# An exploratory analysis of objective responses to neoadjuvant chemotherapy: results from a randomised phase III trial evaluating first-line carboplatin-paclitaxel regimens for ovarian, fallopian tube or primary peritoneal carcinoma (ICON8)

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## Summary

**Background**

Platinum-based neoadjuvant chemotherapy (NACT) followed by delayed primary surgery (DPS) is an established strategy for women with newly diagnosed, advanced stage epithelial ovarian cancer. Although this therapeutic approach has been validated in randomised, phase III trials, evaluation of response to NACT using Response Evaluation Criteria in Solid Tumours (RECIST) and CA125 was not reported. We describe RECIST and Gynecologic Cancer InterGroup (GCIG) CA125 responses in patients receiving platinum-based NACT followed by DPS in the phase III trial, ICON8.

**Methods**

ICON8 was an international, multicentre, randomised, phase III trial in which women ≥18 years old with an Eastern Cooperative Oncology Group performance status of 0-2, life expectancy >12 weeks and newly diagnosed International Federation of Gynecology and Obstetrics (FIGO; 1988) stage IC-IIA high-grade serous, clear cell or any poorly differentiated/grade 3 histological subtype or any FIGO (1988) stage IIB-IV epithelial cancer of the ovary, fallopian tube or primary peritoneum were randomised (1:1:1) to receive either intravenous (IV) carboplatin (AUC5/6) and IV paclitaxel (175mg/m$^2$ by body surface area [BSA]) on day 1 of every 21-day cycle (control arm) or IV carboplatin (AUC5/6) on day 1 and IV paclitaxel (80mg/m$^2$ by BSA) on days 1, 8 and 15 of every 21-day cycle (dose-fractionated paclitaxel arm) or IV carboplatin (AUC2) and IV paclitaxel (80mg/m$^2$ by BSA) on days 1, 8 and 15 of every 21-day cycle (dose-fractionated carboplatin and paclitaxel arm). Randomisation occurred using a minimisation method and patients where stratified according to GCIG group, disease stage and timing and outcome of cytoreductive surgery. Neither patients nor clinicians were masked to their allocated group. The scheduling of surgery and use of NACT were determined by local multidisciplinary case review. In this post-hoc

exploratory analysis of ICON8, progression-free survival (PFS) was analysed using the landmark method and defined as the time interval between the date of pre-surgical planning radiological tumour assessment to the date of investigator-assessed clinical or radiological progression or death, whichever occurred first. This is different to the intention-to-treat primary PFS efficacy analysis of ICON8, which defined PFS as the time from randomisation to the date of clinical or radiological progression or death, whichever occurred first. This post-hoc exploratory analysis includes only women recruited to ICON8 that were planned for NACT followed by DPS and had RECIST v1·1 and/or GCIG CA125 evaluable disease. ICON8 is closed for enrolment and follow-up, and registered with ClinicalTrials.gov, number: NCT01654146.

**Findings**

Between June 6, 2011 and November 28, 2014, 1,566 women were enrolled in ICON8. Seven hundred and seventy-nine women were planned for NACT followed by DPS (NACT-DPS). In the NACT-DPS population, 94% had FIGO stage IIIC/IV disease. Five hundred and sixty-four women had RECIST evaluable disease at trial entry and the complete or partial response rate (CR/PR) was 62% (348/564). Seven hundred and twenty-seven women were evaluable by GCIG CA125 criteria at the time of diagnosis and 84% (610/727) had a CA125 response. The median PFS was 14·4 months (95% CI [confidence interval] 9·2-28·0 months; 297 events) for RECIST CR/PR and 13·3 months (95% CI 8·1-20·1 months; 171 events) for RECIST stable disease (SD). The median PFS for those women with a GCIG CA125 response was 13·8 months (95% CI 8·8-23·4 months; 544 events) and 9·7 months (95% CI 5·8-14·5 months; 111 events) for those without. Complete cytoreduction (R0) was achieved in 56% (187/335) of women with RECIST CR/PR and 42% (73/172) with RECIST SD. Complete cytoreduction (R0) was achieved in 50% (290/576) and 30% (30/101) of women

5

with and without a GCIG CA125 response, respectively. The median follow-up was 29.5 months (interquartile range: 15.6-54.3 months) for the NACT-DPS population.

**Interpretation**

The RECIST-defined radiological response was lower than frequently quoted to patients in the clinic. RECIST v1·1 and GCIG CA125 responses to NACT for epithelial ovarian cancer should not be used as individual predictive markers to stratify patients likely to benefit from DPS, but instead used in conjunction with the patient's clinical capacity to undergo cytoreductive surgery. A patient should not be denied surgery based solely on the lack of a RECIST v1·1 or GCIG CA125 response.

