# A Randomised Phase II trial to examine Modified Vaccinia Ankara-5T4 Vaccine in Patients with Relapsed Asymptomatic Ovarian Cancer (TRIOC)

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## ABSTRACT

Immunotherapy directed at 5T4 tumour antigen may delay the need for further chemotherapy. An attenuated Modified Vaccinia Ankara Virus containing the gene encoding for 5T4 (MVA-5T4) was studied in asymptomatic relapsed ovarian cancer.

**Objectives:** to assess the effectiveness and safety of MVA-5T4 as treatment for asymptomatic relapsed ovarian cancer.

**Methods:** TRIOC was a phase II randomized (1:1), placebo-controlled double-blind multicentre study. The primary aims: to assess the effectiveness and safety of MVA-5T4 as a treatment for asymptomatic relapsed ovarian cancer patients. Eligible patients had FIGO (International Federation of Gynaecology and Obstetrics) stage IC1-III or IVA epithelial ovarian, fallopian tube or primary peritoneal carcinoma**,** Eastern Cooperative Oncology Group (ECOG) 0-1, with relapse as defined by CA-125 rise to ≥2 x upper limit of normal (ULN) or low volume disease on CT scan. The primary endpoint was disease progression (including deaths from ovarian cancer) at 25 weeks (PR-25). Following a brief trial suspension, the trial restarted as a single arm study. The revised single arm design required 45 evaluable patients treated with MVA-5T4 to detect a 25-week progression rate of 50%, assuming an expected 70% rate without MVA-5T4 ; 85% power with 1-sided 5% significance[1].

**Results**: 94 eligible patients were recruited, median age was 65 years (range 42 to 82), median follow up 34 months (2 to 46). 59 patients received MVA-5T4 and 35 placebo. The median number of MVA-5T4 injections received was 7 (range 0-9), compared to a median of 6 (1-12) for patients receiving placebo. Median progression free survival (PFS) was the same in both arms (3.0 months). The 25-week progression rate (primary outcome) was similar in both arms: 80.0% for patients treated with MVA-5T4 and 85.7% for those on placebo (risk difference -5.7%, 95% CI -21.4 to 10.0) Median time to clinical intervention was improved with MVA-5T4: 7.6 (6.7-9.5) vs 5.6 (4.9-7.6), p-0.17.

**Conclusion:** MVA-5T4 vaccination in patients with asymptomatic relapse was well-tolerated but did not improve the progression rate at 25 weeks, patients who received MVA-5T4 tended to receive clinical intervention later than those on placebo.

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## What is already known on this topic

Immunotherapy in ovarian cancer has limited role despite the evidence of immune activation. Many patients relapse with an asymptomatic slowly progressive disease. Those who relapse after a long disease-free interval with a low bulk of cancer or those who have CA-125-only relapse are ideally suited for evaluation of immune-based strategies. 5T4 is an oncofoetal antigen that is expressed on the cell surface and has been identified as a target for immunotherapy. This study was the first study targeting 5T4 in patients with low volume, asymptomatic relapsed ovarian cancer.

## What this study adds

This is a first clinical trial of MVA-5T4 vaccine that consists of a highly attenuated vaccinia virus containing the gene encoding for the human tumour associated antigen 5T4. The trial was designed for patients with relapsed asymptomatic ovarian cancer with CA125 relapse and/or low volume on imaging. Although it shows limited activity of the vaccine, patients in the MVA-5T4 arm tended to receive clinical intervention later than those on placebo.

## How this study might affect research, practice, or policy

The results of the study will encourage trials of a combination immunotherapy as vaccines alone are unlikely to have an effect on progression free and overall survival.

## INTRODUCTION

Ovarian cancer is the second most common gynaecological malignancy in the Western world.

There is evidence that ovarian cancer is under immune surveillance [2]. A study reported by Zhang et al in 2003 showed that 5-year overall survival correlates with the presence or absence of tumour infiltrating lymphocytes (TILs) in favour of patients who show an immune response (38% versus 4.5%, respectively, p<0.001) [2] The Cancer Genome Atlas Network reported the presence of an immunoreactive molecular subtype of ovarian tumours, which displayed an enrichment of genes and signalling pathways associated with immune cells and longer overall survival (OS) [3]. Despite the signs of immune activation, immunotherapy in ovarian cancer has a limited role due to many immunosuppressive mechanisms. It is well recognized that with cancer progression, the tumour microenvironment changes and becomes increasingly immunosuppressive due to development of immune tolerance, propagation of immunosuppressive regulatory T cells, secretion of immunosuppressive cytokines and, exhaustion of proinflammatory T cells (review in [4]). Welters et al demonstrate that the success of vaccination in vulvar cancer correlates with the frequency of specific regulatory cells residing in the tumour , and that these suppressive cells were more prevalent in larger lesions than smaller tumours, resulting in a worse response to vaccination [5].

