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A study protocol for Adaptive ChemoTherapy for Ovarian cancer (ACTOv): A multicentre phase II randomised controlled trial to evaluate the efficacy of Adaptive Therapy (AT) with carboplatin, based on changes in CA125, in patients with relapsed platinum-sensitive high grade serous or high grade endometrioid ovarian cancer.

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Complete List of Authors:	Mukherjee, Uma; Cancer Research UK and UCL Cancer Trials Centre Hockings, Helen; St Bartholomew's Hospital, Counsell, Nicholas; Cancer Research UK and UCL Cancer Trials Centre Patel, Apini; University College London Hospitals NHS Foundation Trust, Narayanan, Priya; University College London Hospitals NHS Foundation Trust Wilkinson, Katie; University College London, CRUK & UCL Cancer Trials Unit Dhanda, Harjot; CR UK & UCL Cancer Trials Centre, Robinson, Kathy; Cancer Research UK and UCL Cancer Trials Centre McNeish, Iain; Imperial College London, Anderson, Alexander; Moffitt Cancer Center, Integrated Mathematical Oncology Miller, Rowan; University College London Hospitals NHS Foundation Trust; St Bartholomew's Hospital Gourley, Charlie; University of Edinburgh Western General Hospital, Institute of Genetics and Cancer Graham, Trevor; The Institute of Cancer Research, Lockley, Michelle; Queen Mary University of London Faculty of Medicine and Dentistry, Barts Cancer Institute; University College London Hospitals NHS Foundation Trust, Oncology
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A study protocol for Adaptive ChemoTherapy for Ovarian cancer (ACTOv): A multicentre phase II randomised controlled trial to evaluate the efficacy of Adaptive Therapy (AT) with carboplatin, based on changes in CA125, in patients with relapsed platinum-sensitive high grade serous or high grade endometrioid ovarian cancer.

Authors and affiliations:
U. Mukherjee,[1] H. Hockings,[2] N. Counsell,[1] A. Patel,[3] P. Narayanan,[3] K. Wilkinson,[1] H. Dhanda,[1] K. Robinson,[1] I. A. McNeish,[4] A. R. A. Anderson,[5] R. E.Miller,[1,2,3] C. Gourley,[6] T. A. Graham,[7] M. Lockley*[1,3,8]

1. University College London Cancer Trials Centre, London, UK
2. St Bartholomew's Hospital, London, UK
3. University College London Hospital, London, UK
4. Ovarian Cancer Action Research Centre, Department of Surgery and Cancer, Imperial College London, UK
5. Gynecologic Oncology Program, Moffitt Cancer Center, Tampa, FL, USA.
6. Cancer Research UK Scotland Centre, Institute of Genetics and Cancer, University of Edinburgh, UK
7. Centre for Evolution and Cancer, Institute of Cancer Research, London, UK
8. Centre for Cancer Genomics and Computational Biology, Barts Cancer Institute, Queen Mary University of London, London, UK

***Corresponding author:**
Professor Michelle Lockley
Centre for Cancer Genomics and Computational Biology
Barts Cancer Institute, Queen Mary University of London
John Vane Science Centre
Charterhouse Square, London, EC1M 6BQ

+44 (0)20 7882 3582 Email: m.lockley@qmul.ac.uk
https://www.bartscancer.london/staff/professor-michelle-lockley

Abstract:

Introduction: Adaptive ChemoTherapy in Ovarian cancer (ACTOv) is a phase II, multicentre, randomised controlled trial, evaluating an Adaptive Therapy (AT) regimen with carboplatin in women with relapsed, platinum-sensitive high grade serous or high grade endometrioid cancer of the ovary, fallopian tube and peritoneum whose disease has progressed at least 6 months after day 1 of the last cycle of platinum-based chemotherapy. AT is a novel, evolutionarily informed approach to cancer treatment, which aims to exploit intra-tumoral competition between drug-sensitive and drug-resistant tumour subpopulations by modulating drug dose according to a patient's own response to the last round of treatment. ACTOv is the first clinical trial of AT in this disease setting.

Methods and analysis: 80 patients will be randomised 1:1 to standard therapy (control) or AT (investigational) arms. The starting and maximum carboplatin dose in both arms is Area Under the Curve x 5 according to absolute nuclear medicine Glomerular Filtration Rate. The AT regimen will modify carboplatin dose according to changes in the serum biomarker CA125, a proxy measure of total tumour burden. Patients will receive treatment intravenously every 21 days for a maximum of 6 and 12 cycles in the control and investigational arms respectively. The primary endpoint is modified progression-free survival (investigator-assessed using RECIST v1.1 compared to the baseline rather than radiological nadir), clinical progression, or death from any cause and secondary endpoints will include acceptability, deliverability, compliance, toxicity, CA125 measurements, quality of life and overall survival. ACTOv is open to National Health Service hospitals throughout the United Kingdom, recruitment is anticipated to take 36 months across 10 sites and will be managed by the Cancer Research UK & University College London Cancer Trials Centre.

Ethics and dissemination: The trial has been reviewed and received approval from the London – Dulwich Research Ethics Committee (REC). Results of the trial will be disseminated through publication in peer-reviewed journals.

Trial registration: ClinicalTrials.gov: NCT05080556

Strengths and limitations of the study

- ACTOv is the first clinical trial exploring Adaptive Therapy in ovarian cancer and with carboplatin. AT could potentially be beneficial in multiple cancer types for patients receiving diverse, systemic anticancer therapies.
- ACTOv is an inclusive clinical trial that does not specify the number of prior chemotherapy regimens and will enrol patients with ECOG (Eastern Cooperative Oncology Group) performance status 0-2. ACTOv patients will therefore be representative of real world practice.
- RECIST v1.1 (Response Evaluation Criteria in Solid Cancers) defines disease progression by comparison with radiological nadir. AT responds to an increase in disease burden by increasing drug dose, thus RECIST v1.1 could result in AT being discontinued early and a potential benefit of AT being underestimated. ACTOv addresses this by comparing with the baseline CT to define the primary endpoint of modified Progression Free Survival.
- Since ACTOv is the UK's first experience testing AT, multiple secondary endpoints will assess acceptability to patients and applicability to a socialized healthcare setting. These include: acceptability (patients approached who accept randomisation); deliverability (treatment cycles delivered as per protocol); Quality of Life including: EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30, QLQ-OV28, EQ-5D) and the Fear of Progression index (FOP-Q SF).
- The evolutionary dynamics of carboplatin resistance will be interrogated in longitudinal blood and biopsy samples. This high frequency sampling and downstream biological analysis will provide insights into the mechanistic basis of AT to facilitate 2nd generation clinical trials.

Introduction

Ovarian cancer is the leading cause of gynaecological-related mortality with approximately 7,000 new cases and 4,000 deaths in the UK each year.[1] High grade serous ovarian carcinoma is the most common pathological subtype accounting for approximately 70% of cases, whilst high grade endometrioid ovarian carcinoma exhibits comparable clinical behaviour and accounts for another 10%.[2] For the purposes of the ACTOv trial they will be considered together and collectively termed high grade ovarian carcinoma (HGOC). Despite favourable responses to primary treatment with cytoreductive surgery, carboplatin and paclitaxel chemotherapy, followed by maintenance bevacizumab and poly ADP ribose polymerase (PARP) inhibitors for certain patients,[3] more than 80% of women will experience disease relapse,[4] which is currently incurable.

When relapse occurs more than 6 months after the most recent course of platinum chemotherapy, it is referred to as 'platinum-sensitive' and is treated with repeated administration of platinum-containing chemotherapy at each subsequent relapse, regardless of the number of prior chemotherapy treatments.[3],[5] Combination chemotherapy is often used based on clinical trials that demonstrated small survival advantages for women in first platinum-sensitive relapse. For example, carboplatin and paclitaxel increased progression-free survival (PFS) by 3 months and 2-year overall survival (OS) by 7% compared to other platinum-containing regimens,[6] while the combination of carboplatin and Caelyx (pegylated liposomal doxorubicin) further extended PFS compared to carboplatin and paclitaxel (11.3 vs 9.4 months respectively)[7] but with no increase in overall survival (OS).[8] There is no randomised evidence to support the use of combination chemotherapy in second or later relapse[9] and single agent carboplatin may be administered at a dose of AUC5 (area under the curve x 5) every 21 days for up to six cycles. This has the advantage of minimising treatment-related toxicities, particularly in heavily pre-treated patients.[10] The disease course is characterised by diminishing chemotherapy effectiveness at each successive treatment[5] and median survival for recurrent platinum-sensitive ovarian cancer is approximately 3 years.[11] Ultimately, nearly all women with relapsed ovarian cancer will die with platinum-resistant disease and new therapeutic strategies are urgently needed.