**Funding**

# Research in context

## Evidence before the study

Prior to this study, three randomised, phase III trials, CHORUS, EORTC 55971 and JCOG 0602, had demonstrated that survival outcomes for women diagnosed with FIGO stage III/IV ovarian cancer treated with 3/4 cycles of platinum-based neoadjuvant chemotherapy (NACT) followed by delayed primary surgery (DPS) were not inferior to those in women receiving immediate primary surgery followed by platinum-based adjuvant chemotherapy.[2-5] However, none of these trials evaluated Response Evaluation Criteria in Solid Tumours (RECIST) and CA125 responses to NACT. We searched PubMed and clinical trial registries, up to 1st June 2020, for studies that reported the RECIST and/or GCIG CA125 response to NACT in epithelial ovarian cancer. We used search terms including 'ovarian cancer', 'primary cytoreductive surgery', 'delayed primary surgery', 'interval debulking surgery', 'neoadjuvant chemotherapy', 'pre-operative chemotherapy', 'RECIST' and 'CA125'. No prospective clinical trials were identified. We concluded therefore, that there were no robust data to counsel patients about response rates, nor data to guide clinicians about proceeding with DPS based upon RECIST and GCIG CA125 responses to NACT for epithelial ovarian cancer.

## Added value of the study

In the international, multicentre, randomised, phase III trial, ICON8, 779 patients diagnosed with International Federation of Gynecology and Obstetrics (FIGO; 1988) stage IC-IV epithelial ovarian cancer entered the trial with a plan to receive NACT followed by DPS. In these patients, RECIST version 1·1 and Gynecologic Cancer InterGroup (GCIG) CA125 responses to NACT were gathered prospectively allowing us to perform an post-hoc exploratory analysis and report the RECIST complete or partial response (CR/PR) rate and GCIG CA125 response rate following platinum-based NACT in predominantly FIGO stage

III/IV high-grade serous carcinoma. In addition, we were able to demonstrate that median progression-free survival was similar for women with RECIST CR/PR and those with RECIST stable disease (SD) following platinum-based NACT.

**Implications of all the available evidence**

The data from the CHORUS, EORTC 55971 and JCOG 0602 trials as well as this post-hoc exploratory analysis of ICON8 provide robust evidence that women diagnosed with FIGO stage III/IV epithelial ovarian cancer who are treated with platinum-based NACT should be considered for DPS even if they achieve only RECIST SD. Moreover, this post-hoc exploratory analysis of ICON8 demonstrates that neither RECIST v1·1 nor GCIG CA125 response should be used in isolation to stratify patients likely to benefit from DPS.

## Introduction

Ovarian cancer is the commonest cause of gynaecological cancer-related death in Europe and North America.[1] Although immediate primary surgery (IPS) followed by adjuvant platinum-based chemotherapy is considered standard therapy for women with advanced stage disease, neoadjuvant chemotherapy (NACT) followed by delayed primary surgery (DPS) is a recognised treatment option for women in whom IPS is contraindicated. This therapeutic approach has been validated in three randomised, phase III trials, which reported non-inferior survival between IPS followed by adjuvant chemotherapy versus NACT followed by DPS in International Federation of Gynecology and Obstetrics (FIGO) stage III/IV ovarian cancer.[2-5] Although the findings from these trials provide clear evidence for NACT followed by DPS in advanced disease, evaluation of response rates to NACT using RECIST and CA125 were not reported.[2-5] The absence of published response evaluation data for NACT has contributed to wide variation in surgical practice in women with radiologically-defined 'stable disease'.[6] Establishing robust and reproducible criteria for evaluating response to NACT is pivotal in standardising DPS and improving outcomes for women diagnosed with ovarian cancer.

ICON8 was an randomised, phase III trial that sought to determine whether first-line chemotherapy with dose-fractionated carboplatin and/or paclitaxel improved progression-free survival (PFS) and overall survival (OS) in women diagnosed with FIGO stage IC-IV epithelial ovarian cancer.[7,8] The intention-to-treat (ITT) primary PFS efficacy analysis showed no significant improvement in PFS between standard three-weekly carboplatin plus paclitaxel versus either three-weekly or weekly carboplatin plus weekly paclitaxel.[7] The eligibility criteria for ICON8 permitted women to enter the trial with a plan to receive NACT followed by DPS, if this was deemed the most appropriate management at local multidisciplinary case review. In these patients, both Response Evaluation Criteria in Solid Tumour version 1·1 (RECIST v1·1) and Gynecologic Cancer InterGroup (GCIG) CA125

responses to NACT were prospectively evaluated.[9,10] In this post-hoc exploratory analysis of ICON8, we aimed to investigate whether objective treatment responses to NACT impacted PFS and cytoreduction rates and could be used to guide surgical treatment decisions.

