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Evidence and experience for the management of metastatic renal cell carcinoma ☆

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AIMS AND SCOPE

The last 7 years have seen the treatment landscape for metastatic renal cell carcinoma (mRCC) dramatically change as the understanding of the molecular background of the disease has grown. With the increase in treatment options, however, comes the question of how best to maximise patient benefits based on the available medicines. This topic was the key focus of a Pfizer meeting held at the 8th European International Kidney Cancer Symposium (EIKCS) in Budapest, Hungary (3–4 May 2013), where leading oncology experts reviewed the latest clinical trial evidence and discussed the importance of real world experience in treating patients with mRCC. This report offers an overview of the discussion on how best to integrate clinical trial data, guideline recommendations and real world experience in order to make treatment decisions that will provide the maximum benefit for each individual patient.

1. Introduction

Only 7 years ago, there was a significant unmet need in the treatment of metastatic renal cell carcinoma (mRCC) – immunotherapy was the only treatment available to patients, and only a small subset of patients (~5%) were responsive in terms of long-term outcome.

The approval of sunitinib followed by six other targeted agents to date have enabled significant improvements for patients in progression free survival (PFS) (Fig. 1), overall response rate (ORR) and overall survival (OS) compared with immunotherapy [1–7].

mRCC has become a dynamic therapeutic area, where options for first-, second- and third-line treatments have made long-term survival a realistic goal. As a consequence, the clinical focus has shifted towards how to best maximise long-term benefits for each individual patient by optimising the treatment selection and management based on both clinical trial results and real world experience.

On this basis, Pfizer organised and funded a meeting at the 8th European International Kidney Cancer Symposium (EIKCS) that aimed to review how best to integrate clinical trial data with real world experience when selecting and managing treatments in first-, second- and third-line settings.

Achieving long-term survival requires a careful selection of treatment for each individual patient combined with an effective management of adverse events (AEs) and dosing to maximise treatment duration. How can physicians best use the

☆ Highlights of the '*The evolving mRCC treatment landscape: Building on evidence and experience*' meeting held at the 8th European International Kidney Cancer Symposium (EIKCS) on 3rd May, 2013 in Budapest, Hungary

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Fig. 1 – The availability of targeted agents for the treatment of mRCC has significantly improved patients' median progression free survival. Slide courtesy of Professor Manuela Schmidinger, 2013.

latest clinical trial evidence with their clinical observations to choose the most appropriate treatment sequence for their patients?

Reviewing the recent developments in mRCC treatment, Doctor James Larkin, from the Royal Marsden Hospital (London), discussed the most recent treatment guidelines issued by the European Society for Medical Oncology (ESMO) and highlighted the critical updates to the recommendations in second- and third-line treatments.

Focusing on the most recent clinical data on first-line treatments, Doctor Camillo Porta from IRCCS San Matteo University Hospital Foundation (Pavia) provided an in-depth look at the challenges and opportunities that non-inferiority trials offer and how to put their results in context when making decisions in the clinic.

Finally, Professor Manuela Schmidinger from the Medical University of Vienna brought the discussion back to the patient, illustrating how real world experience has influenced treatment decisions through a number of patient case studies.

2. The mRCC treatment landscape: Where are we now?

Doctor James Larkin, Royal Marsden Hospital, London, UK

James Larkin is a Consultant Medical Oncologist at The Royal Marsden, London, United Kingdom (UK), specialising in the treatment of patients with cancer of the kidney and cancers of the skin, including melanoma. Dr. Larkin received a first in Natural Sciences from the University of Cambridge and undertook clinical training at the University of Oxford, qualifying in 1996. He underwent general medical training in London, and in 2001 won a Medical Research Council Fellowship for a Clinician, carrying out laboratory research at The Institute of Cancer Research (ICR), which led to the award of a PhD. He completed specialist training at The Royal Marsden and was appointed a Consultant in 2008.

His research interests include the individualisation of patient treatment in kidney cancer and melanoma, and the combination of novel targeted therapies to treat these diseases. He is UK Chief Investigator for a number of clinical trials in melanoma and kidney cancer and has been awarded research grants from bodies including Cancer Research UK, Wellcome Trust and the European Framework Programme. He is a member of the National Cancer Research Institute (NCRI) Melanoma Clinical Studies Group and Chair of both the NCRI Renal Cancer Clinical Studies Group and The Royal Marsden/ICR Committee for Clinical Research.

