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Review

Evaluation of treatment options for patients with advanced renal cell carcinoma: Assessment of appropriateness, using the validated semi-quantitative RAND corporation/University of California, Los Angeles methodology

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Abstract A diverse range of treatment options and interventions are available for the management of renal cell carcinoma (RCC), allowing clinicians to tailor therapy to best meet their patient's needs and situation. However, choosing from the plethora of options can be problematic. RCC treatment guidelines advise on the most efficacious agents based upon specific clinical trial populations, but these do not always take into account all the patient factors that influence the suitability of treatment options for individual patients.

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This study used the validated RAND/UCLA (RAND corporation/University of California, Los Angeles) 'appropriateness methodology' to integrate clinical efficacy data with expert opinion concerning the use of specific RCC treatment options for particular patient scenarios, in an attempt to facilitate the widespread implementation of patient-focussed treatment choices. Use of the methodology has allowed us to develop treatment algorithms for patients with locally-advanced RCC and for those with metastatic disease post-nephrectomy or with primary tumour *in situ*. The algorithms take into account patient-specific characteristics such as tumour histology, prior treatment and known risk factors to advise whether a particular treatment intervention is appropriate, not appropriate or of uncertain appropriateness.
Use of this methodology aims to develop a formalised process by which expert opinion can be integrated with clinical data and used as an additional source of information that can provide further guidance concerning difficult treatment decisions when data are absent or sparse.

1. Introduction

The development of therapies that target the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin pathways (mTOR) have made a significant impact on the treatment of patients with advanced RCC. The targeted agents differ in terms of their biological effects, clinical efficacy, adverse event profiles and the patient populations in which they have been studied.[1] Treatment guidelines for RCC[2,3] have been developed based on clinical trial data but the appropriateness of a specific therapy to a particular situation depends in part on factors such as the extent and aggressiveness of the disease, prior treatment regimens and prognostic factors. Available RCC treatment guidelines may not always take into account these and other factors such as patient history which can have an important influence on clinical decision making. Another consideration is that guidelines can be either general or specific, and can be interpreted variably depending on the specialty of the treating physician (e.g. urologist, medical oncologist). There are many treatment choices available and it would be better if possible, to tailor therapy to meet the needs of each individual RCC patient based on the biology of their disease. A step towards tailoring therapy also requires that the available treatment options are prioritised to best suit the individual.[63]

Evidence is continually being developed with regards the efficacy and toxicity of new therapies. However, this evidence and the views of opinion leaders are not always rapidly transferred to community oncologists treating patients with advanced RCC. Collecting existing and emerging evidence and integrating it with expert opinion represents an important educational need. In 2006, Halbert et al.[4] reviewed the clinical evidence and integrated it with expert opinion, utilising the validated RAND corporation/University of California, Los Angeles (RAND/UCLA) appropriateness methodology,[5] to reach a consensus on the appropriateness of the available RCC treatment. The methodology has been utilised in oncology and applied to consider the applicability of treatments for breast cancer, melanoma,[6] colorectal cancer,[7,8] haematological malignancies and pancreatic cancer.[9]

In this study, we reviewed new evidence that has been published since the Halbert analysis and integrated the findings with the opinions of leaders in RCC treatment from across Europe, using the same RAND/UCLA methodology. This exercise becomes even more relevant given that the first randomized phase III trial with a targeted agent (Sorafenib) was published in 2005[67] and that almost each year since then an additional targeted agent has been approved by the FDA and EMA.

2. Methods

The consensus panel method developed by RAND/UCLA combines evidence-based review with the practical experience of clinicians and leaders in the field.

2.1. Literature review

Comprehensive literature review identified studies that assessed the use of systemic therapies in the treatment of metastatic RCC. The MEDLINE database was searched from February 2005 to July 2010 for English language articles using the search terms *kidney cancer*, *metastatic renal cell carcinoma*, *carcinoma renal cell* and *clinical trial*, as keywords; a search of the bibliographies of relevant articles and reviews identified additional publications. Abstracts from the websites of the American Society of Clinical Oncology, the European Society of Medical Oncology (ESMO) and the European Association of Urology (EAU) published to July 2010 were also reviewed. A broad perspective was taken, to include published evidence from non-randomised phase 1 and 2 studies. The literature review was used to identify data informing on the efficacy of RCC treatments and to support the development of patient scenarios for use in the RAND/UCLA assessment process.

