Article Type: Research Article

Title: A Phase IB open-label, dose-escalation study of NUC-1031 in combination with carboplatin for recurrent ovarian cancer

Authors: Farasat Kazmi[1], Shibani Nicum[2], Rene L. Roux[2], Laura Spiers[1], Chat Gnanaranjan[3], Ajithkumar Sukumaran[4], Hani Gabra[4], Essam Ghazaly[5], Nigel W. McCracken[6], David J. Harrison[5,6], and Sarah P. Blagden[1]

Affiliation List:

1) Early Phase Clinical Trials Unit, Department of Oncology, University of Oxford, Oxford, UK; 2) Churchill Hospital, Oxford University Hospitals Trust, Oxford, UK 3) Barts Cancer Institute, Charterhouse Square, London, UK 4) Ovarian Cancer Action Research Centre, Imperial College London, UK; 5) School of Medicine, University of St Andrews, St Andrews, UK. 6) NuCana plc, 3 Lochside Way, Edinburgh, UK.

Running Title: NUC-1031 in recurrent ovarian cancer

Key words: Acelarin; NUC-1031; platinum-resistance; recurrent ovarian cancer

Additional Information:

- **Financial support:** The study was sponsored by Imperial College London and funded by NuCana plc.
- **Corresponding Author:** Dr Sarah Patricia Blagden, Associate Professor of Experimental Cancer Medicine, University of Oxford, Department of Oncology,

Churchill Hospital, Oxford, OX3 7LE, UK. Telephone: +44 (0)1865 227212; Email: sarah.blagden@oncology.ox.ac.uk

- **Conflicts of Interest:** DH receives salaried support from NuCana plc. NMcC is an employee of NuCana plc.
- **Word Count:** 5114
- **Number of Figures:** 3
- **Number of Tables:** 6
- **Number of Supplementary Tables:** 2
- **Number of Supplementary Figures:** 4

Translational Relevance:

The anti-metabolite gemcitabine has shown some evidence of synergy with platinum however it is rarely used in the management of platinum-resistant ovarian cancer (PROC). In this PRO-002 study, the ProTide NUC-1031 which is a phosphoramidate modification of gemcitabine was successfully administered with carboplatin in 25 heavily pre-treated patients with recurrent ovarian cancer (OC), of whom 15 (60%) were platinum-resistant and 9 (36%) had prior exposure to gemcitabine. The recommended Phase II combination dose (RP2CD) was defined as 500 mg/m^2 NUC-1031 (days 1 & 8) with carboplatin AUC5 (day 1) given every 3 weeks for up to 6 cycles. At this dose, strong efficacy was observed, even in platinum-resistant and gemcitabine-pre-treated patients, and myelosuppression was mild. The safety, pharmacokinetic (PK) and efficacy profile of NUC-1031 plus carboplatin indicates this combination could be a novel and effective treatment strategy for recurrent OC.

Abstract

Purpose: NUC-1031 is a first-in-class ProTide modification of gemcitabine. In PRO-002, NUC-1031 was combined with carboplatin in recurrent ovarian cancer (OC).

Experimental Design: NUC-1031 was administered on days 1 & 8 with carboplatin on day 1 every 3 weeks for up to 6 cycles. Four dose cohorts of NUC-1031 (500, 625 and 750 mg/m^2) with carboplatin (AUC4 or 5) were investigated. Primary endpoint was RP2CD. Secondary endpoints included safety, investigator-assessed objective response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS) and pharmacokinetics (PK).

Results: 25 women with recurrent OC, a mean of 3.8 prior lines of chemotherapy and a median platinum-free interval (PFI) of 5 months (range: 7 - 451 days) were enrolled, 15/25 (60%) platinum-resistant; 9 (36%) partially platinum-sensitive and 1 (4%) platinum-sensitive. Of the 23 response-evaluable: there was 1 confirmed complete response (CR, 4%), 5 partial responses (PR, 17%) and 8 (35%) stable disease (SD). The ORR was 26% and CBR was 74% across all doses and 100% in the RP2CD cohort. Median PFS was 27.1 weeks. NUC-1031 was stable in the plasma and rapidly generated high intracellular dFdCTP levels that were unaffected by carboplatin.

Conclusions: NUC-1031 combined with carboplatin is well tolerated in recurrent OC. Highest efficacy was observed at the RP2CD of 500 mg/m^2 NUC-1031 on days 1 & 8 with AUC5 carboplatin day 1, every 3 weeks for 6 cycles. The ability to deliver carboplatin at AUC5 and the efficacy of this schedule even in patients with platinum-resistant disease makes this an attractive therapeutic combination.

Introduction

The anti-metabolite chemotherapy gemcitabine (2'-2'-difluorodeoxycytidine; dFdC) has been used for the treatment for breast, ovarian, non-small cell lung, pancreatic, bladder and other cancers since the 1990s.(1-3) Like other nucleoside analogues, gemcitabine is a prodrug and is dependent on active transport into the cancer cell and subsequent step-wise enzymatic metabolism to gemcitabine monophosphate (dFdCMP), diphosphate (dFdCDP) and triphosphate (dFdCTP).(4, 5) The cytotoxic activity of gemcitabine is attributable to dFdCTP which is mis-incorporated into replicating DNA (in the place of deoxycytidine) resulting in masked chain termination and cell death.(4, 5) In addition, the intermediate metabolite gemcitabine diphosphate (dFdCDP) inhibits ribonucleotide reductase and prevents the formation of deoxycytidine, a pyrimidine nucleoside essential for DNA synthesis.(5) The first step in this activation process, the conversion of gemcitabine to dFdCMP, is rate-limited by the availability of the enzyme deoxycytidine kinase (dCK) which is typically expressed at low levels in resistant OC.(5) Additionally, the enzyme cytidine deaminase (CDA) that is often highly expressed in resistant OC degrades the majority of gemcitabine to an inactive metabolite, 2′,2′-difluorodeoxyuridine (dFdU).(6)

NUC-1031 is a ProTide form of gemcitabine that is chemically synthesised to overcome these limitations.(7) It is comprised of pre-activated gemcitabine monophosphate (dFdCMP) protected by a biolabile phosphoramidate motif.(7) NUC-1031 enters the cell independent of the Human Equilibrative Nucleoside Transporter (hENT1) channel whereupon the motif is cleaved by intracellular esterases releasing dFdCMP.(7) Having bypassed the first rate-limiting phosphorylation step by the enzyme dCK, dFdCMP is then rapidly converted to the active metabolites dFdCDP and dFdCTP.(7) In a 68-patient Phase I dose-escalation and expansion first-in-human (FIH) study, NUC-1031 displayed good efficacy and tolerability when given I.V. on days 1, 8 and 15 in 28-day cycles in heavily pre-treated patients with advanced cancers, including gynecological malignancies.(8) High levels of dFdCTP were detected in patients' peripheral blood mononuclear cells (PBMCs).(8) Importantly, grade 3/4

myelosuppression was minimal at doses of 825 mg/m^2 and below.(8) A recommended Phase II monotherapy dose range for NUC-1031 was defined as 825 mg/m^2. In light of the favourable impact on bone marrow function observed with NUC-1031, we conducted PRO-002 to explore giving NUC-1031 alongside AUC4 or 5 carboplatin in patients with recurrent OC. By testing four different dosing schedules, an efficacious dose of NUC-1031 was identified that could be given alongside AUC5 carboplatin with minimal myelotoxicity. This was defined as 500 mg/m^2 NUC-1031 given on days 1 & 8 every 3 weeks with AUC5 carboplatin given on day 1 every 3 weeks, both for up to 6 cycles.

