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New Systemic Approaches in the Treatment of Metastatic Renal Cell Carcinoma

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1. Introduction

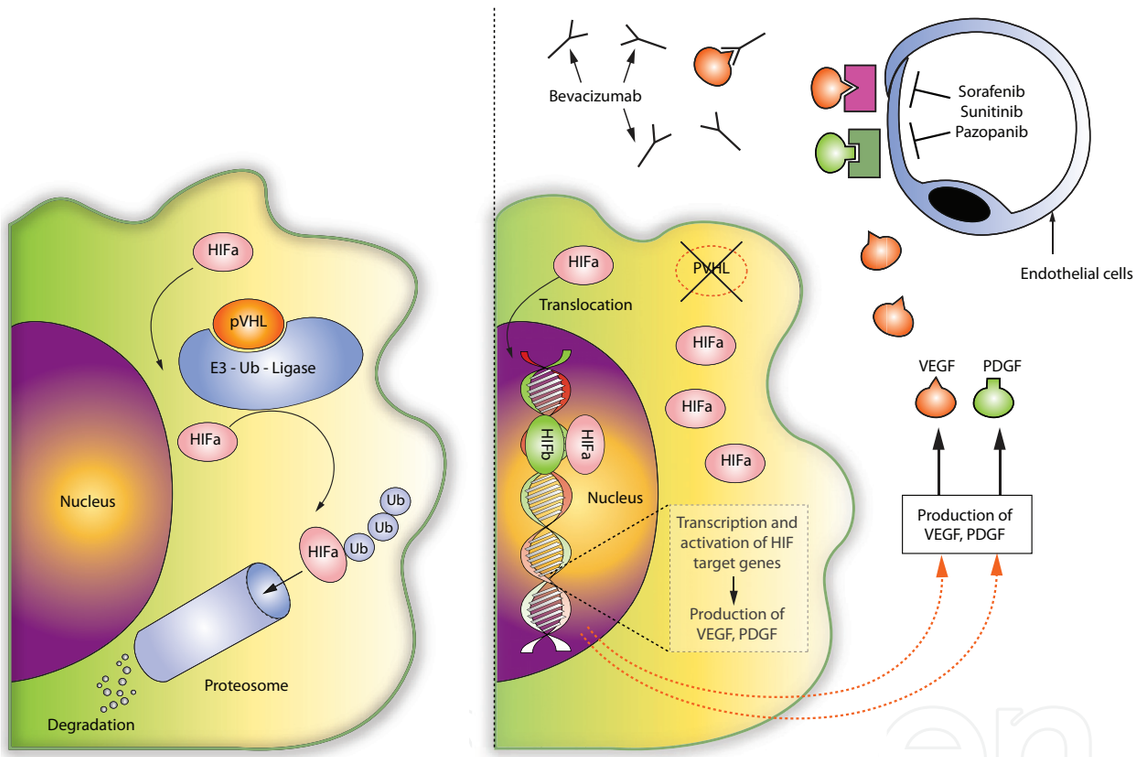
Cancer of the kidney comprises approximately 3% of all cancers in males and 2% in females according to Cancer Research UK statistics. (http://info.cancerresearchuk.org) Similar figures are seen globally. The majority (around 90%) of kidney cancers are Renal Cell Carcinomas (RCC), and clear cell carcinomas (adenocarcinomas) are the most common histological subtype. (Cohen & McGovern, 2005) The remaining 20-25% are papillary (Type I and II) (10-15%), chromophobe (4%) and collecting duct (including the rare medullary variant) (<1%) RCCs. (Cohen & McGovern, 2005) Up to a third of patients present at initial diagnosis with evidence of distant metastases, and a third of patients who undergo nephrectomy will have a recurrence within 5 years. These patients are considered candidates for systemic therapy. (Molina & Motzer, 2008)

2. Molecular pathogenesis

2.1 Clear-cell variant renal cell carcinoma

Unravelling of the biology, genetics and intracellular molecular signalling pathways of RCC has greatly improved our understanding of this disease. (Tan *et al*, 2010) The discovery of von Hippel-Lindau (VHL) tumour suppressor gene as a critical oncogene in the pathogenesis of renal cell carcinoma (clear-cell as well as some of the non-clear-cell variant) has greatly revolutionised the systemic therapy for renal-cell carcinoma where previously treatment had been disheartening. (Choueiri *et al*, 2008; Cohen & McGovern, 2005) The VHL protein (pVHL) encoded by the VHL tumour suppressor gene serves to regulate the normal cellular response to oxygen deprivation through its interaction with hypoxia-inducible factor (HIF). HIF is a heterodimeric (HIF-α/β) gene transcription factor that consists of an unstable α-subunit and a stable β-subunit. In the presence of normal oxygen tension (or normoxic state), VHL protein is the substrate recognition of an E3 ubiquitin ligase complex that targets HIF-α subunits for destruction by the proteasome as illustrated in Figure 1. (Kamura et al, 2000; Ohh et al, 2000) In the absence of functional VHL proteins, either as a result of mutation or hyper-methylation of the VHL gene as seen in majority of sporadic

cases of RCC (equivalent to a physiological hypoxic state), the pVHL-HIF-α interaction is disrupted due to loss of oxygen-dependent hydroxylation of HIF-α subunits leading to their intracellular accumulation. (Maxwell et al, 1999) HIF-α subunits are able to then translocate into the nucleus where they heterodimerize with the HIF-β subunits forming transcriptional factor complexes that induce transcription of various hypoxia-response genes. (Amato, 2011) This in turn leads to the increased production of downstream pro-angiogenic factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor alpha and beta (TGF-α and TGF-β) as illustrated by Figure 1. (Kim & Kaelin, 2004) It is noteworthy that angiogenesis holds the key to tumour survival when the rapidly growing tumour outstrips its own existing blood supply. It utilized the effective HIF mechanism to promote its own survival, growth and progression (metastasis). (Vaupel, 2004)



(a) (b)

Fig. 1. (a) Normoxia/normal VHL gene (b) Hypoxia/inactivated tumour suppressor VHL gene

2.2 Non clear-cell variant renal cell carcinoma

Papillary RCC is the second most common histological subtype of the non-clear cell variant of RCC. (Cohen & McGovern, 2005) It can be further categorized histologically into papillary types I and II with emerging data suggesting an underlying different genetics and molecular pathways. (Furge et al, 2010) Papillary type I RCC is associated with activating mutations of methyl-nitroso-nitroguanidine-induced (MET) oncogene. (Choi et al, 2006; Dharmawardana et al, 2004) These mutations results in ligand-independent activation of intracytoplasmic

tyrosine kinase domains which subsequently activate the hepatocyte growth factor/MET pathway. (Choi et al, 2006; Sudarshan & Linehan, 2006) Papillary type II RCC, in contrast is attributed to mutation of the fumarate hydratase (FH) tumour suppressor gene. (Linehan et al, 2007) FH is a tricarboxylic acid (Kreb) cycle enzyme that has a crucial role in aerobic cellular metabolism. (Isaacs et al, 2005) Mutation of FH (inactivation) leads to the generation of a pseudo-hypoxic state with subsequent upregulation of the HIF-α subunits. The mutated FH enzyme allows the accumulation of fumarate which in turn leads to inhibition of HIF-prolyl hydroxylase (HPH), a critical enzymatic regulator of intracellular HIF-α. When HPH is inactivated, the hydroxylation of HIF is disrupted leading to failure of recognition by pVHL; thus preventing the VHL-dependent proteosomal degradation of HIFs. Accumulation of HIF-α leads to downstream transcriptional overexpression of pro-angiogenic factors as described in the previous section. (Isaacs et al, 2005)

Chromophobe RCC accounts for 4% of all RCC. (Cohen & McGovern, 2005) Whilst the exact mechanism underlying its pathogenesis is not well established, the VEGF-angiogenic pathway was again implicated in view of the elevated levels of VEGF and its receptor mRNA in this variant of RCC. The KIT oncogene and the folliculin (FLCN) gene associated with the hereditary form of chromophobe/oncocytic RCC hybrid (Birt-Hogg-Dubé Syndrome) are other molecular targets identified in this variant. (Pavlovich et al, 2002; Yamazaki et al, 2003; Zbar et al, 2002) Due to the rarity of collecting duct RCC (including the virulent medullary variant), the underlying pathogenesis has not been identify. (Oudard et al, 2007a)

3. Prognostic indicators

For patients with recurrent or metastatic disease, a question often faced by the treating physician is their prognosis as treatment is being contemplated. In metastatic RCC, numerous studies have been undertaken to investigate the prognostic markers for metastatic RCC. (Tan et al, 2010) Five prognostic markers linked to the overall survival rate of patients with metastatic RCC have been identified. These include performance status, absence or presence of prior nephrectomy, serum lactate dehydrogenase, corrected serum calcium and haemoglobin level. (Motzer *et al*, 1999) Based on these criteria, patients could be grouped into three prognostic risk categories: favourable (0 risk features), intermediate (1-2 risk features) and poor (≥3 risk features) according to the Memorial Sloan-Kettering Cancer Centre (MSKCC) risk classification. (Motzer *et al*, 1999) Previous radiotherapy, time to systemic therapy, and the presence of hepatic, pulmonary, and retroperitoneal nodal metastasis were found to be independent prognostic factors in later studies. (Mekhail *et al*, 2005) The stratification of the different prognostic factors of renal carcinoma in clinical studies is important to allow comparison of therapies and to gain insight into the cohort of patients that would most benefit from the investigational agent.

When comparing with the clear-cell variant of RCC, localized papillary RCC when resectable, has a more favourable prognosis than conventional clear cell. (Cheville *et al*, 2003; Patard *et al*, 2005) However, metastatic papillary RCC portends a worse prognosis than their clear-cell counterpart. (Margulis *et al*, 2008) The type II papillary variant is thought to be more aggressive than type I with a higher propensity to metastasize early and progress rapidly. (Motzer *et al*, 2004) Chromophobe RCC is considered a good prognostic variant

and is associated with earlier stage tumour and longer overall survival compared to clear-cell RCC. In the metastatic setting, the reports from the medical literature are however conflicting. (Beck *et al*, 2004; Cindolo *et al*, 2005; Klatte *et al*, 2008; Motzer *et al*, 2002) Collecting duct RCC is associated with a grave prognosis, with up to one-third of patients presenting with metastatic disease on initial presentation. (Motzer *et al*, 2002)

4. Systemic treatment of metastatic renal cell carcinoma

Metastatic RCC is inherently refractory to chemotherapy and hormonal therapies. (Harris, 1983; Yagoda & Bander, 1989) The response rate of these treatment options are in the order of 10% thereby rendering RCC notoriously difficult to treat. (Yagoda & Bander, 1989) Solitary metastatic lesions may be surgically resected however beyond surgery, the only systemic options available prior to the era of targeted therapy were interferon alpha (IFN-α) and interleukin 2 (IL-2). (Oudard *et al*, 2007b) Allogeneic stem cell transplantation to induce a graft-versus-tumour response has also been examined but at the expense of significant life-threatening toxicities. This is therefore not recommended outside a clinical trial setting. (Barkholt *et al*, 2006; Gommersall *et al*, 2004; Rini *et al*, 2002) Patients with good prognostic features had a response rate of 10-20% to IFN-α and IL-2 and a modest improvement of median survival by ~2.5 months with IFN-α. (1999; Coppin et al, 2005) High dose IL-2 (infusion therapy requiring hospitalization) conferred a durable but small long term disease remission of ~5% in clinical responders. (Fyfe *et al*, 1995; McDermott *et al*, 2005) Both cytokine treatments especially with high dose IL-2 are toxic and difficult to administer. The classical side-effects of flu-like syndrome, depression with suicidal episodes from IFN-α; (Cohen & McGovern, 2005; Motzer *et al*, 1996) hypotension, oliguria, capillary-leak syndrome with secondary multi-organ failure, somnolence and confusion from IL-2 would render both treatments very onerous to patients. (Cohen & McGovern, 2005; Parton *et al*, 2006) Moreover the reported mortality rate of 4% from IL-2 would dilute any modest survival advantage gained. (Fyfe *et al*, 1995) Not surprisingly, the underlying enthusiasm in utilizing these agents as frontline therapy in metastatic RCC has been dampened with the advent of targeted therapies.

