5 Konstantinopoulos PA, Barry WT, Birrer M, et al. Olaparib and α-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. *Lancet Oncol* 2019; published online March 14. http://dx.doi.org/10.1016/S1470-2045(18)30905-7.

6 Rehman FL, Lord CJ, Ashworth A. The promise of combining inhibition of PI3K and PARP as cancer therapy. *Cancer Discov* 2012; **2:** 982–84.

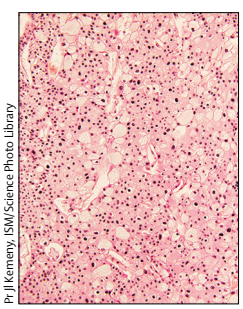
7 Liu JF, Barry WT, Birrer M, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol* 2014; **15:** 1207–14.

8 Brown JS, O'Carrigan B, Jackson SP, Yap TA. Targeting DNA repair in cancer: beyond PARP inhibitors. *Cancer Discov* 2017; **7:** 20–37.

9 Lee JM, Nair J, Zimmer A, et al. Prexasertib, a cell cycle checkpoint kinase 1 and 2 inhibitor, in *BRCA* wild-type recurrent high-grade serous ovarian cancer: a first-in-class proof-of-concept phase 2 study. *Lancet Oncol* 2018; **19:** 207–15.

10 Leijen S, van Geel RMJM, Sonke GS, et al. Phase II study of WEE1 inhibitor AZD1775 plus carboplatin in patients with TP53-mutated ovarian cancer refractory or resistant to first-line therapy within 3 months. *J Clin Oncol* 2016; **34:** 4354–61.

A well organised effort to metastatic non-clear-cell renal cell carcinoma



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Our understanding of renal cortical tumours and their variable metastatic potential has dramatically evolved over the past 25 years, with concurrent advances in pathology, molecular biology, and genomics. What was once considered a single disease with different histopathological features (eg, chromophilic or granular) is now understood to be a heterogenous group of more than 30 tumours with distinct genomic and metabolic defects and clinical behaviours ranging from benign, to indolent with limited metastatic potential, to highly malignant and metastatic. Conventional clear-cell renal cell carcinoma accounts for 70% of renal cortical tumours that metastasise, and is characterised by a loss of chromosome 3p with dysregulation of the hypoxia inducible factor α pathway with subsequent stimulation of downstream growth and angiogenic factors that promote growth, progression, and metastases of renal cancer.[1] Clear-cell renal cell carcinoma and its molecular pathways have been the focus of randomised and prospective clinical trials of cytokines, tyrosine kinase inhibitors, mTOR inhibitors, and immunologically active checkpoint blockade inhibitors, alone or in combination, with a dramatic three-fold increase in median overall survival achieved in the past decade depending on risk group.[2]

Despite the exciting progress with clear-cell renal cell carcinoma, an unmet oncological need exists for the 30% of renal cortical tumours termed non-clear-cell renal cell carcinoma. Non-clear-cell renal cell carcinoma includes papillary (*MET* gene mutations and chromosome 7 amplifications), chromophobe (numerous chromosomal losses and altered p53), distal nephron (collecting duct, renal medullary), translocation, and tumours with distinct metabolic derangements (fumarate hydratase and succinate dehydrogenase germline deficient). Some non-clear-cell renal cell carcinomas cannot be precisely diagnosed and are called unclassified. The clear-cell and non-clear-cell renal cell carcinomas can have sarcomatoid differentiation, which is associated aggressive metastatic behaviour, decreased survival, and treatment refractoriness. When oncologists initially attempted to treat patients with metastatic non-clear-cell renal cell carcinoma and its sarcomatoid variants, treatment with cytokines, systemic chemotherapies, and tyrosine kinase inhibitors all led to dismal results in single-centre reports with fewer than 10% of patients responding and, if so, for only a matter of a few months.[3–5] Despite using similar tyrosine kinase and mTOR inhibitor therapies known to be effective in clear-cell renal cell carcinoma, 252 patients with non-clear-cell renal cell carcinoma had worse overall survival when compared with metastatic clear-cell renal cell carcinoma (12·8 months [95% CI 11·0–16·1] *vs* 22·3 months [20·7–23·5]) in a large study[6] published by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) in 2013.