The traditional ethos of using maximum tolerated dose chemotherapy to kill the greatest number of cancer cells strongly selects for drug-resistant sub-clones.[12, 13] Thus, when cancers relapse, repeated treatment with the same therapy is less effective.[14] This situation is exemplified by HGOC in which repeated administration of platinum chemotherapy inevitably leads to the emergence of resistant cancer cells, followed by treatment failure.[15] The evolution of resistance is often energetically costly to cancer cells, rendering resistant cells less fit than sensitive cells when therapy

is absent.[16] In cancer this means that whilst a resistance adaptation may confer a fitness advantage during drug exposure, [17],[18] resistant population growth may conversely be restricted when fitter, sensitive cells remain within the tumour.[19],[20] Fitness costs associated with drug resistance have been demonstrated both in pre-clinical models and in patients, including those treated with BRAF-targeted therapy in melanoma,[21] doxorubicin in breast cancer[19] and epidermal growth factor receptor (EGFR) blockade in metastatic colorectal cancer.[22] In ovarian cancer, preliminary data derived from a novel panel of matched platinum-sensitive and resistant HGOC models showed that sensitive cells were fitter in the absence of drug and were able to outgrow resistant cells in *in vitro* and *in vivo* co-cultures.[23]

Adaptive Therapy (AT) is an evolutionarily informed treatment paradigm, which aims to exploit the intra-tumoral competition for resources between drug-sensitive and drug-resistant tumour cell subpopulations.[24],[25] By prescribing dose reductions (dose modulation) and 'drug holidays' (dose skipping), AT allows drug sensitive cancer cells to grow and competitively suppress drug-resistant cells, thereby re-sensitising the tumour for the next round of treatment.[13],[17],[26],[21] AT primarily aims to maintain drug-sensitive subclones, that ideally remain the dominant population within a tumour, such that currently available drugs may be effective for longer, potentially prolonging tumour control and extending survival (Figure 1). This novel approach acknowledges that, within the palliative setting, the aim is to prolong time to progression rather than to cure.[27]

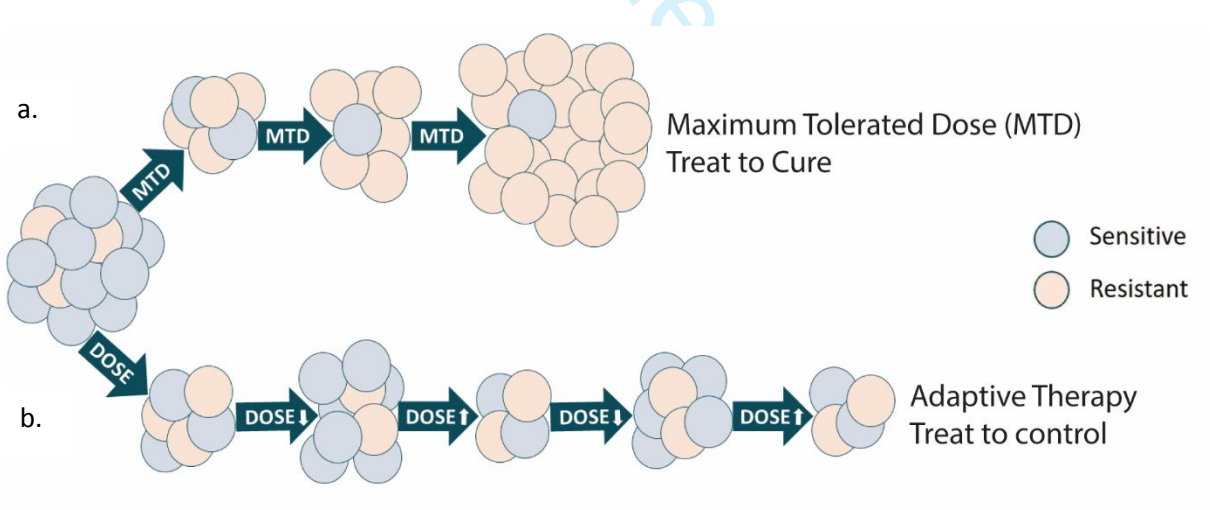

Figure 1 (a) Maximum tolerated dose (MTD) kills drug-sensitive cells allowing preferential proliferation of the remaining drug-resistant cells. (b) Adaptive Therapy (AT): Dose reductions following treatment response allow sensitive cells to proliferate and repopulate the tumour, maintaining drug sensitivity and thus tumour control over the long term.

It has been postulated that AT may modulate the tumour microenvironment by inhibiting angiogenesis, increasing tumour antigenicity and intra-tumoral immune responses, analogous to metronomic therapy.[17, 28-30] However, in contrast to the fixed periodic scheduling of metronomic chemotherapy,[31] AT makes treatment decisions based on response to the previous round of therapy (e.g. tumour shrinkage or growth), and ideally evolutionary dynamics (e.g. fractions of sensitive and resistant cells).

AT has been studied pre-clinically in breast cancer,[32],[33] colorectal cancer[34] and melanoma,[35],[36],[21] where it has been shown to stabilise tumour volume and in some cases, prolong PFS.[32, 35] Dose modulation and dose skipping AT have been used in different models with differing effects.[19, 32, 34, 37] *In silico* modelling demonstrated that drug holidays worked better in tumours which drifted towards a more resistant phenotype, whilst dose modulation controlled tumours with less drug if the initial tumour had a moderate degree of drug sensitivity.[19] Conversely, in murine breast cancer xenografts, dose modulation controlled tumour growth for longer than dose skipping in both aggressive and less aggressive tumour models.[32] In murine HGOC xenografts, carboplatin dose modulation AT significantly improved survival compared to standard dosing and maintained tumour size at baseline for at least 20 weeks.[23] Furthermore, dose modulation AT using the PARP inhibitor Olaparib achieved comparable tumour control to standard continuous therapy in murine HGOC xenografts and simulated patients but with significantly reduced cumulative drug dose.[37]

Clinically, dose skipping AT with androgen deprivation therapy has been used successfully to treat men with castration resistant prostate cancer resulting in an increase in time to progression compared to standard daily dosing.[38] The same treatment approach of adaptive abiraterone treatment based on prostate specific antigen (PSA) levels has been taken forward in the larger randomised ANZadapt study.[39] Other AT clinical trials currently open to recruitment include those investigating personalised scheduling of vismodegib based on *in silico* tumour modelling in advanced basal cell carcinoma,[40] adaptive chemotherapy based on radiological response in rhabdomyosarcoma[41] and BRAF-targeted therapy in melanoma based on ctDNA levels,[42] or on LDH levels and imaging [43].

ACTOv is a proof-of-concept trial exploring the use of dose modulation AT in patients with relapsed HGOC. Patients will be treated with 3-weekly carboplatin either at a fixed dose (AUC5) as per current standard of care (control arm) or according to an AT regimen (investigational arm). The AT regimen will modify carboplatin dose in each cycle according to real time changes in each patient's serum CA125, which is a reliable surrogate measure of total tumour burden and an established marker of

disease response and progression in ovarian cancer.[44] ACTOv will assess whether AT with carboplatin can prolong disease control compared to standard carboplatin dosing. Research blood and biopsy samples will be collected longitudinally from all patients to interrogate the evolutionary dynamics that underpin carboplatin response in circulating tumour DNA (ctDNA). These unique data will be correlated with drug dose and treatment response to optimise future AT regimens.

Methods

Trial design

ACTOv is a multicentre, phase II randomised controlled trial that will recruit women with platinum-sensitive relapsed HGOC whose disease has progressed at least 6 months after day 1 of the last cycle of platinum-based chemotherapy. Patients will be randomised in a 1:1 allocation ratio between the control arm (Arm 1, Standard dosing) and investigational arm (Arm 2, Adaptive Therapy, Carboplatin dose as per **Table 1**). Treatment will be administered intravenously (IV) every 21 days for a maximum of 6 and 12 cycles in the control and investigational arms respectively. A feasibility assessment will be conducted after the first 20 patients have been randomised to ensure that the overall trial objectives are achievable.

Participants

Participants entering ACTOv must satisfy the eligibility criteria summarised in **Table 2**.

Key inclusion criteria	Key exclusion criteria
1. Female, aged ≥18	1. Non-epithelial ovarian cancer, carcinosarcoma, low-grade serous and endometrioid carcinomas, mucinous & clear-cell carcinomas
2. ECOG performance status 0-2	2. Requiring treatment with combination chemotherapy regimens
3. Histologically proven diagnosis of high grade serous or high grade endometrioid carcinoma of the ovary, fallopian tube or peritoneum	3. Known hypersensitivity to carboplatin
4. Most recent regimen must have included platinum (cisplatin or carboplatin)	4. Persisting ≥ grade 2 Common Terminology Criteria for Adverse Events (CTCAE) version 5adverse events/toxicity (except alopecia and neuropathy) from previous anti-cancer treatment
5. Previous treatment with PARP inhibitor (except for patients with contraindication to PARP inhibitor treatment)	5. Treatment with any other investigational agent, or participation in another interventional clinical trial within 28 days prior to randomisation
6. Response by CT or MRI or by Gynecologic Cancer InterGroup (GCIG) CA125 response criteria to most recent platinum treatment	6. Major surgery within 14 days before anticipated start of treatment.

