Reviewer’s report

Title: Safety and Pharmacokinetics of Novel Selective Vascular Endothelial Growth Factor Receptor-2 Inhibitor YN968D1 in Patients with Advanced Malignancies

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Reviewer: Peter Fong

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Overall, an interesting and worthy to be reported study of yet another small molecule VEGFR2 inhibitor. Unfortunately, being a first in human study, some of the data reported in the manuscript is slightly patchy. There is no pharmacodynamic correlate within the study but the incidence of hypertension is “reassuring” somewhat. The weight of the discussion leans too much towards response and clinical benefit without some key “traditional” outcomes one expects to be reported from a Phase I study.

Major Compulsory Revisions

Abstract – Results – “The intake of food prior to dosing had no relevant impact on the PK”. This statement as not substantiated in any part of the manuscript. Was this trial designed a priori to be a food effect bioavailability and fed bioequivalence study? If so, please mention it in the methods section, provide details and provide the PK data for apatinib levels in the fasted and fed situation.

Background – paragraph 2 and 3 – statements of “9 times of inhibition to VEGFR2”, “mildly inhibits c-Kit and c-Src” and “on the basis of encouraging preclinical data” are vague and confusing: Please provide the reference and details of the preclinical data. Is there an update to the AACR proceedings from 2006?

Methods - Study design – It is unusual for fever caused by infection during administration of study drug to be excluded from assessment of possible DLT. The statement is ambiguous and suggests that neutropenic fever is also excluded as a DLT. Please clarify if the preclinical studies of apatinib revealed any evidence myelosuppression or pyrexia. Please provide justification for the above.

Methods - Pharmacokinetic analyses – Was PK analyses performed for all dose levels from 250 to 1000mg once daily? The methods section suggests this was not. Please clarify. Was any PK performed for the patients dosed at 250 and 1000mg/day?

Could the authors confirm if any pharmacodynamic (PD) studies were undertaken?

Results – Dose escalation – it is confusing how many patients were actually
treated at their initially assigned dose levels during dose escalation. Please state the number of patients for each dose cohort for both the dose escalation and PK phase. The number of patients treated during the PK analysis aspect was 28 yet 32 patients were assessable for PK analysis, please clarify. Is there any PK data for the 1000mg/day dose level, especially for the 2 patients with DLT? This is important not only because no PD data has been reported, as in the section of Results – PK – a statement was made that there was no relationship between drug related AE, dose and extent of apatinib exposure, yet there is only data for the 750mg/day dose. The final statement of “interpatient variability of apatinib PK does not affect its clinical safety” is therefore not substantiated by the data presented thus far.

Results – Table 2 - 12 patients were treated at dose level 750mg/day but only 11 patients were analysed for the mean PK parameters in Table 3. Please clarify the discrepancy.

Results – PK – No results are shown for the 250mg, 500mg, 850mg and 1000mg/day dose cohort, yet it is mentioned that cmax and AUC increased with dose. I do not believe this conclusion can be reached on the available information presented in the manuscript. The data in Table 2 is only a reflection of the 750mg/day dose cohort.

Results – tumour response – 38 of 47 patients were evaluable for tumour response. Please provide the reasons for the 9 patients who were not. Furthermore, if only 22 out of 30 colorectal and gastric cancer patients were evaluable for response by RECIST, this means that of the total of 47 patients, 8 out of 9 unevaluable patients were either colorectal or gastric cancer patients. The proportion of evaluable to unevaluable colorectal and gastric cancer patients is rather high. Whilst tumour response is not a primary endpoint of a first in human phase I study, the manuscript asserts strongly the “substantial antitumor activity of apatinib and the discussion leans heavily towards response assessment. Although the activity observed is encouraging, it is premature and the authors should reflect this in a balanced manner in the discussion.

Discussion – 2nd paragraph – There is no data submitted thus far to substantiate the statement that the mean half-life was constant over all dose groups. Likewise, there is no PK data to support a dose of 850mg daily. Please provide the supporting data.

Discussion – please clarify the statement of “significant interpatient variability with apatinib provided individual data for dose justification”. It is unclear what you are trying to convey, the interpatient dose variability at 750mg is not hugely different to some oncology Phase I trials of small molecule TKI’s. You have demonstrated that there were more dose reductions required at the 850mg/day dose level compared to 750mg/day but there is no collaborative PK data. The statement of “these data indicated no apparent relationship between drug-related toxicity and plasma.........” is not substantiated.

Discussion - Of the patients who responded, how many were at the 750mg/day
dose level vs. 850mg/day? What justification is there for 850mg/d to be the RP2D if there is not an insignificant proportion requiring dose reduction?

Minor Essential Revisions

Methods – Study design - It is unclear what the primary and secondary objectives of this phase I trial are. Please outline these clearly.

Methods - Pharmacokinetic analyses – The authors assert that the apatinib concentrations were determined by “fully validated LC/MS methods”, please insert a reference pertaining to this methodology.

Results – tumour response – please define “experienced control of the disease”. It would be useful to mention all the tumour types that were associated with a partial response to apatinib (n=7). Similarly in the conclusion, is it not appropriate to state there was striking activity in a broad range of solid tumours unless detailed.

Discussion – paragraph 5 – “patients who experienced dose reduction could keep control of disease to 5.4 months”. This is unclear, does this mean that only patients who needed a dose reduction had disease stabilisation of 5-6 months or was this also observed in those who did not need a dose reduction for toxicitiy reasons. It is probably reflected also by the biology of the tumour rather than an ability to tolerate apatinib. Other explanations for example resistance to small molecule VEGFR inhibiting TKI's exist and probably deserve to be mentioned.

Discussion – 7th paragraph – IC50 units missing. Please state the duration of PR of the GIST patient(s). Note Table 1 states there is only 1 GIST patient but discussion states 2 patients.

Please cite the 2009 GI ASCO proceedings correctly.

Conclusions – It is not appropriate to state there was striking activity in a broad range of solid tumours.

Table 4 – it may read better if the Grade 1/2 and 3/4 adverse events were displayed as columns rather than rows.

Discretionary Revisions

Study design – please clarify how the first dose level of 250mg/day was selected.

Poor choice of reference (ref 1) for overview of VEGFR family of proteins.

Figure 2 is not very convincing for a PR on the resolution of the image submitted.

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

Quality of written English: Needs some language corrections before being
published

**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