competitive Landscape	• Multiple inhibitors and one degrader in the clinic (Ph1/2).

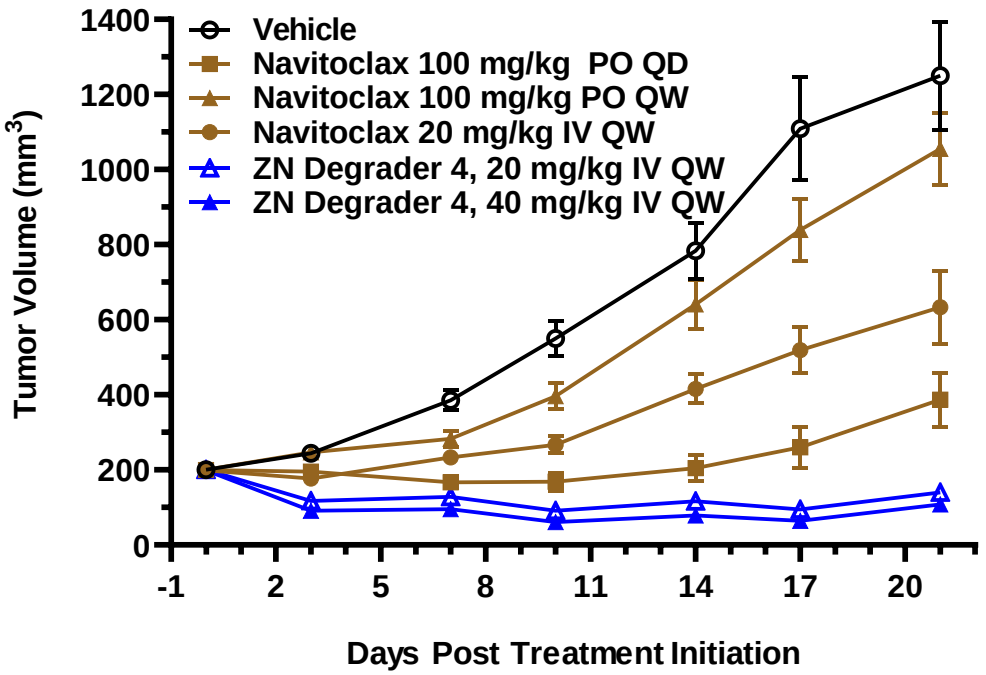


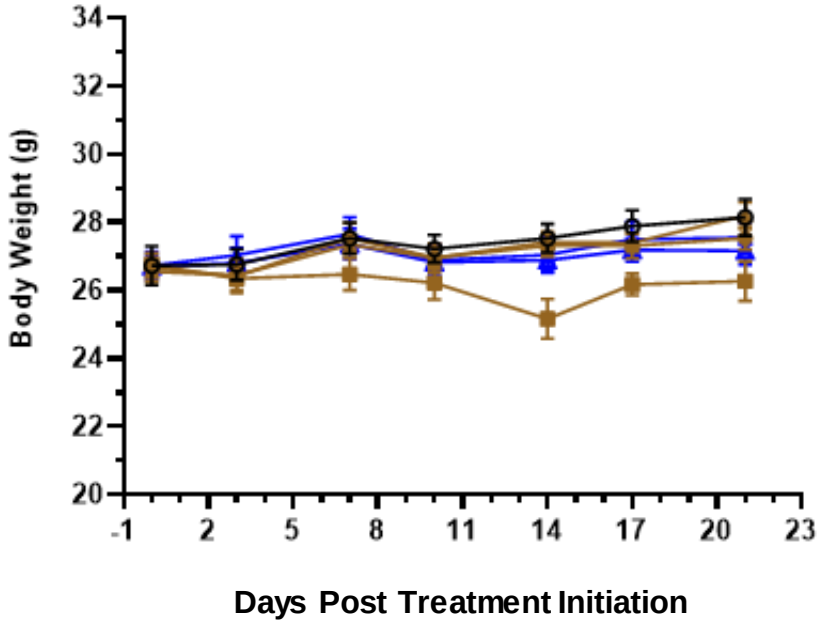
Declared development candidate and initiated IND enabling activities

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., Cnacer Cell Int., 2020, 20(254)
5. cbioportal.org 6. Wilson WY et al., Lancet Oncol., 2010; 11(12):1149-1159 7. Khan et al. Nature Med 12, 1938-1947 (2019) 8. He et al. Nature Comm 11, (2020)

Figure from: Delbridge, A. R. D., et. al. Nat Rev Cancer 16, 99-109 (2016)

