but occult disease represent a minority of patients with relapsed prostate cancer, and with the current stage migration arising from the use of more sensitive staging techniques, such as prostate-specific membrane antigen (PSMA)-PET isotope scanning, even fewer men will fall into this category. Will funding approval based on the findings from this trial encompass men affected by this stage migration, or will a further study be required? Also, focused local treatment of oligometastases (eg, with radiation therapy) might be effective in delaying disease progression,[5] and is as well tolerated, and potentially cheaper, than systemic therapy. In more advanced metastatic disease, the benefit of using this class of drugs has been shown both before and after docetaxel chemotherapy.[6–8] How are these treatment approaches best combined to optimal effect?

Conversely, there is a question about whether this class of drugs should be introduced at the start of the disease trajectory. There is long-standing evidence that treating disease earlier rather than later, and hence treating smaller volume disease before progression to symptomatic disease, improves overall survival.[9,10] This principle underlies the use of adjuvant therapy to eliminate microscopic disease and prevent subsequent relapse. The evidence that these drugs are active in castration-resistant prostate cancer is a strong indicator that they should be tested in early disease settings. There are only two randomised trials of the use of these drugs in the adjuvant setting: a study of apalutamide (NCT02531516), with analysis expected in 2026; and a study of enzalutamide with radiotherapy in men with high-risk disease (NCT02446444), which has a primary endpoint of overall survival at 5 years and a secondary endpoint of HRQOL, with analysis expected in 2021. The latter trial includes an exemplary component not included in trials to date, but which is crucial to the appropriate use of new drugs: an analysis of incremental cost-effectiveness to manage the pressures from effective novel therapies on health-care resources.

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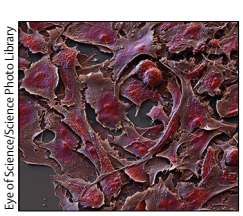
Extending the scope of PARP inhibitors in ovarian cancer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In the past decade, trials with inhibitors of oral poly (ADP-ribose) polymerase (PARP), a key enzyme involved in the repair of DNA damage, have led to a major change in the treatment of advanced ovarian cancer. A key element of the success of this class of drug is deficiency in the homologous recombination repair (HRR) pathway, which repairs DNA double-strand breaks. This deficiency is often seen in *BRCA*-mutated tumours, since functioning BRCA proteins have a major role in preserving the complex DNA repair pathway. However, other mechanisms apart from *BRCA* mutations can also result in HRR pathway alterations and consequently lead to a clinical benefit from PARP inhibitors.[1] Study of DNA damage response and manipulation of the process is now recognised as an important area of research and could lead to better cancer treatments.[2] Precise measurement of HRR is difficult, but in ovarian cancer it is most closely related to the platinum sensitivity of the

tumour. Tumours that become platinum resistant—an inevitable consequence of recurrence—rarely respond to PARP inhibitors.

Olaparib, niraparib, and rucaparib are PARP inhibitors used to treat ovarian cancer. They are more active in tumours with a *BRCA* mutation but are also licensed as maintenance therapy following a response to platinum-based treatment. In patients who have varying degrees of HRR pathway alterations, treatment with these drugs prolongs the time to disease progression. Most tumours eventually become resistant to PARP inhibitors, although a small cohort of patients continue without disease progression for many years.[3]

Repair of both double-strand and single-strand DNA breaks is a complex process, involving several proteins and more than one repair pathway. Similarly, a wide range of mechanisms underlie tumour resistance to PARP inhibitors, and many strategies are being pursued to prevent or overcome it.[4] In *The Lancet Oncology*, Panagiotis Konstantinopoulos and colleagues[5] used the PI3K inhibitor alpelisib in combination with the PARP inhibitor olaparib in patients with epithelial ovarian cancer and breast cancer. The rationale for this combination was that PI3K inhibition has been shown to lead to a downregulation of BRCA1 and BRCA2 proteins, increasing the degree of HRR deficiency.[6] In the absence of competent repair pathways, cells become sensitised to PARP inhibitors. This group previously tested the combination of olaparib and cediranib, a VEGF receptor inhibitor, and found a synergistic effect of the two molecularly targeted drugs, but this was in a population of patients with tumours likely to be sensitive to platinum-based drugs and therefore PARP inhibitors.[7] In the phase 1 study of alpelisib and olaparib in the current issue of *The Lancet Oncology*, nearly all the patients with epithelial ovarian cancer had platinum-resistant or refractory disease (26 [93%] of 28), and thus they were unlikely to benefit from a PARP inhibitor, especially in the absence of a *BRCA* mutation. The most common treatment-related adverse events reported in the study were generally manageable: hyperglycaemia (five [16%] of 32 patients), nausea (three [9%]), and increased alanine aminotransferase concentrations (three [9%]). Although toxicity was the primary endpoint, the response to this combination was much higher than would be expected from either drug alone in this group of patients. Most patients had ovarian cancer (four had breast cancer); of the 28 patients with epithelial ovarian cancer included in the analysis, ten (36%) had a partial response and their median duration of response was 5·5 months (IQR 2·2–6·8). 14 (50%) of 28 patients with epithelial ovarian cancer had stable disease.

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Around 50% of high-grade serous ovarian tumours are estimated to have a degree of HRR deficiency and are likely to benefit from PARP inhibitors.[3] However, many tumours will not respond to initial treatment, or will eventually become resistant to platinum-based drugs. Exploiting DNA damage response pathways, as is the case with PARP inhibitors, requires a detailed knowledge of these mechanisms in cells.[8] Other approaches currently being explored include the use of inhibitors of other pathways (eg, CHK1), alone in *BRCA* wild-type platinum-resistant tumours or—in the case of the Wee1 inhibitor—in combination with chemotherapy.[9,10] Although developing new therapies for patients with platinum-resistant ovarian cancer remains important, more research is needed to enhance the activity of PARP inhibitors in patients who would have otherwise only had a short-term benefit. Similarly, reintroducing a PARP inhibitor following progression on treatment by adding another molecularly targeted agent (such as a PI3K inhibitor) is an attractive strategy, as a growing number of patients have become resistant to PARP inhibitors. Identifying targetable pathways and more rationally designed trials with DNA damage response inhibitors is needed to extend the substantial clinical benefits that have been seen with PARP inhibitors.

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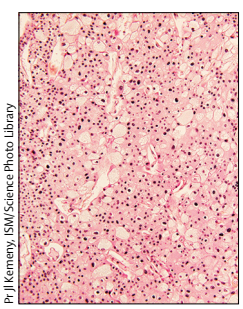
A well organised effort to metastatic non-clear-cell renal cell carcinoma



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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,