Title

A phase I trial of CT900, a novel α-folate receptor-mediated thymidylate synthase inhibitor, in patients with solid tumours with expansion cohorts in patients with high grade serous ovarian cancer

Running title

α-folate receptor-mediated thymidylate synthase inhibitor

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Abstract

Background

CT900 is a novel small molecule thymidylate synthase inhibitor that binds to α-folate receptor (α-FR) and thus is selectively taken up by α-FR-overexpressing tumours.

Patients and Methods

A 3+3 dose escalation design was used. During dose escalation, CT900 doses of 1-6 mg/m^2 weekly and 2-12 mg/m^2 every 2 weeks (q2Wk) intravenously were evaluated. Patients with high-grade serous ovarian cancer (HGSOC) were enrolled in the expansion cohorts.

Results

109 patients were enrolled, 42 patients in the dose escalation and 67 patients in the expansion cohorts. At the dose/schedule of 12 mg/m^2/q2Wk (with and without dexamethasone, n=40), the most common treatment related adverse events were fatigue, nausea, diarrhoea, cough, anaemia and pneumonitis, which were predominantly grade 1 and grade 2. Levels of CT900 greater than 600 nM needed for growth inhibition in preclinical models were achieved for >65 hours at a dose of 12 mg/m2. In the expansion cohorts, the overall response rate (ORR), was 14/64 (21·9%). Thirty-eight response-evaluable patients in the expansion cohorts receiving 12 mg/m^2/q2Wk had tumour evaluable for quantification of α-FR. Patients with high or medium expression had an objective response rate of 9/25 (36%) compared with 1/13 (7·7%) in patients with negative/very low or low expression of α-FR.

Conclusions

The dose of 12 mg/m^2/q2Wk was declared the recommended phase II dose/schedule. At this dose/schedule, CT900 exhibited an acceptable side effect profile with clinical benefit in patients with high/medium α-FR expression and warrants further investigation.

Statement of translational relevance

α-FR is overexpressed in a variety of solid tumours including high grade serous ovarian, ovarian cancer, triple negative breast cancer and non-small cell lung cancer. CT900 is a small molecule thymidylate synthase (TS) inhibitor that binds to and is taken up by α-FR. This is the first clinical trial to show reproducible single agent responses caused by a small molecule in α-FR-overexpressing cancers. The toxicity profile did not show classical TS inhibitor toxicity such as myelosuppression suggesting differential α-FR mediated uptake in tumour tissue. This trial is proof of concept for developing α-FR targeting small molecules which are selectively taken up in α-FR-overexpressing tumours for patient benefit and are an alternate approach to antibody drug conjugates that already target α-FR.

Introduction

The α-folate receptor (α-FR) is highly overexpressed during malignant transformation (1) and is known to be expressed on the entire surface of tumour cells in ovarian cancer, triple-negative breast cancer, endometrial cancer, mesothelioma and lung cancer (2-11).
Up to 90% of ovarian cancers are reported to constitutively express α-FR, whereas it is scarcely expressed in non-malignant tissues (6), making it an important cancer drug target (12). Multiple therapeutic approaches, including antibodies, folate drug–drug conjugates and antibody–drug conjugates, have been used and, despite promising results from early phase trials, there are currently no approved α-FR targeted anticancer drugs (12).

CT900 (also known as ONX-0801 and BCG945) is a novel, cyclopentaquinazoline-based, α-FR targeted thymidylate synthase inhibitor that specifically enters cancer cells following binding to α-FR and does not utilise the reduced folate carrier (RFC) (13,14). CT900, however, does not have a classic small-molecule or antibody-cleavable linker–payload structure of several other α-FR-targeted therapies, such as vintafolide (15) or mirvetuximab soravtansine (16).

A multicentre, open-label, dose-escalation, phase I clinical study in adult patients with histologically- or cytologically-proven solid tumours was conducted with the primary aim to identify a recommended dose and schedule for phase II evaluation by establishing the maximum tolerated

dose (MTD) and establishing a safety profile. Secondary aims included defining a pharmacokinetic profile and tertiary aims included establishing anti-tumour activity, evaluating pharmacodynamic activity and evaluating correlations of clinical response to α-FR in archival tumour tissue.

Methods

Study conduct

This multicentre, open-label, dose-escalation, phase I clinical study (EudraCT number: 2013-000569-34; ClinicalTrials.gov identifier: NCT02360345)(17) of CT900 was co-sponsored by The Institute of Cancer Research (ICR) and The Royal Marsden NHS Foundation Trust (RM). The study was conducted in accordance with Good Clinical Practice (GCP) legislation and the ethical principles enunciated in the Declaration of Helsinki (October 2013). Approval from the Medicines and Healthcare products Regulations Agency (MHRA) and the relevant Research Ethics Committee (REC) was obtained before the start of the study. All patients provided fully informed written consent.

The study comprised two stages: the dose escalation phase, in which the maximally tolerated dose (MTD) was determined, and the expansion phase, in which evaluable patients were treated at the MTD and schedule to further support the design of subsequent studies of CT900.

Inclusion criteria

Main inclusion criteria for the dose escalation included patients with advanced cancers who had received standard of care treatment, age at least 18 years with measurable or evaluable disease, life expectancy of at least 12 weeks and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The patients were required to have adequate organ bone marrow, renal and liver function routine for phase I oncology trials (details in protocol attached). In addition, patients were required to have a forced vital capacity (FVC) of >70% and a diffusion capacity for carbon monoxide corrected for haemoglobin (DLCOc) of >60%. The expansion cohorts were limited to patients with high-grade serous ovarian cancer.