James Larkin opened his presentation by highlighting the necessary components for achieving longer-term survival in mRCC (Fig. 2).

While efficacy has been demonstrated for first-line treatment options, and physicians understand that managing these agents effectively and proactively is critical to achieving the best outcome, longer-term survival is now also dependent on developing the best sequencing strategy with treatments following first-line therapies. This option is only now truly being implemented in day-to-day practice as, for the first time, physicians and patients have proven efficacious treatments available to them in both second- and third-line settings.

The recent RCC treatment guidelines, published by ESMO in October 2012, use the most comprehensive review of clinical evidence to provide recommendations for treatment – guidance that enables physicians to extend the lives of their patients with mRCC. The current update represents a step forward in the management of mRCC with the inclusion, for the first time, of a next-generation VEGF receptor tyrosine kinase inhibitor (TKI) – recommending axitinib in second-line and a third-line option with everolimus [8].

The evidence for axitinib in second-line is based on the AXIS trial, the first phase III, head-to-head study against a targeted agent in second-line mRCC. Patients with clear cell mRCC who had failed on one first-line treatment with sunitinib, bevacizumab + interferon alpha (IFN-α), temsirolimus or cytokines ($n = 723$) were randomised to receive either 5 mg axitinib twice a day (BID) or 400 mg sorafenib BID. The pri-

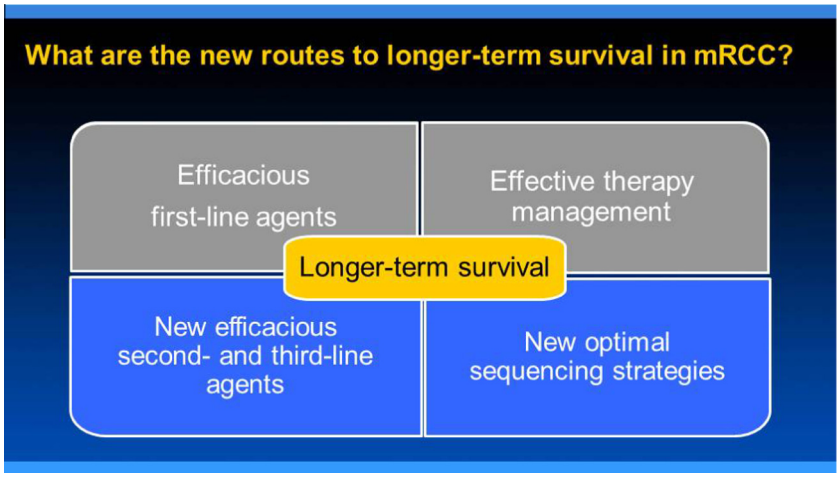

Fig. 2 – There are four necessary components to achieving longer-term survival for patients with mRCC. Slide courtesy of Doctor James Larkin, 2013.

mary endpoint of the trial was achieved in the Intent-To-Treat (ITT) population, with patients on axitinib achieving a median duration of progression free survival (mPFS) of 6.8 months significantly superior to 4.7 months for patients receiving sorafenib (HR 0.67; $p < 0.0001$) [9].

Looking more closely at the largest patient subgroup, patients who had first-line treatment with sunitinib ($n = 389$) achieved a mPFS of 4.8 months when given axitinib in second-line, compared with 3.4 months for sorafenib (Hazard Ratio [HR] 0.741; $p = 0.011$), a 41% longer mPFS with axitinib in second-line, post-sunitinib versus sorafenib. In the second largest subgroup, patients who had first-line treatment with cytokines ($n = 251$) achieved an mPFS of 12.1 months with axitinib versus 6.5 months with sorafenib (HR 0.464; $p < 0.0001$) [9].

Dr. Larkin highlighted that, in addition to these important efficacy results, the other critical information given in the trial was on AEs. Firstly, AEs, such as hypertension and fatigue, would be expected with a potent TKI, as they are on-target side effects that indicate the treatment is effective. Secondly, the list of AEs allows physicians to identify which of the side effects can be effectively managed, such as hypertension and nausea, and those that may be more difficult, such as alopecia. Dr. Larkin warned, however, that physicians do need to keep in mind that some AEs, such as alopecia, may not be medically serious, but are not trivial for a patient, and discussions with patients should be comprehensive and clear from the beginning of treatment.

