A Randomized Clinical Trial Investigating Olaparib, Durvalumab (MEDI4736) and UV1 as Maintenance Therapy in BRCAwt Patients with Recurrent Ovarian Cancer
ENGOT-OV56/NSGO-CTU-DOVACC

TPS5615

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BACKGROUND & RATIONALE

- Most ovarian cancers (OC) are diagnosed at an advanced stage and despite initial therapy, the disease will often relapse and require further treatment. Thus, there is a need for novel therapeutic options.
- PARP inhibitors lead to increased tumour neoantigen, and modulation of the tumour microenvironment, which may facilitate a more profound anti-tumour immune response.
- UV1 is a therapeutic cancer vaccine directed against telomerase. Since telomerase is an essential enzyme and universally expressed by most tumor cells, it represents a unique cancer antigen as a basis for immunotherapy (IO).
- The rationale for integrating immunotherapy as maintenance therapy following chemotherapy is based on preclinical studies which have shown that chemotherapy induces immunogenic cell death leading to increased recognition of the tumor by the immune system.
- The proposed study is evaluating the use of the therapeutic cancer vaccine UV1 in combination with olaparib and the PD-L1 inhibitor, durvalumab as maintenance therapy after response to platinum-based chemotherapy.

KEY INCLUSION CRITERIA

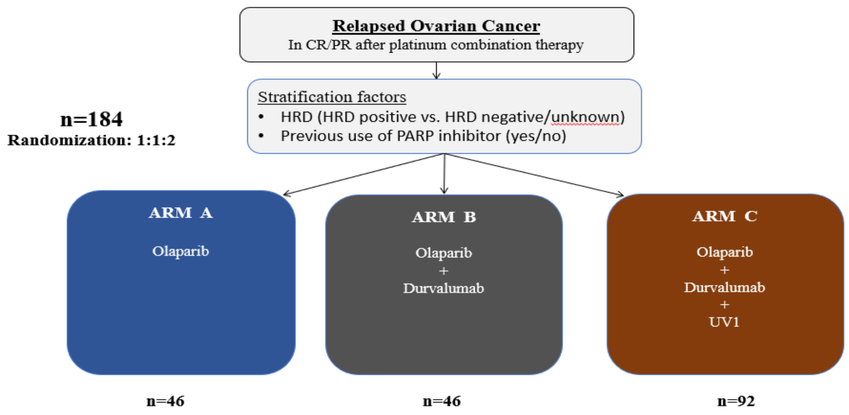
- Histologically diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer, excluding mucinous or low-grade serous histology
- Radiological or histological confirmation of relapse disease ≥ 6 months after last chemotherapy
- Patients who are non-gBRCAmut or tBRCAwt
- Have completed at least two lines, but no more than 4 lines, of chemotherapy.
- Be either PARPi naive or earlier treated with PARPi and not progressed during 6 months of PARPi therapy
- Must have, CR or PR on the post-treatment scan following completion of the last chemotherapy course.
- Patient consents to Myriad myChoice® HRD test.
- Must be included in the study within 10 weeks of completion of the final dose of chemotherapy.
- Must have normal organ function measured within 28 days prior to administration of study treatment

KEY EXCLUSION CRITERIA

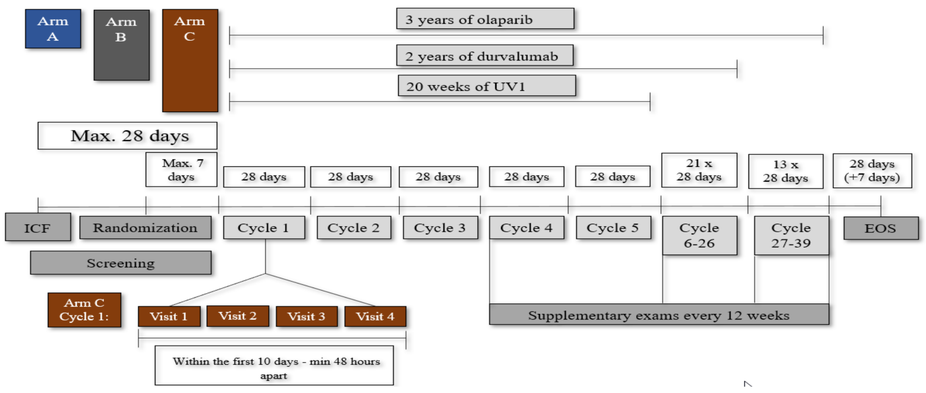
- Previous immunotherapy (for example anti-PD-1/L1).
- Other malignancy unless curatively treated with no evidence of disease for ≥ 5 years, except adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1 endometrial carcinoma.
- Resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (e.g., unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation > 470 ms, electrolyte disturbances, etc.), or patients with congenital long QT syndrome.
- Patients with myelodysplastic syndrome/acute myeloid leukemia or with features suggestive of MDS/AML.
- Patients with symptomatic uncontrolled brain metastases.
- Concomitant treatment with bevacizumab within the last 3 weeks.
- Concomitant therapy with any other anticancer therapy or chronic use of systemic corticosteroids of more than 10mg prednisolone daily.

STUDY DESIGN

ENGOT-OV56/NSGO-CTU-DOVACC (NCT04742075)



STUDY ARMS, DOSING & DURATION OF TREATMENT



Arm A (olaparib):
• Olaparib 300 mg tablets twice daily for 36 months or until progressive disease or unacceptable toxicity.

Arm B (olaparib plus durvalumab):
• Olaparib 300 mg tablets twice daily for 36 months or until progressive disease or unacceptable toxicity.
• Durvalumab 1500 mg IV every 4 weeks for 24 months or until disease progression or unacceptable toxicity.