4.1 VEGF ligands and receptor inhibitors

Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and other angiogenic ligands once produced are able to circulate freely to to interact with cell surface receptors on the endothelial cell. Upon binding of these ligands to their cognate receptors, a cascade of intracellular signalling takes place resulting in downstream activation of Raf and mitogen-activated protein kinase (MAPK) (via phospholipase C-γ). This ultimately leads to the promotion of tumour angiogenesis, endothelial cell survival, proliferation, and migration. (Cebe-Suarez et al, 2006) The discovery of these complex VEGF signalling pathways presented an opportunity as therapeutic targets to treat metastatic RCC. VEGF signaling blockade can be achieved by either the removal of the circulating ligand with monoclonal antibody (bevacizumab) or by inhibiting its receptors with tyrosine kinase inhibitors (TKIs) as illustrated by Figure 1. (Jonasch et al, 2011) The four anti-VEGF therapies approved as of 2011: sunitinib, sorafenib, pazopanib and bevacizumab have revolutionized the treatment of metastatic RCC leading to significant improvement in progression-free survival (PFS) and in some instances overall survival (OS). (Tan et al, 2010)

4.1.1 Sunitinib

Sunitinib is an oral multi-kinase inhibitor that targets several VEGF receptors (VEGF-1, VEGF-2, VEGF-3) and other tyrosine kinase receptors (PDGFR, c-Kit, FLT-3, CSF-1R, and RET). (Abrams et al, 2003; Kim et al, 2006; Mendel et al, 2003; Murray et al, 2003; O'Farrell et al, 2003) Earlier uncontrolled trials showed sunitinib to be active in patients with advanced malignancies including RCC. (Faivre *et al*, 2006)

4.1.1.1 Sunitinib Intermittent Dosing (4 Weeks On / 2 Weeks Off)

The initial phase II study of sunitinib in patients with cytokine-refractory metastatic renal cell cancer assessed the clinical efficacy and safety of sunitinib as second-line therapy. (Motzer et al, 2006) The sixty three patients who failed cytokine-based therapy received 50mg of sunitinib for 4 weeks followed by a 2 week break (4/2), in a 6 week cycle. Forty percent (n=25) of patients had partial response (PR) and 27% (n=17) additional patients demonstrated stable disease (SD) for ≥3 months. The median time to progression and survival were 8.7 months and 16.4 months respectively. (Motzer et al, 2006)

A larger phase II multicentre trial similarly confirmed the anti-cancer efficacy of sunitinib in cytokine refractory patients with metastatic RCC. One hundred and six patients were enrolled and an overall objective response (ORR) of 44% was noted with 1% (n=1) and 43% (n=45) demonstrating a CR and PR respectively. (Motzer et al, 2007b) An additional 22% (n=23) showed SD for ≥ 3 months. The median duration of response for the 46 responding patients was 10 months whilst the median progression free survival (PFS) was 8.3 months. (Motzer et al, 2007b)

As the ORR of sunitinib seen in phase II trials far exceeded the rates previously reported for cytokine therapy as first line treatment of metastatic disease (42% vs. 10–15%), an international landmark phase III trial comparing sunitinib with INF-α for patients with metastatic clear-cell RCC was undertaken. (Costa & Drabkin, 2007; Motzer et al, 2007a) Seven hundred and fifty treatment naïve patients with clear-cell histology and good performance status (ECOG 0 or 1) were randomized in a 1:1 ratio to receive either sunitinib (dose as per earlier studies) or INF-α (9×10^6 units subcutaneously thrice weekly). (Desai *et al*, 2007; Motzer *et al*, 2007a) The median duration of treatment was 6 months (1-15 months) in the sunitinib group and 4 months (1-13 months) in the IFN-α group. The median PFS assessed by an independent third-party review was 11 months in the sunitinib group and 5 months in the IFN-α group, corresponding to a Hazard Ratio (HR) of 0.42 (95% CI 0.32–0.54; $p < 0.001$). (Motzer et al, 2007a) The investigators' assessment showed similar results, with a PFS of 11 months in the sunitinib and 4 months in the IFN-α group. An updated analysis published in 2009 has shown the ORR of 47% for sunitinib and 12% for IFN-α ($p< 0.000001$), with a median PFS of 11 months and 5 months, respectively, for sunitinib and IFN-α ($p< 0.000001$), similar to the original report. (Motzer *et al*, 2009) These results were uniformly seen, regardless of patient's age, gender and prognostic category. (Motzer *et al*, 2009) Patients on sunitinib also experienced a median OS in excess of 2 years. The OS was 26.4 months for sunitinib and 21.8 months for IFN-α ($p = 0.051$). (Motzer *et al*, 2009) A separate exploratory analysis of patients on both treatment arms who did not receive post-study cancer treatment showed the median OS with sunitinib was twice as long as IFN-α (28.1 months versus 14.1 months respectively, $p=0.003$). (Motzer *et al*, 2009) Based on these positive results, sunitinib has replaced INF-α in the first line treatment of metastatic RCC.

In addition to the aforesaid clinical trials, sunitinib was also evaluated in an expanded-access programme, designed to allow access to sunitinib in patients with metastatic RCC who would otherwise be excluded from the clinical trials. (Gore et al, 2009) Over 4500 patients, including older patients (≥65 years-old; n=1414), those with poorer performance status (ECOG PS ≥2; n=582), non-clear cell histology (n=288) and with brain metastases (n=320) were enrolled in this international, open-label study, thus resembling a more "real-world" setting. (Gore et al, 2009) Patients received a median of five sunitinib treatment cycles, with 56% of patients receiving more than 6 months of sunitinib therapy for a median duration of 15.6 months. In the total evaluable study population (n=4349), the median PFS was 10.9 months and median OS was 18.4 months. (Gore et al, 2009) The median PFS closely resembles the phase III study demonstrating consistent efficacy across patients within and outside clinical trials. No differences were noted in median PFS and OS between patients with or without prior cytokine therapy. Subgroup analysis of elderly patients demonstrated median PFS and OS of 11.3 and 18.2 months respectively. (Gore et al, 2009) In patients with poorer performance status, median PFS and OS were 5.1 months and 6.7 months respectively and lastly in patients with brain metastases with an overall poorer prognosis, a median PFS of 5.6 months and median OS of 9.2 months were observed. (Gore et al, 2009)

4.1.1.2 Sunitinib Continuous Dosing

Sunitinib has also been examined in an open-label multicentre phase II trial using continuous once daily dosing at a dose of 37.5 mg. (Escudier *et al*, 2009b) One hundred and seven patients were randomised equally to either morning or evening dose for a median 8.3 months. Forty three percent of patients had dose reduction to 25mg due to grade 3-4 adverse effects. (Escudier *et al*, 2009b) The ORR was 20%, with a median duration of response of 7.2 months, median PFS of 8.2 months and OS of 19.8 months. (Escudier *et al*, 2009b) The tolerability of the morning and evening dosing as well as the reporting quality of life (QoL) whilst on therapy was similar. Grade 3 diarrhoea, fatigue/asthenia and hand-foot syndrome were however noted more in the evening dosing cohort. This continuous regimen appeared promising and certainly deserves further investigation as this dosing schedule may benefit patients who are not able to tolerate the intermittent sunitinib dosing of 50mg and where one is concerned that the intermittent 37.5mg is suboptimal.

Sunitinib standard dosing schedule (50mg/day; 4 weeks on, 2 weeks off) was compared with continuous dose (37.5 mg/day) in a phase II trial (EFFECT) for patients with locally recurrent clear-cell RCC or metastatic RCC who had received no previous systemic therapy for advanced disease. The intermittent schedule when compared with the continuous schedule showed a trend to improved ORR (32.2% vs. 28.1%; p=0.444) and median PFS (8.5 months vs. 7.0 months; p=0.070). No difference were noted between the median OS (23.1 months vs. 23.5 months, p=0.615). (Motzer *et al*, 2011b) Interestingly the median OS was lower than the phase III sunitinib vs. INF-α trial which had a median OS of 26 months. The phase III trial had a higher number of patients with better baseline prognostic features (better performance status and more patients had underwent nephrectomy) which may account for better survival results. (Motzer *et al*, 2011b; Motzer *et al*, 2007a)

4.1.2 Sorafenib

Sorafenib is an oral multi-kinase inhibitor that inhibits Raf (Raf-1, B-Raf, and mutant *b-raf V600E*), VEGF (VEGF-2, VEGF-3), PDGFR (PDGFR-α, PDGFR-β), c-KIT, FLT3 and RET.