Treatment schedules

For the dose escalation portion of the study, patients were dosed either weekly (qWk) or once every 2 weeks (q2Wk). A period of 4 weeks was considered one cycle (four doses in the qWk schedule and two doses in the q2Wk schedule). The first two cycles were considered to be the dose-limiting toxicity (DLT) window. Following the establishment of the recommended phase II dose and an amendment, two further schedules were studied: once every 2 weeks with dexamethasone prophylaxis (q2Wk-steroid) or once every 3 weeks (q3Wk) **(Figure 1)**.

Patients could initially receive up to six cycles of treatment. Patients in the q3Wk cohort could have up to eight cycles if they completed six cycles without pulmonary toxicity or disease progression. The limit of the total number of cycles based on data from a previous unpublished trial of this drug Eudra CT 2009-012933-31 where pulmonary toxicity was shown to occur at a median cumulative dose of 162 mg/m^2. Pharmacokinetic modelling suggested relevant concentrations approximately 10 mg/m^2 , thus at 12 mg/m^2 of CT900 administered once every two weeks (24 mg/m^2/month or cycle), 6 months of treatment would reach a cumulative dose of 144 mg/m^2 which would be lower than 162 mg/m^2.

Patients who received less than 75% of the planned doses of CT900 in the first two treatment cycles for reasons other than toxicity in either phase were replaced. Patients had to receive two cycles of CT900 to be evaluable for dose escalation decisions in the dose escalation phase.

Study design

The study used a 3+3 dose escalation design during dose escalation. Each cohort consisted of three patients, and this was expanded to six evaluable patients if a DLT was observed. The qWk and q2Wk cohorts in the expansion were recruited to in parallel. The recommended phase II dose was based on a minimum of six patients. The expansion cohort was started as a q2Wk schedule and following that three further expansion cohorts i.e. 6 mg/m^2, 12 mg/m^2/q2Wk and 12 mg/m^2/q3Wk were recruited to in parallel **(Figure 1)**.

Criteria for evaluation

Safety and tolerability

Safety and tolerability of CT900 were assessed by monitoring the nature and frequency of adverse events (AEs) using National Cancer Institute Common Terminology Criteria for
Adverse Events version 4.0 (NCI CTCAE v4.0) and laboratory abnormalities (biochemistry, haematology, urinalysis), pulmonary function tests (PFTs), vital signs, electrocardiogram (ECG), and physical examination. The dose limiting period window was 2 cycles (8 weeks for the weekly and once every 2 weekly schedules and 6 weeks for the once every three week schedules).

Pharmacokinetics

The plasma concentration/time data were analysed using non-compartmental methods. The PK parameters determined for CT900 included area under the plasma concentration versus time curve (AUC) from zero to the last value above the limit of quantification (AUC_{last}), from zero extrapolated to infinite time (AUC_{∞}), and from zero to 24 h (AUC_{0-24}); maximum observed plasma concentration (C_{max}); time to C_{max} (T_{max}); terminal elimination half-life ($t_{1/2}$); terminal rate constant (λz); clearance (CL) and steady state volume of distribution (V_{ss}).

Pharmacodynamics

Patients who provided a separate, optional consent underwent an ^{18}F-FLT PET/CT (3′-Deoxy-3′-[^{18}F]-fluorothymidine (FLT) positron emission tomography/ computed tomography) scan at either dose escalation or dose expansion. Each patient received an ^{18}F-FLT PET/CT scan at baseline and a second scan 16–26 h after the first dose of CT900. Maximum standardised uptake value (SUV_{max}) was quantified.

Efficacy

To enrol, patients were required to have measurable disease according to the Response Evaluation Criteria in Solid Tumours version 1·1 (RECIST v1·1). For patients with ovarian cancer, CA125 levels were assessed according to the Gynecologic Cancer InterGroup (GCIG) criteria. Clinical and radiological assessments were used to assess response to CT900. All complete responses (CR) and partial responses (PR) were confirmed by two consecutive observations not less than 4 weeks apart. Disease response in ovarian cancer patients was determined by CA125 levels according to GCIG criteria. All patients who met the eligibility criteria received at least two cycles of study medication and had a baseline assessment of disease were evaluable for response by RECIST v1·1.

Predictive biomarkers

α-FR expression in tumour biopsy samples was primarily evaluated using the Ventana FOLR1 (FOLR1-2·1) CDx assay (Roche Diagnostics), which comprises an immunohistochemistry-compatible murine monoclonal antibody (Clone FOLR1-2·1) with high specificity for human α-FR. Samples were scored by the percentage of cells with greater than or equal to 2+ membranous staining intensity (PS2+ Scoring). Patients were then classified as follows based on PS2+ scoring percentage: 0–24%, negative/very low; 25–49%, low; 50–74%, medium; and ≥75%, high (18-21). Sample images of the Ventana assay are shown in the supplementary information **(Supplementary Figure 1)**.

α-FR expression in tumour biopsy samples was also assessed using an in-house immunohistochemical assay with a commercially available monoclonal antibody (BN3.2) developed by ICR to detect the protein. Patients were scored based on the level of staining observed at the cell membrane and the proportion of cells that were stained positive **(Supplementary data)**.

Statistical methods

All analyses in this study were descriptive in nature. Descriptive summaries of continuous variables included the mean, median, standard deviation, range and, where appropriate, 95% confidence interval (CI) and/or interquartile range (IQR). Descriptive summaries of categorical variables included number of patients with an observation (n) and proportion (%).

Role of the funding source

This is an academically sponsored study. Funding was provided by the following pharmaceutical companies: Onyx pharmaceuticals, BTG international and Carrick Therapeutics. In addition to the academic sponsors, Carrick Therapeutics was involved in the analysis, interpretation, writing of the report and decision to submit the paper for publication.

Data availability

Qualified scientific and medical researchers can request patient level anonymised clinical data for research purposes. These will be reviewed by sponsor prior to granting access and decisions depend on purpose/scientific merit of the proposal and availability of the data. Requests to be sent to corresponding author.

