Reviewer’s report

Title: Nal-IRI with 5-fluorouracil (5-FU) and leucovorin or gemcitabine plus cisplatin in advanced biliary tract cancer - The NIFE trial (AIO-YMO HEP-0315) an open label, non-comparative, randomized, multicenter phase II study

Version: 0 Date: 20 May 2019

Reviewer: Ursa Brown-Glaberman

Reviewer's report:

This is a summary of a planned clinical trial. The trial is not complete and no original data is available / presented. This is very odd. Generally reports on trials in progress are reserved for poster presentations as national meetings, not submitted for publication. This manuscript reads as though it were taken directly from the clinical research protocol, including bulleted inclusion / exclusion criteria, etc.

In addition, there are several other major flaws.

1) The background discussion should describe in more detail the prior irinotecan based protocols in BTC. What was the PFS at 4 months on those trials and with the current standard of care? A table would be useful to summarize this data.

2) What is the clinical significance of PFS at 4 months? Why was this chosen as the primary endpoint. I suspect it was chosen for statistical / sample size reasons, but it seems very arbitrary.

3) A rational for the use of Nap-IRI in BTC should be better delineated. The fact that it worked in advanced pancreas cancer is not sufficient.

4) There is quite extensive literature / current work related to targeted therapy in BTC. Up to 30% of these cancers have a targetable mutation / alteration (FGFR, HER2, BRAF, etc). This should be reviewed / addressed in the manuscript and in the discussion in relation to planned correlative studies.

My major suggestion would be to wait until the trial is complete and submit full results as manuscript at that time.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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