7. Pre-trial CT or MRI-confirmed disease progression ≥ 6 months after day 1 of the last cycle of platinum-containing chemotherapy	7. Has a disease or condition that contraindicates the use of an investigation drug or puts the patients at high risk for treatment-related complications
8. Measurable disease by RECIST v1.1 on a CT scan conducted within 28 days prior to randomisation (If non-measurable disease could be eligible if they meet GCIG CA125 progression criteria)	8. Malignancy treated within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS) of the breast, Stage 1, grade 1 endometrial carcinoma
9. CA125 ≥ 100iU/l at screening	9. Patients with symptomatic uncontrolled brain or meningeal metastases.
10. Expected to commence treatment within 7 days post randomisation	10. Patients with spinal cord compression unless considered to have received definitive treatment for this and with clinically stable disease.
11. Adequate bone marrow, liver and renal function	11. Pregnant or breast-feeding women and women of childbearing potential (unless effective methods of contraception are used from informed consent, throughout the study treatment and for at least 6 months after last dose of trial drug(s)).
12. Negative pregnancy test at screening and prior to trial treatment and willing to use highly effective contraception during and for six months after last dose of trial drug	12. Inability to attend or comply with treatment or follow-up scheduling
13. Informed consent and compliant with treatment and follow up.	

Table 2: Eligibility Criteria for the ACTOv trial.

Trial Treatments

Carboplatin dose in both arms will be determined by absolute nuclear medicine Glomerular Filtration Rate (NM GFR), rather than calculated renal clearance. This will be measured prior to the first cycle of carboplatin. The starting carboplatin dose and also the maximum carboplatin dose in both arms is AUC5 based on absolute NM GFR.

Patients in both arms will provide CA125 and research bloods up to 72 hours before every planned chemotherapy treatment including the first cycle. Patients in Arm 1 (standard dosing) will receive six cycles at the same dose of AUCx5. The AT regimen (Arm 2) will modify carboplatin dose according to changes in the serum biomarker CA125, indicating that patient's own tumour response to the last round of chemotherapy (**Table 1**). Briefly, when CA125 declines by >25%, the dose will be reduced by one AUC at the next cycle. Each fall in CA125 (>25%) will continue to trigger additional, further dose reductions at the subsequent treatment and carboplatin may even be omitted entirely following a

very good CA125 response (decrease in CA125 to ≤10% baseline or to ≤upper limit of normal (ULN)).[45] If CA125 increases by >25%, the dose at the next treatment cycle will be increased by one AUC until AUC5 is reached. If the CA125 continues to increase in subsequent cycles, patients will continue to receive the same dose of AUC5 unless they undergo clinical deterioration or the next scheduled CT scan (either as mandated or to investigate clinical deterioration) demonstrates protocol defined disease progression. The AT regimen outlined in **Table 1**, is derived from the regimen used in preliminary animal experiments, which demonstrated a significant improvement in survival.[23] This regimen has subsequently been adapted for patients. In the pre-clinical AT regimen, a 20% change in tumour volume triggered a 50% modification to the carboplatin dose,[23] whereas in ACTOv, in order to avoid potential harm due to under-dosing, the dose will be modified by 20% (1 x AUC) in response to a 25% change in CA125. In-house clinical databases of CA125 responses in patients receiving single agent carboplatin chemotherapy (courtesy of Prof Charlie Gourley) were used to confirm that CA125 changes of this magnitude would be achievable and relevant.

Investigational arm: Adaptive Therapy (3 weekly carboplatin)	
Starting dose & max dose	**AUC5 (based on NM GFR)**
≤25% change in CA125	Repeat same dose
>25% decrease in CA125, but not reaching ≤10% baseline or ≤ ULN (compared to start of preceding cycle)	Decrease dose by 1 AUC
>25% increase in CA125 (compared to start of preceding cycle)	Increase dose by 1 AUC (Max AUC 5)
CA125 decrease to ≤10% baseline or to ≤ ULN	Omit dose and repeat CA125 in 3 weeks
Restarting treatment after dose omission	AUC2

Table 1: Adaptive Therapy dosing schedule in the investigational arm (Arm 2).

In both arms, absolute NM GFR will be re-measured if the patient experiences ≥ 20% change in serum creatinine indicating renal toxicity during subsequent cycles. Haematological toxicities will be managed with GCSF and blood product support and, if necessary, treatment delay. Dose reductions are not permitted in Arm 2 (AT) but may be used in Arm 1 (dose reduction level -1 = AUC4 and level -2 = AUC3.5) if other measures have failed.

Treatment will be continued until there is unacceptable toxicity, radiological progression or clinical deterioration due to the underlying cancer up to a maximum of 6 and 12 cycles in the control and investigational arms respectively. Progression will be defined either radiologically or clinically and not

by serum CA125. CA125 increase is expected with AT and might indicate that the carboplatin dose should be increased according to **Table 1**. Asymptomatic progression during trial treatment and surveillance (i.e. up to week 46) will be detected by one of the mandated trial CT scans of chest, abdomen and pelvis at weeks 9, 19, 31, 43 and 55 (+/- 7 days at each visit) (**Figure 2**).

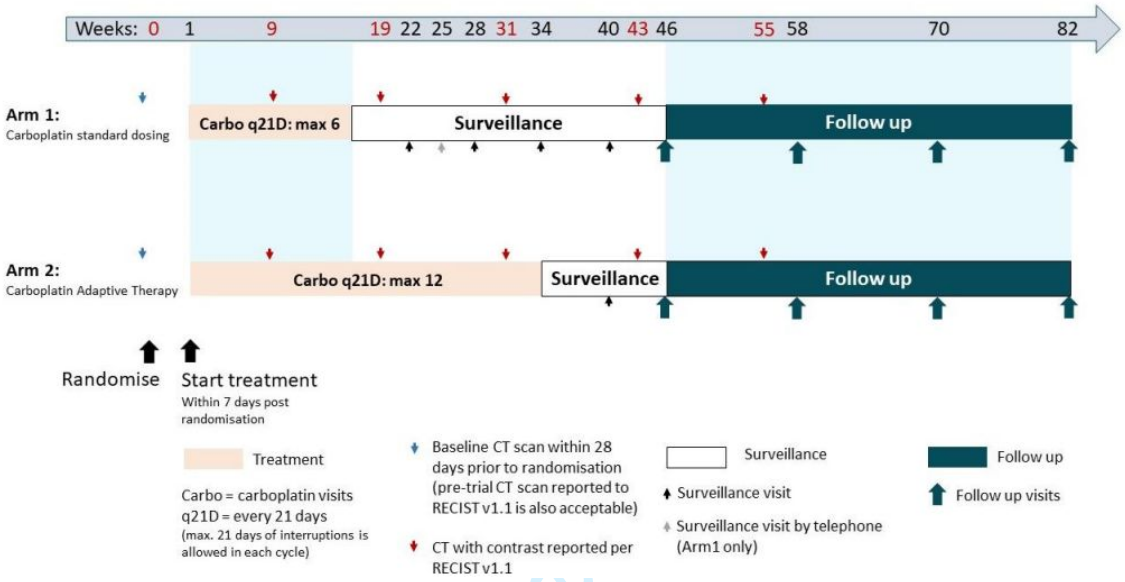

Figure 2 Schematic of protocol defined visits

Tumour assessment

All CT scans in ACTOv will be reported to RECIST v1.1. RECIST v1.1 defines radiological response as a ≥30% reduction in tumour volume compared to the baseline CT scan, while disease progression is defined as a ≥20% increase compared to the radiological nadir.[46] AT is predicted to cause fluctuations in disease burden over time and aims to control these changes by modulating drug dose. Thus, defining disease progression by comparison with the nadir CT could result in AT being stopped prematurely and any potential benefit from AT being underestimated. ACTOv has addressed this by mandating that all CT scans will be compared to both the baseline trial CT and the radiological nadir CT. Treatment in both arms may continue in cases where there is RECIST-defined radiological progression compared to the radiological nadir and radiological progression will only be defined by comparison with the baseline CT. Progression in ACTOv may also be defined clinically and in addition, investigators have the option of discontinuing trial treatment at any time for clinical reasons.

Endpoints

Primary endpoint: modified progression-free survival (mPFS), which is defined as the time from date of randomisation to either: (i) Protocol defined radiological progression measured by RECIST v1.1, compared to the baseline trial CT and not the radiological nadir; (ii) Clinical deterioration, defined at the discretion of the treating clinician, specifically due to the underlying cancer but in the absence of protocol defined radiological progression; (iii) Death from any cause in the absence of disease progression.

Analysis of the primary endpoint will be on an intention-to-treat basis for all eligible patients, with patients censored at their date last seen if no event is observed.

