Reviewer's report

Title: Targeting of CD34+CD38- cells using Gemtuzumab Ozogamicin (Mylotarg) in combination with Tipifarnib (Zarnestra) in Acute Myeloid Leukaemia

Version: 1 Date: 15 June 2012

Reviewer: Judith Karp

Reviewer's report:

The authors have conducted a provocative study that could form a basis for a novel combinatorial therapy for AML, perhaps with particular focus on older adults.

Major revisions:

1. The authors need to expand their explanations/discussion of their counter-intuitive and perhaps paradoxical findings. On the one hand, there appears to be strong CD33 expression in a presumptively primitive LSC population in 11/36 primary samples, raising the question of whether or not the true LSC population was being measured in those patients. On the other hand, to the activity of GO in the LSC population in an apparently "off-target" CD33-independent fashion (previously reported by these investigators, but without any mention to potential mechanism -- is this simply related to free calicheamycin?). The last paragraph of the discussion states that the lack of relationship between GO and CD33 expression is unsurprising -- this off-handed statement requires succinct explanation and not just references.

2. The discussion surrounding chk2 activation and eventual cell death is highly speculative (pg 17), particularly since inhibition of DNA damage-induced chk2 activation has been demonstrated repeatedly to enhance drug cytotoxicity.

3. Table 1 is critically important to the eventual clinical relevance of these preclinical data. As such, it might benefit from some clarification and perhaps breaking out some of the data into another table. The authors may want to consider reorganizing the table according to cytogenetic groupings (e.g., favorable, normal/intermediate,, FLT3+, adverse, not done) -- alternatively, the table could be reorganized by level of CD34+/38- (e.g., from <1% to >50%). These groupings would provide some meaningful clinical context and perhaps illuminate potential clinically-relevant features that shed light on response to combinatorial therapy.

Minor revisions:

1. Pg 10 (bottom): NPM1 is misspelled (NMP1)

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.