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Clinical Trial Protocol

Phase II randomized study of first-line carboplatin and paclitaxel in combination with pembrolizumab, followed by maintenance pembrolizumab alone or with nesuparib, in mismatch-repair proficient, advanced or recurrent endometrial cancer (PENELOPE)

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ABSTRACT

Background: Although recent clinical trials proved survival benefit from the addition of immune checkpoint inhibitors to standard chemotherapy, treatment of mismatch repair-proficient (pMMR) advanced or recurrent endometrial cancer (arEC) is challenging. As poly(ADP-ribose) polymerase (PARP) inhibitors enhance the effects of immune checkpoint inhibitors when combined, improvement of survival is expected by dual maintenance in this population. The PENELOPE trial will investigate the efficacy and safety of dual maintenance with nesuparib, an orally active PARP1/2 and tankyrase 1/2 inhibitor, and pembrolizumab after paclitaxel/carboplatin plus pembrolizumab (TCP) treatment in patients with pMMR arEC.
Methods: In this multicenter, randomized, open-label, non-comparative phase II trial, patients with pMMR arEC, naïve to first-line chemotherapy, will be enrolled. Six patients will be enrolled in stage 1 (safety run-in) and treated with TCP for 6 cycles followed by dual maintenance with nesuparib and pembrolizumab. The study will proceed to stage 2 (dose expansion) if less than 33% of patients in stage 1 experience a dose-limiting toxicity. Otherwise, additional patients will be enrolled in stage 1 at a lower dose level. In stage 2, 80 patients will be randomized (1:1) to: arm A) TCP followed by maintenance

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Conflict of Interest
John Kim is an employee of Onconic Therapeutics, Inc.

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with pembrolizumab; arm B) TCP followed by dual maintenance with nesuparib and pembrolizumab. Patients are planned to receive maintenance treatment up to 14 cycles every 6 weeks. Primary endpoint is investigator-assessed progression-free survival (Response Evaluation Criteria in Solid Tumors 1.1) of each arm vs. historical control, which is the placebo arm for pMMR patients in the NRG-GY018 study, and key secondary endpoints are overall survival, overall response rate, disease control rate, duration of response, and safety. Enrollment began in Q4 2024.

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INTRODUCTION

Endometrial cancer (EC) is a global burden as it is the sixth most common cancer among women worldwide [1]. In the United States, EC is estimated to be the fourth most common cancer diagnosed in women in 2025 [2]. In accordance with the increase of obesity and westernized life style, the incidence of EC has gradually increased in East Asia [3,4]. While early-stage EC has an excellent prognosis with a favorable 5-year survival rate, advanced or recurrent EC (arEC) exhibits poor response rates to conventional chemotherapy, highlighting importance of treatment with new agents based on histological and molecular features [5,6].

Clinical trials have demonstrated antitumor activity of the immune-checkpoint inhibitors (ICIs) in EC patients. Recent phase III randomized controlled trials, NRG-GY018 [7], RUBY [8], and AtTEnd [9], proved that the addition of an ICI (pembrolizumab, dostarlimab, and atezolizumab, respectively) to standard chemotherapy resulted in significantly longer progression-free survival (PFS) than with chemotherapy alone in patients with arEC. Meanwhile, these 3 trials consistently showed that the effective size of adding an ICI to combination chemotherapy on PFS was smaller in mismatch-repair (MMR)-proficient (pMMR) cohort, compared to those in MMR-deficient cohort. Especially, pMMR ECs are generally characterized as “immune-cold” tumors, showing low neoantigen burden, weak T-cell infiltration, and limited benefit from programmed cell death protein 1 (PD-1) blockade alone [10]. Therefore, a critical unmet need remains in the management of pMMR tumors, which account for three-fourths of EC.