BCL-xL IV Degrader is More Efficacious than BCL-xL Inhibitor (Navitoclax) in MOLT4 (T-ALL) Models

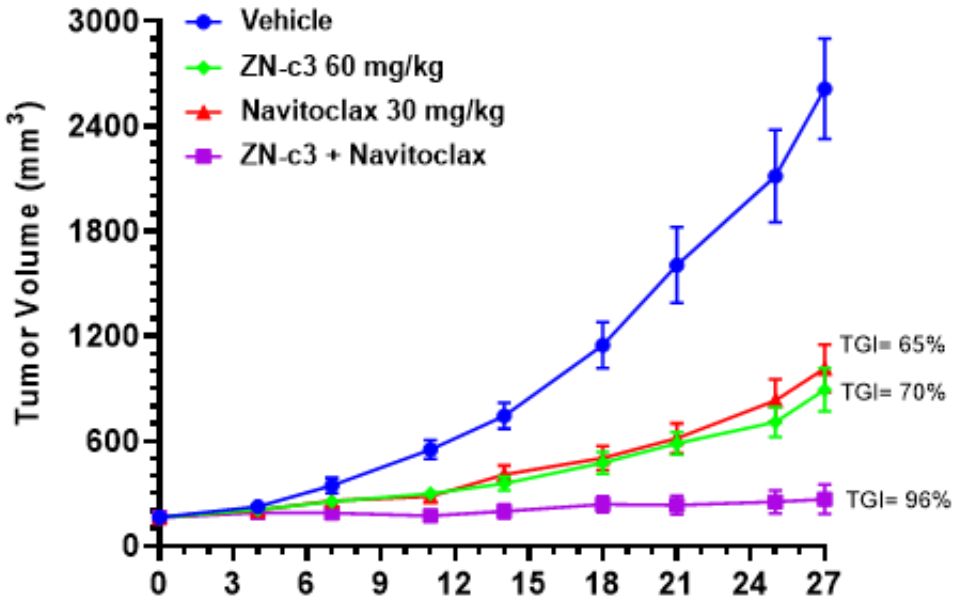


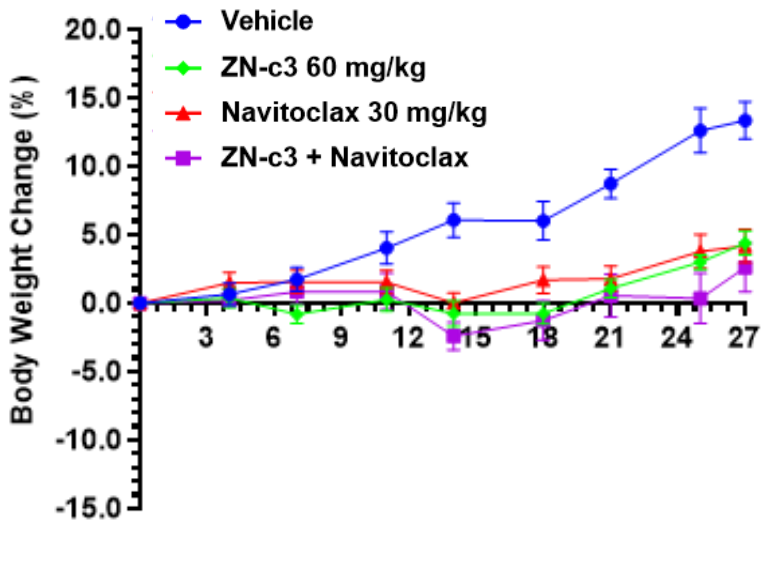


- BCL-xL degrader demonstrates excellent efficacy in the MOLT4 tumor model (T-ALL) and is well-tolerated at efficacious doses
- BCL-xL degrader is more efficacious than Navitoclax

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

Azenosertib Combined with a Low Dose of Navitoclax (BCL-xL Inhibitor) Results in Synergistic Anti-tumor Activity in the T-ALL model MOLT-4[1]





- The MOA of the combination of the BCL-xL therapeutic and azenosertib represents a novel approach which results in synergistic anti-tumor activity.
- Development of the BCL-xL degrader offers an opportunity to combine with other anti-cancer agents, such as azenosertib.