Arm C (olaparib plus durvalumab plus UV1):
• *Olaparib 300 mg tablets twice daily for 36 months or until progressive disease or unacceptable toxicity.
• Durvalumab 1500 mg IV every 4 weeks for 24 months or until disease progression or unacceptable toxicity.
• Eight UV1 vaccinations during the first 5 month: Four UV1 vaccinations during the first 10 days. From cycles 2-5 single UV1 vaccination every 4th week.

The UV1 vaccination includes sargramostim, used as a vaccine adjuvant, at a dose of 75 µg and UV1 at a dose of 300 µg.
Sargramostim is a granulocyte-macrophage-colony-stimulating factor.
*Sargramostim and UV1 should be administered **intradermally** and injected at the **same injection site** (McBurney's point) each time.*

After 36 months of olaparib treatment, further treatment is at the physician's discretion.

STUDY INFORMATION

Sponsor: NSGO-CTU ,Copenhagen, Denmark
ENGOT-model: A
Study Chair: Mansoor Raza Mirza
Study Statistician: Rene dePont Christensen**,** NSGO-CTU
Project Managers: Kirsten Pors, Signe Gybel Frederiksen, Ulrikke Ji Mee Willerslev
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Link to online poster

Contact Dr. Mirza

OBJECTIVES & ENDPOINTS

Primary objective:
• To compare the preliminary efficacy of maintenance treatment with olaparib (arm A) to that of olaparib plus durvalumab & UV1 (arm C)

Secondary objectives:
• To compare the preliminary efficacy of maintenance treatment with olaparib plus durvalumab (arm B) to that of olaparib plus durvalumab and UV1 (arm C)
• To compare the preliminary efficacy of maintenance treatment with olaparib to that of olaparib plus durvalumab and UV1 according to stratification factors
• To evaluate Patient Reported Outcomes (PROs) in treatment arms
• To compare the preliminary efficacy of maintenance treatment according to PD-L1 status
• To evaluate safety in treatment arms

Primary endpoint:
• Progression-free survival (PFS) arm A versus C

Secondary endpoints:
• PFS arm B versus arm C
• Assessment of PROs
• PFS assessed by blinded independent central review (BICR)
• Efficacy according to stratification factors
• Efficacy according to PD-L1 status
• Overall survival (OS)
• Time to first subsequent therapy (TFST)
• Subsequent progression (PFS2)
• Time to second subsequent therapy (TSST)
• Objective Response Rate (ORR)
• Disease Control Rate (DCR)

TRIAL STATISTICS

For the sample size calculation in DOVACC, we use the following assumptions for median PFS:
DOVACC Median PFS arm A: 9.3 months
DOVACC Median PFS arm B: 11.3 months
DOVACC Median PFS arm C: 15.3 months
These are relevant, as the BRCAwt population in the NOVA trial is comparable to the DOVACC population, and our assumed median PFS values, are strongly based on results from the overall non-gBRCA cohort in NOVA (median PFS 9.3 months) *(Mirza et al, NEJM, 2016).*
For the DOVACC study an accrual of 24 months, a follow-up period of 36 months from the last enrolled subject, a randomization of 1:1:2 (arm A: B: C), and a withdrawal probability of 23% is assumed.
"With assumptions as stated, 2:1 (arm C: A) randomization in favor of novum, a one-sided alpha of 0.075, a power=0.8, HR=0.61 and a drop-out rate of 23%, Stata version 15.1 built-in sample size function for log-rank based designs "power log-rank" was used. This produced a requirement for 96 events and taking drop-out into account a resulting sample size of 125 subjects.
This however does not take into account the limited accrual and follow-up time of 24 and 36 months respectively. Using this, the probability of an un-censored event can be calculated to be roughly 0.9. Factoring this in we arrive at a total sample size of approximately 139 for the comparison A vs. C."
All in all, 184 (arm A:46 + arm B:46 + arm C:92) subjects must be enrolled.

PARTICIPATING ENGOT GROUPS & STUDY STATUS

- NSGO-CTU: Nordic Society of Gynaecological Oncology – Clinical Trial Unit
- NOGGO: Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie
- AGO-Austria: Die Arbeitsgemeinschaft für Gynäkologische Onkologie Austria
- BGOG: Belgium and Luxembourg Gynaecological Oncology Group
- HeCOG: Hellenic Cooperative Oncology Group
- DGOG: The Dutch Gynecological Oncology Group

COUNTRY/ GROUP	DATE OF APPROVAL	# TOTAL PLANNED SITES	# SITES ACTIVATED	STATUS
Denmark	CA: 02.07.21 EC: 20.08.21	4	4	Recruiting
Norway	CA 07.12.21 EC: 17.09.21	4	4	Recruiting
Sweden	CA: 07.02.22 EC: 27.04.22	3	1	Recruiting
Finland	CA 06.04.22 EC: 19.05.22	3	3	Recruiting
Lithuania	CA: 06.01.22 EC: 06.01.22	2	2	Recruiting
ENGOT GROUPS				
Austria (AGO-Austria)	CA: 09.03.23 EC: 10.03.23	4	-	SIVs scheduled
Belgium (BGOG)	CA: 20.01.23 EC: 24.04.23	4	-	SIV planning in progress
The Netherlands (DGOG)	CA: 10.03.23	3	-	Pending EC re-submission
Greece (HeCOG)	CA: 27.04.23 EC: 24.04.23	5	-	SIV planning in progress
Germany (NOGGO)	CA: 03.05.22 (V2.1) 03.02.23 (V2.2) EC: 23.01.23 (V.2.2)	4	-	SIVs ongoing
TOTAL	-	**36**	**14**	-