BMJ Open

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

Uma Anne Mukherjee ,[1] Helen Hockings ,[2] Nicholas Counsell ,[1] Apini Patel ,[3] Priya Narayanan,[3] Katie Wilkinson ,[1] Harjot Dhanda ,[1] Kathy Robinson,[1] Iain McNeish ,[4] Alexander R A Anderson ,[5] Rowan Miller ,[2,3] Charlie Gourley ,[6] Trevor Graham ,[7] Michelle Lockley [3,8]

To cite: Mukherjee UA, Hockings H, Counsell N, *et al*. 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. *BMJ Open* 2024;**14**:e091262. doi:10.1136/bmjopen-2024-091262

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-091262).

Received 16 July 2024
Accepted 22 November 2024

For numbered affiliations see end of article.

Correspondence to
Professor Michelle Lockley; m.lockley@qmul.ac.uk

ABSTRACT

Introduction Adaptive ChemoTherapy for 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 intratumoral 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) ×5 according to absolute nuclear medicine glomerular filtration rate. The AT regimen will modify the 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 1.1 (Response Evaluation Criteria in Solid Cancers) compared with the baseline prerandomisation scan rather than 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 UK, recruitment is anticipated to take 36 months across 10 sites and will be managed by the Cancer Research UK and 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 number NCT05080556.

INTRODUCTION

Ovarian cancer treatment

Ovarian cancer is the leading cause of gynaecological-related mortality with approximately 7000 new cases and 4000 deaths in the UK each year.[1] High-grade serous ovarian carcinoma is the most common pathological subtype accounting for approximately 70% of cases, while 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

STRENGTHS AND LIMITATIONS OF THE STUDY

⇒ Adaptive ChemoTherapy in Ovarian cancer (ACTOv) is the first clinical trial exploring adaptive therapy (AT) 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 1.1 (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 1.1 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 (PFS). This application of RECIST 1.1 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 six cycles of carboplatin AUC5 (area under the curve). In contrast, those in arm 2 (AT) 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 PFS 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 on 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).

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 their 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 with other platinum-containing regimens,[6] while the combination of carboplatin and Caelyx (pegylated liposomal doxorubicin) further extended PFS compared with 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 (area under the curve) every 21 days for up to six cycles. This has the advantage of minimising treatment-related toxicities, particularly in heavily pretreated 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 subclones.[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 preclinical models and in patients, including those treated with BRAF-targeted therapy in melanoma,[21] doxorubicin in breast cancer[19] and epidermal growth factor receptor 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 cocultures.[23]

AT is an evolutionarily informed treatment paradigm, which aims to exploit the intratumoral 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 resensitising the tumour for the next round of treatment.[13 17 21 26] 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]

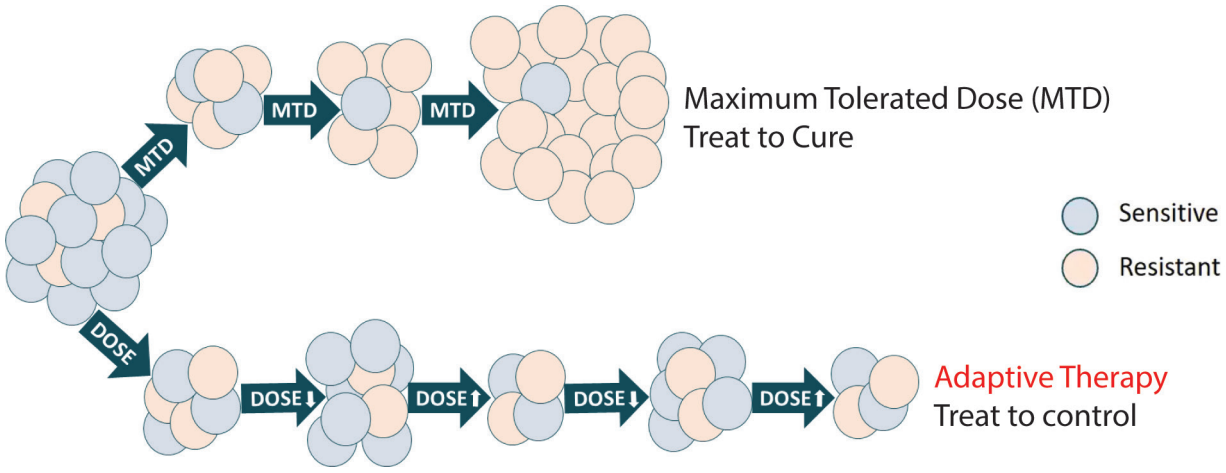

Figure 1 Schematic showing the theoretical basis of adaptive therapy (AT). Maximum tolerated dose (MTD, top row) kills drug-sensitive cells allowing preferential proliferation of the remaining drug-resistant cells. Adaptive Therapy (AT, bottom row) prescribes dose reductions following treatment response to 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 and increasing tumour antigenicity and intratumoral 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 (eg, tumour shrinkage or growth) and ideally evolutionary dynamics (eg, fractions of sensitive and resistant cells).

