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Study Protocol

Prospective Single-Arm Study of Endocrine Therapies With Ovarian Function Suppression in Premenopausal Node-Positive Early Breast Cancer Patients With Low Genomic Risk (INTERSTELLAR Trial, KBCSG-25)

Sung Gwe Ahn [1,2], **Sung Hoon Sim** [3], **Taewoo Kang** [4], **Eun-Kyu Kim** [5], **Jeong Eon Lee** [6], **Hyeong-Gon Moon** [7,8], **Jee Hyun Ahn** [9], **Woosung Lim** [10], **Hyun Jo Youn** [11], **Hyun-Ah Kim** [12], **Chang Ik Yoon** [13], **Jisun Kim** [14], **Byeongju Kang** [15], **Min Ho Park** [16], **Su Hwan Kang** [17], **Lee Su Kim** [18], **Soong June Bae** [1,2], **Yoonwon Kook** [1,2], **Kwan Ho Lee** [19], **Han-Byoel Lee** [7,8], **Wonshik Han** [7,8], **Yeon Hee Park** [20]

[1]Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[2]Institute for Breast Cancer Precision Medicine, Yonsei University College of Medicine, Seoul, Korea
[3]Center for Breast Cancer, National Cancer Center, Goyang, Korea
[4]Breast Surgery and Biomedical Research Institute, Pusan National University Hospital, Pusan National University, Busan, Korea
[5]Breast Care Center, Seoul National University Bundang Hospital, Seoul, Korea
[6]Division of Breast Surgery, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[7]Department of Surgery, Seoul National University College of Medicine, Seoul, Korea
[8]Cancer Research Institute, Seoul National University, Seoul, Korea
[9]Division of Breast Surgery, Department of Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[10]Department of Surgery, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Korea
[11]Department of Surgery, Jeonbuk National University Medical School, Jeonju, Korea
[12]Department of Surgery, Korea Cancer Center Hospital, Korea Institute of Radiological and Medical Sciences, Seoul, Korea
[13]Division of Breast Surgery, Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
[14]Division of Breast Surgery, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[15]Department of Surgery, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[16]Department of Surgery, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Gwangju, Korea
[17]Department of Surgery, Yeungnam University College of Medicine, Daegu, Korea
[18]Department of Surgery, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Korea
[19]Department of Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
[20]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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Correspondence to
Sung Gwe Ahn
Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, 20 Eonju-ro 63-gil, Gangnam-gu, Seoul 06229, Korea.
Email: asg2004@yuhs.ac

Yeon Hee Park
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
Email: yhparkhmo@skku.edu

ORCID iDs
Sung Gwe Ahn
https://orcid.org/0000-0002-8778-9686
Sung Hoon Sim
https://orcid.org/0000-0002-1503-1075
Taewoo Kang
https://orcid.org/0000-0002-6279-0904
Eun-Kyu Kim
https://orcid.org/0000-0003-1318-0939

ABSTRACT

Purpose: While postmenopausal women with low recurrence scores in genomic assay may safely forgo adjuvant chemotherapy, the RxPONDER trial demonstrated that premenopausal

Jeong Eon Lee
https://orcid.org/0000-0003-0037-2456
Hyeong-Gon Moon
https://orcid.org/0000-0002-9981-0286
Jee Hyun Ahn
https://orcid.org/0000-0003-4176-3277
Woosung Lim
https://orcid.org/0000-0002-2863-9346
Hyun Jo Youn
https://orcid.org/0000-0002-2407-8537
Hyun-Ah Kim
https://orcid.org/0000-0001-9713-2605
Chang Ik Yoon
https://orcid.org/0000-0002-7273-8886
Jisun Kim
https://orcid.org/0000-0002-4884-6107
Byeongju Kang
https://orcid.org/0000-0002-3589-5559
Min Ho Park
https://orcid.org/0000-0002-7046-3874
Su Hwan Kang
https://orcid.org/0000-0002-6508-006X
Lee Su Kim
https://orcid.org/0000-0002-9965-0032
Soong June Bae
https://orcid.org/0000-0002-0012-9694
Yoonwon Kook
https://orcid.org/0000-0002-0756-738X
Kwan Ho Lee
https://orcid.org/0000-0002-6526-3333
Han-Byoel Lee
https://orcid.org/0000-0003-0152-575X
Wonshik Han
https://orcid.org/0000-0001-7310-0764
Yeon Hee Park
https://orcid.org/0000-0003-4156-9212

