In this issue:

- Avelumab + axitinib vs sunitinib for advanced RCC
- Pembrolizumab + axitinib vs sunitinib for advanced RCC
- HRQoL of patients with advanced RCC treated with nivolumab + ipilimumab vs sunitinib
- Cost-effectiveness of first-line nivolumab + ipilimumab vs sunitinib for metastatic RCC
- Germline mutations in cancer susceptibility genes in advanced RCC
- Comparative effectiveness of management options for patients with small renal masses
- Cabozantinib in advanced non-clear-cell RCC
- Immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic RCC receiving sunitinib
- Abnormal oxidative metabolism in CCPAP tumours
- Efficacy and safety of an individualised schedule of sunitinib for metastatic RCC

Abbreviations used in this issue:

- CCPAP = clear cell papillary renal cell carcinoma
- CN = cytoreductive nephrectomy
- EQ-5D-3L = EuroQol five-dimensional three level
- FACT-G = Functional Assessment of Cancer Therapy General
- FKSI-19 = Functional Assessment of Cancer Therapy Kidney Symptom Index-19
- HRQoL = health-related quality of life
- ICER = Institute for Clinical Evaluation
- IMPD = mitochondrial DNA
- ICPI = index of cancer proliferation and invasiveness
-ller = mitogen-activated protein kinase (MAPK)
- mDNA = mitochondrial DNA
- mTOR = mammalian target of rapamycin
- mut = mutation
- OS = overall survival
- PD-L1 = programmed death ligand 1
- PD-1 = programmed death-1
- PI3K = Phosphatidyl inositol 3-kinase
- PD-L1 = programmed cell death 1
- PFS = progression-free survival
- PO = partial response
- rRNA = ribosomal RNA
- RCC = renal cell carcinoma
- R FDA = radiofrequency ablation
- TKI = tyrosine kinase inhibitor
- VEGFR = vascular-endothelial growth factor receptor

Welcome to the 4th issue of Renal Cancer Research Review.

Welcome to the Research Review for Renal Cancer and thanks for reading. Recent months’ publications have explored the practicalities and experience of combination immunotherapy in advanced RCC, cemented a new strategy in the management of patients with advanced clear cell kidney cancer, shown the growing utility of multitargeted agents in patients with non-clear cell kidney cancer and explored the unusual aspects of one rare form of kidney cancer. Also included in this issue is an important manuscript that demonstrates that registration of a drug or combination of drugs is merely the beginning and that we must continue to question, probe and improve treatments so that we can extend the benefits of our increasing armamentarium of agents to as many patients as possible.

Kind Regards,

Dr Craig Gedye

Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma

Authors: Motzer RJ, et al

Summary: This phase III trial randomly assigned untreated patients with advanced renal-cell carcinoma (RCC) to receive avelumab plus axitinib (n=442) or sunitinib (n=444). Among the 63% of patients with programmed death ligand 1 (PD-L1) positive tumours the median progression-free survival (PFS) was 13.8 months with avelumab plus axitinib, compared with 7.2 months with sunitinib; in the overall population, the median PFS was 13.8 months, compared with 8.4 months. The objective response rate (ORR) among the patients with PD-L1-positive tumours was 55.2% with avelumab plus axitinib and 25.5% with sunitinib; at a median follow-up for overall survival (OS) of 11.6 months and 10.7 months in the two groups, 37 patients and 44 patients had died, respectively.

