# Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial

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See Comment page 920

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See Online for appendix

## Summary

**Background** The primary analysis of the JGOG 3016 trial showed that a dose-dense paclitaxel and carboplatin regimen significantly improves progression-free and overall survival compared with the conventional regimen as first-line chemotherapy for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer. We report the long-term follow-up results for survival.

**Methods** This randomised controlled trial was done at 85 centres in Japan. Patients with stage II–IV ovarian cancer were randomly assigned to receive conventional treatment (carboplatin area under the curve [AUC] 6 mg/mL per min and paclitaxel 180 mg/m² on day 1) or dose-dense treatment (carboplatin AUC 6 mg/mL per min on day 1 and paclitaxel 80 mg/m² on days 1, 8, and 15). The treatments were repeated every 3 weeks for six cycles; responding patients had three additional cycles. The randomisation was done centrally by telephone or fax, stratified by residual disease, stage, and histological type. The primary endpoint was progression-free survival; overall survival was a secondary endpoint. Long-term information on adverse events was not collected. Efficacy analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00226915.

**Findings** 637 patients were enrolled, of whom 631 were analysed (312 assigned to the dose-dense regimen, 319 to the conventional regimen). Median follow-up was 76·8 months (IQR 68·9–85·6). Median progression-free survival was significantly longer in the dose-dense treatment group than in the conventional treatment group (28·2 months [95% CI 22·3–33·8] *vs* 17·5 months [15·7–21·7]; hazard ratio [HR] 0·76, 95% CI 0·62–0·91; p=0·0037). Median overall survival was 100·5 months (95% CI 65·2–∞) in the dose-dense treatment group and 62·2 months (52·1–82·6) in the conventional treatment group (HR 0·79, 95% CI 0·63–0·99; p=0·039).

**Interpretation** Dose-dense treatment offers better survival than conventional treatment and is a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer.

**Funding** Japanese Gynecologic Oncology Group, Bristol-Myers Squibb.

## Introduction

A combination of paclitaxel and carboplatin is the standard first-line chemotherapy regimen for treatment of ovarian cancer. In the most recent consensus statements for management of ovarian cancer[1] from the 4th International Ovarian Cancer Consensus Conference, the Gynecologic Cancer InterGroup recommended the use of paclitaxel 175 mg/m², administered intravenously over 3 h, followed by carboplatin as an intravenous infusion over 30–60 min at an area under the curve of 5–6 mg/mL per min repeated every 3 weeks for six cycles. Further treatment options recommended by the group include intraperitoneal treatment for patients with small-volume residual disease and dose-dense weekly paclitaxel in combination with carboplatin every 3 weeks. These recommendations were based on the results of JGOG 3016,[2] in which the Japanese Gynecologic Oncology Group showed that progression-free survival was significantly improved in patients taking dose-dense paclitaxel and carboplatin (28·0 months), compared with those taking conventional paclitaxel and carboplatin every 3 weeks (17·2 months), as a first-line chemotherapy regimen for stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (hazard ratio [HR] 0·71, 95% CI 0·58–0·88; log-rank p=0·0015).

Dose-dense paclitaxel and carboplatin prolonged progression-free survival by 11 months in the primary analysis at a median follow-up of 29 months, despite a higher proportion of patients discontinuing treatment in the dose-dense paclitaxel and carboplatin group (53% *vs* 37%).[2] Overall survival at 3 years was 72·1% in the dose-dense group and 65·1% in the conventional group (HR 0·75, 95% CI 0·57–0·98; p=0·03). Severe haematological and non-haematological toxic effects, including

neuropathy, were much the same between groups except for anaemia, which was significantly more common in the dose-dense paclitaxel and carboplatin group. Here, we report the long-term follow-up results for progression-free and overall survival from a post-hoc analysis.

