565TiP: A Phase 1/2 dose-escalation and expansion study of ZN-c5, an oral selective estrogen receptor degrader (SERD), as monotherapy and in combination with palbociclib in patients with advanced estrogen receptor (ER)+/HER2– breast cancer

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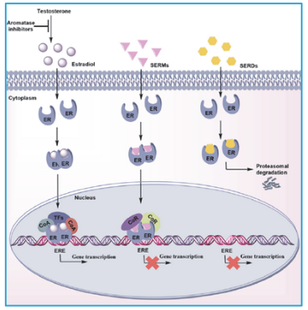
Introduction

- Most patients with estrogen receptor (ER) positive/human epidermal growth factor receptor (HER2) negative breast cancer (BC) are diagnosed at an early stage, receive adjuvant endocrine therapy (ET), and have a good prognosis.[1] However, a subset of patients relapse while on or after adjuvant ET and are placed on first-line ET. After initially responding, they experience disease progression.[1-3]
- Fulvestrant, the only approved selective estrogen receptor degrader (SERD) that binds and selectively degrades the ER, has significant anti-tumor activity following ET failure. However, it is limited by a requirement for intramuscular administration, leading to suboptimal exposure and injection-related adverse events such as pain and ecchymosis.[3,4]
- ZN-c5 is a novel and potentially potent SERD (**Figure 1**) with oral bioavailability, which demonstrated activity in estrogen-dependent tumor models.[5]

Figure 1. Mechanism of Action for SERDs[2]

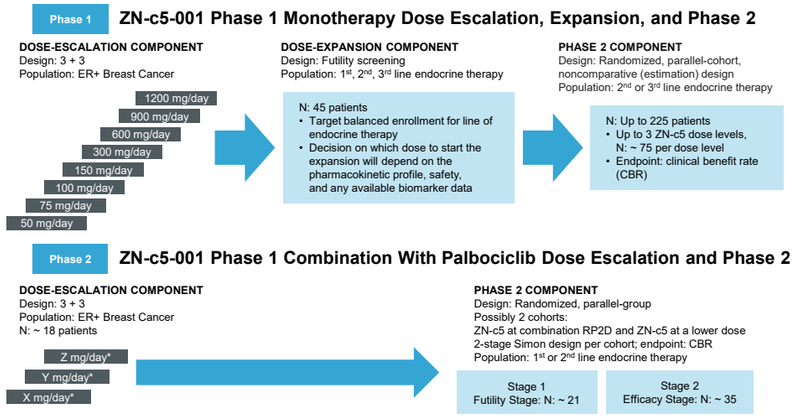


CoA, coactivator; CoR, corepressor; ER, estrogen receptor; ERE, estrogen response element; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulators; TF, transcription factor.

Methods

Study Design

Figure 2. Study Design



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Methods (continued)

Study Design (cont'd)

- Open-label multicenter study with 5 components (**Figure 2**):
  - Phase 1
    - Monotherapy Dose Escalation
    - Monotherapy Expansion
    - Combination Dose Escalation
  - Phase 2
    - Monotherapy Phase 2
    - Combination Phase 2

Patients

Inclusion Criteria

- Male or female; age ≥18 years
- Histologically or cytologically confirmed diagnosis of advanced adenocarcinoma of the breast
- ER-positive and HER2-negative
- Documented prior response to ET for advanced or metastatic disease lasting >6 months or disease recurrence after at least 24 months of adjuvant ET (not applicable if treatment-naïve)
- Prior hormonal therapy:
  - Monotherapy Expansion Cohort: up to 2 prior lines for advanced/metastatic BC
  - Monotherapy Phase 2: 1 or 2 prior lines for advanced/metastatic BC
  - Combination Phase 2: up to 1 prior line for advanced/metastatic BC
- Prior chemotherapy:
  - Monotherapy Dose-Escalation Cohort: up to 2 prior lines for treatment of advanced/metastatic BC
  - Monotherapy Phase 2: no prior regimens for the treatment of advanced/metastatic BC
  - Monotherapy Expansion, Combination Dose-Escalation and Combination Phase 2 Cohorts: up to 1 prior line for the treatment of advanced/metastatic BC
- Evaluable or measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Eastern Cooperative Oncology Group Performance Status ≤2

Exclusion Criteria

- Any of the following within the specified window prior to the first dose of study drug:
  - Tamoxifen, aromatase inhibitor, fulvestrant or other anti-cancer ET <14 days, any chemotherapy or investigational drug <28 days or 5 half-lives (whichever is shorter)
  - Prior radiotherapy <14 days, major surgery <28 days, minor surgery <7 days
- Brain metastases that require immediate treatment or are clinically or radiologically unstable
- Leptomeningeal disease that requires or is anticipated to require immediate treatment
- Life-threatening metastatic visceral disease or symptomatic pulmonary lymphangitic spread

Treatment

- ZN-c5 is administered orally, once or twice daily, with continuous dosing. The daily dose depends on the cohort under assessment.
- Palbociclib is administered orally, once daily, 21 days on and 7 days off in a 28-day cycle.
- In both the Monotherapy and Combination Dose-Escalation cohorts of the study, dose limiting toxicities (DLT) will be assessed during Cycle 1.
- A cohort will be expanded from 3 to 6 patients if 1 of the initial 3 patients demonstrates DLT.

Endpoints

- Primary endpoints are summarized in **Table 1**.

Table 1. Primary Endpoints

Monotherapy Dose Escalation and Combination Dose Escalation
• DLTs
Monotherapy Expansion
• Safety and tolerability
Monotherapy and Combination Phase 2
• CBR: percentage of patients who have at least 1 confirmed response of CR, PR, or SD lasting at least for 24 weeks prior to any evidence of progression (as defined by RECIST v1.1).

CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Study Sites

There are active study sites in Belarus, Bosnia, Bulgaria, Czech Republic, Hungary, Lithuania, Russia, Serbia, Ukraine, and in the United States (**Figure 3**)

Figure 3. Study Sites

Conclusions

The trial is ongoing.

References

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Disclosure

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