2.2. Consensus panel

A pool of panellists was identified from ESMO faculty lists, European Medical Advisors to the Kidney Cancer Association and authors of key clinical trial reports. Twelve experts were invited to participate and 11 accepted. The expert panel comprised recognised European RCC experts, and included nine oncologists and two urologists from eight countries. All were clinical researchers who regularly publish in the field of RCC management.

The study was designed to have two panel meetings. During the first, the lead investigator and research team described the aim of the study and the clinical scenarios under consideration; the clinical scenarios to be assessed were then discussed, revised and finalised by the panel members. The final versions of case histories and computed tomography scans for each scenario and a copy of the systematic literature review were then sent to each panel member, who used the materials to score the treatment/intervention choices for each scenario. An example of a case history and the associated treatment/intervention-scoring sheet is presented as Supplementary Information. At the second panel meeting the results of the scoring exercise, and specifically those scenarios with 'disagreement' were discussed. The objective was to reach consensus, where possible.

2.3. Clinical scenarios

The clinical scenarios were developed based on patient characteristics that were considered by the panel to have a material effect on treatment decisions. Patient characteristics used to describe the clinical scenarios were agreed by the lead investigator and panel members at the first panel meeting and comprised: tumour histology (clear cell or non-clear cell), prognostic score, surgical risk, tumour staging, prior systemic therapy and prior nephrectomy.

Combinations of the selected patient characteristics were used to develop clinical scenarios for locally-advanced and metastatic disease. Care was taken to ensure that only patient characteristics that had been prospectively agreed upon were included in the clinical scenarios. The scenarios involving locally-advanced tumours took into account nodal involvement, according to the TNM classification, and surgical risk. A total of 34 such patient scenarios were developed.

Scenarios for metastatic disease involved nephrectomised patients, those with the primary tumour *in situ*, those treated with first-line systemic therapy and those who had not received prior treatment:

- In scenarios where patients had not undergone partial or radical nephrectomy (i.e. the primary tumour was *in situ*), prognostic risk (high/low/intermediate) and surgical risk were used to classify patients.
- In scenarios where patients had not received prior therapy, prognostic risk (high/low/intermediate) was taken into account. The MSKCC prognostic score was used as the predominant criteria for defining risk.
- Four scenarios were included for patients with non-clear cell histology (papillary, chromophobe, oncocytic and collecting duct carcinomas).
- For patients who had not undergone partial or radical nephrectomy, treatment options included surgery with or without systemic therapy.
- Various systemic treatments were listed as options for those with prior nephrectomy, including cytokine therapy, bevacizumab, sunitinib, sorafenib, pazopanib, temsirolimus and everolimus.

The American Society of Anaesthesiologists (ASA) classification[68] was used to distinguish two surgical risk categories: good surgical risk (ASA category 1–2) and bad surgical risk (ASA category 3–4). Prognostic risk for patients with metastatic RCC was determined based on the Memorial Sloan-Kettering Cancer Centre criteria[10] and the TNM Classification of Malignant Tumours[69] was used to classify tumour stage. Other parameters taken into account included Karnofsky performance status[11] and laboratory values.

2.4. Classifying the appropriateness of treatment

The clinical scenarios and treatment/intervention options were grouped based on generic descriptions. Panel members then scored the appropriateness of each treatment/intervention for each scenario on a scale of 1 (inappropriate) to 9 (most appropriate). An example of a clinical scenario with the relevant scoring sheet is presented as Supplementary Data. Disagreements between panel members were resolved as far as possible at the second meeting, as per the RAND/UCLA methodology. This was done by having specific discussions within the panel and then re-scoring for each of the treatment options with 'disagreement'. The scores for each treatment/intervention choice for each scenario were compiled together and treatments/interventions were then classified at one of three appropriateness levels:

(1) *Appropriate:* a median panel score of 7–9, without disagreement.
(2) *Uncertain:*
   (a) a median panel score of 4–6,
   (b) 'disagreement' (defined as at least 4 panellists scoring in the low range [1–3] and at least 4 panellists scoring in the high range [7–9]).