Trial Registration
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Presentation
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Conflict of Interest
Lee HB and Han W report being members of the board of directors and holding stock and ownership interests in DCGen Co. Ltd. The other authors declare no conflicts of interest related to this work.

women with 1–3 positive nodes (pN1) derive significant benefit from adjuvant chemotherapy regardless of low recurrence scores. The INTERSTELLAR trial is evaluating whether ovarian function suppression (OFS) combined with adjuvant endocrine therapy (ET) can offer comparable efficacy to chemotherapy in this specific patient population.

Methods: INTERSTELLAR is a prospective, multicenter, single-arm, non-inferiority cohort study enrolling premenopausal women aged ≤ 50 with pT1–2, estrogen receptor +/human epidermal growth factor receptor 2 −, pN1 breast cancer. Genomic risk is assessed using OncoFREE®, a next-generation sequencing-based assay developed in the Republic of Korea. Patients classified as low genomic risk (Decision Index ≤ 20) receive OFS combined with either an aromatase inhibitor or tamoxifen for 5 years, while patients with high genomic risk receive standard adjuvant chemotherapy followed by ET. The primary endpoint is 5-year distant disease-free survival (DDFS). Non-inferiority will be established if the lower bound of the 97.5% one-sided confidence interval exceeds 93.1%, benchmarked against a historical control DDFS of 96.1% derived from the RxPONDER trial. The study plans to enroll 604 patients total, with a target of 380 evaluable low-risk patients after accounting for expected genomic risk distribution and study dropout rates.

Discussion: Our results may establish evidence supporting the omission of adjuvant chemotherapy in premenopausal women with low genomic risk scores and limited nodal involvement (p-N1), potentially reducing treatment-related morbidity while preserving comparable oncologic outcomes.

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Keywords: Antineoplastic Agents, Hormonal; Aromatase Inhibitors; Breast Neoplasms; Premenopause; Receptors, Estrogen

INTRODUCTION

Multigene assays have revolutionized treatment decision-making for patients with estrogen receptor (ER) +/human epidermal growth factor receptor 2 (HER2) − breast cancer [1-3]. In postmenopausal women, these genomic tests reliably identify patients with low recurrence score who can safely forgo adjuvant chemotherapy, regardless of nodal status (N0 or N1) [1-3]. However, this paradigm has been challenged by the RxPONDER trial, which demonstrated a significant chemotherapy benefit in premenopausal women with node-positive (N1) disease despite low recurrence scores [1].

This discrepancy between postmenopausal and premenopausal outcomes raises fundamental questions about the mechanisms underlying chemotherapy benefit in ER+ breast cancer. Traditionally, high recurrence scores correlate with increased chemotherapy benefit in luminal breast cancer, while low recurrence score suggest minimal chemotherapy benefit [4-8]. This finding of chemotherapy efficacy in premenopausal women with low-risk genomic profiles and N1 disease warrants mechanistic investigation.

Many investigators hypothesize that the observed chemotherapy benefit in premenopausal women may be primarily attributed to chemotherapy-induced amenorrhea rather than direct cytotoxic effects [9-12]. If this hypothesis is validated, comparable oncologic outcomes might be achievable by replacing chemotherapy with targeted ovarian function suppression (OFS) in this specific patient population, potentially eliminating chemotherapy-related toxicities while

Data Availability

This manuscript presents a study protocol. Data collection is currently underway. In accordance with the ICMJE data sharing policy, the authors have agreed to make the data available upon request. The full trial protocol and statistical analysis plan are available from the corresponding authors (Sung Gwe Ahn, Yeon Hee Park) upon reasonable request and can be accessed through the Korean Breast Cancer Society Study Group data repository.

