Rebuttal to `The COMPARZ study presented at ESMO 2012: how pliable is non-inferiority?´

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Concerning the previously published letter to the editor:
The COMPARZ study presented at ESMO 2012: how pliable is non-inferiority?
L. Van den Hove, Belg J Med Oncol 2013;7(1):3-7
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Dear editor,

We would like to thank you for giving GSK the opportunity to respond to the *Letter to the Editor* published in the first issue of the Belgian Journal of Medical Oncology 2013 by L. Van den Hove, Medical Advisor at Pfizer in Belgium.[1] In his letter, Dr. Van den Hove challenged your comments regarding the COMPARZ data and provided his view on the trial results which were recently presented at the ESMO congress 2012 by Professor Robert Motzer.[2,3] We would like to take this opportunity to clarify the points raised by Dr. Van den Hove.

COMPARZ is a randomised, open label, phase III study designed to evaluate the efficacy and safety of pazopanib compared to sunitinib in subjects with advanced or metastatic renal cell cancer (mRCC) who have not received prior systemic therapy. The primary endpoint was progression-free survival (PFS) by independent review (Independent Review Consulting, IRC), and the study was powered to demonstrate non-inferiority of pazopanib versus sunitinib. The study met its primary endpoint of non-inferiority between both treatment arms with a hazard ratio (HR) for PFS of 1.047 (95%CI: 0.8982-1.2195). Study design and the non-inferiority criteria (margin) were prospectively defined, discussed with renal cancer experts and regulatory authorities in Europe. Van den Hove questions the timing of the disease assessment scans and Patient Reported Outcomes (PRO) questionnaires. In COMPARZ, disease assessments for all subjects were scheduled to occur at screening/baseline and then every six weeks to week 24 and then every twelve weeks thereafter until disease progression, death, unacceptable toxicity, or withdrawal of consent. It is important to maintain a fixed disease assessment schedule that is not impacted by post randomisation factors, especially when comparing two agents with differing dosing schedules (continuous for Votrient versus intermittent for Sutent). In fact, the six-weekly timing of disease assessments has been previously used in sunitinib studies, for example, in the Pfizer-sponsored EFFECT trial and the MD Anderson's single-arm sunitinib trial in non-clear cell renal cell cancer (NCT00465179).[4,5]

Four Health-Related Quality of Life (HRQoL) questionnaires were given to patients during the study. These were given at baseline/pre-dose Day 1 (with the exception of the Cancer Therapy Satisfaction Questionnaire (CTSQ) as this questionnaire is only relevant once treatment has started) and then day 28 (± 3 days) of every cycle through to Cycle 9. It can be argued that assessing HRQoL at day 28 of the sunitinib cycle might bias against sunitinib as the reported QoL scores will not capture the two-week holiday period in which patients are expected to recover from any treatment-related toxicities. However, when evaluating two agents with differing dosing schedules (intermittent versus continuous), capturing disease-related toxicities

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during treatment is important, and there is probably no ideal time to assess QoL. Assessments carried out at day 42 could be seen as biasing against Votrient as at this time point patients are at the end of a two-week treatment break with Sutent while patients in the other treatment arm are on continuous Votrient treatment, thus assessing that HRQoL on day 28 of a cycle allows for a comparison of QoL during a time when both patient groups are on active treatment for the previous four weeks. In addition:

- The CTSQ and the Supplementary Quality of Life Questionnaire (SQLQ) both ask questions about the patient's experiences over the last four weeks and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-19 assess QoL over the last 7 days; therefore, the QoL instruments are not solely assessing treatment-related QoL scores at day 28 of the cycle.
- The study results from COMPARZ are further supported by the results of a second randomised study, presented at ESMO 2012 that compared HRQoL (but not efficacy) of patients receiving pazopanib versus patients receiving sunitinib (PISCES).[6] In this randomised, crossover, double-blind study patients were randomised to receive treatment with sunitinib followed by pazopanib or vice versa over a 22-week period. Analyses of HRQoL scores showed pazopanib-treated patients to experience less fatigue, hand/foot soreness, and mouth/throat soreness compared to sunitinib-treated patients. Two of the HRQoL instruments used in PISCES (FACIT-F and SQLQ) were also used in COMPARZ. In PISCES these two instruments were completed by patients more frequently (every two weeks) and capture more frequently the impact on QoL of the patients treated with the 4/2 sunitinib dosing regimen. The very similar and statistically significant results of these two instruments in both the PISCES and COMPARZ trial, despite the differences in timing, suggest that the impact of timing of QoL assessment in COMPARZ is likely to be minor.

Van den Hove's *Letter to the Editor* also states that the per protocol (PP) analysis failed to confirm the result of the intent to treat (ITT) population analysis that was reported at ESMO 2012. The primary analysis, pre-specified in the COMPARZ protocol, was progression-free survival (PFS) as assessed by IRC, to be performed on the ITT population. The study was only powered for the primary analysis to be performed on the ITT population and was accepted as appropriate by the trial steering committee, European regulators and ethics committees. Importantly, the Committee for Medicinal Products for Human Use (CHMP) also reviewed the study analysis plan since the study was conducted to meet specific regulatory obligations and accepted the choice of primary endpoint and analyses. The CHMP has subsequently concluded that the COMPARZ study has demonstrated that pazopanib is non-inferior to sunitinib. The analysis on the PP population was a pre-specified sensitivity analysis and a subgroup of the ITT population, and the study was not powered appropriately to assess this subgroup. Importantly, the results of the PP PFS analysis (HR=1.07; 95%CI: 0.91-1.25) were consistent with the primary analysis and, with overlapping confidence intervals, further demonstrates the robustness of the ITT analysis results.

In conclusion, COMPARZ is the largest trial conducted to date in advanced RCC and demonstrates non-inferior efficacy for patients receiving pazopanib as compared to sunitinib. In addition, it highlights a differentiated safety profile between the two agents with better HRQoL scores for patients receiving pazopanib, results that were recently confirmed in the PISCES trial.[6]

References

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