Evidence has been accumulated since the 1970s and results of large population-based studies have documented that childhood cancer survivors have a 3 times higher risk of being diagnosed with a second malignancy following cancer treatment than the general population.[7] Furthermore, overwhelming evidence in adult patients with cancer suggests that immunosuppression increases the risk of post-transplant cancer.[8] However, no evidence is available concerning the risk of a subsequent cancer in childhood cancer survivors when treated with immunosuppressive agents.

Childhood cancers differ substantially from adult cancers, in tissue origin, risk factors, and treatment protocols.[9] This raises the question of whether immunosuppressive protocols should be modified in childhood cancer survivors, or whether these survivors should be treated as patients with adult cancers.

Elevated risk of cancer in patients receiving immunosuppressive medications has been reported among adult kidney transplant recipients with risk estimates two to 12 times higher than population comparisons, whereas a risk 30 times higher has been reported in childhood transplant recipients.[10] These findings might indicate that childhood cancer survivors who have had a transplant in childhood have a very high risk of second cancers, but for those having the transplant later in life, cancer risk is still unknown.

More research should be vigorously pursued to learn about appropriate immunosuppression in this high-risk group. From a clinical perspective, until this knowledge is available, monitoring for de novo or recurrent malignancies to prevent or detect and treat cancers at an earlier stage is of primary concern.

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Targeting lineage plasticity in prostate cancer

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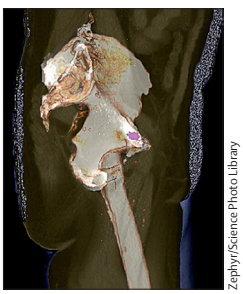
In cancer biology, the term lineage plasticity denotes a process by which cancer cells change from one morphological and functional cell type to another (and back), under the influence of particular environmental pressures. In the context of prostate cancer therapy, lineage plasticity refers to a shift in cellular phenotype from an androgen receptor-dependent adenocarcinoma to an androgen receptor-indifferent neuroendocrine or small-cell carcinoma, which might occur as a consequence of ongoing androgen deprivation therapies.[1] These neuroendocrine prostate cancers are difficult to define histologically (except in the case of pure small-cell prostate cancers) but are clinically characterised by inadequate responses to androgen deprivation therapy and novel hormonal therapies. Early data have suggested that patients with these neuroendocrine prostate tumours might also have suboptimal responses to taxane chemotherapies, perhaps showing greater sensitivity to platinum agents.



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In an effort to better characterise these androgen receptor-indifferent prostate cancers, the MD Anderson group has previously proposed clinical criteria to define this entity, which they have termed aggressive variant prostate cancer.[2] For aggressive variant prostate cancer to be diagnosed, patients must exhibit at least one of the following seven characteristics: histological small-cell prostate cancer, visceral-only metastases, osteolytic bone metastases, bulky (>5 cm) lymphadenopathy or primary tumour, low prostate-specific antigen concentration (<10 ng/mL) plus high-volume (≥20) bone metastases, elevated lactate dehydrogenase or carcinoembryonic antigen levels, or short response (<6 months) to primary androgen deprivation therapy.

In *The Lancet Oncology*, Paul Corn and colleagues[3] report the results of a randomised phase 1–2 trial, which compared the activity of cabazitaxel (25 mg/m^2) alone or combined with carboplatin (area under the curve 4 mg/mL per min) in men with metastatic castration-resistant prostate cancer, with a secondary analysis stratified by presence or absence of aggressive variant prostate cancer features. The study hypothesis was that the addition of a platinum to a taxane would improve outcomes in men with metastatic castration-resistant prostate cancer. The study showed that median progression-free survival was longer in men receiving cabazitaxel plus carboplatin versus cabazitaxel alone (7·3 months [95% CI 5·5–8·2] *vs* 4·5 months [3·5–5·7], hazard ratio 0·69 [0·50–0·95], p=0·018). As hypothesised, the added value of the platinum agent was greatest in men with clinical aggressive variant prostate cancer features (hazard ratio 0·58, 95% CI 0·37–0·89, p=0·013) compared with those without aggressive variant prostate cancer features (hazard ratio 0·74, 95% CI 0·46–1·21, p=0·23), suggesting that the aggressive variant prostate cancer phenotype was the driver of this clinical benefit.