We now have a wealth of clinical trial data to inform our treatment decisions in second-line, but clinical experience

Case Study: Sunitinib from Prof Schmidinger:
Managing AEs to Maximise Patient Response

Patient: Male, 64 years

History:

- October 2011 – Nephrectomy due to clear cell RCC, pT3b, pNx, pM+, G2
- November 2011 – Diagnosed with metastatic disease with sites in lung, lymph nodes, bone and liver
- MSKCC prognosis: Intermediate
- ECOG: 0

Treatment:

- Sunitinib, 50 mg 4/2 initiated November 2011

Details:

- After beginning initial treatment, patient experienced hypertension grade 2, was prescribed antihypertensive agents, and achieved partial remission
- 11 months after starting treatment, experienced minor disease progression
- At this time, patient was no longer experiencing hypertension and had discontinued antihypertensive agents
- Dose was escalated to 62.5 mg 4/2, and patient experienced again hypertension grade 2 (no additional side effects)
- Patient is still continuing treatment with an ongoing PFS of 17 months

remains vital to drive optimal patient outcome. Non-interventional, population-based studies indeed also provide insights into outcomes with agents in real-life clinical settings and in patients who may not necessarily be included in clinical trials.

Advancing from second-line treatment, physicians should now consider treatment in the third-line setting to achieve a long-term continuum of care. The only treatment recommended at this stage in this setting, post two TKIs, is everolimus, based on the best available evidence to date: the RECORD-1 trial results. In this phase III trial, mRCC patients who received prior treatment with a TKI were randomised to receive either everolimus or placebo ($n = 416$). Importantly, only 21% of patients in the trial received everolimus in second-line, the remaining 79% received the treatment in a subsequent setting (Fig. 3) [10,11].

Based on the 108 patients (26%) who had received two previous TKIs, the results demonstrate clear activity for everolimus in third-line, achieving a mPFS of 4 months in patients previously treated with sunitinib and sorafenib, compared to a mPFS of 1.84 months in patients receiving placebo (HR 0.32; $p < 0.001$) [12,13].

Returning to the question of how physicians can apply the results of these trials to their patients, Dr. Larkin stated it is important to draw on real world experience, as patients in the clinic may be different from those in a clinical trial. While efficacy remains the key driver for treatment selection, choices may also be informed and affected by safety profiles and side effects, especially with patients who may have additional health considerations.

In conclusion, efficacy and evidence support the use of axitinib in second-line after first-line treatment with sunitinib, with everolimus as the proven option for treatment in third-line. Based on the highest level of evidence, reflected by the recently updated ESMO 2012 RCC treatment guidelines, the recommended treatment sequence to maximise patient outcomes is TKI–TKI–mTOR inhibitor.

'*We all have to use our clinical experience to maximise the benefits of this sequence for our patients, helping control the mRCC in our patients for as long as we can,*' stated Dr. Larkin.

3. First-line treatment of mRCC: Providing clinical context

Doctor Camillo Porta, IRCCS San Matteo University Hospital Foundation, Pavia, Italy
Camillo Porta is a Senior Staff Member of the Unit of Medical Oncology at the IRCCS San Matteo University Hospital Foundation in Pavia, Italy. He is also an Adjunct Professor of Medical Oncology at the Post-graduate Schools of Medical Oncology, Biotechnology and General Surgery at the University of Pavia.

After specialising in medical oncology with honours at the University of Pavia, Dr. Porta undertook an Oncology Research Fellowship at the IRCCS San Matteo University Hospital. His research interests include free radicals in cancer; immunology of tumours; development of novel anticancer agents; and the biology of malignant mesothelioma, hepatocellular carcinoma and renal cell carcinoma. Dr. Porta was awarded a prize from Schering-Plough in 1997 for his experimental work on free radicals, free radical scavengers and cancer, and the Gaetano Fichera Memorial Prize in Medical Oncology from the University of Pavia in 1999. Dr. Porta is the author of more than 150 original papers published in peer-reviewed journals, including the *New England Journal of Medicine*, *The Lancet*, *Lancet Oncology*, *European Urology*, *Proceedings of the National Academy of Sciences*, and *the Journal of Clinical Oncology*. He is Editor-in-Chief of *Oncology Reviews* and is a reviewer of several international journals.

