Reviewer's report

Title: Expression profiling of blood samples from an SU5416 Phase III metastatic colorectal cancer clinical trial: a novel strategy for biomarker identification.

Authors:

Dr Samuel E DePrimo (samuel-deprimo@sugen.com)
Lily M Wong (lily-wong@sugen.com)
Dr Deepak B Khatry (deepak-khatry@sugen.com)
Susan L Nicholas (susan-nicholas@sugen.com)
William C Manning (bill-manning@sugen.com)
Beverly D Smolich (beverly-smolich@sugen.com)
Anne-Marie O'Farrell (marie-ofarrell@sugen.com)
Julie M Cherrington (julie-cherrington@sugen.com)

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Reviewer: Dr Arul Chinnaiyan

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the compulsory revisions

Comments to authors
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Please note that both your comments and answers to the questions below will be forwarded to the authors, and published on the site if the article is accepted.

1. Comments (Please number your comments and divide them into: discretionary revisions - which the authors can choose to ignore - and compulsory revisions - which the authors must address.)

This is a well written study in which the authors have used gene expression profiling of peripheral blood mononuclear cells to identify a small cohort of genes that are associated with a treatment regimen that consisted of the anti-angiogenesis drug SU5416. The study certainly would be much more impressive if the authors could identify gene predictors of SU5416 treatment efficacy rather than mere exposure. But considering this is at the proof of concept stage, their findings are still remarkable especially regarding the ability to predict SU5416 treatment in a non-invasive fashion.

a) Discretionary revisions

1. As is now becoming standard practice in the field, the authors should include supplementary material of the gene expression data used in this study.

b) Compulsory revisions
1. Minor points: Table 3 "Affymetrix" is spelled incorrectly.; Page 32 was left blank?

2. The authors used "Difference Call (DC) scores" to identify their gene predictors of SU5146 treatment. It would also be useful if they used a more transparent methodology such as SAM (Significance Analysis of Microarrays) Analysis to generate “q values” or estimated lowest false discovery rates. This will associate a statistical parameter with the genes they identify and take into account the multiple inference scenario (as is the case in this set of experiments).

3. In Figure 2, the authors have summarized their microarray and QRT-PCR data by generating histograms of “%patients with an increase in expression”. Two-fold is considered up-regulated. How was this determined and is this an appropriate cut-off for Affymetrix data (relative to spotted cDNAs)? It is also important to visualize the data on a per patient basis as the current histogram consolidates the data. A representation of the actual expression levels of these markers +/- SU5416 would also be more convincing.

Competing interests:

None declared.