British Journal of Cancer (2010) 103, 1307 – 1308

www.bjcancer.com

Letter to the Editor

Comment on 'Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-α2a compared with sunitinib'

C Charbonneau*,[1] and R Sandin[2]

[1]Global Outcomes Research, Pfizer Oncology, New York, NY, USA; [2]Global Outcomes Research, Oncology, Pfizer AB, Sollentuna, Sweden

British Journal of Cancer (2010) **103,** 1307 – 1308. doi:10.1038/sj.bjc.6605886 www.bjcancer.com
Published online 14 September 2010

Sir,

Mickisch *et al* (2010) recently reported a comparison of the costs of managing adverse events resulting from treatment of first-line metastatic renal cell carcinoma (mRCC) with sunitinib or bevacizumab plus interferon-α2a across several European countries. The authors concluded that such costs were lower for bevacizumab plus interferon-α2a than for sunitinib in a number of countries, including the United Kingdom.

Given the dramatic change in the treatment landscape for mRCC, we agree with the authors that economic evaluations become increasingly important, as decision makers with scarce resources must choose among several available targeted therapies. However, we fundamentally disagree that costs associated with management of adverse events can be decoupled from other significant factors, most notably, clinical benefit and drug/treatment cost. The cost of adverse event treatment in RCC is likely to be less than 2 – 3% of total costs (Benedict *et al*, 2009; Remák *et al*, 2009; Calvo *et al*, 2010; Thompson Coon *et al*, 2010), depending on the country in question and, therefore, virtually unimportant for the choice of treatment. Moreover, we disagree that the two regimens have comparable efficacy, as stated by Mickisch *et al* (2010), which flatly contradicts two recently published meta-analyses that suggest sunitinib provides a superior progression-free survival (PFS) benefit (Mills *et al*, 2009; Thompson Coon *et al*, 2009).

A UK study by Thompson Coon *et al* (2010), commissioned and funded by the Health Technology Assessment program on behalf of the UK National Institute for Health and Clinical Excellence (NICE), is used here as an illustrative example of a comprehensive economic evaluation, as it can be compared with the UK results from Mickisch *et al* (2010).

Unlike the analysis by Mickisch *et al* (2010), in which drug administration costs and initial drug acquisition costs were not considered, ostensibly to avoid country-specific confounders in the analysis, Thompson Coon *et al* (2010) comprehensively included drug treatment costs, costs associated with routine patient follow-up, management of treatment-related adverse events, diagnosis of disease progression, and best supportive care. It was shown that the costs associated with treating adverse events represented less than 1% of total costs due to the low incidence of severe and costly adverse events. Moreover, sensitivity analyses showed that the hazard ratios for survival and the drug prices and utilities associated with treatment were the most important factors.

There is also evidence to indicate that Mickisch *et al* (2010) may have overestimated the costs associated with adverse event management. For example, according to their analysis, the cost for treating grade 3/4 thrombocytopenia in the United Kingdom is €3372 per event; however, the UK National Health Service (NHS, 2010) reference cost database, a standardized means of assessing the costs of healthcare in the United Kingdom, estimates this cost at £1746, or €2012 (OANDA, 2010), approximately 40% lower.

This clearly shows that adverse event costs should not be assessed independently of survival benefits and treatment costs when choosing therapy. In addition, evidence supporting the clinical efficacy of each regimen suggests that sunitinib has the strongest data to date as first-line mRCC therapy (Motzer *et al*, 2009), with a PFS of 11 months and overall survival of more than 2 years (26.4 months).

Furthermore, Benedict *et al* (2009) recently reported findings from a cost-effectiveness analysis in which sunitinib was found to be more effective (e.g., gains of 0.16 quality-adjusted life years) and less costly (i.e., savings of $67 798 over 10 years) than bevacizumab plus interferon-α2a (as well as sorafenib and temsirolimus), when indirectly compared as first-line mRCC therapy from a US third-party payer perspective. And, again, unlike the study by Mickisch *et al* (2010), this was a comprehensive analysis, which included drug treatment costs, costs associated with routine patient follow-up, management of treatment-related adverse events, diagnosis of disease progression, and best supportive care. It was subsequently demonstrated in sensitivity analyses that, although the overall findings for sunitinib were robust to changes in most parameters, the results, similar to those for Thompson Coon *et al* (2010), were most influenced by the hazard ratios for survival, and the drug prices and utilities associated with treatments, thus providing further evidence that management of adverse events, although important, cannot be used in isolation when making treatment choices. In addition, comparable findings have been reached in similar analyses recently reported for patients receiving first-line

*Correspondence: Dr C Charbonneau;
E-mail: Claudie.Charbonneau@pfizer.com
Published online 14 September 2010

mRCC therapy in both Sweden and Spain (Remák *et al*, 2009; Calvo *et al*, 2010).