Author Contributions

Conceptualization: Ahn SG; Data curation: Ahn SG; Formal analysis: Ahn SG; Funding acquisition: Ahn SG, Han W; Investigation: Ahn SG, Kook Y; Methodology: Ahn SG, Bae SJ, Kook Y, Han W, Park YH; Project administration: Ahn SG, Sim SH, Kang T, Kim EK, Lee JE, Moon HG, Ahn JH, Lim W, Youn HJ, Kim HA, Yoon CI, Kim J, Kang B, Park MH, Kang SH, Kim LS, Kook Y, Lee KH, Lee HB, Park YH; Resources: Ahn SG, Sim SH, Kang T, Kim EK, Lee JE, Moon HG, Ahn JH, Lim W, Youn HJ, Kim HA, Yoon CI, Kim J, Kang B, Park MH, Kang SH, Kim LS, Bae SJ, Kook Y, Lee KH, Lee HB, Park YH; Software: Ahn SG; Supervision: Ahn SG, Han W, Park YH; Validation: Ahn SG; Visualization: Ahn SG; Writing - original draft: Ahn SG; Writing - review & editing: Ahn SG, Sim SH, Kang T, Kim EK, Moon HG, Ahn JH, Lim W, Youn HJ, Kim HA, Yoon CI, Kim J, Kang B, Park MH, Kang SH, Kim LS, Bae SJ, Kook Y, Lee KH, Lee HB, Han W, Park YH.

preserving therapeutic efficacy. Given that chemotherapy is associated with significant acute toxicities (myelosuppression, nausea, fatigue) and long-term complications (cardiotoxicity, neuropathy, cognitive impairment), identifying patients who can safely avoid it represents a critical unmet clinical need.

To address this critical knowledge gap and evaluate the oncologic equivalence of endocrine therapy (ET) alone compared with chemotherapy plus ET in premenopausal patients with pN1, ER+/HER2− breast cancer and low genomic risk, we designed the INTERSTELLA trial—a single-arm prospective cohort study. Genomic risk categorization is performed using the OncoFREE®, a next-generation sequencing (NGS)-based multigene assay developed in Republic of Korea.

METHODS

Patients

The INTERSTELLAR trial is a prospective, multicenter, single-arm, non-inferiority cohort study (**Figure 1**) [13]. This study is coordinated by the Korean Breast Cancer Society Study Group (KBCSG) and overseen by a Steering Committee oversees its implementation. Premenopausal women aged 35 to 50 years with pT1–2 ER+/HER2− breast cancer and 1–3 lymph node metastases are eligible for enrollment. Patients with micrometastasis are eligible for enrollment. Premenopausal status is defined as: (1) women within 6 months of their last menstrual period, or (2) women who have undergone hysterectomy or have unclear menopausal status with serum follicle-stimulating hormone levels < 30 mIU/mL. All participants will undergo testing with OncoFREE®, an NGS-based breast cancer prognostic multigene assay developed and available in the Republic of Korea [14]. This multicenter trial is conducted across 17 academic hospitals. The study protocol has been approved by the Institutional Review Boards (IRBs) of the Gangnam Severance Hospital (3-2022-0192) and all participating centers, with the initial approval granted on July 5, 2022. All patients must provide written informed consent before enrollment.