## Methods

### Participants

JGOG 3016 was a randomised, controlled trial[2]—details of the study have been published previously. The study was done in 85 centres in Japan. Patients with histologically identified stage II–IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were eligible. If the results of only cytological examinations were available, patients had to meet the following criteria: (1) a cytological diagnosis of adenocarcinoma, (2) an abdominal mass more than 2 cm in diameter on abdominal images, and (3) a CA125:carcinoembryonic antigen (CEA) ratio[3] of more than 1:25 or no evidence of gastrointestinal cancer if the CA125:CEA ratio was less than or equal to 1:25. Patients also had to be aged 20 years or older, have an Eastern Cooperative Oncology Group performance status of 0–3, and have adequate organ function. Patients were excluded if they had an ovarian tumour with a low malignant potential or a synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ.

All patients gave written informed consent before enrolment. The study was approved by the institutional review boards of all participating centres.

### Randomisation and masking

We did randomisation centrally by telephone or fax, stratified by residual disease (≤1 cm *vs* >1 cm), International Federation of Gynecology and Obstetrics stage (stage II *vs* stage III *vs* stage IV), and histological type (clear-cell or mucinous *vs* serous or other) with an option to avoid imbalances greater than two within each institution. The randomisation sequence was generated by an independent registration office using a validated computer system. The trial was open-label.

### Procedures

Patients were randomly assigned to receive paclitaxel and carboplatin as either a conventional regimen or a dose-dense regimen. Both groups received carboplatin at a dose calculated to produce an area under the curve (AUC) of 6 mg/mL per min on day 1 of a 21-day cycle, given as an intravenous infusion over 1 h. Patients given the conventional regimen also received paclitaxel, 180 mg/m² on day 1, given as a 3 h intravenous infusion. In the dose-dense group, paclitaxel was given as a 1 h intravenous infusion at a dose of 80 mg/m² on days 1, 8, and 15. The dose of carboplatin was calculated with the formula of Calvert using creatinine clearance instead of the glomerular filtration rate. Creatinine clearance was calculated with the formula of Jelliffe.[4] Irrespective of the calculated doses, the maximum absolute dose given to each patient was limited to 1000 mg. Treatments were repeated every 3 weeks for six cycles. Patients with measurable lesions who had a partial response or a complete response received three additional cycles of chemotherapy.

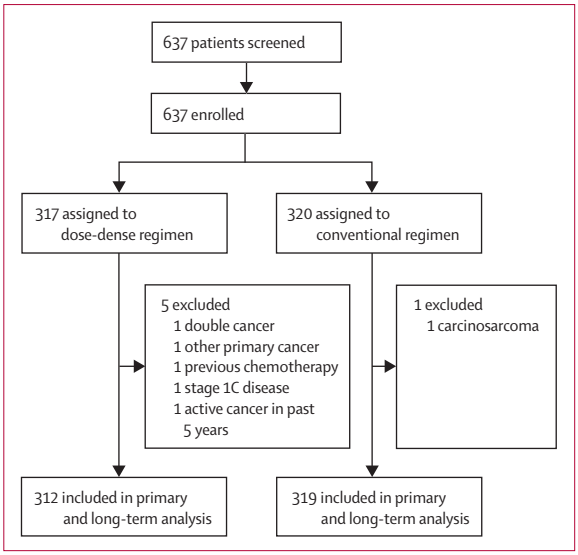


*Figure 1:* **Trial profile**

Patients in both groups had to have an absolute neutrophil count of 1000 cells per μL or greater and a platelet count of 75 000 platelets per μL or greater to receive subsequent cycles of treatment. Patients taking the dose-dense regimen also had to have an absolute neutrophil count of 500 cells per μL or greater and a platelet count of 50 000 platelets per μL or greater before they received paclitaxel on days 8 and 15. Treatment was delayed for a maximum of 3 weeks. The carboplatin dose was reduced when febrile neutropenia occurred, an absolute neutrophil count of less than 500 cells per μL persisted for 7 days or longer, platelet count was less than 10 000 platelets per μL, platelet count was 10 000–50 000 platelets per μL accompanied by signs of bleeding, or treatment was delayed because of haematological toxic effects for more than 1 week. The dose of paclitaxel was reduced in patients with grade 2 or higher peripheral neuropathy. Patients could have interval debulking surgery after two to four cycles of chemotherapy, secondary debulking or second-look surgery after six cycles of chemotherapy, or both.