Patients with ovarian cancer, who relapse after a long disease-free interval with a low bulk of cancer, who are not suitable for secondary cytoreductive surgery or those who have CA-125-only relapse, may be ideal candidates for evaluation of immune-based strategies.

5T4 is an oncofetal antigen that is expressed on the cell surface and has been identified as a target for immunotherapy. 5T4 is expressed on human trophoblast cells and most human tumors, including ovarian cancer [6 7]. 5T4 is absent in most normal tissues. 5T4 is expressed in ovarian cancer and its expression correlates with advanced stage of disease (FIGO stages III and IV) (P=0.033)[8]. To date, MVA-5T4 has been tested a total of 580 patients in 11 phase I/II and II clinical trials and 1 phase III clinical trial in colorectal, renal, and prostate cancer subjects , the safety profile was consistent and there was evidence of strong immunological response to MVA-5T4 [9-17].

We conducted a clinical trial of MVA-5T4 (TroVax®), a vaccine that consists of an attenuated vaccinia virus (MVA) containing the gene encoding for the human tumor

antigen (5T4) under transcriptional control of a modified VV promoter, mH5. The trial was designed for patients with relapsed asymptomatic ovarian cancer with CA125 relapse and/or low volume on imaging to assess the clinical efficacy and immunological responses to MVA-5T4. The vaccine was designed to induce T cell specific response as well as antibody response to 5T4 antigen and MVA.

# Methods

## Trials Design

TRIOC was originally designed as a phase II randomized (1:1), placebo-controlled double-blind multicenter study. The primary aims were to assess the effectiveness and safety of MVA-5T4 as a treatment for asymptomatic relapsed ovarian cancer patients. The study was sponsored by University College London. Ethical (GTAC182) and Regulatory Clinical Trials Agreement (CTA:2011-001836-44) approvals were obtained and all participants gave written informed consent.

Patients were randomized (1:1) to receive MVA-5T4 at a dose of 1 x $10^9$ $TCID_{50}$/mL in 1mL or matching placebo by intramuscular injection. Injections were scheduled for the weeks 1, 2, 4, 7, 10, 13, 19 and 25. The schedule was based on previously published clinical trials of 5T4 -based vaccination [12 14 15] No dose modifications were permitted. Treatment was discontinued in the event of confirmed progression or a grade ≥3 toxicity thought to be related to treatment.

Patients were followed up for a maximum of 2 years. A CT or MRI scan of the abdomen and pelvis and CT scan of the chest was performed at weeks 13 and 25 and then at 2 months after treatment completion, and thereafter 3-monthly until 1 year after the end of treatment. All scans were assessed using RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 and immune-related response criteria (irRC)[18]. Progressive disease by RECIST 1.1 was confirmed by a repeat scan 8 weeks after to assess response by irRC.

Quality of life was assessed by EORTC (Response Evaluation Criteria in Solid Tumours) quality of life (QLQ) C-30 and OV-28 at baseline, at each vaccination visit, at the first post-treatment visit and at 5 and 11month visits.

## Change of Design

Recruitment started in December 2013. However, the trial was suspended in August 2016 due to an issue over the quality control of two MVA-5T4 vaccine vials containing tiny particles. The patient was unblinded and no further patients received this batch of vaccine. In total 11 patients who had already started MVA-5T4 did not receive a further dose of it while the manufacturing process was investigated. 18 patients (including 7 patients on placebo) were withdrawn during the trial suspension, but outcome data (including safety data) was still collected from them. A full investigation confirmed that the product was safe. However, due to limited allocated drug supply, and a fixed expiration date, the trial was redesigned as a single-arm open-label study, to maximize the number of patients given MVA-5T4. Recruitment re-started in May 2017. All patients randomized before the suspension remained blinded, except the single patient whose treatment triggered the investigation.

Patients were enrolled at hospital sites and randomized using a third-party interactive web response system with a minimization approach stratified by radiological disease, relapse status ($1^{st}$ vs $2^{nd}$), histological subtype and hospital site. Investigators and patients were blinded to the assignment interventions.

