Exploratory outcome analyses according to stage and/or residual disease in the ICON7 trial of carboplatin and paclitaxel with or without bevacizumab for newly diagnosed ovarian cancer

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HIGHLIGHTS

- Post hoc analyses of ICON7 explored bevacizumab by stage and extent of residual disease after upfront surgery for OC.
- The progression-free survival (PFS) benefit from bevacizumab was seen consistently in all subgroups explored.
- The PFS hazard ratio was 0.77 (95% CI, 0.59-0.99) in 411 patients with stage IIIB-IV disease and no visible residuum.
- No OS difference was detected overall or in any subgroup except the previously reported 'high-risk' subgroup.
- Adding bevacizumab to front-line chemotherapy improves PFS irrespective of stage/residual disease.

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ABSTRACT

Objective. In the randomized phase 3 ICON7 trial (ISRCTN91273375), adding bevacizumab to chemotherapy for newly diagnosed ovarian cancer significantly improved progression-free survival (PFS; primary endpoint) but not overall survival (OS; secondary endpoint) in the intent-to-treat (ITT) population. We explored treatment effect according to stage and extent of residual disease.

Methods. Patients with stage IIIB-IV or high-risk (grade 3/clear-cell) stage I-III ovarian cancer were randomized to receive six cycles of carboplatin and paclitaxel either alone or with bevacizumab 7.5 mg/kg every 3 weeks followed by single-agent bevacizumab for 12 further cycles (total duration 12 months). Post hoc exploratory analyses of subgroups defined by stage and extent of residual disease at diagnosis within the stage IIIB-IV population (European indication) was performed.

Results. The PFS benefit from bevacizumab was seen consistently in all subgroups explored. The PFS hazard

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1. Background

The anti-angiogenic agent bevacizumab is an established treatment option for newly diagnosed disease and recurrent ovarian cancer, based on significantly improved progression-free survival (PFS) in five large randomized phase 3 trials [1–5]. However, the optimal timing and patient selection for bevacizumab have been longstanding topics of debate, and an overall survival (OS) benefit remains elusive. Exploratory biomarker research in subsets of patients has yielded inconsistent results [6–9] and findings have not been validated in prospective trials or even in exploratory analyses of other relevant datasets. In the absence of molecular markers predicting treatment effect, clinical characteristics remain some of the most important factors in treatment decision-making.

In the open-label randomized phase 3 ICON7 trial, PFS was significantly improved in patients receiving bevacizumab combined with front-line carboplatin and paclitaxel and then continued as a single agent for up to a total of 12 months compared with patients receiving the same chemotherapy alone. The hazard ratio (HR) for PFS was 0.81 (95% confidence interval [CI], 0.70–0.94; P = 0.004) [2]. No OS difference was detected in the intent-to-treat (ITT) population [10]. However, exploratory analyses suggested improved OS with bevacizumab-containing therapy in a prede

sion of bevacizumab to chemotherapy in the ITT population, exploratory analyses of the protocol-specific final OS analysis suggested that OS was improved with bevacizumab in the subgroup of patients with stage IV disease [11]. This pattern was maintained in a recently reported OS analysis with longer follow-up [12].

FIGO stage at diagnosis and extent of residual disease after debulking surgery are both established prognostic factors in ovarian cancer. FIGO stage has long been recognized as one of the most powerful determinants of OS prognosis [13–17]. The correlation between maximal cytoreduction (to no residual disease) and improved outcome is also well documented [13,18–28]. However, relatively little is known about the interaction between these factors in relation to prognosis, and it is unclear whether surgical intervention or patient- and disease-related factors are the main drivers of variation in prognosis [29].

In a series of 408 patients with stage IIIC ovarian cancer, cytoreduction to no visible residual disease had a greater impact on OS than the extent of metastatic disease before surgery [20]. However, other reports suggested that factors beyond cytoreductive effort are important in predicting survival [30,31]. In an analysis of the GOG-0182 trial, patients with minimal residual disease after primary cytoreductive surgery had worse PFS and OS than patients with complete resection [32]. Interestingly, among patients with complete resection, those

![Fig. 1. Distribution of the study population (treatment arms pooled) according to residual disease and stage. Subgroups in shaded boxes correspond to the Medical Research Council-defined ‘high-risk’ subgroup. NOS, not otherwise specified.](http://creativecommons.org/licenses/by-nc-nd/4.0/).
with greater disease burden before complete resection had worse PFS and OS than those with low disease burden. Clearly complete resection at primary debulking surgery has better outcomes than incomplete surgery, even if achieved before chemotherapy. Moreover, when patients were stratified by residual disease category according to the 1998 FIGO classification, patients with minimal macroscopic residual disease (resection grade 0 or 1) appear to have outcomes between those of patients with stage I disease and those with stage II disease (residual disease vs inoperable stage III and stage IV disease), planned interval between surgery and chemotherapy (<4 vs ≥4 weeks), and Gynecologic Cancer Intergroup group.

