TPS5635 **Poster Session**

PENELOPE: A randomized phase II trial of first-line carboplatin and paclitaxel in combination with pembrolizumab, followed by maintenance pembrolizumab with or without nesuparib, in patients with newly diagnosed advanced or recurrent MMR-proficient endometrial cancer.

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Background: Clinical trials have demonstrated antitumor activity of the immune checkpoint inhibitors in endometrial cancer patients. Two landmark phase III RCTs, NRG-GY018 and RUBY, proved that the addition of pembrolizumab or dostarlimab to standard chemotherapy resulted in significantly longer progression-free survival (PFS) than with chemotherapy alone in patients with advanced or recurrent endometrial cancer. Meanwhile, both two trials consistently showed that the effective size of adding an immune checkpoint inhibitor to combination chemotherapy on PFS was smaller in MMR-proficient (pMMR) cohort, compared to those in MMR-deficient (MMRd) cohort. As poly(ADP-ribose) polymerase (PARP) inhibitors enhance the effects of immune checkpoint inhibitors when combined, improvement of PFS is expected by dual maintenance with pembrolizumab and a PARP inhibitor. Although the phase III DUO-E trial demonstrated elongated PFS from paclitaxel/carboplatin plus durvalumab followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer, this trial is not designed to prove that addition of olaparib maintenance provides extra survival benefits. Nesuparib is a newly synthesized small-molecule chemical compound that inhibits both PARP-1&2 and tankyrase. The PENELOPE trial will investigate whether the addition of nesuparib to pembrolizumab maintenance after paclitaxel/carboplatin plus pembrolizumab treatment further improves PFS in patients with advanced or recurrent pMMR endometrial cancer. **Methods:** In this multicenter, open-label phase II clinical trial, patients with pMMR, stage III/IV or recurrent endometrial cancer, naïve to first-line chemotherapy, will be enrolled. Six patients will be enrolled in Stage 1 (safety run-in) and treated with TCP (paclitaxel/carboplatin + pembrolizumab 200 mg; q3w for six cycles) followed by maintenance treatment with P (pembrolizumab 400 mg; q6w up to 14 cycles) + N (nesuparib 150mg PO once a day; up to 14 months). 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 lower dose level. In Stage 2, 80 patients will be randomized (1:1) to: arm A) TCP followed by maintenance treatment with P; arm B) TCP followed by maintenance treatment with P + N (150mg or 100mg PO once a day; up to 14 months). Patients will receive maintenance treatment until disease progression. Primary endpoint is investigator-assessed PFS (RECIST 1.1) of arm B vs. arm A, and key secondary endpoints are overall survival, overall response rate, disease control rate, duration of response, and safety. Enrollment began in Q4 2024. Clinical trial information: NCT06502743. Research Sponsor: Onconic Therapeutic INC.