## Participants

Eligible patients had stage IC1-III or IVA epithelial ovarian, fallopian tube or primary peritoneal carcinoma (high grade serous, endometroid and mucinous histology). They were ECOG 0-1, had asymptomatic platinum-sensitive relapse as defined by CA-125 rise to ≥2 x ULN or low volume disease on CT scan (low volume radiological disease was defined as radiologically visible disease excluding intra-hepatic, parenchymal liver or splenic metastases, ascites or pleural effusion thought to require drainage within the next 2 months). All patients had cytoreductive surgery as part of their first line treatment and ≥6-month period between completion of last platinum-based chemotherapy and relapse. Maintenance treatment was permitted but discontinued upon entry to the trial.

## Primary Endpoints

The primary endpoint was disease progression (including deaths from ovarian cancer) at 25 weeks. The date of progression was taken as the earliest occurrence of the following: i) progression by RECIST 1.1 with confirmatory irRC 8 weeks later, ii) progression by irRC with confirmatory irRC 8 weeks later or iii) clinical intervention required for symptoms of progression.

Secondary endpoints were irRC response at 25 weeks, progression-free survival, time to clinical intervention, incidence of clinical intervention at 25 weeks, CA-125 doubling time, overall survival and quality of life.

Immunological endpoints included antibody and cellular responses against both 5T4 and the MVA viral vector.

## Statistical methods

The initial trial was designed as a two-arm study, to directly compare endpoints between the MVA-5T4 and placebo groups. At 25 weeks, 70% were expected to progress or die from ovarian cancer (RECIST-defined progression) in the Placebo group [19]. We aimed to detect a progression rate of 50% in the MVA-5T4 group. Based on a direct comparison of proportions (using 70 vs. 50%), 80% power and one-sided test of statistical significance of 15%, we required 42 patients per group. To allow for non-evaluable patients and loss to follow-up, 50 women needed to be recruited per group (i.e. 100 in total)

Following the trial suspension, the primary design was changed to a single-arm trial. For the revised single-arm design, we required 45 evaluable patients treated with MVA-5T4 to detect a progression rate of 50%, assuming an expected 70% rate without MVA-5T4 (A'Hern design: 85% power with 1-sided 5% significance[1]). As well as analysing all patients treated, additional analyses were performed on the subset of patients whose treatment was not impacted by the trial suspension, and on the subset treated as per the final protocol. Analyses comparing the outcomes of randomized patients to those recruited to the single-arm study were also performed.

PFS, OS and time to clinical intervention were assessed using Kaplan-Meier methods, measured from registration until protocol-defined progression (PFS), clinical intervention (time to clinical intervention) or death from any case (PFS, OS-Overall survival). Patients who did not experience an event of interest were censored at the date last seen. Health-related quality of life was analysed used repeated measures regression, with adjustment for baseline scores. To account for multiple scales being tested, only p-values <0.01 were considered statistically significant in quality of life analyses. Analyses comparing the outcomes of randomized patients to those recruited to the single arm study were performed.

Immunological endpoints included antibody and cellular responses against both 5T4 and the MVA viral vector. The IFN-γ ELISPOT was used to monitor T cell responses, as previously described [11 13]. Flow cytometry was performed using a FACSCalibur flow cytometer. T cell function was tested by mixed lymphocyte proliferation assay, as previously described [2 11 17]. MVA- and 5T4-specific antibody titers were determined by ELISA as described previously [17]
Further exploratory analyses investigated potential pre-treatment predictors of treatment benefit: haemoglobin, haematocrit, Mean Corpuscular Haemoglobin Concentration (MCHC), baseline 5T4 antibody, serum C-reactive protein (CRP), platelets, neutrophils, lymphocytes, 5T4 immune response surrogate and neutrophil to lymphocytes ratio, as well as Glasgow prognostic index (GPS).

To assess 5T4 expression in archival tissue we followed a previously published protocol using deparaffinization, horse serum and an Avidin Biotin block before incubation with an anti-TPBG (5T4) antibody produced in rabbit (HPA010554; Sigma-Aldrich). Detection of the primary antibody was performed using Vectastain Elite ABC-HRP Kit, Peroxidase (Vector Laboratories) with a diaminobenzidine reaction and hematoxylin counterstaining. For 5T4 IHC expression, human placenta and kidney FFPE tissue with and without primary antibody were used as positive and negative controls.

For the antibody response and potential predictors of treatment benefit, the association between pre-treatment variables and maximum absolute responses were reported as Spearman's correlation coefficients (with corresponding p-values). Associations between pre-treatment variables and responder categories were

reported as odds ratios (with corresponding 95% confidence intervals) from logistic regression models.

