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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ledermann JA, Embleton AC, Raja F, et al, on behalf of the ICON6 collaborators. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; **387:** 1066–74.

Supplementary Appendix

Ledermann JA, Embleton AC, Raja F, et al. Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; **387:** 1066–74.

Table of Contents

A – Timeline of key trial milestones

Date	Milestone
01-Jan-2007	Funded by Cancer Research UK as an investigator-initiated academic trial, with additional support from AstraZeneca (AZ). To be carried out as a multi-stage trial involving an initial safety stage at selected sites, to be followed by wider international participation in two efficacy stages.
10-Dec-2007	Stage I (safety) recruitment begins at 14 sites in UK and Canada, using 30mg dose.
05-Nov-2008	IDMC meet and recommend dose reduction based on concerns about tolerability of 30mg dose and the decision of AZ to develop 20mg as the standard dose for its own pivotal trials (in other diseases).
13-Nov-2008	Trial Management Group (TMG) meet and decide to immediately conclude randomisation to 30mg dose and restart Stage I (safety) at 20mg dose. All patients reconsented to the new Patient Information Sheet.
18-Nov-2009	Revised Stage I (20mg) completed (published: http://dx.doi.org/10.1038/bjc.2011.334).
17-Dec-2009	IDMC meet and approve trial progression to efficacy stages. PFS to be employed as endpoint for moving from Stage II to Stage III. Planned sample size for the final stage was 2000 patients, with OS as the primary endpoint. Over time 78 sites open in UK, Canada, Australia and Spain.
14-Sep-2011	MRC Clinical Trials Unit informed by AZ that the company would discontinue cediranib development due to insufficiently strong results in their pivotal trials in other indications. At this point, 387 patients had been randomised in ICON6 and no outcome analyses had been scheduled or performed. Consultations between MRC Clinical Trials Unit and AZ regarding continuing supply of cediranib clarified that ICON6 recruitment would need to cease by end of 2011 due to limited remaining supply and shelf-life of clinically formulated drug. It was not possible for AZ to fund the substantial cost of formulation of additional clinical supplies.
28-Sep-2011	TMG (which had no access to any outcome data) met to discuss how to salvage useful clinical data from the trial with the newly limited sample size of 400-500. A proposal was made to redesign the trial: • using PFS as the primary endpoint (to maximise the number of events) • OS thus becoming a secondary endpoint • the primary comparison to be between Arms A and C (that is, the control chemotherapy only arm vs the 'full' treatment of concurrent + maintenance cediranib) as maintenance of anti-angiogenesis for a prolonged period seemed to be key to the benefit of bevacizumab in emerging results This plan, based on 440 patients on the 20mg dose, yielded 80% power to detect a clinically meaningful difference in PFS between arms A and C.
09-Nov-2011	The IDMC (which had still seen no analysis of the accumulating data, blinded or unblinded) agree in principle the protocol amendment, v7. AZ are informed of the revised plan.
06-Dec-2011	Independent Trial Steering Committee meet and approve the protocol amendment.
23-Dec-2011	Recruitment complete; final number randomised = 486.

01-Oct-2012	Pre-planned number of PFS outcome events reached (176 events in arms A + C). An estimated 20% of patients still on trial drug had not yet reached the originally scheduled 18 months of therapy needed to test the maintenance question (arm C), so analysis delayed to improve power. No analyses of the outcome data were done at this time (or at any point between trial initiation and 19-Apr-2013, as indicated below). IDMC agree that the delay is the right approach to ensure robust conclusions.
19-Apr-2013	Data snapshot from database for outcome analysis.
01-July-2013	TMG and AZ informed of results of outcome analysis.
30-Sep-2013	Results presented publically at the Presidential Session of the European Cancer Congress in Amsterdam, NLD.

