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Platinum Priority – Editorial

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Time to Focus on the Rare—Encouraging Progress in the Management of Non–clear Cell Renal Cell Carcinoma

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Our misconception that renal cancer is a single disease entity that should be managed the same surgically and medically has hampered our progress in the management of non–clear cell renal cell carcinoma (nccRCC). The majority of our advances in the management of renal cancer have been in the realm of clear cell renal cell carcinoma (ccRCC). We have made relatively few strides in the non–clear cell subtypes. Once metastatic, nccRCC is characterised by resistance to traditional systemic therapies and poor survival [1–3].

The European Association of Urology (EAU) Renal Cell Carcinoma Guideline Panel conducted a systematic review of the data available on the systemic treatment of advanced nccRCC [4]. The panel concluded that there was little evidence that nccRCCs are less responsive to mammalian target of rapamycin inhibitors and vascular endothelial growth factor–targeted therapy than ccRCC, and made a weak recommendation that sunitib may be marginally better than everolimus for the systemic treatment of advanced nccRCC [4]. As a follow-on from this, in this month's issue of *European Urology*, Giles et al [5] make a compelling "call to action" for increased collaboration and research into nccRCC. They preferentially use the term rare kidney cancer (RKC), which they deem more inclusive than nccRCC. The authors highlight three key shortcomings of the current lines of investigation into RKCs and make recommendations for improvement.

First, Giles et al [5] highlight that the current approach of considering all RKCs to be one disease is flawed. RKCs encompass over a dozen histological entities that vary widely in their prognosis and response to treatments [6]. The strategy of continuing to consider them one disease is likely to lead us in to the same pitfalls as considering all RCCs to be the same, and should be abandoned. We must assess the different subtypes separately regardless of the small numbers involved.

Furthermore, we continue to use predominantly histological criteria rather than molecular/genetic profiling to classify tumours and target treatment. We now know that tumours within the same histological class behave and respond to treatment differently [4–8]. For example, response rates to foretinib (oral broad kinase inhibitor targeting MET among other receptors) were 50% in those with papillary RCC (pRCC) who had germline MET mutation, compared with 8% in those who did not have the MET mutation [7], and MET-driven pRCC has significantly better progression-free survival and overall response rates with savolitinib (selective MET inhibitor) compared with MET-independent pRCC (6.2 mo and 18% vs 1.4 mo and 0%; $p < 0.001$) [8]. We also know that the molecular patterns of tumours cross histological class boundaries. A comprehensive pan-RCC molecular analysis by Chen et al [9] shows that tumours share greater molecular similarity with tumours grouped in different histological categories. In the light of this knowledge, use of histological classification alone seems inadequate and begs two questions: (1) is our stringent adherence to established histological boundaries preventing advancement in this disease? and (2) are the overall poor outcomes of systemic treatments because of the heterogeneity of the population being studied rather than "failure" of the drugs? Perhaps we should shift to a molecular classification of tumours, for example, MET amplified, VHL altered, SDH deficient, PDL1 expressing, in addition to the traditional histological subtypes. Molecular/genetic profiling of tumours prior to inclusion in trials offers a much more comprehensive way of assessing diagnosis,

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prognosis, and treatment response [5]. PAPMET (NCT02761057) is one such trial. The availability of rapid and inexpensive mutation testing in the near future will simplify the process of molecular classification and allow targeted therapy to be just that—targeted. This shift in classification of tumours may, in turn, lead to the development of more successful combinations of targeted therapy, for example, would pRCC that has both MET and FH mutations respond best to a combination of MET kinase inhibitor (eg, cabozantinib) and vascular endothelial growth factor receptor blocker (eg, bevacizumab)?

Second, the authors allude to a lack of inclusion of RKCs in RCC trials and very few trials look at RKCs alone. In an effort to increase interest in this area, they suggest that RKCs be classified as an orphan disease. Although when bundled together, they give an incidence of >5 per 10 000 (the threshold for an orphan disease), when subtypes are considered individually they give an incidence low enough to be an orphan disease. This will encourage pharmaceutical companies to develop drugs in this niche area by taking advantage of orphan drugs legislations such as tax incentives (Europe 1999; Orphan Drugs Act 1983; Rare Diseases Act 2002).

Finally, the relatively small numbers of RKCs scattered across the world necessitates international multicentre collaboration to allow progress in this disease [4,5]. The authors suggest the use of international registries such as the International mRCC Database Consortium or the USA-based National Clinical Trials Network biorepository to centralise tissue specimens for research. In an effort to support this, they have created a portal (http://rarekidneycancer.org). This portal does not appear to be at full functionality as yet, but it has a valuable clinical trial search feature indexing over 300 clinical trials for RKCs. The use of technology to make it easier for clinicians and patients to access specialist advice and trials; enter data about treatment outcomes; and encourage patients to participate in trials will be essential for research and development into RKCs. Likewise, links to international registries through the RKC website will help. The authors recommend that we should treat RKCs in specialist centres and within clinical trials wherever possible. RKCs currently treated outside of clinical trials represent missed opportunities for development in this area.

Whilst in several aspects this paper revisits many of the conclusions and recommendations of the EAU RCC Guideline Panel review [4] and other similar reviews on the subject [10], the authors' intention to inspire action in the field of RKCs is highly laudable and deserves a reaction from clinicians, academics, and pharmaceutical companies.

Conflicts of interest: The author has nothing to disclose.

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