Treatment guidelines are extremely important tools that provide physicians with a critical review of the available evidence to support first-line treatment decisions. Numerous guidelines are available; however the five levels of evidence and grades of recommendation adopted by the ESMO 2012

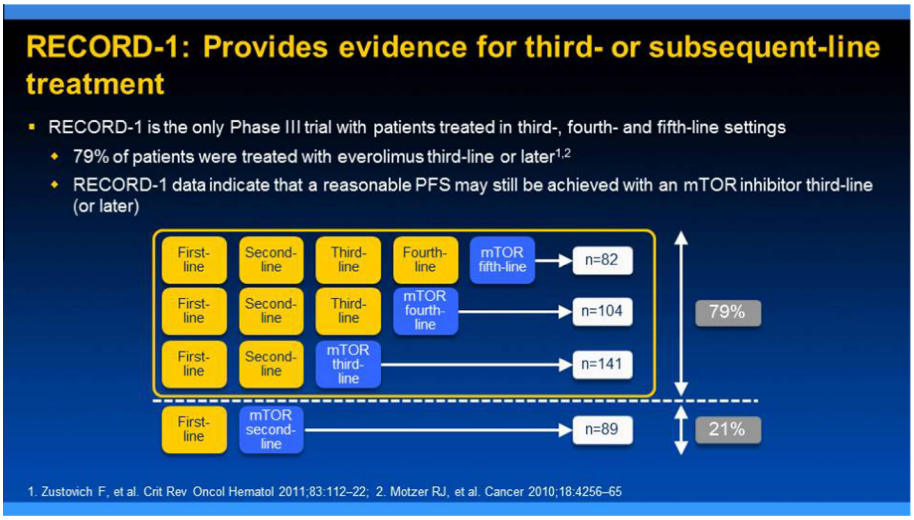

Fig. 3 – Patients who had received prior treatment with a TKI were randomised in the RECORD-1 phase III trial to receive either everolimus or placebo. 21% of patients in the trial received everolimus in second-line, the remaining 79% received the treatment in a subsequent setting. Slide courtesy of Doctor James Larkin, 2013.

RCC treatment guidelines make them a unique and robust resource.

First-line treatment of mRCC has been revolutionised with the approval in European countries of three treatments for good and intermediate prognosis patients, sunitinib, pazopanib and bevacizumab + IFN-α, and temsirolimus for poor prognosis patients. Efficacy is the key driver when selecting first-line treatment, but treatment choice is also informed by robust evidence and guideline recommendations, patient characteristics, experience and patient preference.

The ESMO 2012 RCC treatment guidelines differentiate sunitinib from the other treatment options, as it alone has the highest level of evidence and grade of recommendation for good and intermediate prognosis patients, together with temsirolimus as the recommendation for poor prognosis patients. The rationale behind this recommendation is evident when the results from the pivotal trials are examined. Sunitinib has shown an unsurpassed efficacy across multiple clinical endpoints: mPFS (11 months), median overall survival (mOS, 26.4 months), and ORR (47%) versus IFN-α (Fig. 4) [1,3,5–7,14–16].

Following the publication of the ESMO 2012 RCC treatment guidelines, however, results from the COMPARZ trial were announced at the 2012 ESMO Congress, providing additional information that could impact treatment choice in first-line. The question, Dr. Porta asked, is whether they should.

The aim of the open label, phase III COMPARZ non-inferiority trial was to provide a direct comparison of the efficacy, safety and tolerability of pazopanib and sunitinib in first-line mRCC. As the first non-inferiority (NI) trial in mRCC, the primary objective was to determine whether patient response to pazopanib was not clinically inferior to sunitinib, which was defined as being met if the upper bound of 95% confidence interval (CI) for HR < 1.25, though the European Medicines Agency (EMA) had requested ⩽ 1.22 [4].