As poly(ADP-ribose) polymerase (PARP) inhibitors enhance the effects of ICIs when combined, improvement of PFS is expected by dual maintenance with a PARP inhibitor and an ICI [11,12]. PARP inhibition provides a mechanistic strategy to “heat up” the tumor microenvironment and promote conditions favorable for T-cell activation and effective checkpoint inhibition by inducing DNA damage and cytosolic DNA accumulation, activating the cGAS–STING pathway, stimulating type I interferon release, and enhancing antigen presentation, while simultaneously driving programmed death-ligand 1 (PD-L1) upregulation on tumor cells [13-15]. In part 2 of the phase III RUBY trial, PFS was significantly improved in patients with pMMR arEC who received paclitaxel/carboplatin plus dostarlimab followed by maintenance dostarlimab with niraparib maintenance, compared to those who received paclitaxel/carboplatin plus placebo followed by placebo maintenance [16]. Similarly, the phase III DUO-E trial demonstrated elongated PFS from paclitaxel/carboplatin

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plus durvalumab followed by maintenance durvalumab with olaparib in patients with pMMR arEC [17]. Furthermore, olaparib plus durvalumab maintenance showed longer PFS, compared to durvalumab maintenance alone (median, 15.0 vs. 9.9 months). Nevertheless, both 2 trials were not designed to prove that addition of PARP inhibitor maintenance to ICI maintenance provides extra survival benefits [16,17].

Nesuparib is an orally active small molecule that functions as a dual inhibitor of PARP1/2 and tankyrase (TNKS) 1/2. In a phase I study, nesuparib demonstrated an objective response rate (ORR) of 28.2% and a disease control rate (DCR) of 64.1% in patients with advanced solid tumors. Furthermore, nesuparib achieved a 57.1% of ORR in heavily pretreated patients with *BRCA*-mutated or homologous recombination-deficient ovarian cancer, underscoring its broad therapeutic potential across various tumor types [18]. In preclinical studies, nesuparib significantly enhanced tumor immunogenicity in pancreatic cancer cells by upregulating antigen presentation pathways and immune response genes [19] and demonstrated superior antitumor efficacy than olaparib in *BRCA* wild-type gastric cancer xenograft models by modulating Wnt/β-catenin and Hippo signaling pathways [20]. Emerging evidence indicates that aberrant Wnt/β-catenin signaling is a major driver of "immune-cold" tumor phenotypes by suppressing chemokine expression, impairing dendritic cell recruitment, and limiting $CD8^+$ T-cell infiltration, thereby conferring resistance to PD-1/PD-L1 blockade [21]. In addition, TNKS inhibition attenuates Wnt/β-catenin signaling by stabilizing Axin, restoring antigen presentation, and T-cell trafficking into the tumor microenvironment [22,23]. This provides a mechanistic rationale that nesuparib, which uniquely combines PARP and TNKS inhibition, may induce a more profound conversion of pMMR tumors from immune-cold to immune-hot compared with PARP inhibition alone. Consequently, the dual activity of nesuparib could potentiate synergy with pembrolizumab, offering greater clinical benefit in pMMR arEC.

Thus, we hypothesized that combining nesuparib with pembrolizumab, a humanized anti-PD-1 antibody, may improve outcomes in patients with pMMR arEC.

MATERIALS AND MEHTODS

1. Objectives

The PENELOPE trial aims to evaluate the efficacy and safety of first-line carboplatin and paclitaxel in combination with pembrolizumab, followed by maintenance pembrolizumab alone or in combination with nesuparib, in pMMR arEC.

2. Trial design

The PENELOPE is a multicenter, randomized, open-label, non-comparative phase II trial, involving 6 sites from Korea. Institutional Review Board approval was obtained from each site. This study is composed of 2 stages: safety run-in (stage 1) and dose expansion (stage 2).

In stage 1, patients are treated with TCP (paclitaxel 175 mg/m^2 IV + carboplatin area under the curve [AUC] 5.0 IV + pembrolizumab 200 mg IV; q3w for 6 cycles) followed by dual maintenance with pembrolizumab (400 mg; q6w up to 14 cycles) and nesuparib (150 mg PO once a day × 6 weeks; up to 14 cycles). The lower dose level of nesuparib in stage 1 is 100 mg PO once a day.