## Methods

### Study design and participants

ICON8 was an international, Gynecologic Cancer InterGroup (GCIG), multi-centre, randomised, phase III trial in which patients were recruited from United Kingdom, Australia, New Zealand, Mexico, South Korea and Republic of Ireland. At least one patient was recruited at each of the 117 trial sites (appendix pp 1-3). Inclusion criteria included newly diagnosed FIGO (1988) stage IC-IIA high-grade serous, clear cell or any poorly differentiated/grade 3 histological subtype or any FIGO (1988) stage IIB-IV epithelial cancer of the ovary, fallopian tube or primary peritoneum; were ≥ 18 years old; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; a life expectancy >12 weeks; and adequate bone marrow, liver and renal function (haemoglobin ≥90 grams per L; platelet count ≥100 × $10^9$ per L; absolute neutrophil count [ANC] ≥1·5 × $10^9$ per L; bilirubin ≤1·5 × upper limit of normal [ULN] and aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≤3 × ULN in the absence of parenchymal liver metastases or ≤5 × ULN in the presence of parenchymal liver metastases; directly measured Glomerular Filtration Rate [GFR] ≥30 mL per min or a calculated creatinine clearance ≥60 mL per min). Exclusion criteria included non-epithelial ovarian cancer; peritoneal cancer that was not Müllerian origin including mucinous histology; borderline tumours/tumours of low malignant potential; prior systemic anti-cancer therapy for ovarian cancer; previous malignancies ≤5 years prior to randomisation apart from adequately treated carcinoma in situ of the cervix, breast ductal carcinoma in situ, non-melanomatous skin cancer or previous/synchronous

FIGO (2009) stage IA grade 1 or 2 endometrioid cancers with no lymphovascular space invasion; pre-existing grade ≥2 neuropathy; any other disease/metabolic dysfunction that in the opinion of the investigator would put the subject at high-risk of treatment-related complications or prevent compliance with the trial protocol; previous radiotherapy to the abdomen or pelvis; planned intraperitoneal cytotoxic chemotherapy; planned maintenance treatment with systemic anti-cancer therapy following completion of protocol treatment and prior to protocol defined progression; sexually active women of childbearing potential not willing to use adequate contraception; pregnant or lactating women who are breastfeeding; treatment with other investigational agent prior to protocol defined progression; history or clinical suspicion of central nervous system metastases; known hypersensitivity to carboplatin, paclitaxel or their excipients (appendix pp 4-5). In this post-hoc exploratory analysis, only patients who were planned to receive NACT followed by DPS (NACT-DPS) were included.

All patients provided written informed consent prior to enrolment. The protocol had the appropriate national ethics committee approval for the countries in which the study was conducted. The trial was performed in accordance with the national laws and regulations of the countries in which it was being performed. All protocol amendments were approved by relevant ethics committees and regulatory bodies (appendix pp 6-7). The trial was also performed in accordance with Good Clinical Practice guidelines and provisions of the Declaration of Helsinki.

**Randomisation and masking**

Eligible patients were randomised (1:1:1) using a minimisation method of random element to one of three treatment arms. The minimisation was stratified by the following three stratification factors: GCIG group (Australia New Zealand Gynaecological Oncology Group

[ANZGOG]; Grupo de Investigación en Cáncer de Ovario y Tumores Ginecológicos de México [GICOM]; Korean Gynecologic Oncology Group [KGOG]; Cancer Trials Ireland – formerly Irish Clinical Oncology Research Group), disease stage (FIGO stage IC high grade serous, clear cell or grade 3 carcinoma; FIGO stage IIA high grade serous, clear cell or grade 3 carcinoma; FIGO stage IIB; FIGO stage IIC; FIGO stage IIIA; FIGO stage IIIB; FIGO stage IIIC; FIGO stage IV) and timing and outcome of surgery of IPS arm (IPS plus FIGO stage IC–III with no visible residual disease; IPS plus FIGO stage IC–III with residual disease ≤1 cm; IPS plus FIGO stage IV or FIGO stage IC–III with residual disease >1 cm; no surgery currently planned; DPS was planned). Patients were randomly assigned using the Medical Research Council Clinical Trials Unit at University College London randomisation telephone service. Patients and clinicians were not masked to their allocated group.

**Procedures**

Treatment arms included, Arm 1 (control arm): intravenous (IV) carboplatin AUC5 or AUC6 (capped at 900mg) and IV paclitaxel 175mg/m$^2$ by body surface area (BSA; capped at 350mg) on day 1 of every 21-day cycle; Arm 2 (dose-fractionated paclitaxel): IV carboplatin AUC5 or AUC6 (capped at 900mg) on day 1 and IV paclitaxel 80mg/m$^2$ by BSA (capped at 160mg) on days 1, 8 and 15 of every 21-day cycle; Arm 3 (dose-fractionated carboplatin and paclitaxel): IV carboplatin AUC2 (capped at 300mg) and IV paclitaxel 80mg/m$^2$ by BSA (capped at 160mg) on days 1, 8 and 15 of every 21-day cycle. The protocol defined dose levels for carboplatin and paclitaxel as: 3-weekly carboplatin AUC5 (starting dose), AUC4 (dose level -1) and AUC3.5 (dose level -2) by directly measured GFR or calculated GFR (Wright formula) or AUC6 (starting dose), AUC5 (dose level -1) and AUC4.5 (dose level -2) by calculated GFR (Cockcroft-Gault or Jelliffe formulae); weekly carboplatin AUC2 (starting

dose), AUC1.67 (dose level -1) and AUC1.5 (dose level -2); weekly paclitaxel 80mg/m$^2$ (starting dose), 60mg/m$^2$ (dose level -1) and 45mg/m$^2$ (dose level -2).