B – Relationship with previously presented results

Source Data Verification, Quality Check of data entry and Blinded Independent Central Review

Following the primary presentation of results at ECC 2013[1] AstraZeneca made the decision to review the data quality of this academically-led trial in preparation for possible regulatory review for licensing of cediranib in patients with relapsed ovarian cancer. Third-party Source Data Verification (SDV) was carried out for key Case Report Forms (CRFs) compared to the original source of information, a Quality Check (QC) of data entry of these CRFs and a Blinded Independent Central Review (BICR) of disease progression/non progression on imaging was conducted. This resulted in numerous data point changes in the database, locked on 20-Aug-2014. The same data cut-off of 19-Apr-2013 was used, but the changes led to variation between the original analysis/presentation and the updated data used in the preparation of this manuscript. However, the net effect was a nearly identical PFS. There was a minor change in the OS result compared to the original presentation as ten additional deaths either became apparent, or in the case of two patients their date of death was revised to be prior to the data cut-off, during the SDV and QC process. Consequently, these deaths were included in the revised analysis. There was no material change in PFS when a sensitivity analysis was performed using the blinded imaging central review (BICR).

Censoring rule for overall survival

Consistent with an AstraZeneca standard approach for OS analyses, a censoring rule different from MRC's original one was applied to the revised (cleaned) OS data. Instead of using the date of the last patient visit prior to data cut-off (as originally), the revised approach brings censoring forward to the data cut-off date for any patients who were confirmed alive at a later date on the basis of receipt of one of the following forms: follow up, SAE, or death. This approach was undertaken in order to achieve the effect of a 'survival sweep' as would have been performed if OS had been the primary endpoint, and does produce some numerical differences between the OS results presented at ECC 2013 and this paper.

Note that the figures quoted below are prior to the inclusion on the analysis of an extremely late reported patient death, which pertained to prior to the data cut off. Consequently these figures will differ by one event to that reported in the main body of text. This has been done so that any contrasts between factors are being made on a comparable basis.

To summarize the changes made, 64 (54%) patients in the reference arm and 80 (49%) in maintenance arm had an OS event in the update. Of reference arm patients eligible for having a revised censoring time, those without an event, nine (17% of 54) had a death at their next recorded visit, 38 (70%) had a follow up visit and 7 (13%) had no further information available. The pattern was similar on the maintenance arm with ten (11% of 85) patients having a death at their first subsequent visit, 64 (74%) with a follow up and 11 (13%) with no further information. No death events were captured using an SAE event.

50 patients in the reference arm and 74 in the maintenance arm had their censoring date brought forward to the date of cut-off (19-Apr-2013); given the 2:3:3 ratio of randomisation this was not unexpected. The most striking differences were in the median change in days, as the reference arm gained an average of 93 days (IQR: 36–130) whereas the maintenance arm gained 48 days (21–95). It is difficult to say whether three months shift versus a month and a half in the standard analysis suggests that the reference arm patients had been less closely followed and it cannot be excluded that this is due to a less stringent follow up in the control arm. Given the blinded nature of the trial we feel this would more likely be a random finding, which however may have contributed to some observed narrowing of the OS difference between the two arms when compared to the original presentation.

Note that the use of the revised censoring approach does not alter the number of survival events incorporated in the analysis, only the addition of time to individual cases found after the cut-off date of 19-Apr-2013 to have been alive on that date.

The effect of this censoring, in comparison to the standard approach outlined in the SAP, on the test of difference between the two arms using the log-rank test is that the p-value of 0·07 reduced to 0·1. Strong evidence for non-proportionality was still present at p=0·002, in comparison to 0·003. The RMST estimate (over three years) was very similar at 2·6 (1·02–4·11) months difference when compared to the revised standard estimate of 2·5 (1·01–4·05) months.

The HR varied marginally at 0·76 (0·55–1·05) for the censoring rule over 0·74 (0·53–1·03). The situation was similar for median survival times with 19·6 months (17·1–26·5) in the reference arm for the standard

censoring group and 21·0 months (17·7–27·6) in the modified censoring analysis. The maintenance arm changed marginally from 25·7 months (23·5–29·0) to 26·5 months (23·8–31·8).