Secondary endpoints: (i) acceptability (patients approached who accept randomisation); (ii) deliverability (treatment cycles delivered as per protocol); (iii) compliance (cumulative carboplatin dose); (iv) toxicity (adverse events categorised by CTCAE v5.0);[47] (v) Quality of Life measured using EORTC questionnaires: [48] QLQ-C30 (suitable for all cancer types), QLQ-OV28 (ovarian cycle specific), EQ-5D (descriptive profile of health state: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, a single summary index and a visual analogue scale); (vi) Fear of Progression (FOP-Q SF); [49] (vii) CA125 measurements; (viii) further treatment upon progression; (ix) overall survival.

Acceptability and deliverability are both important factors in determining the feasibility of the novel AT approach and will provide key data to support future AT trials. Given that ACTOV is the first AT trial using intravenous chemotherapy with dose modifications based on concurrent measurements of disease burden (CA125), deliverability will be the principle indicator of the practicality of AT for both prescribers and dispensing pharmacy units. Cumulative carboplatin dose is included as a secondary endpoint because this is expected to be different between the two arms and could influence disease response and treatment-related toxicity. Quality of life and fear of progression indices will clarify the impact of variations to dose and schedule on patients.

Exploratory biological studies: Research blood samples will be collected from all patients at baseline, 3-weekly during treatment, 6-weekly during surveillance and at 12-weekly follow-up visits. Research biopsies are optional from all patients at baseline and will also be requested if appropriate at the end of treatment and again at disease relapse. Cell-free DNA (cfDNA) will be extracted from patient blood and tumour DNA extracted from biopsies for downstream analysis aimed at quantifying the impact of drug dosing regimens on the evolution of carboplatin-resistance.

Sample size

A total sample size of N=80 is required to detect an improvement in median mPFS from 5 months in the control arm to 7.5 months with AT, representing a hazard ratio (HR) of 0.667, with 80% power at the one-sided 20% significance level. This assumes a 3-year recruitment period, 1 year of additional follow-up from the last patient randomised and a drop-out rate of up to 10% per year. Eligible patients will be randomised equally between the two trial arms using minimisation and stratified by the number of prior lines of chemotherapy (1, 2 or ≥ 3), length of platinum-free interval (6 to 12 months or >12 months), and BRCA status (positive [pathological mutation only], wild type [including variants of unknown significance] or unknown).

Patient and Public Involvement:

The ACTOv trial protocol was developed in close consultation with our local Patient Involvement Advisory Group (PIAG) at Barts Cancer Institute (BCI), London, UK. This resulted in the proposed treatment schedule in which all patients will attend three-weekly for pre-treatment blood tests including CA125, prior to consultation with their clinical team as per standard of care (SOC). AT dose will be varied according to CA125 and in some cases may be omitted altogether. Ovarian cancer patients are accustomed to dose omissions during weekly chemotherapy, usually after a prior blood test showing low blood counts, and so the PIAG felt that this felt this would be familiar and acceptable to patients and would allow patients to plan around regular three-weekly visits. Treatment will continue until progressive disease or toxicity for a maximum of 6 cycles in the standard treatment arm or 12 cycles (9 months) in the AT arm. The BCI PIAG was satisfied with this longer duration of AT since long-term, three-weekly IV maintenance bevacizumab is an established SOC. We have also benefited from patient involvement via the UK Gynae Trials Group and a dedicated patient representative is a member of our Trial Management Group. She has led development of our Patient Information Sheet and Consent Form and plays a key role in disseminating information regarding the trial through patient and public forums and other communication channels.

Ethics and dissemination:

The trial has received favorable ethical approval from the London – Dulwich Research Ethics Committee (REC), reference number 22/LO/0543, with three amendments between 2021 and 2024. The current protocol version is v4.0, dated 05 Jan 2024.

The results from this trial will be submitted for publication through peer-reviewed journals, and the key findings will be presented at national and international conferences. All publications and presentations relating to the trial will be authorised by the Trial Management Group (TMG). The first

publication of the trial results will be in the name of the TMG on behalf of the trial participants. The writing committee will be formed by contributing members of the TMG. Contributing site Principal Investigators (PIs) will be added as co-authors. Trial participants and funders will be acknowledged in all publications.

Summary

ACTOv is a phase II randomised controlled trial to investigate the efficacy of AT in patients with relapsed platinum-sensitive high grade serous or high grade endometrioid cancer of the ovary, fallopian tube and peritoneum. The trial opened to recruitment on 10 March 2023 and the first patient was randomised on 24 May 2023. It is anticipated that the required 80 randomised patients will take 3 years to recruit across 10 UK centres. The primary endpoint is modified PFS and secondary endpoints include acceptability, deliverability, compliance and safety, quality of life, fear of progression, further treatments and OS. Exploratory translational studies will look at ctDNA collected at different timepoints to measure how resistant and sensitive cell populations grow and shrink during therapy and to see whether this correlates with standard clinical measures of disease response including changes in CA125 and radiological disease burden measured by RECIST v1.1. The aim is to see whether AT can achieve significant patient benefit by prolonging drug-sensitivity and extending tumour control, and to optimise AT regimens for future clinical testing.

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Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Trial status: The trial is currently open to recruitment.

Authors' contributions: UM, HH, NC and ML: original draft of the manuscript; HH, NC, AP, PN, IM, ARAA, RM, CG, TG, ML study conception, design and methodology; NC statistics; KW, HD: Project management and data collection; KR: patient representative; All authors revised, edited and approved the final version of the protocol paper.

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A study protocol for Adaptive ChemoTherapy for Ovarian cancer (ACTOv): A multicentre phase II randomised controlled trial to evaluate the efficacy of Adaptive Therapy (AT) with carboplatin, based on changes in CA125, in patients with relapsed platinum-sensitive high grade serous or high grade endometrioid ovarian cancer.

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A study protocol for Adaptive ChemoTherapy for Ovarian cancer (ACTOv): A multicentre phase II randomised controlled trial to evaluate the efficacy of Adaptive Therapy (AT) with carboplatin, based on changes in CA125, in patients with relapsed platinum-sensitive high grade serous or high grade endometrioid ovarian cancer.

Authors and affiliations:

U. Mukherjee,[1] H. Hockings,[2] N. Counsell,[1] A. Patel,[3] P. Narayanan,[3] K. Wilkinson,[1] H. Dhanda,[1] K. Robinson,[1] I. A. McNeish,[4] A. R. A. Anderson,[5] R. E. Miller,[1,2,3] C. Gourley,[6] T. A. Graham,[7] M. Lockley*[1,3,8]

1. Cancer Research UK and University College London Cancer Trials Centre, London, UK
2. St Bartholomew's Hospital, London, UK
3. University College London Hospital, London, UK
4. Ovarian Cancer Action Research Centre, Department of Surgery and Cancer, Imperial College London, UK
5. Gynecologic Oncology Program, Moffitt Cancer Center, Tampa, FL, USA.
6. Cancer Research UK Scotland Centre, Institute of Genetics and Cancer, University of Edinburgh, UK
7. Centre for Evolution and Cancer, Institute of Cancer Research, London, UK
8. Centre for Cancer Genomics and Computational Biology, Barts Cancer Institute, Queen Mary University of London, London, UK

***Corresponding author:**

Professor Michelle Lockley
Centre for Cancer Genomics and Computational Biology
Barts Cancer Institute, Queen Mary University of London
John Vane Science Centre
Charterhouse Square, London, EC1M 6BQ

+44 (0)20 7882 3582 Email: m.lockley@qmul.ac.uk
https://www.bartscancer.london/staff/professor-michelle-lockley

Abstract:

Introduction: Adaptive ChemoTherapy in Ovarian cancer (ACTOv) is a phase II, multicentre, randomised controlled trial, evaluating an Adaptive Therapy (AT) regimen with carboplatin in women with relapsed, platinum-sensitive high grade serous or high grade endometrioid cancer of the ovary, fallopian tube and peritoneum whose disease has progressed at least 6 months after day 1 of the last cycle of platinum-based chemotherapy. AT is a novel, evolutionarily informed approach to cancer treatment, which aims to exploit intra-tumoral competition between drug-sensitive and drug-resistant tumour subpopulations by modulating drug dose according to a patient's own response to the last round of treatment. ACTOv is the first clinical trial of AT in this disease setting.

Methods and analysis: 80 patients will be randomised 1:1 to standard therapy (control) or AT (investigational) arms. The starting and maximum carboplatin dose in both arms is Area Under the Curve (AUC) x 5 according to absolute nuclear medicine Glomerular Filtration Rate. The AT regimen will modify carboplatin dose according to changes in the serum biomarker CA125, a proxy measure of total tumour burden. Patients will receive treatment intravenously every 21 days for a maximum of 6 and 12 cycles in the control and investigational arms respectively. The primary endpoint is modified progression-free survival (investigator-assessed using RECIST v1.1 compared to the baseline pre-randomisation scan rather than to the radiological nadir), clinical progression, or death from any cause. Secondary endpoints will include acceptability, deliverability, compliance, toxicity, CA125, quality of life and overall survival. ACTOv is open to National Health Service hospitals throughout the United Kingdom, recruitment is anticipated to take 36 months across 10 sites and will be managed by the Cancer Research UK & University College London Cancer Trials Centre.