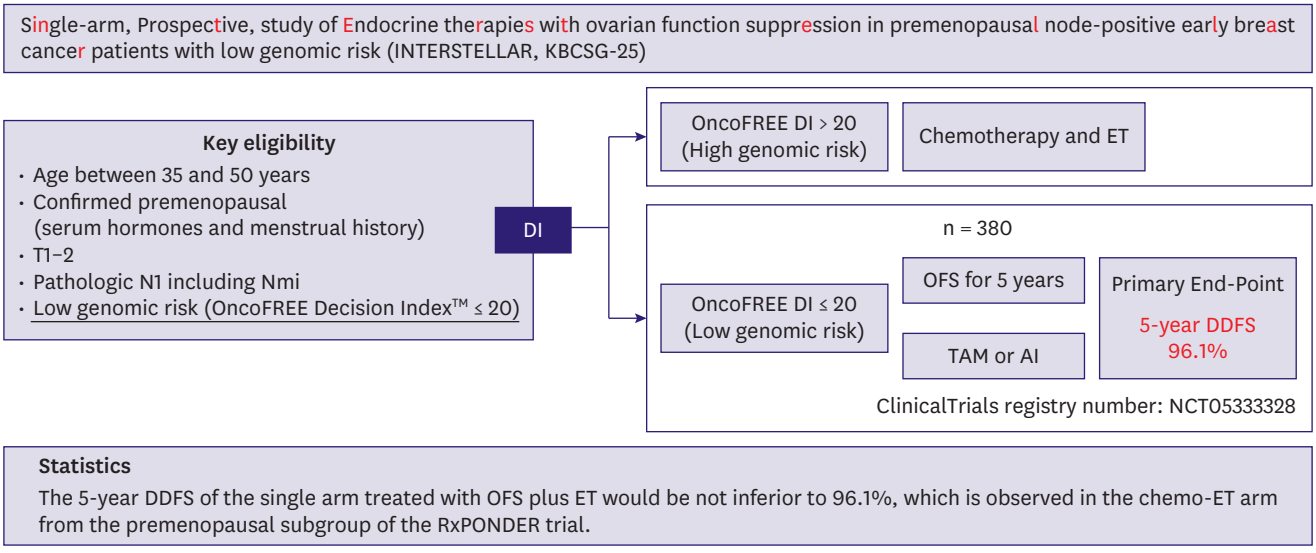

Figure 1. Schema of the study.
DI = Decision Index; ET = endocrine therapy; OFS = ovarian function suppression; TAM = tamoxifen; AI = aromatase inhibitor; DDFS = distant disease-free survival.

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A formal independent data monitoring committee was not established. Safety oversight is performed by designated safety monitors approved by the IRBs of participating centers, and trial conduct is periodically reviewed during meetings of the KBCSG Steering Committee. No interim efficacy or safety analyses are planned. This study was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials 2025 guidelines to ensure methodological transparency and reproducibility. The study protocol version 6.0 (dated 28 April 2025) has been approved by 15 of 17 participating centers' IRBs, with approvals pending at the remaining centers. The overall schedule of participant enrollment, intervention, and assessments is summarized in **Figure 2** [15]. This trial is registered at ClinicalTrials.gov (NCT05333328).

OncoFREE® multigene assay

OncoFREE® is a NGS-based multigene assay developed for prognostic risk stratification and treatment decision guidance in hormone receptor-positive, HER2− early breast cancer [14,16,17]. The assay analyzes 179 genes to quantify the risk of distant metastasis according to the Decision Index (DI), with a cut-off value of 20 used to stratify patients into low-risk (DI < 20) and high-risk (DI ≥ 20) groups for determining the need for adjuvant chemotherapy.

Assay validation and performance

OncoFREE® has been extensively validated in multiple clinical cohorts, demonstrating strong concordance with Oncotype DX and robust prognostic performance [16]. The assay effectively stratifies patients by distant metastasis-free survival, with particular utility in younger patients aged ≤ 50 years. Long-term validation studies with up to 10 years of follow-up have

	Trial period							
	Enrollment		Post-allocation					Close-out
Timepoint	$-t_i$ to 0	0	6	12	24	36	48	60
Enrollment		X						
Eligibility screen	X							
Informed consent		X						
Baseline demographics, physical exam, ECOG PS		X						
Imaging and laboratory tests		X						
OncoFREE® assay		X						
Intervention/comparator								
ET (AI or TAM) + OFS		X →	→	→	→	→	→	X
Assessments								
Baseline variables (FSH, E2, AMH, pathology)		X						
Outcome variables (DDFS, iDFS, OS, LDFI, FACT-B+4, PRO)			X	X	X	X	X	X
Safety assessments (AEs, vitals, labs, physical exam)			X	X	X	X	X	X
Other data (OFS adherence, imaging, hormone monitoring)			X	X	X	X	X	X

Target timepoints: baseline (0), follow-up every 6 12 months up to 60 months.
Arrow indicates continuous intervention (OFS + ET).

