Welcome to the 6th issue of Renal Cancer Research Review.

The leading article explores first-line immuno-oncology combination therapies in metastatic renal cell carcinoma in a real-world setting. The study compared immuno-oncology/VEGF inhibitor combinations with ipilimumab and nivolumab. Reassuringly the outcomes of these combinations seem similar to those reported in clinical trials and again are similar to each other. Another study of targeted therapies for advanced renal cell carcinoma in a real-world setting found worse survival with more treatment discontinuation due to toxicity than in clinical trials. The paper highlights ongoing refinement in practice is warranted long after a drug is registered to ensure the benefits in clinical trials are effectively translated into routine clinical practice. There are also a number of articles in this issue with a focus on surgical outcomes. A British audit reports closer guideline adherence was exhibited by higher surgical volume centres. In addition treatment of T1 tumours using partial nephrectomy rather than radical nephrectomy increased with increasing high volume, and complication rate decreased with increasing high volume. Results from the SURTIME study suggests patients with metastatic kidney cancer do not have more surgical complications irrespective of whether they are treated with sunitinib before or after surgery. A prospective study reports during extended follow up the majority of small renal masses in patients on active surveillance display indolent behaviour and the risk of progression to metastatic disease remains low. I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,
Dr Craig Gedye
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First-line immuno-oncology combination therapies in metastatic renal-cell carcinoma: Results from the International Metastatic Renal-cell Carcinoma Database Consortium

Authors: Dudani S, et al

Summary: The study compared 113 metastatic renal-cell carcinoma (mRCC) patients treated with immuno-oncology (IO)/vascular endothelial growth factor (VEGF) inhibitor combinations and 75 treated with ipilimumab and nivolumab. For IO+VEGF combinations versus ipilimumab/nivolumab, first-line response rates were 33% versus 40%, time to treatment failure was 14.3 versus 10.2 months (p = 0.2), time to next treatment was 19.7 versus 17.9 months (p = 0.4), and median overall survival (OS) was immature but not statistically different (p = 0.17). The authors reported adjusted hazard ratios for time to treatment failure, time to next treatment, and OS were 0.71 (p = 0.14), 0.65 (p = 0.11), and 1.74 (p = 0.14), respectively. 34% of patients received second-line treatment. In patients receiving subsequent VEGF-based therapy, second-line response rates were lower in the IO+VEGF group than in the ipilimumab/nivolumab group (15% vs 45%), though second-line time to treatment failure was not significantly different (3.7 vs 5.4 months; p = 0.4).

Comment: The International Metastatic Renal-cell Carcinoma Database Consortium (IMDC) has been tracking outcomes from patients taking treatment for kidney cancer for many years, and has revealed real-world outcomes and generated many ideas for people taking VEGF/tyrosine kinase inhibitor (TKI). Now the IMDC publishes its first results of people taking immunotherapy agents, as first line therapy, either alone or in combination with VEGFR TKI. Reassuringly the outcomes of these combinations seem similar to those reported in clinical trials, and again not surprisingly similar to each other. Also, unsurprisingly people who took a VEGFR TKI + IO agent in the first line did not experience as good a response to a 2nd line TKI. But what this data doesn’t show us are the answers to the questions that patient’s cancers are asking, but that first-line trials are NOT asking. Whose kidney cancer could be controlled with a single agent PD1 inhibitor alone? Who will be failed by PD1/PDL1 but benefit from adding broader immunotherapy with CTLA4 inhibitor? Who will be failed by immunotherapy completely? Who should avoid the expense and side effects of taking the immunotherapy and VEGFR TKI together?


Immunohistochemical expression of renin is a prognostic factor for recurrence in nonmetastatic renal cell carcinoma

Authors: de Almeida E Paula F, et al

Summary: The study cohort consisted of 498 patients with nonmetastatic clear cell renal cell carcinoma (cRCC) who underwent partial or radical nephrectomy. Nuclear renin was qualitatively positive in 72% of cases and negative in 28%. Quantitatively, an equal number of cases had ≤35% or >35% renin-positive nuclei. The investigators found the absence of renin expression was associated with high-grade tumours, greater microscopic venous invasion (P = 0.046), and renal vein invasion (P = 0.020). Qualitatively negative renin expression was an unfavourable prognostic factor for disease-free survival rates (DFS) (RR = 2.923, P < 0.001). In terms of quantitative renin expression, a cutoff of ≤35 was associated with worse DFS (RR = 4.085, P < 0.001).