(Carlomango 2006, Wilhelm 2004) A phase II randomized discontinuation trial in 202 patients with metastatic RCC who failed previous systemic treatments were treated with sorafenib at 400 mg BD. (Ratain et al, 2006) Seventy-three patients exhibited tumour shrinkage of more than 25%. Sixty-five patients with stable disease at 12 weeks were randomly assigned to sorafenib (n=32) or placebo (n=33). Patients on sorafenib experienced prolonged median PFS (24 weeks) when compared to placebo (6 weeks) (p = 0.087). (Ratain et al, 2006) A second phase II trial comparing sorafenib with INF-α as first line treatment was undertaken in treatment naïve patients with metastatic RCC. Patients were randomised to receive sorafenib 400mg BD or IFN-α (9 million units thrice weekly). There was an option of dose escalation to sorafenib 600mg BD or crossover from INF-α to sorafenib upon disease progression. There was no significant improvement in PFS of sorafenib vs. placebo, 5.7 months vs. 5.8 months respectively. The ORR was 5% with sorafenib and 9% with IFN-α. (Escudier *et al*, 2009c)

A subsequent multi-centre placebo controlled phase III trial (TARGET) randomised 903 patients with metastatic clear-cell RCC on 1:1 to receive either placebo or sorafenib 400mg BD. The study cohort consisted of patients who previously received cytokine therapies with IFN-α, IL-2 or a combination of both, or radiotherapy, or had a nephrectomy. After 3 months of therapy, sorafenib resulted in a higher ORR (57% vs. 34%) and statistically significant longer PFS (5.5 months vs. 2.8 months; $p < 0.001$ with a HR of 0.44) when compared with placebo. (Escudier *et al*, 2007b) This was consistent with an earlier phase II second line trial that found PFS benefit was independent of age over or under 70 years, prognostic risk, prior cytokine therapy, lung, liver, bone or brain metastases, time from diagnosis, or whether or not the patient had clinical cardiovascular disease. (Beck *et al*, 2011; Escudier *et al*, 2007b) The latter included patients with ischemic heart disease, a previous myocardial infarction, left ventricular dysfunction, hypertension, epistaxis or central nervous system ischemia. (Beck *et al*, 2011) Patients on the placebo arm were permitted to cross over to sorafenib on diagnosis of progressive disease. In the first interim analysis, a trend towards better OS was noted in patients taking sorafenib, and this was unchanged in the final analysis (17.8 vs. 15.2 months, respectively, HR= 0.88; p = 0.146). (Escudier *et al*, 2007b; Escudier *et al*, 2009a) However, after placebo patients who crossed over on progression were censored, the difference in OS became significant (17.8 vs. 14.3 months; HR = 0.78; p = 0.029). (Escudier *et al*, 2007b)

Sorafenib has also been evaluated in two open-label expanded access studies in Europe (The European Advanced Renal Cell Carcinoma Sorafenib (EU-ARCS) and North America ARCCS (NA-ARCCS). The NA-ARCCCS offered insights into sorafenib in the real world setting. (Beck *et al*, 2008; Beck *et al*, 2011; Stadler *et al*, 2010) In Europe, about 1155 patients who failed at least one line of systemic therapy or were unsuitable for cytokine therapy received sorafenib 400mg BD until treatment intolerance or disease progression. Interim analysis revealed a median PFS of 6.9 months (95% CI: 6.2 – 7.5 months). (Beck *et al*, 2008) The North American access study enrolled 2515 patients in total with 2504 patients having received at least one cycle of sorafenib and therefore evaluable. Patients who had received no prior systemic therapy were allowed enrolment. Except for the difference in the median time from diagnosis (0.6 years vs. 2.2 years), prior nephrectomy rates (77% vs. 89%) and the incidence of >2 sites of metastatic disease prior to study entry (30% vs. 38%), the baseline characteristics were mostly balanced for patients who were treatment-naïve and patients who had at least one prior systemic treatment. The rate of disease progression was similar

for fist-line sorafenib patients and patients who had received at least on e prior systemic treatment (16% vs. 17%). Similarly the rates of PFS and disease control (ORR + stable disease) were 83% vs. 84% in the first-line and prior systemic therapy cohorts, respectively. (Eisenhauer *et al*, 2009) These results demonstrate that sorafenib provides similar benefit in first- and second- or later line patient populations in a non-randomised, open access trial. (Stadler *et al*, 2010)

4.1.3 Pazopanib

Pazopanib is an oral multi-targeted receptor tyrosine kinase inhibitor that inhibits VEGF (VEGF-1, VEGF-2, VEGF-3), PDGF (PDGF-α, PDGF-β) and c-KIT. (Hutson *et al*, 2010) Pazopanib showed activity in a phase I trial with 2 partial responders and 4 patients achieving disease stability out of a total 12 patients. (Hurwitz *et al*, 2009) Subsequently, a randomised phase II study to determine the ORR, duration of response and PFS was undertaken on patients with predominantly clear-cell histology who had never been treated or had failed one line of non-multi-kinase therapy. This study was originally designed as a randomized discontinuation study but revised to an open-label study after a planned interim analysis undertaken at 12 weeks showed a response rate of 38%. (Hutson *et al*, 2010) This was confirmed to be similar on an independent review. The final analysis of this trial showed an ORR (CR + PR) of 33.8% with similar response rate between the treatment naïve cohort (34%; 95% CI 26% to 41%) and patients with one previous line of therapy (37%; 95% CI 26% to 49%). The median duration of response was 68 weeks. The estimated median PFS was 11.9 months for pazopanib vs. 6.2 months for placebo. (Rini & Al-Marrawi, 2011)

Pazopanib was subsequently tested in a phase III trial where a total of 233 treatment-naïve and 202 cytokine-pretreated patients with advanced clear-cell RCC were randomized in a 2:1 ratio to pazopanib (n = 290) or placebo (n = 145). (Sternberg *et al*, 2010) Placebo with best supportive care was thought to be an acceptable comparator arm due to the inaccessibility of other tyrosine kinase inhibitors (sunitinib or sorafenib) in some centres at the time of study initiation. Moreover, utilizing placebo control in a randomised double blind design enabled better characterization of the safety and efficacy of the profile of pazopanib. Placebo with best supportive care remained as the comparator arm as cytokines as the standard of care were challenged due to their underlying toxicities. The PFS in the pazopanib arm compared with placebo was significantly prolonged in the overall study population (9.2 months vs. 4.2 months, HR 0.46; $p < 0.0001$), in treatment naïve patients (11.1 months vs. 2.8 months, HR: 0.40, $p < 0.001$) and in cytokine-pretreated patients (7.4 months vs. 4.2 months; HR 0.54, $p < 0.001$). The response rate was 30% with pazopanib versus 3% in the placebo group and the median duration of response was 58.7 weeks. The final OS results were updated at the European Society of Medical Oncology meeting in 2010. A median OS of 22.9 vs. 20.5 months were noted in the pazopanib and placebo arms respectively ($p=0.224$). The lack of significant benefit was attributed to the early, high rate and prolonged duration of cross-over from placebo to pazopanib. In fact, more placebo than pazopanib patients received subsequent treatment (66% vs. 30% respectively) with 54% of patients on placebo crossing over to the active arm, some occurred as early as week 6 into therapy. (Rini & Al-Marrawi, 2011; Sternberg, 2010) The efficacy of pazopanib as first line therapy is comparable and is an alternative agent in patients who do not tolerate sunitinib. As yet, no head-to-head efficacy data are available to show superiority or non-inferiority between

pazopanib and sunitinib and phase III trial (COMPARZ) is currently underway. (NCT00720941, 2011)

4.1.4 Bevacizumab

Bevacizumab is a humanized monoclonal antibody that uniquely targets the VEGF molecule and thus inhibiting this ligand with all of the receptors to which it binds. (Gommersall *et al*, 2004) A randomized phase II trial randomized 116 patients with metastatic clear-cell RCC to either placebo, low-dose (3 mg/kg given fortnightly) or high-dose bevacizumab (10 mg/kg given fortnightly). Accrual was halted when an interim analysis revealed a time to disease progression (TTP) benefit in the (high-dose) bevacizumab arm. A significant prolongation of TTP was observed in the high dose bevacizumab group ($p<0.001$; HR 2.55) compared to the placebo, and a smaller TTP benefit of borderline significance was reported for those receiving low-dose bevacizumab ($p=0.053$; HR 1.26). An objective partial response rate of 10.3% in the high-dose bevacizumab arm was noted. (Yang *et al*, 2003) Further data of bevacizumab as monotherapy was derived from a study comparing bevacizumab (10mg/kg; fortnightly) with placebo and bevacizumab with erlotinib (150mg bd), a small-molecule epidermal growth factor receptor (EGFR) inhibitor. Whilst the combination arm was well tolerated, it failed to demonstrate the superiority of this combination over bevacizumab alone. (Bukowski *et al*, 2007b) In both trials, the vast majority of patients treated with bevacizumab demonstrated some degree of tumour shrinkage, although in most instances the extent of tumour shrinkage did not meet the Response Evaluation Criteria in Solid Tumour (RECIST) criteria for PR. Interestingly the efficacy data from these two trials suggest the presence of clinical activity of bevacizumab monotherapy for metastatic RCC. (Elaraj *et al*, 2004) This is in clear contrast with other tumour types (non-small cell lung cancer, metastatic colorectal carcinoma, and metastatic breast carcinoma) where clinical benefit of single-agent bevacizumab without accompanying chemotherapy has been limited. (McDermott & George, 2010)

Two parallel large multicentre randomized international trials both examined the clinical efficacy of bevacizumab and IFN-α versus IFN-α alone, the previous standard of care for systemic treatment of patients with metastatic RCC. (Escudier *et al*, 2007c; Rini *et al*, 2008) Both trial (AVOREN, n=649; CALGB 90206 Intergroup Study, n=732), randomized treatment-naïve patients to IFN-α (9×10^6 units thrice weekly) and bevacizumab (10 mg/kg fortnightly) or placebo and IFN-α. The only difference was that the AVOREN study was placebo-controlled and the CALBG 90206 Intergroup study was an open labelled trial. (McDermott & George, 2010)

In the AVOREN study, the ORR was higher in the bevacizumab arm (31.4% vs. 12,8%, $p=0.0001$) with 70% of this group of patients demonstrating tumour shrinkage compared to 39% of patients on the IFN- α and placebo arm. The median PFS after a median follow-up of 22 months demonstrated a better median survival in the bevacizumab arm (10.2 months vs. 5.5 months; $p = 0.0001$). The improvement in PFS was evident irrespective of age, tumour subtype (clear cell or mixed), baseline VEGF level, and creatinine clearance. When stratified according to the MSKCC criteria, significant PFS benefits are seen in the low- and intermediate-risk groups but not detected in the poor risk category. As the number of patients enrolled in this poor subgroup were small (<10% of the enrolled patient), it is difficult to undertake any meaningful interpretation. (Escudier *et al*, 2007c)

A subsequent unplanned retrospective analysis revealed that PFS benefits was similar in 39% (n=131) of bevacizumab patients who received either 6 X 10^6 IU or 3 X 10^6 IU instead of 9 X 10^6 IU due to treatment related toxicity. The ORR for the reduced-dose group and full-dose group were 34% vs. 31% respectively and median duration of tumour response in turn was 13.6 months vs. 13.5 months respectively. This suggested that the dose of IFN-α could be reduced without compromising efficacy in patients who could not treatment related toxicities of IFN-α. (Melichar *et al*, 2008)

At the time of final OS analysis, only a trend towards OS was seen (23 months vs. 21.3 months, p = 0.1291). The effects of crossover to the bevacizumab arm, as well as the availability of second-line therapies where at least 35% received the TKIs (sunitinib and sorafenib) in both treatment arms, could well have compounded the results. An exploratory analysis showed that median OS was longer in patients receiving subsequent TKI therapy after bevacizumab plus IFN-α (n=113) compared with patients receiving TKIs after IFN plus placebo (n = 120) 38.6 months vs. 33.6 months respectively. (Escudier *et al*, 2007a)

In the Intergroup CALBG 90206, the ORR for active arm versus the control arm was 25.5% vs. 13.1% ($p<0.0001$) and the median PFS was in turn 8.4 months vs. 4.9 months ($p<0.0001$) respectively. (Rini *et al*, 2008) Only a trend in improved median OS was noted (18.3 months vs. 17.4 months, $p = 0.097$) and the trial did not achieve its primary end point, OS. The HR for progression was 0.71, which overlap with the AVOREN trial.