Radiological studies to assess the status of all measurable lesions noted at baseline were repeated after two, four, and six cycles of chemotherapy. After patients discontinued the protocol treatment, disease status was assessed every 3 months for the first 2 years and every 6 months thereafter. Follow-up monitoring included clinical examinations and estimation of CA125 concentration; routine CT scans were not necessary but were requested if the CA125 concentration increased or symptoms of relapse developed.

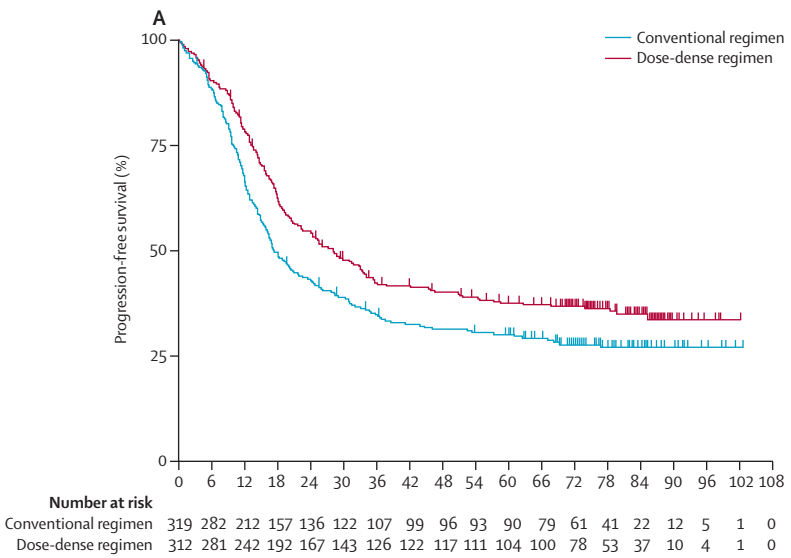


***Figure 2:*** **Kaplan-Meier analyses of survival by treatment regimen**
Progression-free survival (A) and overall survival (B) in each treatment group.

The primary endpoint was progression-free survival, secondary endpoints were overall survival, response rate, and adverse events. In the present analysis we assessed long-term progression-free survival and overall survival. Long-term information on adverse events was not collected.

### Statistical analysis

This post-hoc analysis of the trial was triggered after a median of more than 5 years' follow-up in the surviving patients, with a data cutoff date of Oct 31, 2011. The planned analyses of progression-free survival and overall survival included data on eligible patients according to the intention-to-treat principle. Progression-free survival was defined as the time from the date of randomisation to the date of the first occurrence of any of: death from any cause, appearance of any new lesions that could be measured or assessed clinically, or meeting the CA125 criteria for disease progression.[5] Overall survival was defined as the time from the date of randomisation to the date of death resulting from any cause. In January, 2005, the protocol was amended to have a sample size of 600 patients. This sample size would enable the detection of a 31·3% improvement (from 16 months to 21 months) in median progression-free survival with 80% power, two-sided log-rank test, at an alpha level of 0·05, an accrual of 3 years, and a follow-up of 1·5 years.

We evaluated survival by the Kaplan-Meier method, and compared treatment groups with the log-rank test. We used a Cox proportional hazards model to calculate HRs and 95% CIs. We also used a Cox proportional hazards model to assess the effect of treatment after adjustment for histological subtypes, residual disease, and performance status. Subgroup analyses included a log-rank test stratified for factors used for randomisation and interaction analyses based on stratification factors. All the analyses were done with SAS software (version 9.2).

This study is registered with ClinicalTrials.gov, number NCT00226915.

### Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. NK, FT, and HM had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between April 28, 2003 and Dec 28, 2005, 637 patients were enrolled. 631 patients (312 patients in the dose-dense regimen group and 319 patients in the conventional regimen group) were evaluable in the analysis of long-term outcomes (figure 1).

