Dear Chris

In response to the ACD we are pleased to see that the Committee recognises that sorafenib has demonstrated both clinical and statistical significance in terms of overall survival, progression-free survival and tumour response. However, we are very disappointed that such a clinically effective treatment option, the first to demonstrate clinical effect in this patient group for over a decade, will be denied to NHS patients, despite it being able to extend their life expectancy by 50%. The proposed recommendation will mean that patients with advanced RCC, a rare cancer, will now only be able to receive cytokine therapy or supportive care as part of routine clinical practice in England and Wales, severely limiting the clinical options available to oncologists.

The proposed recommendation from the Committee will have a devastating impact on both patients and their family. If this recommendation stands the NHS will be denying life extending treatments to vulnerable people at a point in their lives when they rely on the NHS the most. Essentially, the decision will mean that the Committee and the NHS will have let these patients down and cut any final hope they may have during their valuable last few months of life.

There is both rising incidence and rising mortality due to renal cell carcinoma in the UK. The decision by the Committee to not recommend use of these important therapies for patients who have either limited or non-existent alternatives is contradictory to the Department of Health's commitment to ensure that the NHS provides world class cancer care, as outlined in the recent Cancer Reform Strategy. The UK already has one of the lowest expenditure per capita for sorafenib within Europe, with 13 countries having higher expenditure, including Greece, the Czech Republic and Slovakia. The UK position will continue to fall as a result of the proposed guidance. Decisions such as this will also mean that the UK continues to rank poorly in cancer survival compared to our European counterparts.

The guidance poses several questions in light of the recently published End of Life Care Strategy. By denying these life extending drugs, the guidance provides no recommendation on what clinicians should do and what patients should expect from the NHS in preparation for their end of life. The guidance makes no attempt to estimate what would be a cost-effective end of life package that represents optimal care whilst remaining within the Committee's judgement on what constitutes value for money for the NHS, leaving patients with an uncertain last few months of life. Furthermore, the guidance offers no proposed education or training to health care professionals in explaining to patients why they are deemed not worth treating by the NHS and how they will now be managed.

The Strategy states that "it is difficult, if not impossible, to calculate the cost of end of life care in this country". The academic group assumed a minimal supportive care package would be provided to patients, contrary to the aims of the End of Life Care Strategy. Ironically, the proposed guidance now means that the Department of Health and NICE should begin to consider whether providing high quality supportive care at the end of someone's life will be a cost-effective use of public money given that it may not have sufficient impact on quality of life to achieve a favourable incremental cost/QALY ratio. Our own cost estimates of supportive care for advanced RCC patients show that, even without the cost of sorafenib being included in the calculation, extending life in the way that sorafenib has proven to do, would only just be deemed cost-effective by NICE based on a £20,000 per QALY threshold. Whilst we recognise that the Committee has to be mindful of the need to take into account the effective use of NHS resources, we disagree that the QALY is the appropriate outcome to measure the benefit of oncology products, particularly in advanced stage disease. Although the health state utility attempts to adjust time by modifying it for the preference (or fear) of a health state, it does not account for people's valuation of their time. When people have less time available, for example, if they have short life expectancy, they will value any time available much more highly than if they have more many years of life left. Unfortunately, the QALY approach, even accounting for discounting based on Treasury financial investment recommendations, does not take this into account. This therefore results in a perverse situation where the NHS values the addition of 6 months of life to someone with only a few months to live the same as if it were given to someone with 30 years to live. The implication of this is that the NHS is implicitly devaluing the benefit of time these life extending drugs provide for advanced stage disease at a point when patients value their time most highly.

Throughout the ACD, the document mentions that the Phase III sorafenib trial, TARGET, was

terminated early. In the way that it is written, readers may interpret this as the manufacturer's decision and that this may have compromised the results of the trial. Please can you add that the cross-over decision was based on ethical grounds, and recommended by the independent monitoring group after sorafenib had demonstrated a clinically significant increase in progression free survival over placebo. The pre-planned secondary analyses with the placebo arm censored did show a statistically significant overall survival advantage.

The ACD comments on further possible research areas within the RCC field. We would like to bring to the Committee's attention that Bayer has remained committed to investing in and undertaking research on sorafenib in the UK, including a large scale (n=1656), UK specific phase III trial, SORCE.

Please find below a list of additional comments relating to specific sections of the ACD that we would like the Committee to take into account for the wording of the FAD.

4.1.21

Bokowski et al. (2007; JCO Vol 30 (3)) reported that the median time to health status deterioration was significantly greater for subjects on sorafenib than those on placebo ($p<0.0001$ by log rank test). Health status deterioration was defined as a greater or equal than four point drop in FKSI-10 total score, progression or death).

4.1.24

Please change "appears" to "demonstrated"
Please add "on ethical grounds" i.e. "terminated early on ethical grounds"

4.2.6

Title should be unsuitable for immunotherapy

Please remove the statement "although the precise range of ICERs is not reported numerically in the manufacturer submission" as these were available to PenTAG within the fully enabled and transparent economic models provided. Otherwise, please add that Tornado diagrams were provided in the submission to demonstrate the results of the one way sensitivity analysis. It was not our intention to not provide these values numerically.

4.4.7

Sorafenib is licensed for patients unsuitable for cytokine therapy. By not allowing this group to receive any of the clinically effective treatments available, NICE is denying patients the ability to both relieve symptoms and extend their lives. As this group has no other treatments available they have the highest unmet clinical need of all advanced RCC patients; denying them treatment when nothing else is available is unjust.

4.4.15

Please add "on ethical grounds" i.e. "…was terminated early on ethical grounds and people…"

4.4.15

The Committee believe that in clinical practice patients will receive additional therapies. The Committee should be mindful that, as a result of denying these new drugs to patients, that this statement will no longer be correct in England and Wales, although it is highly appropriate for all the other countries who regularly fund treatment with sorafenib. Only patients recruited into clinical trials will be able to receive other therapies and this is not reflective of clinical practice throughout the NHS.

We would therefore ask the committee to reconsider their proposed decision in denying sorafenib to patients where no further treatment options available to them. In particular:

- We do not believe that that using the QALY for advanced RCC patients is a suitable and sound basis for making recommendations to the NHS in this patient group.
- The decision will be inequitable to those patients who are unsuitable for cytokine therapy and therefore will not be eligible for any treatment at all.

Finally, Bayer believes that sorafenib should be available to clinically eligible RCC patients. We are currently in discussions with the Department of Health about schemes that may allow patients access to sorafenib in the event that NICE rejects the use of sorafenib in the NHS.

Kind Regards