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Second-line chemotherapy in advanced biliary cancer: the present now will later be past

We have read with great interest the recent paper by Lamarca et al. [1], in which the authors conducted a systematic review of the literature to evaluate the level of evidence behind the use of second-line chemotherapy for patients with advanced biliary tract cancer (aBTC). The authors collected data of 761 patients from 14 phase II trials and 9 retrospective analyses, reporting a mean overall survival (OS) of 7.2 months and a mean progression-free survival (PFS) of 3.2 months. Response rate and disease control rate (DCR) were 7.7% and 49.5%, respectively, suggesting that a cohort of aBTC patients may benefit from second-line chemotherapy. We really thank the authors for their efforts: due to the paucity of reliable data in this setting, the topic is of great interest. In order to further reduce the impact of study heterogeneity on the results, we suggest to the authors to exclude the reports of targeted agents and limit the analyses to chemotherapy only: this could be particularly important when alternative end points (such as PFS) are being investigated as surrogate for OS in pooled series.

Our group has recently conducted a retrospective evaluation of 300 patients with aBTC who underwent second-line chemotherapy [2]. Our results are consistent with those of Lamarca, with a median PFS of 3.2 months and a 34% DCR. Second-line chemotherapy in aBTC therefore represents an unresolved issue and prospective randomized trials are needed. Ongoing ABC-06 trial (NCT 01926236) is the first randomized phase III trial comparing mFOLFOX chemotherapy with active symptom control (ASC) alone. If we completely agree with the ABC-06 investigators that ASC is correct as control arm from a strict scientific perspective, we could speculate if it is still acceptable in the light of the abovementioned results [1, 2]: are we taking the chance not to achieve the answers we really need? Lessons learned from pancreatic cancer tell us that the original design of the CONKO group phase III study in second-line setting (with a similar design to the ABC-06 trial) was prematurely closed because ASC was not accepted by participating centres and a new trial was performed with 5-fluorouracil as control arm, even though a formal demonstration of the value of second-line chemotherapy was lacking at the time [3, 4]. Since both the report from Lamarca et al. and our paper do not allow to identify a preferable second-line regimen, would a single-agent chemotherapy arm (e.g. fluoropyrimidine) be a more suitable comparator for mFOLFOX? Our group has recently completed a randomized phase II study to assessing the therapeutic activity of capecitabine alone or in combination with mitomycin C as second-line therapy (NCT01530503). In order to strength the value of fluoropyrimidines in this setting, we sought for OS differences between patients receiving gemcitabine-based first-line chemotherapy and fluoropyrimidine-based second-line chemotherapy and patients receiving the reverse sequence: in our series, neither second-line OS [6.0 versus 7.8 months, hazard ratio (HR) 0.769; 95% confidence interval (CI) 0.165–1.373] nor OS calculated from the beginning of first-line (15.7 versus 14.9 months, HR 1.054; 95% CI 0.450–1.658) differ between these two groups.

In their review, the authors underline the need for prognostic factors to better select aBTC patients with higher chances of benefit from rescue chemotherapy [1]. Different retrospective series tried to identify prognostic factors in patients with aBTC in first line [5]. In our retrospective series, performance status, CA19.9 level, surgery on primary tumour and first-line PFS were identified as independent prognostic parameters at multivariate analysis for second-line chemotherapy: such factors can be combined and different patient subgroups can be thus identified by means of these easily available variables [2]. We claim that prospective trials such as the ABC-06 could be intriguing opportunities in order to validate our prognostic score: we should not miss the opportunity to make the times really change in aBTC management.

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disclosure

The authors have declared no conflicts of interest.

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Reply to the letter to the editor 'Second-line chemotherapy in advanced biliary cancer: the present now will later be past' by Vivaldi et al.

We thank Vivaldi et al. for their supportive comments [1] regarding our published work [2]. We agree in one major respect: the need for prospective randomised second-line trials in advanced biliary tract cancer. Our systematic review identified a cohort of patients able to receive second-line chemotherapy with results comparable with the retrospective series by Vivaldi et al. A re-analysis excluding trials with targeted agents, as suggested, does not alter our conclusions (Table 1).

Vivaldi et al. express concern regarding two aspects of the ABC-06 study (a 162-patient randomised phase III study comparing Active Symptom Control (ASC) versus ASC plus FOLFOX chemotherapy, developed by the UK National Cancer Research Institute Hepatobiliary Subgroup, NCT01926236): a non-chemotherapy control arm and potential recruitment difficulties of such a design, citing as an example the CONKO-003 trial [3].

A major limitation of currently available evidence (level C, heavily subject to selection bias and non-representative of the whole patient group) is that a number of questions remain unanswered: is there a survival benefit of chemotherapy over ASC [a protocol-led proactive approach (contrasting with Best Supportive Care, a 'hands-off' approach) for which OS has not been defined]? If so, what is the magnitude of that benefit? What is the impact of toxicity and, importantly, what is the effect on patient-reported outcomes? It is incumbent on us to offer our patients 'informed' choice regarding pros/cons of treatment for what appears to be a modest gain [median progression-free survival (PFS) of 3.2 months in both analyses]. These questions, along with additional translational research, are addressed by ABC-06. Changing the control arm to single-agent chemotherapy (e.g. capecitabine or 5-fluorouracil), as suggested, would fail to answer the main survival question of ABC-06. There is insufficient evidence to select monotherapy as the current standard of care and a 'negative' study of combination chemotherapy versus monotherapy would leave us in the same position we are in now: with no standard of care, a status persisting for too long in first line before an adequately powered prospective phase III study [4].

We shared concerns regarding physician/patient acceptability; a preparatory physician survey across 17 major centres showed unanimous agreement regarding equipoise between the treatment arms. Furthermore, both the trial design and the patient information sheet were supported by AMMF—The Cholangiocarcinoma Charity (UK). We are reassured by the current high rate of acceptance of the trial (61% consent rate of patients approached for ABC-06) along with the oversight of patient welfare provided by the IDMC. A similar degree of physician/patient engagement has recently resulted in completion of another study, also comparing chemotherapy with ASC, in oesophago-gastric cancer [5].

Finally, the sample size of ABC-06 limited us to three stratification factors; review of previously published literature led us to include first-line PFS (as suggested by Vivaldi et al.), disease stage and serum albumin. A future pooled analysis of homogeneous datasets may improve our understanding of prognostic factors with greater statistical power and we look forward to such a collaboration. Only robust clinical trials will allow 'the present' to 'later be past'.

Table 1. Excluding the trials employing targeted therapies as suggested by Vivaldi et al. did not alter the conclusions of our analysis

	All studies	Targeted therapies studies excluded
Weighted mean OS (95% CI) (months)	7.2 (6.2–8.2)	7.4 (6.4–8.5)
Weighted mean PFS (95% CI) (months)	3.2 (2.7–3.7)	3.3 (2.8–3.9)
Weighted mean RR (95% CI) (%)	7.7 (4.6–10.9)	8.1 (4.2–12)
Weighted mean DCR (95% CI) (%)	49.5 (41.4–57.7)	49.5 (39.9–59.2)
Correlation OS/DCR (*r*; *P* value)	0.19; 0.45	0.23; 0.4
Correlation OS/RR (*r*; *P* value)	0.34; 0.16	0.39; 0.13
Correlation OS/PFS (*r*; *P* value)	0.54; 0.01	0.59; 0.01

OS, overall survival; PFS, progression-free survival; RR, response rate; DRC, disease control rate; CI, confidence interval; *r*, correlation index.