Chemotherapy was interrupted for an ANC less than $1 \cdot 0 \times 10^9$ per L (Arms 1 & 2 day 1; Arm 3 days 1, 8, 15) or ANC less than $0 \cdot 5 \times 10^9$ per L (Arm 2 days 8, 15), a platelet count of less than $75 \times 10^9$ per L (Arms 1 & 2 day 1; Arm 3 days 1, 8, 15) or a platelet count less than $50 \times 10^9$ per L (Arm 2 days 8, 15). Treatment resumed without dose reduction if haematological toxicity recovered within 7 days. If recovery occurred after 7 days or dose-limiting haematological toxicity occurred (febrile neutropenia, grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding) protocol-defined dose reductions were recommended. Chemotherapy was interrupted for grade ≥2 sensory or motor neuropathy, grade ≥3 mucositis, grade ≥3 AST/ALT increase, grade ≥2 rash or any other treatment-related grade ≥3 CTCAE (version 4·0). Paclitaxel was permanently discontinued if there was a delay in restarting paclitaxel for ≥3 weeks due to grade 2 sensory or motor neuropathy, or grade ≥3 sensory or motor neuropathy or any other treatment-related grade ≥4 CTCAE (version 4·0). Hypersensivity reactions to carboplatin and/or paclitaxel were managed according to standard local practice. Docetaxel could not be used as a substitute for paclitaxel in patients who experienced hypersensivity reactions that prohibited further administration of paclitaxel. Single-agent carboplatin was accepted as protocol treatment if patients were unable to tolerate paclitaxel. Three-weekly cisplatin (75mg/m$^2$ by BSA) in combination with 3-weekly paclitaxel (80mg/m$^2$ by BSA) could be used as a substitute for carboplatin in patients who experienced hypersensivity reactions that prohibited further administration carboplatin.

Protocol treatment was also discontinued due to any of the following reasons: progression whilst on therapy, unacceptable toxicity, inter-current illness that prevented

further treatment, withdrawal of consent for treatment by the patient or any alterations in the patient's condition that justified the discontinuation of treatment in the investigator's opinion.

The trial protocol strongly recommended that DPS was performed as close to cycle 3 day 22 as possible, and within a maximum of ten days after this, provided that haematological recovery had occurred. Only under exceptional circumstances, where patients were deemed unsuitable for DPS following three cycles of NACT, could additional cycles of NACT be given. The maximum number of cycles of NACT permitted was six. The final decision to perform DPS was made by the local treating multidisciplinary team. The outcome of DPS was defined as either complete cytoreduction (R0): the absence of any macroscopically visible disease; optimal cytoreduction: largest deposit of residual disease ≤1cm in diameter or; suboptimal cytoreduction: >1cm diameter deposit of residual disease at the end of debulking surgery.[11] Adjuvant chemotherapy was planned to commence between one to six weeks after DPS. The maximum total number of cycles of chemotherapy permitted (neoadjuvant plus adjuvant) was six.

All patients recruited to ICON8 had cross-sectional imaging of the abdomen and pelvis +/- thorax (preferably CT, but MRI was permitted) as part of radiological tumour assessment. However, RECIST v1·1 measurable disease was not required for trial entry. In the NACT-DPS population the baseline scan was performed prior to randomisation and within 6 weeks prior to cycle 1 day 1 of NACT. Subsequently, cross-sectional imaging using the same imaging modality as the baseline scan was performed pre-operatively as part of the surgical planning process ('the pre-surgical planning radiological tumour assessment'), during cycle 3 or 4 of NACT. For patients undergoing DPS, a post-operative CT or MRI occurred four weeks +/- seven days after surgery. In all trial patients, an end of primary-treatment scan occurred within six weeks +/- two weeks after day 1 of their last cycle of chemotherapy. At subsequent follow-up visits, cross-sectional imaging was performed only if

there were clinical symptoms suggestive of relapse/progression +/- evidence of GCIG CA125 progression. Any patient with asymptomatic CA125 elevations and no radiological evidence of disease progression according to RECIST v1·1 underwent routine 3-monthly repeat scans until protocol defined disease progression. All patients recruited to ICON8 had a serum CA125 level measured at baseline, within 7 days prior cycle 1 day 1 of NACT and then within 72 hours prior to day 1 of each subsequent cycle of NACT. A pre-surgical serum CA125 level was requested within the protocol, but not mandated. Subsequently, CA125 levels were measured at each follow-up visit. The protocol did not mandate that a serum CA125 level was measured on the same day as the baseline or surgical planning scan.

All adverse events were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4·0 and were collected at baseline, at every chemotherapy cycle and at DPS. Only CTCAEs that occurred in the NACT-DPS population are included in this post-hoc exploratory analysis of ICON8.