Stratification by MSKCC risk factors revealed the median PFS to be 11.1 months vs. 5.7 months in patients with absent risk factors (26%), 8.4 months vs. 5.3 months in patients with one or two risk factors (64%), and 3.3 months vs. 2.6 months in patients with three or more risk factors (10%), for the bevacizumab combination and INF-α monotherapy treatment groups, respectively. When stratified by the MKSCC risk factors, the median OS for bevacizumab / INF-α respectively was 32.5 months vs. 33.5 months for the favourable-risk group (26% of patients, p=0.524); 17.7 months vs. 16.1 months for the intermediate-risk group (64% of patients, p = 0.174) and lastly 6.6 months vs. 5.7 months for the poor risk group (p =0.25). (McDermott & George 2011, Rini *et al*, 2010)

Whilst no cross-over was allowed for the IFN-α monotherapy arm, 56% of study patients proceeded to at least one subsequent further systemic therapy in the form of a TKI. The patients who received second-line therapy were subsequently analysed and showed a median OS of 31.4 months vs. 26.8 months (p=0.079) in the bevacizumab/IFN-α and IFN-α monotherapy arms respectively. Amongst the patients who did not, the survival duration were 13.1 months vs. 9.1 months (p=0.059) respectively. (Rini *et al*, 2010)

Both trials were statistically robust and showed clear benefits in the median PFS arms with an overlapping HR and doubling of PFS when comparing the placebo/IFN-α arm with bevacizumab/IFN-α arm. (McDermott & George, 2010) The effects of crossover to the active bevacizumab arm in the AVOREN trial, as well as the permission of second-line therapies in both trials would account for the dilution of the actual overall survival benefits in both trials. (McDermott & George, 2010) Despite the lack of overall survival benefit and the notable toxicity of IFN-α with a large percentage of patients in the phase III trials undertaking dose reduction (40 – 60%), the combination of bevacizumab and IFN- α received Food and Drug Administration (FDA) approval for use as frontline of metastatic RCC.

4.2 mTOR Inhibitors

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that plays a crucial role in angiogenesis and regulation of cell cycle through a series of complex tightly regulated pathways. (Amato, 2011) mTOR activity is affected by a host of factors that influence cell functioning including nutrients (glucose, amino acid), energy depletion, as well as external signals such as cytokines, hormones, and growth factors. It also reacts to cellular stresses such as hypoxia, heat shock, oxidative stress, DNA damage and lastly a change in the microenvironment (pH or osmostic cell pressure). (Amato, 2011) The key pathway is via the phsophotidylinositol 3 kinase-protein kinase (P13K – AKT) pathway which is dysregulated in many cancers. (Amato, 2011; Beuvink *et al*, 2005) Activation of mTOR leads to phosphorylation of down-stream substrates (4E-binding protein-1 and protein S6 kinase) which in turn promotes mRNA translation, stimulation of protein synthesis and entry into the G_1 phase of cell cycle as illuastrated in figure 2. (Beuvink *et al*, 2005) Another important role of mTOR is the encoding and subsequent production of HIF-1α which drives angiogenesis, growth and survival of the cancer cells. The selective inhibition of this complex pathway by the mTOR inhibitors is achieved by binding to the intracellular protein FK506 binding protein 12 (FKBP-12) and causing inhibition of the kinase activity of the mTOR. (Amato, 2011) The two mTOR inhibitors, registered for the treatment of metastatic RCC are temsirolimus and everolimus.

4.2.1 Temsirolimus

The mTor inhibitor temsirolimus is similar to sirolimus (rapamycin) which has been used as an immunosuppressant in renal transplantation for many years. (Hudes *et al*, 2007) It affects cell division by inhibition of mTOR dependent protein translation, via binding to an intracellular protein (FK506 Binding Protein 12; FKBP12) resulting in a protein-drug complex. Temsirolimus is administered as a weekly intravenous infusion at 25mg. It is metabolised by CYP3A4 to active metabolite sirolimus and has a half-life of about 9 to 27 hours. (Hudes *et al*, 2007)

It was approved in 2007 by FDA as a first-line therapy in treatment-naïve metastatic RCC with poor prognostic features. Phase I and II trials of temsirolimus alone, or combined with IFN-α, found anti-tumour effects and stable disease in patients refractory to cytokine therapies. (Hidalgo *et al*, 2006; Raymond *et al*, 2004) In addition to that, another phase II trial on heavily pre-treated patients observed a median survival of 15 months. (Atkins *et al*, 2004) These encouraging results subsequently led to the development of an international multicentre phase III trial where 626 treatment-naïve patients with poor prognostic factors were randomized to temsirolimus (25 mg i.v. weekly), IFN-α (3×10^6 units, with an increase to 18×10^6 units s.c. thrice weekly) or the combination of temsirolimus (15 mg weekly) and IFN-α (6×10^6 thrice weekly). (Atkins *et al*, 2004) This was a pivotal trial that enrolled patients with poor prognostic factors only unlike previous studies with VEGF inhibitors which only recruited patients with good and intermediate risk features. The poor prognostic patients consisted of at least three or more of the 6 poor MSKCC prognostic factors. Another notable characteristic of recruitment is the enrolment of up to 20% of non-clear cell renal cell histological subtype. This is the only randomised study available so far for patients with the non-clear cell histology. (Atkins *et al*, 2004)

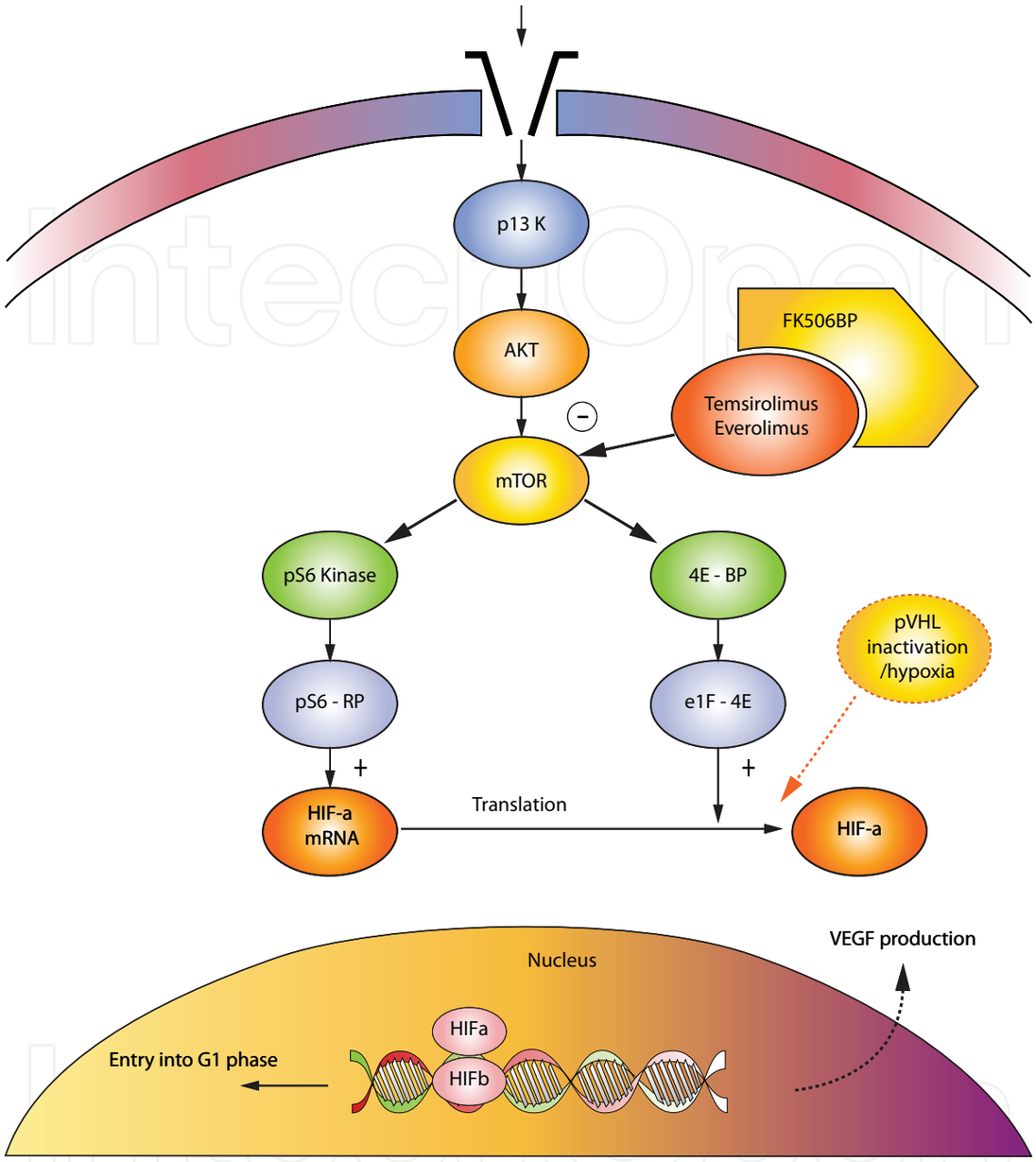


Fig. 2. External stimuli (growth factors)

Patients who received temsirolimus alone experienced a longer median OS (10.9 vs. 7.3 months; $p = 0.008$) and PFS (3.8 vs. 1.9 months; $p < 0.001$) compared with those who received INF-α alone. (Hudes *et al*, 2007) Patients in the combination therapy group had the most grade 3 or 4 adverse events leading to more dose reductions or delays. Their mean temsirolimus dose intensity was 10.9 mg per week vs. 23.1 mg per week for patients on temsirolimus alone. The median PFS in the temsirolimus, temsirolimus and IFN-α and IFN-α alone were 3.8, 3.7 and 1.9 months, respectively, and the median OS in turn was 10.9 months, 8.4 months and 7.3 months. (Hudes *et al*, 2007) Notably, older patients and patients with a higher serum LDH (> 1.5 fold the upper limit of normal) had better OS. (Hudes *et al*, 2007)

Clinicians are now faced with the challenge of treating patients who are refractory to VEGF targeted therapy as there is paucity of data in this area. The only published prospective randomised trial looking at this cohort of patients was RECORD-1 looking at everolimus vs. placebo. (Motzer *et al*, 2008) The few abstracts published on second line treatment with temsirolimus are all single institution case series confirming a modest activity in the second line setting with a median PFS of up to almost 4 months.