Comment: First reported at ESMO last year and updated at the ASCO GU meeting in February, the phase III trial of avelumab and axitinib was published in the NEJM last month. The checkpoint immunotherapy revolution continues to march onwards and outwards, and in this manuscript (and the following) we see the first mature data that demonstrates that it is safe and feasible to combine PD1/PD1 antibodies with vascular-endothelial growth factor receptor (VEGFR) inhibitors, or at least some VEGFR tyrosine kinase inhibitor (TKI). Remember that the first combination of these drug classes, pazopanib and pembrolizumab, was extremely toxic with high levels of hepatotoxicity. Partnerships in this space have rapidly formed with a variety of combinations at various stages of development. Avelumab/axitinib has the longest follow-up to date, and with a secure partnership between Pfizer and EMD Serono, would seem most likely to come to the clinic soon. Avelumab at a dose of 10mg/kg IV fortnightly was offered with the standard starting dose of axitinib (5mg BD). Toxicity remains high, with effectively all patients experiencing some adverse event, and 70% of patients suffering a grade 3 toxicity, whether they took the avelumab/axitinib combination or sunitinib. Toxicities appear to be additive rather than multiplicative; toxicities appeared to be able to be attributed to each agent and dose modification could be implemented. It is important to remind ourselves that in this trial, as in every other modern trial, the comparator sunitinib arm has been constrained to the 4 weeks on, 2 weeks off dose schedule… that is almost never used in reality. Like every other modern study in advanced kidney cancer, this therefore limits what we can say about the comparative effectiveness of the combination given that it was up against a strawman. The PFS was reported as extended compared to the handcuffed-schedule of sunitinib, but overall survival was somewhat tellingly not reported in the intention-to-treat population, being buried in the Supplementary Data. As we’ll discuss later, with so many treatments and combinations of treatments now available for people suffering kidney cancer, the expectations of our patients are rising, and we can now dare to dream about durable long-term outcomes. Likewise, with so many combinations and agents competing with each other, important scientific questions are taking a second place to commercially vital questions. We raise more questions than we answer.


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, testis, 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.
Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma

Authors: Rini BI, et al

Summary: In this open-label, phase 3 trial, patients with previously untreated advanced RCC were randomly allocated to receive pembrolizumab plus axitinib (n=432) or sunitinib (n=429). The authors reported the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab-axitinib group and 78.3% in the sunitinib group. Median PFS was 15.1 months in the pembrolizumab-axitinib group and 11.1 months in the sunitinib group; ORR was 59.3% and 35.7%, respectively. They also noted Grade 3 or higher adverse events occurred in 75.8% of patients in the pembrolizumab-axitinib group and in 70.6% in the sunitinib group.

Comment: Published and presented back-to-back with the avelumab/axitinib data, the other leading combination of checkpoint immunotherapy and anti-angiogenic agents, pembrolizumab plus axitinib, was also reported in the NEJM last month. With an early similar design and sample size, pembrolizumab (at a fixed dose three-weekly) and standard axitinib was compared with sunitinib in the usual fashion, (i.e. with the sunitinib schedule tied to a chair and beaten with the fire-hose). The patient population was perhaps slightly more favourable in terms of risk factors compared to the avelumab/axitinib population, and certainly the patients in the sunitinib control arms seemed to fare slightly better.

Pembrolizumab/axitinib was once again met with adverse events in all patients, grade 3 events in three-quarters of patients, attributable to treatment in almost two-thirds of patients; again this was added to the sunitinib on trial, but hopefully no one is cruel enough to enforce this outdated 4/2 dosing schedule on patients in real-world settings. Comparative effectiveness with the pembrolizumab/axitinib combination appeared higher compared to sunitinib, but again this must be taken with a grain of salt; not only was dose-reduction the only allowed modification, but the fraction of patients taking a second-line of therapy after progressing on sunitinib was modest, with only 60% of patients taking a second-line therapy, and only 40% of patients taking an immunotherapy agent in the second-line. Given our increasing appreciation that performance status is one of the most important predictors of benefit from checkpoint immunotherapy, it is important to recognise that this trial, as well as CheckMate 214 (avelumab/axitinib), CheckMate-214 (pembrolizumab/nivolumab) and Imfinzi 151 (atezolizumab/bevacizumab) all have limitations in implementation into the real-world.

None of these studies addresses the key question from a patient’s perspective – is a combination of agents (with greater patient and payment toxicity) superior to taking agents in a sequential fashion? Does adding the VEGFR TKI increase the chance of durable benefit from immunotherapy – is there an immunotherapeutic synergy or are we simply seeing the additive effect of two partially effective agents?