Results

Demographics

A total of 109 patients were enrolled in the study (42 patients in the dose escalation and 67 patients in the expansion cohorts) between 2013 and 2019. The male-to-female ratio of 11:98 reflected the expansions conducted in patients with ovarian cancer. The median age of patients was 62 (range 55–67) years, and the median number of previous lines of treatment was 5 (range 1–13) **(Table 1)**.

Dose escalation

Two schedules were explored in parallel: qWk and q2Wk **(Figure 1)**. During the dose escalation cohort, there was only one protocol-defined DLT within the first 8 weeks in the qWk schedule: cellulitis at 2 mg/m^2, which occurred in a patient with ovarian cancer who had extensive pre-existing oedema of the abdominal wall. The DLT necessitated an expansion to six patients in the cohort. One patient treated at 4 mg/m^2/qWk developed a grade 3 pneumonitis after completing six cycles of treatment. Thus, although 6 mg/m^2/qWk and 12 mg/m^2/q2Wk were considered tolerable by protocol-defined criteria (i.e., no DLTs in the first 8 weeks of treatment), the decision was made to explore 12 mg/m^2/q2Wk in the expansion.

Following treatment of 25 patients at 12 mg/m^2/q2Wk, three further cohorts were explored to evaluate tolerability and efficacy. These were 6 mg/m^2/q2Wk, 12 mg/m^2/q2Wk-steroid prophylaxis, and 12 mg/m^2/q3Wk.

Tolerability

Once a week schedule

The qWk schedule explored dose levels of 1, 2, 4, and 6 mg/m^2 and a total of 21 patients were treated. There were three drug-related NCI CTCAE ≥grade 3 events: anaemia (6 mg/m^2 in Cycle 3), cellulitis (2 mg/m^2 in Cycle 1) and pneumonitis (4 mg/m^2 after completing Cycle 6) **(Supplementary Table 1)**. The grade 3 cellulitis that occurred was a DLT; therefore, the 2 mg/m^2/qWk cohort was expanded to six patients.

Once every two weeks schedule

The q2Wk schedule explored dose levels of 2, 4, 8, and 12 mg/m^2 (n=21). This schedule was better tolerated than the qWk schedule, with only one drug-related grade 3 event of anaemia recorded (8 mg/m^2 in Cycle 1) **(Supplementary Table 2)**.

Expansion cohorts

Two expansion cohorts explored doses other than 12 mg/m^2/q2Wk. These were 6 mg/m^2/q2Wk (n=14) and 12 mg/m^2/q3Wk (n=13). Drug-related ≥grade 3 toxicities included anaemia (two patients at 6 mg/m^2/q2Wk), alanine aminotransferase increase (one patient at 6 mg/m^2/q2Wk) and hyponatremia (two patients at 12 mg/m^2/q3Wk) **(Supplementary Table 3)**.

Two expansion cohorts explored 12 mg/m^2/q2Wk: one without prophylactic steroids (n=25) and the other with prophylactic steroids (n=15). Drug-related NCI CTCAE ≥grade 3 events were anaemia (two patients in the 12 mg/m^2/q2Wk-steroid cohort), diarrhoea (one patient each in the 12 mg/m^2/q2Wk and 12 mg/m^2/q2Wk-steroid cohorts), influenza-like illness (one patient at 12 mg/m^2/q2Wk), and atrial fibrillation (one patient at 12 mg/m^2/q2Wk). The most common side effects (all grades) reported with 12 mg/m^2/q2Wk (without or with steroid prophylaxis) were fatigue (53%), nausea (40%), diarrhoea (23%), cough (23%), anaemia (20%), and pneumonitis (20%) **(Table 2)**. All these side effects were grade 1-2 apart from two cases each of grade 3 diarrhoea and grade 3 anaemia. The use of steroid prophylaxis had minimal impact on the tolerability profile.

Ten cases of pneumonitis were reported in the expansion cohorts (n=67) and were considered adverse effects of special interest. One patient in the 4 mg/m^2/qWk dose escalation cohort had grade 3 pneumonitis, observed radiologically, after completing six cycles of treatment. There were no signs of pneumonitis on CT scans after Cycle 2 and Cycle 4 in this patient. There were no cases of fatal pneumonitis during the trial. All other cases were grade 1-2 and were diagnosed radiologically.

Overall, there was no clinically significant difference in tolerability between the 12 mg/m^2/q2Wk and 12 mg/m^2/q2Wk-steroid cohorts **(Table 2)**.

Pharmacokinetics

The pharmacokinetic parameters are shown in Table 2. At the 12 mg/m^2 dose level the geometric mean of the C_{max} was 5101 ng/mL (percentage coefficient of variation of the geometric mean [CV% Geo Mean], 12·2) and the geometric mean of the AUC_{last} was 85,858 h*ng/mL (CV% Geo Mean, 22) **(Table 3).** The terminal half-life was 28.7 h. The plasma concentration exceeded the target concentration of 600 nM for over 65 h which is predicted to be efficacious based on preclinical studies (13) **(Supplementary Figure 2)**.

Pharmacodynamics

Seven patients treated with CT900 at 12 mg/m^2/q2Wk underwent FLT PET/CT studies pre-treatment and 16-24 h post-treatment to study changes in SUV_{max} in ^{18}F-FLT PET/CT scans. There was a increase in SUV_{max} in tumour post-treatment in 6 of 7 patients (p=0.016) **(Figure 2A)**. An example of an increase in ^{18}F-FLT PT signal in ovarian cancer metastasis is shown in **(Figure 2B)**. One further patient treated at 6 mg/m^2/q2Wk underwent PET scans at the same time and had a pre- and post-treatment SUV_{max} of 6.14 and 9.61, respectively.