4.2.2 Everolimus

Everolimus is a derivative of rapamycin used in transplant medicine. Everolimus is an orally administered mTOR inhibitor with activity in patients with advanced clear-cell RCC who have failed VEGF-targeted therapies (sorafenib, sunitinib or both). (Motzer *et al*, 2008) Everolimus is converted to a main metabolite hydroxy everolimus is converted to a main metabolite hydroxy everolimus by the cytochrome 3A4 enzyme. The 30-hour half-life maintains a relative steady state achievable with the daily dosage regimen of 10mg/day. (Amato, 2011)

In RECORD-1, a double-blind placebo-controlled phase III trial, 410 patients with advanced clear-cell RCC which had progressed after sunitinib, sorafenib or both, were randomized in a 2:1 ratio to everolimus 10 mg once daily or placebo plus best supportive care. Regardless of age, gender, prognostic group, previous treatment with sorafenib, sunitinib or both, prolongation of PFS (4.9 vs. 1.9 months; $p< 0.0001$) was found with everolimus over placebo. (Motzer *et al*, 2008) However there was lack of difference for median OS (14.8 months vs. 14.4 months) as majority (80%) of patients in the placebo plus best supportive arm were allowed to cross over after the unbinding at the second interim analysis. This important landmark phase III trials proved the efficacy of mTOR inhibitors following VEGF therapy and as such received FDA registration for patients who have progressed following therapy with sunitinib and sorafenib. (Motzer *et al*, 2008)

5. New agents in clinical development

A number of second generation small molecule multi-targeted agents have been investigated in Phase II and III studies treating patients with metastatic RCC. (Fisher *et al*, 2011) These include axitinib and tivozanib which are in advanced clinical development, as well as dovitinib and others. (Fisher *et al*, 2011)

5.1 Axitinib

Axitinib is a potent oral agent that inhibits VEGFR-1, -2 and -3. It is rapidly absorbed with peak plasma concentration occurring 1 - 2 hours after administration on an empty stomach, terminal half-life of 3 – 5 hours, and bioavailability of 58%. (Pithavala *et al*, 2010) Dose-limiting toxicities seen in phase I studies were hypertension and mucositis, and in a phase II study, common adverse events also included diarrhoea and fatigue. ((Rixe *et al*, 2007b)

Axitinib has been investigated in a number of different cancers including cytokine-refractory metastatic RCC. A second line study in 52 patients using starting doses of axitinib 5 mg twice daily, resulted in two complete and 21 partial responses (ORR of 44.2%). The median response duration was 23 months and median overall survival was 29.9 months.

(Rixe *et al*, 2007b) Updated 5 year OS data from this study were presented in abstract form in 2011. (Motzer *et al*, 2011a) The 5 year survival rate was 20.6%. The ten patients surviving for more than five years had ORR 100% compared with 30% in <5 year survivors, took axitinib for longer (median 5.8 years vs. 0.67 years) and were fitter, with baseline ECOG PS of 0 in 80% of the longer term survivors compared with 53% in <5 year survivors. However they were all similar age, gender and risk factors. No unexpected new toxicities were seen with prolonged use of axitinib.

In a phase III second line study (AXIS), patients received axitinib at doses titrated up to 10mg BD or sorafenib 400mg BD. (Rini *et al*, 2011b) The 723 patients had progressive disease after one prior first line treatment (sunitinib, bevacizumab, temsirolimus or cytokines). The ORR was 19.4% for axitinib vs. 9.4% for sorafenib ($p=0.0001$) and significantly longer PFS (12.1 versus 6.5 months, $p<0.0001$) was seen in patients on the axitinib arm. Patients who had previously received cytokines were found to have significantly ($p<0.0001$) better PFS with axitinib (12.1 months) than sorafenib (6.5 months). This also occurred in those having prior sunitinib (4.8 vs. 3.4 months, $p=0.0107$). As part of the same trial, patient-reported kidney specific symptom and function assessments were secondary endpoints. (Cella *et al*, 2011) Outcomes according to validated tools were similar for both drugs during treatment, however as patients had a PFS with axitinib, this delayed worsening of the composite endpoint of cancer symptoms, progression or death compared with sorafenib.

5.2 Tivozanib

Tivozanib is an oral quinoline urea derivative small molecule TKI. It is a potent and selective inhibitor of VEGFR-1, -2 and -3 as well as inhibiting c-kit and PDGFR at higher concentrations. In 272 patients with advanced or metastatic RCC who had not received prior VEGF targeted therapy, tivozanib has shown promising efficacy and acceptable safety and tolerability in a phase II study reported in abstract form in 2011. (Nosov *et al*, 2011) All patients initially took tivozanib 1.5 mg daily for 16 weeks, and were then stratified according to response into stopping or continuing tivozanib, or if disease had stabilized, being randomised between tivozanib and placebo. Patients receiving placebo that developed progressive disease, or completed the double blind phase were allowed to restart tivozanib. Overall, 84% of patients demonstrated PR or SD by Week 16, ORR was 30%, disease control rate (DCR) was 85% and median PFS 11.7 months. Highest efficacy for tivozanib was in patients with clear-cell histology who had undergone a nephrectomy, who achieved an ORR of 36%, DCR of 88% and median PFS of 14.8 months. Commonest adverse effects included hypertension (45%) which was grade 3/4 in 12%, and dysphonia (22%). A low incidence of drug-related diarrhoea (12%), asthenia (10%), fatigue (8%), dyspnoea (6%), cough (5%), anorexia (5%), stomatitis (4%), hand-foot syndrome (4%) and proteinuria (3%) was reported. Overall median PFS, DCR and ORR were 11.7 months, 85% and 30%, respectively. Patients with clear-cell RCC who had undergone nephrectomy had PFS of 14.8 months and ORR of 36% with tivozanib. Phase III evaluation of tivozanib in nephrectomised patients with advanced clear cell RCC is on-going.

A phase Ib open-label study found tivozanib could be combined with temsirolimus at full dose/schedule in patients with advanced RCC (with clear cell component) who had failed up to one prior VEGF-targeted therapy. (Kabbinavar *et al*, 2011) Tivozanib was given orally

daily for 3 weeks on, 1 week off (1 cycle) and IV temsirolimus was given once weekly. A standard 3+3 dose escalation design was used at four levels from 0.5 mg to 1.5 mg per day and 15 to 25 mg per week of tivozanib and temsirolimus, respectively. There were 28 patients (26 male) of median age 62 years and Karnofsky Performance Status from 100 to 80. Median duration of treatment was 21.1 weeks. Treatment-related adverse events seen in ≥10% of patients were: fatigue (20 all grades/4 grade 3), decreased appetite (14/0), stomatitis (13/2), thrombocytopenia (10/4), diarrhoea (16/2), nausea (13/1), constipation (10/1), and dypsnoea (10/1). There were no grade 4 events, and no dose limiting toxicities. The MTD for the combination of tivozanib and temsirolimus was 1.5 mg/day and 25 mg/week, respectively. PR was seen in 28%, SD in 64% and DCR (PR and SD>24weeks) of 48%. The combination of tivozanib with temsirolimus was well tolerated and showed encouraging clinical activity in patients with advanced RCC.

5.3 Dovitinib

Dovitinib is a potent oral inhibitor of angiogenic factors, including the fibroblast growth factor (FGFR) and VEGF receptors. The maximum tolerated dose of dovitinib is 500 mg daily on a 5 day on/ 2 day off dosing schedule in 28 day cycles. A phase II study of dovitinib in clear-cell metastatic RCC patients previously treated with a VEGFR inhibitor and/or mTOR inhibitor was reported in 2011. (Angevin *et al*, 2011) (NCT1217931, 2011) In 51 patients best overall responses were PR in 8%, and SD ≥ 4 months in 37%. Median PFS and OS were 6.1 and 16 months respectively. Fifty nine patients median age 60 years and ECOG PS 0 or 1 were evaluable for safety. The most common adverse events were nausea (73%; grade 3 : 9%), diarrhoea (64%; grade 3: 9%), vomiting (56%; grade 3: 5%), decreased appetite (48%; grade 3: 7%), asthenia (36%; grade 3: 12%), and fatigue (36%; grade 3: 10%). An on-going phase 3 trial is comparing dovitinib with sorafenib in patients who have had one previous VEFR- and mTOR-targeted therapy.

6. Combination therapy in metastatic RCC

Despite being in the era where increasing numbers of VEGF and mTOR inhibitors are at the clinician's disposal, their optimal use in patients with metastatic RCC has not been fully ascertained. Undeniably these agents have conferred significant survival benefits compared to historical series, however most patients eventually develop resistance and relapse after 6 months to 3 years of therapy. (Jonasch *et al*, 2011) This underscores the strong need to develop novel treatment strategies to achieve better clinical outcomes. This could be achieved by the use of combinations of anti-angiogenic agents or with mTOR inhibitors, chemotherapy or immunotherapy. Sequencing treatment with different anti-VEGF agents as well as with mTOR inhibitors and immunotherapeutic agents could be another solution which will be discussed subsequently. (Jonasch *et al*, 2011)

The concept of combining two (or more) targeted agents is biologically plausible as each agent may affect different targets simultaneously potentially resulting in additive or synergistic effects and achieving better clinical outcomes. (Hutson, 2011) Using a combination of drugs which target the same pathway (e.g. VEGF) at two or more different levels, has been termed "vertical blockade". In contrast, "horizontal blockade" occurs when the different pathways are blocked simultaneously by one or multiple agents in combination. (Hutson, 2011) It should be

noted that combination therapy is often undertaken at the cost of increased toxicities as evidenced by some of the phase I trials where sunitinib was combined with temsirolimus, bevacizumab or everolimus. (Feldman *et al*, 2009; Rini *et al*, 2009)

6.1 VEGF-ligands or receptor inhibitors / mTOR plus immunotherapy combination

This is best illustrated by the two single arm phase II studies combining sorafenib with standard dose of IFN-α which conferred higher ORR (approximately 30%) and longer PFS (7 – 12 months) when compared with phase III data of sorafenib monotherapy. (Gollob *et al*, 2007; Ryan *et al*, 2007) However, in a randomised phase II study comparing sorafenib monotherapy with sorafenib /low-dose IFN-α combination, a very similar response rates and longer PFS were demonstrated equally in both arms. Interpretation of these phase II data required caution given the small number of patients recruited in comparison with the more robust phase III sorafenib vs. placebo trial. (Jonasch *et al*, 2010)

The AVOREN and CALBG 90206 trial demonstrated that the bevacizumab / IFN-α combination had achieved better clinical outcome when compared with IFN-α alone. (Escudier *et al*, 2007c; Rini *et al*, 2008) Unfortunately, the lack of bevacizumab as a control arm did not help address the question as to whether the addition of IFN-α to bevacizumab was able to achieve a more superior outcome compared to bevacizumab alone. A small randomised phase II study comparing erlotinib and bevacizumab with bevacizumab alone reported a non-statistical small PFS difference of 0.5 months (9.0 months vs. 8.5 months; p=0.58). Although this is small benefit may be clinically irrelevant, this trial provided insight into the clinical efficacy of bevacizumab as monotherapy. (Bukowski *et al*, 2007b)