AT has been studied preclinically in breast cancer,[32 33] colorectal cancer[34] and melanoma,[21 35 36] 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, while 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 with 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 with 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 continue therapy or to receive a treatment break until disease progression, when treatment was reinstated. 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 with 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. Patients with

first or any subsequent relapse will be included, and there is no maximum number of prior treatments stipulated for eligibility. Patients with homologous recombination repair deficient tumours (HRD) 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 ≥100 iU/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 cut-off of ≥200 iU/L excluded 52 of 186 patients whereas a cut-off of ≥100 iU/L excluded 25 of 186 patients. The cut-off of ≥100 iU/L was therefore chosen by the ACTOv investigators as an appropriate level that would enable CA125 changes to be appreciated while maintaining trial inclusivity. The remaining eligibility criteria are summarised in table 1. All participants will provide written informed consent on the currently approved version of the consent form (see online supplemental material) before any trial-specific procedures are conducted.

Trial treatments

All patients in both arms will receive carboplatin intravenously 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 the 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 the 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.[45] 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)).[46] 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 preclinical 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 underdosing, the dose will be modified by 20% (1× 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.

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 (ie, up to week 46) will be detected by one of the mandated trial CT scans of the 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 1.1. RECIST 1.1 defines radiological response as a ≥30% reduction in tumour volume compared with the baseline CT scan, while disease progression is defined as a ≥20% increase compared with the radiological nadir.[47] 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 with 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 with 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 remeasured 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

Table 1 Eligibility criteria for the ACTOv trial

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 anticancer treatment.
5. Patients with homologous recombination repair deficient tumours (including germline or tumour BRCA mutation and/or tumour HRD positive) must have previously received a PARP inhibitor (Note: 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.[53]	6. Major surgery within 14 days before the anticipated start of treatment and need to have recovered from any effects of major surgery.
7. Pretrial CT or MRI-confirmed disease progression ≥6 months after day 1 of the last cycle of platinum-containing chemotherapy (cisplatin or carboplatin) and requiring treatment with further platinum-based 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 1.1 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).[53]	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 ≥100 iU/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 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 postrandomisation.	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 breastfeeding 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. Women of child-bearing potential must have a negative pregnancy test at screening and prior to trial treatment and be willing to use highly effective contraception during and for 6 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.	

ACTOv, Adaptive ChemoTherapy for Ovarian cancer; ECOG, Eastern Cooperative Oncology Group; PARP, poly ADP ribose polymerase; RECIST, Response Evaluation Criteria in Solid Cancers.

(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

Table 2 Adaptive therapy dosing schedule in the investigational arm (arm 2)

Investigational arm: adaptive therapy (three weekly carboplatin)	
Starting dose and 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 with start of preceding cycle)	Decrease dose by 1 AUC
>25% increase in CA125 (compared with 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

AUC, area under the curve; NM GFR, nuclear medicine glomerular filtration rate ; ULN, upper limit of normal.

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 the date of randomisation to either: (1) protocol-defined radiological progression measured by RECIST 1.1, compared with the baseline trial CT and not the radiological nadir (radiological progression compared with baseline disease volume rather than smallest disease volume); (2) clinical deterioration, defined at the discretion of the treating clinician, specifically due to underlying cancer but in the absence of protocol defined radiological progression; (3) death from any cause in the absence of disease progression.

Secondary endpoints

(1) Acceptability (patients approached who accept randomisation); (2) deliverability (treatment cycles delivered as per protocol); (3) compliance (cumulative carboplatin dose); (4) toxicity (adverse events categorised by CTCAE v5.0 (Common Terminology Criteria for Adverse Events))[48]; (5) quality of life measured using European Organisation for Research and Treatment of Cancer (EORTC) questionnaires[49]: 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); (6) Fear of Progression (FOP-Q SF)[50]; (7) CA125 measurements; (8) further treatment on progression (time-to-next treatment (measured from randomisation), treatment received and response to this treatment)); (9) overall survival (OS).