At the time of the final follow-up (Oct 31, 2011), median follow-up was 76·8 months (IQR 68·9–85·6) for patients with censored data. 426 patients had progressed or died and 307 deaths had been recorded.

Both progression-free survival and overall survival were significantly longer in the dose-dense regimen group than in the conventional regimen group (figure 2). Median progression-free survival was 28·2 months (95% CI 22·3–33·8) in the dose-dense regimen group and 17·5 months (15·7–21·7) in the conventional regimen group (HR 0·76, 95% CI 0·62–0·91; p=0·0037). Median overall survival was 100·5 months (95% CI 65·2–∞) in the dose-dense regimen group versus 62·2 months (52·1–82·6) in the conventional regimen group (HR 0·79, 95% CI 0·63–0·99; p=0·039). 5-year overall survival was 58·7%

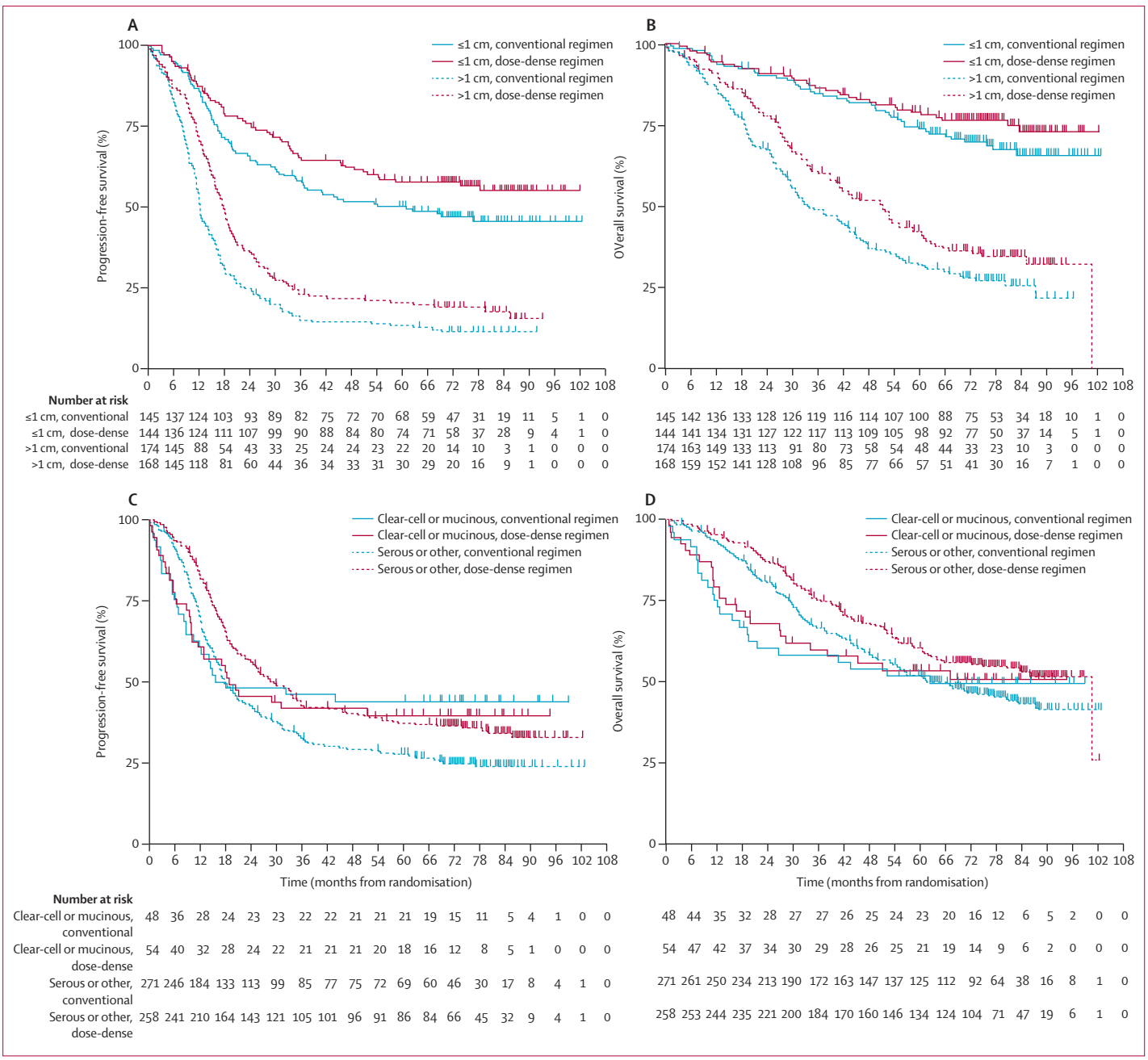


***Figure 3:*** **Kaplan-Meier analyses of survival by treatment regimen in subgroups**
Progression-free survival (A) and overall survival (B) in each treatment group, stratified by residual disease (≤1 cm *vs* >1 cm), and progression-free survival (C) and overall survival (D) in each treatment group, stratified by histological type.

(95% CI 52·9–64·1) in the dose-dense group versus 51·1% (45·4–56·6) in the conventional regimen group.

Figure 3 and the appendix show survival by the stratification subgroups. Median progression-free survival in patients with residual disease at least 1 cm was higher for those dose-dense regimen group than for those in the conventional regimen group (17·6 months, 95% CI 15·6–19·4 *vs* 12·1 months, 11·2–14·3; HR 0·71, 95% CI 0·56–0·89; p=0·0029; figure 3A). Median progression-free survival in patients with residual disease less than 1 cm tended did not differ significantly between groups (not reached *vs* 60·9 months, 35·0–∞; HR 0·74, 95% CI 0·53–1·04; p=0·08; figure 3A). Median overall survival of patients with residual disease at least 1 cm was better in the dose-dense regimen group versus the conventional regimen group (51·2 months,