A randomised three-arm trial was undertaken comparing temsirolimus (25mg) / bevacizumab (10mg/kg) combination with sunitinib alone and with IFN-α ($9X\ 10^6$ IU thrice weekly) / bevacizumab (10mg/kg) combination in patients with advanced RCC (TORAVA). A total of 171 treatment naïve patients were recruited in a 2:1:1 ratio and was equally distributed into the three arms. The reported median FPS was similar (8.2 months) for both temsirolimus (25mg) / bevacizumab (10mg/kg) (experimental) arm and sunitinib (comparator) arm. The duration for bevacizumab / IFN-α was however up to 16.8 months. The patients in the experimental arm experienced a high number of discontinuation from treatment for reasons other than progression (51%) when compared to the sunitinib arm (12%) and bevacizumab / IFN-α arm (38%). (Negrier *et al*, 2011) Furthermore up to 77% in the experimental arm experienced a grade 3 or higher toxicity. The trial again highlighted the lack of survival benefit due to a toxic combination that is poorly tolerated and the investigators appropriately commented that this combination would not be recommended for first-line treatment in patients with metastatic RCC. (Negrier *et al*, 2011) Similarly, when temsirolimus was prescribed in conjunction with IFN-α in a phase III trial for patients with poor prognostic advanced RCC, the overall survival benefit was worst in the tmesirolimus / IFN-α arm compared to temsirolimus monotherapy arm. Once again, toxicity prevailed in the combination arm and therefore the temsirolimus / IFN-α combination is not recommended as standard practice yet outside a clinical trial for treatment of advanced RCC. (Hudes *et al*, 2007)

6.2 VEGF-ligands or receptor inhibitors / mTOR combination

Sorafenib like sunitinib was also investigated in combination with bevacizumab in two phase I studies. In one the study of patients with metastatic RCC, the median time to

progression was 11.2 months and the partial response rate was 46%. (Sosman *et al*, 2008) In the second trial which included 39 patients with solid tumours (with 3 patients with RCC), PR or disease stabilisation of ≥4 months was observed in 59% of the assessable patients, and a PR was achieved in one of the 3 patients with RCC. (Azad *et al*, 2008) The combination arm required dose reduction of both agents and resulted in a considerably lower maximum tolerated dose compared to maximal tolerated dose of the single agent. It is postulated that bevacizumab most likely enhanced the side-effects of sorafenib such as hypertension and hand-foot syndrome. (Azad *et al*, 2008; Sosman *et al*, 2008) When sunitinib was combined with bevacizumab, a high incidence of haematological and vascular toxicities (including microangiopathic haemolytic anaemia) and hypertension were observed. (Feldman *et al*, 2009) Again bevacizumab was likely responsible for the exaggeration of the side-effects of sunitinib which would have been otherwise manageable.

Finally, a phase II trial examining the feasibility, tolerability, and efficacy of multiple combinations of currently available therapies are being tested in the Eastern Cooperative Oncology BeST trial. The four arms are bevacizumab (10mg/kg), bevacizumab (5mg/kg) /temsirolimus (25 mg), bevacizumab (5mg/kg) and sorafenib (200mg twice daily)/ temsirolimus (25mg). (NCT00378703, 2006) This trial will provide insight into the efficacy of bevacizumab monotherapy and the clinical tolerability and efficacy of lowered dose of bevacizumab and sorafenib dose in conjunction with temsirolimus where previously significant toxicities was noted on the earlier phase II studies.

7. Sequencing therapy in metastatic RCC

Sequencing the systemic treatment of metastatic RCC has several potential benefits. Sequential treatment is less toxic than combination therapy and thus allowing patients to be exposed to a more optimal dose (and subsequent higher total accumulative dose) resulting in improved clinical efficacy. It also creates a treatment continuum with the goal of maintain responding patients on treatment for as long as clinically feasible. Lastly, targeting the different pathway at different point in time theoretically offers the benefit of overcoming the resistance to the individual agents. (Bellmunt, 2009)

7.1 Antiangiogenic therapy after immunotherapy

A phase II study published in 2003 examined the role of bevacizumab (10mg/kg) post progression on immunotherapy demonstrated a time-to-progression (TTP) of 4.8 months. (Yang *et al*, 2003) Two phase II trials mentioned earlier on similarly examined the efficacy of sunitinib post immunotherapy revealed promising survival benefits which subsequent led to the landmark phase III trial comparing sunitinib with IFN-α. (Motzer *et al*, 2006; Motzer *et al*, 2007b) The phase III sorafenib trial vs. placebo (TARGET) also recruited patient who had cytokine therapy and observed a doubling of PFS benefit of 2.8 to 5.6 months. (Escudier *et al*, 2007b) More recently, in a phase II trial examined the use of axitinib post cytokine therapy demonstrated a TTP of 15.7 months. (Rixe *et al*, 2007b) Whilst it is possible to compare the results of each individual phase II trials and rank them to their clinical benefit, a proper conducted phase III is essential to determine the best anti-angiogenic agent to use post-cytokine therapy.

7.2 mTOR blockade after anti-angiogenic therapy

The best illustrating example is the RECORD-1 trial which investigated the benefits of everolimus vs. placebo with best supportive care post progression on sunitinib, sorafenib or both. Of note 71% of patients had received prior sunitinib whilst 55% sorafenib. Patient that received everolimus achieved an additional of 3-month of PFS benefit regardless whether they received sunitinib or sorafenib. No overall survival benefits were noted due to large numbers of patients from placebo crossing over to everolimus arm (80%). (Motzer *et al*, 2008)

An on-going trial (RECORD-3) will randomly assign patients between either everolimus or sunitinib where at first sign of progression, patients would cross over to sunitinib if they were on everolimus and vice versa. The primary end point of this trial is to assess whether PFS after first-line treatment for patients who received everolimus will be non-inferior to patients who receive sunitinib after first-line therapy. (NCT00720941, 2011)

7.3 Serial anti-angiogenic agents

Axitinib has been investigated in both phase II and III second-line trials in advanced RCC. The results of the survival benefits have so far been encouraging especially in the phase III trial comparing with sorafenib. (Dutcher *et al*, 2008) Further trials will be undertaken clarify the outcomes. Specifically, in the Sequential Two-agent Assessment in Renal Cell Carcinoma Therapy (START) two hundred and forty treatment-naïve patients with clear-cell component mRCC will be randomly assigned to receive bevacizumab, pazopanib, or everolimus. On first progression or intolerance to therapy, patients will be randomly assigned to one of two of the remaining agents. The primary end point is the detection of the longest combination of the TTP. (NCT1217931, 2011)

A retrospective study described the efficacy of sorafenib or sunitinib in the first-line setting in 49 patients with metastatic RCC as well as the subsequent derived benefit after switching to the alternative agent on progression. (Dudek *et al*, 2009) The TTP for patients treated with sunitinib or sorafenib (after initial treatment) was 5.8 and 5.1 months respectively (p=0.299). However, sequential treatment with sorafenib followed by suntinib resulted in a trend toward improved TTP (p = 0.115). Similarly, the median OS was better for patients who received sorafenib followed by sunitinib (23.5 months) than if they received sunitinib after sorafenib (10.4 months; p=0.061). This analysis of median survival did not include patients who did not need to cross over. This retrospective study suggested the benefit of utilizing sorafenib as first line may improve duration of disease control if a subsequent agent is used and certainly warrants further investigation. (Dudek *et al*, 2009) The SWITCH trial is a prospective phase III trial which will randomize patients to upfront sunitinib and switching to sorafenib on progression versus switching from sorafenib to sunitinib on progression. The primary end point is the PFS and hopefully this trial will show further insight into which anti-VEGF treatment sequence will confer better clinical outcome in patients with metastatic RCC. (NCT00732914, 2010)

8. Systemic treatment for non-clear-cell RCC

The treatment for advanced non-clear-cell RCC is less well established than the clear-cell variants and the evidence to guide treatment is limited. Majority of the data is derived from

expanded access trials, retrospective series, and subset analyses of major trials. (Tazi el *et al*, 2011) The phase III sunitinib trial virtually excluded all patients with non-clear-cell RCC. In spite of this, sunitinib was made available to all patients with clear-cell and non-clear-cell histology in a subsequent multi-centre, international, non-randomized expanded access compassionate trial. (Motzer *et al*, 2007a) A total of 588 patients with non-clear cell histology (not characterized further) received sunitinib and of that, 437 evaluable patients demonstrated an ORR of 11% (n=48) with 46 partial responders and 2 complete responders) and 57% had stable disease (n=250) for at least 3 months. (Gore *et al*, 2009) The median OS was 13.4 months. The ORR of 11% was lower than the original phase III study and was thought to due to the non-mandatory reporting of the disease response and the reliance of local practice to detect any change in the disease burden. The authors of the study therefore concluded that sunitinib is active in subjects with non-clear- cell histology amongst other subsets of patients (poor performance status, brain metastasis and patients of ≥ 65 years old) which were not enrolled in the original trial. (Motzer *et al*, 2002)

One of the largest retrospective series for papillary RCC was a multi-centre review consisting of 41 patients treated with either sunitinib or sorafenib. The response rate was disappointing with an ORR of 5% for all comers but was higher at 17% for sunitinib. The PFS was statistically longer for patients treated with sunitinib (11.9 months) when compared with sorafenib (5.1 months; $p < 0.001$). The PFS for sunitinib was comparable to the phase III clear-cell trial suggesting clinical efficacy in sunitinib for papillary carcinoma. (Choueiri *et al*, 2008) In contrast, two small phase II studies showed little-to-no clinical response and disease stability being the best clinical response for only a short duration of 1.4 to 3 months. (Plimack *et al*, 2010; Ravaud *et al*, 2009)

The efficacy of sorafenib in the treatment of advanced papillary variant is best demonstrated in the Advance Renal cell Carcinoma Sorafenib Expanded Access Program in North America. One hundred and fifty eight patients with papillary RCC were enrolled. Of the 107 patients with papillary RCC that could be evaluated, 84% (n=90) demonstrated 3 PR and 87 SD for a duration of 8 weeks or more. Sixteen percent (n=17) of patients showed early progression of disease. (Beck *et al*, 2008)

The phase III international, multicentre trial, comparing temsirolimus, IFN-α, or combination of both, is the first trial that prospectively recruited all histological subtypes of RCC. Twenty percent (n=120) were classified as non-clear cell RCC without further subclassification at the outset due to the absence central pathology review. (Hudes *et al*, 2007) An improvement in the median OS and median PFS were seen in the temsirolmus monotherapy arm compared to the combination temsirolimus/IFN-α or IFN-α monotherapy arm. Subsequent exploratory subset analyses based on tumour histology determined that 55 patients that had papillary RCC also demonstrated an OS and PFS benefit when treated with temsirolimus. (Schmidt *et al*, 2001) The OS and PFS for temsirolimus vs. IFN-α were 11.6 months vs. 4.3 months and 7.0 months vs. 1.8 months respectively. These results led to the subsequent FDA approval of temsirollimus as treatment for non-clear-cell histology in advanced RCC. Everolimus has demonstrated efficacy in the pivotal trial for patients with clear-cell RCC, post progression on sunitinib, sorafenib or both in the RECORD-1 trial. (Motzer *et al*, 2008) This has prompted the development of an open-label, single arm, multi-centre phase II examining the efficacy of everolimus as first-line systemic therapy for patients with advanced papillary RCC. (Amato,

2011) Central confirmation of histology and subclassification into type I and II will be undertaken. This trial which is still recruiting will hopefully show further insight into the treatment of papillary RCC which thus far has been disappointing.