Ethics and dissemination: The trial has been reviewed and received approval from the London – Dulwich Research Ethics Committee (REC). Results of the trial will be disseminated through publication in peer-reviewed journals.

Trial registration: ClinicalTrials.gov: NCT05080556

Strengths and limitations of the study

- ACTOv is the first clinical trial exploring Adaptive Therapy in ovarian cancer and with carboplatin. AT could potentially be beneficial in multiple cancer types for patients receiving diverse, systemic anticancer therapies.
- ACTOv is an inclusive clinical trial that does not specify the number of prior chemotherapy regimens and will enrol patients with ECOG (Eastern Cooperative Oncology Group) performance status 0-2. ACTOv patients will therefore be representative of real-world practice.
- RECIST v1.1 (Response Evaluation Criteria in Solid Cancers) defines disease progression by comparison with radiological nadir. AT responds to an increase in disease burden by increasing drug dose, thus RECIST v1.1 could result in AT being discontinued early and a potential benefit of AT being underestimated. ACTOv addresses this by comparing with the baseline CT to define the primary endpoint of modified Progression Free Survival. This application of RECIST v1.1 is a potential limitation as it will prevent direct comparison with existing literature.
- Patients in Arm 1 (Standard Therapy) will all receive a maximum of 6 cycles of carboplatin AUC5. In contrast, those in Arm 2 (Adaptive Therapy) will continue for a maximum of 12 cycles and the dose is expected to differ between cycles and between patients. Thus, a potential limitation is that any improvement in progression-free survival in either arm could be due to an increased cumulative carboplatin dose. Conversely, a higher cumulative carboplatin dose could be detrimental by increasing treatment-related toxicity and diminishing future platinum sensitivity. ACTOv will resolve these factors by secondary endpoints that will measure cumulative drug dose, toxicity and further treatment upon progression.
- Since ACTOv is the UK's first experience testing AT, a lack of familiarity with this approach could limit recruitment. Multiple secondary endpoints will assess this including: acceptability (patients approached who accept randomisation); deliverability (treatment cycles delivered as per protocol); Quality of Life including: EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30, QLQ-OV28, EQ-5D) and the Fear of Progression index (FOP-Q SF).

Introduction

Ovarian cancer treatment

Ovarian cancer is the leading cause of gynaecological-related mortality with approximately 7,000 new cases and 4,000 deaths in the UK each year.[1] High grade serous ovarian carcinoma is the most common pathological subtype accounting for approximately 70% of cases, whilst high grade endometrioid ovarian carcinoma exhibits comparable clinical behaviour and accounts for another 10%.[2] For the purposes of the ACTOv trial they will be considered together and collectively termed high grade ovarian carcinoma (HGOC). Despite favourable responses to primary treatment with cytoreductive surgery, carboplatin and paclitaxel chemotherapy, followed by maintenance bevacizumab and poly ADP ribose polymerase (PARP) inhibitors for certain patients,[3] more than 80% of women will experience disease relapse,[4] which is currently incurable.

When relapse occurs more than 6 months after the most recent course of platinum chemotherapy, it is referred to as 'platinum-sensitive' and is treated with repeated administration of platinum-containing chemotherapy at each subsequent relapse, regardless of the number of prior chemotherapy treatments.[3,5] Combination chemotherapy is often used based on clinical trials that demonstrated small survival advantages for women in first platinum-sensitive relapse. For example, carboplatin and paclitaxel increased progression-free survival (PFS) by 3 months and 2-year overall survival (OS) by 7% compared to other platinum-containing regimens,[6] while the combination of carboplatin and Caelyx (pegylated liposomal doxorubicin) further extended PFS compared to carboplatin and paclitaxel (11.3 vs 9.4 months respectively)[7] but with no increase in OS.[8] There is no randomised evidence to support the use of combination chemotherapy in second or later relapse[9] and single agent carboplatin may be administered at a dose of AUC5 every 21 days for up to six cycles. This has the advantage of minimising treatment-related toxicities, particularly in heavily pre-treated patients.[10] The disease course is characterised by diminishing chemotherapy effectiveness at each successive treatment[5] and median survival for recurrent platinum-sensitive ovarian cancer is approximately 3 years.[11] Ultimately, nearly all women with relapsed ovarian cancer will die with platinum-resistant disease and new therapeutic strategies are urgently needed.

Adaptive Therapy

The traditional ethos of using maximum tolerated dose (MTD) chemotherapy to kill the greatest number of cancer cells strongly selects for drug-resistant sub-clones.[12 13] Thus, when cancers relapse, repeated treatment with the same therapy is less effective.[14] This situation is exemplified by HGOC in which repeated administration of platinum chemotherapy inevitably leads to the emergence of resistant cancer cells, followed by treatment failure.[15] The evolution of resistance is often

energetically costly to cancer cells, rendering resistant cells less fit than sensitive cells when therapy is absent.[16] In cancer this means that while a resistance adaptation may confer a fitness advantage during drug exposure, [17,18] resistant population growth may conversely be restricted when fitter, sensitive cells remain within the tumour.[19,20] Fitness costs associated with drug resistance have been demonstrated both in pre-clinical models and in patients, including those treated with BRAF-targeted therapy in melanoma,[21] doxorubicin in breast cancer[19] and epidermal growth factor receptor (EGFR) blockade in metastatic colorectal cancer.[22] In ovarian cancer, preliminary data derived from a novel panel of matched platinum-sensitive and resistant HGOC models showed that sensitive cells were fitter in the absence of drug and were able to outgrow resistant cells in *in vitro* and *in vivo* co-cultures.[23]

Adaptive Therapy (AT) is an evolutionarily informed treatment paradigm, which aims to exploit the intra-tumoral competition for resources between drug-sensitive and drug-resistant tumour cell subpopulations.[24,25] By prescribing dose reductions (dose modulation) and 'drug holidays' (dose skipping), AT allows drug sensitive cancer cells to grow and competitively suppress drug-resistant cells, thereby re-sensitising the tumour for the next round of treatment.[13,17,26,21] AT primarily aims to maintain drug-sensitive subclones, that ideally remain the dominant population within a tumour, such that currently available drugs may be effective for longer, potentially prolonging tumour control and extending survival (Figure 1). This novel approach acknowledges that, within the palliative setting, the aim is to prolong time to progression rather than to cure.[27]

It has been postulated that AT may modulate the tumour microenvironment by inhibiting angiogenesis, increasing tumour antigenicity and intra-tumoral immune responses, analogous to metronomic therapy.[17 28-30] However, in contrast to the fixed periodic scheduling of metronomic chemotherapy,[31] AT makes treatment decisions based on response to the previous round of therapy (e.g. tumour shrinkage or growth), and ideally evolutionary dynamics (e.g. fractions of sensitive and resistant cells).

AT has been studied pre-clinically in breast cancer,[32,33] colorectal cancer[34] and melanoma,[35,36,21] where it has been shown to stabilise tumour volume and in some cases, prolong PFS.[32 35] Dose modulation and dose skipping AT have been used in different models with differing effects.[19 32 34 37] *In silico* modelling demonstrated that drug holidays worked better in tumours which drifted towards a more resistant phenotype, whilst dose modulation controlled tumours with less drug if the initial tumour had a moderate degree of drug sensitivity.[19] Conversely, in murine breast cancer xenografts, dose modulation controlled tumour growth for longer than dose skipping in both aggressive and less

aggressive tumour models.[32] In murine HGOC xenografts, carboplatin dose modulation AT significantly improved survival compared to standard dosing and maintained tumour size at baseline for at least 20 weeks.[23]

Clinically, dose skipping AT with androgen deprivation therapy has been used successfully to treat men with castration resistant prostate cancer resulting in an increase in time to progression compared to standard daily dosing.[38] The same treatment approach of adaptive abiraterone treatment based on prostate specific antigen levels has been taken forward in the larger randomised ANZadapt study.[39] The STAR trial was a phase 2/3 study carried out in patients with inoperable loco-regional or metastatic disease clear cell renal cell carcinoma, who all received standard dosing schedules of oral tyrosine kinase inhibitor treatment (either sunitinib or pazopanib) for 24 weeks before randomisation to either continuing therapy or to receive a treatment break until disease progression, when treatment was re-instated. Non-inferiority between the groups could not be concluded and there was no clinically meaningful reduction in life expectancy between either group. Thus, the authors concluded that treatment breaks might be a feasible and cost-effective option with lifestyle benefits in such patients.[40] Other AT clinical trials currently open to recruitment include those investigating personalised scheduling of vismodegib based on *in silico* tumour modelling in advanced basal cell carcinoma,[41] adaptive chemotherapy based on radiological response in rhabdomyosarcoma[42] and BRAF-targeted therapy in melanoma based on circulating tumour DNA levels,[43] or on LDH levels and imaging. [44]

Methods

Trial design

ACTOv is a multicentre, phase II randomised controlled trial that will recruit women with platinum-sensitive relapsed HGOC whose disease has progressed at least 6 months after day 1 of the last cycle of platinum-based chemotherapy. Patients will be randomised in a 1:1 allocation ratio between the control arm (Arm 1, Standard therapy) and investigational arm (Arm 2, Adaptive Therapy). ACTOv will assess whether AT with carboplatin can prolong disease control compared to standard carboplatin dosing. A feasibility assessment will be conducted after the first 20 patients have been randomised to ensure that the overall trial objectives are achievable.