| | Progression-free survival | | Overall survival | |
|---|---|---|---|---|
| | Adjusted HR (95% CI) | p value | Adjusted HR (95% CI) | p value |
| Conventional regimen *vs* dose-dense regimen | 0·72 (0·60–0·88) | 0·0009 | 0·79 (0·63–0·99) | 0·0403 |
| Stage | | | | |
| II *vs* III | 3·33 (2·24–4·94) | <0·0001 | 3·24 (1·92–5·47) | <0·0001 |
| II *vs* IV | 4·49 (2·86–7·06) | <0·0001 | 4·27 (2·40–7·59) | <0·0001 |
| Residual disease (≤1 cm *vs* >1 cm) | 2·17 (1·75–2·71) | <0·0001 | 2·58 (1·96–3·39) | <0·0001 |
| Performance status (0–1 *vs* 2–3) | 1·50 (1·11–2·03) | 0·0085 | 1·70 (1·23–2·35) | 0·0015 |

HR=hazard ratio.

***Table:*** **Results of multivariate analysis for progression-free survival and overall survival**

40·1–58·3 *vs* 33·5 months, 29·3–43·6; HR 0·75, 95% CI 0·57–0·97; p=0·0027; figure 3B), but it did not differ significantly between treatment groups in patients with residual disease less than 1 cm (not reached *vs* not reached; HR 0·76, 95% CI 0·49–1·19; p=0·23; figure 3B). According to histological subtype, progression-free and overall survival of patients with serous or other histological subtypes was longer in the dose-dense regimen group than in the conventional regimen group (median progression-free survival 28·7 months, 95% CI 24·0–35·3 *vs* 17·5 months, 15·8–21·1; HR 0·70, 95% CI 0·57–0·86; p=0·0007; median overall survival 100·5 months, 65·2–∞ *vs* 61·2 months, 52·6–82·6; HR 0·76, 95% CI 0·59–0·97; p=0·0252; figure 3C, 3D). In patients with clear-cell or mucinous tumours, progression-free and overall survival did not differ significantly between treatment groups (median progression-free survival 18·7 months, 9·9–∞ *vs* 16·7 months, 8·5–∞; HR 1·06, 95% CI 0·63–1·76; p=0·84; median overall survival not reached *vs* 62·2 months, 19·0–∞; HR 0·92, 95% CI 0·53–1·61; p=0·776; figure 3C, 3D).