Comment: Kidney cancer is well known as a hyper-vascular tumour, with a high density of blood vessels, many bleeding complications and response to drugs that block blood vessel biology. The molecular mechanisms that drive this hypervascularity vary in different people’s cancers however, with some cancers using usual pathways, whereas more aggressive dedifferentiated cancers use less typical mechanisms. One molecule that is associated with these mechanisms is renin, better known as a pathway for blood pressure regulation in the renin-angiotensin system (RAS). People with low levels of renin in their kidney cancers have worse prognosis than people who’s kidney cancers express renin. This is further data to support the importance of the RAS in kidney cancer biology, and provides an interesting biological connection to the observation that people with kidney cancer taking RAS inhibitors such as ACE inhibitors or angiotensin-II receptor antagonists have a markedly improved overall survival.


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Abstract
A phase I study of alpha-1,3-galactosyltransferase-expressing allogeneic renal cell carcinoma immunotherapy in patients with refractory metastatic renal cell carcinoma

Authors: Hahn AW, et al
Summary: The group assessed safety and maximum tolerated dose of HyperAcute Renal (HAR) immunotherapy in 18 patients with refractory mRCC. HAR was injected intradermally weekly for 4 weeks then biweekly for a further 2 months. Two grade 3 adverse events (AEs) were attributed to HAR; lymphopenia and injection site reaction. No grade 4/5 AEs occurred. The study cohort was randomly assigned to nivolumab plus ipilimumab or sunitinib (550 vs 546 in the intention-to-treat population; 425 vs 422 intermediate-risk or poor-risk patients), and 125 vs 124 favourable-risk patients). With extended follow-up (median follow-up 32.4 months), in intermediate-risk or poor-risk patients nivolumab plus ipilimumab continued to be superior to sunitinib in terms of OS (median not reached vs 26.6 months; HR 0.66, p<0.0001), PFS (median 8.2 months vs 8.3 months; HR 0.77, p=0.0014), and the proportion of patients achieving an objective response (178 [42%] of 425 vs 124 [29%] of 422; p=0.0001).

Comment: Yes, but I have this other question… This publication from the Checkmate 214 trial, now with long-term follow-up data once again shows that OS of people with intermediate and unfavourable risk cRCC taking combination immunotherapy is longer on average than prescribed sunitinib. The outcomes in patients with IMDC good risk disease in this dataset have started to converge, with people being failed by sunitinib presumably taking nivolumab in the second-line setting and at least some of them deriving benefit. What this data still doesn’t answer are who can be predicted to respond to immunotherapy and thus avoid sunitinib toxicity, and likewise who can be predicted to fail by immunotherapy and who should best be treated with VEGFR TKI? This trial exemplifies how far the field has come in recent years as the risk factors based on the IMDC, based on angiogenic properties of cancer, don’t predict the immune response to therapy. What an amazing situation that we face and must catch-up to help people more.


Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: Extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial

Authors: Motzer RJ, et al
Summary: The study cohort was randomly assigned to nivolumab plus ipilimumab or sunitinib (550 vs 546 in the intention-to-treat population; 425 vs 422 intermediate-risk or poor-risk patients), and 125 vs 124 favourable-risk patients). With extended follow-up (median follow-up 32.4 months), in intermediate-risk or poor-risk patients nivolumab plus ipilimumab continued to be superior to sunitinib in terms of OS (median not reached vs 26.6 months; HR 0.66, p<0.0001), PFS (median 8.2 months vs 8.3 months; HR 0.77, p=0.0014), and the proportion of patients achieving an objective response (178 [42%] of 425 vs 124 [29%] of 422; p=0.0001).