The primary endpoint was PFS; the trial was also powered to detect a difference in OS (secondary endpoint). Post hoc exploratory analyses of subgroups defined by stage at diagnosis and extent of residual disease were performed to assess consistency of PFS and OS across subgroups.

Investigators assigned FIGO staging according to the 1998 FIGO classification, and reported extent of residual disease as optimal (≤1 cm) or suboptimal (>1 cm) according to the classification scheme at the time the trial was designed. Further details of the extent of residual disease were collected retrospectively to provide better understanding of the population treated in the ICON7 trial, particularly in light of the GOG-0218 trial evaluating front-line bevacizumab in a slightly different population that was reported in previous publications [2,10]. In summary, women with newly diagnosed ovarian cancer that was either high-risk early-stage (FIGO stage I-IIA, grade 3, or clear-cell histology) or advanced (FIGO stage IIIB-IV) were randomized after primary surgery (unless disease was inoperable) to receive six cycles of chemotherapy (carboplatin area under the curve 5 and paclitaxel 175 mg/m², both administered on day 1 every 3 weeks) either alone or in combination with bevacizumab 7.5 mg/kg every 3 weeks continued for up to 12 months in the absence of disease progression or unacceptable toxicity. Patients had to have Eastern Cooperative Oncology Group performance status 0–2 and adequate coagulation parameters and liver, renal, and bone marrow function. Patients with uncontrolled hypertension were excluded, as were patients for whom further surgery was planned.

The design of the international open-label randomized phase 3 ICON7 trial has been described in previous publications [2,10]. In summary, women with newly diagnosed ovarian cancer that was either high-risk early-stage (FIGO stage I-IIA, grade 3, or clear-cell histology) or advanced (FIGO stage IIIB-IV) were randomized after primary surgery (unless disease was inoperable) to receive six cycles of chemotherapy (carboplatin area under the curve 5 and paclitaxel 175 mg/m², both administered on day 1 every 3 weeks) either alone or in combination with bevacizumab 7.5 mg/kg every 3 weeks continued for up to 12 months in the absence of disease progression or unacceptable toxicity. Patients had to have Eastern Cooperative Oncology Group performance status 0–2 and adequate coagulation parameters and liver, renal, and bone marrow function. Patients with uncontrolled hypertension were excluded, as were patients for whom further surgery was planned.

The stratification factors were: combined FIGO stage and residual disease (stage I–III and ≤1 cm residual disease vs stage I–III and >1 cm residual disease vs inoperable stage III and stage IV disease), planned interval between surgery and chemotherapy (<4 vs ≥4 weeks), and Gynecologic Cancer Intergroup group.

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Tumors were assessed by computed tomography (CT) after cycles 3 and 6, and then 9 and 12 months after randomization. After treatment discontinuation, CT scans were performed every 6 months.
until 3 years after randomization, and then as clinically indicated. Disease progression was assessed by investigators according to Response Evaluation Criteria in Solid Tumors (2000); radiological or clinical evidence of progression was required.

2.2. Statistical analysis

The data cutoffs for these analyses were November 30, 2010, for PFS, representing the updated primary PFS analysis requested by regulatory authorities [2], and March 31, 2013, for OS, representing the prespecified final OS analysis [10]. The 2010 cutoff for PFS was chosen to avoid potential bias in PFS estimates during the extended OS follow-up, when CT scans were performed only as clinically indicated. PFS was defined as the interval between the date of randomization and the date of first progression or death, whichever occurred first. Patients who were alive without disease progression were censored at the date of last clinical follow-up visit (i.e., using the same approach as the primary trial analyses). In sensitivity analyses, patients who were alive and progression-free were censored at the date of their last tumor assessment.

Although the subgroup analyses reported here were not prespecified in the primary and secondary objectives of the trial, a statistical analysis plan was developed (after study completion) and agreed before performing these exploratory analyses. The main aim was to assess consistency of treatment effects.

