564TiP: A Phase 1b dose-escalation study of ZN-c5, an oral selective estrogen receptor degrader (SERD), in combination with abemaciclib in patients with advanced estrogen receptor (ER)+/HER2– breast cancer

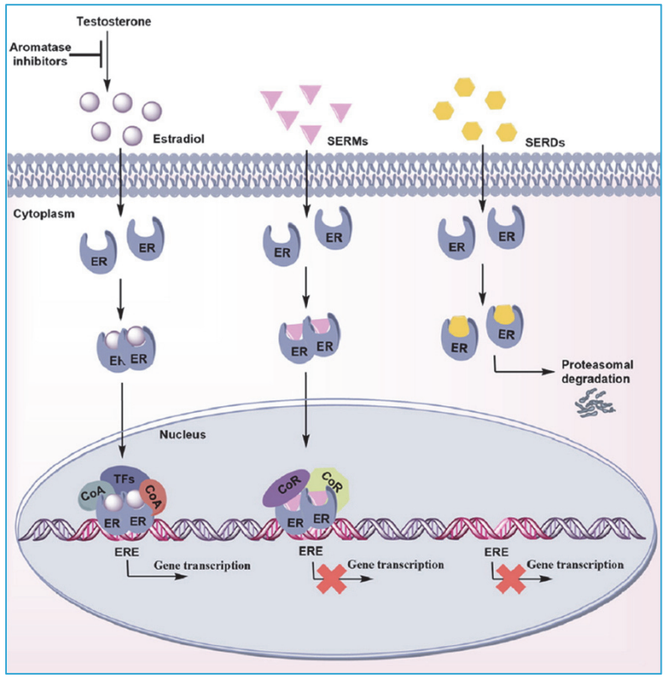
G.P. Keogh[1], S. Papish[2], W. Piskorski[3], M. Ułańska[4], B. Jackson[5], M. Suster[5], M. Ptaszynski[5], L. Mina[6]

[1] Charleston Oncology, Charleston, SC, USA; [2] Summit Health Cancer Center, Florham Park, NJ, USA; [3] Clinical Trials Center of the Jagiellonian Center of Innovation, Krakow, Poland; [4] Copernicus Memorial Hospital, Łódź, Poland; [5] Zentalis Pharmaceuticals, New York, NY, USA; [6] Banner MD Anderson Cancer Center, Gilbert, AZ, USA

Introduction

- Hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2–) breast cancer (BC) accounts for nearly 70% of all BC in the United States.[1]
- Despite first-line endocrine therapy (ET), about 50% of patients with HR+/HER2– BC experience recurrence within 5 years.[2]
- Fulvestrant, a selective ER degrader (SERD), binds and degrades the ER and is active in patients with HR+/HER2– BC for whom first-line ET failed. However, it is limited by a requirement for intramuscular injection, which is inconvenient, may result in injection-site reactions, and limits exposure to the drug.[3]
- Combining of a SERD (**Figure 1**) with a cyclin-dependent kinase (CDK) 4/6 inhibitor is now the standard of care for first- and later-line treatment for ER+/HER2– BC.[4]
- ZN-c5 is a novel, orally bioavailable SERD with demonstrated activity in ER+ tumor models,[5] and it is being combined with the CDK4/6 inhibitor abemaciclib in patients with advanced BC.

Figure 1. Mechanism of Action for SERDs[6]



CoA, coactivator; CoR, corepressor; ER, estrogen receptor; ERE, estrogen response element; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; TF, transcription factor.