## RESULTS

94 patients were recruited from 12 centers in the UK between December 2013 and October 2017, 59 received MVA-5T4 and 35 placebo. 69 were randomized prior to the change in the design of the study and an additional 25 were enrolled in the single arm study. Median age was 65 (range 42 to 82), and median time since prior chemotherapy was 18 months (range 7 to 86). The characteristics of the patients given MVA-5T4 as part of the randomized phase were similar to those in the single arm study (Table 1). The median follow up was 34 months (range 2 to 46).

The median number of MVA-5T4 injections received was 7 (range 0-9), compared to a median of 6 (1-12) for patients receiving placebo. The most common reason for stopping treatment before the $8^{th}$ injection was disease progression (40.7% MVA-5T4; 54.3% placebo), followed by trial suspension (13.6%; 14.3%) and unacceptable toxicity (8.5%; 2.9%). Toxicity that resulted in discontinuation of treatment was due to adverse and serious adverse events such as fatigue, vomiting, arthralgia, myalgia, dizziness and headache (Supplementary Table 1).

The 25-week progression rate (primary outcome) was similar in both arms: 80.0% for patients treated with MVA-5T4 and 85.7% for those on placebo (risk difference -5.7%, 95% CI -21.4 to 10.0). Excluding those whose MVA-5T4 treatment was impacted by the trial suspension gave a risk difference of -0.9% (-16.5 to 14.6), while in the pre-specified per protocol analysis (patients who had ≥5 treatment injections, unaffected by trial suspension) it was -12.1% (-30.5% to 6.3%). Median PFS was 3.0 months in both treatment arms.

Clinical intervention was defined by symptoms that required systemic treatment: ascites, pleural effusion, malignant bowel obstruction or other symptoms related to progressive disease demonstrated on imaging (Table 2). There was a lower proportion of patients requiring clinical intervention by week 25 in the MVA-5T4 arm (29% vs 51% placebo, p=0.03), however this did not translate to a significant improvement in time to clinical intervention (HR 0.74, 95% CI 0.47-1.15, p=0.17); Figure 1.

A total of 44 deaths were reported during follow up, all attributed to disease progression. The median overall survival was 30.6 months in the MVA-5T4 arm versus 39.7 months with placebo (HR 1.58, 95% CI 0.84-2.95, p=0.15); Figure 2.

The safety population included all patients who received at least one injection. Treatment with MVA-5T4 was well tolerated (Supplementary Table 2). The most reported grade 3/4 toxicities were gastrointestinal disorders (5.2% in MVA-5T4 vs 11.4% in placebo) such as abdominal pain, bloating, constipation, diarrhoea, dyspepsia, flatulence and nausea as well as nervous system disorders (8.6% vs 2.9%) such as lethargy, headache, dizziness, peripheral sensory neuropathy, dysgeusia, and amnesia. The incidence of any grade 3/4 toxicity in the MVA-5T4 arm was 27.6% compared to 22.9% in the placebo arm. Quality of life was generally similar between the two treatment arms with no significant differences between treatment arms for the QLQ C30 functional scales or symptom scales and no significant differences in the QLQ OV28 symptom scales over the duration of the study.

94 patients were assessed for immune response. 72 archival tumor blocks were available for analysis of which 54 were evaluable (those with ≤10% tumor content were excluded). Out of the 54 tumors, 11 (20%) did not show any 5T4 expression and of the blocks that showed 5T4 staining, 21 (39%) showed weak expression of 5T4.

Patients were more likely to mount a positive antibody response if they received the active treatment compared to patients who received placebo; 5T4 (53/57 [93%] MVA-5T4 vs 12/34 [35%] placebo, p<0.001) and MVA (54/57 [95%] MVA-5T4 vs 1/34 [3%] placebo, p<0.001).

There was no evidence that MVA-5T4-treated patients were more likely to mount a positive 5T4 cellular response than placebo (6/57 [11%] MVA-5T4 vs 2/34 [6%] placebo, p=0.5). There was also no evidence that antibody response to either 5T4 or MVA was associated with a significant benefit in terms of PFS or time to clinical intervention. There was, however, evidence to suggest that patients who achieved higher maximum MVA cellular responses, had significantly better time to clinical intervention (HR for 100 unit increase in maximum cellular response 0.92, 95% CI

0.88-0.97, p<0.01) (Figure 3). 5T4 cellular response was not associated with clinical benefit. Figure 3 shows the time to clinical intervention in patients who developed a high MVA cellular response as compared to patients who had a low response.