Participants

ACTOv will enrol patients with platinum-sensitive, high grade serous or high grade endometrioid carcinoma of the ovary, fallopian tube or peritoneum progressing on or more than 6 months after day 1 of the last cycle of platinum-based chemotherapy. Patients with first or any subsequent relapse will be included and there is no maximum number of prior treatments stipulated for eligibility. Patients must have received a PARP inhibitor in any prior line of treatment (unless there is a contraindication to PARP inhibitor treatment) to exclude the risk of bias if patients were to receive a PARP inhibitor following completion of ACTOv treatment. A baseline CA125 of ≥100iU/L is required. We derived this by examining our in-house database of 186 patients with relapsed high grade serous ovarian carcinoma receiving carboplatin monotherapy. We found that a CA125 cutoff of ≥200iU/L excluded 52 of 186 patients whereas a cutoff of ≥100iU/L excluded 25 of 186 patients. The cutoff of ≥100iU/L was therefore chosen by the ACTOv investigators as an appropriate level that would enable CA125 changes to be appreciated while maintaining trial inclusivity. Remaining eligibility criteria are summarised in **Table 1**. All participants will provide written informed consent on the current approved version of the consent form (see supplementary material) before any trial-specific procedures are conducted.

Key inclusion criteria	Key exclusion criteria
1. Female, aged ≥18 years.	1. Non-epithelial ovarian cancer, carcinosarcoma, low-grade serous and endometrioid carcinomas, mucinous and clear-cell carcinomas.
2. ECOG performance status 0-2.	2. Patients requiring treatment with combination chemotherapy regimens.
3. Histologically proven diagnosis of high grade serous or high grade endometrioid carcinoma of the ovary, fallopian tube or peritoneum.	3. Known hypersensitivity to carboplatin.
4. Most recent regimen must have included platinum (cisplatin or carboplatin).	4. Persisting ≥ grade 2 Common Terminology Criteria for Adverse Events (CTCAE) version 5 adverse events/toxicity (except alopecia and neuropathy) from previous anti-cancer treatment.
5. Previous treatment with PARP inhibitor (except for patients with contraindication to PARP inhibitor treatment).	5. Treatment with any other investigational agent, or participation in another interventional clinical trial within 28 days prior to randomisation.
6. Response by CT or MRI or by Gynecologic Cancer InterGroup (GCIG) CA125 response criteria to most recent platinum treatment.[45]	6. Major surgery within 14 days before anticipated start of treatment and need to have recovered from any effects of major surgery.
7. Pre-trial CT or MRI-confirmed disease progression ≥ 6 months after day 1 of the last cycle of platinum-containing chemotherapy.	7. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding contraindicating the use of an investigation drug or puts the patients at high risk for treatment-related complications.
8. Measurable disease by RECIST v1.1 on a CT scan conducted within 28 days prior to randomisation (If non-measurable disease, could be eligible if they meet GCIG CA125 progression criteria).[45]	8. Other factors that the Investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results.
9. CA125 ≥ 100iU/l at screening.	9. Malignancy treated within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in

	situ (DCIS) of the breast, stage 1, grade 1 endometrial carcinoma.
10. Agree to provide additional research blood samples at the same time as blood draws prior to each carboplatin treatment, 6-weekly during surveillance and at 12- weekly follow-up visit.	10. Patients with symptomatic uncontrolled brain or meningeal metastases. Patients can receive a stable dose of corticosteroids before and during the study as long as these were started at least 4 weeks prior to treatment.
11. Expected to commence treatment within 28 days post randomisation.	11. Patients with spinal cord compression unless considered to have received definitive treatment for this and with clinically stable disease for 28 days prior to randomisation.
12. Adequate bone marrow, liver and renal function.	12. Pregnant or breast-feeding women and women of childbearing potential (unless effective methods of contraception are used from informed consent, throughout the study treatment and for at least 6 months after last dose of trial drug(s)).
13. Negative pregnancy test at screening and prior to trial treatment and willing to use highly effective contraception during and for six months after last dose of trial drug.	13. Inability to attend or comply with treatment or follow-up scheduling.
14. Informed consent and compliant with treatment and follow up.	

Table 1: Eligibility Criteria for the ACTOv trial.

Trial treatments

All patients in both arms will receive carboplatin intravenously (IV) every 21 days and the dose will be determined by absolute nuclear medicine Glomerular Filtration Rate (NM GFR), rather than calculated renal clearance. The starting and maximum carboplatin dose in both arms is AUC5 based on absolute NM GFR. Patients in Arm 1 will receive a fixed dose (AUC5) as per current standard of care. Patients in both arms will provide blood for CA125 measurement up to 72 hours before every planned chemotherapy treatment including the first cycle. The AT regimen in Arm 2 will modify carboplatin dose in each cycle according to real time changes in each patient's serum CA125, a reliable surrogate measure of total tumour burden and an established marker of disease response and progression in

ovarian cancer.[46] The AT regimen is shown in **Table 2**. Briefly, when CA125 declines by >25%, the dose will be reduced by one AUC at the next cycle. Each fall in CA125 (>25%) will continue to trigger additional, further dose reductions at the subsequent treatment and carboplatin may even be omitted entirely following a very good CA125 response (decrease in CA125 to ≤10% baseline or to ≤ upper limit of normal (ULN)).[47] If CA125 increases by >25%, the dose at the next treatment cycle will be increased by one AUC until AUC5 is reached. If the CA125 continues to increase in subsequent cycles, patients will continue to receive the same dose of AUC5.

The AT regimen outlined in **Table 2**, is derived from the regimen used in preliminary animal experiments, which demonstrated a significant improvement in survival.[23] This regimen was subsequently adapted for patients. In our pre-clinical AT regimen, a 20% change in tumour volume triggered a 50% modification to the carboplatin dose,[23] whereas in ACTOv, in order to avoid potential harm due to under-dosing, the dose will be modified by 20% (1 x AUC) in response to a 25% change in CA125. In-house clinical databases of CA125 responses in patients receiving single agent carboplatin chemotherapy were used to confirm that CA125 changes of this magnitude would be achievable.

Investigational arm: Adaptive Therapy (3 weekly carboplatin)	
Starting dose & maximum dose	AUC5 (based on NM GFR)
≤25% change in CA125	Repeat same dose
>25% decrease in CA125, but not reaching ≤10% baseline or ≤ ULN (compared to start of preceding cycle)	Decrease dose by 1 AUC
>25% increase in CA125 (compared to start of preceding cycle)	Increase dose by 1 AUC (Max AUC 5)
CA125 decrease to ≤10% baseline or to ≤ ULN	Omit dose and repeat CA125 in 3 weeks
Restarting treatment after dose omission	AUC2

Table 2: Adaptive Therapy dosing schedule in the investigational arm (Arm 2).

Treatment will be continued up to a maximum of 6 and 12 cycles in the control and investigational arms respectively unless there is unacceptable toxicity, radiological progression or clinical deterioration due to the underlying cancer. Progression will be defined either radiologically or clinically and not by serum CA125 because CA125 increase is expected with AT and might indicate that the carboplatin dose should be increased according to **Table 2**. Asymptomatic progression during trial treatment and surveillance (i.e. up to week 46) will be detected by one of the mandated trial CT scans of chest, abdomen and pelvis at weeks 9, 19, 31, 43 and 55 (+/- 7 days at each visit) (**Figure 2**).

Tumour assessment

All CT scans in ACTOv will be reported to RECIST v1.1. RECIST v1.1 defines radiological response as a ≥30% reduction in tumour volume compared to the baseline CT scan, while disease progression is defined as a ≥20% increase compared to the radiological nadir.[48] AT is predicted to cause fluctuations in disease burden over time and aims to control these changes by modulating drug dose. Thus, defining disease progression by comparison with the nadir CT could result in AT being stopped prematurely and any potential benefit from AT being underestimated. ACTOv has addressed this by mandating that all CT scans will be compared to both the baseline trial CT conducted within 28 days of randomisation as well as the radiological nadir on any other trial mandated CT. Treatment in both arms may continue in cases where there is RECIST-defined radiological progression compared to the radiological nadir and radiological progression will only be defined by comparison with the baseline CT. Progression in ACTOv may also be defined clinically and in addition, investigators have the option of discontinuing trial treatment at any time for clinical reasons.