(3) *Inappropriate:* a median panel score of 1–3, without disagreement.

3. Results

3.1. The evidence base

A total of 65 studies were identified as suitable for the RAND/UCLA methodology, including: nine sunitinib studies,[12–20] 12 sorafenib studies,[21–32] nine bevacizumab studies,[13,33–40] two temsirolimus studies,[41,42] three studies with everolimus,[70–73] and two pazopanib studies;[43,44] 21 cytokine studies (10 with interferon alpha[18,38,41,45–51], eight with interleukin 2[52–59], and three with a combination of interleukin 2 and interferon alpha).[64–66] There were also three studies on cytoreductive nephrectomy.[45,60,61] Specific efficacy data for non-clear RCC were taken from two studies, one retrospectively evaluating the effect of a combination of sunitinib and sorafenib[62] and the other being a subgroup analysis of the temsirolimus registrative trial.[41] Data published or included in databases after July 2010 have not been included in the review in line with agreed methodology. Complete results of the systematic review are summarised in Table 1; the details with references are available as Supplementary Data files.

Table 1 presents a summary of the clinical benefit (objective response, complete response, progression-free survival [PFS] and overall survival [OS]) achieved with the interventions identified during systematic review of the literature.

3.2. Appropriateness of treatment options

Table 2 groups the clinical scenarios identified by the principal investigator and panel of experts and describes how they were classified by the panel as appropriate, inappropriate, and of uncertain appropriateness. The panel identified a total of 575 treatment options in 34 clinical scenarios, which were grouped under six categories. Of the 575 treatment/interventions identified, 80 options (13.91%) were considered appropriate, 385 options (66.95%) were considered inappropriate and for 110 options (19.13%) the appropriateness of the treatment/intervention was considered uncertain. Of the 110 options of uncertain appropriateness, only 17 were classified as such because of 'disagreement' between panel members as defined by the RAND/UCLA methodology. The scenarios/treatments on which panel members disagreed were re-scored after discussion at the second panel meeting as per the RAND/UCLA methodology following which the number of options where there was disagreement was reduced to 8 (1.39%) and these are detailed in Table 3.

Figs. 1–3 summarise the overall findings and present the treatment options for patients with different disease types, with each colour coded to identify appropriate (green), inappropriate (red) and uncertain (yellow) options. The data in these figures form the core of the results of this study.

4. Discussion

There was a high degree of concordance among the panellists concerning the appropriateness/inappropriateness of therapies for most of the clinical scenarios considered. This can be attributed to the robust and clear evidence from clinical trials that can be used to guide the evaluation of the suitability of different agents. Disagreement was seen for only eight treatment options/scenarios (1.5%) of the total of 575 options; seven cases of disagreement involved enrolment of patients into a clinical trial with an investigational agent and the remaining case related to the use of temsirolimus in patients with oncocytic carcinoma.

The proportion of options where there was uncertainty regarding appropriateness, as defined by the methodology, was quite high (approximately 19%). These clinical scenarios are of interest, as the uncertainty could be due either to insufficient evidence to support use of a specific treatment in a particular clinical situation or a lack of clarity as to the message to be taken from conflicting data. Anecdotally a particularly high degree of uncertainty was seen for some patient scenarios, such as locally-advanced disease involving aggressive tumours, metastatic disease in patients who had received prior TKI therapy with or without prior nephrectomy and patients with non-clear cell histology. The uncertainty most likely reflects the lack of prospective evidence in these clinical settings at the time this study was being conducted.

Pazopanib or sunitinib were generally considered appropriate for the treatment of patients with metastatic disease who had not received prior systemic therapy, which is in line with published phase III evidence. Some differences in applicability were seen for the two treatments. In patients with metastatic disease and an *in situ* primary tumour the appropriateness of pazopanib was considered uncertain in high-risk situations, while sunitinib was considered appropriate. However, in patients with metastatic disease who had undergone prior nephrectomy, both treatments were considered appropriate. Clearer definition of the most appropriate treatment option for such patients may be achieved when the results of ongoing trials are reported, such as head-to-head-comparisons of the various agents. Bevacizumab was considered appropriate for use in patients who had undergone partial or radical nephrectomy with low/intermediate-risk metastatic disease.

