Quality of life, long-term survivors and long-term outcome from the ABC-02 study

John Bridgewater *,1, Andre Lopes 2, Daniel Palmer 3, David Cunningham 4, Alan Anthoney 5, Anthony Maraveyas 6, Srinivasan Madhusudan 7, Tim Iveson 8, Juan Valle 9,11 and Harpreet Wasan 10,11 on behalf of the ABC-02 investigators 12

1UCL Cancer Institute, UCL, London WC1E 6DD, UK; 2UCL and CRUK Clinical Trials Centre, UCL, London W1T 4TJ, UK; 3Institute of Translational Medicine, University of Liverpool, Liverpool L69 3BX, UK; 4Department of Medicine, Royal Marsden Hospital, Sutton SM2 5PT, UK; 5Department of Oncology, St. James’s Hospital, Leeds LS9 7TF, UK; 6Department of Oncology, Castle Hill Hospital, Hull HU16 5JQ, UK; 7Department of Oncology, Nottingham University Hospitals, Nottingham NG7 2UH, UK; 8Department of Oncology, Southampton University Hospitals, Southampton SO16 6YD, UK; 9The University of Manchester, Manchester M20 4BX, UK and 10Hammersmith Hospital, London W12 0HS, UK

Background: The ABC-02 (Advanced Biliary Tract Cancer) study established cisplatin and gemcitabine (CisGem) as the standard first-line chemotherapy for patients with locally advanced or metastatic biliary tract cancer (BTC). We examine quality of life (QoL), describe the long-term survivors and provide a long-term outcome.

Methods: A total of 410 BTC patients were randomised to receive either CisGem or gemcitabine alone (Gem); 324 patients consented to complete EORTC QLQ-C30 and EORTC QLQ-PAN26 QoL questionnaires; 268 (83%) patients returned at least one QoL questionnaire (134 in each arm). Long-term survivors were defined as those surviving over 2 years and we performed a final analysis of the primary outcome; overall survival (OS).

Results: Most QoL scales showed a trend favouring the combined CisGem arm, including functional and symptomatic scales, although the differences were not statistically significant. Forty-five (11%) patients survived at least 2 years (34 received CisGem and 11 Gem) and 21 (5%) 3 years or more (14 received CisGem and 7 Gem). After a median follow-up of 9.2 months and 398 deaths, the median OS was 11.7 months for CisGem and 8.1 months for Gem (hazard ratio (HR) = 0.65, 95% CI: 0.53–0.79, P < 0.001).

Conclusions: The survival advantage of CisGem compared to Gem was not associated with an improvement or deterioration of QoL. Long-term survivors were more likely to have received CisGem and the long-term OS is identical to that previously described.

Biliary tract cancers (including cholangiocarcinoma and cancers of the gallbladder and ampulla of Vater, BTC) are uncommon cancers with a poor prognosis (de Groen et al, 1999). The standard of care for advanced biliary tract cancers (ABC) was established following publication of the ABC-02 (Advanced Biliary Tract Cancer) trial, which demonstrated that the addition of cisplatin to gemcitabine (CisGem vs Gem) significantly improved overall survival (OS) and progression-free survival by 3.6 months and 3 months, respectively compared to gem alone (Valle et al, 2010). These data were supported by a similar Japanese phase 2 study (Okusaka et al, 2010) and a subsequent meta-analysis of these data with ABC-02 (Valle et al, 2013).

Maintaining quality of life is a key goal of treatment and impacts on the decision patients make with respect to treatment.

*Correspondence: Professor J Bridgewater; E-mail: j.bridgewater@ucl.ac.uk

1Joint senior authors.

12The recruiting sites and principal investigators in the ABC-02 study are listed at the end of the paper.

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Of particular concern for the ABC-02 study was the potential impact of cisplatin-related fatigue, which numerically increased in episodes of biliary sepsis, a difficult and common problem in BTCs, may have had.

We report quality of life in the ABC-02 study. Additionally we wished to document the global impact that any change in episodes of biliary sepsis, a difficult and common problem in BTCs, may have had.

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High scores indicate good QoL for functional responses (e.g. physical functioning), but poor QoL for symptomatic responses (e.g. pain). The aim of the analysis is to assess whether having a bad quality of life at baseline is associated with risk of death, and the results suggest that this is the case for some of the scales. We reported univariate and multivariate OS cox model.