Comment: Are PD1 and PD1L antibodies equally effective in cancer checkpoint immunotherapy? This clinically relevant question (and in fact, should we give a combination?) will likely never be answered in clinical trials as it would be commercially suicidal. So we must resort to dodgy cross-trial comparisons. In lung cancer the different immunotherapy drugs don’t look all that different, we’ll never know the answer in melanoma, but in bladder cancer there is a hint that anti-PD1 antibodies might be more potent, and in kidney cancer it is also looking like anti-PD1 antibodies might have an edge, with the avelumab/axitinib combination appearing less active than pembrolizumab/axitinib, and the combination in this paper, atezolizumab + bevacizumab failing to best badly-prescribed sunitinib in this randomised phase III study. The activity of atezolizumab alone is unknown, and it may have gone into the ring with a weak partner, as there is very little benefit of bevacizumab in renal cell carcinoma. In any case, with only surrogate endpoints showing any difference, and no OS benefit likely, this combination is unlikely to see further development in kidney cancer.

Reference: Lancet 2019 Jun 15;393(10189):2404-2415

NIVOLUMAB PLUS BEVACIZUMAB VERSUS SUNITINIB IN ADVANCED RENAL CELL CARCINOMA: EXTENDED FOLLOW-UP OF EFFICACY AND SAFETY RESULTS FROM A RANDOMISED, CONTROLLED, PHASE 3 TRIAL

Atezolizumab plus bevacizumab versus sunitinib in patients with previously untreated metastatic renal cell carcinoma (IMmotion151): A multicentre, open-label, phase 3, randomised controlled trial

Authors: Rini BI, et al
Summary: Patients with first-line mRCC were randomly assigned to atezolizumab plus bevacizumab (n=454) and sunitinib (n=461); 40% had PD-L1 positive disease. Median follow-up was 15 months at the primary progression-free survival (PFS) analysis and 24 months at the OS interim analysis. In the PD-L1 positive population, the median PFS was 11.2 months in the atezolizumab plus bevacizumab group versus 7.7 months in the sunitinib group (HR 0.74; p=0.0217). In the intention-to-treat population, median OS had an HR of 0.93 and the results did not cross the significance boundary at the interim analysis. Treatment-related grade 3-4 AEs were reported in 40% of patients in the atezolizumab plus bevacizumab group and 54% in the sunitinib group.

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Reference: Lancet Oncol 2019 Jun 15;1;1;1891;2404-2415

VHL synthetic lethality signatures uncovered by genotype-specific CRISPR-Cas9 screens

Authors: Sun N, et al
Summary: The researchers performed parallel genome-wide CRISPR screens in two pairs of isogenic ccRCC cell lines that differed only in the Hippel-Lindau (VHL) status. The results confirmed a role for mTOR signalling in renal carcinoma. In addition they identified DNA damage response and selenocysteine biosynthesis pathways as novel synthetic lethal targets in VHL-inactivated cancer cells.

Comment: One of the coolest new technologies that the DNA sequencing revolution has delivered to us over the last ten years is the idea of functional genomic screening. By planning out a huge library of tiny pieces of DNA that will block the RNA transcribed from a gene, scientists have been able to find targets in cancer that might respond to a “critical hit”. Cancers have disorganised DNA, and in some cases this means they are particularly dependent on a gene or pathway to stay alive; if you could block that pathway then the cancer would be exquisitely vulnerable. Doing a test-tube model of this killing mechanism has been called “synthetic lethality”. The most famous recent example is the use of PARP inhibitors in people whose cancers have a defect in a DNA-repair gene. Like anything else in science sometimes the results of these synthetic lethality functional genomics screens were a bit rough and blurry. In this paper, the authors use a stronger form of DNA blocking called CRISPR where the gene in question is effectively cut out of the genome. This technology has been applied to kidney cancer cell lines, where the VHL gene is very commonly lost in most people with clear-cell kidney cancer. By using this more powerful screen, new therapeutic targets have been suggested in kidney cancer such as selenium metabolism and the aforementioned DNA-defect repair pathways.