Of the pre-treatment factors analysed, only GPS and 5T4 immune response surrogate had a predictive value in terms of clinical benefit[20]. Patients with a high GPS (defined as ≥1) had worse PFS in the MVA-5T4 arm (hazard ratio of 2.66 (CI 1.18-6.01), p=0.02), but not in the placebo arm (HR 0.71 (CI 0.27-1.91) p=0.5) (interaction p=0.04). A similar pattern was seen for time to clinical intervention; for patients in the MVA-5T4 arm the HR was 2.58 (CI 1.13-5.89, p= 0.02), compared to a HR of 0.6 (CI-0.23-1.59, p=0.3) in the placebo arm (interaction p=0.03).

The 5T4 immune response surrogate predicted patients who derive benefit from MVA-5T4 in terms of time to symptomatic progression (HR 0.99 (CI 0.98-1.00) p=0.05), but not PFS.

# DISCUSSION

## Summary of Main Results

The results of immunotherapy trials in ovarian cancer have so far been disappointing. Some studies looking at the immune environment show promising results with evidence of immune activation, but with low rates of clinical response[21] [22].

Based on preclinical and clinical results demonstrating a good immunological response to a 5T4 antigen[9-11 14 15], expressed in many solid tumors, we conducted a trial in ovarian cancer using a genetically modified vaccina Ankara virus containing the human tumor associated antigen, 5T4. Only patients who had no symptoms relating to their relapsing cancer were eligible for the study. This study captured patients who did not immediately require chemotherapy or surgery and could potentially benefit from an immunological treatment approach.

Disease progression at 25 weeks did not differ between the two arms and there was no evidence of an overall survival benefit to the vaccine. However, there was a trend towards improvement in time to clinical intervention with MVA-5T4 treatment (HR-

hazard ratio- 0.74), with fewer patients requiring clinical intervention by week 25 than those given placebo (29% vs 51%). Vaccination with MVA-5T4 resulted in measurable immunological responses with increased levels of antibodies against 5T4 and MVA. Interestingly the cellular responses were mainly directed at MVA and there was no evidence that MVA-5T4 patients were more likely to mount a positive 5T4 cellular response (p=0.5).

## Results in the Context of Published Literature

These results can potentially be explained by the low immunogenicity of 5T4 and high immunogenicity of the MVA vector in patients with ovarian cancer. Interestingly several trials that looked at MVA 5T4 vaccination in other tumor types reported a better cellular response to MVA 5T4 vaccination[9 11-13 15 23]. A trial of vaccination of colorectal cancer patients showed that most patients developed 5T4 -specific cellular responses and there was a positive association between the development of a 5T4 (but not MVA) antibody response and patient survival or time to disease progression [13]. Similarly, in a trial of patients with renal cancer, many patients developed a high 5T4 antibody response, which was associated with longer survival within the MVA-5T4-treated group [15]. The nature of immune response development in ovarian cancer is perhaps more complex and evaluation of tumour tissue prior to immunotherapy trial enrolment may be the key to a better clinical response. The inclusion of only women with asymptomatic recurrence did not permit taking biopsies at the time of the trial enrolment.

There are several clinical trials that combine immunotherapy agents with small molecule drugs, for example bevacizumab, atezolizumab and chemotherapy or PARP inhibitors and the response rates are encouraging with some women achieving CR and high rates of clinical benefit (up to 95% in platinum sensitive relapse ) (reviewed in [24]).

We have found that some previously described clinical indicators of immune response can offer valuable predictive information. Patients with a high Glasgow Prognostic Index had a worse PFS in the MVA-5T4 arm and those patients developed symptoms sooner than patients who had a low Glasgow Prognostic

Index. This correlation was previously published, and it should be utilized in future clinical trials and in clinical practice [25]

## Strengths and Weaknesses

This study explored an immune treatment approach in a group of women who are not normally offered clinical trials of novel agents. The population of women in the study did not have cancer related symptoms, and some had no measurable disease but a CA-125 progression only. Patients in this clinical scenario may be better suited for an immunotherapy-based approach and this is a strength of the study.

The weaknesses of the study include a change of the design to a single arm study, discontinuation of treatment for patients during trial suspension as well as lack of fresh tumour tissue, which is a frequent hurdle in clinical trials, and it often limits our understanding of tumour environment and how it evolves with cancer progression.