Figure 1. Quality of life across the five measurable time points for six QoL scales. For each score the mean quality of life is provided with its 95% confidence interval. (A–F) Represent appetite loss, financial difficulties, constipation, satisfaction with health care, digestive symptoms and hepatic symptoms, respectively.
Quality of life, long-term survivors and long-term outcome: the ABC-02 study

### RESULTS

**Quality of life.** A total of 268 (83%) patients returned at least one QoL form (134 in each arm), though only 259 (80%) returned the baseline form and 134 (41%) of the patients returned the QoL form at 12 weeks (Supplementary Table S1). Missing data due to deaths and due to other causes are similar between treatment groups, with a slightly higher percentage of missing data due to deaths in the Gemcitabine arm. Only 11 (3%) patients returned all five forms.

Table 1 shows the association between QoL scores and survival. A better survival outcome seems to be related with higher score levels in global health (HR 0.63, 99% CI: 0.44–0.91, P = 0.006), functional symptoms (HR 0.77, 99% CI: 0.53–1.11, P = 0.06), physical functioning (HR 0.56, 99% CI: 0.34–0.92, P = 0.003) and sexual functioning (HR 0.69, 99% CI: 0.46–1.02, P = 0.01) at baseline. A worst survival experience seem to be associated with higher baseline score levels in the scales related with appetite loss (HR 1.42, 99% CI: 0.96–2.10, P = 0.02), nausea and vomiting (HR 1.98, 99% CI: 0.94–4.17, P = 0.02), pain (HR 1.50, 99% CI: 0.94–2.38, P = 0.02), digestive symptoms (HR 1.42, 99% CI: 0.90–2.25, P = 0.05) and pancreatic pain (HR 1.39, 99% CI: 0.90–2.15, P = 0.05). Supplementary Figure S1A and B show Kaplan–Meier plots for survival outcomes amongst patients who scored high and low in the global health functioning and physical functioning scales, respectively.

Treatment mean differences in the QoL scales at 12 weeks adjusted for baseline (ANOVA analysis) are presented in Figure 1 and Table 2. The ANCOVA results imply a difference not statistically significant in the direction favouring the combined treatment arm for most of the scales. After controlling for baseline quality of life and baseline characteristics, only appetite loss and baseline depression levels in the scales related with appetite loss (HR 1.42, 99% CI: 0.96–2.10, P = 0.02), nausea and vomiting (HR 1.98, 99% CI: 0.94–4.17, P = 0.02), pain (HR 1.50, 99% CI: 0.94–2.38, P = 0.02), digestive symptoms (HR 1.42, 99% CI: 0.90–2.25, P = 0.05) and pancreatic pain (HR 1.39, 99% CI: 0.90–2.15, P = 0.05). Supplementary Figure S1A and B show Kaplan–Meier plots for survival outcomes amongst patients who scored high and low in the global health functioning and physical functioning scales, respectively.

Table 2. Treatment difference in quality of life at 12 weeks, adjusting for quality of life at baseline (analysis of covariance)

