Reviewer's report

Title: E7080, a multi-targeted tyrosine kinase inhibitor suppresses tumour cell migration and invasion

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Reviewer: Faye Johnson

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In this manuscript the authors incubate 6 cancer cell lines in vitro with the multi-targeted kinase inhibitor E7080 and observe no effect on cell number using an MTT assay. In two cell lines (DX3, U2OS) E7080 inhibited PDGFR-beta and FRS2 (surrogate for FGFR1) and cellular migration and invasion. In one cell line (U2O2), PDGFR-beta knock down inhibited invasion. Invasion was not inhibited in a cell line that did not express PDGFR-beta.

The topic is relevant and the paper is well-written. The techniques are straight-forward and the data are clean and well-presented. However, the study is superficial with no real insight into cancer biology, mechanism, or future clinical application of E7080.

Major Compulsory Revisions

More sophisticated studies of E7080 have been done in animal models and E7080 has undergone phase I testing, so it is not clear what the current study adds to our knowledge. It is a strictly an in vitro study of 2 cancer cell lines. The authors contend that by evaluating E7080’s direct anti-tumor effects, one will be able to better define a population that may benefit from E7080. This assertion is problematic for three main reasons: 1) There is no insight provided as to how one would use the information in this study to prospectively identify patients who would be more like to benefit from E7080. 2) E7080 inhibited migration/invasion in 2 of 6 cell lines with no effect on survival or proliferation. At clinically relevant concentrations (< 1 micromolar), the effect on invasion was incomplete (only about 15% in U2OS cells). Drugs that have a more striking and universal effect on invasion (e.g. Src inhibitors) have been identified, but no clear role in patient care has yet been identified for them in solid tumors. 3) Imatinib is a drug that inhibits PDGFR. Despite multiple laboratory studies and clinical trials, it is ineffective in nearly all solid tumors.

The study does not clearly establish that E7080 inhibits invasion via an effect on PDGFR. At concentrations where PDGFR is completely inhibited (1 micromolar) there is only about a 15% reduction in invasion (Figure 5B). The parallel effects of siRNA and the lack of invasion is a line without PDGFR expression are helpful, but without “add-back” experiments in which overexpression (or dominant negative or gatekeeper mutants) of PDGFR abrogates the effect of E7080, the language here should be softened to “suggests” rather than “indicates.”
Minor Essential Revision
The authors should provide more detail about how the invasion assays were performed.

Discretionary Revisions
1. The last sentence of the abstract is not convincing. It could be replaced by the sentence on page 13, line 6.
2. Page 4, introduction. FGFR amplification has been observed in lung cancer also.
3. The cultured cells should be validated.
5. It is not clear how a drug that inhibits invasion would be useful in the adjuvant setting. The goal of adjuvant therapy is to destroy existing micro metastasis and thus one would want a drug that induced cancer cell death.

Level of interest: An article whose findings are important to those with closely related research interests

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.