Trial registration: Clinicaltrials.gov registry number NCT02303912.

Patients and Methods:

This open-label, Phase IB combination dose-escalation/ expansion study was conducted at two clinical centres in the United Kingdom: the Churchill Hospital, Oxford and the Hammersmith Hospital, London. The study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.(9) The protocol was approved by the West London Research Ethics Committee and all patients provided written informed consent before undergoing any study procedures. The primary objective of the study was to determine the RP2CD of NUC-1031 (on days 1 and 8) and carboplatin (on day 1) given in a 21-day schedule for up to six cycles. Secondary objectives were to evaluate the safety and tolerability of the combination and its efficacy by objective response rate (ORR), clinical benefit rate (CBR), progression-free survival (PFS) and best overall response (BOR), utilising the evaluation criteria determined by the Gynecologic Cancer Intergroup (GCIG) and Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.(10-12) Research objectives included assays to explore the relationship between NUC-1031 pharmacokinetics (PK), pharmacodynamics (PD) and clinical activity.

Eligible patients were aged ≥18 years with Eastern Cooperative Oncology Group (ECOG) performance score 0-2, adequate organ function, histologically-confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer (here collectively termed “ovarian cancer” or OC), and evaluable recurrent disease on radiological imaging (in accordance with RECIST v1.1 criteria). Patients must have had a platinum-free interval (PFI) of ≤24 months. PFI was defined as the time since last (adjuvant or non-adjuvant) platinum (carboplatin or cisplatin) or platinum-containing chemotherapy until start of subsequent non-platinum therapy or consent for PRO-002 (whichever occurred first).(13) Exclusion criteria included prior allergy to gemcitabine or carboplatin and symptomatic central nervous system metastases.

NUC-1031 was administered I.V. on days 1 and 8 every 21 days via a Groshong® or Peripherally Inserted Central Catheter (PICC). Initially, consistent with the Phase I study (8), NUC-1031 was administered in a 10-15 minute bolus injection but, in March 2016, this was substituted by a 250ml saline solution formulation of NUC-1031 that was administered over 30 minutes. Carboplatin was administered via a one-hour IV infusion on day 1 of each 21-day cycle, immediately prior to the administration of NUC-1031. Based on the findings of the PRO-001 (Phase I) study (8), a dose below the MTD of 750 mg/m^2 was chosen as the starting dose of NUC-1031 to combine with carboplatin AUC4. The dose was escalated sequentially in cohorts of 3 to 6 patients using an accelerated titration method (Table 1) with alternating escalation of NUC-1031 and carboplatin with each planned cohort. Dose-escalation stopped when the maximum tolerated dose (MTD)/RP2CD had been determined. The MTD was defined as the highest dose level for which fewer than 2 out of 6 (or <33%) patients experienced dose-limiting toxicities (DLTs). The expansion cohort was then dosed at the MTD to confirm the RP2CD.

Computed tomography (CT) based tumor assessments were conducted according to RECIST v1.1 criteria at screening and weeks 9 and 18. Serum CA125 was measured at baseline and at day 1 of each treatment cycle. Safety parameters were continually assessed and based on adverse events (AEs) graded according to the National Cancer Institute

Common Terminology Criteria for Adverse Events version 4.03, 2009, clinical laboratory data and physical examinations. In view of the association between gemcitabine and pulmonary toxicity, lung function assessments, comprised of spirometry, lung volumes and gas transfer, were performed at baseline and at the end of study participation.(14) Blood samples were collected for PK analysis at set time points after the end of NUC-1031 infusion (pre-dose, end of infusion, 30 minutes, 2 hours, 24 hours) on cycle 1 day 1. A DLT was defined as any of the following occurring during first treatment cycle: grade 3 or 4 non-hematological toxicity (excluding nausea/vomiting/diarrhea or rash that responded to standard medical treatment), grade 3 or 4 nausea/vomiting/diarrhea that occurred despite standard medical treatment, grade 4 neutropenia lasting >7 days, febrile neutropenia, grade 4 thrombocytopenia, any toxicity related to NUC-1031 that was unresolved after a treatment delay of >14 days or isolated/recurrent toxicity that was judged by the investigator to be a DLT. The use of granulocyte colony-stimulating factor was permitted from cycle 2 only.

Efficacy and Safety Analyses

ORR with exact binomial 95% confidence intervals (CIs) and Kaplan-Meier estimates for PFS (based on clinical symptoms and/or RECIST v1.1 progression) were calculated; safety analyses were descriptive. With respect to primary objectives and endpoints, no specific hypotheses were tested statistically. The primary focus was on determining the RP2CD, the safety profile, and the identification of a range of biologically active doses and the PK of NUC-1031 in patients with OC. Baseline characteristics of the patients, together with safety, PK, biomarker and anti-tumor activity summaries were provided by dose level of NUC-1031/carboplatin and overall. No formal interim analysis was performed in this study. Safety, PK and PD biomarker data were reviewed on an ongoing basis in line with the cohort progression criteria. Progression was defined as date of objective progression by RECIST criteria, by CA125 (GCIG) criteria or the date of symptomatic progression, whichever occurred first.

Pharmacokinetic (PK) analysis

Review of preliminary safety and available PK data from the dose-escalation was performed after completion of each dosing cohort. Blood samples (0.05, 0.55, 2.05, and 24 hours) were collected for PK analyses at set time points after the end of NUC-1031 infusion on cycle 1 day 1. Plasma was assayed for NUC-1031, dFdC, and dFdU and PBMCs for dFdCTP using ultra-performance liquid chromatography tandem mass spectrometry (UPLC MS/MS).(15) Given the relatively sparse PK sampling employed during the study, a Bayesian post-hoc approach utilising a base population model was taken to estimate PK parameters (C_{max}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{1/2,}$, V_{ss} and CL) for patients who provided concentration-time observations.

Pharmacokinetic modelling

The base population PK model was developed using Non-Linear Mixed Effects (NONMEM) using Phase 1b PK data (PRO-001) as part of the ongoing development of NUC-1031(16).The model was built in a stepwise manner with NUC-1031 being characterised first followed by dFdC and then dFdU. Random variability (ETAs) were tested for clearance (CL) and volume (V). The evaluation of the model was based on the values given by the objective function (-2log likelihood), the Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC) and the coefficient of determination of linear regression of the observed versus predicted values. A visual predictive check (VPC) was performed to assess whether the model was predictive.

Statistical analysis

Sample size calculations were based on a Fleming design.(17) No formal statistical analyses were planned or performed on safety or efficacy data.