In summary this approach to censoring has increased the median survival in the reference arm, bringing it somewhat closer to OCEANS[2] (median OS for the PL arm was 35·2 months), CALYPSO[3] (30·7 months in the CD arm and 33·0 months in the CP arm) and ICON4[4] (29 months paclitaxel plus platinum-based chemotherapy), though it has also reduced the observed OS difference due to the median change in days for the placebo arm being almost double that of the maintenance arm. The apparent disparity in observed median OS between ICON6 and analogous trials will be addressed in a separate manuscript. As the number of survival events that we will have in this trial is relatively small, and fewer than half of these had occurred at the time of data cut-off, we may yet observe strengthening or weakening of benefit in terms of OS.

C – Sensitivity analyses

Summary of pre-planned sensitivity analyses

We performed several pre-planned sensitivity analyses to assess the robustness of both the primary PFS and OS results. These included models stratifying by the randomisation factors (exposure to bevacizumab, first line paclitaxel, planned chemotherapy regimen, greater than 6 months since end of first line, GCIG group), both individually and jointly, and an unstratified model of 486 patients including the 30 patients randomised at the start of the trial to cediranib 30mg dose. All made a negligible difference to both the overall test of equality of survivor functions and the estimate of this difference.

For completeness, and to ensure all randomised patients contribute data, we will describe the results of the full 486 patients at both 20 mg and 30 mg doses in full. Consistent with the primary analysis of PFS the log-rank test of a difference between Arms A and C provided strong evidence of a benefit at $p<0.001$, with 120/125 (96%) and 154/177 (87%) of events having occurred. The hazard ratio was similarly consistent at 0.56 (CI 0.44–0.72). As there was no strong evidence to declare non-proportional hazards (p=0.08) the median is an appropriate measure of the size of the difference, with a 2.4 month gain in arm C (8.8 months to 11.1 months). A greater difference was observed using the RMST method, with a 3.2 month gain over the reference from 9.3 to 12.5 months.

We also looked at the effect of cediranib on both PFS and OS for time from first histological diagnosis as reported at screening. The median period from this first diagnosis to randomisation was 1·6 years overall (IQR 1·2–2·3) and was balanced across all arms. PFS was consistent with time from randomisation with a strong treatment effect (HR 0·74, 95% CI 0·58–0·95, p=0·02), reflected in an improvement of 5 months in median time to progression from 26·8 months to 31·9. OS shows a slightly diluted effect when compared to the original planned OS assessment of last visit prior to data cut-off (HR 0·78, 95% CI 0·56–1·08, p=0·1) but is still generally consistent with both the planned and revised censoring rules for the secondary analyses, with a median survival improvement of 8.1 months from 43·6 to 51·7 months.

Blinded Independent Central Review of progression scans

In comparison to the revised PFS results summarized in the main body of the paper, using Blinded Independent Central Review the number of patients in the analysis set was reduced by 4% in each arm, 5 in

Arm A and 6 in Arm C, in the primary comparison (A vs. C) due to the inclusion of only those patients with at least 1 scan or radiological report provided for review. In this primary comparison the observed progression events decreased by 24 overall. This meant that overall 85% (230/271) of patients observed an event as opposed to 90% previously (254/282). The reference arm received a reduction of 6% in absolute terms from 96% (113) to 90% (102) and the maintenance arm reduced 5% from 86% (141) to 81% (128). On the reference arm one patient (1%) had a progression newly identified and 8 patients (7%) had progressions discounted. The maintenance arm was rather similar in that two patients (1%) had progressions added and 13 (8%) had theirs omitted.