## Implications for Practice and Future Research

The change in clinical practice over the last few years and the use of PARP inhibitors in the maintenance setting has altered the clinical picture and future immunotherapy trials in ovarian cancer. We are unlikely to have many women with asymptomatic relapse who are not on treatment, as most of those women will be on a maintenance therapy. Combining immunotherapy agents might offer more effective treatment options in recurrent ovarian cancer. The molecular and immune heterogeneity of ovarian cancer indicates that the combination of immunotherapy treatment together with targeted agents such as PARP inhibitors, as well as drugs that target the immune suppressors, like TGF-β or IL-10 may be the way forward. The idea of immune stimulation in a “low volume” relapsed disease setting might be explored further with new approaches and combinations of targeted therapy and immunotherapy. Recent studies with vaccines in the adjuvant setting, targeting tumour antigens such as NY-ESO-1 have suggested a survival benefit [21] but these may well be overtaken by check-point inhibitors in combination with targeted agents such as PARP inhibitors. Studies such as KEYNOTE-162 (niraparib/pembrolizumab) and MEDIOLA (Olaparib/durvalumab) combining PARP inhibitors and check-point inhibitors show promising results, with the latter demonstrating overall response rate

of 74.2% in the non-BRCA patients and over 90% in patients with BRCA mutation [26] [27] . Targeting early relapsed disease in patients on treatment with PARP inhibitors by adding immunomodulating agents may be an attractive option to explore.

Access to fresh tissue to evaluate the immune microenvironment and better ways to assess immune activation using peripheral blood will help us to understand the dynamic changes that occur during immune modulation.

## Conclusion

In summary, our trial did not demonstrate an improvement in cancer progression at 25 weeks but MVA-5T4 was a safe and well tolerated treatment that showed some evidence of immune activation that might influence the development of clinical symptoms. Therefore, there may still be a role for using anti-cancer vaccines in advanced ovarian cancer.

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## Figure 1:

## Time to clinical intervention by treatment arm for A) all patients and B) per protocol population (≥5 injections and unaffected by trial suspension)

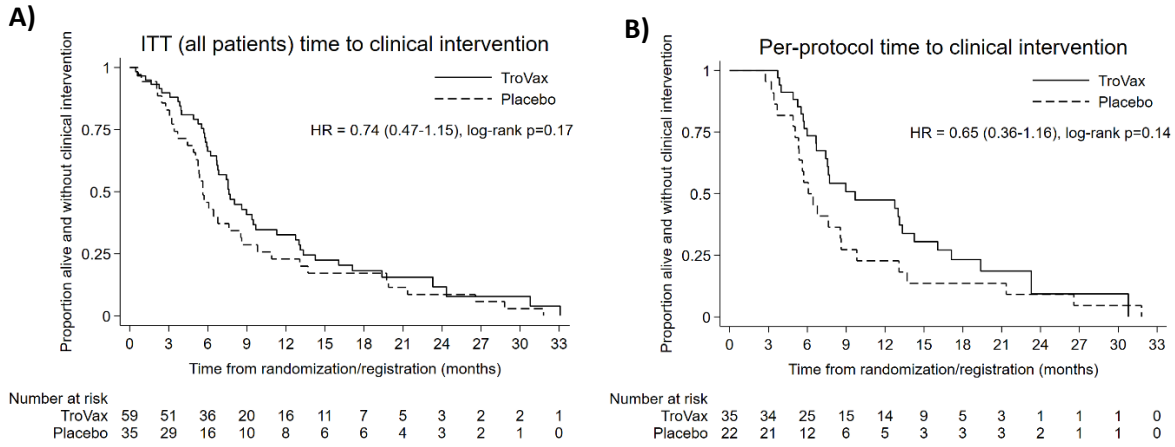

Figure 2:

