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A phase II, multicenter, open-label study of abemaciclib and letrozole in patients with estrogen receptor-positive rare ovarian cancer: ALEPRO trial

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ABSTRACT

Background Low-grade serous and endometrioid ovarian cancers and adult-type granulosa cell tumors are rare ovarian malignancies that show high estrogen receptor positivity. Recurrences of these subtypes of ovarian cancer are often treated with conventional chemotherapy, although response rates are disappointing.

Primary Objective To determine the overall response rate of the combination therapy of abemaciclib and letrozole in patients with estrogen receptor-positive rare ovarian cancers.

Study Hypothesis The combination therapy of abemaciclib and letrozole will provide a clinically meaningful therapeutic benefit, with an overall response rate of >25%.

Trial Design This is a phase II, international, multicenter, open-label, single-arm study to evaluate the efficacy and safety of abemaciclib and letrozole in patients with advanced, recurrent, and/or metastatic estrogen receptor-positive, rare ovarian cancer. The study will follow a tandem two-stage design.

Major Inclusion/Exclusion Criteria Patients must have histologically confirmed low-grade serous/endometrioid ovarian cancer or adult-type granulosa cell tumor with estrogen receptor positivity on immunohistochemistry. Patients need to have recurrent and measurable disease according to Radiologic Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A maximum of two prior lines of endocrine therapy are allowed, and patients cannot have previously received a cyclin-dependent kinase inhibitor. Patients with platinum-refractory disease are not allowed in any stage of the study.

Primary Endpoint Investigator-assessed confirmed overall response rate, defined as the proportion of patients with a complete or partial response according to RECIST v1.1.

Sample Size 40 to 100 patients will be included, depending on the results of the interim analysis. Patients will be included in Belgium, France and the Netherlands.

Estimated Dates for Completing Accrual and Presenting Results Patient recruitment will be completed by the end of 2025 and reporting of the final study results will be done by the end of 2027.

Trial registration number NCT05872204

INTRODUCTION

Ovarian cancer comprises a heterogeneous group with a large number of different histological subtypes. Low-grade serous and endometrioid ovarian cancers, both epithelial ovarian tumors and adult-type granulosa cell tumor, a sex-cord stromal tumor, are rare subtypes of ovarian tumors. They have distinct molecular, histological, and clinical characteristics and are known for their chemotherapy resistance, especially if compared to the most common form of ovarian cancer, high-grade serous ovarian cancer. The standard of care for low-grade serous/endometrioid ovarian cancer consists of debulking surgery and platinum-based chemotherapy. Low-grade serous ovarian cancer has reported overall response rates to chemotherapy ranging between 2.1% and 17% in the recurrent setting.[1 2] For adult-type granulosa cell tumors, a systematic review by Brink et al revealed an overall response rate of 30% to chemotherapy in recurrent disease.[3]

These rare subtypes of ovarian cancer show a high expression of the estrogen receptor. Therefore, they are considered to be potentially responsive to endocrine therapy. In recent years, endocrine therapy is often applied for recurrent low-grade serous ovarian cancer with a reported response rate of 9% to 14%.[4 5] Aromatase inhibitors show the highest response rates. In adult-type granulosa cell tumors, several meta-analyses and the phase II PARAGON study showed overall response rates of aromatase inhibitors ranging between 11% and 18%.[3 6–8] The available evidence suggests that endocrine therapy might be effective in this patient population. However, there is no consensus on the therapeutic modalities nor on the selection criteria needed to define which patients will benefit from a specific endocrine therapy. Most reports consist of relatively small numbers of patients who were unselected for estrogen receptor positivity and these patients are often heavily pre-treated, which may mask the true efficacy of endocrine therapy. The poor response rates on conventional

chemotherapy as well as on endocrine therapy fuel the search for alternative treatment strategies.