Management of toxicity

In both arms, absolute NM GFR will be re-measured if the patient experiences ≥ 20% change in serum creatinine indicating renal toxicity during subsequent cycles. Modifications to carboplatin dose to prevent future haematological toxicity are discouraged. Isolated haematological toxicities should be managed by delaying the next carboplatin dose (maximum 21 days) and with supportive measures including Granulocyte colony-stimulating factor and blood products as per standard of care. In Arm 1 only, if haematological recovery occurs beyond 7 days but within 21 days, carboplatin dose reductions can be considered to AUC 4 (dose level -1). If this is insufficient in a subsequent cycle, a further reduction to AUC 3.5 (dose level -2) is permitted. Modifications to carboplatin dose to prevent future haematological toxicity are not permitted in Arm 2. If supportive measures are insufficient to safely continue with treatment within 21 days, the patient will need to discontinue study treatment.

Sample collection

Research blood samples will be collected from all patients at baseline, 3-weekly during treatment, 6-weekly during surveillance and at 12-weekly follow-up visits. Research biopsies are optional from all patients at baseline and will also be requested if appropriate at the end of treatment and again at disease relapse. Samples will be kept for use in future peer-reviewed research projects that will be conducted outside of the trial protocol.

Statistical considerations

Primary endpoint: Modified progression-free survival (mPFS), which is defined as the time from date of randomisation to either: (i) Protocol defined radiological progression measured by RECIST v1.1,

compared to the baseline trial CT and not the radiological nadir (radiological progression compared to baseline disease volume rather than smallest disease volume); (ii) Clinical deterioration, defined at the discretion of the treating clinician, specifically due to the underlying cancer but in the absence of protocol defined radiological progression; (iii) Death from any cause in the absence of disease progression.

Secondary endpoints: (i) acceptability (patients approached who accept randomisation); (ii) deliverability (treatment cycles delivered as per protocol); (iii) compliance (cumulative carboplatin dose); (iv) toxicity (adverse events categorised by CTCAE v5.0);[49] (v) Quality of Life measured using EORTC questionnaires: [50] QLQ-C30 (suitable for all cancer types), QLQ-OV28 (ovarian cycle specific), EQ-5D (descriptive profile of health state: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, a single summary index and a visual analogue scale); (vi) Fear of Progression (FOP-Q SF); [51] (vii) CA125 measurements; (viii) further treatment upon progression (time-to-next treatment (measured from randomisation), treatment received and response to this treatment); (ix) overall survival.

Sample size

A total sample size of N=80 is required to detect an improvement in median mPFS from 5 months in the control arm to 7.5 months with AT, representing a hazard ratio (HR) of 0.667, with 80% power at the one-sided 20% significance level. This assumes a 3-year recruitment period, 1 year of additional follow-up from the last patient randomised and a drop-out rate of up to 10% per year. Eligible patients will be randomised equally between the two trial arms using minimisation and stratified by the number of prior lines of chemotherapy (1, 2 or ≥ 3), length of platinum-free interval (6 to 12 months or >12 months), and BRCA status (positive [pathological mutation only], wild type [including variants of unknown significance] or unknown).

Statistical methods

Analysis of the primary endpoint will be on an intention-to-treat basis for all eligible patients, with patients censored at date last seen if no event is observed. Patients will not be replaced. The trial arms will be compared using a log-rank test, with Kaplan-Meier methods used to describe mPFS and provide estimates of the median and 6- and 12-month rates. Cox regression will be used to estimate the HR, both unadjusted and after adjusting for randomisation stratification factors. If there is clear evidence of non-proportional hazards, then restricted mean survival times will be analysed. Analyses of secondary endpoints will generally be descriptive in nature, and estimates presented with two-sided 95% confidence intervals.

Patient and public involvement:

The ACTOv trial protocol was developed in close consultation with our local Patient Involvement Advisory Group (PIAG) at Barts Cancer Institute (BCI), London, UK. This resulted in the proposed treatment schedule in which all patients will attend three-weekly for pre-treatment blood tests including CA125, prior to consultation with their clinical team as per standard of care. AT dose will be varied according to CA125 and in some cases may be omitted altogether. Ovarian cancer patients are accustomed to dose reductions and omissions during chemotherapy, usually after a prior blood test showing low blood counts or due to other non-haematological toxicity. The PIAG felt that dose reductions and omissions would therefore be familiar and acceptable to patients and would allow patients to plan around regular three-weekly visits. Treatment will continue until progressive disease or toxicity for a maximum of 6 cycles in the standard treatment arm or 12 cycles (9 months) in the AT arm. The BCI PIAG was satisfied with this longer duration of AT since long-term, three-weekly IV maintenance bevacizumab is an established standard of care. We have also benefited from patient involvement via the UK Gynae Trials Group and a dedicated patient representative is a member of our Trial Management Group (TMG). She has led development of our Patient Information Sheet and consent form and plays a key role in disseminating information regarding the trial through patient and public forums and other communication channels.

Ethics and dissemination:

The trial has received favourable ethical approval from the London–Dulwich Research Ethics Committee (REC), reference number 22/LO/0543, with three amendments between 2021 and 2024. The current protocol version is v4.0, dated 05 Jan 2024.

The results from this trial will be submitted for publication through peer-reviewed journals, and the key findings will be presented at national and international conferences. All publications and presentations relating to the trial will be authorised by the TMG. The first publication of the trial results will be in the name of the TMG on behalf of the trial participants. The writing committee will be formed by contributing members of the TMG. Contributing site Principal Investigators will be added as co-authors. Trial participants and funders will be acknowledged in all publications.

Discussion

ACTOv is a proof-of-concept, phase II randomised controlled trial and the first study to investigate the efficacy of dose modulation AT with carboplatin in patients with relapsed, platinum-sensitive high grade serous or high grade endometrioid cancer of the ovary, fallopian tube and peritoneum. Carboplatin is generally well-tolerated and so there is no upper limit on patient age and patients with ECOG performance status 0, 1 and 2 are eligible. Since single agent carboplatin is more often used in

later lines of therapy, ACTOv allows any number of prior chemotherapy regimens. This means that ACTOv patients are likely to be older, less fit and have more heavily pre-treated disease compared to participants in most clinical trials. These patients have few therapeutic options and the emphasis in their care is to use anticancer therapy to reduce cancer-related symptoms without causing excess toxicity. ACTOv could therefore be very appealing for this patient group.

The number of potential AT regimens we could have tested in humans is limitless, so the ACTOv AT regimen is based on our preclinical work[23]. There were important considerations in adapting this mouse AT regimen for human patients. One concern was that prescribing dose reductions could result in worse patient outcomes by administering insufficient carboplatin dose. To address this, our AT regimen requires a greater change in tumour burden to trigger a smaller change in drug dose compared to the regimen that was successful in mice. The risk here is that the ACTOv regimen is insufficiently 'adaptive', and that drug dose would not reduce sufficiently to stimulate re-growth of drug sensitive populations. This is a particular concern in the heavily pre-treated ACTOv cohort. Interrogation of our patient database provided reassurance by revealing that 63% of patients receiving single agent carboplatin for their second relapse would be prescribed a dose reduction according to our final AT regimen. The trial protocol, including this AT regimen, was developed in close collaboration with patient representatives and the UK Gynaecological Oncology Group. In addition, our protocol has been subject to extensive peer review including from both of our academic funders (Barts Charity and the AntiCancer Fund), our sponsor (University College London) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). The most compelling endorsement of our AT regimen is the fact that clinical investigators have opened ACTOv in 10 hospitals around the UK and are actively recruiting their patients.

AT is predicted to preserve drug sensitivity and utilise lower drug dose at each administration and so it is generally continued for longer than standard maximum tolerated dose (MTD) treatment. In our mouse experiment, carboplatin AT controlled tumour growth until the experiment was stopped at 20 weeks, even though median survival had not been reached[23]. In other clinical experience with AT such as the abiraterone trial in prostate cancer, AT was continued until progression or toxicity and was well tolerated[38]. ACTOv patients in Arm 1 will receive six cycles of carboplatin AUC5 as per standard of care[52]. Those in Arm 2 will continue AT for a maximum of 12 cycles so that analysis of trial outcomes can be conducted without undue delay. An obvious concern with longer treatment duration is that AT will result in greater cumulative drug dose, which could result in greater toxicity, although we note that carboplatin side effects are familiar and manageable. Moreover, our protocol includes multiple

strategies for managing toxicity, including terminating trial treatment and we have included multiple measures of toxicity and quality of life as secondary trial endpoints.

