

Introduction

- Neoadjuvant carboplatin-paclitaxel (CT) administered once every 3 weeks with delayed primary surgery (DPS) after 3 cycles is a standard-of-care option for women with bulky FIGO stage IIIC-IV EOC where complete cytoreduction at primary surgery is deemed unlikely
- This approach is supported by two published randomised trials demonstrating that it is not inferior to upfront surgery and has lower perioperative morbidity (*Vergote et al, NEJM, 2010; Kehoe et al Lancet, 2015*).
- Radiological and biochemical response to neoadjuvant CT have however not been prospectively evaluated nor compared with DPS outcome and progression-free survival (PFS) in large patient cohorts.

Background to ICON8

- The Japanese JGOG3016 trial demonstrated a clinically significant improvement in survival over three weekly CT by administering paclitaxel in a weekly dose-dense schedule at the expense of increased toxicity
- ICON8 is a randomised three-arm phase III trial that compares the efficacy and safety of two regimens incorporating weekly paclitaxel to standard three-weekly chemotherapy in a predominantly European population
- ICON8 allowed patients to enter after primary surgery or receive neoadjuvant chemotherapy (NACT) with planned DPS providing an ideal opportunity to prospectively evaluate response to NACT.

Trial Design

Diagnosis of Stage IC-IV EOC/PPC/FTC

After immediate primary surgery or planned to receive NACT plus delayed primary surgery

Stratification factors:  
GCIG group  
Disease stage  
Timing and outcome of surgery

Randomise 1:1:1

Arm 1  
Carboplatin AUC 5 q3w  
Paclitaxel 175mg/m<sup>2</sup>q3w

Arm 2  
Carboplatin AUC 5 q3w  
Paclitaxel 80mg/m<sup>2</sup> q1w

Arm 3  
Carboplatin AUC 2 q1w  
Paclitaxel 80mg/m<sup>2</sup> q1w

Eligibility Criteria

- Histologically confirmed (minimum core biopsy) epithelial ovarian, fallopian tube, Mullerian primary peritoneal carcinomas or ovarian carcinoma
- FIGO (1988) staging
  - Stage Ic/IIa – high grade histology
  - Stage IIb-IV – all histological types
- ECOG PS 0-2
- Adequate haematological, renal and hepatic function for carboplatin-paclitaxel chemotherapy
- No prior systemic therapy or planned maintenance therapy for ovarian cancer

Surgery

Patients underwent either:

- Initial Debulking surgery with post-operative chemotherapy (immediate primary surgery – IPS)
- NACT followed by debulking surgery and post-operative chemotherapy (DPS)

Surgical strategy was decided on an individual patient basis prior to trial entry by a specialist gynaecological oncology multidisciplinary team at each investigative site.

Statistical Design

- Sample size for whole trial: 1485 patients

NACT and DPS Protocol Guidelines

- Cytoreductive surgery was strongly advised to be conducted after three cycles of NACT. However, sites could request to perform surgery later for clinical or logistical reasons. The final decision to proceed with DPS was made by the treating multidisciplinary team
- It was recommended that DPS was performed in the 10 day window after day 22 of the preoperative chemotherapy cycle.
- Day 15 of the final preoperative chemotherapy cycle was omitted in weekly treatment arms
- Participants received post-operative chemotherapy to complete six cycles of protocol treatment commencing a maximum of 6 weeks after DPS.

Response Assessment

- Radiological response to NACT was evaluated using RECIST v1.1
- Cross-sectional imaging of abdomen/pelvis was mandated at baseline and during preoperative chemotherapy cycle, 4 weeks post-DPS and at end of chemotherapy.
- During follow-up, imaging was only mandated if clinical examination/symptoms were suggestive of recurrence or there was GCIG CA125 progression
- Serum CA125 was measured three-weekly per protocol during treatment and response evaluated using GCIG criteria

Patient Characteristics

- 1566 patients were recruited to ICON8
- 779 patients entered with planned delayed primary surgery after NACT

		DPS pts N=779
Age	Median IQR	64 56-69
Stage	IC/IIA	4
	IIB/IIC	8
	IIIA/IIIB	34
	IIIC	507
	IV	229
ECOG status	0	311
	1	380
	2	86
Histological Type	Serous high grade	578
	Serous low grade	14
	Serous (no grade specified)	22
	Clear cell	12
	Endometrioid	5
	Mixed/other	148