In estrogen receptor-positive advanced and metastatic breast cancer endocrine therapy remains the therapeutic cornerstone. The addition of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor (eg, ribociclib, abemaciclib or palbociclib) to endocrine therapy has remarkably improved the outcome of patients with estrogen receptor-positive advanced and/or metastatic breast cancer.[9] A CDK4/6 inhibitor targets the cell cycle machinery and can overcome some mechanisms of endocrine resistance in this patient population. Given the similarities between estrogen receptor-positive advanced breast cancer and estrogen receptor-positive advanced ovarian cancer, we hypothesize that the same drug combination including abemaciclib and letrozole can show efficacy in these subtypes of rare ovarian cancer. Additionally, a phase II clinical trial of ribociclib and letrozole in patients with recurrent estrogen receptor-positive ovarian and endometrial cancer showed significant efficacy in patients with low-grade serous ovarian cancer.[10] In this trial, partial or complete responses were achieved in all of the three included patients with low-grade serous ovarian cancer. Additionally, in recurrent estrogen receptor-positive endometrioid endometrial cancer, letrozole plus a CDK4/6 inhibitor showed encouraging evidence of activity.[11 12]

The aim of this study is to determine the response rate to endocrine therapy in combination with CDK4/6 inhibitors and the duration of response in this study population with limited therapeutic options. Additionally, the safety and quality of life of patients will be monitored and (epi)genomic signatures that correlate with endocrine response or resistance will be explored. The clinical and exploratory results of this study will hopefully lead to better guidance regarding the use of endocrine therapy in these rare estrogen receptor-positive ovarian cancers.

METHODS

Trial Design

ALEPRO is a phase II, multicenter, open-label, single-arm clinical study that aims to evaluate the efficacy, safety, and quality of life in patients with persistent, recurrent, and/or metastatic low-grade serous/endometrioid ovarian cancers and adult-type granulosa cell tumors treated with abemaciclib and letrozole. These patients will have previously received at least one line of systemic treatment for persistent, recurrent, and/or metastatic disease.

The study design is outlined in Figure 1. In a preliminary phase (stage 1), 20 patients per tumor cohort will be enrolled after screening for estrogen receptor positivity on immunohistochemistry. Eligible patients will receive treatment with abemaciclib orally 150 mg twice daily and letrozole orally 2.5 mg once daily.

An interim analysis with early stopping rules for futility will be performed when 15 patients per cohort have completed 24 weeks of treatment. The primary efficacy analysis to determine the overall response rate will be based on the response evaluable population in each tumor cohort. If clinical activity is observed in a cohort, 30 additional patients will be enrolled in that cohort during the potential expansion phase (stage 2). If a cohort shows minimal clinical activity, defined as ≤1 response in 15 patients, or unacceptable toxicity, it will not undergo expansion. In total, approximately 40 to 100 subjects are projected to be enrolled in this study.