1. Izadi, H.; et. al. Cancer Res (2022) 82 (12_Supplement): 2605.
TGI: Tumor Growth Inhibition ALL: Acute Lymphoblastic Leukemia MOLT-4 model is BCL-xL dependent, but is not on BCL-2
Navitoclax data based on evaluation of comparable proxy chemical compound purchased from commercial sources rather than obtained from the pharmaceutical company developing the compound

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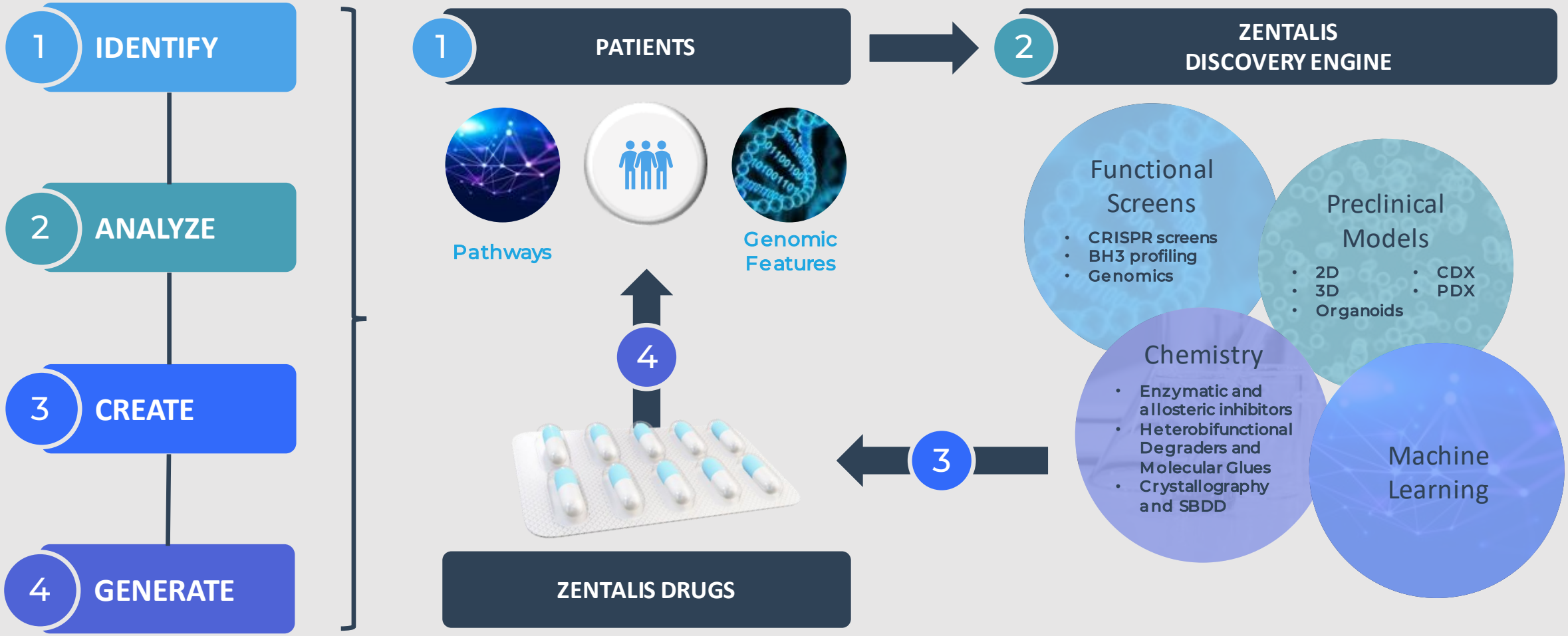
Conclusions

Utilizing the Highly Efficient Integrated Discovery Engine to Generate Potentially Best-In-Class Drugs



2023 Key Milestones

Azenosertib (ZN-c3) Wee1 Inhibitor

1Q 2023	✓ Initiate enrollment in the BRAF mutant colorectal cancer BEACON regimen combination clinical trial in collaboration with Pfizer
1H 2023	Provide preclinical rationale for Cyclin E1 enrichment strategy at a scientific conference
1H 2023	Declare monotherapy RP2D and provide update on dose optimization activities, program timelines and potential paths to registration
2H 2023	Results from Phase 1b ovarian chemotherapy combination trial, including clinical translational data on Cyclin E1 amplification / overexpression

ZN-d5 BCL-2 Inhibitor

2H 2023	Provide interim clinical data and declare RP2D for Phase 1/2 monotherapy trial in amyloidosis
2H 2023	Provide preliminary data from clinical trial of azenosertib + ZN-d5 in relapsed / refractory acute myeloid leukemia

Integrated Discovery Engine

2023	Continue to advance the BCL-xL protein degrader program through IND enabling studies
2023	Advance ongoing research on protein degrader programs of undisclosed targets

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