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ACKNOWLEDGEMENTS: The authors are supported by a Cancer Research UK Centre grant, an Experimental Cancer Medicine Center grant, National Institute for Health Research Biomedical Research Center funding, and support from Movember, Prostate Cancer UK and the Prostate Cancer Foundation.

Perhaps more than any other malignancy, systemic therapy for metastatic prostate cancer has focused on a single oncogenic target: the androgen receptor (AR). Dramatic regressions following castration occur in the vast majority of patients, first demonstrated in the seminal work of Charles

Huggins in 1941 [Huggins 1941]. Even in the castration resistant setting, the cancer remains androgen driven in most patients [Ang 2009], a concept that has been unequivocally proven by the clinical success of abiraterone acetate, and enzalutamide. Even docetaxel, a broad spectrum antineoplastic, is thought to exert at least part of its effect against prostate cancer through preventing microtubule dependent translocation of the AR from the cytoplasm to the nucleus [Thadani-Mulero 2012]. Yet despite successes in targeting the AR, resistance invariably develops to these agents, with recent evidence suggesting this is due in at least some cases, maddeningly, to ongoing activity of the AR [Buttigliero 2015]. Indeed the fact that resistance and disease progression are frequently heralded by a rising PSA indicate ongoing activity of the AR. Hence, interest in targeting this pathway remains.

Recently a number of novel therapies that either directly or indirectly target the AR have been developed with purported theoretical advantages over abiraterone or enzalutamide: orteronel and VT464 offer more selective inhibition of CYP17 C17,20-lyase with less effect on 17α-hydroxylase compared to abiraterone, potentially decreasing mineralocorticoid toxicity, with VT-464 not requiring steroid co-administration; galeterone acts as a dual inhibitor of C17,20-lyase and AR antagonist, and also doesn't require steroid co-administration; and ARN-509, an AR antagonist that shows higher potency and lower CNS penetration than enzalutamide. All of these agents are currently undergoing evaluation in clinical trials [Bambury 2015].

In this month's issue of European Urology, Massard and colleagues address another addition to the field, ODM-201. Like enzalutamide and ARN-509, it functions as an AR antagonist by interacting with the ligand binding C-terminus domain, and prevents nuclear translocation of the

AR. However, it has a higher AR binding affinity than either enzalutamide or ARN-509, it is active against some forms of mutant AR which enzalutamide and ARN-509 are not, and it does not cross the blood brain barrier and as such it is not thought to predispose to seizures [Fizazi 2014; Fizazi 2015]. In order to understand the current study, one must be familiar with the clinical development of ODM-201. In brief, the phase I/II ARADES trial [Fizazi 2014] found that doses of ODM-201 up to 1800mg daily were well tolerated with no dose-limiting toxicities in patients with metastatic CRPC and no maximum tolerated dose identified, with the most common toxicities being fatigue, diarrhea, arthalgias, back pain, and headache. Patients were then randomized to receive 200mg, 400mg, or 1400mg of ODM-201 daily, with three different cohorts of patients represented in each dose level: chemotherapy- and CYP17 inhibitor-naive; post chemotherapy and CYP17 inhibitor-naive; and post CYP17 inhibitor. PSA and objective response rates were similar across the dose levels, with chemotherapy- and CYP17 inhibitor-naive patients unsurprisingly showing the highest response rates. Based on this data, the randomized phase III ARAMIS trial of ODM-201 versus placebo in high-risk non-metastatic CRPC (NCT02200614) was planned, with a selected daily dose of 1200mg; however, the aforementioned ARADES trial used 100mg capsules, therefore patients in ARAMIS would be required to take an unpalatable twelve capsules per day. Hence the current trial, which evaluated the comparative pharmacokinetic profiles of two different 300mg tablets with the original 100mg capsules, followed by an extension phase where thirty chemotherapy- and CYP17 inhibitor-naive patients were treated with a daily dose 1200mg of ODM-201.

Importantly, this trial showed similar bioavailability between the tablets and capsules when taken with food, with a doubling of plasma exposure when either tablet formulation is taken with food

compared to the fasted state. Furthermore, this study confirmed the previously demonstrated safety profile, with no dose reductions and only grade 1 treatment related adverse events. In the extension phase clear evidence of antitumour activity was seen with with ≥50% PSA declines in 83%, objective radiographic response in 29% of those evaluable, and a median time to radiographic progression of 66 weeks.

This trial serves as an important bridge between the ARADES and the ongoing ARAMIS trials by demonstrating equivalency between three different formulations of ODM-201, meaning that patients in ARAMIS will thankfully only have to swallow four pills a day instead of twelve, and can still expect the same safety and efficacy previously demonstrated with this drug. While the authors highlight that no seizures have been seen is this trial or ARADES despite the inclusion of patients with prior or elevated risk of seizure, the small number of patients studied to date prevent one from making any firm conclusions about this. And while the theoretical lower risk of seizure is interesting, it is likely of little clinical relevance. Seizures due to enzalutamide are rare, at least in patients without risk factors. The frequency in patients at risk is currently unknown, but is currently being evaluated in an ongoing phase IV trial (NCT01977651). While it is true that these patients are currently precluded from receiving enzalutamide, they can usually be safely treated with abiraterone. Many health jurisdictions only allow an individual to receive one of these agents, and indeed current evidence doesn't support their sequential use [Bianchini 2014; Azad 2015]. The efficacy analysis done frankly doesn't add any more information to what has previously been demonstrated in ARADES. While the response rates seen in this trial are impressive, the only reliable conclusion that can be drawn is that this drug warrants further evaluation, a conclusion that was already made after ARADES.

In many ways, the development of ODM-201 highlights the recent successes and future challenges for drug development in CRPC. Prior to the introduction of abiraterone and enzalutamide, the response rates seen with ODM-201 would have been considered staggering, but now this kind of activity is expected of novel AR targeting drugs. And while ODM-201 is clearly highly active, it is likely to struggle to find regulatory approval, a fact that is highlighted by the example of orteronel, another highly active AR targeting drug that failed to demonstrate an OS advantage in metastatic CRPC in two large placebo controlled phase III trials, likely due to the availability of abiraterone and enzalutamide to patients upon progression [Fizazi 2015, Saad 2015]. Hence the developers of ODM-201 appear to have learned from this cautionary tale, and are seeking to develop this drug in a space not already filled by abiraterone or enzalutamide, in non-metastatic CRPC, and by targeting a primary endpoint, metastases free survival, that will not to be affected by post-progression therapies. With the availability of approved agents with overlapping mechanisms of action, it has become extremely difficult to demonstrate an OS advantage. And since there are no accepted surrogate endpoints for OS in CRPC, the bar is now set much higher. Thus new agents are now being evaluated either in combination studies, select patient niches, or biomarker selected populations, as opposed to traditional placebo controlled trials in unselected populations. While ODM-201 is clearly well tolerated and highly active, whether it will succeed in the long, hard climb to regulatory approval remains to be seen.

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