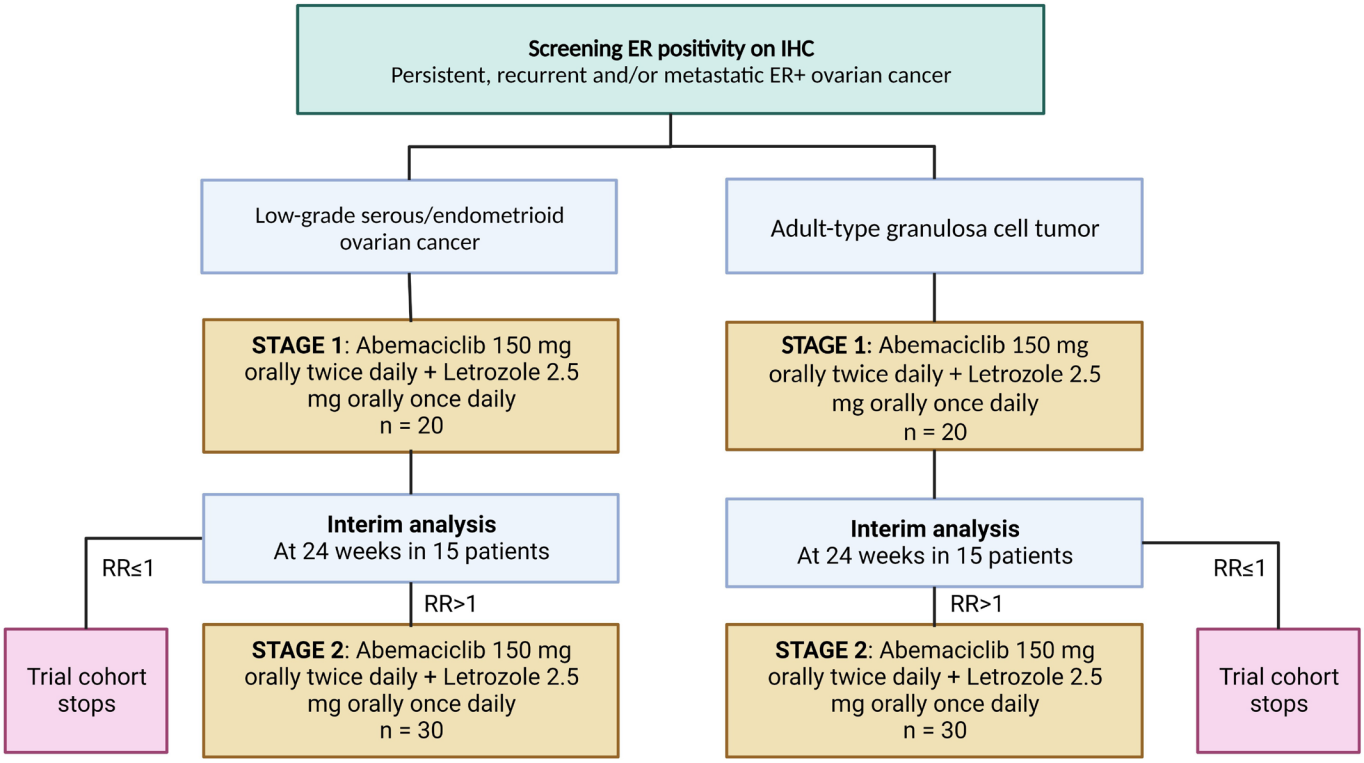

Figure 1 ALEPRO study design. ER, estrogen receptor status; IHC, immunohistochemistry; RR, response rate. Created with BioRender.com.

Participants

Participants eligible for inclusion must be women ≥18 years old and have a histologically confirmed diagnosis of low-grade serous/endometrioid carcinoma of the ovary, fallopian tube or peritoneum (cohort 1) or adult-type granulosa cell tumor (cohort 2) and estrogen receptor positivity on immunohistochemistry, as defined by the local pathologist. Patients must have recurrent, evaluable, and measurable disease by Radiologic Evaluation Criteria in Solid Tumors (RECIST) v1.1. For stage 1 of the trial, only patients where platinum is still an option are eligible, with no limitations in prior chemotherapy regimens and a maximum of two prior endocrine therapy regimens. For stage 2, patients where platinum is still an option are eligible, with no limitations in prior chemotherapy regimens and a maximum of two prior endocrine therapy regimens. However, 10 patients where platinum is not an option are allowed per cohort. Patients who were previously treated with letrozole or another aromatase inhibitor are allowed, but are capped at 10 patients in each cohort. Patients are ineligible if they are platinum refractory.

Primary Endpoints

The primary efficacy endpoint is investigator-assessed confirmed overall response rate, defined as the proportion of patients with a complete or partial response. This will be determined by the investigator according to RECIST v1.1 and will be assessed every 3 months.

The secondary endpoints include progression-free survival, overall survival, duration of response, clinical benefit rate, safety, and quality of life. Progression-free survival and clinical benefit rate will be determined according to RECIST v1.1 and will be based on the intention-to-treat population. For patients who do not have documented disease progression or death at the time of analysis, progression-free survival will be censored on the day of the last tumor assessment. Patients who are still alive at the time of overall survival analysis will be censored at the last date they were known to be alive.

In order to better define which patient population would benefit from endocrine therapy in combination with CDK4/6 inhibitors, exploratory analyses will be performed. These include estrogen and progesterone receptor expression and the correlation of this receptor expression with overall response and clinical benefit rate. Additionally, genetic and epigenetic analyses will be executed to explore biomarkers of response and resistance to endocrine therapy and CDK4/6 inhibitors.

Sample Size

Assuming a target overall response rate of 30%, a sample size of 50 patients per tumor cohort is deemed sufficient to provide adequate precision for the overall response rate point estimate. Under these assumptions, the lower bound of the two-sided 95% Clopper-Pearson exact confidence interval would rule out a historical response rate of ≤15%.

Statistical Methods

The rarity of these cancer types calls for an alternative view of the statistical design, as described by the Rare Cancers Europe initiative.[13] A Bayesian adaptive clinical trial design will be followed, allowing aspects of the study to change while it is ongoing, based on analyses of data obtained from the enrolled patients.[14] Historical data will serve as a comparator.