The authors then explored molecular definitions of aggressive variant prostate cancer, using immunohistochemical and circulating tumour DNA (ctDNA) analyses. Previous studies from the MD Anderson group had suggested that inactivation or loss of the tumour suppressor genes *TP53*, *PTEN*, and *RB1* (at least two of the three) was associated with the clinical features of aggressive variant prostate cancer.[4] Experimental data have confirmed these findings, particularly with respect to combined alterations in *TP53* and *RB1*, which are strongly linked to prostate cancer lineage plasticity and anti-androgen resistance.[5,6] In this study, the molecular classifications of positivity for aggressive variant prostate cancer by immunohistochemistry or ctDNA were even more strongly indicative of platinum benefit than the clinical aggressive variant prostate cancer criteria. To this end, the added progression-free survival benefit of carboplatin was only observed in men who were positive for aggressive variant prostate cancer by immunohistochemistry (hazard ratio 0·29, 95% CI 0·10–0·85) and not in patients who were not (1·44, 0·66–3·13), with a significant statistical interaction ($p_{interaction}$=0·0024). Similarly, the additional benefit of carboplatin was restricted to those with, but not without aggressive variant prostate cancer by ctDNA criteria ($p_{interaction}$=0·029). These data not only suggest that patients with metastatic castration-resistant prostate cancer without molecular aggressive variant prostate cancer features might not require the addition of carboplatin to cabazitaxel, but also that such patients might be harmed by the added side-effects of combination chemotherapy.

The results of this study raise several questions. First, in men with clinically defined or molecularly defined aggressive variant prostate cancer, is a taxane agent even needed? Is it possible, for example, that these patients are more resistant to taxane agents? Or, alternatively, might they be so sensitive to platinum that combination chemotherapy is not required? Second, if a platinum drug is the preferred approach, then which platinum agent is best: carboplatin, cisplatin, or something else? Because patients with aggressive variant prostate cancer appear to respond better to DNA-damaging agents, perhaps a platinum should be combined with a topoisomerase inhibitor for optimal results, although this might cause greater toxicity. Also, might oral platinum agents, such as satraplatin, have a role?[7] Third, what other types of patients with metastatic castration-resistant prostate cancer might benefit less from taxane drugs and more from platinum agents? Several preliminary publications have suggested that tumours with DNA-repair-deficiency mutations, particularly *BRCA2* alterations, might derive a greater benefit from platinum chemotherapy.[8,9] Although improved outcomes were not observed in the combination group of the this trial in men with *BRCA2* alterations on ctDNA analysis, this hypothesis deserves

further study in dedicated randomised trials. Finally, the biological mechanisms underpinning potential platinum sensitivity in prostate cancers undergoing lineage plasticity are unclear and require further study. It is also unknown whether platinum treatment reverses lineage plasticity after it has occurred, and whether this might sensitise these cancers to androgen receptor-directed therapies again.

Optimal management of aggressive variant prostate cancer represents an unmet medical need, and new clinical trials specifically addressing this entity are clearly indicated. This study adds to the body of evidence suggesting that such patients need to be managed differently. A randomised phase 3 trial testing the platinum–taxane combination in patients with metastatic castration-resistant prostate cancer and molecularly defined aggressive variant prostate cancer is planned.

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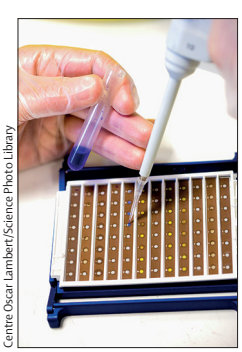
A new screening tool for FGFR inhibitor treatment?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Major advances in targeted therapy and immunotherapy has revolutionised the treatment of cancer. With the advent of personalised medicine, a one-size-fits-all approach is no longer appropriate.[1] Our aim to personalise cancer treatment based on the molecular landscape of tumours has led to development of biomarker-driven strategies to improve treatment outcomes.

The mammalian FGFR family consists of four tyrosine kinase receptors (FGFR1–4) with 22 distinct ligands identified to date.[2] Activation of FGFR results in receptor dimerisation, transphosphorylation of receptor kinase domains, and activation of downstream RAS–MAPK, PI3K–AKT, and STAT signalling pathways. FGFR signalling is involved in cellular proliferation, differentiation, and migration, thus aberrant activation of the pathway due to FGFR amplification, mutations, or gene fusions has been implicated in pathogenesis of several cancers, such as *FGFR3* mutation in urothelial carcinoma.[3] Considering the fact that FGFR is a potential therapeutic target, several non-selective FGFR tyrosine kinase inhibitors such as dovitinib and lenvatinib have been investigated. In March, 2015, lenvatinib was approved by the US Food and Drug Administration for metastatic, radioactive iodine-refractory differentiated thyroid carcinoma.[4] Since non-selective FGFR tyrosine kinase inhibitors target other related receptors such as vascular endothelial growth factor receptors and platelet-derived growth factor receptors in addition to FGFRs, their use is limited by the occurrence of off-target side-effects that result in cardiovascular and liver toxicities.[2,5] This limitation led to the development of selective FGFR tyrosine kinase inhibitors—ie, FGFR1–3 inhibitors, FGFR4 inhibitors, and pan-FGFR inhibitors. In general, selective FGFR inhibitors have a favourable safety profile. On April 12, 2019, erdafitinib was approved by the US Food and Drug Administration for patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* or *FGFR2* genetic alterations who had progressed on platinum-based