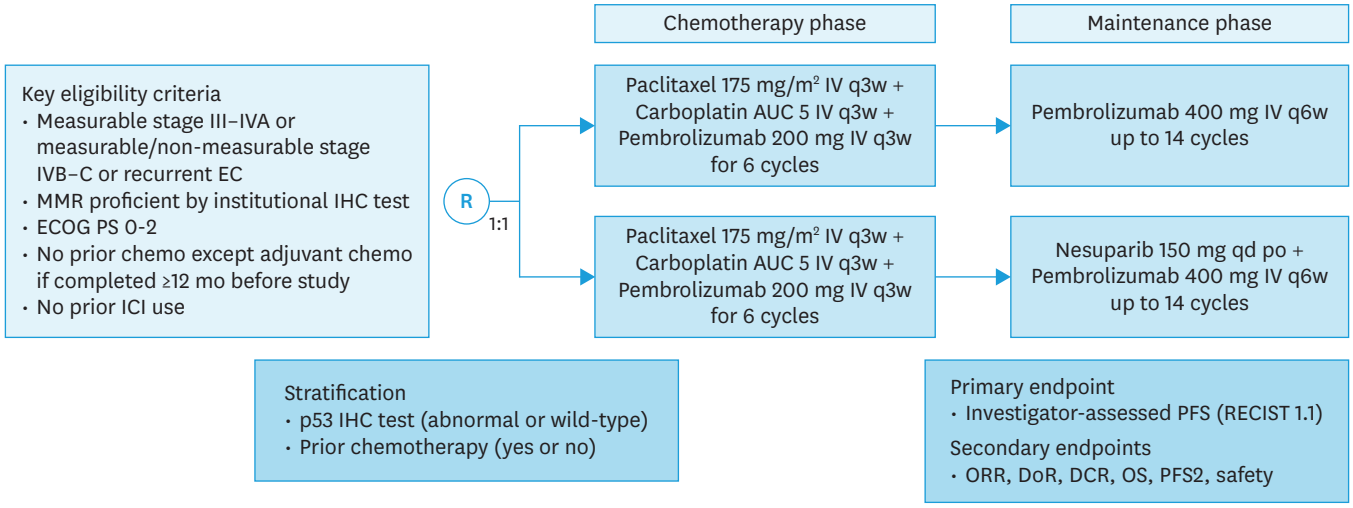

Fig. 1. Trial design.
AUC, area under the curve; DCR, disease control rate; DoR, duration of response; EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; MMR, mismatch repair; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

In stage 2, patients will be randomized 1:1 to receive TCP (paclitaxel 175 mg/m² IV + carboplatin AUC 5.0 IV + pembrolizumab 200 mg IV; q3w for 6 cycles) followed by pembrolizumab maintenance (400 mg; q6w up to 14 cycles) (arm A) or TCP (paclitaxel 175 mg/m² IV + carboplatin AUC 5.0 IV + pembrolizumab 200 mg IV; q3w for 6 cycles) followed by dual maintenance with pembrolizumab (400 mg; q6w up to 14 cycles) and nesuparib (150 mg or 100 mg PO once a day × 6 weeks; up to 14 cycles) (arm B) (**Fig. 1**).

Patients will receive maintenance treatment until disease progression, intolerable toxicity, or withdrawal of patient consent. Dose reductions of paclitaxel, carboplatin, and nesuparib are allowed for treatment-related toxicities. Tumor measurements will be performed every 9 weeks for the first 9 months, and every 12 weeks during maintenance. Tumor response will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [24].

