Reviewer's report

Title: What does a modified-Fibonacci dose-escalation actually correspond to?

Version: 2 Date: 21 March 2012

Reviewer: William Mietlowski

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Major Compulsory Revisions

1. The issue of dose increment is not often addressed in Oncology Phase I dose escalation trials and the literature search performed by the authors may be a useful resource. However, I feel that the authors have not made the best use of this resource and have focused on some relatively trivial aspects. The authors have not mentioned the accelerated titration design (Simon et al 1997 Journal of the National Cancer Institute) in which dose doubling is used until there is one dose limiting toxicity or two patients with at least two Grade II toxicities at least possibly related to drug when a 40% increment is used. The authors also do not mention the Bayesian logistic regression model with escalation with overdose control (BLRM-EWOC) (Babb et al 1998 Statistics in Medicine, Neuenschwander et al 2008 Statistics in Medicine) which uses a model based approach to determine the potentially unsafe doses. The maximum dose increment may be capped at a doubling but a smaller dose increment can be used if the EWOC criterion is not met or there are other safety concerns. These approaches let the emerging data determine the future dose increment subject to a cap rather than a fixed algorithm.

2. The 6th edition of Holland-Frei Cancer Medicine (Kufe DW, Pollock RE, Weichaelbaum RR et al, editors, Hamilton, Ontario, BC Decker, 2003) mentions that the modified Fibonacci search scheme is the most often used method of dose escalation which can result in the highest number of patients receiving ineffective doses because of the rapid tapering off of the dose escalation. The reference mentions that the modified Fibonacci search is preferred when the dose response curve in the animal toxicology studies is steep. This should be mentioned. Note that the BLRM-EWOC model could incorporate a steep dose response curve in the prior, perhaps as an element of a mixture prior if the animal to man extrapolation is unclear.

3. Given the concern about treating a high number of patients with ineffective doses, an interesting question would be how often among the 81 studies was at least one of the actual dose increments employed substantially higher (e.g. 50% greater) than that specified by the modified Fibonacci search. If there are clear descriptions of dose levels among the 105 studies with other designs, perhaps the same calculation can be done for the other designs (complaince with the design).
4. The term dose level is unclear since dose de-escalation can occur. If there is
de-escalation after the 3rd cohort to the dose of the 2nd cohort, is the dose for
the 4th cohort counted as the 2nd dose level or the 4th dose level?

5. There are some major errors in table 2. The max of the actual dose is less
than both the median actual dose and mean actual dose in dose levels 3 through
7.

6. The calculation of the incremental ratio of the median dose in Table 3 may be
problematic. For example, the entry for dose level 7 (1.529) appears to be the
ratio of the median dose at dose-level 7 (11.93 based on 32 studies) and the
median dose at dose-level 6 (7.80 based on 43 studies). I think that the
increment ratio should be based on the studies that have both a 6th and 7th dose
level (presumably n=32). Therefore, a median of the 32 incremental ratios may
be more meaningful.

7. A good reference about the low rate of using innovative designs in Phase I
cancer trials is given by Rogatko et al 2007 Journal of Clinical Oncology. This
should be added to the references.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests.'