Results

Between 27 November 2014 and 10 November 2016, 25 eligible patients were enrolled in the study. At the time of data cut-off on 30 May 2017, no patients remained on study; 18 having successfully completed treatment and 7 having discontinued (3 due to disease progression, 2 to adverse events, 1 to unmanageable toxicity, and 1 to physician decision). All 25 patients were considered toxicity-evaluable. Two patients discontinued the study before their first post-enrolment (9 week) CT scan for toxicities that had not resolved to baseline within 2 weeks and the remaining 23 participants were response-evaluable. Twenty (80%) out of the 25 patients were included in the CA125 evaluable-for-response set; the remaining 5 patients (20%) did not have a baseline CA125 level of ≥2×upper limit of normal (ULN). See Table 2 for patient characteristics. Patients had a mean age of 64 years (range 37 - 77 years) and the majority had a good performance status (92% ECOG PS 0 or 1). All had primary ovarian cancer and 23/25 (92%) had serous histology. The majority of study patients (15/25, 60%) had platinum-resistant disease with a platinum-free interval (PFI) of <6 months, the median PFI amongst them was 5 months (range: 7 - 184 days). Of the remaining 10 patients, 9 (36%) had partially platinum-sensitive disease with a median PFI of 8 months (range 195-311 days) and one (4%) was platinum-sensitive with a PFI of 14.8 months. Patients had received a mean of 3.8 prior lines of treatment (median 3, range 2-8), including first-line treatment. Nine (35%) had received gemcitabine as part of a preceding regimen, 3 of whom entered PRO-002 having progressed immediately after gemcitabine and carboplatin treatment. BRCA testing was not universally conducted at the time of the study so BRCA status was unknown for 14 (56%) patients; 5 of the remaining 11 (20%) were BRCA wild-type and 6 (24%) were confirmed BRCA mutation carriers (5 with BRCA1 and 1 with BRCA2 mutations).

Patients were sequentially recruited into the study: 6 were recruited into Cohort 1, 1 into Cohort 2, 12 into Cohort 2B and 6 into Cohort 3 (Table 1). Eighteen (72%) patients completed all 6 cycles of study treatment, whilst 7 discontinued prematurely for progressive disease or other reasons. Among the 25 treated patients, a mean of 5.1 cycles of NUC-1031

plus carboplatin were administered. Across all dose levels, 68% and 81% of planned doses of NUC-1031 and carboplatin were administered, respectively. The majority of patients had dose reductions and dose modifications of both drugs and 12 (48%) patients required ≥1 NUC-1031 dose reduction. Summarised in Table 3.

Safety: All 16 patients in the dose-escalation part of the study were DLT-evaluable. Amongst them, 4 experienced at least one DLT during cycle 1 of their treatment. The first was a DLT of grade 4 thrombocytopenia in a patient in Cohort 1 (750 mg/m^2 NUC-1031 & carboplatin AUC4) prompting the enrolment of a further 3 patients to this dose level. The same patient had 4 additional DLTs: G3 fatigue, G3 febrile neutropenia, G4 leucopenia, G4 neutropenia. As no further DLTs were observed in Cohort 1, the carboplatin dose was escalated to AUC5 and given with 750 mg/m^2 NUC-1031 for Cohort 2. The first patient to be enrolled in this cohort experienced grade 3 neutropenia before C1D8 which was not a DLT but required a dose interruption and reduction. In view of the rapid emergence of this AE, the investigators agreed to discontinue enrolment in this cohort and opened Cohort 2B in which the carboplatin was given at AUC5 alongside 500 mg/m^2 NUC-1031. Three patients were recruited to this cohort and no DLTs were observed. Cohort 3 was then opened exploring 625 mg/m^2 NUC-1031 & carboplatin AUC4. Six patients were enrolled in this cohort, and 4 DLTs were observed in 3 patients: G4 thrombocytopenia in one, G3 fatigue in one, and G3 fatigue with G3 hyponatremia in the third. The MTD was therefore defined as 500 mg/m^2 NUC-1031 and carboplatin AUC5 (dose used in Cohort 2B). Cohort 2B was then expanded to include an additional 9 patients (to 12 in total) which confirmed this as the RCP2D.

Across the dose-escalation and expansion parts of the study, the majority of patients (88%) experienced an AE of G3 or higher and underwent at least one dose modification of NUC-1031 (84%) and carboplatin (68%) (Table 4). A total of 24 (96%) patients experienced at least one grade 1 or 2 treatment-related AE. The most common grade 1 or 2 AEs observed across all doses that were causally attributable to carboplatin or NUC-1031 were: neutropenia (68%), hypomagnesemia (64%), nausea (52%), fatigue (48%), anemia (48%),

leukopenia (48%) and transaminitis (48%) (Table 5). Neutropenia was the principal reason for dose modification (76%). Although the numbers of patients per cohort were too small for formal statistical comparison, across all cohorts, grades 1-4 myelosuppression (anemia, neutropenia and thrombocytopenia) were NUC-1031 dose-dependent, affecting 67% of patients in Cohort 1 (NUC-1031 750 mg/m^2) and 58% in Cohort 2B (NUC-1031 500 mg/m^2). No allergic reactions to carboplatin or NUC-1031 were observed in any study participants.

Pharmacokinetic Model

The base population PK model that best described NUC-1031 and its metabolites dFdC and dFdU is shown in Supplementary Figure 1. Based on AIC and goodness of fit (GOF) plots, a three compartment model was found as the most appropriate model to describe the data for NUC-1031. The rate of conversion of NUC-1031 to dFdC was also described in a three compartment model, whereas a single compartment model was used for the conversion of dFdC to dFdU. Population PK parameters of NUC-1031 and its metabolites dFdC and dFdU are shown in Supplementary Table 2. GOF plots for NUC-1031, dFdC and dFdU are shown in Supplementary Figure 2. The R squared values of the linear regression for NUC-1031, dFdC and dFdU were found to be 0.77, 0.53 and 0.88, respectively. The predictive nature of the model to determine the PK of NUC-1031 and its metabolites dFdC and dFdU is shown in Supplementary Figure 3.

This model was used to estimate PK parameters for each of the 21 participants who provided evaluable concentration-time observations. The individual post-hoc PK parameter estimates obtained from the final model were then used to calculate PK exposure parameters for each analyte. The base population PK model provided an adequate fit to the individual observed plasma concentration-time data for NUC-1031, dFdC, and dFdU (Supplementary Figure 4).

Pharmacokinetics

Twenty-one participants had evaluable PK samples: 8 participants from Cohort 2B (NUC-1031 500 mg/m^2), 6 participants from Cohort 3 (NUC-1031 625 mg/m^2) and 7 participants from Cohort 1 and 2 (NUC-1031 750 mg/m^2). Three PK datasets were not obtained.

The mean infusion times for NUC-1031 500 mg/m^2, 625 mg/m^2 and 750 mg/m^2 dose levels were 19.3 (range 9-30), 14.7 (range 5-26) and 26.6 (range 14-30) minutes, respectively. Similar to PRO-001, AUC_{0-t} and C_{max} were used to compare PK between doses and in relation to potential interactions.(8) Following administration, NUC-1031 achieved substantially higher concentrations than its metabolites dFdU and dFdC on day 1 as shown in Figure 1.