| QoL response | Treatment mean difference* in quality of life at 12 weeks (99% CI) | P-value | Treatment mean difference* in quality of life at baseline (99% CI) | P-value |
|--------------|------------------------------------------------------------------|---------|------------------------------------------------------------------|---------|
| **Global health status** | | | | |
| Global health | 6.9 (−2.5 to +16.3) | 0.06 | 5.9 (−4.0 to +15.8) | 0.12 |
| **Functional scale** | | | | |
| Social functioning | 9.6 (−2.2 to +21.4) | 0.04 | 8.3 (−4.0 to +20.6) | 0.08 |
| Emotional functioning | 3.3 (−6.5 to +13.2) | 0.38 | 2.3 (−8.0 to +12.7) | 0.56 |
| Cognitive functioning | 2.4 (−5.9 to +10.7) | 0.45 | 2.8 (−5.8 to +11.3) | 0.40 |
| Role functioning | −0.2 (−11.4 to +11.0) | 0.96 | 0.8 (−10.8 to +12.4) | 0.86 |
| Physical functioning | −0.4 (−7.9 to +7.1) | 0.88 | −1.1 (−9.0 to +6.8) | 0.73 |
| **Symptom scale** | | | | |
| Appetite loss | −15.7 (−27.8 to +3.5) | 0.001 | −13.2 (−25.8 to +0.55) | 0.007 |
| Financial difficulties | −11.6 (−24.6 to +1.3) | 0.02 | −11.7 (−25.0 to +1.5) | 0.02 |
| Nausea and vomiting | −5.4 (−13.2 to +2.4) | 0.07 | −3.0 (−10.8 to +4.7) | 0.31 |
| Pain | −4.8 (−15.2 to +5.6) | 0.23 | −3.7 (−14.5 to +7.1) | 0.37 |
| Insomnia | −4.5 (−16.4 to +7.4) | 0.33 | −4.9 (−17.4 to +7.7) | 0.31 |
| Fatigue | −3.9 (−14.0 to +6.3) | 0.32 | −3.5 (−14.2 to +7.3) | 0.40 |
| Constipation | −1.1 (−13.2 to +11.0) | 0.81 | 0.37 (−11.9 to +12.7) | 0.94 |
| Diarrhoea | −0.2 (−9.6 to +9.2) | 0.95 | −0.02 (−9.8 to +9.8) | 0.99 |
| Dyspnoea | 4.8 (−6.6 to +16.2) | 0.27 | 5.2 (−6.7 to +17.1) | 0.25 |
| **Biliary tract cancer-specific** | | | | |
| Satisfaction with health care | 12.1 (−0.2 to +24.5) | 0.01 | 11.1 (−1.6 to +23.8) | 0.02 |
| Sexual functioning | −4.7 (−22.0 to +12.6) | 0.48 | −7.2 (−25.5 to +11.0) | 0.30 |
| Digestive symptoms | −14.1 (−25.7 to −2.5) | 0.002 | −13.4 (−25.7 to −0.98) | 0.006 |
| Hepatic | −5.6 (−12.1 to +0.9) | 0.03 | −5.3 (−12.1 to +1.5) | 0.04 |
| Pancreatic pain | −3.9 (−12.1 +4.3) | 0.22 | −3.5 (−12.0 +4.9) | 0.28 |
| Body image | −3.6 (−15.8 to +8.7) | 0.45 | −2.0 (−14.7 to +10.8) | 0.69 |
| Altered bowel habit | −0.7 (−11.0 to +9.6) | 0.86 | −1.7 (−12.6 to +9.3) | 0.69 |

*Models adjusted for baseline characteristics: gender, disease status, primary tumour site, tumour histology, ECOG performance status, prior therapy and age group.

**Scores range from 0–100 for all endpoints.**

**For the global health and functional scales (including satisfaction with health care and sexual functioning) 0 indicates poor health and 100 good health.**

**For all other scales, 0 indicates no symptoms and 100 high level of symptoms.**

**-values (two-sided) are unadjusted for multiple comparisons, so 99% CIs are shown.**
digestive symptoms were statistically significant at the 1% level ($P = 0.007$ and $P = 0.006$, respectively; Figures 1A and B), both in favour of CisGem. Our findings suggest some evidence of treatment differences in favour of CisGem in hepatic function, financial difficulties and dissatisfaction with health-care scales (Figure 1C, E and F).

There is no evidence of a treatment effect in the difference in mean QoL scores, over all five time points, for any of the QoL responses at the 1% level (Supplementary Table S2). Responses in the constipation scale showed a difference in the direction favourable the combined treatment arm at a 5% level ($P = 0.001$ vs 10%, respectively). A difference favouring the CisGem arm was seen in digestive symptoms, global health, social functioning, appetite loss, financial difficulties, insomnia and satisfaction with health-care scales, but our findings do not suggest evidence of a statistical difference (Figure 1D and B).