**Outcomes**

The co-primary outcomes of ICON8 were PFS and OS. Secondary outcomes of ICON8 included toxicity, quality of life and health economics. In the primary PFS efficacy analysis, PFS was calculated from the date of randomisation to the date of first clinical or radiological progression or death from any cause, whichever came first. In the primary efficacy analysis, OS was calculated from the date of randomisation to the date of death from any cause. The primary PFS efficacy analysis, including toxicity, and the quality of life analysis of ICON8 have been reported previously.[7,8] In this post-hoc exploratory analysis we assessed the RECIST v1·1 and GCIG CA125 response to platinum-based chemotherapy in women enrolled on ICON8 who were planned for NACT followed by DPS. In addition, we evaluated

median PFS, using a landmark analysis, and compared the extent of surgical cytoreduction with RECIST v1·1 and GCIG CA125 responses.

**Statistical analysis**

Sample size calculations for the main ICON8 trial have been reported previously.[7] As this analysis was performed in an exploratory manner, no formal power calculations have been performed. In this post-hoc exploratory analysis, PFS analysis used a landmark method, in which PFS was calculated from the date of pre-surgical planning radiological tumour assessment to the date of investigator-assessed clinical or radiological progression or death from any cause, whichever occurred first. The median PFS data described in this analysis are therefore shorter than the primary PFS efficacy analysis (appendix p 13). Asymptomatic elevations in CA125 were not used to define disease progression. This post-hoc exploratory analysis includes mature data of investigator-assessed radiological responses using RECIST v1·1 and central evaluation of CA125 responses using GCIG criteria.

Objective responses are reported according to RECIST v1·1 and GCIG CA125 criteria.[9, 10] The RECIST v1·1 response was determined by comparing the baseline scan and the pre-surgical planning radiological tumour assessment. The GCIG CA125 response was determined by comparing the cycle 1 day 1 CA125 value with either the cycle 3 or 4 day 1 CA125 value or the pre-surgical CA125 value, which ever occurred last. Patients were excluded from being considered in this post-hoc exploratory analysis if they did not have RECIST v1·1 or GCIG CA125 measurable disease.

Categorical variables are presented as number (percentage) with differences between groups analysed using the Chi-square test. Missing data are indicated in tables, but not included in the calculation of percentages. Continuous variables were presented as median (interquartile range [IQR]). Time-to-event analyses used landmark analysis as described

above and are presented using Kaplan-Meier curves and median (95% confidence intervals [CI] event-free survival. Statistical significance was determined by a two-sided p-value at the 95% level. All statistical analyses were performed in Stata version 16·1. The final trial database lock was 31st March 2020. This study is registered with ClinicalTrials.gov, number: NCT01654146.

**Role of the funding source**

# Results

Between June 6, 2011 and November 28, 2014, 1,566 women were enrolled to ICON8.[7] Seven hundred and seventy-nine (50%) of the 1,566 women were planned to receive NACT followed by DPS after local multidisciplinary case review. Demographic data for this population are presented in Table 1. The median follow-up for the NACT-DPS population was 29·5 months (IQR 15·6-54·3 months). One hundred and thirty (17%) of the 779 women in the NACT-DPS population had incomplete radiology follow-up data (104/130) or non-target lesions reported at baseline that were not described on subsequent follow-up imaging (26/130); these women were therefore excluded from this post-hoc exploratory analysis (Figure 1). Of the remaining 649 women with complete RECIST-evaluable radiology

datasets, 564 (87%) had measurable disease by RECIST v1·1 (Figure 1). Data from these 564 women were used to determine the RECIST response. The overall RECIST complete or partial response (CR/PR) rate following NACT was 62% (348/564) and did not differ between treatment arms (Table 2). RECIST progressive disease (PD) during NACT occurred in 6% (33/564) (Table 2). The majority of women (156/183) with RECIST stable disease (SD) had a reduction in the size of marker lesions, with a median reduction of 14% (IQR 5-23%) (Figure 2A). Seven hundred and twenty-seven (93%) of the 779 women in the NACT-DPS population had a baseline CA125 of twice the upper limit of normal range (Figure 1). Data from these 727 women were used to determine the GCIG CA125 response. Six hundred and ten (84%) of the 727 women had a GCIG CA125 response to NACT (Table 2 and Figure 2B). Both RECIST and GCIG CA125 response data were available for 534 women (Table 3). Among the group of women with a GCIG CA125 response, a substantial proportion did not have a RECIST response: of 453 women with a GCIG CA125 response and RECIST-evaluable disease, 33% (148/453) had RECIST SD or PD (Table 3). Of the same 453 women, 91% (413/453) had a reduction in the size of the marker lesion(s).