Efficacy

Twelve patients with high-grade serous ovarian cancer entered the dose escalation cohort in whom 4/11 (36·4%) partial responses were observed.

Sixty-four patients with high-grade serous ovarian cancer were treated on the expansion cohorts and were evaluable for response. The overall response rate (ORR) determined by CT or MRI, regardless of α-FR status, was 14/64 (21·9%) (95% confidence interval [CI] 12·5–34) **(Figure 3A)**.

Thirty-eight response-evaluable patients in the expansion cohorts treated at 12 mg/m^2/q2Wk had tumour evaluable for the Ventana FOLR2·1 assay. For patients who received treatment in the 12 mg/m^2/qWk cohorts, the RECIST v1·1 ORR was 9/25 (36%) (95% CI 18–57·5) in patients with medium or high α-FR expression compared with 1/13 (7·7%) (95% CI 0·2–36) in patients with negative/very low or low expression of α-FR **(Figure 3B**, **Supplementary Table 4)**.

In the medium and high α-FR expressing patients treated at 12 mg/m^2/q2Wk, 5/25 (20%) (95% CI 6·8–40·7) patients received treatment for ≥16 weeks and 2/25 (8%) (95% CI 1–26) received treatment for ≥24 weeks **(Supplementary Table 5)**.

Of interest, three patients had previously received a α-FR targeted antibody drug conjugate prior to study entry and 1 of these 3 patients had a partial response.

Recommended phase II dose

Grade 3 pneumonitis was observed radiologically in one patient on the qWk schedule at a dose of 4 mg/m^2 after six cycles, which is outside the DLT window. Treating additional patients on weekly schedules would likely have increased the incidence of this event, thus weekly schedules were not considered for evaluation in expansions.

Within the q2Wk dosing schedules, 12 mg/m^2/q2Wk was the highest dose reached. At this dose, there is a plasma concentration >600 nM for >65 h. An increase in the ^{18}F-FLT PET signal has been shown to correspond to thymidylate synthase activity in preclinical models (22) and it was possible to show pharmacodynamic activity of CT900 within tumours of patients treated at 12 mg/m^2/q2Wk using this approach. Not

accounting for α-FR expression status, the RECIST v1·1 response rates in the medium and high α-FR expressing patients were lower in the 6 mg/m^2/q2Wk (0/9 [0%]) and 12 mg/m^2/q3Wk (1/5 [20%]) cohorts than in the 12 mg/m^2/q2Wk (9/25 [36%]) cohorts. Furthermore, there was no significant improvement in toxicity or reduction in radiological incidence of pneumonitis with the addition of prophylactic dexamethasone. Taking all these factors into consideration, the dose of 12 mg/m^2/q2Wk was considered the recommended phase II dose.

Discussion

This is the first publication about clinical results of CT900 and has multiple novel aspects. It is the first α-FR-targeted drug that has thymidylate synthase inhibitor properties that is internalized by the α-FR but is not linked to an antibody or folic acid moiety by a linker (13) to be evaluated in a clinical trial (13,15). This is in contrast to antibody-drug conjugates that target α-FR and have maytansine payloads (16), or small molecules that target α-FR and have vinca payloads (15). This is also the first report of a small molecule binding to α-FR that has shown single agent responses in α-FR overexpressing cancers. This provides proof of concept for further drug development opportunities focussing on α-FR as a target.

CT900 exhibited an acceptable side effect profile. The majority of AEs, experienced during the study, were reported as unrelated and mild or moderate in severity and were generally typical for patients with an advanced malignancy. A drug related, predominantly low-grade pneumonitis was observed in 10/109 (9%) patients on CT900, manifesting as radiological changes rather than significant symptomatic impairment. The addition of steroid prophylaxis did not alter this clinical picture. The cases of pneumonitis were reported prior to the first reported case of COVID 19 infections in the UK where the trial was run and were not associated with fever and thus are unlikely to be associated with COVID 19 infections. With appropriate pulmonary monitoring, long-term administration of CT900 appears feasible. The α-FR is known to be expressed on the luminal surface of alveolar cells. Pneumonitis was observed in 2.9% and 9% of patients in trials of another α-FR targeted agent, mirvetuximab soravtansine, used as a single agent (20) and when combined with bevacizumab respectively (23).

After a single IV infusion, CT900 PK showed low variability in C_{max}. Total plasma concentration after infusion of 12 mg/m^2 CT900 was maintained above >600 nM for at least 65 h, a concentration when corrected for plasma binding that has shown efficacy *in vitro* in α-FR expressing cells (13). Preclinical studies with BCG945/CT900 have shown that thymidylate synthase (TS) inhibition causes increase in thymidine uptake which can be measured by the increase in ^{18}F-FLT PET signals in tumor tissue (22). A subset of patients underwent pre and post treatment ^{18}F-FLT PET scans and showed an increase in ^{18}F-FLT PET signals, post treatment in tumour tissue, consistent with TS inhibition in tumor tissue.

This study showed the significant clinical benefit of identifying patients with solid tumours which expressed α-FR. In line with the mechanism of action of CT900, patients with a high or medium α-FR expression determined by an immunohistochemical assay showed an objective response rate of 36%.

This phase I study has thus used toxicity-pharmacokinetic-pharmacodynamic-biomarker of sensitivity, all important pillars of the pharmacological audit trial to optimize and recommend a phase II dose and schedule CT900 (24).