**Long-term survivors.** Survival analysis and analysis of baseline characteristics and treatment of patients by grouped length of follow-up is shown in Table 3. A total of 69 (17%) patients have been followed up for $\leq 3$ months, 296 (72%) patients between 3–24 months and 45 (11%) patients for $> 24$ months. Median survival among the 45 long-term survivors is 31.4 months. There is a trend between the following factors and survival time: CisGem treatment, disease status and ECOG performance status ($P < 0.001$, $P = 0.028$ and $P < 0.001$, respectively). There is a survival advantage for patients receiving CisGem compared with Gem (HR: 0.65, 95% CI: 0.53–0.79, $P < 0.001$), with 17% of the CisGem patients being followed up for at least 24 months in comparison with 5% of Gemcitabine-alone patients. Our findings suggest that the higher the ECOG performance status the poorer the survival, and that a performance status of 2 is associated with worst prognosis (ECOG 2, HR: 2.35, 95% CI: 1.68–3.28, $P < 0.001$). Locally advanced patients have a better survival prognosis than the patients with metastatic disease (HR 1.34, 95% CI: 1.07–1.69, $P = 0.01$). A higher percentage of locally advanced patients were followed up for $> 24$ months compared with metastatic disease (14% vs 10%, respectively). Our findings did not show evidence that gender, primary tumour site, tumour histology, priority therapy and age were associated with survival.

**Long-term primary outcome analysis.** With a median follow-up of 9.2 months, 398 (97%) patients have died as of March 2012 compared to 327 when previously reported (Valle et al, 2010). Of the 12 patients not known to have died, 9 have been followed up for at least 24 months; the other 3 patients were all lost to follow-up within 6 months of randomisation. As nearly all the patients have died, long-term follow-up can be considered as long-term survival. The median OS was 11.7 months for CisGem and 8.1 months for Gem (HR = 0.65, 95% CI: 0.53–0.79, $P < 0.001$, Figure 2).

### Table 3. Baseline characteristics and treatment of patients, by grouped length of follow-up

| Follow-up period | Univariate cox model | Median survival time (95% CI) | HR (95% CI) | P-value | 0–3 months (N = 69) n (%) | 3–24 months (N = 296) n (%) | > 24 months (N = 45) n (%) | P-value for trend |
|------------------|---------------------|-----------------------------|-------------|---------|-------------------------|---------------------------|------------------------|-----------------|
| Treatment        |                     |                             |             |         | 43 (21)                 | 152 (74)                  | 11 (5)                 | $< 0.001$       |
| Gemcitabine alone | 8.1 (7.0–9.1)       | 1                           |             | <0.001  |                         |                           |                        |                 |
| Gemcitabine + Cisplatin | 11.7 (9.6–14.0) | 0.65 (0.53–0.79)             |             |         |                         |                           |                        |                 |
| Gender           |                     |                             |             |         | 35 (16)                 | 155 (72)                  | 26 (12)                | 0.75            |
| Female           | 9.6 (8.3–11.1)      | 1                           |             |         |                         |                           |                        |                 |
| Male             | 9.1 (7.9–11.7)      | 1.09 (0.90–1.33)             |             | 0.38    |                         |                           |                        | 0.5             |
| Disease status   |                     |                             |             |         | 11 (11)                 | 78 (75)                   | 15 (14)                | 0.086           |
| Locally advanced disease | 13.3 (8.1–15.0) | 1                           |             | 0.01    |                         |                           |                        |                 |
| Metastatic disease | 8.8 (8.1–10.0)     | 1.34 (1.07–1.69)             |             |         |                         |                           |                        | 0.028           |
| Primary tumour site |                 |                             |             |         | 19 (13)                 | 115 (77)                  | 15 (10)                | 0.053           |
| Gallbladder      | 9.6 (8–11.7)       | 0.96 (0.78–1.19)             |             | 0.93    |                         |                           |                        | 0.78            |
| Bile duct        | 8.8 (8–10.7)       | 1                           |             |         |                         |                           |                        |                 |
| Ampulla          | 11.8 (6.8–14)      | 1 (0.62–1.62)                |             |         |                         |                           |                        |                 |
| Tumour histology |                     |                             |             |         | 61 (16)                 | 273 (72)                  | 43 (11)                | 0.37            |
| Adenocarcinoma   | 9.6 (8.3–11.1)     | 1.27 (0.88–1.82)             |             | 0.21    |                         |                           |                        | 0.16            |
| Other            | 7.2 (4.5–10.8)     |                             |             |         |                         |                           |                        |                 |
| ECOG performance status |         |                             |             |         | 11 (8)                  | 98 (75)                   | 21 (16)                | 0.001           |
| 0                | 11.9 (9.7–14.3)    | 1.29 (1.04–1.61)             |             | <0.001  |                         |                           |                        |                 |
| 1                | 9.3 (7.9–11)       | 2.35 (1.68–3.28)             |             |         |                         |                           |                        |                 |
| 2                | 5.7 (3.4–7.1)      |                             |             |         |                         |                           |                        |                 |
| Prior therapy    |                     |                             |             |         | 42 (18)                 | 163 (68)                  | 28 (12)                | 0.053           |
| None             | 8.0 (6.8–10.1)     | 1.03 (0.82–1.30)             |             | 0.79    |                         |                           |                        | 0.27            |
| Any prior therapy | 9.8 (8.7–11.6)    |                             |             |         | 49 (16)                 | 230 (74)                  | 31 (10)                | 0.94            |
| Age (years)      |                     |                             |             |         | 22 (15)                 | 111 (75)                  | 15 (10)                | 0.23            |
| 23–60            | 9.3 (8–12.2)       | 1                           |             | 0.61    |                         |                           |                        |                 |
| 60–70            | 9.7 (7.9–11.8)     | 1 (0.80–1.25)                |             |         |                         |                           |                        |                 |
| 70–84            | 9.1 (7–10.7)       | 1.13 (0.86–1.48)             |             |         |                         |                           |                        |                 |