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 an HR (hazard ratio) 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 dropout 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 (6–12 months or >12 months) and BRCA (Breast Cancer gene) 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 the date last seen if no event is observed. Patients will

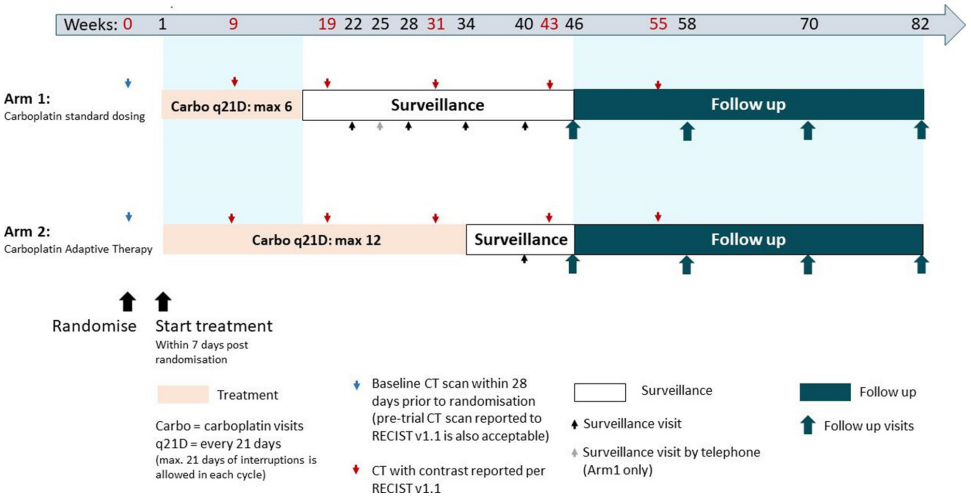

Figure 2 Schematic of protocol-defined visits.

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-month 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 will be presented with two-sided 95% CIs.

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 for 3weekly pretreatment 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 3weekly 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, 3weekly intravenous 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 the 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 5 January 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 coauthors. 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 (Eastern Cooperative Oncology Group) 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 pretreated disease compared with 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 with the regimen that was successful in mice. The risk here is that the ACTOv regimen is insufficiently 'adaptive', and that the drug dose would not reduce sufficiently to stimulate regrowth of drug-sensitive populations. This is a particular concern in the heavily pretreated 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 use lower drug dose at each administration, and so it is generally continued for longer than standard 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.[51] 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 a 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 52] 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 the 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 the 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.

Author affiliations
[1]Cancer Research UK and UCL Cancer Trials Centre, London, UK
[2]St Bartholomew's Hospital, London, UK
[3]University College London Hospitals NHS Foundation Trust, London, UK
[4]Division of Cancer, Department of Surgery and Cancer, Imperial College London, London, UK
[5]Integrated Mathematical Oncology, Moffitt Cancer Center, Tampa, Florida, USA
[6]Institute of Genetics and Cancer, University of Edinburgh Western General Hospital, Edinburgh, UK
[7]Centre for Evolution and Cancer, The Institute of Cancer Research, London, UK
[8]Centre for Cancer Evolution, Barts Cancer Institute, Queen Mary University of London, London, UK

X Alexander R A Anderson @ara_anderson, Trevor Graham @trevoragraham and Michelle Lockley @dr_lockley

Acknowledgements We acknowledge the Cancer Research UK and UCL Cancer Trials Centre and University College London who sponsor the trial. We would like to thank the Gynaecological Tumour Group UK, local investigators and trials teams at our recruiting sites and the Barts Gynae Tissue Bank (Research Ethics Committee reference: 20/EE/0193) who manage all patient samples. Finally, we thank all ACTOv patients and their families.

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

Funding This work was supported by funders of the ACTOv trial: Barts Charity (MGU0598), the Anticancer Fund (RCT-A80-2021) and the Jon Moulton Charity Trust

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Uma Anne Mukherjee http://orcid.org/0000-0001-6693-8788
Helen Hockings http://orcid.org/0000-0003-4509-6387
Nicholas Counsell http://orcid.org/0000-0002-0688-9192
Apini Patel http://orcid.org/0009-0004-2096-4840
Katie Wilkinson http://orcid.org/0009-0001-4343-6483
Harjot Dhanda http://orcid.org/0009-0003-9870-6422
Iain McNeish http://orcid.org/0000-0002-9387-7586
Alexander R A Anderson http://orcid.org/0000-0002-2536-4383
Rowan Miller http://orcid.org/0000-0002-2400-1716
Charlie Gourley http://orcid.org/0000-0002-2377-7221
Trevor Graham http://orcid.org/0000-0001-9582-1597
Michelle Lockley http://orcid.org/0000-0002-9281-5789

REFERENCES

1 Cancer Research UK. Ovarian cancer statistics. Available: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer [Accessed 2 Apr 2024].
2 Köbel M, Kalloger SE, Huntsman DG, *et al*. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. *Int J Gynecol Pathol* 2010;29:203–11.
3 Colombo N, Sessa C, du Bois A, *et al*. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. *Ann Oncol* 2019;30:672–705.