In the multivariate analysis, after adjustment for prognostic variables, treatment with the dose-dense regimen was associated with a significantly better progression-free and overall survival (table). Stage III or IV disease, residual disease at least 1 cm, and a poor performance status were associated with poor progression-free survival and overall survival (table). We did ad-hoc analyses to assess the effect of treatment delays, dose reductions, and dose intensity of carboplatin and paclitaxel. Dose reductions, treatment delays of chemotherapy, or lower relative dose intensity (<80%) of carboplatin were not independent prognostic factors for overall survival (data not shown). Only lower relative dose intensity (<80%) of paclitaxel was associated with a poor overall survival (HR 1·42, 95% CI 1·12–1·81; p=0·004) according to multivariate analysis.

## Discussion

A combination of platinum and a taxane has been a cornerstone of treatment of epithelial ovarian, fallopian tube, and peritoneal cancer for more than 15 years. The addition of a third cytotoxic drug provides no benefit, including in both triplet combinations and sequential doublets.[6] However, improvements might be made through changes in scheduling, dose intensity, or delivery.[7] We have shown that a dose-dense regimen improves progression-free and overall survival after 5 years of follow-up. The long-term results of this study, in which each group received the same dose and schedule of carboplatin, reinforce this strategy as a potential standard of care (panel).

We did not assess long-term adverse events in the present study. In the original report,[2] anaemia was more common in the dose-dense regimen group versus the conventional regimen group (69% *vs* 44%), but other haematological toxic effects, grade 3 or 4 hypersensitivity reactions (1·9% *vs* 1·6%), and neurotoxicity (7% *vs* 6%) were not significantly different between groups.

Median overall survival in the optimally resected group (with residual disease <1 cm) who received the conventional regimen was better than that in previous trials done in Europe and the USA. This and other studies have shown that Asian patients with ovarian cancer have significantly better survival than do non-Hispanic white patients.[9,10] The study by duPont and colleagues[9] enrolled patients from South Korea and Japan in the Gynecologic Oncology Group 218 phase 3 study with advanced-stage ovarian cancer.[8] Overall survival was significantly higher in Asian patients when adjusted for age, stage, residual disease, performance status, and histology. Future studies should explore biological differences, environmental factors, socioeconomic factors, and response to treatment to clarify the racial and ethnic differences in survival.

In the stratification subgroup analyses, the greatest benefit was achieved in the group of patients with residual disease of 1 cm or more and who had serous or other histology (not clear-cell or mucinous). The improvement in median overall survival (33·5 to 51·2 months) was greater than the improvement in median progression-free survival (12·1 to 17·6 months) for patients with residual disease of 1 cm or more. The reason for this difference is unclear, although subsequent treatment could affect this outcome. The proportion of patients who received subsequent treatments (chemotherapy including platinum *vs* non-platinum chemotherapy) after discontinuation of the protocol treatment did not differ between both groups (data was not shown). However, we did not assess the patients who received subsequent treatment with weekly paclitaxel. The dose-dense regimen might have had a favourable effect in the optimally resected group: progression-free survival was longer in this group. More patients or more events will be needed to detect the effect on overall survival. We report no advantage for clear cell or mucinous histological types, suggesting that other

*Panel:* **Research in context**

**Systematic review**

We searched PubMed, the abstracts of major oncology congresses (American Society of Clinical Oncology and European Society for Medical Oncology), and ClinicalTrials.gov. We used MeSH and full-text search terms for advanced ovarian cancer, chemotherapy, and phase 3 clinical trials, limiting our results to English language articles and abstracts published or presented in the past 2 years. For PubMed, the search was: (advanced[All Fields] AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])) AND ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields]) AND (Clinical Trial, Phase III[ptyp] AND ("2010/07/05"[PDAT] : "2013/07/05"[PDAT]) AND English[lang]). For conferences, the search was: "ovarian cancer" or "advanced ovarian cancer", manually limited to abstracts. The last search was done on July 5, 2013. We identified 14 results in PubMed. The most promising treatment was bevacizumab[8] combined with first-line chemotherapy of carboplatin and paclitaxel for advanced ovarian cancer. The use of bevacizumab during and up to 10 months after carboplatin and paclitaxel chemotherapy prolongs median progression-free survival by about 4 months.

