Systemic Treatment of Advanced Papillary Renal Cell Carcinoma: Where Next?

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Bernard Escudier and colleagues are to be congratulated for successfully recruiting and reporting the RAPTOR study in this edition of EJC (*1*). This phase 2 trial evaluated the efficacy and safety of the orally administered mammalian target of rapamycin (mTOR) inhibitor everolimus in papillary renal cell carcinoma (pRCC). Whilst everolimus and the related intravenously-administered agent temsirolimus are approved globally for the treatment of RCC, the evidence base for these approvals is contingent on phase 3 studies conducted predominantly in clear cell RCC (ccRCC), the commonest (~75% of cases) histological subtype of the disease (*2*). Historically, non-clear cell RCC has to some extent been regarded as homogeneous from the perspective of systemic therapy, but in fact it is heterogeneous with papillary and chromophobe subtypes the commonest entities, accounting for roughly 10% and 5% respectively of the overall incidence of RCC. Rarer subtypes include medullary, translocation and collecting duct; it is further noteworthy that 5-10% of kidney cancers cannot be assigned by pathologists into one of these categories and as such are labelled as unclassifiable. Indeed a major strength of the RAPTOR study is central pathology review and as such it is striking that a diagnosis of pRCC on local pathology review was overturned on central review in just over 20% of patients.

What has the RAPTOR study told us apart from the importance of central pathology review in pRCC? First, everolimus was, consistent with experience to date in RCC, relatively well tolerated. Second, some anti-tumour activity was evident, although it is not easy in single arm phase 2 studies to be confident about the relative level of efficacy in comparison with other available agents. Two prospective randomised phase 2 studies in non-clear cell RCC, ASPEN and ESPN, are of interest in this regard. Both compared everolimus with the multi-targeted kinase inhibitor sunitinib, a standard of care 1st line treatment option for advanced clear cell RCC. An interim analysis of ESPN conducted after the enrolment of 68 patients of whom 27 (40%) had papillary RCC showed a survival detriment in the everolimus arm and led to early closure of the trial. At final analysis, median survivals were similar at around 15 months for both arms with median progression-free survival also similar at around 5 months

for the overall group and also for the papillary subset. In ASPEN, 108 patients were randomised, of whom 70 (65%) had papillary histology. In the overall group progression free survival favoured sunitinib (HR 1.4, p=0.16, median 8.3 versus 5.6 months) with heterogeneity noted as a consequence of both prognostic risk group (favouring everolimus in poor risk disease but sunitinib in good and favourable risk) and histological subtype (favouring sunitinib for papillary histology). Taken together these data show that efficacy outcomes in pRCC with sunitinib and everolimus are inferior to those in ccRCC but that the preferred order of therapy is probably sunitinib followed by everolimus.

Perhaps the real take home message from the RAPTOR, ASPEN and ESPN studies is the need to go back to basics when designing clinical trials in pRCC and indeed in other histological subtypes of the disease. There is ample molecular information to help us make predictions about therapeutic efficacy. Critically, despite their common cell of origin in the proximal tubule, pRCC and ccRCC are molecularly distinct cancers. ccRCC is characterised by the loss of the Von Hippel Lindau (VHL) protein, and the resultant upregulation of the hypoxia-inducible factor (HIF) pathway provides a sound rationale for VEGF inhibition with drugs such as sunitinib in this RCC subtype. On the other hand, VHL alterations are not reported in papillary RCC, thus there is no particular reason to predict *a priori* that sunitinib or similar agents should have significant activity in pRCC. Indeed, there is no single gene alteration that is pervasive in pRCC (*3, 4*) in the way that VHL is in ccRCC. As such it is unlikely that there will be a suitable targeted therapy approach that fits most pRCCs.

A recent report from the Cancer Genome Atlas (*5*) has revealed significant heterogeneity within pRCC, with multiple, molecularly distinct sub-groups defined by genetic, expression and methylation patterns. Around 80% of type 1 pRCCs are characterised by mutations of the MET gene or gain of chromosome 7 where MET is located and Laurence Albiges and colleagues have previously noted that MET amplification correlates with increased MET expression (*6*). Foretinib, a MET/VEGF inhibitor showed a high response rate in patients with germline mutations in MET, however this was not the case for somatically acquired MET mutations (*7*), suggesting that the surrounding genetic/signaling pathway context plays a role and that we cannot extrapolate from the germline setting. Type 2 pRCC presented a more complex picture with multiple individual subgroups (*5*), one of which was characterised by mutation or promoter methylation of CDKN2A and associated with poor

survival. Another subtype was defined by mutations in chromatin modifiers including SETD2, PBRM1 and BAP1. Mutations in these genes are also seen in ccRCC and therefore represent a potentially common therapeutic target for both RCC subtypes. It is worth noting however that such mutations in ccRCC are accompanied by the loss of the short arm of the chromosome 3 (3p) and therefore loss of the wild type allele (SETD2, PBRM1 and BAP1 are all located on 3p) leading to complete inactivation of these genes, whilst in pRCC the wild type allele is frequently preserved (*5*). These differences could lead to different responses to the targeting of chromatin modifiers. Other subtypes were characterised by the CpG island methylator phenotype (CIMP) which showed a Warburg-like metabolic shift and associated with poor prognosis, increased expression of the NRF2-antioxidant response element (ARE) pathway and up regulation of the Hippo pathway through mutations in NF2. Targeting any of these pathways could represent therapeutic opportunities in pRCC. Finally, gene mutations in pRCC also include components of the mTOR pathway, such as TSC1/2. In the context of ccRCC these alterations have been linked to extreme responders to mTOR therapy in a retrospective analysis (*8*).

A further issue that may need consideration is intratumour heterogeneity, which has been well characterised in clear cell RCC through multi-region tumour profiling (*9*). Analyses to date have shown that loss of the short arm of chromosome 3 and VHL mutations are the only consistently clonal events in clear cell RCC, although it remains to be seen whether this is true of all disease stages. This degree of intratumour heterogeneity is important because many other reported driver events are subclonal i.e. do not affect every region of the tumour over space and time. The extent of intratumour heterogeneity in pRCC has been analysed in 4 cases and the most advanced tumour displayed extensive subclonal diversification involving the STED2 gene. Given this observation further studies which incorporate multi-region tumour profiling are necessary to provide a rational basis for attempting to target the driver events revealed in recent studies (*3*-*5*). As such perhaps a tractable future approach to clinical trial design in this disease lies with molecular characterisation of each tumour and matching against drugs with potentially appropriate mechanisms of action in a ‘basket’ type trial design. This poses considerable logistical challenges but if we are to improve outcomes for patients with this and other rare tumour types and subtypes, these are challenges that the community must address.

Conflict of Interest Statement

James Larkin is a non-remunerated consultant for Novartis, Pfizer, Bristol Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Roche/Genentech, Glaxo Smith Kline (GSK) and Eisai and receives institutional research support from Pfizer, BMS, Novartis and MSD.

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