Independent commentary by Dr Craig Gedye

Dr Gedye is a physician/scientist, dual trained as a medical oncologist, clinical trialist and basic science researcher. He works for patients with melanoma, brain, kidney, prostate, tests, and bladder cancer at the Calvary Mater Newcastle, and is the Clinical Research Director at the NSW Statewide Biobank. He chairs the Renal Cancer Subcommittee for ANZUP Cancer Trials Group, and is the coordinating principal investigator for the KeyPAD and UNISON trials. He undertakes translational and basic cancer research at the Hunter Medical Research Institute, University of Newcastle. Dr Gedye’s research focus is on cancer heterogeneity; why treatments work for some patients but not others. This challenging research spans the translational spectrum from patient experience to basic science.
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CR = complete response; HR = hazard ratio; mOS = median overall survival; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma.


Please refer to the Approved Product Information before prescribing. The Product Information is available upon request from BMS Medical Information Department: 1800 067 567 or can be accessed at http://www.medicines.org.au/files/bqpopdiv.pdf

PBS INFORMATION: OPDIVO monotherapy – Authority required (STREAMLINED) for the treatment of patients with advanced (Stage IV) clear cell variant renal cell carcinoma.

OPDIVO in combination with YERVOY – Authority required (STREAMLINED) for the treatment of patients with intermediate/poor-risk, previously untreated advanced clear cell variant renal cell carcinoma. Refer to PBS Schedule for full authority information.

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30-month follow-up: mOS not reached vs 26.6 months with sunitinib (HR 0.66; p<0.0001); investigator-assessed CR 11% vs 1% with sunitinib (p-value not reported) in intermediate/poor-risk, treatment-naïve advanced RCC

PBS INFORMATION: OPDIVO and YERVOY (IPILIMUNAB) COMBINATION THERAPY.

Immune-related adverse reactions are seen more frequently, and are more severe, with OPDIVO and YERVOY combination therapy than with OPDIVO or YERVOY monotherapy. Immune-related adverse reactions can involve any organ system. The majority of these initially manifest during treatment; however, a minority can occur weeks to months after discontinuation. Some immune-related adverse reactions can be permanent (such as thyroid dysfunction and diabetes mellitus). Life-threatening or fatal immune-related adverse reactions that have occurred include colitis, intestinal perforation, hepatitis, pneumonitis, hypophysitis, adrenal insufficiency, toxic epidermal necrolysis, myocarditis, encephalitis and myasthenia gravis (see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse Effects). Early diagnosis and appropriate management are essential to minimise life-threatening complications (see Section 4.2 Dose and method of administration). Monitoring at least prior to each dose is recommended. Advise patients of the importance of immediately reporting possible symptoms. Physicians should consult the YERVOY product information prior to initiation of OPDIVO in combination with YERVOY. The combination of OPDIVO and YERVOY should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy in the treatment of cancer.
Guideline adherence for the surgical treatment of T1 renal tumours correlates with hospital volume: An analysis from the British Association of Urological Surgeons Nephrectomy Audit

Authors: Tran MGB, et al

Summary: This retrospective study analysed data from 13 045 kidney tumours that underwent radical nephrectomy or partial nephrectomy in the period 2012-2016. The authors showed closer guideline adherence by higher surgical volume centres. They also noted there was an increase in partial nephrectomy as an increase over time, (59.7% in 2012 to 44.9% in 2016). There was an association between annual hospital volume and the proportion of T1 tumours treated with partial nephrectomy rather than radical nephrectomy (from 18.1% in centres performing <25 cases/year to 61.8% in centres performing >100 cases/year). Overall and major complication rate decreased with increasing high volume for all patients including those treated with partial nephrectomy.

Comment: Further data from registries, this time from the UK, showing that kidney cancer surgery may be best organised into high-volume sites. Comparative analysis in this retrospective audit showed that high-volume sites were more likely to adhere to management guidelines, more likely to use partial rather than radical nephrectomy, and had a lower complication rate than low-volume sites. As with other cancer surgery subspecialties, it appears that kidney cancer surgery outcomes might be optimised by ensuring surgery is performed in high-volume sites.