In order to determine whether RECIST response to NACT could be used to predict patient survival or the effectiveness of DPS, PFS and extent of surgical cytoreduction were evaluated according to RECIST response. A pre-planned analysis of the primary PFS efficacy analysis of ICON8 had already shown no significant difference in median PFS between the three NACT treatment regimens and therefore all three arms were combined in this post-hoc exploratory analysis using a landmark method, which utilised time of pre-surgical planning radiological tumour assessment as the start point for PFS.[7] The median PFS was 14·4 months (95% CI 9·2-28·0 months; 297 events) for RECIST CR/PR and 13·3 months (95% CI 8·1-20·1 months; 171 events) for RECIST SD (Figure 3A). Data on surgical outcome were available for 536 (95%) of 564 women with RECIST-evaluable disease, of whom, 67 (13%)

did not undergo DPS (Table 4). When including only those women who underwent DPS, the median PFS was 15·0 months (95% CI 9·5-28·0 months; 273 events) for RECIST CR/PR and 14·0 months (95% CI 9·5-23·8 months; 143 events) for RECIST SD (appendix p 14). Evaluation of the 130 women with incomplete radiology follow-up data demonstrated a shorter median PFS (12·5 months, 95% CI 7·5-17·2 months; 118 events) compared to those with a complete RECIST-evaluable radiology dataset (15·4 months, 95% CI 10·1-25·3 months; 584 events) (appendix p 15). In those women with RECIST-evaluable disease in the NACT-DPS population, median PFS correlated with extent of surgical cytoreduction, and those who had complete (R0) cytoreductive surgery had the best median PFS irrespective of the RECIST response categorisation to NACT (appendix pp 16-17). Forty two percent (73/172) of women with RECIST SD following NACT had complete cytoreduction, although this percentage was significantly lower than for those with RECIST CR/PR (56% [187/335]; Chi-square test for SD versus CR/PR, p=0·0040) (Table 4). Interestingly, 48% (14/29) of women with RECIST PD had complete cytoreduction (Table 4).

A similar analysis was conducted to determine the clinical impact of CA125 response assessment prior to DPS. The median PFS for those women with a GCIG CA125 response was 13·8 months (95% CI 8·8-23·4 months; 544 events) and 9·7 months (95% CI 5·8-14·5 months; 111 events) for those without (Figure 3B). Data on surgical outcome were available for 677 (93%) of 727 women with GCIG CA125 evaluable disease, of whom 101 did not undergo DPS (Table 4). When including only those women who underwent DPS, the median PFS was 14·2 months (95% CI 9·3-25·0 months; 490 events) and 10·5 months (95% CI 6·6-15·6 months; 73 events) for those women with and without a GCIG CA125 response, respectively (appendix p 18). Complete cytoreduction was achieved in 50% (290/576) and 30% (30/101) in women with and without a GCIG CA125 response, respectively (Chi-square test, p<0.0010) (Table 4). Delayed primary surgery did not take place in 40% (40/101) of

women who did not have a GCIG CA125 response, compared to 11% (61/576) of those with a CA125 response (Chi-square test, p<0.0010) (Table 4).

In order to determine whether combining the outcomes from both conventional response assessment modalities would identify a patient group unlikely to benefit from DPS, the rate of complete cytoreduction in patients with RECIST SD was evaluated according to GCIG CA125 response (appendix p 8). No significant difference in the rate of complete cytoreduction versus all other surgical outcomes was apparent (Chi-square test for R0 versus all other outcomes, p=0·18). However, it was notable that a greater number of women with RECIST SD and a GCIG CA125 response underwent surgery compared to those with RECIST SD and no GCIG CA125 response (109/121 [90%] versus 32/47 [68%], respectively), thereby making it challenging to draw any meaningful clinical conclusions (appendix p 8). The persistence of ascites has been shown to impact on the outcomes of ovarian cancer surgery.[12] In those ICON8 patients who had ascites at the commencement of NACT and achieved a best RECIST response of SD, the rate of complete cytoreduction versus all other surgical outcomes did not differ significantly between those groups with persistent or resolved ascites at pre-surgical imaging (Chi-square test for R0 versus all other outcomes, p=0·48) (appendix p 8).

All CTCAEs in the NACT-DPS population that occurred during NACT and DPS, separated according to RECIST responses, are outlined in the supplementary material (appendix pp 9-12). There were no differences in CTCAEs experienced by patients with RECIST CR/PR versus SD.

The number of reported non-high-grade serous cases with RECIST and/or GCIG CA125 measurable disease was too small to make any definitive conclusion regarding the differences in treatment response between each histological subtype.

**Discussion**

This exploratory analysis of treatment responses to first-line platinum-based NACT in women with newly diagnosed FIGO stage IC-IV epithelial ovarian cancer demonstrates a number of key findings. Firstly, we show that the RECIST response rate (CR or PR) following NACT for predominantly high-grade serous carcinoma (HGSC) is approximately 60%. This response rate is lower than that often quoted to patients in the clinic, but is consistent with historically reported rates from other randomised, phase III trials investigating first-line carboplatin-taxane chemotherapy in smaller subsets of patients with measurable disease after upfront surgery.[13,14] To our knowledge, data from this study represent the first and only prospective evidence reporting RECIST responses to first-line platinum-based NACT in epithelial ovarian cancer.

Secondly, we show that a best response of RECIST SD following first-line platinum-based NACT should not preclude DPS. Both the outcome of cytoreductive surgery and the median PFS were similar between women with RECIST PR and SD. This finding supports the use of DPS in all women with RECIST CR, PR or SD and is in keeping with the treatment protocols followed in the CHORUS and EORTC 55971 trials, which did not mandate a response to NACT prior to undergoing DPS.[2,3] In contrast, the geographical variation seen in surgical management practice for advanced stage ovarian cancer outside of clinical trials indicates that lack of treatment response may impact negatively on the decision to proceed with DPS, a factor that might also explain, in part, the higher percentage of patient with RECIST SD compared to those with CR/PR not undergoing surgery in ICON8.