CT900 therefore has the potential to help address the significant unmet medical need and poor outcomes for patients with platinum resistant high-grade serous ovarian cancer where current control treatment arms in randomized trials have a response rate of 4-12% and progression free survival of 3.5-4.4 months (20,25). Of note, apart from Mirvetuximab Soravtansine with an ORR of 22-34%, there have little single agent objective responses seen with any α-FR targeting drugs (12,20,26). The authors acknowledge the progression free intervals in patients with CT900 was modest and ways of maximizing this should be explored. Preclinical studies have found synergistic combinations of TS inhibitors and poly (ADP-ribose) polymerase (PARP) inhibitors (27) and we have shown synergistic growth inhibition caused by the combination of CT900 and PARP inhibition in a α-FR overexpressing preclinical model **(Supplementary Figure 3)**. This is a possible path for further development. Further clinical trials of CT900 as a single agent or in combination in α-FR overexpressing tumours such as HGSOC are warranted.

Data sharing statement

The protocol and patient information sheets will be available as part of the publication. Anonymized data will be made available upon reasonable request from academic groups made to the sponsors following publication.

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BJ conducted the statistical analysis.

BJ and MP verified the underlying data.

UB and SB drafted the manuscript.

SB, VM, JEA, AIG, AB, IGF, ML, RR, FR, RR BG, SC, NT, JP, TP, MP, AZ, AT, BJ, SM, EA, AM, JL, JDB, RJ, EH, NC, BB and UB reviewed the manuscript.

All authors confirm that they had full access to all the data in the study and accept responsibility to submit the manuscript for publication.