*Follow-up time is near enough an exact proxy for survival. Yet, there are 12 patients who did not die. So, although the FUP time and survival time are almost the same they are not exactly the same. That is the reason that we use follow-up time instead survival time.

*Note that there are two P-values. The first is for any difference between follow-up duration and covariate groupings; the second is for trend.

*A non-parametric test for linear trend developed by Cuzick (1985) has been calculated to assess if the covariates are associated with follow-up time.

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DISCUSSION

Although ABC-02 has defined the standard of care for BTC patients, the survival benefit is modest and most patients do not survive beyond a year. QoL is therefore pivotal to globally evaluate this benefit, particularly in the context of a disease with multiple symptoms that can often be difficult to manage. Our data demonstrate that QoL is not adversely affected despite a modest non-significant increase in some toxicities such as neutropenia.

Research on QoL in ABC is challenging. Assessing the QoL of ABC patients is critically important in a population who are often unwell from both local (obstructive jaundice, biliary sepsis, bowel obstruction and liver pain) and systemic consequences (malaise, fatigue and depression) of advanced disease. This is the likely reason for missing data (20% at baseline and 59% at 12 weeks) reflecting a common problem of QoL studies in unwell cancer patients. Extant data reflect both a lack of appropriate instruments and study compliance realities. Heffernan et al (2002) described the FACT-G scale for hepatobiliary malignancies, but to date it has been used only in pancreas cancer studies with no survival benefit (Rocha Lima et al, 2004; Moinpour et al, 2010). EORTC QoL scales have been described for liver metastasis (LMC21) (Kavadas et al, 2003) and pancreas (PAN26) (Fitzsimmons et al, 1999), the latter used here, but are limited by not being BTC specific. It is likely that a recently validated BTC instrument will be used for BTC in the future (EORTC QLQ-BIL21; Friend et al, 2011). This is a mostly a combination of PAN26 and LMC21 and requires phase 4 evaluation across multiple ethnic groups before general adoption. Limitations of our data include the missing data (Table 1; Supplementary Table S1) and the assumption that all these data are balanced between the treatment arms. Nevertheless, these are the only data describing QoL in the context of a treatment-defining study for ABC and as such set the standard for subsequent investigation.

The majority of long-term outcomes are described in surgical series and there are no published data for the long-term survival of patients presenting with advanced disease. These data describe a cohort of long-term survivors and are consistent with an increasing appreciation that ABC are sensitive to chemotherapy (Eckel et al, 2011). Ongoing studies in second and subsequent line therapies will continue to build a therapeutic hierarchy for ABC, such as the UK National Cancer Research Institute ABC-06 study (Lamarca et al, 2014). The added efficacy of Cisplatin to gemcitabine across multiple variables including primary tumour site (bile duct, gall bladder and ampulla) is confirmed, suggesting that although they may be molecularly heterogeneous (Jiao et al, 2013) their sensitivity to cisplatin is similar.

CONCLUSION

The survival benefit of CisGem compared to Gem in ABC is not paralleled by a benefit in QoL. A qualitative description of long-term survivors and the long-term primary outcome analysis supports the survival benefit. We recommend that CisGem remains the standard of care for ABC.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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970

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