This exploratory analysis of ICON8 also shows that GCIG CA125 criteria inadequately documents response to NACT. While the prognosis of women without a GCIG CA125 response to NACT is worse than those in whom a CA125 response is achieved, almost half (49%) of those patients with non-responding disease by GCIG CA125 criteria

achieved at least optimal cytoreduction at DPS and 30% achieved complete (R0) cytoreduction, findings that were evident even in the subgroup of patients with RECIST SD (appendix p 8). Therefore, GCIG CA125 criteria should not be used in isolation to determine which patients are considered appropriate for DPS.

It should be noted that, in order to reduce bias associated with comparing outcomes in different response cohorts, this exploratory analysis used a landmark method, in which PFS was determined from the date of pre-surgical planning radiological tumour assessment, as opposed to the ITT primary PFS efficacy analysis where PFS was determined from time of randomisation.[7] For this reason, the PFS values reported in this exploratory analysis cannot be directly compared with those reported in the primary analysis and are approximately 2 months shorter (appendix p 13).

This large evaluation in a clearly-defined patient population demonstrates the difficulties in using current well-defined unidimensional radiological and biochemical response surrogates to assess the therapeutic impact of NACT in advanced high-grade ovarian cancer. Both response criteria predict imperfectly the ability to achieve complete or optimal cytoreduction at interval surgery; a more robust surrogate for survival, or indeed patient PFS. We recommend therefore that neither RECIST nor CA125 assessments should be considered as stand-alone measures to stratify patients likely to benefit from DPS, but instead used in conjunction with the patient's clinical capacity (e.g. performance status and co-morbidities) to undergo cytoreductive surgery. This conclusion is unsurprising given the complex, multi-site, biologically heterogeneous nature of HGSC.[15,16] One notable limitation to this conclusion is that we have not considered more sophisticated evaluation methodology for radiological and CA125 data. More detailed analysis of the trends in CA125 during NACT may demonstrate a more accurate percentage-change or rate-of-change that correlates with RECIST response and/or provides enhanced discrimination of surgical outcomes at

DPS.[17] Equally the development of volumetric or radiomics algorithms to analyse CT data may also improve our ability to provide meaningful predictors of outcome that can guide individual treatment decisions in the clinic.[18]

The data reported in this study have identifiable limitations. Treatment responses, defined through RECIST and GCIG CA125, were not a predefined secondary outcome. Nonetheless, response evaluation data were collected prospectively and this exploratory analysis includes 83% (649/779) and 93% (727/779) complete data for RECIST and CA125 outcomes respectively. While 17% (130/779) patients who had incomplete radiological follow-up had shorter PFS than those with complete radiological data, this is unlikely to bias the overall conclusions of the study. Secondly, 20% of cases were described as "serous (no grade specified)" or "other" and yet NACT is currently most frequently used in women diagnosed with FIGO stage IIIC/IV HGSC. It is important to note that recruitment to the trial almost entirely predated the 2014 World Health Organisation re-classification of ovarian tumours and we expect the majority of unknown histiotypes would now be reclassified as HGSC using current immunohistochemical panels. Thirdly, treatment responses in other rarer forms of epithelial ovarian cancer (e.g. low-grade serous, clear cell, endometrioid) remains insufficiently defined by our study because of the paucity of cases. Fourthly, the *BRCA1/2* status of enrolled patients was unknown, and yet tumours with *BRCA1/2* mutations are often highly sensitive to platinum-based chemotherapy.[19,20] Thus, the overall findings of this study may not be completely applicable to *BRCA*-mutant tumours. When ICON8 was originally opened, universal germline and somatic *BRCA1/2* testing was not performed in all patients diagnosed with epithelial ovarian cancer and instead restricted to those women with a higher risk of hereditary ovarian and/or breast cancer syndrome.[21,22] Moreover, none of the published phase III trials involving NACT evaluated *BRCA1/2* status and so the same criticism applies to all available datasets.[2-5] We also recognise that by combining patients

with RECIST CR/PR this may underestimate the survival outcomes of those patients with RECIST CR. Nonetheless, our approach was performed in an exploratory setting, focused on differentiating patients with and without a conventional radiologically-defined treatment response (CR/PR versus SD or PD) and the small proportion of patients with RECIST CR precluded a separate analysis of this group. It is also notable that ICON8 did not involve concurrent bevacizumab therapy as part of NACT.[23-26] Indeed, the addition of bevacizumab to first-line carboplatin-paclitaxel NACT for epithelial ovarian cancer may improve treatment responses further, although this has yet to be confirmed and may be uncovered in the follow-on phase III trial, ICON8b.[27,28] Also, it is noteworthy that 6% of patients planned for NACT followed by DPS had FIGO stage IC-IIIB ovarian cancer, whereas the standard of care approach for these FIGO stages' of disease is IPS followed by adjuvant chemotherapy.[29] For accuracy, the FIGO staging for all these patients was verified by the trial site, although no specific rationale for the local multidisciplinary team decision was collected. We expect there were patient-specific factors (e.g. performance status and co-morbidities), disease-specific (widespread miliary peritoneal disease) and/or logistical factors at each trial site that led to this therapeutic approach being utilised in these cases. Finally, we acknowledge that the histological chemotherapy response score (CRS) data for FIGO stage IIIC/IV HGSC have not been collected in ICON8 as the Böhm et al. CRS system was published after completion of recruitment into ICON8.[30] Therefore, CRS reporting was not routinely undertaken at the time of the study.