Unstratified Cox regression analyses were used to estimate HRs for PFS and OS, presented with corresponding 95% CIs. Medians were estimated using the Kaplan-Meier approach. As nonproportional hazards were detected in the overall population of ICON7 [2], restricted means were also calculated with associated 95% CIs for each subgroup. There was no adjustment for multiplicity. Consequently, no P-values are presented.

3. Results

3.1. Patient population

The distribution of patients according to stage and residual disease is shown in Fig. 1 and Table 1. In 41 patients classified as ‘optimally debulked, no further details of residual disease were available. These patients were included in the subgroup with visible residual disease.

3.2. Efficacy

The median duration of follow-up was 28 months for PFS and 49 months for OS. Fig. 2 shows analyses by FIGO stage. For PFS, the subgroups for all stages indicate more favorable outcome with bevacizumab (HR<1 in all subgroups). The 95% CIs are difficult to interpret because of the imbalance in sample size between the subgroups (e.g. 163 patients with stage II disease, 1045 patients with stage III disease). Nevertheless, in all subgroups defined by stage, the direction of treatment effect favored bevacizumab. In contrast, the pattern for OS is less clear. When interpreting these findings, the extremely low event rates in the stage I and II subgroups compared with the stage III and IV subgroups should be noted: OS analyses are based on only 15 events (13%) in the stage I subgroup and 27 (17%) in the stage II subgroups.
In all three analyses of the stage IIIB subgroup, the bevacizumab-containing and chemotherapy-alone arms was similar and also the ITT population [2]. The absolute difference in PFS between the shape of the curves for the visible residual disease subgroup (Fig. 4iii) did not cross 1. Of note, the Kaplan-Meier curves for PFS within this subgroup systematically diverged from each other, indicating that bevacizumab-containing therapy versus 9.6 months with chemotherapy alone. In contrast, no OS was observed in either the entire stage IIIB subgroup or the subgroups further classified according to the presence/absence of residual disease (Figs. 3 and 4). The 95% CIs for the OS HR crossed 1 in all cases, indicating no difference in OS. This observation is consistent with results in the ITT population. Among the broader group of patients with stage III/IV disease, the important prognostic effect of visible residual disease extent was clearly reflected in the ITT population. The 95% CI of the HR for the smaller subgroup with stage IIIB–IV disease and no visible residual disease (n = 411) was wide but did not cross 1. Of note, the Kaplan-Meier curves for PFS within this subgroup remained clearly separated over time (Fig. 4ii), in contrast to the shape of the curves for the visible residual disease subgroup (Fig. 4iii) and also the ITT population [2]. The absolute difference in PFS between the bevacizumab-containing and chemotherapy-alone arms was similar in all three analyses of the stage IIIB–IV subgroup (all patients, those with visible residual disease, and those with no visible residual disease): approximately 3 months as estimated by the restricted mean and approximately 5 months as estimated by the median. In contrast, no OS difference was observed in either the entire stage IIIB–IV subgroup or the subgroups further classified according to the presence/absence of residual disease (Figs. 3 and 4). The 95% CIs for the OS HR crossed 1 in all cases, indicating no difference in OS. This observation is consistent with results in the ITT population. Within the smaller subgroup of 43 patients with stage IV disease and no visible residuum after debulking surgery, the PFS HR was 0.88 (95% CI, 0.45–1.72). Median PFS was 19.0 months with bevacizumab-containing therapy versus 13.0 months with chemotherapy alone. In the subgroup of 158 patients with stage IV disease with visible residuum after debulking surgery, the PFS HR was 0.63 (95% CI, 0.45–0.89) and median PFS was 13.2 months with bevacizumab-containing therapy versus 9.6 months with chemotherapy alone. Similar patterns were seen for OS in patients with stage IV disease: in those with no visible residuum, the HR was 0.80 (95% CI, 0.36–1.76; median OS 49.2 vs 41.6 months with bevacizumab-containing therapy vs chemotherapy alone, respectively), while in those with visible residuum, the HR was 0.69 (95% CI, 0.47–1.02; median OS 36.8 vs 26.3 months, respectively).