4 Jayson GC, Kohn EC, Kitchener HC, *et al*. Ovarian cancer. *Lancet* 2014;384:1376–88.
5 Hanker LC, Loibl S, Burchardi N, *et al*. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. *Ann Oncol* 2012;23:2605–12.
6 Parmar MKB, Ledermann JA, Colombo N, *et al*. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. *Lancet* 2003;361:2099–106.
7 Wagner U, Marth C, Largillier R, *et al*. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. *Br J Cancer* 2012;107:588–91.
8 Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, *et al*. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. *J Clin Oncol* 2010;28:3323–9.
9 Raja FA, Counsell N, Colombo N, *et al*. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. *Ann Oncol* 2013;24:3028–34.
10 Dizon DS, Dupont J, Anderson S, *et al*. Treatment of recurrent ovarian cancer: a retrospective analysis of women treated with single-agent carboplatin originally treated with carboplatin and paclitaxel. The Memorial Sloan-Kettering Cancer Center experience. *Gynecol Oncol* 2003;91:584–90.
11 Griffiths RW, Zee Y-K, Evans S, *et al*. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and fallopian tube. *Int J Gynecol Cancer* 2011;21:58–65.
12 Gillies RJ, Verduzco D, Gatenby RA. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. *Nat Rev Cancer* 2012;12:487–93.
13 Gatenby RA. A change of strategy in the war on cancer. Nature 2009;459:508–9.
14 Marine JC, Dawson SJ, Dawson MA. Non-genetic mechanisms of therapeutic resistance in cancer. *Nat Rev Cancer* 2020;20:743–56.
15 Bowtell DD, Böhm S, Ahmed AA, *et al*. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. *Nat Rev Cancer* 2015;15:668–79.
16 Gatenby RA, Brown JS. Integrating evolutionary dynamics into cancer therapy. *Nat Rev Clin Oncol* 2020;17:675–86.
17 Gatenby RA, Silva AS, Gillies RJ, *et al*. Adaptive therapy. *Cancer Res* 2009;69:4894–903.
18 Strobl MAR, West J, Viossat Y, *et al*. Turnover Modulates the Need for a Cost of Resistance in Adaptive Therapy. *Cancer Res* 2021;81:1135–47.
19 Gallaher JA, Enriquez-Navas PM, Luddy KA, *et al*. Spatial Heterogeneity and Evolutionary Dynamics Modulate Time to Recurrence in Continuous and Adaptive Cancer Therapies. *Cancer Res* 2018;78:2127–39.
20 Hansen E, Woods RJ, Read AF. How to Use a Chemotherapeutic Agent When Resistance to It Threatens the Patient. *PLoS Biol* 2017;15:e2001110.
21 Sun C, Wang L, Huang S, *et al*. Reversible and adaptive resistance to BRAF(V600E) inhibition in melanoma. Nature 2014;508:118–22.
22 Siravegna G, Mussolin B, Buscarino M, *et al*. Erratum: Clonal evolution and resistance to EGFR blockade in the blood of colorectal cancer patients. *N Med* 2015;21:827.
23 Hockings H, Lakatos E, Huang W, *et al*. Adaptive therapy achieves long-term control of chemotherapy resistance in high grade ovarian cancer. *bioRxiv* 2023.
24 Strobl MAR, Gallaher J, West J, *et al*. Spatial structure impacts adaptive therapy by shaping intra-tumoral competition. *Commun Med (Lond)* 2022;2:46.
25 Viossat Y, Noble R. A theoretical analysis of tumour containment. *Nat Ecol Evol* 2021;5:826–35.
26 Gatenby R, Brown J. The Evolution and Ecology of Resistance in Cancer Therapy. *Cold Spring Harb Perspect Med* 2018;8:a033415.
27 Thomas F, Donnadieu E, Charriere GM, *et al*. Is adaptive therapy natural? *PLoS Biol* 2018;16:e2007066.
28 Browder T, Butterfield CE, Kräling BM, *et al*. Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer. *Cancer Res* 2000;60:1878–86.
29 Galluzzi L, Humeau J, Buqué A, *et al*. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat Rev Clin Oncol* 2020;17:725–41.
30 Muraro E, Vinante L, Fratta E, *et al*. Metronomic Chemotherapy: Anti-Tumor Pathways and Combination with Immune Checkpoint Inhibitors. *Cancers (Basel)* 2023;15:2471.