Figure 2. Participant timeline: schedule of enrollment, interventions, and assessments.
ECOG PS = Eastern Cooperative Oncology Group Performance Status; ET = endocrine therapy; AI = aromatase inhibitor; TAM = tamoxifen; OFS = ovarian function suppression; FSH = follicle stimulating hormone; AMH = anti-müllerian hormone; DDFS = distant disease-free survival; iDFS = invasive disease-free survival; OS = overall survival; LDFI = locoregional disease-free interval; FACT-B = Functional Assessment of Cancer Therapy-Breast; PRO = patient reported outcome; AE = adverse effect.

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confirmed the assay's ability to identify high-risk patients who may benefit from adjuvant chemotherapy and low-risk patients who can safely avoid it [17].

Sample processing in current study

Formalin-fixed paraffin-embedded tissue blocks are centrally collected from all participating institutions and tested with OncoFREE®. All samples undergo rigorous quality control assessment prior to analysis. If enrolled patients have multiple tumors meeting the inclusion criteria, the assay is performed for up to a maximum of three tumors, with each tumor assessed independently for DI calculation and risk stratification.

Treatment procedure

Patients with low genomic risk (DI ≤ 20) receive OFS plus either an aromatase inhibitor (AI) or tamoxifen (TAM) for five years. The choice of OFS partner (AI vs. TAM) and the selection of chemotherapy regimen in high-risk patients were left to the treating physician's discretion. TAM usage is capped at 30% of the study population. Although AI with OFS is prioritized based on current evidence for premenopausal high-risk patients, this allowance provides flexibility for clinical scenarios where TAM with OFS may be more appropriate based on physician judgment and patient-specific factors. Both monthly and tri-monthly OFS administration are permitted. Adjuvant CDK4/6 inhibitors are not permitted for the low genomic risk group. Patients with high genomic risk receive chemotherapy followed by ET and will be followed for survival analysis as a secondary endpoint. Adjuvant CDK4/6 inhibitors and enrollment in clinical trials exploring novel drugs are permitted for patients with high genomic risk.

Sample-size calculation

We hypothesize that the 5-year distant disease-free survival (DDFS) of the single arm treated with OFS plus ET would be non-inferior to 96.1%, which was observed in the chemotherapy plus ET arm from the premenopausal subgroup of the RxPONDER trial. A one-sided test with a non-inferiority margin of 3% and statistical power of 80% at a significance level of 0.05 resulted in a required sample size of 380 patients with low genomic risk. Assuming that 70.0% of patients will be designated as low genomic risk by OncoFREE® and accounting for a 10.0% drop-out rate, 604 patients will be enrolled.

Statistical analysis plan

Data from study participants will be categorized into three analysis sets: Safety set, Full Analysis (FA) set, and Per-Protocol (PP) set. The FA set will serve as the main analysis population, with additional analyses performed on the PP set. Safety analyses will be conducted using the Safety set.

For the primary efficacy endpoint, the 5-year DDFS value and its 97.5% one-sided confidence interval lower limit will be presented. Non-inferiority will be established if the difference between the lower limit of the 97.5% one-sided confidence interval and the 5-year DDFS of the RxPONDER trial (96.1%) is greater than -3% (study group minus historical control). Survival analyses will be conducted using both the Competing Risk model and, additionally, Kaplan-Meier Analysis.

The primary endpoint of this study is to demonstrate that the 5-year DDFS in the study group is non-inferior to the historical control group (chemotherapy plus hormone therapy).

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The secondary endpoints were presented as below:

1. Secondary endpoints for the low-risk group
   1.1. Two-year DDFS
   1.2. Five-year invasive disease-free survival (iDFS): time from enrollment to first invasive recurrence (local, regional, or distant), second invasive cancer (contralateral breast cancer or other cancer), or death from any cause.
   1.3. Five-year overall survival (OS): time from enrollment to death from any cause.
   1.4. Five-year locoregional disease-free interval (LDFI): time from enrollment to confirmation of locoregional recurrence of breast cancer.
   1.5. Quality of life assessment at baseline, 2 years, and 5 years (Functional Assessment of Cancer Therapy-Breast [FACT-B])
   1.6. Patient-reported outcomes at baseline, 6 months, 2 years, and 5 years
2. Secondary endpoints for the high-risk group
   2.1. Two-year DDFS
   2.2. Five-year iDFS
   2.3. Five-year OS
   2.4. Five-year LDFI
   2.5. Quality of life assessment at baseline, 2 years, and 5 years (FACT-B)

Trial progress

Recruitment was initiated on February 1, 2024. As of the end of April 2025, a total of 102 patients have been screened, and 86 have been enrolled. Of these, 55 (62.5%) patients with low DI were enrolled into the primary study cohort. Thirty-one patients (37.5%) with high DI received chemotherapy.