Among the broader group of patients with stage III/IV disease, the important prognostic effect of extent of residual disease was seen clearly in the median PFS and OS values in both the control arm and the investigational arm. The magnitude of bevacizumab treatment effect on PFS (as indicated by the HR) was similar in patients with versus without visible residual disease, suggesting that the extent of visible residual disease does not appear to be predictive for bevacizumab treatment effect. In clinical practice, this finding suggests that despite the better prognosis associated with complete resection compared with visible residual disease after maximal debulking, in both subgroups, PFS outcomes can be improved further by adding bevacizumab to chemotherapy. Regarding OS in the subgroup of patients with stage III–IV disease, neither a benefit nor a detrimental effect from bevacizumab was demonstrated either in those with complete resection or in those with visible residual disease. In the stage IV subgroup, there was a trend toward improved OS with bevacizumab but the 95% CI crossed 1, even in the small subgroup with visible residual disease. In the stage IV subgroup, there was a trend toward improved OS with bevacizumab but the 95% CI crossed 1, even in the small subgroup with visible residual disease. This contrasts with observations from GOG-0218, but as noted below, these exploratory subgroup analyses should be interpreted with caution. Only in the previously reported prespecified subgroup of patients with stage III residuum >1 cm, stage IV, or inoperable disease (‘high-risk’ subgroup) has the PFS benefit translated into an OS benefit [10].

These analyses have limitations that should be considered. Firstly, these exploratory subgroup analyses were not prespecified in the primary analyses [2] and no adjustment was made for multiplicity of

| Stage and residuum | No. of events/patients (%) | Median, months | Restricted mean, months | HR (95% CI) |
|-------------------|---------------------------|----------------|-------------------------|-------------|
|                  |                           | Reference | Bevacizumab | Reference | Bevacizumab | Bevacizumab better | Reference better |
| PFS               |                           |           |             |           |             |                   |               |
| III/IV 0 cm       | 240/461 (52)              | 21.9      | 25.9        | 26.2      | 28.6        | 0.82 (0.64–1.06)   |               |
| III/IV >0–<1 cm   | 260/340 (76)              | 12.9      | 17.4        | 19.1      | 20.0        | 0.98 (0.77–1.25)   |               |
| III/IV >1 cm      | 324/388 (84)              | 10.6      | 16.4        | 15.1      | 19.6        | 0.69 (0.56–0.86)   |               |
| OS                |                           |           |             |           |             |                   |               |
| III/IV 0 cm       | 166/461 (36)              | NR        | NR          | 49.3      | 49.0        | 1.06 (0.78–1.44)   |               |
| III/IV >0–<1 cm   | 211/340 (62)              | 43.1      | 44.1        | 40.8      | 41.6        | 0.91 (0.70–1.20)   |               |
| III/IV >1 cm      | 258/388 (64)              | 31.3      | 38.9        | 35.2      | 39.2        | 0.84 (0.66–1.07)   |               |

Fig. 5. Subgroup analyses by stage and residual disease status in the stage III/IV subgroup. CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

Sensitivity analyses within all of these subgroups showed very similar results (data not shown).

3.3. Safety

Analyses of safety within the various subgroups defined above showed no relevant differences (Supplementary Table S1).

4. Discussion

In these post hoc exploratory analyses, adding bevacizumab to carboplatin and paclitaxel chemotherapy improved PFS in most of the evaluated subgroups, consistent with the ITT population. The main patient populations appearing not to derive a PFS improvement from adding bevacizumab to chemotherapy were those with stage I or II disease, although small sample sizes and low event rates in these subgroups limit interpretation. In the subgroup of patients with stage IIIB–IV disease, representing the approved bevacizumab indication in Europe, a PFS improvement was seen irrespective of the presence or not of visible residual disease.

Efficacy in the stage IIIB–IV subgroup was consistent with results in the ITT population for both PFS and OS. Within the subgroup of patients with stage IIIB–IV disease, the important prognostic effect of visible residual disease extent was clearly reflected in the median PFS and OS values in both the control arm and the investigational arm. The magnitude of bevacizumab treatment effect on PFS (as indicated by the HR) was similar in patients with versus without visible residual disease, suggesting that the extent of visible residual disease does not appear to be predictive for bevacizumab treatment effect. In clinical practice, this finding suggests that despite the better prognosis associated with complete resection compared with visible residual disease after maximal debulking, in both subgroups, PFS outcomes can be improved further by adding bevacizumab to chemotherapy. Regarding OS in the subgroup of patients with stage IIIB–IV disease, neither a benefit nor a detrimental effect from bevacizumab was demonstrated either in those with complete resection or in those with visible residual disease. In the stage IV subgroup, there was a trend toward improved OS with bevacizumab but the 95% CI crossed 1, even in the small subgroup with visible residual disease. This contrasts with observations from GOG-0218, but as noted below, these exploratory subgroup analyses should be interpreted with caution. Only in the previously reported prespecified subgroup of patients with stage III residuum >1 cm, stage IV, or inoperable disease (‘high-risk’ subgroup) has the PFS benefit translated into an OS benefit [10].