For patients with the primary tumour *in situ* everolimus, pazopanib, sorafenib or sunitinib were all considered appropriate second-line therapies, with the choice of agent depending on prior treatment. For nephrectomised patients pazopanib, sorafenib and sunitinib were considered appropriate second-line regimens following initial cytokine therapy. More data is needed to inform on the most suitable treatment option for individual patients in this disease setting.

Table 1
Systematic review of the efficacy of interventions for the management of renal cell carcinoma.

Treatment	No of trials	Objective response % (range)	Complete response % (range)	Median PFS months (range)	Median PFS months (range)–comparator	Median OS months (range)	Median OS months (range)–comparator
Sunitinib	9	35.8 (0, 52)	2 (0, 6)	9.3 (6, 11)	5	20.2 (16, 26.4)	21.8
Sorafenib	12	17.7 (7, 50)	1 (0, 2.5)	8.6 (2.1, 25.1)	3.7 (2.8–5.6)	17 (4.3, 27)	15.2–15.9
Bevacizumab	9	25.9 (12, 52)	2.3 (1, 4)	9.7 (8.1, 11)		20.5 (17.2, 25.4)	
Everolimus	3	15 (1, 30)	0	7.9 (4.3, 11.2)	1.8–1.9	18.5	
Temsirolimus	2	28.4	–	5.1	3.1	10.4 (9.7, 11.2)	7.3
Pazopanib	2	30	–	11.1 (9.2, 13)	4.2	–	
IFN-alpha	10	13.8 (4.8, 31)	1.8 (1, 3)	4.9 (3, 8)	6.4 (4.7–11)	14.4 (6.3, 31)	12.97 (7–18)
IL2	8	15.6 (6.5, 23.2)	5.7 (3, 8.4)	11.3 (3.1, 19.5)	3.1	16.5 (11.5, 23)	9.4 (12.5–17)
IL2 + IFN	3	9.3 (4.9, 16.6)	3.3	3.1		12.8 (12.5, 13)	
Nephrectomy	3	19	5	12		40.2 (15,57.6)	6–7

Table 2
The appropriateness of specific groups of treatment options according to clinical scenario.

Groups	Total options	Appropriate treatment number (%)	Inappropriate treatment number (%)	Appropriateness uncertain (including disagreement) number (%)
Total	575	80 (13.91%)	385 (66.95%)	110 (19.13%)
Locally advanced tumour	260	15 (5.77%)	200 (76.92%)	45 (17.31%)
Metastatic RCC with *in situ* primary tumour and prior therapy	126	17 (13.49%)	90 (71.43%)	19 (15.08%)
Metastatic RCC with *in situ* primary tumour and no prior therapy	72	17 (23.61%)	40 (55.56%)	15 (20.83%)
Metastatic RCC with prior nephrectomy with prior therapy	63	17 (26.98%)	29 (46.03%)	17 (26.98%)
Metastatic RCC with prior nephrectomy and no prior therapy	18	8 (44.44%)	8 (44.44%)	2 (11.11%)
Non-clear cell carcinoma	36	6 (16.67%)	17 (47.22%)	13 (36.11%)

Table 3
Treatment options identified in the literature were there was panel disagreement as to the appropriateness of that treatment.

Setting	Patient characteristics	Treatments
Locally advanced tumour with clear cell histology	$T_3N_{1-2}M_O$, bad surgical risk	Nephrectomy + clinical trial with investigational agent
Locally advanced tumour with clear cell histology	$T_3N_{1-2}M_O$, bad surgical risk	Intended nephrectomy + clinical trial with investigational agent
Locally advanced tumour with clear cell histology	$T_4N_0M_0$, bad surgical risk	No planned nephrectomy + clinical trial with investigational agent
Locally advanced tumour with clear cell histology	$T_4N_{1-2}M_O$, good surgical risk	No planned nephrectomy + clinical trial with investigational agent
Metastatic RCC with clear cell histology	*In situ* primary tumour with prior temsirolimus therapy	Nephrectomy + clinical trial with investigational agent
Metastatic RCC with clear cell histology	*In situ* primary tumour with low/intermediate prognostic risk, bad surgical risk and no prior systemic therapy	Nephrectomy + clinical trial with investigational agent
Metastatic RCC with clear cell histology	*In situ* primary tumour with high prognostic risk, bad surgical risk and no prior systemic therapy	Nephrectomy + clinical trial with investigational agent
Metastatic RCC with oncocytic cell histology	Not available	Systemic therapy with temsirolimus