DISCUSSION

The INTERSTELLAR trial aims to investigate the oncologic equivalence of OFS plus ET without chemotherapy for premenopausal women with ER+/HER2− breast cancer and low genomic risk scores. While several pivotal trials have established the treatment landscape for this patient population, critical questions regarding optimal therapeutic approaches remain unanswered.

Chemotherapy benefit was demonstrated in premenopausal women with ER+/HER2− breast cancer and intermediate 21-gene recurrence score in the TAILORx trial [2,3], and this chemotherapy efficacy in genomic low-risk premenopausal women was further validated by the MINDACT trial using the 70-gene signature [18]. Similarly, the RxPONDER trial demonstrated reduced disease recurrence with adjuvant chemotherapy in premenopausal women with pN1, ER+/HER2− disease, and low genomic risk recurrence scores [1]. Importantly, these landmark trials did not mandate OFS in the ET alone arm for premenopausal women, leaving unanswered whether OFS could potentially replicate the benefits of chemotherapy in this subset.

Previous trials were conducted in the United States or Europe, where the proportion of premenopausal breast cancer patients is significantly lower than in Asia [19,20], leading to the underrepresentation of younger women. The ongoing INTERSTELLAR trial, being conducted in Asia where the proportion of premenopausal patients is relatively higher than in Western countries, is therefore both timely and relevant. The OncoFREE® test, developed

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and validated in the Korean population to better reflect the characteristics of younger Asian patients [14,16], may offer additional value in evaluating oncologic equivalence in node-positive premenopausal women within this trial.

Current National Comprehensive Cancer Network guidelines suggest that chemotherapy may be considered for premenopausal pN1 patients with ER+/HER2− tumors and Recurrence Score ≤ 25, based on gene expression assay results [21]. The NRG-BR009 (OFSET) phase III trial directly addresses this uncertainty by randomizing 3,960 premenopausal patients with pN0–1 disease and RS ≤ 25 to OFS+ET with or without chemotherapy, using invasive breast cancer-free survival as the primary endpoint [22]. This study seeks to determine whether chemotherapy provides incremental benefit beyond the estrogen deprivation achieved through OFS in genomic low-risk patients, potentially refining adjuvant decision-making for N1 cases.

A distinguishing feature of the OFSET trial is the inclusion of adjuvant CDK4/6 inhibitors. The MONARCHE and NATALEE trials have demonstrated benefit from adding CDK4/6 inhibitors to chemo-ET in high-risk, ER+/HER2− breast cancer patients [23-26]. In particular, the NATALEE trial results support adjuvant ribociclib use in N1 patients [23,26]. In contrast, the INTERSTELLAR trial excludes adjuvant CDK4/6 inhibitors, including ribociclib. Our primary objective is to evaluate the oncologic safety of treating N1 patients with genomic-low risk using OFS+ET alone, without CDK4/6 inhibitors. Radiotherapy represents another variable affecting outcomes, with regional radiotherapy permitted in the study according to investigator discretion.

Ethnicity can influence treatment responses. Asian women generally have a lower body mass index (BMI), whereas a high BMI or obesity is associated with poorer breast-cancer outcomes [27-29]. A similarly low BMI among Asian women, compared with other ethnic groups, was also observed in the RxPONDER trial [30]. Because our study enrolled only Korean participants, these demographic characteristics should be considered when interpreting the results.

The INTERSTELLAR trial addresses persistent clinical uncertainty regarding oncologic safety of adjuvant OFS plus ET without chemotherapy in premenopausal patients with N1 disease. These results may establish evidence supporting the omission of adjuvant chemotherapy in premenopausal women with low genomic risk despite limited nodal involvement (N1), potentially reducing treatment-related toxicity while preserving oncologic outcomes.

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