In conclusion, this large exploratory analysis provides the first robust evaluation of response using internationally recognised radiological and biochemical criteria to NACT in a well-annotated trial population of women with advanced ovarian cancer. It demonstrates that neither response modality should be used in isolation to determine a patient's eligibility for DPS and that surgery, with the goal of complete cytoreduction, still provides clear clinical

benefit for the majority of women with RECIST SD after 3 to 4 cycles of NACT. These findings should be validated prospectively in future clinical studies investigating NACT treatment strategies. We recommend that *BRCA1/2* mutation status, CRS and the presence/absence of ascites prior to DPS are collected in appropriate cases to improve clinical utility.

**Contributors**

ARC, IAM, ECJ, J-WK and JAL led and coordinated the main ICON8 study design. ARC, IAM, ECJ, ADC, J-WK and JAL are members of the trial management group. IAM, RL, GD, RG, JK, CP, CJP, MH, DG-R, ML, SE, JS, AA, AZ, SW, RJ, KS, AW, J-WK, SS, GCJ, JAL and ARC contributed to recruitment and data collection in ICON8. For this exploratory analysis of ICON8, RDM, IAM, ADC, ECJ and ARC analysed the data, which were interpreted by all co-authors. RDM, IAM, ADC and ARC drafted this manuscript, and the final version was approved by all co-authors.

**Declaration of interests**

ADC, ECJ, RL, GD, JK, CP, CJP, MH, DG-R, SE, JS, AA, AZ, J-WK, SS, GJC and JAL declare no conflicts of interest. RDM declares personal fees and travel expenses from AstraZeneca, outside the submitted work. IAM declares personal fees from Carrick Therapeutics, Clovis Oncology, Roche, Scancell, Tesaro and personal fees and grants from AstraZeneca, outside the submitted work. RJ declared personal fees from Amgen, and personal fees and travel expenses from AstraZeneca, Clovis Oncology and Tesaro, outside the submitted work. ML declares personal fees from Roche outside the submitted work. AW declares personal fees from AstraZeneca and Roche, and personal fees and travel expenses from Tesaro, outside the submitted work. RMG declares personal fees from AstraZeneca, Clovis, GSK/Tesaro, Immunogen and Sotio, travel/conference registration fees from AstraZeneca and GSK and grants from Boehringer Ingelheim and Lilly/Ignyta, outside the submitted work. RMG is also a principal investigator for trials sponsored by Astrazeneca, GSK, Pfizer, Lilly and Immunogen, outside the submitted work. SW declares personal fees and travel expenses from AstraZeneca, Clovis Oncology and GSK, outside the submitted work. KS declares conference fees from GSK, outside the submitted work. ARC declares

personal fees for AstraZeneca, Clovis Oncology and GSK, research funding from AstraZeneca and travel expenses from Clovis Oncology and Tesaro, outside the submitted work.

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**Figures**


**Figure 1: CONSORT diagram for post-hoc exploratory analysis.** 564 patients had RECIST measurable disease at trial entry. 727 had a baseline CA125 of twice the upper limit of normal range and were evaluable for response by GCIG CA125 criteria. Key: NACT, neoadjuvant chemotherapy.

**Figure 2A. Waterfall plot showing percent change in RECIST marker lesions (capped at 100%).** Key: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; dashed grey lines represent +20% and -30% change in marker lesions from baseline.

**Figure 2B. Waterfall plot showing percent change in CA125 level from baseline (capped at 100%).** Key: dashed grey lines represent -50% change in CA125 level from baseline.

**Figure 3A. Kaplan-Meier estimates of progression-free survival according to RECIST response (landmark method).** The RECIST CR/PR population included 347 patients and the RECIST SD population included 183 patients. Key: CR/PR, complete or partial response; SD, stable disease. The median PFS was 14·4 months (95% CI 9·2-28·0 months; 297 events) for RECIST CR/PR and 13·3 months (95% CI 8·1-20·1 months; 171 events) for RECIST SD.

**Figure 3B. Kaplan-Meier estimates of progression-free survival according to GCIG CA125 response (landmark method).** The CA125 response population included 605 patients and the CA125 no response population included 114 patients. The median PFS for those patients with a GCIG CA125 response was 13·8 months (95% CI 8·8-23·4 months; 544 events) and 9·7 months (95% CI 5·8-14·5 months; 111 events) for those without.