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A randomized phase II study to evaluate the efficacy and safety of Trastuzumab deruxtecan versus CDK4/6 inhibitor-based endocrine therapy as first-line therapy of hormone receptor-positive and HER2-low/ultralow advanced breast cancer patients classified as non-luminal subtype according to gene expression profiling: the PONTIAC study

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BACKGROUND

- Human epidermal growth factor receptor 2 (HER2)-low and HER2-ultralow breast cancer (BC), represents approximately 85% of all HR-positive(HR+)/HER2-negative (HER2-) tumors [1].
- HR+/HER2- BC exhibiting non-luminal subtypes by PAM50 profiling are associated with a more aggressive clinical behavior and reduced sensitivity to endocrine therapy (ET) [2].
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate that has demonstrated to improve clinical outcomes in endocrine-resistant pts with HR+ and HER2-low/ultralow advanced BC (ABC) as shown in DESTINY-Breast04 and DESTINY-Breast06 phase III trials [3, 4].
- T-DXd has shown improved efficacy across all intrinsic PAM50 subtypes, including luminal A, luminal B, and HER2-enriched types [3, 4] .
- Here, the PONTIAC study evaluates the safety and efficacy profiles of T-DXd compared with ET plus a CDK4/6 inhibitor as first-line therapy in pts with HR+ and HER2-low/ultralow ABC classified as non-luminal according to PAM50 gene expression profiling.

STATISTICS

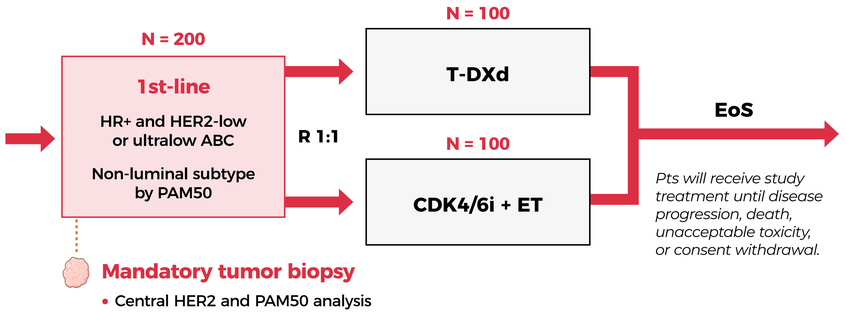
- Progression-free survival (PFS) distributions will be estimated with the Kaplan-Meier method and compared using a stratified log-rank test at two-sided 5% significance level.
- A sample size of 200 pts (79 and 130 events in HER2-low and all pts, respectively) will allow to detect a hazard ratio of 0.526 (HER2-low pts) and 0.608 (all pts) with 80% power.
- An interim analysis with the possibility of stopping the trial for futility will be carried out when 36% of the information is available.

TRIAL DESIGN

The PONTIAC study is an international, multicenter, randomized, two-arm phase II trial (NCT06486883).

KEY INCLUSION CRITERIA

- Adult pts with HR+ and centrally confirmed HER2-low (IHC 1+, IHC 2+ & ISH-) or ultralow (IHC 0 with membrane staining in ≤ 10% of tumor cells) ABC.
- Non-luminal subtype by central PAM50 analysis.
- No prior therapy for advanced disease.
- Pre-screening central PAM50 analysis will be conducted in:
  - Endocrine-resistant pts.
  - Endocrine-sensitive pts, who meet at least one of the following criteria:
    - Estrogen receptor expression ≤ 50% positive stained cells and/or
    - High histological grade and/or Ki67 > 50% and/or
    - Non-luminal subtype as per local PAM50 analysis in the primary tumor and/or
    - Presence of liver metastases.
- ECOG PS 0-1.
- Evaluable disease according to RECIST v.1.1.



Treatment

- T-DXd: 5.4 mg/kg, IV, Q3W.
- CDK4/6i: Physician's choice including palbociclib, ribociclib, and abemaciclib.
- ET: Physician's choice including fulvestrant, letrozole, anastrozole, and exemestane.

Pre- and perimenopausal women and men randomized in the CDK4/6i + ET arm must receive LHRH agonists.

PRIMARY OBJECTIVES

- PFS by investigator assessment according to RECIST v.1.1 in:
  - HER2-low pts
  - All pts (HER2-low and HER2- ultralow)

SECONDARY OBJECTIVES

- OS
- ORR, CBR, TTR, DoR, TTF, TFSC, PFS2, TFST, and best percentage of change in tumor burden as per RECIST v.1.1
- HRQoL
- Safety and toxicity according to the NCI-CTCAE v.5.0

Stratification factors

- Type of disease (visceral vs. non-visceral);
- PAM50 intrinsic subtype (basal-like vs. others);
- HER2 protein expression (HER2-low vs. HER2-ultralow).

Abbreviations: **ABC:** Advanced breast cancer; **CBR:** Clinical benefit rate; **CDK4/6i:** CDK4/6 inhibitor; **DoR:** Duration of response; **ECOG PS:** Eastern Cooperative Oncology Group performance status; **EoS:** End of study; **ET:** Endocrine therapy; **HER2:** Human epidermal growth factor receptor 2; **HR:** Hormone receptor; **HRQoL:** Health-related quality of life; **IHC:** Immunohistochemistry; **ISH:** *In situ* hybridization; **IV:** Intravenous; **LHRH:** Luteinizing hormone-releasing hormone; **NCI-CTCAE:** National Cancer Institute-Common Terminology Criteria for Adverse Events; **ORR:** Objective response rate; **OS:** Overall survival; **PFS:** Progression-free survival; **PFS2:** Progression-free survival 2; **pts:** Patients; **Q3W:** Every three weeks; **R:** Randomization; **RECIST:** Response Evaluation Criteria in Solid Tumors; **T-DXd:** Trastuzumab deruxtecan; **TTF:** Time to treatment failure; **TFSC:** Time to first subsequent chemotherapy; **TFST:** Time to first subsequent therapy; **TTR:** Time to response.

TRIAL ENROLLMENT

The PONTIAC trial initiated recruitment in Q3 2025. Currently, 23 sites are activated and the study is authorized in 10 countries. The number of potentially recruiting sites is expected to be 87.

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