3. Participants

Adult women (≥19 years of age) with confirmed pMMR arEC of any histologic subtype except for carcinosarcoma are eligible for enrollment. Tumor MMR status will be evaluated in tumor cells from a formalin-fixed, paraffin-embedded tumor tissue sample, using institutional immunohistochemical staining of 4 MMR proteins (MLH1, MSH2, PMS2, and MSH6). Patients with newly diagnosed 2023 International Federation of Gynecology and Obstetrics (FIGO) stage III or IVA disease should have measurable disease according to the RECIST version 1.1, while patients with stage IVB–C or recurrent disease can be included, regardless of the presence or absence of measurable disease [24,25]. Patients who have received previous adjuvant chemotherapy are eligible if their chemotherapy-free interval is ≥12 months. The receipt of previous radiation or hormonal therapy is permitted. Among the inclusion criteria were institutional results on immunohistochemical analysis of MMR status, which should be pMMR, an available biopsy specimen for central immunohistochemical assessment, and an Eastern Cooperative Oncology Group Performance Status scale of 0, 1, or 2. Archival tissue of sufficient quality must be submitted or a mandatory pretreatment biopsy must be performed in each case. Key exclusion criteria are prior treatment with any kind of immune checkpoint inhibitor (anti–PD-1 or anti–PD-L1 agent) or PARP inhibitor.

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4. Endpoints

The primary endpoints of stage 1 and stage 2 are dose-limiting toxicity (DLT) rate and investigator-assessed PFS, respectively. PFS is defined as the time interval from randomization to the first documentation of disease progression or death from any cause. Secondary endpoints include ORR, duration of response, DCR, overall survival, PFS2, and safety. The comparisons of PFS between the arms A and B are descriptive and non-analytical.

Exploratory endpoints aim to identify predictive biomarkers of response and resistance to pembrolizumab with or without nesuparib, such as PD-L1 expression, homologous recombination deficiency (HRD), homologous recombination repair (HRR) gene alterations, and tumor mutational burden (TMB). For stage 1 only, evaluation of the pharmacokinetics of nesuparib and its major metabolite, M1, will be evaluated during dual maintenance therapy.

5. Sample size

Six patients will be enrolled in stage 1. The study will proceed to stage 2 if less than 33% of patients in stage 1 experience a DLT. Otherwise, 6 additional patients will be enrolled in stage 1 at the lower dose level (nesuparib 100 mg PO once a day × 6 weeks; up to 14 cycles).

Stage 2 is designed to perform 2 separate comparisons for PFS: arm A versus historical control, which is the placebo arm for pMMR patients in the NRG-GY018 study; and arm B versus historical control. Each comparison is structured as a single-arm, 2-stage phase II trial. The sample size was determined using the one-sample log-rank test. Herein, hazard ratio of 0.576 was assumed, which is translated as a 20% increase from 12-month PFS rate (%) of the historical control (i.e., 48%–50% in the arms A and B vs. 28%–30% in the historical control). The study plans for a type I error of 5% (1-sided), type II error of 20% (80% power), with an 18-month accrual period, a minimum 18-month follow-up, and one interim analysis. A total of 72 patients (36 per arm) are needed, adjusting for a 10% dropout rate, leading to the enrollment of 80 patients (40 per arm) [26].

6. Randomization

In stage 2, randomization will be performed within 1 week prior to C1D1. Eligibility will be confirmed before randomization using stratified block randomization with stratification factors including institutional results on immunohistochemical analysis of p53 (abnormal vs. wild-type) and prior chemotherapy (yes or no). Patients will be randomized via the Interactive Web Response System.

7. Statistical methods

Stage 1 will evaluate the feasibility of the dual maintenance with pembrolizumab and nesuparib in patients with pMMR arEC. Feasibility is defined as a DLT rate less than 33%.

In stage 2, statistical analyses will be performed based on the investigator's assessment according to the treatment arm and strata assigned at screening. The primary efficacy endpoint (PFS) will be estimated using the Kaplan–Meier method. The median PFS and a 95% confidence interval will be calculated per the treatment arm, and one-sample log-rank test will be used for comparisons with the historical control. For comparisons between the 2 treatment arms, the stratified log-rank test will be used.