Another important consideration is that differences in cumulative drug dose between the treatment arms and between individual AT-treated patients could explain any differences in PFS observed. Previous ovarian cancer clinical trials have established that prolonged courses of chemotherapy do not result in additional clinical benefit overall[5 53] but the relationship between cumulative dose and patient outcome following personalised AT regimens is unknown. In our mouse experiment, cumulative carboplatin dose was higher in the AT arm, but this was not associated with increased toxicity, and because AT improved survival, the dose of carboplatin per day was not significantly different between standard and AT. Conversely, in another recent study of dose modulation AT using the PARP inhibitor, olaparib, AT achieved comparable tumour control to standard continuous therapy in murine HGOC xenografts and simulated patients but with significantly reduced cumulative drug dose.[37] ACTOv will unpick this relationship by analysing the number of treatment cycles and the cumulative carboplatin dose according to trial arm and in relation to PFS (primary endpoint), toxicity and OS. The secondary endpoint of 'further treatment' will determine whether cumulative drug dose impacts future platinum sensitivity by recording whether the next treatment is platinum-based, as well as response to that treatment.

ACTOv is an important step in evaluating AT in a randomised clinical trial setting. As well as demonstrating whether AT appeals to patients and investigators it will evaluate whether AT can achieve patient benefit by prolonging drug-sensitivity and extending tumour control. The selected trial endpoints will provide evidence to optimise AT regimens for future clinical testing and inform the design of second-generation studies.

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Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Trial status: The trial is currently open to recruitment.

Authors' contributions: UM, HH, NC and ML: original draft of the manuscript; HH, NC, AP, PN, IM, ARAA, RM, CG, TG, ML study conception, design and methodology; NC statistics; KW, HD: Project management and data collection; KR: patient representative; All authors revised, edited and approved the final version of the protocol paper. ML acted as guarantor

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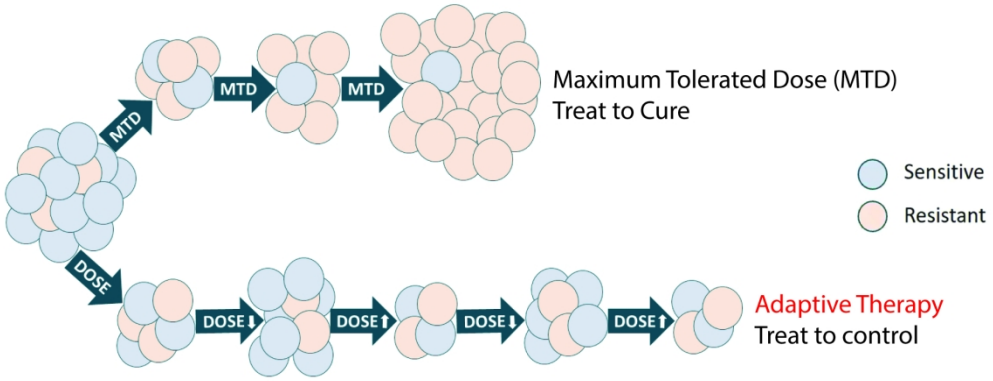
Figure legends

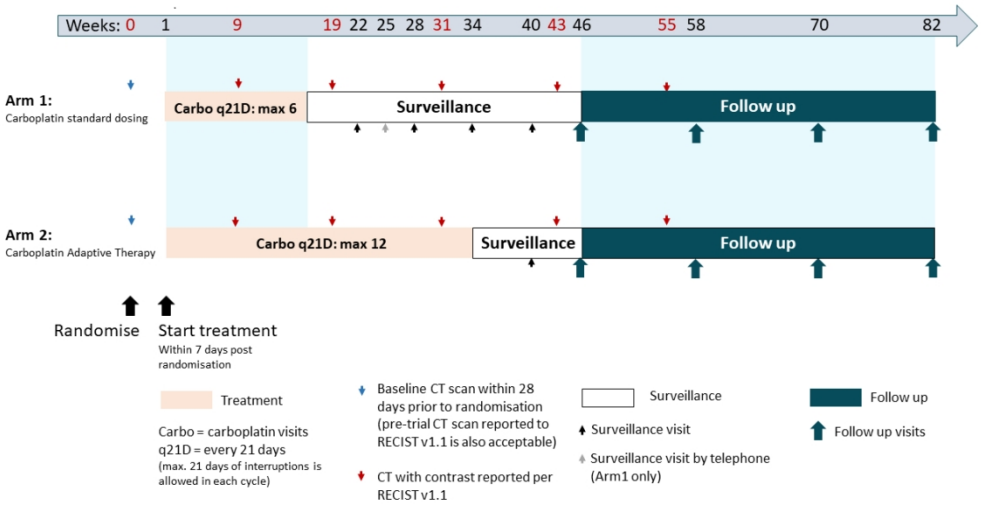
Figure 1: Schematic showing the theoretical basis of adaptive therapy. (a) Maximum tolerated dose (MTD) kills drug-sensitive cells allowing preferential proliferation of the remaining drug-resistant cells. (b) Adaptive Therapy (AT): Dose reductions following treatment response allow sensitive cells to proliferate and repopulate the tumour, maintaining drug sensitivity and thus tumour control over the long term.

Figure 2: Schematic of protocol defined visits



Schematic showing the theoretical basis of adaptive therapy. (a) Maximum tolerated dose (MTD) kills drug-sensitive cells allowing preferential proliferation of the remaining drug-resistant cells. (b) Adaptive Therapy (AT): Dose reductions following treatment response allow sensitive cells to proliferate and repopulate the tumour, maintaining drug sensitivity and thus tumour control over the long term.

163x68mm (300 x 300 DPI)



Schematic of protocol defined visits

108x60mm (300 x 300 DPI)

(Form to be printed on hospital/institution headed paper)

Site Name: _____

Patient Study ID: ACT-_____

CONSENT FORM

Name of Study: **ACTOv: Adaptive ChemoTherapy for Ovarian cancer:**

A multicentre phase II randomised controlled trial to evaluate the efficacy of Adaptive Therapy (AT) with carboplatin, based on changes in CA125, in patients with relapsed platinum-sensitive high grade serous or high grade endometrioid ovarian cancer

Name of Principal Investigator: <<insert name of Principal investigator>>

IRAS No.: 1003954

		Please initial box
1.	I confirm that I have read and understand the information sheet dated 22nd September 2022 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐
3a.	I understand that relevant sections of my medical notes, and data collected during the study, may be viewed at the hospital site or remotely by individuals from the study sponsor (University College London) and its representatives, including CR UK and UCL Cancer Trials Centre (UCL CTC), my NHS Trust/Health Board and from relevant regulatory authorities, where it is relevant to my taking part in this research. I give permission for these organisations/individuals to have access to my data.	☐
3b.	I understand that data collected about me and my treatment may also be shared with other researchers. This research may involve private or commercial companies. I understand that, for such sharing, personal data items that could allow researchers to directly identify me would be removed and a code used to link the information instead.	☐

		Please initial box
3c.	I understand that these parties mentioned above (researchers) may be in regions outside of the UK and EU/EEA where data protection laws have different levels of protection to those in the UK and EU/EEA.	☐
4.	I agree to my General Practitioner (GP) being informed of my participation in this study. I also agree to my GP being involved in the study and providing information about me (relevant to my participation in the study) to the study team.	☐
5.	I understand that information collected about me and my treatment will be used to support other ethically approved research in the future, and may be shared with researchers in other organisations. I understand that, for such sharing, UCL CTC would ensure that personal data items that could allow researchers to directly identify me are removed and a code used to link the information instead.	☐
6.	I agree to give the additional research samples for use in future ethnically and scientifically approved research related in the UK or overseas, including genetic studies. This research may involve private or commercial companies. If this research leads to a new commercial discovery, such as the development of a new treatment or medical test, I understand I will not benefit financially from this. I understand that giving my samples is voluntary and that I am free to withdraw my approval for their use at any time without giving any reason and without my medical treatment or legal rights being affected.	☐
7.	I agree to take part in the above study.	☐

Please initial box

	Optional consent	
8.	**Tissue sample (biopsy) collection:** I agree to give the additional tissue samples (biopsies) collected pre-treatment, at the end of treatment and if the cancer grows back for use in other future ethically approved research studies. I understand that giving my samples is voluntary and that I am free to withdraw my approval for their use at any time without giving any reason and without my medical treatment or legal rights being affected. **This is optional, if you do not wish to take part in this please do not initial the box.**	YES ☐ NO ☐
9.	**For women of child bearing potential:** (initial the N/A box if this does not apply to you) Should I become pregnant during the study, I give permission for the above individuals to have access to any of my medical notes and information collected about my pregnancy. **This is optional, if you do not wish to take part in this please do not initial the box.**	N/A ☐ ☐

Name of Patient _____ Date _____ Signature _____

Name of person taking consent (designated responsible person) _____ Date _____ Signature _____

Instructions to sites: When completed: Take 2 copies. Original and 1 copy to be kept in medical notes and investigator site file, and a copy to be given to the patient.