For patients with non-clear cell carcinoma, sunitinib was considered as an appropriate option for the treatment of metastatic papillary cancer, while temsirolimus was considered appropriate for chromophobe tumours. The disagreement seen with regards the use of temsirolimus in patients with oncocytic carcinoma is thought to be due to a general lack of evidence to support the use of this treatment option.

Several limitations of this RAND/UCLA assessment exercise in patients with RCC should be noted, for instance, the case histories and scenarios that could be assessed were limited by practical constraints, in terms of the maximum number of permutations that could realistically be scored. This led to some treatment possibilities and clinical situations not being represented. In addition, the option to score the appropriateness of

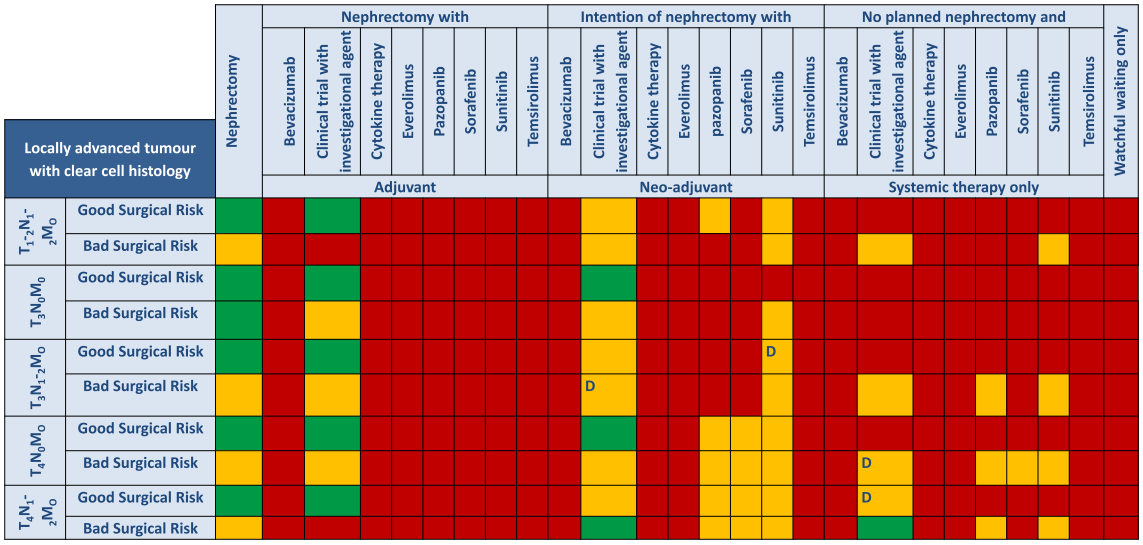

Fig. 1. Appropriate treatment options for patients with locally-advanced renal cell carcinoma. Green = appropriate treatment option, red = inappropriate treatment option, and yellow = treatment options of uncertain appropriateness. The letter D denotes a treatment option classified as uncertain due to disagreement within the expert panel.