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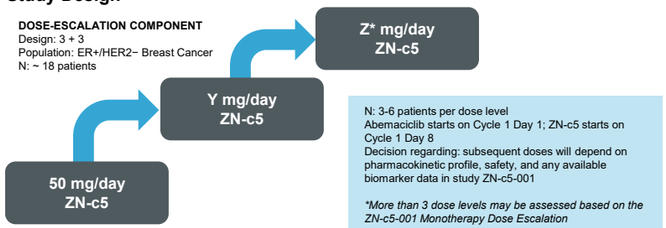
Methods

Study Design (cont'd)

- Open-label, multicenter dose escalation study (**Figure 2**):

Figure 2. Study Design



Patients

Inclusion Criteria

- Male or female; age ≥18 years
- Histologically or cytologically confirmed diagnosis of advanced adenocarcinoma of the breast
- ER+ (>10% positive stained cells by immunohistochemical methods)
- HER2– based on the most recent tumor biopsy, per the 2018 guidelines of the American Society of Clinical Oncology and College of American Pathologists
- No prior chemotherapy for the treatment of advanced/metastatic disease
- Up to 1 prior hormonal-based therapy for the treatment of advanced/metastatic disease
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Eastern Cooperative Oncology Group Performance Status ≤1

Exclusion Criteria

- Timing for discontinuation of prior therapy vs Cycle 1 Day 1:
  - Tamoxifen, aromatase inhibitor, fulvestrant, or other anti-cancer ET <14 days
  - Any investigational drug therapy <28 days or 5 half-lives
  - Prior radiotherapy <28 days (except for palliative radiotherapy to peripheral sites without residual toxicity)
  - Any prior systemic adjuvant chemotherapy regardless of the stop date, but the patient must have recovered to eligibility levels from prior toxicity
  - Major surgery <28 days, minor surgery <7 days
- Prior hematopoietic stem cell or bone marrow transplantation
- Prior treatment with ZN-c5
- Prior treatment with CDK4/6 inhibitors
- Brain metastases that require immediate treatment or are clinically or radiologically unstable
- Presence of life-threatening metastatic visceral disease or symptomatic pulmonary lymphangitic spread
- Other known active cancer(s)

Treatment

- Treatment cycles are 28 days:
  - For the first 7 days of Cycle 1 (C1D1 – C1D7), all subjects will ingest abemaciclib alone. On Day 8, ZN-c5 will be added to the regimen. For the remainder of the study, all subjects will take both study medications together.

Endpoints

- Endpoints are summarized in **Table 1**.

Table 1. Endpoints

Primary
• Observed dose-limiting toxicities (DLTs) in DLT-evaluable subjects during Cycle 1 • Incidence and severity of adverse events, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v 5.0
Secondary
• As defined by RECIST v1.1 – Objective response rate – Duration of response – Clinical benefit rate, defined as complete response + partial response (PR) + stable disease lasting at least for 24 weeks prior to any evidence of progression. PR will be included only for subjects with measurable disease • ZN-c5 (and its potential metabolites as applicable) and abemaciclib (and its metabolites) plasma pharmacokinetic parameters: maximum plasma concentration, time to maximum plasma concentration, area under the curve to the time of last measurement, elimination half-life, and trough concentration, as applicable
Exploratory
• Biomarkers (including but not limited to ER degradation, Ki-67, and estrogen receptor 1 [ESR1] mutations) • ZN-c5 concentrations (and its potential metabolites as applicable) in tumor tissue

Study Sites

There are active study sites in Poland and the United States (**Figure 3**)

Figure 3. Study Sites

Conclusions

The trial is ongoing.

References

1. National Cancer Institute. 2021. https://seer.cancer.gov/statfacts/html/breast-subtypes.html. **2.** Wangchinda P, Ithimakin S, et al. *World J Surg Oncol.* 2016;14(1):223. **3.** Blackburn SA, et al. *Expert Rev Anticancer Ther.* 2018;18(7):619-628. **4.** National Comprehensive Cancer Network. 2021. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. **5.** Samatar AA, et al. *Cancer Res.* 2020;80(16 Suppl):4373. **6.** Patel HK, Bihani T. *Pharmacol Ther.* 2018;186:1-24.

Disclosure

Dr Keogh: none.