The mean AUC_{0-24} of NUC-1031 increased with increasing dose whereas the mean AUC_{0-24} of dFdC decreased with increasing dose. The mean AUC_{0-24} of dFdU was found to be similar between doses. The mean C_{max} of NUC-1031 and dFdU increased between Cohort 2B (NUC-1031 500 mg/m^2) and Cohort 3 (NUC-1031 625 mg/m^2) but was lower in Cohort 1 and 2 (NUC-1031 750 mg/m^2). The mean C_{max} of dFdC decreased with increasing dose (Supplementary Table 2). The reduction in NUC-1031 and dFdU C_{max} values in Cohort 1 and 2 can be explained by significantly longer infusion times for NUC-1031 in Cohort 1 and 2 (NUC-1031 750 mg/m^2) with mean infusion time of 27 mins versus 19 and 14 mins for Cohorts 2B and 3 respectively, resulting in lower amounts of NUC-1031 infused per minute and subsequent reduced concentrations from which to calculate the C_{max} (plasma and PBMC) values. Intracellular concentrations of the active anti-cancer metabolite dFdCTP remained high throughout the 24-h PK sampling window with median C_{max} values of 2.66, 4.16 and 3.22 µg/mL at 500, 626 and 750 mg/m^2, respectively (Supplementary Appendix 1). C_{max} values generated during the PRO-001 study at the 500 and 625 mg/m^2 doses were very similar to those seen for PRO-002, with median values of 3.31 and 4.09 µg/mL respectively and higher for the 750 mg/m^2 dose with a median C_{max} of 8.44 µg/mL.(8)

A comparison of the PRO-002 PK parameters with those generated during the PRO-001 study indicates that combination with carboplatin did not alter the PK profile of NUC 1031.(8)

In Cohort 2B (NUC-1031 500 mg/m^2), Cohort 3 (NUC-1031 625 mg/m^2), and Cohort 1 and 2 (NUC-1031 750 mg/m^2), the median concentrations of NUC-1031 AUC_{0-24} and C_{max} were 118 µg/h/mL and 412 µg/mL, 176 µg/h/mL and 573 µg/mL and 259 µg/h/mL and 499 µg/mL respectively. These values were similar to the median AUC_{0-24} and C_{max} values generated following administration of 500, 625 and 750 mg/m^2 NUC-1031 alone (PRO-001 study): 122 µg/h/mL and 654 µg/mL, 161 µg/h/mL and 419 µg/mL and 272 µg/h/mL and 718 µg/mL, respectively. These results demonstrate that there was no clinically relevant PK drug-drug interaction between NUC-1031 and carboplatin.

Efficacy

Radiological response to treatment was determined using CT scans conducted at weeks 9 and 18 and compared to baseline scans according to RECIST v1.1 criteria (Table 6). Amongst the 23 response-evaluable patients, one (4%) had a confirmed response of a CR, 5 had confirmed PR (22%) resulting in an ORR of 26%, 8 (35%) had stable disease of >6 weeks duration and 8 (35%) progressed on study. Four of the 6 responses occurred in Cohort 2B and two in Cohort 1. One patient in Cohort 3 achieved a PR by their 18-week CT scan but discontinued due to fatigue. CBR, defined as the proportion of patients with a best overall response according to RECIST v1.1 of CR, PR and SD, was highest in Cohort 2B with 11/11 (100%) evaluable patients obtaining clinical benefit from treatment (Figure 2). In terms of CA125 response, five patients were not evaluable as they did not have baseline CA125 levels ≥2×ULN (35 U/mL). Of the remaining 20 who were CA125 response-assessable, 11 (55%) patients showed a CA125 response: 10 (50%) with confirmed PR and 1 (5%) with confirmed CR (Figure 3). The best change in CA125 occurred in Cohorts 2 and 2B with mean changes of 72% and 61%, respectively.

Of the 6 patients (22%) who had a confirmed RECIST v1.1 response in the full analysis set, 1 was platinum-sensitive and 5 were partially platinum-sensitive at study entry. Of the 8 patients with lasting SD, 7 had platinum-resistant and 1 had partially platinum-sensitive disease. Of the 8 patients who progressed between their 9 and 18 week scans, 7 were

platinum-resistant and 1 was partially platinum-sensitive. Overall, all 23 evaluable patients (100%) included in the exploratory analysis had progression at the time of PFS analysis**.** The median PFS duration was 27.1 weeks (6.2 months) (range: 5 - 46 weeks; 95% CI: 19.1 - 29.7).

Discussion

Platinum-based chemotherapies like carboplatin and cisplatin remain at the mainstay of treatment for ovarian cancer and, even in the current era of targeted therapies, the emergence of platinum-resistance has adverse prognostic implications.(12, 13) Strategies to extend or recover platinum sensitivity have been explored by combining platinum-based chemotherapy with other synergistic agents. However, combinations that display synergism *in vitro* can cause additive toxicities in the clinical setting. Gemcitabine, whilst synergising with both carboplatin and cisplatin in cell lines and xenografts, causes severe dose-limiting myelosuppression when given with cisplatin in the clinic.(18) Even in less heavily pre-treated platinum-sensitive patients, carboplatin and gemcitabine are administered at reduced doses of AUC4 (days 1) and 1000 mg/m^2 (days 1 and 8) respectively to lessen myelotoxicity.(12, 13) More recently, this regimen has been superseded by carboplatin and liposomal doxorubicin (PLD), wherein carboplatin can be administered at AUC5 but at a longer cycle length of 4 weeks.(19) When evaluated in patients with partially platinum-sensitive OC in the CALYPSO study, the carboplatin and PLD combination yielded an ORR of 39%.(20)

As preclinical studies showed NUC-1031 bypasses chemoresistance mechanisms, and a first-in-human Phase I study showed it was less myelotoxic than gemcitabine, we questioned whether NUC-1031 could be repositioned in combination with AUC5 carboplatin for the treatment of recurrent partially platinum-sensitive and resistant ovarian cancer. The majority of patients in PRO-002 had PROC and were heavily pre-treated.(8) At the RP2CD of 500

mg/m^2 NUC-1031 and AUC5 carboplatin, treatment was well-tolerated and all 11 evaluable patients in this cohort derived clinical benefit; 6 with best responses of PR and 5 with SD of >6 weeks. Interestingly, 5 of these 11 patients had previously received gemcitabine and one had progressed on a gemcitabine-containing regimen prior to entering PRO-002. These findings support preclinical studies showing that NUC-1031 overcomes resistance mechanisms associated with gemcitabine (7, 21). At this dose of NUC-1031, myelotoxicity was low grade and manageable, enabling the concomitant administration of carboplatin at AUC5. Other toxicities were also minimal, of note no lung toxicity was observed in any dosing cohorts. Although patients were precluded from the study if they had a history of allergy to platinum agents or gemcitabine, we did not observe any *de novo* allergic reactions to carboplatin or NUC-1031 in any of the study participants.

This study had limitations; it was small and the population, although mostly platinum-resistant, was heterogenous as it contained platinum-sensitive, partially platinum sensitive as well as resistant OC patients. The regimen examined would need further evaluation in a larger study to more clearly compare and characterise disease response by platinum-sensitivity and allow comparison with current standard of care regimens. In addition, to reflect standard of care, in PRO-002 radiological tumour assessments were scheduled after every 9 weeks (3 cycles of treatment)- longer than in comparable chemotherapy studies in which imaging is conducted every 4 weeks (10, 11). As a RECIST response is only confirmed if it is maintained for 2 consecutive scans, our reported rates of confirmed ORR and radiological PFS are probably conservative.(10) Finally, at the time of this study, BRCA1/2 gene testing was only approved for OC patients with an indicative familial or personal cancer history and was known for 13 (52%) of the study patients. Of the 23 response-evaluable patients, 6 were BRCA 1 or 2 germ-line carriers (26%), 6 were BRCA negative (26%) and 11 were BRCA unknown (48%). Amongst the patients with best responses, the two CRs were observed in one BRCA-negative patient and one with BRCA-unknown and the 7 PRs were seen in 4 BRCA-negative, 2 BRCA-unknown and 1 BRCA-

positive patients. Although numbers are small, this suggests there was no evidence of superior response to chemotherapy in the BRCA carriers, who were predominantly platinum-resistant at the time of study entry. Instead, response was more aligned with platinum-free interval across the study participants. A comparison of the PRO-002 PK parameters with those generated following monotherapy (PRO-001 study) indicates that combining with carboplatin does not alter the profile of NUC 1031, suggesting there is no clinically relevant PK interaction between NUC-1031 and carboplatin. Overall, this study provides encouraging evidence to support the use of NUC-1031 in combination with carboplatin AUC5 in patients with recurrent ovarian cancer.