Patient-reported outcomes of patients with advanced renal cell carcinoma treated with nivolumab plus ipilimumab versus sunitinib (CheckMate 214): A randomised, phase 3 trial

Authors: Cella D, et al

Summary: The investigators assessed health-related quality of life (HRQoL) in the CheckMate 214 cohort. Patient-reported outcomes were assessed using the Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19), Functional Assessment of Cancer Therapy-General (FACT-G), and EuroQol five dimensional three level (EQ-5D-3L) instruments. Patient-reported outcomes were more favourable with nivolumab plus ipilimumab than sunitinib throughout the first 103 weeks after baseline; with mean change for FKSI-19 total score being −4.02 versus −3.14, and FACT-G total score being −2.77 versus −1.3. In contrast, there was no significant difference between the treatment groups at week 103 in EQ-5D-3L visual analogue rating scale scores. Compared with sunitinib, nivolumab plus ipilimumab reduced risk of deterioration in FKSI-19 total score, FACT-G total score, and EQ-5D-3L visual analogue rating scale score and UK utility scores.

Comment: The combination of nivolumab and ipilimumab is now registered and reimbursed for the first-line treatment of patients with IMDC intermediate or poor risk advanced RCC in Australia (about 70% of patients), and is entering routine practice. One of the major questions facing patients when considering a treatment is how the treatment might impact their quality of life. Though difficult to measure, various standardised questions have been used to try to describe patients’ experiences. The HRQoL data from the CheckMate 214 study was recently released, with few surprises. With the lower dose of ipilimumab (1mg/kg) the frequency of severe side-effects is more muted compared to the original dosing of ipilimumab in combination with nivolumab as seen in the CheckMate 067 trial [1]. However, for the comparison of sunitinib versus nivolumab plus ipilimumab, the former had its legs chained together and then is thrown over the back of the boat leads to a poorer patient experience than one would see in routine regular practice with a VEGFR TKI. Notwithstanding however, nivolumab plus ipilimumab leads to fewer symptoms and better HRQoL than sunitinib in patients at intermediate or poor risk with advanced RCC.


First-line nivolumab plus ipilimumab vs sunitinib for metastatic renal cell carcinoma: A cost-effectiveness analysis

Authors: Wan X, et al

Summary: This article assessed the cost-effectiveness of nivolumab plus ipilimumab versus sunitinib in the first-line setting for patients with metastatic RCC. The authors concluded nivolumab plus ipilimumab provided an additional 0.96 quality-adjusted life-years (QALYs), at a cost of $1083 363 per QALY. Furthermore, nivolumab plus ipilimumab was most cost-effective for patients with PD-L1 expression of at least 1% ($86 390 per QALY).

Comment: A treatment may help more people, and may be associated with a better experience of treatment, but if the cost of the treatment is prohibitive then it cannot help people in the real world. A cost-effectiveness analysis was performed from data in the CheckMate 214 study, under the assumption that patients would take either the combination immunotherapy or the TKI, an assumption that is becoming increasingly difficult to model with so many 2nd line options available to people suffering kidney cancer. In this model, nivolumab plus ipilimumab was estimated to offer an additional QALY at a cost of over USD$100,000. This fits in the general range of the Institute for Clinical and Economic Review (ICER), which conducts drug cost-effectiveness analyses, and generally values one QALY at $100,000 to $150,000 for a treatment to be cost-effective. Again this is largely not surprising as the combination treatment has received approval in North America, Europe and Australia, but with more and more immunotherapy indications being sought, the implications for long-term sustainability of pharmaceutical reimbursement will likely challenge the ICER model, and we will face increasing pressure to make treatments more efficient and effective.


Prevalence of germline mutations in cancer susceptibility genes in patients with advanced renal cell carcinoma

Authors: Carlo MI, et al

Summary: This group examined the prevalence of germline mutations in 267 patients with advanced RCC. Of the study cohort germline mutations were identified in 16.1%; 5.5% had mutations in syndromic RCC-associated genes with CHEK2 and FH being the most frequent. Other than VHL, only 6% of patients taking a second-line therapy, and only 40% of patients taking an immunotherapy agent in the second-line. Given our increasing appreciation that performance status is one of the most important predictors of benefit from checkpoint immunotherapy, it is important to recognise that this trial, as well as CheckMate 214 (avelumab/axitinib), CheckMate-214 (pembrolizumab/nivolumab) and Imfinzi 151 (atezolizumab/bevacizumab) all have limitations in implementation into the real-world.

None of these studies addresses the key question from a patient’s perspective – is a combination of agents (with greater patient and payment toxicity) superior to taking agents in a sequential fashion? Does adding the VEGFR TKI increase the chance of durable benefit from immunotherapy – is there an immunotherapeutic synergy or are we simply seeing the additive effect of two partially effective agents?