LEGENDS

Table 1

Demographics in escalation and expansion

Table 2

Treatment-related toxicities reported in the 12 mg/m^2/q2Wk + Steroid expansion cohort by the dose level assigned and worst recorded NCI CTCAE grade (only up to 10% toxicities tabulated)

*Grade 3 toxicities in bold text; there were no grade 4 toxicities

Table 3

Summary of CT900/Idetrexed Plasma Pharmacokinetic Parameters from dose escalation phase, Cycle 1 Day 1

CV% - percentage coefficient of variation; T_{max} - time to maximum observed plasma concentration; C_{max} - maximum observed plasma concentration; HL λz - half-life terminal rate constant; AUC_{0-24} - area under the plasma concentration versus time curve from zero to 24 h; AUC_{last} - area under the plasma concentration versus time curve from zero to the last value above the limit of quantification; Cl - clearance; V_{ss} - steady state volume of distribution.

Figure 1

Consort diagram

RE - response evaluable patients/cohort

Figure 2

Pharmacodynamic studies of CT900

A) Results in seven patients showing difference in SUV_{max} in pre- and post-treatment scans. B) Representative images of a patient's ^{18}F-FLT PET/CT scan showing increase in uptake of FLT in tumour in post-treatment.

Figure 3

Efficacy of CT900/Idetrexed in expansion cohorts of patients with ovarian cancer

A. Waterfall plot of patients with HGSOC treated on the expansion cohort. Percentage change from baseline in tumour size in the expansion cohort (n=64*). *All patients with at least one complete follow-up scan, n=63 shown on waterfall plot. B. Depth and duration of response of patients receiving 12 mg/m^2/q2Wk based on α-FR expression

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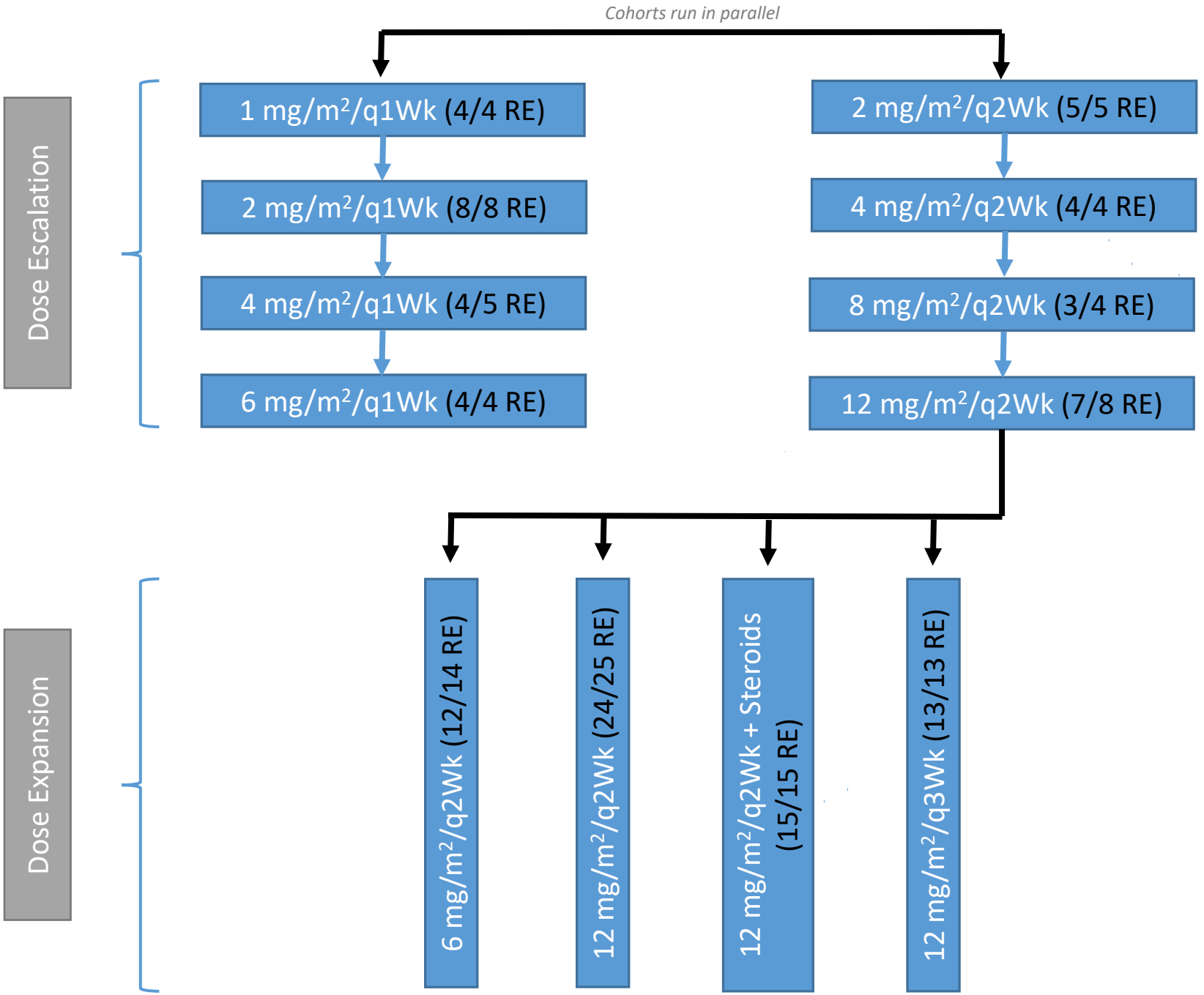
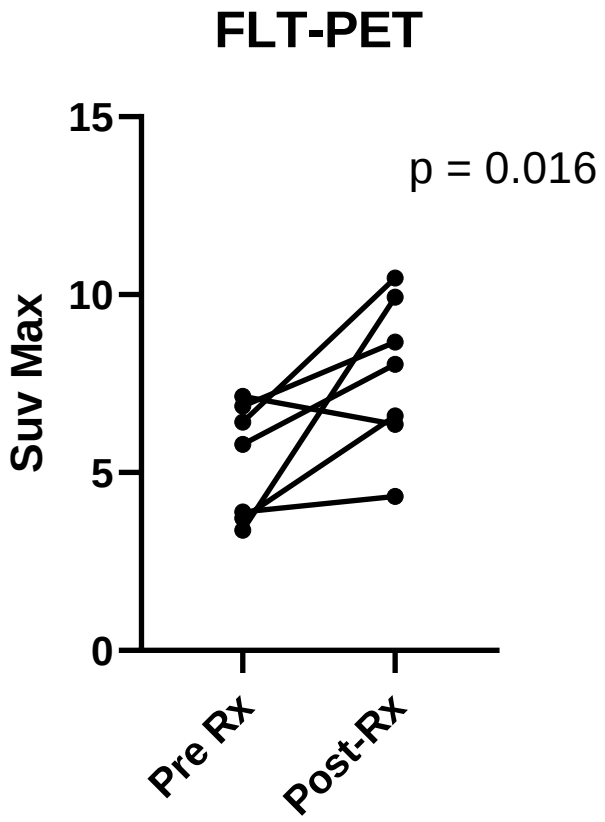