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8. Planned interim analyses

To assess futility, an interim analysis will be conducted at approximately 11.01 months when 23 patients will be enrolled in each arm in stage 2. Comparisons between arm A versus historical control and arm B versus historical control will be conducted independently. Unless DSMB recommends early termination, the final analysis will be conducted when all the patients have been enrolled and have completed an 18-month follow-up period.

9. Trial registration ID

The study was registered at ClinicalTrials.gov (NCT06502743).

DISCUSSION

Although previous phase III trials have shown promising results with ICIs in arEC [7-9,17], there is room for better efficacy in the pMMR subpopulation. To our knowledge, the PENELOPE is the first ongoing study to explore the efficacy and safety of dual maintenance with nesuparib, an orally active PARP1/2 and TNKS 1/2 inhibitor, and pembrolizumab after first-line TCP treatment in patients with pMMR arEC.

The control arm of the PENELOPE is the current standard, based on the study results of the NRG-GY018 study [7]. Considering that adding a PARP inhibitor to an ICI in the maintenance setting has the potential to further improve antitumor activity, reported by the recent phase III trials, RUBY Part 2 [16] and DUO-E [17], the addition of nesuparib maintenance to the current standard may provide extra survival benefits in patients with pMMR arEC.

A notable feature of the PENELOPE trial is that the PENELOPE is completely dedicated to patients with pMMR arEC. The DUO-E trial investigated whether the addition of durvalumab to carboplatin plus paclitaxel, followed by maintenance durvalumab with or without the addition of olaparib, improved survival outcomes in newly diagnosed arEC [17]. However, PFS analysis in the pMMR subpopulation was conducted as an exploratory analysis in the DUO-E [17], while it was one of the primary endpoints in the RUBY Part 2 [16]. Therefore, if positive results are observed, the PENELOPE will be the first study to show significant and clinically meaningful improvement in PFS from dual maintenance with nesuparib and pembrolizumab in this setting.

Interestingly, the PENELOPE has the same inclusion and exclusion criteria as the NRG-GY018 [7]. For example, patients having carcinosarcoma histologic subtype are excluded in both trials. It is expected that the same criteria will facilitate indirect comparisons of the results between the 2 trials. Unlike previous phase III trials [7-9,16,17], the PENELOPE adopted the updated 2023 FIGO staging of EC [25] as it is the most recently designed study.

During systemic therapy, a combination of multiple agents might lead to frequent and severe adverse events (AEs). However, in the NRG-GY018 study, the addition of pembrolizumab to first-line carboplatin and paclitaxel did not increase the frequency of AEs [7]. Also, the incidence of immune-mediated AEs was not greater than what earlier studies found for pembrolizumab alone in patients with EC [27]. In both RUBY Part 2 and DUO-E, dual maintenance with a PARP inhibitor and an ICI was generally well tolerated, with AEs that were manageable [16,17]. Especially, the safety profiles observed in the dual

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maintenance were generally consistent with the known profiles of the individual agents. The PENELOPE trial evaluates whether the delivery of chemotherapy is compromised or not by pembrolizumab and examine the frequency of any treatment discontinuation due to AEs. Events of myelodysplastic syndrome, acute myeloid leukemia, and new primary malignancies will be collected throughout the study and during survival follow-up.

A major advantage of the PENELOPE trial is its detailed translational research plan, using both tumor and blood samples to investigate the tumor microenvironment and biomarkers, such as PD-L1, HRD, HRR gene alterations, and TMB. Novel prognostic and predictive biomarkers and those associated with resistance mechanisms will be identified through multi-omics analyses. In particular, blood samples will be collected serially during the treatment course and survival follow-up for circulating tumor DNA analyses. Minimal residual disease and recurrence risk will be assessed in the study population [28,29]. Such in-depth translational research has the potential to facilitate individualized escalation or de-escalation treatment strategies based on precise prediction of treatment responses in patients with pMMR arEC.

Management of pMMR arEC is challenging, highlighting the need for more extensive investigations. The PENELOPE trial will provide a unique opportunity for dual maintenance in this population.

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