Comment: While cancers are largely caused by exposure to environmental mutagens over time, we are increasingly aware of a hereditary disposition to cancer susceptibility, and the question on every patient’s mind is what does this mean for my kids? Carlo, Offit and colleagues report a cohort study of 254 patients with advanced (stage III or IV) RCC seen in urology and medical oncology clinics over a two-year period. Consenting patients agreed to germline sequencing in parallel to sequencing of their tumour. Germline mutations were identified in 1/6 patients (16.1%). One in twenty patients were found to have a mutation in syndromic RCC-associated genes (7 in FH, 3 in BAP1, and 1 each in VHL, MET, SDHA, and SDHB). The most frequent mutations were CHEK2 (n = 29) and FH (n = 7). Of genes not previously associated with RCC risk, CHEK2 was over represented in patients compared with the general population, with an odds ratio of RCC of 3.0 (95% CI, 1.3-6.8; P = .003). Patients with non–clear cell RCC were more likely to have an RCC-associated gene mutation (9 [11.7%] of 74 vs 3 [1.7%] of 177; P = .001). Of patients with mutations in RCC-associated genes, one-third of patients would not have met current clinical guidelines for genetic testing. The prevalence of germline mutations in people with advanced kidney cancer is greater than previously appreciated, current testing guidelines may not identify all patients that may benefit from screening and people with non-clear cell kidney cancers might have an increased risk versus people suffering clear cell RCC.

Reference: JAMA Oncol 2018 Sep 1;4(9):1228-1235

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OS = overall survival; PBS = Pharmaceutical Benefits Scheme; RCC = renal cell carcinoma.

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Please review full PBS criteria.
Comparative effectiveness of management options for patients with small renal masses: A prospective cohort study

Authors: Alam R, et al

Summary: This prospective study used registry data to explore the comparative effectiveness of partial nephrectomy (PN), radical nephrectomy (RN), radiofrequency ablation (RFA) and active surveillance for small renal masses. Of 638 patients, 231 (36.2%) chose PN, 41 (6.4%) RN, 27 (4.2%) RFA and 339 (53.1%) active surveillance. Cancer-specific survival at 7 years was 98.6% in PN patients and 100% in all other groups. Overall survival at 7 years was 87.9% in PN, 90.2% in RN, 83.5% in RFA and 66.1% in active surveillance patients.

Comment: “At last the Dodo said, ‘everybody has won, and all must have prizes.’” Alice in Wonderland, Lewis Carroll.

McKieran and colleagues report on a longitudinal cohort study where over 600 patients with small (≤4.0 cm) renal masses were followed in the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry. Non-randomised treatment choices were the choice of the participant and their clinician. One-third of patients (36.2%) chose PN, approximately one in twenty (6.4%) chose RN or RFA (4.2%), while approximately half of patients (53.1%) chose active surveillance.

No matter which primary treatment modality was selected, outcomes were excellent. Cancer-specific survival at 7 years was 98.8% in PN patients and 100% in all other groups. Overall survival at 7 years was 87.9%, 90.2%, 83.5% and 66.1% in PN, RN, RFA and active surveillance patients, respectively. While OS appeared worse in the surveillance group than other groups this is very likely attributable to the older age and increased comorbidities in this group of patients. The eGFR was lowest in RN patients but comparable in all other groups. QoL was lowest in active surveillance patients due to lower physical health scores; mental health scores were similar in all groups. Active surveillance is a reasonable option for many patients, given the comparable oncological and mental health outcomes. If intervention is chosen there is no clear winner. Ongoing prospective studies are needed to define if any particular patient group is benefited by a particular treatment modality.


Abstract

Caborzantinib for the treatment of patients with metastatic non-clear cell renal cell carcinoma: A retrospective analysis

Authors: Campbell MT, et al

Summary: This retrospective study included 30 patients with non-clear cell RCC who received cabozantinib; the majority of whom had disease progression on prior VEGFR-TKIs. The authors reported median PFS was 8.6 months and median OS was 25.4 months, with a median follow-up of 20.6 months.