Acknowledgments

The study was designed by the lead investigators and the Sponsor (Imperial Healthcare NHS Trust). The sponsor collected and analysed the data in conjunction with the authors. Phastar provided statistical analysis support. This work was also supported by the BRC, ECMC and CRUK Clinical Centres, and the Ovarian Cancer Action Research Centre, Imperial College London. The study was funded and the investigational drug NUC-1031 was supplied by NuCana plc. We are grateful to Danielle McLean for her support in writing this manuscript and the late Professor Chris McGuigan for synthesising the ProTide NUC-1031.

Figures and legends:

Figure 1: Pharmacokinetic profile of metabolites NUC-1031, dFdU and dFdC. Mean dose-normalised NUC-1031, dFdC, and dFdU plasma concentrations from Cohort 2B (NUC-1031 500 mg/m^2 & carboplatin AUC5) and Cohort 3 (NUC-1031 625 mg/m^2 & carboplatin AUC4) using observed and predicted model concentrations, plotted on a semi-log scale.

Abbreviations: dFdC = Difluorodeoxycytidine; dFdU = 2',2'-difluorodeoxyuridine; dFdCTP = gemcitabine triphosphate; AUC = area under the plasma concentration time curve.

Figure 2: Waterfall chart comparing the best change (%) from baseline of target lesions based on RECIST 1.1. The dashed lines represent the threshold for progressive disease (PD) at +20% and partial response (PR) at -30% from baseline. Twenty two of the 23 evaluable patients are included in this graph as one patient in Cohort 2B did not have any target lesions. Cohort 1 (NUC-1031 750 mg/m^2 & carboplatin AUC4), Cohort 2 (NUC-1031 750 mg/m^2 & carboplatin AUC5), Cohort 2B (NUC-1031 500 mg/m^2 and carboplatin AUC5) and Cohort 3 (NUC-1031 625 mg/m^2 & carboplatin AUC4). Abbreviations: RECIST = Response Evaluation Criteria In Solid Tumors version 1.1; AUC = area under the plasma concentration time curve

Figure 3: Waterfall chart showing best change (%) from baseline of CA125 levels. The dashed line represents a change of 50% from baseline. Cohort 1 (NUC-1031 750 mg/m^2 & carboplatin AUC4), Cohort 2 (NUC-1031 750 mg/m^2 & carboplatin AUC5), Cohort 2B (NUC-1031 500 mg/m^2 and carboplatin AUC5) and Cohort 3 (NUC-1031 625 mg/m^2 & carboplatin AUC4). Abbreviations: AUC = area under the plasma concentration time curve.

Table 1: Number of patients and doses of NUC-1031 and carboplatin by cohort

Table 2: Demographic and clinical characteristics at baseline. Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; MMMT = malignant mixed mesodermal tumor

Table 3: Treatment completion and intensity by cohort

Table 4: Grade 3 /4 Adverse Events. Abbreviations: AE = Adverse Events; CTCAE = Common Terminology Criteria for Adverse Events

Table 5: Grade 1 and 2 Adverse Events Causally Related to Study Drug affecting >5% study participants

Table 6: RECIST responses by cohort. Abbreviations: AUC = area under the plasma concentration time curve; RECIST = Response Evaluation Criteria In Solid Tumors version 1.1.

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Table 1: Number of patients and doses of NUC-1031 and carboplatin by cohort

Cohort	NUC-1031 (Days 1 & 8, every 3 weeks) x 6 cycles	Carboplatin (Day 1 only, every 3 weeks) x 6 cycles	Number of patients (n = 25)
1	750 mg/m^2	AUC4	6
2	750 mg/m^2	AUC5	1
2B	500 mg/m^2	AUC5	12
3	625 mg/m^2	AUC4	6

Table 2: Demographic and baseline characteristics

Number of patients, n (%)	Cohort 1 NUC-1031 750 mg/m^2 + carboplatin AUC4 **n=6** **(%)**	Cohort 2 NUC-1031 750 mg/m^2 + carboplatin AUC5 **n=1** **(%)**	Cohort 2B NUC-1031 500 mg/m^2 + carboplatin AUC5 **n=12** **(%)**	Cohort 3 NUC-1031 625 mg/m^2 + carboplatin AUC4 **n=6** **(%)**	All Patients **n=25** **(%)**
Age, years					
Mean (SD)	63.3 (15.2)	63	63.4 (8.8)	65.8 (9.3)	**64 (10.1)**
Median	68.5	63	63.5	67	**65**
ECOG PS, n (%)					
0	2 (33)	1(100)	8 (67)	3 (50)	**14 (56)**
1	4 (67)	0	4 (33)	1 (17)	**9 (36)**
2	0	0	0	2 (33)	**2 (8)**
BRCA Mutation Status, n (%)					
BRCA 1	1 (17)	0	3 (25)	1 (17)	**5 (20)**
BRCA 2	0	0	0	1 (17)	**1 (4)**
Wild-type	1 (17)	0	3 (25)	1 (17)	**5 (20)**
Unknown	4 (67)	1 (100)	6 (50)	3 (50)	**14 (56)**
Stage at Diagnosis, n (%)					
IIB	1 (17)	0	0	0	**1 (4)**
IIIB	2 (33)	0	1 (8)	0	**3 (12)**
IIIC	1 (17)	0	6 (50)	3 (50)	**10 (40)**
IV	2 (33)	1(100)	5 (42)	3 (50)	**11 (44)**
Histological Grade, n (%)					
Grade 2	0	0	0	1 (17)	**1 (4)**
Grade 3	5 (83)	1 (100)	11 (92)	4 (67)	**21 (84)**
Other	1 (17)	0	0	1 (17)	**2 (8)**
Missing	0	0	1 (8)	0	**1 (4)**
Histological Type, n (%)					
Serous/papillary serous	6*	1	12	4	**23 (92)**
MMMT	0	0	0	1	**1 (4)**
Mucinous	0	0	0	1	**1 (4)**
Other	0	0	0	0	**0**
Number of Prior Chemotherapy Courses n (%)					
2	2 (33)	0	3 (25)	1 (17)	**6 (24)**
3	2 (33)	0	3 (25)	3 (50)	**8 (32)**
4	0	1 (100)	2 (17)	1 (17)	**4 (16)**
5	1 (17)	0	2 (17)	0	**3 (12)**
6	0	0	1 (8)	1 (17)	**2 (8)**
7	0	0	1 (8)	0	**1 (4)**
8	1 (16.7)	0	0	0	**1 (4)**
Prior Gemcitabine, n (%)					
Yes	3 (50)	0	5 (42)	1 (17)	**9 (36)**
No	3 (50)	1 (100)	7 (58)	5 (83)	**16 (64)**
Platinum-free Interval n (%)					
<6 months	4 (67)	0	7 (58)	4 (67)	**15 (60)**

6-12 months	1 (17)	1 (100)	5 (41)	2 (33)	**9 (36)**
>12 months	1 (17)	0	0	0	**1 (4)**
MMMT=malignant mixed mullerian tumor	*One with neuroendocrine differentiation.				