Finally, it has been suggested that toxicities, such as hypothyroidism and cardiotoxicity, may have been underestimated in the phase III sunitinib registration trial used in the analyses cited above, in order to highlight potential concern that the estimates for adverse event management may not adequately reflect everyday clinical practice or long-term use of sunitinib (Porta, 2010). However, this concern has not been borne out in the trial itself, in which long-term follow-up did not result in cumulative toxicity, and previously reported quality of life measures favored sunitinib over interferon (Cella *et al*, 2008; Motzer *et al*, 2009). On the contrary, toxicity with sunitinib has even been shown to be tolerable and manageable in an expanded access program with a broad population of more than 4000 mRCC patients, including subgroups of patients with a traditionally poor prognosis (Gore *et al*, 2009).

In summary, this analysis by Mickisch *et al* (2010) advances a worthy line of investigation of the targeted therapies in mRCC; however, it falls short in demonstrating that costs of adverse event management should be considered in a vacuum or that the clinical benefit gained with sunitinib is outweighed by such costs. Instead, this study serves to highlight the importance of conducting comprehensive cost-effectiveness analyses in order to facilitate treatment choice.

ACKNOWLEDGEMENTS

Medical writing support was provided by Andy Gannon at ACUMED (Tytherington, UK) with funding from Pfizer Inc.

Conflict of interest

The authors, in addition to being full-time employees of Pfizer, are also company stockholders.

REFERENCES

Benedict A, Figlin RA, Charbonneau C, Kreif N, Hariharan S, Négrier S (2009) Economic Evaluation of Sunitinib vs. Sorafenib and Bevacizumab Plus Interferon-alfa Among All Patients and Sunitinib vs. Temsirolimus in Poor-risk Patients as First-line Therapy of Metastatic Renal Cell Carcinoma in the US. Presented at the 8th International Kidney Cancer Symposium, Chicago, IL, USA, 25 – 26 September

Calvo E, Maroto-Rey P, Gonzalez-Larriba JL, López-Brea MF, Castellano DE, Kreif N, Díaz-Cerezo S, Korytowsky B, Martí B (2010) Cost-effectiveness Evaluation of Sunitinib as First-line Treatment for Metastatic Renal Cell Carcinoma in Spain. Presented at the 2010 American Society of Clinical Oncology Genitourinary Cancers Symposium: San Francisco, CA, USA, 5 – 12 March

Cella D, Li JZ, Cappelleri JC, Bushmakin A, Charbonneau C, Kim ST, Chen I, Motzer RJ (2008) Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon-alfa: results from a phase III randomized trial. *J Clin Oncol* **26:** 3763 – 3769

Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, Hariharan S, Lee SH, Haanen J, Castellano D, Vrdoljak E, Schöffski P, Mainwaring P, Nieto A, Yuan J, Bukowski R (2009) Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. *Lancet Oncol* **10:** 757 – 763

Mickisch G, Gore M, Escudier B, Procopio G, Walzer S, Nuijten M (2010) Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-a2a compared with sunitinib. *Br J Cancer* **102:** 80 – 86

Mills EJ, Rachlis B, O'Regan C, Thabane L, Perri D (2009) Metastatic renal cell cancer treatments: an indirect comparison meta-analysis. *BMC Cancer* **9:** 34

Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, Negrier S, Szczylik C, Pili R, Bjarnason GA, Garcia-del-Muro X, Sosman JA, Solska E, Wilding G, Thompson JA, Kim ST, Chen I, Huang X, Figlin RA (2009) Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* **27:** 3584 – 3590

National Health Service reference costs 2008 – 2009 (2010) Published 28 January 2010. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591 (accessed 28 April 2010)

OANDA, the Currency Site (2010) Available at: http://www.oanda.com/currency/converter/ (accessed 29 April 2010)

Porta C (2010) Letter to the editor regarding: 'Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-a2a compared with sunitinib'. *Br J Cancer* **102:** 1196 – 1197

Remák E, Vioix H, Sandström P, Harmenberg U, Ullén A, Sandin R (2009) Cost-Effectiveness Analysis of Sunitinib, Bevacizumab + Interferon-Alfa and Temsirolimus as First-Line Therapy of Metastatic Renal Cell Carcinoma in Sweden. Presented at the International Society for Pharmacoeconomics and Outcomes Research 12th Annual European Congress, Paris, France, 24 – 27 October

Thompson Coon JS, Liu Z, Hoyle M, Rogers G, Green C, Moxham T, Welch K, Stein K (2009) Sunitinib and bevacizumab for first-line treatment of metastatic renal cell carcinoma: a systematic review and indirect comparison of clinical effectiveness. *Br J Cancer* **101:** 238 – 243

Thompson Coon JS, Hoyle M, Green C, Liu Z, Welch K, Moxham T, Stein K (2010) Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. *Health Technology Assessment* **14**(2)**:** 1 – 184, iii – iv