Scheduling and Outcomes of DPS

- DPS was performed in 602 patients (77.3%)
- 536 (68.8%) patients underwent DPS after 3/4 cycles and 65 (8.3%) after 5/6 cycles
- There were no differences in the proportion of patients undergoing surgery or cytoreductive outcomes between the three trial arms
- No improvement in PFS was seen in either weekly dose-dense chemotherapy arms compared to standard three-weekly CT in patients planned for DPS

Response to NACT

- Complete RECIST v1.1 data to evaluate radiological response before planned surgery were available in 539/779 patients (68.2%)
- No differences in response rates were noted between trial arms, therefore a combined analysis was conducted
- RECIST response rate (CR + PR) pre-planned DPS was 61%

RECIST v1.1 response rates

Response	Percentage of patients
PD	6%
SD	33%
PR	57%
CR	4%

- In patients with RECIST SD, the median preoperative change in marker lesions was -14.5%

Percent Change in tumour burden

Response	Percent Change in tumour burden
PD	~10%
SD	~-14.5%
PR	~-30%
CR	~-60%

- CA125 GCIG response data were available for 726 patients
- Overall pre-surgical GCIG response rate was 84%, including 71% in patients with RECIST SD and 77% in those with RECIST PD.

		CA125 response			
		Yes	No	Missing	
RECIST	PD	20 77%	6 23%	6	
	SD	123 71%	50 29%	4	
	PR	266 93%	21 7%	14	
	CR	18 95%	1 5%	2	
Missing		180	41	1	

RECIST Response Categorisation and DPS

- Comparison of DPS feasibility, cytoreductive outcomes and PFS with RECIST ORR was conducted

	PD		SD		PR/CR		Total	
	N=32		N=177		N=322		N=531	
Surgical Feasibility								
Surgery performed	18	56%	141	80%	284	88%	443	83%
Surgery not performed:	14	44%	36	20%	38	12%	88	17%
<i>No disease to excise</i>	0	0%	17	47%	17	45%	34	39%
<i>Patient progressed</i>	4	29%	1	3%	0	0%	5	6%
<i>No reason given</i>	10	71%	18	50%	21	55%	49	56%
Scheduling of DPS								
Surgery performed after C3/4	15	47%	134	76%	251	78%	400	75%
Surgery performed after C5/6	3	9%	7	4%	33	10%	43	8%
Cytoreductive outcome								
Inoperable (open and close surgery)	0	0%	3	2%	5	2%	8	2%
Debulked to no visible residual disease	14	78%	69	49%	166	58%	249	56%
Debulked to ≤1cm residual disease	2	11%	41	29%	74	26%	117	26%
Debulked to >1cm residual disease	2	11%	24	17%	34	12%	60	14%
Missing	0		4		5		9	
Median PFS (months)								
	5.0		14.7		16.4			

Conclusions

- RECIST RR to neoadjuvant chemotherapy in ICON8 was 61% and was not improved by dose-dense chemotherapy
- PD is rare following neoadjuvant chemotherapy and SD by RECIST incorporates many women with definite reduction in disease burden
- GCIG CA125 response criteria appear unreliable in pre-DPS setting and overestimate response compared to RECIST
- Both PFS and complete/optimal debulking rates were similar in SD and CR/PR groups, reinforcing that patients with SD should be offered delayed primary surgery.

Progress of ICON8 Trials Programme

- ICON8 closed to recruitment in November 2014.
- PFS results were presented at ESMO 2017 – weekly dose dense chemotherapy did not improve PFS compared to standard q3w CT.
- OS results are expected in Q3/4 2019
- ICON8B, assessing the use of bevacizumab in combination with weekly dose-dense paclitaxel was opened to recruitment in July 2015

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Contact

- Dr Andrew Clamp: [andrew.clamp@christie.nhs.uk](mailto:andrew.clamp@christie.nhs.uk)
- ICON8 Trial team: [mrccctu.icon8@ucl.ac.uk](mailto:mrccctu.icon8@ucl.ac.uk)