Author Manuscript Published OnlineFirst on March 19, 2021; DOI: 10.1158/1078-0432.CCR-20-4403
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

Table 3: Treatment completion and intensity by cohort

Number of patients, n (%)	**Cohort 1** NUC-1031 750 mg/m^2 + carboplatin AUC4 **n=6 (%)**	**Cohort 2** NUC-1031 750 mg/m^2 + carboplatin AUC5 **n=1 (%)**	**Cohort 2B** NUC-1031 500 mg/m^2 + carboplatin AUC5 **n=12 (%)**	**Cohort 3** NUC-1031 625 mg/m^2 + carboplatin AUC4 **n=6 (%)**	**All Patients n=25 (%)**
Completed all 6 cycles	5 (83)	0	10 (83)	3 (50)	**18 (72)**
Patients who discontinued study treatment	1 (17)	1 (100)	2 (17)	3 (50)	**7 (28)**
• Adverse event	0	0	1 (8)	0	**1 (4)**
• Physician decision	0	0	0	1 (17)	**1 (4)**
• Progressive disease	1 (17)	1 (100)	0	1 (17)	**3 (12)**
• Protocol-specified	0	0	1 (8)	0	**1 (4)**
• Patient-requested	0	0	0	2 (33)	**2 (8)**
NUC-1031 dose modification	6 (100)	1 (100)	10 (83)	4 (67)	**21 (84)**
• NUC-1031 dose reduction	2 (33)	1 (100)	5 (42)	4 (67)	**12 (48)**
NUC-1031 dose intensity (% delivered/planned dose)	79%	25%	77%	40%	**68%**
Carboplatin dose modification	5 (83)	1 (100)	8 (67)	3 (50)	**17 (68)**
• carboplatin dose reduction	1 (17)	1 (100)	4 (33)	1 (17)	**7 (28)**
Carboplatin dose intensity (% delivered/planned dose)	96%	88%	80%	69%	**81%**

Table 4: Grade 3 /4 Adverse Events

System	Cohort 1 NUC-1031 750 mg/m^2 + carboplatin AUC4	Cohort 2 NUC-1031 750 mg/m^2 + carboplatin AUC5	Cohort 2B NUC-1031 500 mg/m^2 + carboplatin AUC5	Cohort 3 NUC-1031 625 mg/m^2 + carboplatin AUC4	All Patients
	(n=6)	(n=1)	(n=12)	(n=6)	**(n=25)**
Patients with any AE of CTCAE Grade 3 or higher	4 (67)	1 (100)	11 (92)	6 (100)	22 (88)
Blood and Lymphatic System Disorders	4 (67)	1 (100)	7 (58)	5 (83)	17 (68)
Neutropenia	4 (67)	1 (100)	5 (42)	3 (50)	13 (52)
Leukopenia	4 (67)	1 (100)	1 (8)	1 (17)	7 (28)
Thrombocytopenia	2 (33)	0	3 (25)	2 (33)	7 (28)
Anemia	1 (17)	0	1 (8)	1 (17)	3 (12)
Lymphopenia	3 (50)	0	0	0	3 (12)
Febrile neutropenia	2 (33)	0	0	0	2 (8)
Leukocytosis	0	1 (100)	0	0	1 (4)
Gastrointestinal Disorders	1 (17)	0	3 (25)	2 (33)	6 (24)
Abdominal pain	1 (7)	0	0	1 (17)	2 (8)
Diarrhea	0	0	1 (8)	1 (17)	2 (8)
Intestinal ischemia	1 (17)	0	0	0	1 (4)
Intra-abdominal hemorrhage	0	0	1 (8)	0	1 (4)
Vomiting	0	0	1 (8)	0	1 (4)
General Disorders and Administration Site Conditions	2 (33)	0	0	2 (33)	4 (16)
Fatigue	2 (33)	0	0	2 (33)	4 (16)
Incarcerated hernia	1 (17)	0	0	0	1 (4)
Infections and Infestations	3 (50)	0	0	1 (17)	4 (16)
Medical device site infection	3 (50)	0	0	0	3 (12)
Infection	1 (17)	0	0	0	1 (4)
Urinary tract infection	0	0	0	1 (17)	1 (4)

System	Cohort 1 NUC-1031 750 mg/m^2 + carboplatin AUC4	Cohort 2 NUC-1031 750 mg/m^2 + carboplatin AUC5	Cohort 2B NUC-1031 500 mg/m^2 + carboplatin AUC5	Cohort 3 NUC-1031 625 mg/m^2 + carboplatin AUC4	All Patients
	(n=6)	(n=1)	(n=12)	(n=6)	**(n=25)**
Injury, Poisoning and Procedural Complications	0	0	2 (17)	0	2 (8)
Infusion-related reaction	0	0	1 (8)	0	1 (4)
Vascular access complication	0	0	1 (8)	0	1 (4)
Metabolism and Nutrition Disorders	4 (67)	0	2 (17)	2 (33)	8 (32)
Hypophosphatemia	2 (33)	0	1 (8)	0	3 (12)
Hypokalemia	2 (33)	0	0	0	2 (8)
Hyponatremia	0	0	0	2 (33)	2 (8)
Hypoalbuminemia	0	0	0	1 (17)	1 (4)
Hypomagnesemia	0	0	1 (8)	0	1 (4)
Renal and Urinary Disorders	1 (17)	0	1 (8)	0	2 (8)
Hematuria	0	0	1 (8)	0	1 (4)
Hydronephrosis	1 (17)	0	0	0	1 (4)
Urinary tract obstruction	1 (17)	0	0	0	1 (4)
Respiratory, Thoracic and Mediastinal Disorders	0	0	1 (8)	0	1 (4)
Pulmonary embolism	0	0	1 (8)	0	1 (4)
Vascular Disorders	0	0	0	1 (17)	1 (4)
Embolism	0	0	0	1 (17)	1 (4)

Table 5: Grade 1 and 2 Adverse Events Causally Related to Study Drug affecting >5% Study Participants

System Organ Class	Cohort 1 NUC-1031 750 mg/m^2 + carboplatin AUC4	Cohort 2 NUC-1031 750 mg/m^2 + carboplatin AUC5	Cohort 2B NUC-1031 500 mg/m^2 + carboplatin AUC5	Cohort 3 NUC-1031 625 mg/m^2 + carboplatin AUC4	All Patients
	n=6 (%)	n=1 (%)	n=12 (%)	n=6 (%)	n=25 (%)
Blood and Lymphatic System Disorders					
Neutropenia	6 (100)	1 (100)	7 (58)	3 (50)	17 (68)
Anemia	5 (83)	1 (100)	4 (33)	2 (33)	12 (48)
Leukopenia	5 (83)	1 (100)	3 (25)	3 (50)	12 (48)
Thrombocytopenia	5 (83)	1 (100)	1 (8)	1 (17)	8 (32)
Lymphopenia	4 (67)	0	2 (17)	3 (50)	9 (36)
Gastrointestinal Disorders					
Nausea	4 (67)	1 (100)	5 (42)	3 (50)	13 (52)
Vomiting	3 (50)	0	1 (8)	3 (50)	7 (28)
Constipation	1 (17)	0	1 (8)	1 (17)	3 (12)
Stomatitis/mucositis	0	0	1 (8)	1 (17)	2 (8)
General Disorders and Administration Site Conditions					
Fatigue	3 (50)	0	5 (42)	4 (67)	12 (48)
Influenza-like illness	0	0	2 (17)	0	2 (8)
Adverse drug reaction (carboplatin)	1 (17)	0	2 (17)	0	3 (12)
Injury, Poisoning and Procedural Complications					
Infusion-related reaction	2 (33)	0	1 (8)	0	3 (12)
Investigations					
Raised Alanine aminotransferase (ALT)	6 (100)	1 (100)	4 (33)	1 (17)	12 (48)
Raised Aspartate aminotransferase (AST)	5 (83)	1 (100)	2 (17)	1 (17)	9 (36)
Raised alkaline phosphatase (ALP)	4 (67)	0	2 (17)	1 (17)	7 (28)
Metabolism and Nutrition Disorders					
Hypomagnesemia	6 (100)	0	8 (67)	2 (33)	16 (64)
Hypophosphatemia	1 (17)	0	1 (8)	0	2 (8)