Erlotinib was examined in a phase II study in treatment naïve patients with locally advanced or metastatic papillary RCC. (Gordon *et al*, 2009) Of the 52 registered patients, 45 were evaluable. The ORR was 11% (n=5) and the DCR was 64% with five partial responders and 24 patients with stable disease. The median OS time was 27 months with a 29% probability of freedom from treatment failure at 6 months. The presence of EGFR receptors scores and staining intensity determined by immunohistochemistry showed no correlation with TTP or OS. The estimated median survival was estimated to be 27 months. (Gordon *et al*, 2009) Combination of erlotinib with bevacizumab is currently underway designed to further evaluate the efficacy of erlotinib. (2010)

As with papillary variant of RCC, the chromophobe variant has also been excluded from many of the initial targeted therapy trials. Not surprisingly the data is even more limited. Furthermore, with the low incidence of 4% and the low likelihood of chromophobe to metastasize, any attempts to recruit patients of this type into a clinical trial is a difficult process. In the sorafenib access program described earlier, an overall DCR of 90% was noted with 5% (n=1) demonstrating partial response and 85% (n=17) of the patients experiencing disease stability for at least 2 months. (Stadler *et al*, 2010) The chromophobe variant were also included in the phase III temsirolimus versus IFN-α trial but the subgroup analysis only focused on papillary variant and the data for chromophobe was therefore not published. Nevertheless the PFS and OS were prolonged in the non-clear cell subgroup, therefore hinting some weak evidence of efficacy in this group of tumour. (Tazi el *et al*)

The strongest treatment evidence for treatment of the rare collecting duct renal cell carcinoma stemmed from a phase II multi-centre trial of 23 treatment-naïve patients who received cisplatin or carboplatin if inadequate renal function with gemcitabine. This variant is very aggressive and patient often presents with more advanced stage and succumbed earlier. This combination was selected based on some similarities in the histological features comparing with transitional cell carcinoma of the urinary bladder. In the trial, there was an observed ORR of 26%. The median PFS and OS were 7.1 months and 10.5 months. (Oudard *et al*, 2007a) To date, there is very little data to support the use of anti-VEGF therapies in this very bad prognostic cancer.

9. Side effects of targeted therapies used in renal cell carcinoma

The clinical benefit of newer targeted agents in metastatic RCC over previous conventional treatment has been shown in Sections 1 to 5 in this chapter. However as with any new treatment, sideeffects must be carefully measured and evaluated against older treatments and supportive or pharmacologic interventions developed for their prevention or control. (di Lorenzo *et al*, 2011) This is essential when considering patients' quality of life (see Section 11) and should allow patients to stay on beneficial treatment for as long as possible. (Bellmunt, 2007) Safety data from clinical trials and post-marketing surveillance have identified that many of the targeted therapies have toxicities that are different from those usually seen with conventional anticancer drugs. (di Lorenzo *et al*, 2011; Ravaud, 2011)

These angiogenesis inhibitors directly or indirectly target the VEGF pathway, and their individual mechanisms are pointers to their toxicities. (Schmidinger & Bellmunt, 2011) They share several adverse effects in common, including hypertension, fatigue, gastrointestinal, skin, and bone marrow effects. The mTOR inhibitors can cause metabolic alterations, immunosuppression and interstitial pneumonitis, whereas hypothyroidism is seen in patients taking sunitinib, potentially sorafenib and pazopanib. (di Lorenzo *et al*, 2011) Suggestions for management are shown below. The importance of patient education with respect to self-management strategies has been emphasized. (Ravaud, 2011)

9.1 Hypertension

Hypertension is a well recognised class side effect commonly observed in cancer patients treated with angiogenesis inhibitors that target the VEGF pathway, but not with mTOR inhibitors. (Izzedine *et al* 2009, diLorenzo 2011) Hypertension is reported with axitinib, bevacizumab, sorafenib, sunitinib and pazopanib. (Escudier *et al*, 2007b; Motzer *et al*, 2007a; Rini *et al*, 2011a; Rixe *et al*, 2007a; Sternberg *et al*, 2010) Hypertension has occurred whether or not the patient has a history of high blood pressure, however incidence may be higher in patients with pre-existing cardiovascular disease. Reversible posterior leukoencephalopathy syndrome is a rare association with hypertension seen with sunitinib and sorafenib where patients in addition experienced seizures and impaired vision thought to be attributed to capillary leakage and vasogenic oedema of the brain. This is reversible with cessation of the implicated agent. (Kapiteijn *et al*, 2007) Hypertension is an independent risk factor for the onset of cardio- and renovascular disease. In patients with metastatic disease, the goal of optimizing blood pressure is to allow continuous and safe administration of the anti-VEGF agents. (Izzedine *et al*, 2009; Keefe *et al*, 2011) Blood pressure monitoring (either daily or multiple times per week) is recommended and the use of antihypertensive medication may be required to avoid potential cardiovascular complications. Algorithms for hypertension management have been developed, (di Lorenzo *et al*, 2011) and treatment should be individualised to the patient. (Izzedine *et al*, 2009) The best anti-hypertensive agents is yet to be determined, however an angiotensin-converting enzyme (ACE) inhibitors is a logical choice if bevacizumab is the underlying cause as they may improve the associated proteinuria. (Keefe *et al*, 2011) Angiotensin II inhibitors, diuretics, hydropyridine calcium channel blockers (CCBs), and β-blockers are also possible anti-hypertensive agents. In patients on anti-hypertensive medications at baseline, an increase in the dose of pre-existing antihypertensive medications may be required. Temporary suspension of therapy may be required to allow for better control of the hypertension. In some cases, severe hypertension with life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis) has led to permanent discontinuation. (Keefe *et al*, 2011) The relationship between hypertension and anti-tumour effect is postulated with several of the drugs used for renal cell cancer and this will be addressed in Section 10.

9.2 Fatigue

Fatigue is the commonest of the constitutional side effects seen with the targeted agents used in metastatic RCC, but is less common than with cytokine treatment. (Adams & Leggas, 2007; di Lorenzo *et al*, 2011; Hutson, 2011; Motzer *et al*, 2007a) The incidence of fatigue in Phase III studies ranged from 14% to 51% for all grades, up to 11% for grade 3–4.

(di Lorenzo *et al*, 2011) Patients with cancer-related fatigue experience a chronic feeling of tiredness or lack of energy that is not relieved by rest. Fatigue can be caused by the targeted therapy and/or aggravated by other factors, such as anaemia, anxiety, hypothyrodism or depression, nutritional status, side effects of other medications or even organ dysfunction. (di Lorenzo *et al*, 2011; Ravaud, 2009) Patients may find it useful to record a daily fatigue diary to see when their energy levels are highest during the day in order to allow themselves time and energy for activities they enjoy. Evidence-based pharmacological interventions remain scarce, but monitoring and treating patients for any aggravating factors may help. If grade 3–4 fatigue persist, it may be necessary to dose reduce or stop treatment. (di Lorenzo *et al*, 2011; Ravaud, 2009)

9.3 Gastrointestinal side effects

Gastrointestinal toxicities are common to most of the targeted therapies for RCC but rarely lead to dose interruptions. (di Lorenzo *et al*, 2011) These include diarrhoea, nausea and to a lesser degree vomiting. Standard protocols used in prevention and treatment of these toxicities in patients having cytotoxic chemotherapy are suitable for use in this setting. Supportive medications will include loperamide (up to 16mg per day) for diarrhoea; dopamine antagonists such as metoclopramide or where necessary 5HT3 receptor antagonists for nausea and vomiting. (di Lorenzo *et al*, 2011)(di Lorenzo 2011) Oral mucositis is also reported with the mTOR inhibitors everolimus and temsirolimus, and the tyrosine kinase receptor inhibitors. Evidence-based guidelines advise good oral hygiene, local anaesthetic mouthwashes or systemic analgesics if required for mouth pain, and avoidance of alcohol based mouthwashes. (see www.mascc.org)

9.4 Dermatological side effects

Various dermatological side effects can be seen with all of the agents used in metastatic RCC. Prevention and management is important to maintain patients' health-related quality of life as well as treatment dose intensity. (Lacouture *et al*, 2011) Toxicities seen include papulopustular (acneiform) rash, hair changes (including alopecia, colour changes), dermatitis enhancement, pruritus, xerosis, skin fissures, paronychia and hand-foot skin reactions (HFSR). (di Lorenzo *et al*, 2011; Lacouture *et al*, 2011) HFSR appears as plaques or blisters with painful tingling or burning sensations in the soles of the feet or palms of the hands, and these effects are particularly common with sorafenib and sunitinib. (di Lorenzo) Avoiding tight shoes, and using moisturiser, emollient creams and topical treatment containing urea or salicyclic acid is suggested. (di Lorenzo *et al*, 2011; Ravaud, 2009) Evidence-based treatment guidelines for managing skin toxicities have recently been published by the MASCC Skin Toxicity Study Group (Lacouture *et al*, 2011) Topical hydrocortisone cream (1 %) and oral antibiotics (doxycycline or minocycline) are the mainstay of prevention of papulopustolar rash or if they are painful. (Lacouture *et al*; Ravaud, 2009)

9.5 Other reported adverse effects

Clinical hypothyroidism defined as a decrease in free thyroxine index with elevated thyroid stimulating hormone levels has been reported in patients taking sunitinib, pazopanib and sorafenib (the latter specifically in Japanese subjects). (di Lorenzo *et al*, 2011) Screening pre-

treatment and on days 1 and 28 each cycle, and use of thyroxine is advised. (di Lorenzo *et al*, 2011)

Heart failure is seen with a number of targeted agents including sunitinib, bevacizumab and sorafenib. (Jarkowski *et al*, 2011) Patients, especially those with pre-existing cardiovascular disease, should be closely monitored especially if they have cardiac risk factors. (Ravaud, 2011) If heart failure occurs it should be managed according to standard protocols, and the offending agent ceased. (Jarkowski *et al*, 2011) Myocardial ischaemia or infarction was significantly more frequent in patients taking sorafenib group (3%) than placebo.

