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European Association of Urology

Editorial

Current Perspectives in Metastatic Renal Cell Carcinoma Treatment: The Role of Mammalian Target of Rapamycin (mTOR) Inhibition

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Renal cell carcinoma (RCC) is the most frequently occurring renal malignancy, and its incidence is increasing both in the United States and in parts of Europe [1–3]. Approximately 25% of patients present with metastatic RCC (mRCC) at diagnosis [4], while 20–30% of patients with localized tumours at the time of nephrectomy relapse after surgery and develop metastasis [5]. Furthermore, mRCC has a poor prognosis and is notoriously resistant to treatment with chemotherapy [2].

Research into the underlying biology and genetics of RCC has led to the identification of two main signalling cascades that have a pivotal role in the development of the disease: the von Hippel-Lindau/hypoxia-inducible factor pathway and the mammalian target of rapamycin (mTOR) pathway [6,7]. Subsequently, novel therapies have been developed to specifically target key components of these signalling pathways involved in tumour growth and angiogenesis [7]. Targeted drugs are becoming the recommended first- and second-line treatment options for patients with mRCC, replacing standard cytokine therapies that have been major constituents in the management of mRCC since the 1990s [7]. Because of their selectivity, targeted agents are generally better tolerated than standard cytotoxic treatments [8]. Results from clinical studies have shown positive efficacy in mRCC following treatment with targeted therapy such as sunitinib [9], sorafenib [10], temsirolimus [11], and the combination of bevacizumab with interferon α [12,13]; all of these agents have been approved for use in mRCC. Everolimus (RAD001), an oral mTOR inhibitor, has also shown activity in the treatment of mRCC, especially in patients who progressed on previous treatment with vascular endothelial growth factor (VEGF)–targeted therapy [14]. Everolimus was approved in March 2009 by the US Food and Drug Administration for treatment of patients with advanced RCC after failure of treatment with sunitinib or sorafenib. European Union approval for use of everolimus in patients with advanced RCC whose disease progressed on or after treatment with VEGF-targeted therapy was granted in August 2009.

Novel therapies have the potential to help reduce the clinical burden of mRCC [2], and continued development of drugs targeting different molecules and pathways involved in the pathology of mRCC have the potential to provide even more effective treatment options for clinicians and an increased benefit for patients. Prognostic and risk factors affect clinical outcomes and facilitate the selection of those patients most likely to respond to treatment with targeted therapies [15,16]. Therefore, treatment algorithms are helpful for determining which patients should receive a particular therapy regimen at a given time point, according to individual patient profiles.

This supplement discusses the current medical landscape for mRCC with particular emphasis on epidemiology, molecular tumourigenic pathways, and current and future treatment options. Recent updates to treatment algorithms (including encouraging data from trials involving everolimus) that help optimize future clinical outcomes are also

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1569-9056/$ – see front matter doi:10.1016/j.eursup.2009.07.006

discussed. Additionally, examples of experience with everolimus in clinical practice are provided.

Conflicts of interest: Dr Patard has been a consultant for Baxter, Bayer, Pfizer, Wilex, and Wyeth. Professor Bracarda has been an Advisory Board Member for Bayer-Schering Pharma, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth and has received honoraria from Novartis. Dr Ravaud is a member of the Global, European and/or French Advisory Boards for Bayer, GlaxoSmithKline, Novartis, Pfizer, Roche, and Wyeth for urologic tumours; institutional funding support for research has been obtained from GlaxoSmithKline, Novartis, and Roche. The authors did not receive honoraria or consultancy fees for writing this manuscript.

Funding support

Novartis Farma S.p.A. (Italy) funded the publication of this paper.

Acknowledgements

Medical writing assistance was provided by Simone Blagg and David Collison with funding from Novartis Farma S.p.A. (Italy).

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