Decreased appetite	0	0	1 (8)	1 (17)	2 (8)
Hypoalbuminemia	0	0	3 (25)	0	3 (12)
Nervous System Disorders					
Dizziness	2 (33)	0	1 (8)	0	3 (12)
Peripheral neuropathy	1 (17)	0	1 (8)	0	2 (8)
Respiratory, Thoracic and Mediastinal Disorders					
Dyspnea	2 (33)	0	0	0	2 (8)

Table 6: RECIST Responses by Cohort

RECIST 1.1 Response	Cohort 1 NUC-1031 750 mg/m^2 + carboplatin AUC4	Cohort 2 NUC-1031 750 mg/m^2 + carboplatin AUC5	Cohort 2B NUC-1031 500 mg/m^2 + carboplatin AUC5	Cohort 3 NUC-1031 625 mg/m^2 + carboplatin AUC4	All RECIST evaluable patients
	n=6 (%)	**n=1**	**n=11 (%)**	**n=5 (%)**	**n=23 (%)**
Best Complete Response (CR)	2 (33)	0	0	0	2 (9)
Best Partial Response (PR)	0	0	6 (54)	1 (20)	7 (30)
Confirmed CR	1 (17)	0	0	0	1 (4)
Confirmed PR	1 (17)	0	4 (36)	0	5 (22)
Stable Disease (SD) > 6 weeks	1 (17)	0	5 (45)	2 (40)	8 (35)
Cumulative Response Assessment					
Best Overall Response (Best CR+PR) - BOR	2 (33)	0	6 (55)	1 (20)	9 (39)
Objective Response Rate (confirmed CR + PR) - ORR	2 (33)	0	4 (36)	0	6 (26)
Clinical Benefit Rate (Best OR + SD > 6 weeks) - CBR	3 (50)	0	11 (100)	3 (60)	17 (74)
Duration of Response					
Median Progression-free survival (PFS - weeks)	27.1	14.3	20.1	29.4	27.1
PFS Range (weeks)	5.0 – 45.0	14.3 – 14.3	17.9 – 40.4	16.9 – 46.0	5.0 – 46.0