In *The Lancet Oncology*, Nieves Martínez Chanzá and colleagues[7] understood that small, single-institutional studies of non-clear-cell renal cell carcinoma would not provide a sufficient foundation to make meaningful progress in this group of advanced tumours. They organised, around a central database, an international consortium of oncologists from 22 centres and found 112 patients with metastatic non-clear-cell renal cell carcinoma of which 66 (59%) were papillary, 17 (15%) translocation, 15 (13%) unclassified, ten (9%) chromophobe, and four (4%) collecting duct. They initiated cabozantinib at 60 mg per day, a small molecule tyrosine kinase inhibitor,

which targets the VEGF receptor, as well as MET and AXL tyrosine kinase receptors, which might lead to resistance to antiangiogenic drugs. This choice was probably made because data from a large prospective randomised clinical trial of metastatic renal cell carcinoma progressing after tyrosine kinase inhibitor treatment indicated that cabozantinib outperformed the mTOR inhibitor everolimus in this second-line setting with median progression-free survival of 7·4 months (95% CI 5·6–9·1) versus 3·8 months (3·7–5·4).[8] In the study by Chanzá and colleagues, of the 112 heterogeneous non-clear-cell renal cell carcinoma patients, 26 (23%) did not have surgical resection of the primary tumour, all but nine (8%) had intermediate-risk or poor-risk disease, and 87 (78%) had either previous tyrosine kinase inhibitor or immunotherapy exposure. The proportion of patients who achieved an objective response was 30 (27%) of 112 (*MET*-driven papillary renal cell carcinoma and altered p53 in chromophobe renal cell carcinoma subtypes had higher proportions of responses), one patient with papillary renal cell carcinoma achieved a complete response, median time to treatment failure was 6·7 months (95% CI 5·5–8·6), and the median overall survival was 12·0 months (9·2–17·0). 51 (46%) patients required a dose reduction, but only five (7%) patients discontinued therapy because of toxicity.

Despite the shortcomings of a retrospective cohort study, absence of central pathology and radiology review, and the complex mixture of non-clear-cell tumour histology, this study provides clinicians with credible information that can guide treatment of these notoriously difficult tumours. Because of the rarity of these tumours, large-scale prospective trials that are successful in metastatic clear-cell renal cell carcinoma will be difficult, if not impossible, to do. Yet, the determination of a such a large group of oncologists to provide real-world care to their patients while obtaining and analysing these data is truly remarkable. Extending their work and organisational skills to more centres, awaiting the arrival of more effective systemic agents, and fine-tuning drug selection based on genomics and other biomarkers might allow these investigators the opportunity for future and increasingly effective attempts to tackle these particularly lethal forms of kidney cancer.

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1 Signoretti S, Flaifel A, Chen YB, Reuter VE. Renal cell carcinoma in the era of precision medicine: from molecular pathology to tissue-based biomarkers. *J Clin Oncol* 2018; **36:** 3553–59.
2 Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. *New Engl J Med* 2017; **376:** 354–66.
3 Motzer RJ, Bacik J, Mariani T, Russo P, Mazumdar M, Reuter V. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear cell histology. *J Clin Oncol* 2002; **20:** 2376–81.
4 Molina AM, Tickoo SK, Ishill N, et al. Sarcomatoid-variant renal cell carcinoma: treatment outcome and survival in advanced disease. *Am J Clin Oncol* 2010; **185:** 433–38.
5 Molina AM, Feldman DR, Ginsberg MS, et al. Phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma. *Invest New Drugs* 2012; **30:** 335–40.
6 Kroeger N, Xie W, Lee JL, et al. Metastatic non-clear cell renal cell carcinoma treated with targeted therapy agents: characterization of survival outcome and application of the International mRCC database consortium criteria. *Cancer* 2013; **119:** 2999–3006.
7 Martínez Chanzá N, Xie W, Asim Bilen M, et al. Cabozantinib in advanced, non-clear-cell renal cell carcinoma: a multicentre, retrospective, cohort study. *Lancet Oncol* 2019; published online Feb 28. http://dx.doi.org/10.1016/S1470-2045(18)30907-0.
8 Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in 662 advanced renal cell carcinoma. *New Engl J Med* 2015; **373:** 1814–23.

Predicting recurrence in patients with localised renal cell carcinoma after nephrectomy

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Although most patients who undergo nephrectomy for clear cell renal cell carcinoma for cT1–T3 N0 disease achieve a complete response, up to 30% will recur.[1] Targeted agents and immune checkpoint inhibitors exist that are clinically beneficial for the treatment of metastatic disease and thus there is a motivation to ascertain whether these also provide a benefit in the adjuvant setting.[2] However, successful use of adjuvant therapy depends on several premises. The first is that the benefits of treating those who need therapy (ie, patients with micrometastatic disease) outweigh the risks of treating those whose disease was organ confined and in whom nephrectomy alone had already been successful. The second consideration is that a survival benefit with