**Interpretation**

Dose-dense carboplatin and paclitaxel is the most active treatment other than targeted treatment with bevacizumab for advanced ovarian cancer. Several confirmatory trials using the dose-dense regimen with or without bevacizumab are now ongoing in Europe and the USA. If these studies confirm the results of JGOG 3016, then it is likely that dose-dense chemotherapy will become an internationally accepted standard of care.

treatment strategies are needed. Both clear cell and mucinous tumours are distinct from high-grade serous cancer and can be classified as type I ovarian cancers, whereas type II tumours comprise the more common high-grade serous carcinomas.[11] A randomised clinical trial (JGOG 3017; University Hospital Medical Information Network in Japan number 000000499) is underway to compare carboplatin and paclitaxel with cisplatin and irinotecan. Standard chemotherapeutic drugs have only modest activity against clear-cell cancer. Greater benefits might be achieved with molecularly targeted treatments, such as sunitinib[12] or mTOR inhibitor.[13]

We calculated the carboplatin dose with the formulas of Calvert and Jellife without adjustment for serum creatinine concentrations. We used the enzymatic peroxidase-antiperoxidase method to estimate the glomerular filtration rate for measurement of serum creatinine. This method can result in an excessive dose of carboplatin and more severe myelotoxicities than the methods used in previous trials.[6,14] Several methods have been proposed to estimate the glomerular filtration rate more accurately,[15–17] but no global consensus exists as to the best method for assessment of renal function as the basis for determining the dose of carboplatin. For this reason, we did not use any adjustment methods to calculate the carboplatin dose. In our post-hoc prognostic analysis, the relative dose intensity of carboplatin was not associated with progression-free or overall survival (data not shown). Therefore, possible excessive doses of carboplatin probably have little effect on survival compared with the different dose schedules for paclitaxel.

The best doses and schedule for a dose-dense regimen of paclitaxel and carboplatin are still unclear. An Italian trial (MITO-7; NCT00660842) is assessing a different schedule of weekly carboplatin and a lower paclitaxel dose than our trial: weekly carboplatin (AUC 2 mg/mL per min) plus weekly paclitaxel (60 mg/m²) compared with carboplatin (AUC 6 mg/mL per min, administered every 3 weeks) and paclitaxel (175 mg/m²). The weekly regimen did not significantly improve progression-free survival compared with the conventional regimen (18·8 months *vs* 16·5 months; p=0·18), but was associated with better quality of life and fewer toxic effects.[18] Other ongoing studies—including the ICON8 trial (NCT01654146), the GOG 262 trial (NCT01167712), and the GOG 262 trial (NCT00951496)—are assessing different schedules and doses in an effort to establish the best dose-dense regimen.

Dose-dense treatment offers a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer. Ongoing studies will clarify the best dose, schedule, and route of administration.

**Contributors**

NK, MY, SI, FT, HM, EK, TS, and KO had the idea for, and designed, the study with the Japanese Gynecologic Oncology Group. MY was the coordinating principal investigator. NK, FT, and HM analysed and interpreted the results. NK wrote the first draft. KO was responsible for the overall planning and conduct of the study. NK, MY, SI, EK, DA, TJ, SK, FT, TS, and KO enrolled patients and collected data. NK, MY, TS, EK, and KO were members of the steering committee. All authors were involved in writing the report and approved the final version of the manuscript.

**Conflicts of interest**

SI has received honoraria from Bristol-Myers Squibb. NK has received honorara from Nippon Kayaku. NK and DA have received grants from Nippon Kayaku. The other authors declare that they have no conflicts of interest.

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