Moreover, both continuous infusion and modulation by leucovorin have failed to increase the efficacy of 5-FU [4, 5]. It gives no advantage in combination with gemcitabine [6]. Above all, continuous infusion is extremely restrictive for patients with a very short life expectancy. Given synergies with many drugs, it is also true that oxaliplatin gives higher response rates in combination, typically in tumors with higher chemosensitivity such as colorectal carcinoma or ovarian carcinomas. Nevertheless, a phase II study of the combination of gemcitabine and oxaliplatin showed modest results, with a median time to progression of 4.5 months, suggesting no evidence of superiority over gemcitabine alone [7]. Although oxaliplatin is usually included in the FOLFOX regimen, Ducreux and colleagues [1] have created a new variant, increasing the confusion. A tremendous number of phase II studies exploring doublets with various combinations of old and new drugs including taxanes, irinotecan, platinum compounds or fluoropyrimidines have been published since the end of the 1990s, showing, at best, marginal improvements. The evolution of this proliferation of phase II studies to phase III studies would take decades. Given the poor prognosis and low probability of obtaining significant improvements with the current cytotoxic drugs, quality of life should remain one of the primary objectives for pancreatic carcinoma. In this regard, the oral route as well as regimens compatible with home chemotherapy should be preferred. A certain number of factors that are predictive of response to chemotherapy, such as CA 19-9, serum albumin, total bilirubin, C-reactive protein or performance status, might be applied. Since the vast majority of the patients do not benefit from current costly regimens, while on the other hand there are good responders with prolonged survival and an increasing variety of drugs, studies should be orientated towards molecular predictive factors of response to a given drug.

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Response to the letter


The authors thank Dr Alliot for his thoughtful letter, and agree with most of his considerations, discussion and well thought-out approach to the possibility of finding molecular predictive factors for specific drugs or regimens. Nonetheless, some misconceptions and/or misunderstandings need to be clarified with respect to the timing and rationale for the published study [1], so that his comments can be considered in the correct context.

Most of the authors of our paper are indeed firm advocates of the fixed rate gemcitabine infusion, which was first prospectively assessed in a comparative trial reported in abstract form in 1999 by Tempero et al. [2] as a more efficient (more active, less toxic) way to administer this agent. This led one of the participants to design the optimal GEMOX (gemcitabine–oxaliplatin) (E.C.) combination later adopted by the GERCOR group in its studies on this disease [3].

Gemcitabine was not approved for the treatment of pancreatic cancer in France until April 1998, given its minimal benefit over what we consider suboptimal (bolus) administration of 5-fluorouracil (5-FU). On the other hand, our choice of
infusional 5-FU (a better way of giving 5-FU, before capecitabine became available) as a control was based on its proven marginal activity in pancreatic cancer reported for a number of published phase III studies (of which, one is referenced in our manuscript: Maisey et al. [4]). Given that our study was initiated at the time that identification of oxaliplatin–5-FU synergy was resulting in an overhaul of the treatment and natural history of advanced colon cancer, and that its activity had been reported in many other settings, we had no other alternative than to choose the correct ethical control to benchmark the combination activity exploration beyond a single-arm phase II trial, which also allowed us to obtain at the same time, once and for all, single-agent data on oxaliplatin activity in pancreatic cancer. We consider that although the results of our trial are modest and have been published in full relatively late, they provide valuable information to many colleagues, and will allow oncologists to avoid needless ‘second guessing’.

The excellent safety profile of the oxaliplatin–5-FU combination provides a valid alternative for the small but prevalent population of patients who cannot be treated with gemcitabine due to its pulmonary toxicity, a short time interval with radiotherapy, or who have failed gemcitabine–platinum-based therapies.

In summary, given that gemcitabine was not available in France at the time of the conception of this study, we considered (and still do) that the study presented was one of the best alternatives available for the treatment of pancreatic cancer patients within a clinical research initiative. Its results were beneficial to a small proportion of long-term responding patients during its conduct, and the oncologic community through its reporting.


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