Figure 1

RE - Response Evaluable patients/cohort

A)



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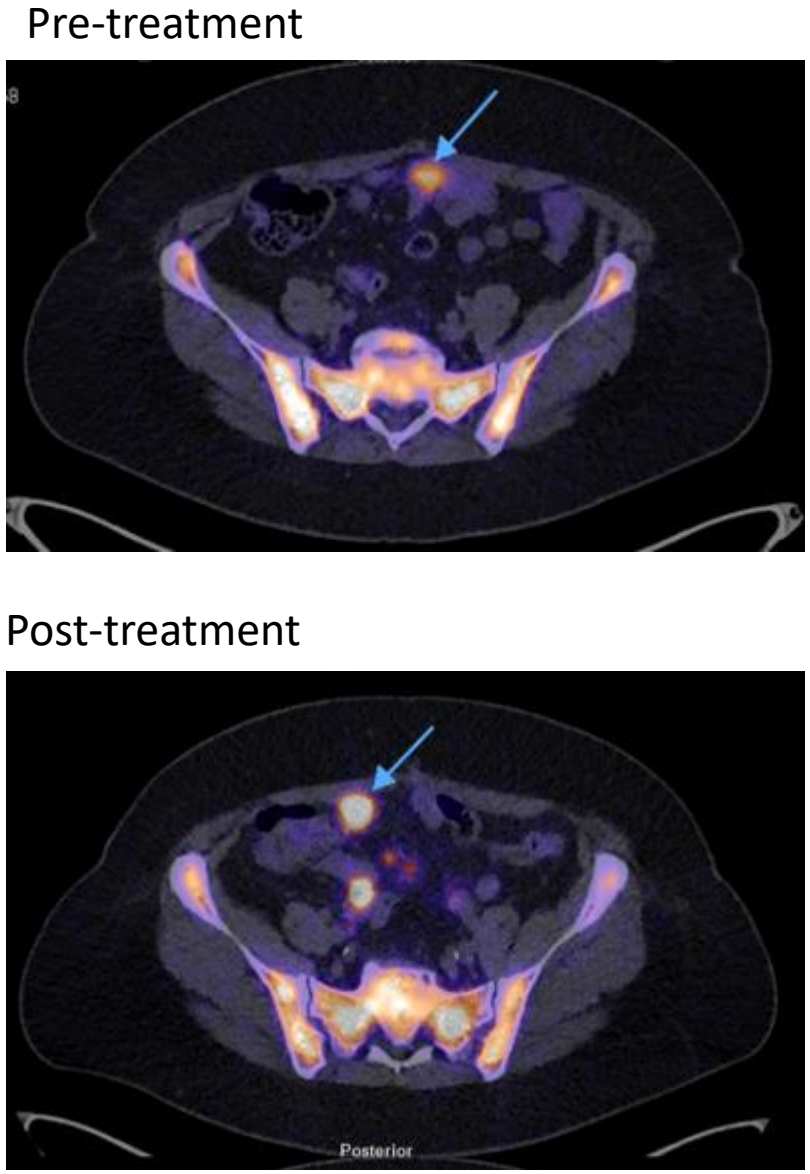
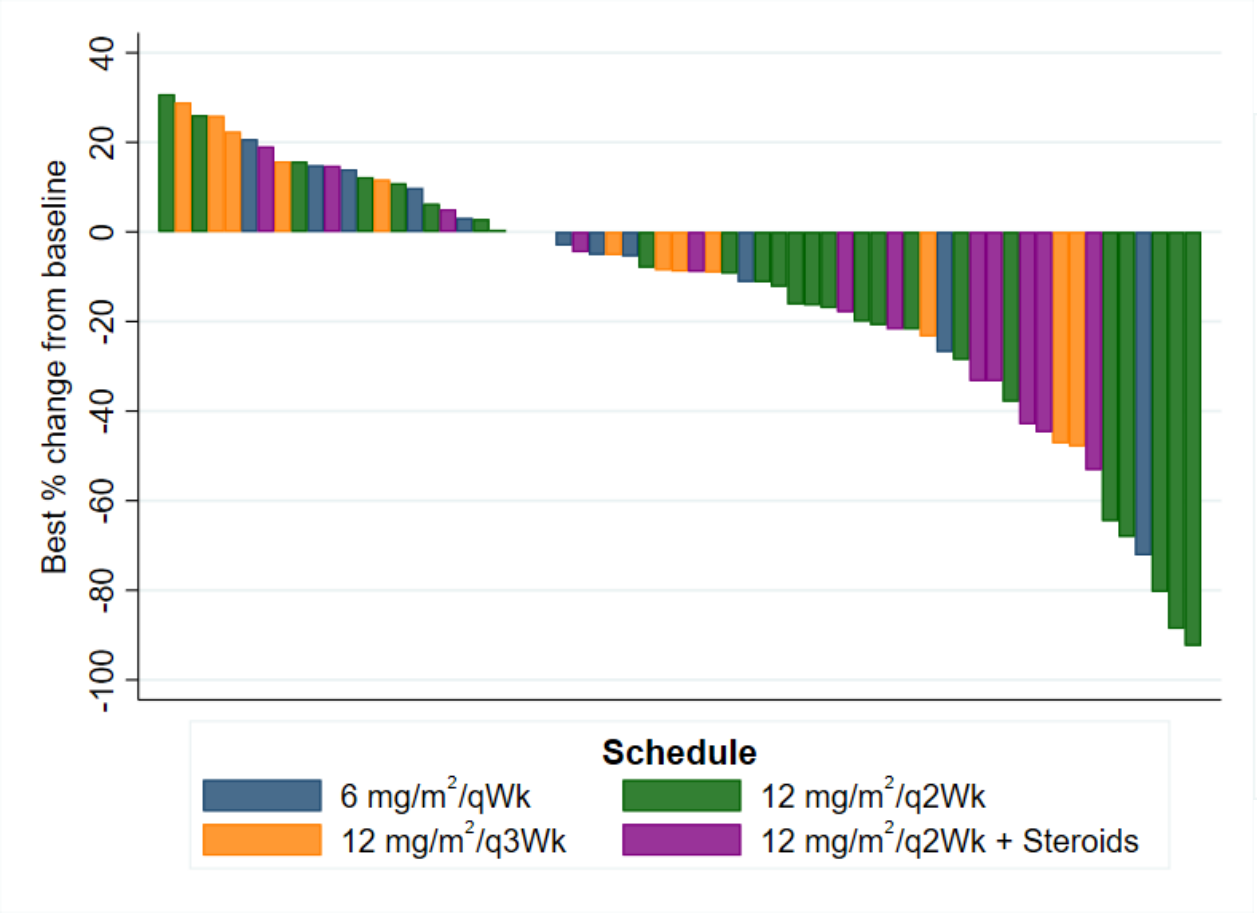