Figure 1: Pharmacokinetic profile of NUC-1031 and metabolites

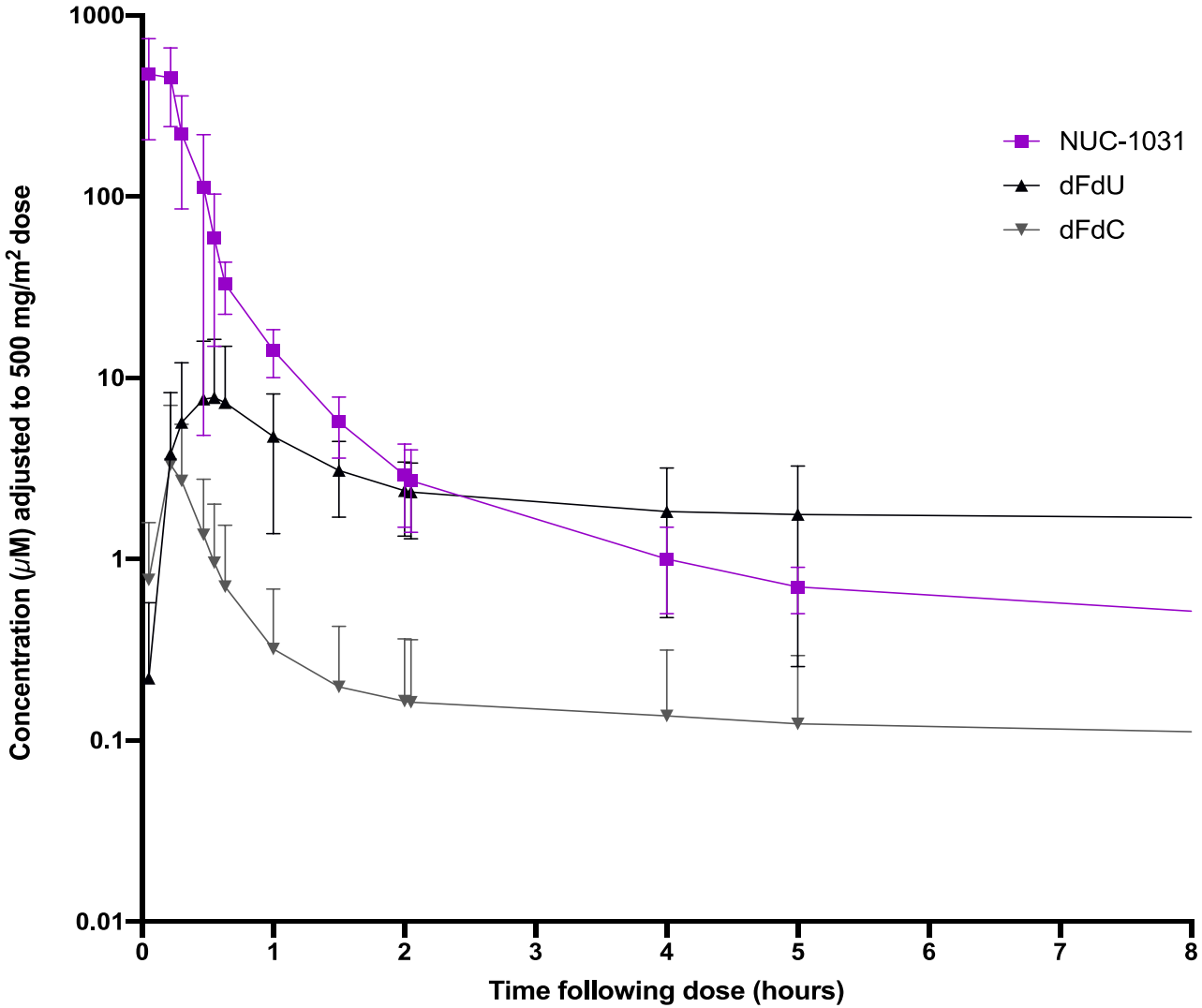
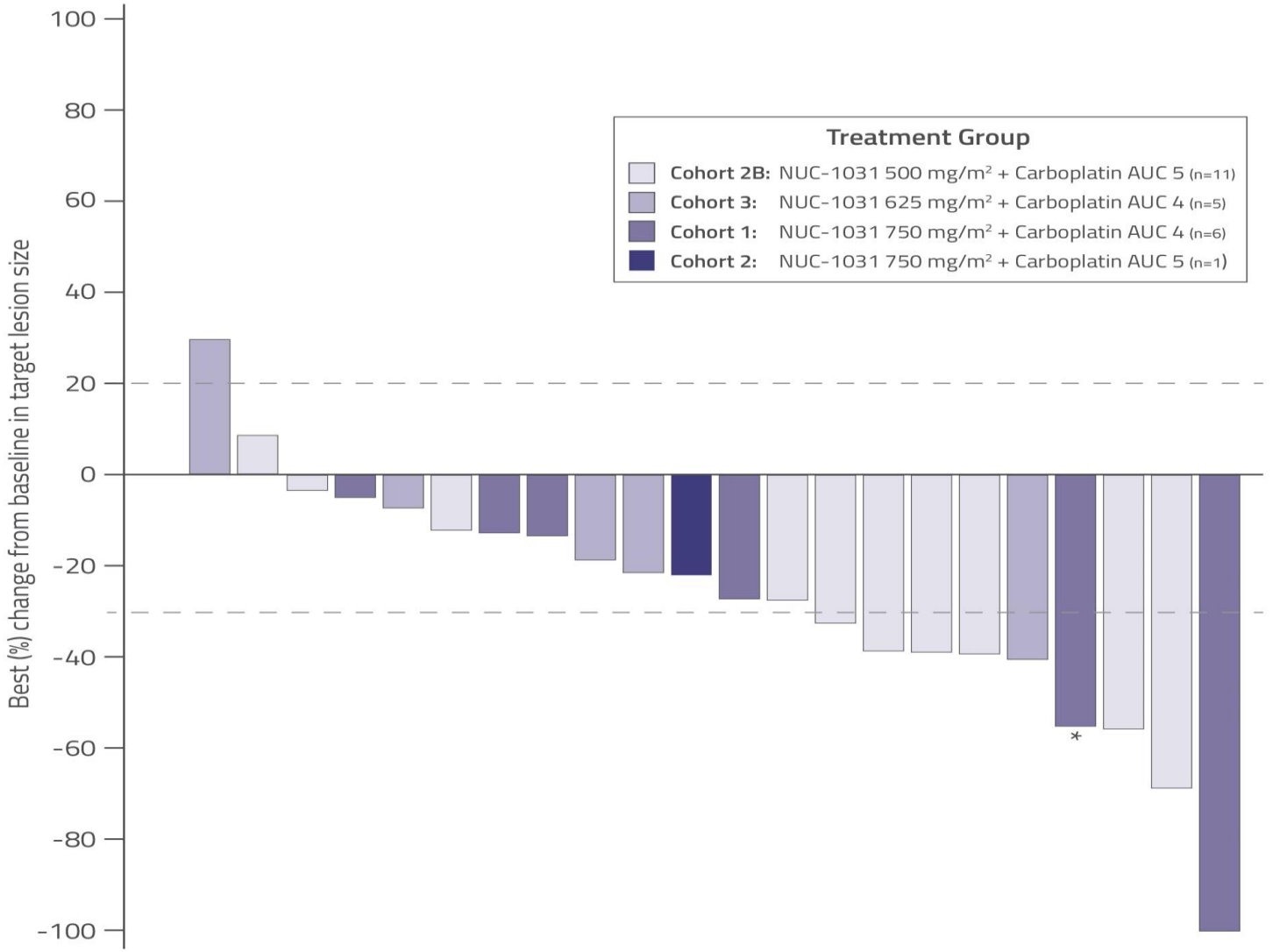
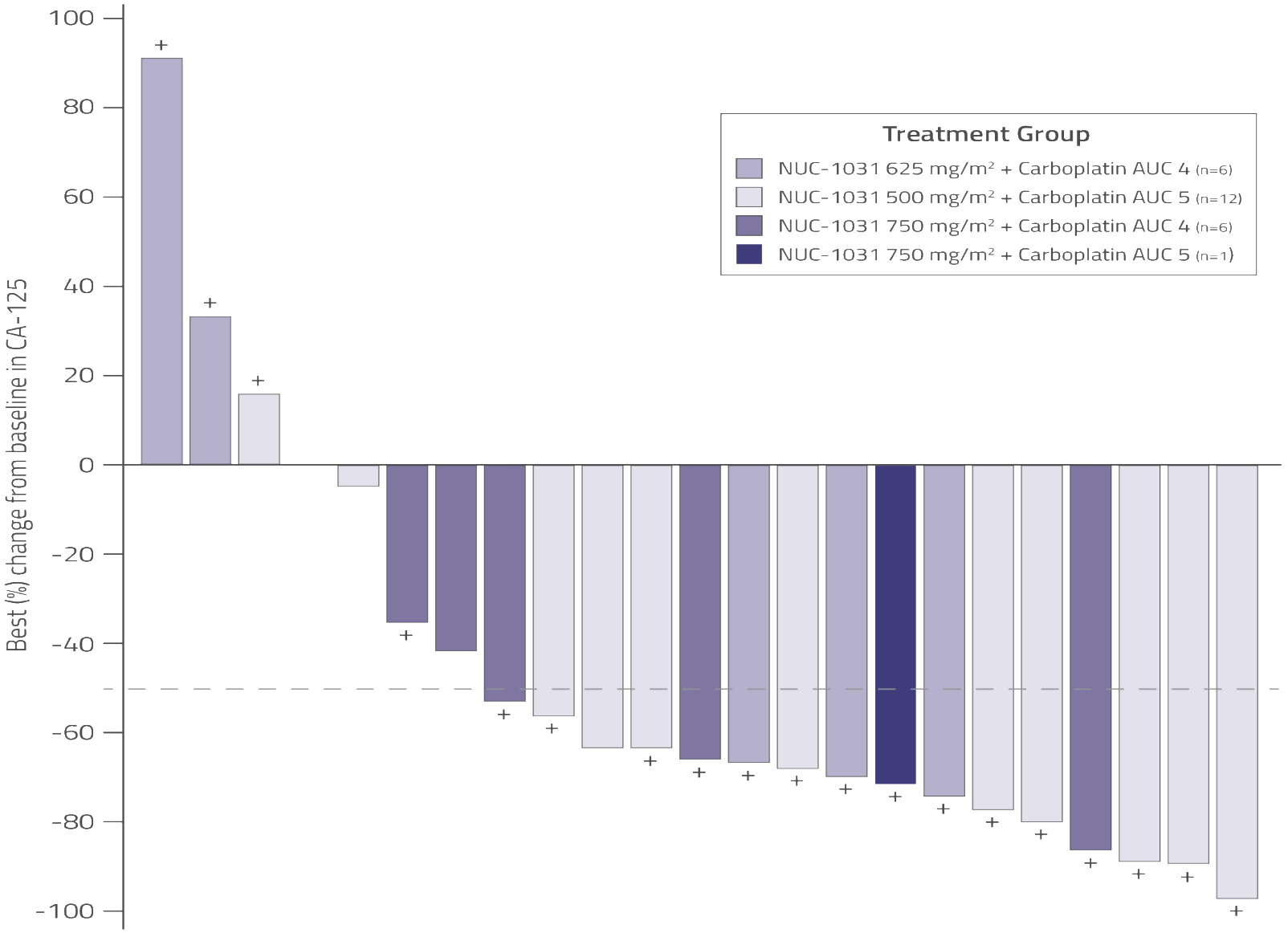


Figure 2: Best RECIST 1.1 responses



*Target lesions were lymph nodes that shrank by >50% in diameter and returned to normal size, qualifying as a CR.

Figure 3: Waterfall chart showing best change (%) from baseline of CA125 levels.



AACR American Association for Cancer Research

Clinical Cancer Research

A Phase IB open-label, dose-escalation study of NUC?1031 in combination with carboplatin for recurrent ovarian cancer

Farasat Kazmi, Shibani Nicum, Rene L Roux, et al.

Clin Cancer Res Published OnlineFirst March 19, 2021.