31 Strobl MAR, Gallaher J, Robertson-Tessi M, *et al*. Treatment of evolving cancers will require dynamic decision support. *Ann Oncol* 2023;34:867–84.
32 Enriquez-Navas PM, Kam Y, Das T, *et al*. Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer. *Sci Transl Med* 2016;8:327ra24.
33 Silva AS, Kam Y, Khin ZP, *et al*. Evolutionary approaches to prolong progression-free survival in breast cancer. *Cancer Res* 2012;72:6362–70.
34 Bacevic K, Noble R, Soffar A, *et al*. Spatial competition constrains resistance to targeted cancer therapy. *Nat Commun* 2017;8:1995.
35 Das Thakur M, Salangsang F, Landman AS, *et al*. Modelling vemurafenib resistance in melanoma reveals a strategy to forestall drug resistance. Nature 2013;494:251–5.
36 Smalley I, Kim E, Li J, *et al*. Leveraging transcriptional dynamics to improve BRAF inhibitor responses in melanoma. *EBioMedicine* 2019;48:178–90.
37 Strobl MAR, Martin AL, West J, *et al*. To modulate or to skip: De-escalating PARP inhibitor maintenance therapy in ovarian cancer using adaptive therapy. *Cell Syst* 2024;15:510–25.
38 Zhang J, Cunningham J, Brown J, *et al*. Evolution-based mathematical models significantly prolong response to abiraterone in metastatic castrate-resistant prostate cancer and identify strategies to further improve outcomes. *Elife* 2022;11:e76284.
39 Study details | Phase II randomised controlled trial of patient-specific adaptive vs. continuous abiraterone or enzalutamide in mcrpc (anzadapt). ClinicalTrials.gov. Available: https://classic.clinicaltrials.gov/ct2/show/NCT05393791#contacts [Accessed 1 May 2024].
40 Brown JE, Royle K-L, Gregory W, *et al*. Temporary treatment cessation versus continuation of first-line tyrosine kinase inhibitor in patients with advanced clear cell renal cell carcinoma (STAR): an open-label, non-inferiority, randomised, controlled, phase 2/3 trial. *Lancet Oncol* 2023;24:213–27.
41 Study details | Adaptive therapy of vismodegib in advanced basal cell carcinoma. ClinicalTrials.gov. Available: https://classic.clinicaltrials.gov/ct2/show/NCT05651828 [Accessed 1 May 2024].
42 Study details | evolutionary therapy for rhabdomyosarcoma. ClinicalTrials.gov. Available: https://clinicaltrials.gov/study/NCT04388839 [Accessed 1 May 2024].
43 Study details | Circulating tumour DNA guided adaptive BRAF and MEK inhibitor therapy (DyNAMIc). ClinicalTrials.gov. Available: https://clinicaltrials.gov/study/NCT06470880 [Accessed 4 Jul 2024].
44 Study details | adaptive BRAF-MEK inhibitor therapy for advance BRAF mutant melanoma. ClinicalTrials.gov. Available: https://clinicaltrials.gov/study/NCT03543969 [Accessed 1 May 2024].
45 Salani R, Backes FJ, Fung MFK, *et al*. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol* 2011;204:466–78.
46 Rustin GJS, Quinn M, Thigpen T, *et al*. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst* 2004;96:487–8.
47 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
48 Common terminology criteria for adverse events (CTCAE) version 5.0. Available: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [Accessed 5 Apr 2024].
49 EORTC quality of life questionnaires. Available: https://qol.eortc.org/questionnaires/ [Accessed 5 Apr 2024].
50 Youssef Y, Mehnert-Theuerkauf A, Götze H, *et al*. Rapid screener for the assessment of fear of progression in cancer survivors: The Fear of progression-Questionnaire Rapid Screener. *Eur J Cancer Care (Engl)* 2021;30:e13400.
51 González-Martín A, Harter P, Leary A, *et al*. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34:833–48.
52 Dizon DS, Weitzen S, Rojan A, *et al*. Two for good measure: six versus eight cycles of carboplatin and paclitaxel as adjuvant treatment for epithelial ovarian cancer. *Gynecol Oncol* 2006;100:417–21.
53 Rustin GJS, Vergote I, Eisenhauer E, *et al*. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). *Int J Gynecol Cancer* 2011;21:419–23.