In the reference arm using the BICR data 18 patients (16% of the total patients assessable in that arm) died without progression, 77 (68%) had progression radiologically-confirmed by BICR as their first documented evidence of progression, seven (6%) progression confirmed but non-radiologically initially and 11 (10%) had no documented progression. The pattern was somewhat similar in the maintenance arm with 12 patients (8%) dying without progression, 104 (66%) with radiologically-confirmed progression, 12 (8%) with progression but no radiologic confirmation and 30 (19%) with no documented progression.

The strength of evidence for a PFS difference in the treatment arms using the log-rank test remained at $p \leq 0.001$, even given the slightly unbalanced reduced number of events in both arms, using progressions defined using the BICR.

The test for non-proportionality p-value was unchanged at 0·06; consequently the primary estimate of this observed difference was a HR of 0·64 (0·49–0·83). This was a very similar, if a little smaller, effect size in favour of maintenance treatment observed in the investigator-based approach.

The RMST for the investigator-based approach gave a 3·1 (95% CI 1·8–4·4) month gain of the maintenance treatment over the reference from 9·4 to 12·5 months. The BICR-based analysis gave a reduction in this gain to 2·9 months from 10·4 to 13·3 months.

Median event times shortened slightly and their corresponding intervals shifted due to the overall reduction of events. The reference arm increased from 8·7 months (7·7–9·4) to 9·4 (8·3–10·1) months with the maintenance also increasing slightly from 11·0 (10·4–11·7) to 11·1 (10·7–12·0).

Kaplan-Meier plots displayed no real differences between the shapes of the curves comparing the two approaches, beyond superficial variations.

D – Definition of progression

For patients with measurable disease at randomisation

Progression is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since trial entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since trial entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)

For patients with non-measurable disease at randomisation

Progression, for patients with non-measurable disease at randomisation, is defined as increasing clinical, radiological or histological evidence of disease since trial entry. All patients, including those with measurable disease whose progression is classified as 'global deterioration without objective evidence of progression and those with non-measurable disease at randomisation, are expected to have a CT or MRI scan at the time of progression to formally document radiological disease status.

E – Quality of Life

Methods

Health related quality of life (QoL) was summarised for their previous week by patient-report, using the EORTC QLQ-C30 and OV28 questionnaires (http://groups.eortc.be/qol/questionnaires_qlqc30.htm). Reporting was always before clinical assessments, and carried out every chemotherapy cycle, 6-weekly for the remainder of year 1, then 3-monthly or until progression. QoL data was collected infrequently after disease progression, but a scheduled assessment took place at 12 months for all post-progression patients still alive. The primary QoL endpoint was Global QoL at the 51-week scheduled follow up, using the QLQ-C30 score on a translated scale from 0 (worst) to 100 (best). For patients who had not progressed the closest QoL form to 51 weeks was used.

Three secondary hypotheses were also defined a priori to assess specific effects of cediranib at different points during a patient's treatment. The early hypothesis was that ascites would resolve more rapidly with cediranib, the mid hypothesis was that women with symptomatic disease at enrolment and treated with cediranib would respond better in global QoL, physical functioning and pain, while the late hypothesis was that maintenance cediranib treatment would prolong impairment of social functioning and fatigue.

F – Collaborators

The ICON6 trial team would like to thank all collaborators, including:

Patients

ICON6 TMG members and staff at the MRC Clinical Trials Unit at UCL – K. Brown, E. Burnett, K. Carlton, E. Clark, A. Cook, C. Davidson, C. Díaz-Montaña, E. Eisenhauer, A. Embleton, L. Farrelly, D. Fry, A. González-Martín, C. Griffin, H. Hirte, G. Jayson, C. Jones, R. Kaplan, S. Kaye, J. Ledermann, S. Mannix, J. Martyn, R. Meyer, F. Nepote, J. Parker, M. Parmar, W. Parulekar, T. Perren, J. Petrie, S. Popoola, W. Qian, F. Raja, G. Rustin, D. Stark, AM. Swart, M. Tomiczek, S. Townsend, M. Vaughan

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Appendix-specific references

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