Initial trial enrolment included 927 patients; however the trial was later combined with a similar phase II trial being conducted in Asia to bring the total number to 1,110. Patients were randomised to receive either pazopanib 800 mg daily on a continuous dosing schedule or sunitinib 50 mg daily on a 4 weeks on/2 weeks off (4/2) schedule. With a mPFS of 8.4 months for patients receiving pazopanib compared with 9.5 months with sunitinib, despite a 1.1 month difference, the results, initially presented at the 2012 ESMO Congress, based on the ITT analysis, seem to indicate non-inferiority of pazopanib versus the standard of care, sunitinib [4].

A number of other NI trials are being conducted in mRCC, and as NI trials become more common, it will be critical for physicians to understand the specificities of analysing the results of these trials (as opposed to superiority trials) in order to determine if and how they should impact clinical practice.

Dr. Porta highlighted that one key to interpreting these NI trials lies in the two patient populations for analysis: the ITT population, which includes all randomised patients (e.g. non-compliant patients, protocol violations, etc.) and the Per Protocol (PP) population, which are only the patients who completed the study without protocol violations. ITT and PP analyses are equally important when drawing conclusions from a NI trial as the PP analysis is the most conservative assessment. Both analyses should, hence, lead to similar conclusions for a robust interpretation of NI trials. Therefore, reporting results from just one of these populations may have an impact on the interpretation of the data.

Returning to the COMPARZ trial, Dr. Porta reviewed the results for these two populations, demonstrating that non-inferiority was only reached in the ITT group, but not in the PP population where the upper bound of the 95% CI crossed the NI margin, as defined by the study protocol (1.25) and the EMA (1.22) [17]. Taking the results from both the ITT and PP analyses into account, as is recommended for NI trials, the level of uncertainty about the reproducibility of this NI trial in the real world remains high.

In addition, the methodology used to collect the quality of life (QoL) data included surveying patients at day 28 of the sunitinib treatment [18], which has been demonstrated to

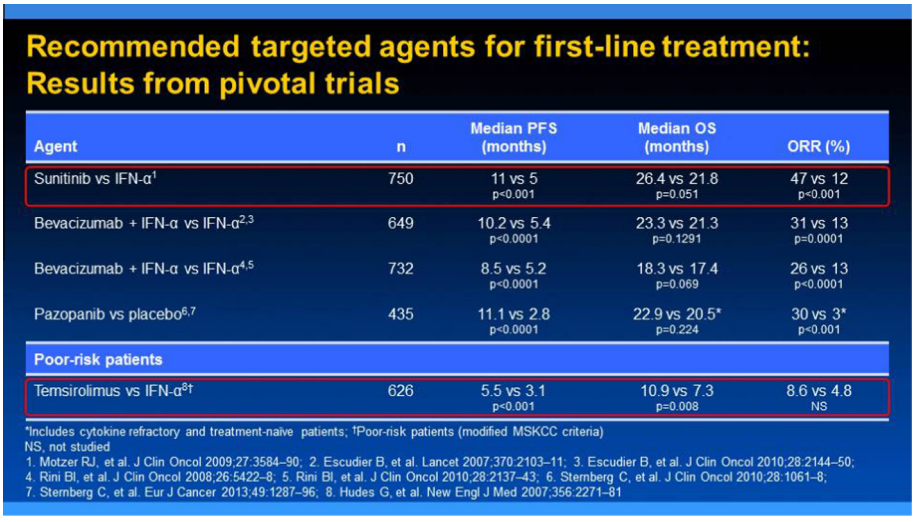

Fig. 4 – Sunitinib has shown an unsurpassed efficacy across mPFS (11 months), mOS (26.4 months) and ORR (47%) versus IFN-α. Slide courtesy of Doctor Camillo Porta, 2013.

Case Study: Sunitinib from Prof Schmidinger:
Optimising First-line Treatment Response by Maximising Treatment Dose/Duration

Patient: Male, 44 years

History:
- November 2010 – Cytoreductive nephrectomy, clear cell RCC, pT3a, pN0, G3
- Metastases included lesion in the left kidney, left adrenal gland, cauda pancreatic, left thoracic wall, left paraaortic lymph nodes, lung, bone and pleural effusion
- MSKCC prognosis: Intermediate

Treatment:
- Sunitinib, 50 mg 4/2 initiated December 2010

Details:
- Patient clearly informed about dose-response
- Experienced hypertension grade 3, stomatitis grade 1 and anorexia with significant weight loss during 4 weeks on treatment
- Dose reduction suggested to manage anorexia, patient declined due to concern over long-term outcome
- Anorexia managed by addition of medroxyprogesteronacetate
- Patient experienced partial remission with current PFS (still ongoing) of 24 months

be the height of toxicity due to the typical 4/2 sunitinib dosing cycle. Despite this, while statistical significance was observed for the two pre-specified primary QoL measurements, the differences in QoL assessments between pazopanib and sunitinib were lower than the validated, minimally important difference, and may not carry a clinically meaningful difference for patients.