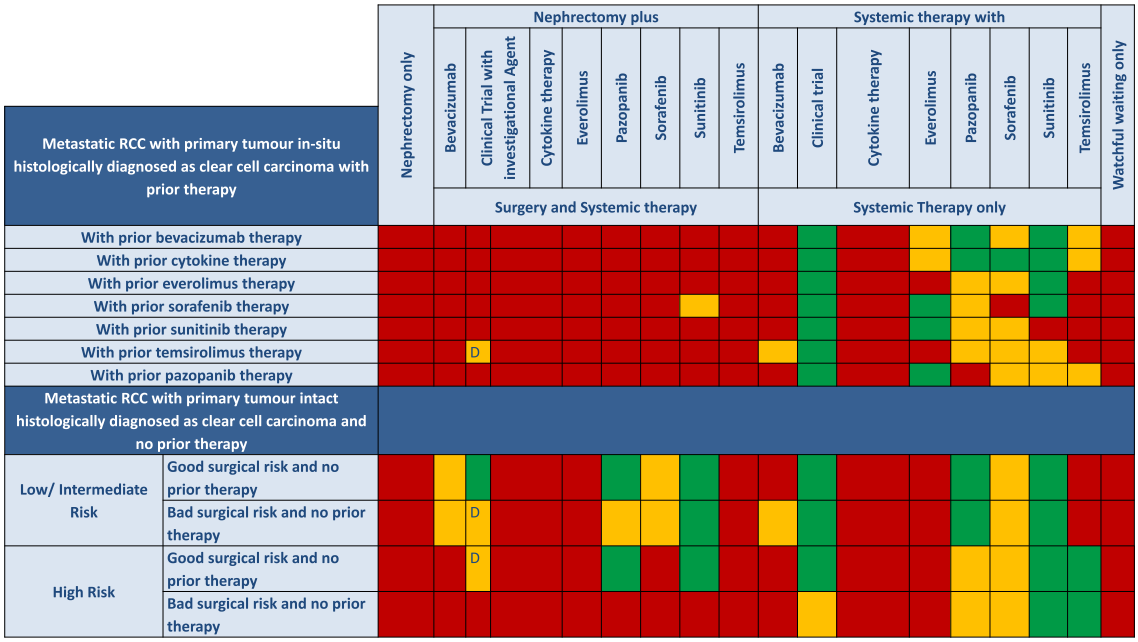

Fig. 2. Appropriate treatment options for patients with metastatic renal cell carcinoma with an *in situ* primary tumour. Green = appropriate treatment option, red = inappropriate treatment option, and yellow = treatment options of uncertain appropriateness. The letter D denotes a treatment option classified as uncertain due to disagreement within the expert panel.

enrolling a patient into a clinical trial with an investigational agent was likely to have been favoured by research-active experts who have ready access to clinical trials. It should also be noted that the prognostic risk criteria used to develop the patient scenarios were based on the Memorial Sloan-Kettering Cancer Centre model, which are not used universally and may be superceded in the future. In future assessments it might be useful to include a mechanism for experts to highlight areas with the greatest need of further study via the RAND/UCLA methodology. There is a need to update this analysis as new data from randomised trials become available.

5. Conclusions

This work has implications for the medical community across Europe involved in the treatment of RCC patients. The scoring exercise should enable oncologists to rapidly