Figure 2

A



B

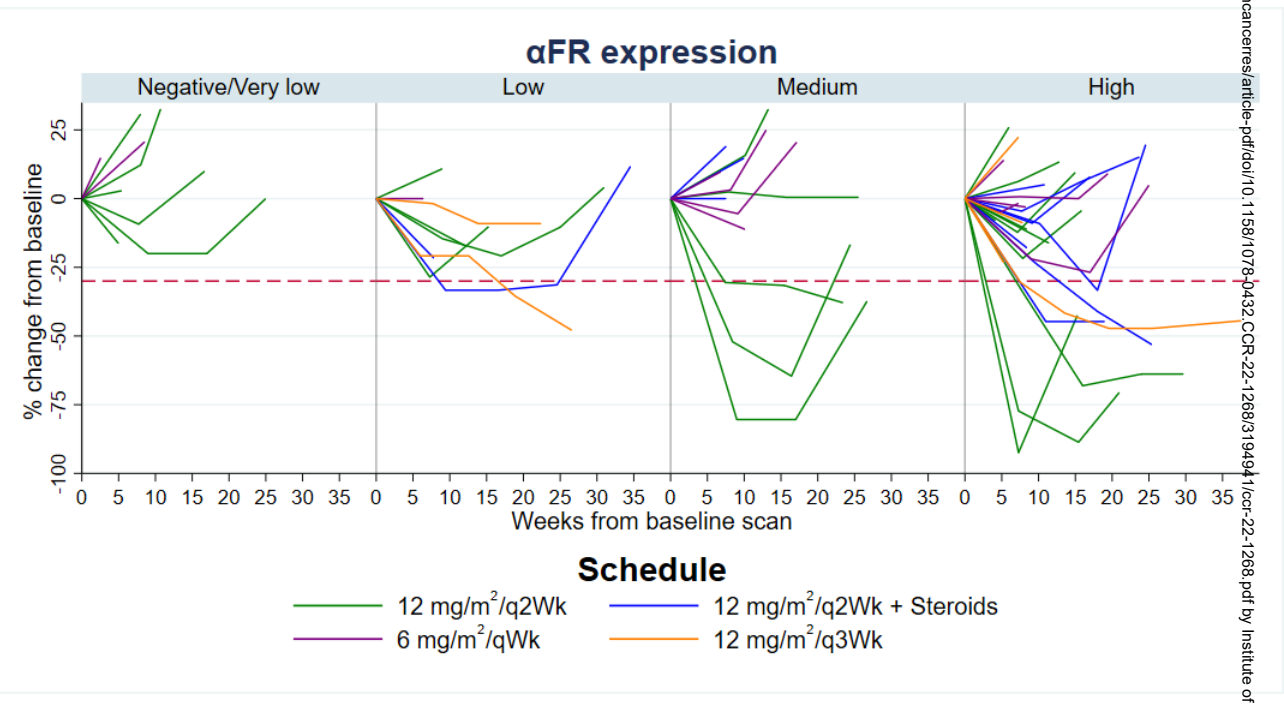


Figure 3

Table 1: Demographics in escalation and expansion

		Escalation		Expansion	
		Total N=42		Total N=67	
		n	%	n	%
Age (years)	Median (IQR)	61·0 (55·0 - 63·8)		62·0 (57·5 - 68·0)	
Sex	Female	31	73·8	67	100.0
	Male	11	26·2	0	0
ECOG Performance Status	0	15	35·7	14	20·9
	1	27	64·3	53	79·1
	Unknown	0	0	0	0
Primary diagnosis	Breast	1	2·4	0	0
	Colonic/Rectal	7	16·7	0	0
	Oesophageal	1	2·4	0	0
	Gastric	1	2·4	0	0
	Head and Neck	1	2·4	0	0
	Ocular	2	4·8	0	0
	Ovarian/Cervical/Endometrial	25	59·5	63	94·0
	Fallopian tube/Omentum/Peritoneum	0	0	4	6·0
	Pancreatic	3	7·1	0	0
	Renal	1	2·4	0	0
Prior lines of Treatment	Median (range)	4 (1 - 12)		5 (1 - 13)	

Table 2: Treatment related toxicities reported in the 12mg/m^2/q2Wk + Steroid expansion cohort by the dose level assigned and worst recorded CTCAE grade (only up to 10% toxicities tabulated)

Preferred Term	12 mg/m^2/q2Wk						12 mg/m^2/q2Wk + Steroids						Total	
	G1		G2		G3		G1		G2		G3			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Fatigue	12	48	1	4	0	0	6	40	2	13·3	0	0	21	53
Nausea	8	32	4	16	0	0	4	26·7	0	0	0	0	16	40
Diarrhoea	4	16	1	4	**1**	4	2	13·3	0	0	**1**	6·7	9	23
Cough	8	32	0	0	0	0	1	6·7	0	0	0	0	9	23
Anaemia	2	8	2	8	0	0	1	6·7	1	6·7	**2**	13·3	8	20
Pneumonitis	0	0	4	16	0	0	1	6·7	3	20	0	0	8	20
Pyrexia	3	12	0	0	0	0	4	26·7	0	0	0	0	7	18
Aspartate aminotransferase increased	3	12	1	4	0	0	3	20	0	0	0	0	7	18
Vomiting	4	16	0	0	0	0	0	0	0	0	0	0	4	10
Chills	2	8	1	4	0	0	1	6·7	0	0	0	0	4	10
Decreased appetite	3	12	0	0	0	0	1	6·7	0	0	0	0	4	10

Cohort (mg/m2)	Descriptive Statistic	Tmax (h)	Cmax (ng/mL)	HL Lambda_z (h)	AUC_{0-24} (h*ng/mL)	AUClast (h*ng/mL)	Cl (mL/h)	Vss (mL)
1	Mean	1.0	402	6.7	1654	1654	1219	7594
	CV%	1.7	7.2	47.6	39.7	39.7	47.7	19.7
	Geometric Mean	1.0	402	6.1	1565	1565	1116	7501
	CV% Geo Mean	1.8	7.2	62.2	43.4	43	57.6	19.0
	Median	1.0	401	7.5	1618	1618	1250	6745
	Range	1.0 - 1.0	374 - 432	3.2 - 9.4	1017 - 2329	1017 - 2329	623 - 1784	6712 - 9324
	N	*3*	*3*	*3*	*3*	*3*	*3*	*3*
2	Mean	0.9	746	12.6	4892	6857	674	8519
	CV%	29.6	14.4	42.1	42.9	63.0	75.1	34.2
	Geometric Mean	0.9	740	11.8	4541	5855	552	8193
	CV% Geo Mean	37.1	14.9	41.9	48.2	75	82.6	32.1
	Median	1.0	759	11.3	4733	6046	523	7407
	Range	0.5 - 1.1	613 - 855	7.5 - 20.0	2516 - 7588	2516 - 12818	244 - 1405	6534 - 12730
	N	*4*	*4*	*4*	*4*	*4*	*4*	*4*
6	Mean	1.0	2030	19.9	15104	25574	460	12024
	N	*1*	*1*	*1*	*1*	*1*	*1*	*1*
12	Mean	1.0	5132	28.7	47191	87560	216	7621
	CV%	1.4	12.4	24.6	13.9	23.5	29.6	11.1
	Geometric Mean	1.0	5101	28.1	46862	85858	207	7586
	CV% Geo Mean	1.4	12.2	22.4	13.0	22	33.0	10.6
	Median	1.0	4830	26.5	45428	83497	221	7333
	Range	1.0 - 1.0	4460 - 6010	23.0 - 41.0	42328 - 58611	68732 - 122559	126 - 303	6986 - 9065
	N	*5*	*5*	*5*	*5*	*5*	*5*	*5*

Table 3: Summary of CT900 Plasma Pharmacokinetic Parameters from dose escalation phase, Cycle 1 Day 1