Moving to optimal treatment options for patients with poor prognosis, Dr. Porta stated that, while the vast majority of trials have not considered patients with poor risk, temsirolimus is the only treatment that has been examined in this population. Survival data from the global trial for advanced renal cell carcinoma (ARCC) showed a 49% increase in median OS with temsirolimus compared with IFN-α, the first and only study to demonstrate a significant improvement in OS for patients with poor prognosis [16].

Overall, when translating results from clinical trials, experience is still an important consideration, as clearly demonstrated for sunitinib. Since its approval 7 years ago, physicians have had the opportunity to learn how to manage patients on sunitinib and its related AEs optimally. Experience in the real world has demonstrated that some toxicities with sunitinib, such as hypertension, can be considered biomarkers of treatment efficacy. Recent data show a link between increased PFS and OS in patients who developed hypertension on treatment compared with patients who did not [19,20]. In addition, clinical experience and published evidence indicate that efficacy is of utmost importance to cancer patients, and patients with mRCC are most often accepting of some AEs based on the understanding that they may be linked to improved efficacy [21].

Efficacy is, and should continue to be, the primary treatment decision driver. In determining the most efficacious treatment, physicians have many tools available to them, including the ESMO 2012 RCC treatment guidelines, which provide a critical review of all available evidence to help clinicians. Based on this assessment, the best recommendation was given to sunitinib for patients with good and intermediate prognosis and temsirolimus for patients with poor prognosis.

'*At the end of the day, it is the physician's choice to choose the best treatment for the patient and it is clear that [sunitinib and temsirolimus] should be regarded as the first-line treatments of choice in their respective risk groups,*' concluded Dr. Porta.

4. Learning from real-life clinical cases

Professor Manuela Schmidinger, Department of Oncology, Medical University of Vienna, Vienna, Austria
Manuela Schmidinger is a Medical Oncologist and Professor of Medicine at the University of Vienna, Vienna, Austria. Having achieved official specialisation in intensive care medicine, she is currently a Senior Physician in the Department of Oncology and Programme Director for mRCC, leading the research programme in the field of kidney cancer and the care of patients with RCC.

Her research interests include prognostic factors and treatment in RCC, TKI-related side effects and quality of life measurements in long-term survivors of cancer. Professor Schmidinger is the author or co-author of more than 50 articles in peer-reviewed journals, including *Anticancer Research*, *Journal of Immunotherapy*, *Supportive Care in Cancer*, *Oncologist*, *Breast Cancer Research and Treatment*, *British Journal of Cancer*, *Journal of Clinical Oncology*, *Cancer* and *Leukaemia & Lymphoma*. She is also the author or co-author of four books in the field of immunology and oncology, including a recent textbook on targeted agents in kidney cancer.

Physicians need to manage the risk that the outcome for patients in daily practice may not meet the expectations from

the trial, as many patients may have co-morbidities and other challenges that can impact response to treatment. Drawing on personal experience with patients, Prof Schmidinger related the important principles that should guide physicians when treating patients.

Avoiding unnecessary treatment discontinuation and maintaining drug dose are two critical factors to maximising treatment benefits for patients. Conducting clear and comprehensive discussions with patients on the subjects of dose/response and the link between certain AEs (e.g. hypertension) and outcome involves the patient in their treatment and provides them with essential information that can impact their treatment decisions.