Comment: See comment below

Reference: Eur J Cancer 2018 Nov;104:188-194

Abstract

Caborzantinib in advanced non-clear cell renal cell carcinoma: A multicentre, retrospective, cohort study

Authors: Martinez Chanza N, et al

Summary: This multicentre, retrospective study included 112 patients with metastatic non-clear cell RCC treated with cabozantinib during any treatment line. Of the study cohort, 59% had papillary histology, 15% had Xp11.2 translocation histology, 13% had unclassified RCC, 18 had stable disease (64.2%) and 6 had progressive disease (21.4%), resulting in a 14.3% ORR and a 78.6% disease control rate. Two patients with papillary RCC who had experienced disease progression on sunitinib achieved durable partial response and stable disease, respectively, following treatment with cabozantinib.

In the Dana-Farber led group, the proportion of patients who achieved an objective response across all histologies was 27% (95% CI 19–36). At a median follow-up of 11 months (IQR 6–18), median time to treatment failure was 6·7 months, median PFS was 7·0 months, and median OS was 12·0 months. The most common adverse events of any grade were fatigue and the most common grade 3 events were skin toxicity.

While we await results from prospective studies, these real-world studies provide evidence supporting the activity and safety of cabozantinib in patients with non-clear cell RCC. Outcomes are at least comparable to historical reports of other TKI such as sunitinib, and studies examining the activity of checkpoint inhibitors and combinations of therapies are eagerly awaited.


Abstract

Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: The SURTIME randomized clinical trial

Authors: Bex A, et al

Summary: Patients with metastatic clear cell RCC and resectable primary tumour, were randomly allocated to immediate cytoreductive nephrectomy (CN) followed by sunitinib therapy versus treatment with 3 cycles of sunitinib followed by CN (in the absence of progression following sunitinib therapy). The 28-week progression-free rate was 42% in the immediate CN arm and 43% in the deferred CN arm. The intention-to-treat OS hazard ratio of deferred versus immediate CN was 0.57, with a median OS of 32.4 months in the deferred CN arm and 15.0 months in the immediate CN arm.

Comment: With the development of TKIs for advanced RCC, a natural question to attempt to improve patients’ outcomes was to examine the effect of tumour debulking using traditional modalities such as surgery. Older studies using cytoreduction showed a small benefit or waited until 3–4 months of therapy were delivered. However more tellingly, the intention-to-treat OS was markedly different between the two groups, and a hazard ratio of deferred vs immediate CN of 0.57 (95% CI, 0.34-0.95; P = .03), with a median OS of 32.4 months (95% CI, 14.5-65.3 months) in the deferred CN arm and 15.0 months (95% CI, 9.3-29.5 months) in the immediate CN arm.

As in the CARMENA study, upfront sunitinib seemed the preferred strategy, and the addition of surgery did not improve outcomes. Again, it is important to reflect on the different practices in the northern hemisphere where CN is a commonly recommended first treatment, versus the common practice in Australia where CN is only considered for isolated patients, and likely still has a role in some patients with a very large or symptomatic primary lesion but limited metastatic lesions.


Abstract
Abnormal oxidative metabolism in a quiet genomic background underlies clear cell papillary renal cell carcinoma

Authors: Xu J, et al

Summary: This group explored the molecular phenotype of a genomically quiet kidney tumour, clear cell papillary renal cell carcinoma (CCPAP). They found the tumours exhibit severe depletion of mitochondrial DNA (mtDNA) and RNA. In addition, the group recorded elevated levels of oxidative stress and accumulation of the sugar alcohol sorbitol.