Reference: BJU Int 2019 Jul 11 [Epub ahead of print]

Abstract

Surgical safety of cytoreductive nephrectomy following sunitinib: Results from the multicentre, randomised controlled trial of immediate versus deferred nephrectomy (SURTIME)

Authors: De Buijn RE, et al

Summary: The study investigated surgical safety in patients randomised 1:1 to immediate cytoreductive nephrectomy (CN) followed by sunitinib versus sunitib followed by deferred CN 24h after the last dose of sunitib. AE's related to surgery in the immediate and deferred arms occurred in 52% and 53% after CN, respectively. Postoperative AEs, 30-day readmission, and in-hospital mortality rates were 6.5%, 13%, and 4.3% in the immediate arm and 2.5%, 7.5%, and 2.5% in the deferred arm, respectively. They concluded there were no differences in surgery time, blood loss, and hospital stay.

Comment: The role of local therapy in people suffering de novo metastatic kidney cancer has been debated and studied intensively, and will no doubt continue to be a subject of interest. During the cytokine era, prospective studies showed that CN made a small improvement in outcomes for people taking interleukin or interferon. The CARMENA and SURTIME trials have confirmed that there is no survival benefit for CN at any time-point in patients intending to take VEGFR TKI, and CN should be seen as a niche procedure for carefully selected patients (e.g. large symptomatic primary cancers). One question that might have muddied the interpretation of these survival results was whether VEGFR TKI prior to surgery actually increased surgical complications, and the short answer is that despite the potential for changes in bleeding and wound healing, there is no major impact. Thus we can be confident that the patient’s clinical situation should guide management, and that we shouldn’t rush into CN for fear of being unable to perform this later.


Abstract

Extended duration of active surveillance of small renal masses: A prospective cohort study

Authors: Whelan EA, et al

Summary: The study cohort included 103 patients with a total of 107 small renal masses undergoing active surveillance. Median follow-up was 55.5 months in patients who continued on active surveillance. At last follow-up 53 patients (51.5%) were alive without metastatic disease. 48 (45.6%) had died of another cause and metastatic disease had developed in 2 (1.9%), including 1 (1.0%) who ultimately died of metastatic renal cell carcinoma. The mean ± SEM linear and volumetric growth rates of all small renal masses were 0.21 ± 0.03 cm per year and 6.15 ± 2.15 cm³, respectively.

Comment: Renal cell carcinoma remains an outlier compared to other cancers in that sometimes no immediate treatment is needed. This report follows a single centre prospective cohort of people presenting with small renal masses, who on discussion with their urologist elected to undertake active surveillance. Only two of 103 patients developed mRCC, only one dying of their renal cancer. Death due to other causes occurred in almost half of the cohort. A small renal mass may be actively surveyed without need for immediate surgical management in well selected and counselled patients.


Abstract

Use of targeted therapies for advanced renal cell carcinoma in the Veterans Health Administration

Authors: Agparil SL, et al

Summary: The retrospective study included 286 patients diagnosed with advanced crRCC between 2010 and 2014. Of the 220 patients treated, the mean number of medications received was 1.9 and the medications most commonly used first were sunitinib (61.8%), pazopanib (17.3%), and temsirolimus (10.9%). The researchers reported median survival from the start of treatment to death was 1.08 years. Furthermore, receipt of temsirolimus vs sunitinib (HR 1.95) as the first targeted therapy was independently associated with an increased hazard of death.

Comment: Lost in translation; this troubling report retrospectively examines the outcomes of people with mRCC treated in the US Veterans Health Administration from 2010-2016. This population of people was treated with targeted therapies for mRCC and experienced outcomes that were markedly inferior to the results of the registralal studies that licensed the drugs being used, e.g. sunitinib and pazopanib. Not only was survival worse but toxicity appeared inferior also, with more treatment discontinuation due to toxicity. This humbling data shows that ongoing refinement and improvements in practice are warranted long after a drug is registered and reimbursed, to ensure that the benefits that might be possible in clinical trials are effectively translated into routine clinical practice.

Reference: Cancer Med 2019 Sep 19 [Epub ahead of print]

Abstract

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