The case of a 44-year-old woman illustrates this point. In September 2012, the patient presented with a history of cough since June 2012, fever and ECOG PS 0. A computed tomography (CT) scan revealed multiple lung lesions, a tumour in the right kidney, most likely RCC, and additional metastases in the liver, bone and pericardium. After a palliative nephrectomy (G3, pT3a, L0 and V1), she was MSKCC (Memorial Sloan-Kettering Cancer Center) and Heng-classified intermediate risk and was put on sunitinib, 50 mg once daily on 4/2 treatment cycle that same month. The patient was informed at the beginning on the incidence, severity and prophylactic measures of the side effects, as well as the possible relationship between dose/response and as a biomarker of successful outcome.

Four days after beginning treatment she was admitted to hospital with chest pain and high blood pressure. Her ECG (electrocardiogram) and cTNT (cardiac troponin T) was normal and a CT showed no evidence of embolism, but her blood pressure was 190/110 mmHg. After she was prescribed analgesics and antihypertensive agents, the treating physician recommended she discontinue sunitinib treatment or request dose reduction. The patient refused based on her understanding of the association with hypertension and efficacy and instead was prescribed additional hypertensive agents. In the end, the patient was right and she experienced a dramatic response within the first weeks of treatment, demonstrating the importance of informing patients about the role of side effects and their potential impact on outcome, as it can be critical in avoiding unnecessary treatment discontinuation.

In addition, when managing patients, physicians need to be critical of what constitutes disease progression due to drug resistance. For example, a male patient, 71 years old, was diagnosed with clear cell mRCC and underwent a nephrectomy in 1989. In December 2008, he underwent a partial resection of liver segment IV due to liver metastases, with new lesions diagnosed in August 2009. His prognosis was favourable based on MSKCC data and he was referred to the department of oncology where he began treatment on sunitinib, 50 mg once daily on 4/2 treatment cycle. He experienced grade 3 hypertension, grade 2 fatigue, and grade 1 diarrhoea and hand-foot syndrome. In November 2009, he achieved partial remission and his dose was reduced to 37.5 mg due to mucositis. He maintained partial remission and achieved complete remission in August 2010 on this dose.

Concerned about the chronic use of medicine, the patient then requested a further dose reduction to 25 mg. Fifteen months after initiating sunitinib treatment, scans indicated that he had disease progression. Instead of assuming treatment resistance, his dose was re-escalated to 50 mg. He has since achieved a PFS of 33 months, and an OS of 42+ months since starting systemic treatment. His progression was due to inappropriate dosing, not treatment resistance, highlighting the need for physicians to question when disease progression indicates apparent resistance due to dose levels or true disease resistance.

Prof Schmidinger concluded that the past 7 years of experience with targeted agents has increased physicians' knowledge substantially on how to best use these new agents, as evidenced by the rapidly growing number of long-term survivors. Therefore, as the field continues to advance, efficacy should continue to remain the primary goal, so that physicians not only select the first-line treatment with care, but must also ensure they are managing it as effectively as possible.

'*If we [. . .] try to get the best out of every treatment line, I think we will achieve survival that surpasses what we have seen in clinical trials,*' concluded Prof Schmidinger.

5. Conclusions

- Efficacy is the key driver of treatment selection.
- Guidelines provide a critical review of available evidence, helping clinicians to select the most appropriate treatment; ESMO 2012 RCC treatment guidelines acknowledge the highest level of evidence for sunitinib and temsirolimus in first-line for their respective patient populations.
- Evidence supports sequencing as TKI–TKI–mTOR inhibitor, with axitinib demonstrating proven efficacy in second-line after first-line sunitinib or a cytokine, and everolimus as the only agent recommended in a third-line setting.
- It is important that every targeted agent, whether in first-, second- and third-line, is used effectively in order to maximise their treatment benefits and obtain optimal clinical outcomes.
- Achieving the best patient outcomes depends on individualising dosing, maximising treatment duration and effectively managing AEs.

Conflict of interest statement

Manuela Schmidinger has received honoraria from, and served as a consultant for, Pfizer, Roche, Astellas, GSK and Novartis, and has received research grants from Pfizer and Roche.

James Larkin has received honoraria from Pfizer, Novartis, GSK and BMS, and research funding from Pfizer and Novartis.

Camillo Porta has acted as a speaker and/or consultant for Pfizer, Bayer-Schering, Roche, GSK, Novartis, Aveo, Astellas, Boehringer-Ingelheim and Recordati, and has received research funding from Bayer-Schering and Novartis.

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