Comment: The dogma of cancer biology is that DNA mutations drive carcinogenesis, and genomic sequencing routinely identifies oncogenic alterations in the majority of cancers. However, some cancers harbor no discernible driver lesion, and the pathway to tumour formation remains less clear. In a beautifully written manuscript, Hakimi and colleagues have worked to describe the exceptional molecular phenotype of a genomically quiet kidney tumour. CCPAP. CCPAP was recently defined as a unique subtype of kidney cancer in the ISUP Vancouver classification meeting, recognised as a subset of clear cell carcinoma with a very good outcome for patients. Hakimi and colleagues show in this manuscript that CCPAP tumours have a largely wild-type nuclear genome, with few DNA mutations or changes, but do exhibit severe depletion of mtDNA and RNA with high levels of oxidative stress, reflecting a shift away from respiratory metabolism. This remarkable change in the mitochondrial compartment also leads to a distinct metabolic phenotype uniquely characterised by accumulation of the sugar alcohol sorbitol within tumours. Clear cell carcinoma often show clearing of the cytoplasm after histology of formalin-fixed paraffin embedded samples, as the lipids accumulated in these tumours are washed out in the staining process – hence clear cells. Immunohistochemical staining of primary CCPAP tumour specimens shows loss of mtDNA-encoded proteins and a lipid-depleted metabolic phenotype, enriched with the presence of glycogen. This elegant study of the genetics of this rarer tumour identifies some easily used clinical biomarkers and emphasises the unique biology of these tumours.

Reference: Elife 2019 Apr 1;8. pii: e38986

The efficacy and safety of sunitinib given on an individualised schedule as first-line therapy for metastatic renal cell carcinoma: A phase 2 clinical trial

Authors: Bjarnason GA, et al

Summary: The objective of this study was to ascertain whether toxicity-driven dose and schedule changes would optimise sunitinib treatment exposure and outcome for individual patients with metastatic RCC. The team concluded individualised sunitinib therapy is feasible, safe and an effective method to manage toxicity.

Comment: The final article we wish to highlight this month is both a triumph of clinical science and a clarion call. The result of careful work from an extended network in Canada over several years, this work gives us a valuable way to improve patient outcomes now, and highlights the challenges ahead of us.

Recognising that the “standard” dosing schedule of sunitinib at 4 weeks on, 2 weeks off was originally proposed on the basis of limited preclinical data; Bjarnason and colleagues recognised that treatment failure with sunitinib seemed to be related to three variables. Firstly, they noted that prolonged breaks off treatment seemed to be associated with loss of tumour control; hence they proposed reducing treatment breaks to just one week. Secondly, they noticed that some patients (≤20%) experienced virtually no side effects on the standard dose and schedule, but also seemed to have a reduced duration of benefit from the treatment, suggesting that these patients pharmacologically underdosed. Thirdly, they noted there were no complications and dry hands; minor nausea but no vomiting; the occasional bout of diarrhea. Patients themselves became attuned to the strategy, self-modifying their schedule to take extra or fewer days of treatment.

With this individualisation of dose and schedule, frankly extraordinary outcomes were achieved. In a single arm phase 2 trial, 117 patients with metastatic clear cell RCC were started on sunitinib 50 mg/day with the aim to treat for 28 days. Treatment breaks were reduced to 7 days. Sunitinib dose and the number of days on therapy were individualised based on toxicity aiming for ≤ grade II toxicity with dose escalation in patients with minimal toxicity. The null hypothesis for the primary end-point was a PFS of 8.5 months with the null hypothesis easily rejected (p < 0.001) with a median PFS of 12.9 months (95% confidence interval [CI]: 9.6–16.5). The median OS was 38.5 months (95% CI: 28.3–not reached), the median OS in the registration study for sunitinib and the registration study for pazopanib was only 22 months respectively. The ORR (46.1%) and stable disease rate (38.5%) translated into a clinical benefit for 84.6% of patients with no decline in quality of life scores during therapy. Complete responses were even seen in some (5%) patients, something never usually reported with VEGFR TKI. Fewer patients were dose reduced (26.5% vs. 50%) or discontinued due to toxicity (7.7 vs. 18–20%) compared to standard sunitinib dosing, and 20 (18.4%) patients were dose escalated to 62.5 mg (12) and 75 mg (8) with a wide individual variation in the optimal dose and treatment duration.

Individualised sunitinib therapy is therefore feasible, safe, manageable and delivers the best efficacy outcomes ever reported for oral vascular endothelial growth factor inhibitors in metastatic renal cell carcinoma. Compared to the registration studies survival was over a year longer.

The sobering epilogue of this remarkable story is that it is 13 years since sunitinib was first registered for renal cell carcinoma; 13 years in which further innovation could have improved outcomes for patients. With five checkpoint inhibitors and many tyrosine kinase inhibitors now available now for patients with advanced renal cell carcinoma, we must work diligently to test new ideas and improve outcomes for all patients.