The Kaplan-Meier method will be used to estimate the median for progression-free survival and overall survival for each tumor cohort, along with the two-sided 95% CI.

Safety analysis will be based on the safety population, defined as all enrolled patients receiving at least one dose of abemaciclib and letrozole. Safety will be assessed through summaries of adverse events, changes in laboratory test results and vital signs, and exposure to the study drug. For each patient, the maximum reported grade of each adverse event will be used in the summaries. Patient-reported outcome measures will be based on the quality of life questionnaires administered during the study. These include the European Quality of Life 5 Dimensions 5 Level Questionnaire (EQ-5D-5L) and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). Descriptive statistics for baseline values, actual values, and the change from baseline will be presented for each scheduled time point.

Ethics Statements

This clinical trial will be conducted in accordance with local and national regulations and the International Council for Harmonisation Good Clinical Practice. Investigators will follow the ethical principles outlined in the Declaration of Helsinki. Written informed consent will be obtained from each potential participant prior to their participation in the study. An independent Data Safety Monitoring Committee will review safety data every 6 months.

DISCUSSION

This international open-label, multicenter, phase II study will assess the efficacy of the combination therapy of abemaciclib and letrozole in patients with recurrent and advanced estrogen receptor-positive rare ovarian cancer. If efficacy can be demonstrated, this combination therapy may become an important new treatment strategy in this study population with limited therapeutic options. Additionally, if safety can be shown, it would be a great improvement for the quality of life of these patients, who would alternatively receive chemotherapy and would endure all its associated side effects.

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Contributors EVN designed and wrote the protocol. TO helped with the implementation of the protocol and wrote the manuscript. All authors contributed

to refinement of the study protocol and approved the final manuscript. EVN acts as guarantor.

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Competing interests EVN reports consulting fees from Regeneron, Oncoinvent, AstraZeneca, Roche, Seagen, Novartis, Merck and Verastem; and receipt of study drug abemaciclib for this study from Eli Lilly. TVG reports grants/contracts from the Fund for Scientific Research-Flanders (FWO); consulting fees (paid to the institution) from AstraZeneca, Eisai, OncXerna Therapeutics, MSD, GSK, ImmunoGen, Seagen, Tubulis and Zentalis; honoraria (paid to the institution) from ImmunoGen, GSK, AstraZeneca; and meeting/travel support from Amgen, Pfizer, Roche, GSK, Novartis, ImmunoGen, MSD, PharmaMar and Sanofi-Aventis. FK reports grants/contracts from GSK, PharmaMar and AstraZeneca; consulting fees from GSK and PharmaMar; honoraria from GSK; expert testimony for GSK and AstraZeneca; meeting/travel support from PharmaMar and AstraZeneca; and advisory board for AstraZeneca. TB reports grants/contracts from Roche; honoraria from Novartis, AstraZeneca and Eli Lilly; and meeting/travel support from AstraZeneca, GSK and MSD. HD reports grants/contracts (paid to the institution) from Gilead; consulting fees (paid to the institution) from GSK and Gilead; honoraria (paid to the institution) from AstraZeneca, GSK, Eli Lilly, Gilead, Amgen, Roche, Leo Pharma, MSD, Daiichi Sannkyo and Teva Pharmaceuticals; meeting/travel support (paid to the institution) from GSK, AstraZeneca, Gilead, Roche, MSD, Pfizer, Teva Pharmaceuticals and PharmaMar; and advisory board (paid to the institution) for GSK, AstraZeneca, MSD, Menarini, Eli Lilly, Pfizer, Gilead, Seagen. FS reports consulting fees from AstraZeneca, GSK Tesaro and MSD; and honoraria from AstraZeneca, GSK Tesaro, MSD and Eisai. IB reports grants from Springer Healthcare and GSK; honoraria from Status Plus Gynaecongres; and participation on the DSMB of the Direct2 study (no payments).TO, ASVR and DL have no competing interests to disclose.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Federal Agency for Medicines and Health Products (FAMHP) Belgium. Reference ID: R&D/ 1320457. Participants gave informed consent to participate in the study before taking part. Ethical approval has been obtained for Belgium (EU CT Number 2023-503533-21-00).

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Data availability statement Data are available upon request.

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