These analyses have limitations that should be considered. Firstly, these exploratory subgroup analyses were not prespecified in the primary analyses [2] and no adjustment was made for multiplicity of

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|-------------------|---------------------------|----------------|-------------------------|-------------|
|                  |                           | Reference | Bevacizumab | Reference | Bevacizumab | Bevacizumab better | Reference better |
| PFS               |                           |           |             |           |             |                   |               |
| III/IV 0 cm       | 240/461 (52)              | 21.9      | 25.9        | 26.2      | 28.6        | 0.82 (0.64–1.06)   |               |
| III/IV >0–<1 cm   | 260/340 (76)              | 12.9      | 17.4        | 19.1      | 20.0        | 0.98 (0.77–1.25)   |               |
| III/IV >1 cm      | 324/388 (84)              | 10.6      | 16.4        | 15.1      | 19.6        | 0.69 (0.56–0.86)   |               |
| OS                |                           |           |             |           |             |                   |               |
| III/IV 0 cm       | 166/461 (36)              | NR        | NR          | 49.3      | 49.0        | 1.06 (0.78–1.44)   |               |
| III/IV >0–<1 cm   | 211/340 (62)              | 43.1      | 44.1        | 40.8      | 41.6        | 0.91 (0.70–1.20)   |               |
| III/IV >1 cm      | 258/388 (64)              | 31.3      | 38.9        | 35.2      | 39.2        | 0.84 (0.66–1.07)   |               |
testing. Therefore, the risk of spurious findings should not be ignored. Secondly, the analyses rely on retrospectively collected information on visible residual disease at the time of primary debulking. Thirdly, because the ICON7 trial recruitment period preceded the introduction of the 2014 FIGO staging system, the analyses use the preceding FIGO staging system. The new staging appears to provide even better prognostic value, at least for stage I–III disease [36]. Finally, we recognize that there is a risk of bias in assessing PFS in an unblinded clinical trial. Despite such limitations, these analyses expand our understanding of frontline bevacizumab-containing therapy by providing an indication of the impact of bevacizumab on outcomes in patients with completely resected advanced-stage ovarian cancer. This finding is pertinent given the practice in some countries and healthcare systems of restricting front-line bevacizumab use to patients meeting the ICON7 criteria for high-risk disease. Our findings also add to the analysis by Horowitz et al. [32], which suggested that initial disease burden remained a significant prognostic indicator despite maximal cytoreduction to no residual disease. Although complete resection remains a key goal in ovarian cancer, it is important to avoid complacency in patients diagnosed with advanced-stage disease to ensure that outcomes are optimized for patients, irrespective of surgical achievements.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2018.08.036.

Conflict of interest statement

AGM has received personal fees from AstraZeneca, Roche, Tesaro, Clovis, and PharmaMar. JP has received grants from Roche during the conduct of the study. JAL has received personal fees from Roche for an advisory board, a research grant and personal fees from AstraZeneca, personal fees from Clovis Oncology and Pfizer, and a research grant from MSD/Merck. EPL has received personal fees and non-financial support from Roche and AstraZeneca, and personal fees from Tesaro, Clovis, and Pfizer. PB has received educational meeting attendee/Chair fees from AstraZeneca, Roche, MSD, and sponsorship to attend conferences from Ipsen and Roche. RSK’s institution has received research grants from Roche. MKBP has received a grant from Roche related to the submitted work. NS is an employee of F. Hoffmann-La Roche Ltd. Medical writing support was provided by Jennifer Kelly, MA (Medi-Kelsey Ltd., Ashbourne, UK), funded by F. Hoffmann-La Roche Ltd.

Role of the funding source

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Author contributions

AGM, AMO, JP, JAL, EPL, GK, MAB, PB, AC, RSK, and TJP enrolled patients. AMO, AMO, ACE, RSK, NS, and TJP developed the concept of this paper. ACE and MKBP performed the statistical analyses. AGM drafted the paper with support from a medical writer and input from AMO, ACE, RSK, NS, and TJP. All authors critically reviewed and revised subsequent drafts and provided final approval for submission.

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