Overall survival for all patients by treatment arm

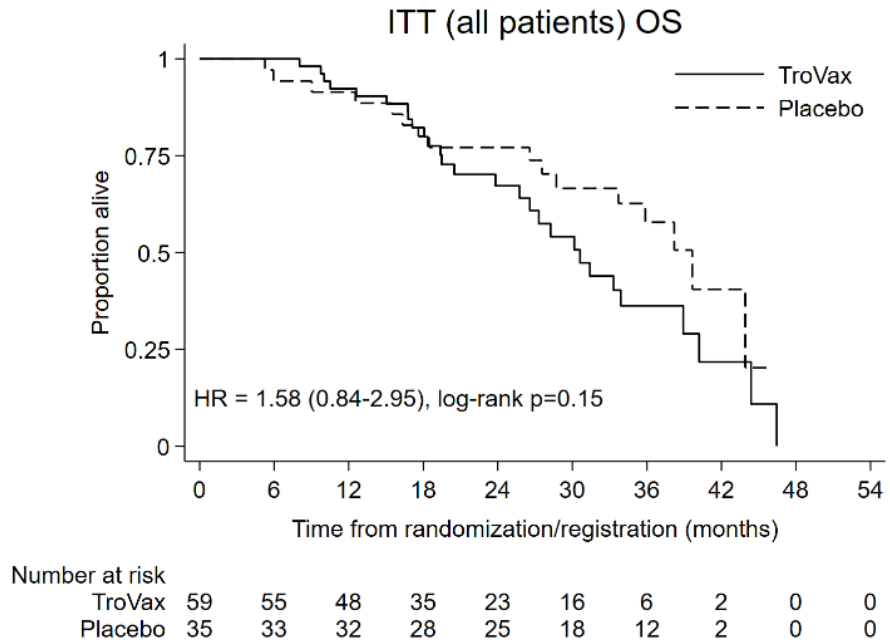


Figure 3.

Time to clinical intervention split by median maximum MVA cellular frequency (Low < 376.7, High ≥376.7)

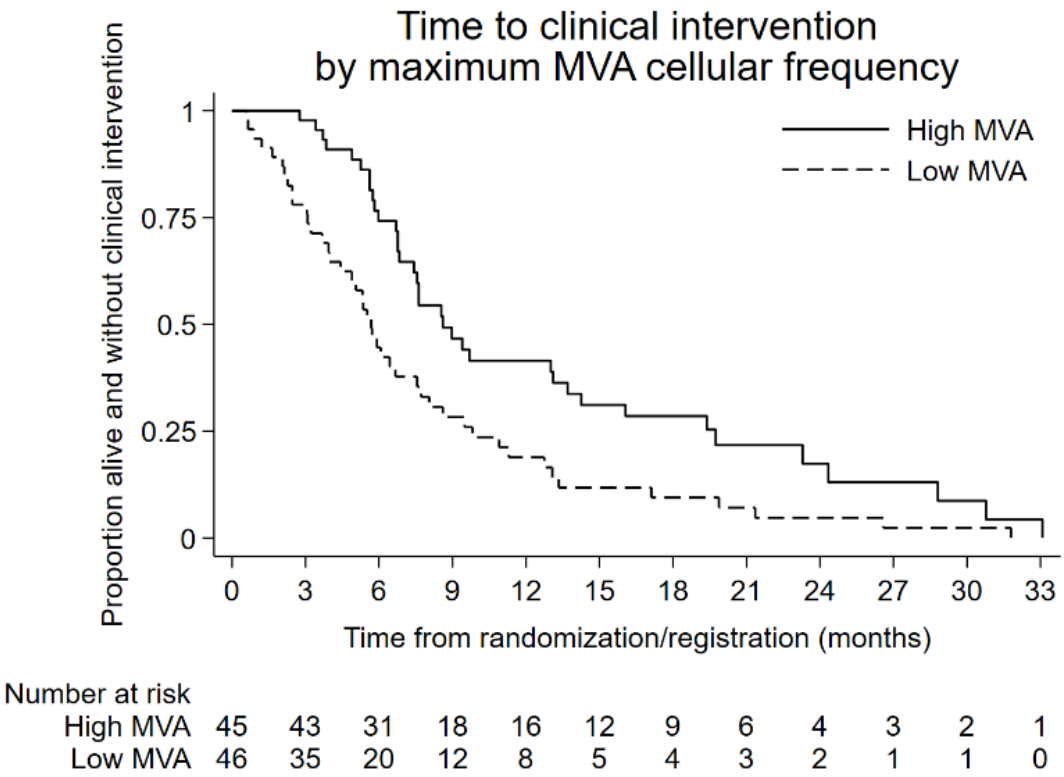


Table 1:

Baseline characteristics of eligible patients (N=94)