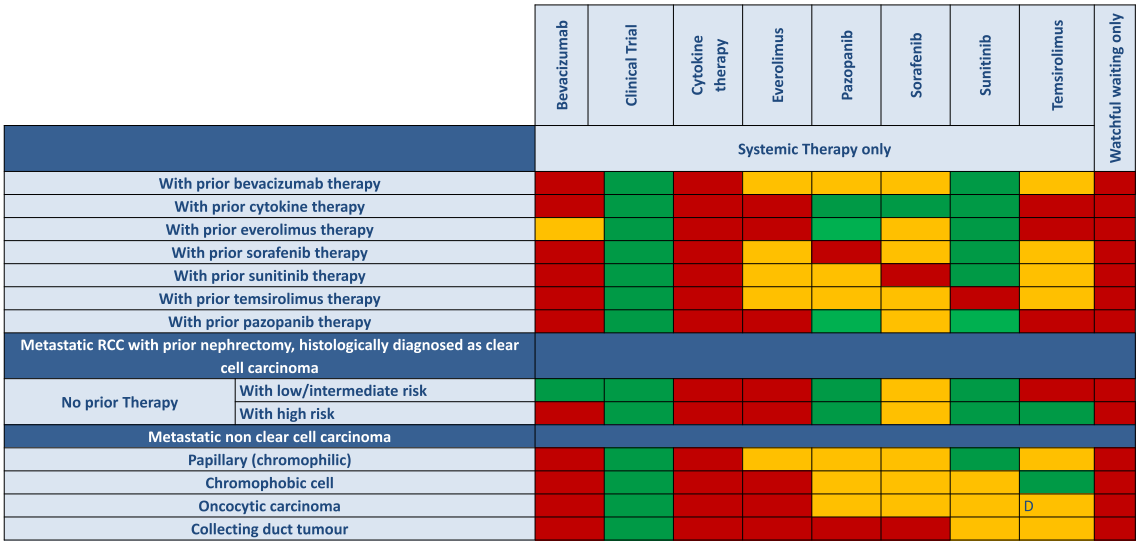

Fig. 3. Appropriate treatment options for patients with metastatic renal cell carcinoma with prior nephrectomy. Green = appropriate treatment option, red = inappropriate treatment option, and yellow = treatment options of uncertain appropriateness. The letter D denotes a treatment option classified as uncertain due to disagreement within the expert panel.

access academic expert opinions in conjunction with the evidence base, particularly as results can be disseminated electronically. We have developed a web-based toolkit that can be utilised in conjunction with the findings of this study, to support colleagues in their decision making when treating patients with renal cancer.

Areas for further research could focus on producing data to help resolve the differences in opinion seen between panel members and to clarify the most appropriate treatment option where expert views appear inconsistent with trial data.

Expert opinion can be a useful additional source of information for difficult treatment questions particularly when data are absent or sparse. The potential use of such information in the development of clinical neural networks and learning tools is under evaluation.

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This project was funded by GSK. GSK selected the principal investigator but had no involvement in the selection of the panel, selection of cases, or any of the factors affecting the result. GSK also had no editorial control on the abstract, manuscript or the poster. The analysis was carried out in its entirety by Double Helix Consulting, London with support from the principal investigator and the panel of experts.

Conflict of interest statement

Martin Gore has been on the speaker bureau and on advisory boards for Roche, GSK, Novartis, Bayer, Pfizer, Schering Plough, Bristol Myers Squibb, Aveo, AstraZeneca, and Astellas.

Joaquim Bellmunt has received lectures fee and honoraria as advisor for GSK, Pfizer, Bayer Healthcare and Roche.

Tim Eisen has Astra Zeneca shareholding (£30 K), is on advisory board for Bayer, Pfizer, Roche, GSK, AVEO. Has been involved in corporate-sponsored research by Astra Zeneca, GSK, Pfizer, Bayer, has received fees from Roche, Bayer, Pfizer, GSK, AVEO.

Bernard Escudier has been an advisor for most of the drug companies involved in RCC treatment including Pfizer, Bayer, Novartis, GSK, Roche, Aveo, and has received honoraria for this activity.

Gerald Mickisch has served as a consultant/speaker for a number of companies over the last 2 years including Astra-Zeneca, Antigenics, Pfizer, Roche, GSK, Novartis, Sanofi, Astellas, Ipsen, Takeda and Wyeth.

Jean-Jacques Patard has acted as a consultant for Pfizer and GSK.

Camillo Porta has acted as a consultant and/or as a speaker for GSK, Pfizer Oncology, Hoffman La Roche, Bayer-Schering Pharma, Novartis Pharma and Boehringer Ingelheim. Furthermore, he has received research grants from Bayer-Schering Pharma and Novartis Pharma.

Alain Ravaud is a member of Global, European and/or French boards for Pfizer, Novartis, GSK, Bayer Schering on urological tumours. He has received institutional research grant/support from Pfizer, Novartis, Roche and accommodation and transport for meetings from Novartis, Pfizer, Bayer.

M. Schmidinger has received honoraria for lectures from and/or acted as an advisor for Pfizer, GSK, Roche, Novartis, Astellas.

Patrick Schöffski has received scientific grants for translational research projects from GSK, Pfizer, Bayer, Novartis, has received honoraria for educational activities in collaboration with GSK, Pfizer, Bayer, Novartis, has given scientific advice to GSK, Pfizer, Bayer, Novartis, Roche.

Cora Sternberg has received speaker or research funding from GSK, Pfizer and Novartis.

Cezary Szczylik has provided consulting services to Pfizer and Bayer, has received honoraris from Bayer, Roche Pfizer and GSK and has received research funding from Bayer.

Enrico de Nigiris: None to declare.

Colin Wheeler: None to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2012.02.058.

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