| Characteristic | MVA-5T4 (N=59) | Placebo (N=35) |
|---|---|---|

| | | |
|---|---|---|
| **Age, median years (range)** | 64 (42 - 82) | 66 (43 - 80) |
| **BMI, median kg/m^2 (range)** | 26.8 (14.8 - 45.4) | 28.2 (18.6 - 51.6) |
| **Time since completing platinum-based chemotherapy, median months (range)** | 17.8 (9.0 - 86.1) | 17.3 (7.3 - 53.2) |
| **ECOG, N (%)** | | |
| 1 | 7 (11.9%) | 3 (8.6%) |
| 0 | 52 (88.1%) | 32 (91.4%) |
| **Stage at original diagnosis, N (%)** | | |
| IIA | 1 (1.7%) | 1 (2.9%) |
| IIB | 1 (1.7%) | 1 (2.9%) |
| IIC | 2 (3.4%) | 0 |
| IIIA | 4 (6.8%) | 3 (8.6%) |
| IIIB | 6 (10.2%) | 1 (2.9%) |
| IIIC | 40 (67.8%) | 25 (71.4%) |
| IV | 2 (3.4%) | 4 (11.4%) |
| IV/IVA | 3 (5.1%) | 0 |
| **Histological subtype, N (%)** | | |
| Clear Cell | 2 (3.4%) | 3 (8.6%) |
| Endometrioid | 2 (3.4%) | 0 |
| High Grade Serous | 55 (93.2%) | 32 (91.4%) |
| **Measurable lesions by RECIST1.1, N (%)** | | |
| Yes | 41 (69.5%) | 20 (57.1%) |
| *Sum of longest diameter, median mm (range)* | *48.0 (9.0 - 112.6)* | *33.0 (15.0 - 68.8)* |
| No | 18 (30.5%) | 15 (42.9%) |

Society of Gynaecologic Oncology – FIGO ovarian cancer staging guidelines (effective 01 Feb 2014), <https://www.sgo.org/clinical-practice/guidelines/new-figo-ovarian-cancer-staging-guidelines/> accessed 18 March 2016

## Table 2:

## Clinical intervention at 25 weeks by treatment arm (N=90)

| Clinical intervention | MVA-5T4 | Placebo | P-value |
|---|---|---|---|
| **ITT (no trial suspensions)** | **N=46** | **N=35** | |
| Ascites or pleural drainage | 3 (6.5%) | 1 (2.9%) | |
| Surgery | 1 (2.2%) | 1 (2.9%) | |
| Chemotherapy | 13 (28.3%) | 15 (42.9%) | |
| Radiotherapy | 3 (6.5%) | 0 | |
| Biological therapy | 3 (6.5%) | 4 (11.4%) | |
| **Any clinical intervention** | **15 (32.6%)** | **18 (51.4%)** | **0.04** |
| **ITT (all patients)** | **N=55** | **N=35** | |
| Ascites or pleural drainage | 3 (5.5%) | 1 (2.9%) | |
| Surgery | 1 (1.8%) | 1 (2.9%) | |
| Chemotherapy | 14 (25.5%) | 15 (42.9%) | |
| Radiotherapy | 3 (5.5%) | 0 | |
| Biological therapy | 3 (5.5%) | 4 (11.4%) | |
| **Any clinical intervention** | **16 (29.1%)** | **18 (51.4%)** | **0.03** |
| **Per-protocol** | **N=34** | **N=22** | |
| Ascites or pleural drainage | 1 (2.9%) | 1 (4.5%) | |
| Surgery | 0 | 0 | |
| Chemotherapy | 7 (20.6%) | 8 (36.4%) | |
| Radiotherapy | 0 | 0 | |
| Biological therapy | 2 (5.9%) | 2 (9.1%) | |
| **Any clinical intervention** | **8 (23.5%)** | **10 (45.5%)** | **0.09** |

Note: 4 patients were lost to follow up before 25 weeks with no reported clinical intervention and so have been excluded from the above analysis.

# Additional Information:

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**Authors' contributions**

Agnieszka Michael -Chief Investigator for the study, overall study responsibility, study design and grant submission, oversight of recruitment, data analysis, manuscript writing,

William Wilson and Alan Hackshaw-statistical study design, data analysis , manuscript writing , data oversight

Sunny Sunshine, Nicola Annels and Hardev Pandha – immunological and translational analysis and writing support.

Richard Harrop, Daniel Blount-Oxford Biomedica study development support, immunological and translational analysis of samples

Rosemary Lord, Shibani Nicum, Stephen Gwyther, Ian McNeish-patient recruitment , study design support, data analysis support, manuscript writing support.

Yen Ngai-project manager, patients' recruitment oversight, study conduct support, data analysis support, manuscript writing support.

Jonathan Ledermann -overall study design and conduct oversight on behalf of the study sponsor

**Ethics approval and consent to participate :** Ethical (GTAC182) and Regulatory (CTA:2011-001836-44) approvals were obtained and all participants gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki

**Consent for publication**- All participants consented for publication of the results of the trial

**Data availability**- The data generated in this study are available within the article and its supplementary data files.

**Competing interests**: There are no conflict of interest to declare

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