Severe and fatal hepatotoxicity (boxed warning) and grade 3 or 4 proteinuria have occurred with pazopanib treatment which necessitates routine monitoring of liver function tests, and urinalyses. (Ravaud, 2011)

Venous and arterial thromboses have been reported in patients on bevacizumab. (Escudier *et al*, 2007c; Rini *et al*, 2008) Both sunitinib and sorafenib are also associated with thromboembolic events although the rates are lower to bevacizumab. (Keefe *et al*, 2011) The role of therapeutic anticoagulation for venous thrombosis and aspirin for arterial thrombosis are currently being undertaken given the increased use of the anti-VEGF agents not only in metastatic RCC but in other advance cancers such as non-small cell lung cancer and colorectal carcinoma. (Keefe *et al*, 2011) Pazopanib has also been associated with arterial thrombotic events including myocardial infarction or ischaemia, cerebrovascular accidents and transient ischaemic attacks. Incidence was 3% of patients on pazopanib compared with none in patients taking placebo. (Sternberg *et al*, 2010) The incidence of haemorrhagic events (all grades) in the pazopanib arm was 13% compared with 5% with placebo. (Sternberg *et al*, 2010)

Other agent-specific side effects include adrenal insufficiency, especially in the setting of increased physical stressors with sunitinib; (Desai *et al*, 2007) hyperglycaemia, hyperlipidaemia and acute infusion reactions with temsirolimus (Hudes *et al*, 2007); and non-infectious pneumonitis in patients receiving everolimus, or temsirolimus. (Ravaud, 2011) Patients with pneumonitis may exhibit few if any symptoms and the diagnosis is radiological. Monitoring is advisable although pneumonitis resolves spontaneously when the mTOR inhibitor is ceased and rarely requires use of corticosteroids. (Hudes *et al*, 2007)

Lastly, thrombotic microangiopathy has been reported in association with suntinib, sorafenib, and bevacizumab, either as combined or as single agents. The manifestations included thrombocytopenia, haemolytic anaemia with schistocytosis, and renal dysfunction. (Kapiteijn *et al*, 2007; Patel *et al*, 2008) The treatment of this condition would involve the cessation of the implicated agent and plasma exchange. (Frangie *et al*, 2007)

10. Hypertension as biomarker of efficacy of sunitinib

Data from the two second-line phase II trials, one first-line phase III trial, and an expanded access study of sunitinib were retrospectively analysed to determine whether there was a relationship between hypertension and anti-tumour effect. (Rini *et al*, 2011a) Hypertension in this context was defined by either maximum or mean systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90 mmHg, measured on days 1 and 28 of each 6-week treatment cycle at any time during the study after the

first dose of sunitinib. (Rini *et al*, 2011a) The ORR was 54.8% in hypertensive patients vs. 8.7% in patients without a maximum SBP of at least 140 mmHg. Median PFS was 12.5 months vs. 2.5 months, and median OS was 30.9 months vs. 7.2 months in the same two cohorts respectively. (Rini *et al*, 2011a) Overall, a better clinical outcome was demonstrated in patients who experienced hypertension and indeed a direct correlation between SBP and DBP and clinical outcome was observed. To determine whether or not antihypertensive medications reduced the anti-tumour efficacy of sunitinib, clinical outcomes were compared in patients using medications with those that were not at baseline, after cycle 1 and cycle 2. No statistical differences were noted in the ORR or the PFS between the two cohorts regardless of the presence of anti-hypertensive treatments at baseline. The median PFS in the treated and not on antihypertensive were 11.3 months and 10.6 months respectively (p=0.20). There was however a significant difference in median OS of more than 10 months with patients on anti-hypertensive medications demonstrating a 31.8 month survival vs. 21.4 months for patients not taking anti-hypertensive agents (p <0.001). The results of median PFS and median OS measured in patients with or without hypertension at the end of cycle 1 and 2 mirrored those obtained at baseline. (Rini *et al*, 2011a) To illustrate, median PFS measured at the end of cycle 1 for patients with and without anti-hypertensive agents were 13.4 months vs. 10.8 months respectively (p=0.31) and at the end of cycle 2, the median PFS were 13.6 months vs. 10.8 months respectively (p=0.15). (Rini *et al*, 2011a)The overall survival benefit at the end of cycle 1 for patients on anti-hypertensive and not on anti-hypertensive were 30.1 months vs. 23.3 months (p=0.155) and for cycle 2 was 31.1 months vs. 23.0 months (p=0.013) respectively. When analysed according to the prognostic factors (ECOG performance status, time from diagnosis to treatment, LDH, platelet count, corrected calcium), treatment induced hypertension remained a statistically significant predictor of survival benefit (p<0.001). (Rini *et al*, 2011a) In spite of these results supporting the hypothesis that hypertension may be a viable biomarker of anti-tumour efficacy, the development of hypertension during sunitinib treatment was neither necessary nor sufficient for clinical benefit in all patients.(Rini *et al*, 2011a)

11. Drug interactions

The targeted agents are predominantly metabolized by the hepatic cytochrome P450 enzyme CYP3A4 which raises the possibility of drug- drug interactions with concomitant medications that are strong inducers or inhibitors of CYP3A4 (Table 1). (Adams & Leggas, 2007; di Lorenzo *et al*, 2011; Kollmannsberger *et al*, 2007b) For example, the CYP3A4 inhibitors that would potentially increase toxicity of targeted agents include antiretroviral agents such as ritonavir, indinavir and nelfinavir, and antibiotics/antifungals such as clarithromycin, ketoconozole, fluconazole, itraconazole and voriconazole. Potent CYP3A4 inducers that decrease therapeutic efficacy of the targeted agents would include antiepileptic medications such as phenytoin and carbamazepine; antibiotics such as rifampicin and rifabutin. (Kollmannsberger *et al*, 2007a) If the interacting concomittant agent cannot be stopped, doses of the targeted agents may need upward or downward adjustment. It is not only drug-to-drug interactions that are of concern, as many patients take supplements or complementary and alternative medicines (CAM) which they may not mention to their treating physicians. (Lees & Chan, 2011) *Hypericum perforatum*, commonly

Targeted agent	Possible clinical effect	Recommended management
sunitinib		
carbamazepine phenytoin primidone	Decreased blood levels of sunitinib, potential for reduced effect	Avoid concurrent use, choose a non-interacting anti-epileptic agent or consider increasing sunitinib dose; monitor closely for effect and tolerability
St John's Wort	Decreased blood levels of sunitinib, potential for reduced effect	Avoid concurrent use
sorafenib		
carbamazepine phenytoin primidone	Decreased blood levels of sunitinib, potential for reduced effect	Avoid concurrent use, choose a non-interacting anti-epileptic agent or consider increasing sorafenib dose; monitor closely for effect and tolerability
warfarin	Increased INR, bleeding	Monitor patient's INR closely
everolimus		
ketoconazole itraconazole fluconazole voriconazole	Increased blood levels of everolimus; potential for toxicity	Avoid concurrent use or consider reducing everolimus dose; monitor closely for effect and tolerability
phenytoin	Decreased blood levels of everolimus, potential for reduced effect	
St John's Wort	Decreased blood levels of everolimus, potential for reduced effect	Avoid concurrent use

Table 1. Selected examples of drug interactions with some targeted agents

known as St John's Wort is a herbal preparation cancer patients may well be taking for its supposed antidepressant benefits. As it is a CYP3A4 enzyme inducer if taken with sunitinib, sorafenib or everolimus, for example, their effects may be decreased. Grapefruit juice is known to be a CYP3A4 enzyme inhibitor and as such may lead to unexpected toxicity if taken with sunitinib. (Kollmannsberger *et al*, 2007a) A comprehensive full medication history incuding prescribed, self-prescribed over the counter and CAM should be taken when any patient is about to start treatment. (di Lorenzo *et al*, 2011; Lees & Chan, 2011) Drug interaction databases should be utilised, since more reports of interactions may appear as experience with these newer therapies increases.

12. Quality of life in patients with renal cell carcinoma receiving targeted therapies

Health-related quality of life (QoL) has been assessed in a number of studies of patients taking newer targeted therapies for RCC (or kidney cancer). Questionnaires used have included the Functional Assessment of Cancer Therapy-General (FACT-G), the FACT-Kidney Symptom Index-15 item (FKSI-15), the FACT-Kidney Symptom Index-Disease related Symptoms (FKSI-DRS), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30 and the Euro QOL 5D (Index and Visual Analogue Scale) utility score (EQ-5D) Index.

Sunitinib has shown improvement over IFN-α with clinically meaningful differences both in kidney cancer related symptoms and overall QoL. (Motzer *et al*, 2007a) Sorafenib when compared with placebo, showed no difference in QoL based on the FACT-G or FKSI-15 mean scores in a sub-analysis of the TARGET trial. However certain symptoms such as fevers, ability to enjoy life, dyspnoea and cough as well as concerns for well being were reported less in the patients on sorafenib. (Bukowski *et al*, 2007a) Quality of life was assessed as a secondary end point in the pazopanib vs. placebo phase III trial (EORTC-QLQ-C30 Version 3) and EQ-5D Index. Patients on pazopanib did not have a clinically different QoL compared with placebo, despite the toxicities that may be expected with pazopanib. (Sternberg *et al*, 2010)

More recently, patient-reported kidney-specific symptom and function assessments as secondary endpoints of the AXIS trial (axitinib vs. sorafenib) were reported at ASCO 2011 (Cella *et al*, 2011). Over 700 patients randomised to axitinib or sorafenib completed FKSI-15 and its disease-related symptoms subscale FKSI-DRS with a completion rate of about 90%. (Cella *et al*, 2011) Overall estimated means in the FKSI-15 and FKSI-DRS mixed-effects models were similar between treatments. The composite time to deterioration (TTD) endpoint, using FKSI-15 or FKSI-DRS, showed a 25% risk reduction for axitinib vs. sorafenib ($p=0.0001$ for both comparisons). Axitinib treatment resulted in patient reported outcomes comparable to sorafenib in patients being treated for second-line metastatic RCC. The PFS benefit demonstrated by axitinib is accompanied by a delay in worsening of the composite endpoint of advanced RCC symptoms, progression, or death compared with sorafenib.

These data reporting on improved or unchanged QoL during treatment with anti-VEGF tyrosine kinase inhibitors (TKIs) are reassuring and may well allay any fears that patient may have and in fact encourage them to proceed on with the treatment. Indeed, the improvement of QoL with some of the TKIs may be attributed to the resolution of their cancer-related-symptoms from the treatment.

In a double-blind, placebo-controlled trial, everolimus 10 mg daily was evaluated using FKSI-DRS and EORTC QLQ-C30. (Beaumont *et al*, 2011) Longitudinal trends for FKSI-DRS scores did not differ between everolimus and placebo. For physical functioning and global QoL, a small but statistically significant decrease was seen with everolimus. All three measures were significantly related to PFS. The authors reported that even when progression of disease was delayed by the new treatment, it did not affect patients' symptoms, functioning, or their QoL, which they proposed is something patients, their family and healthcare providers might expect. (Beaumont *et al*, 2011) Furthermore,

Beaumont and colleagues suggest that for patients receiving first line treatment with a targeted agent, the prospect for clinical benefit may outweigh concerns about health-related QoL. However, in contrast, when these agents are being used in the second- and third-line settings, health-related quality of life may be of more importance to all concerned groups. Continued research is needed into the positive and negative outcomes associated with new treatments for metastatic RCC. (Beaumont *et al*, 2011)

13. Pharmacoeconomics

It is important to determine the optimal setting and sequence of new targeted agents in metastatic RCC to improve patient survival outcomes whilst considering cost-effectiveness. Comparative cost-effectiveness in the first- and second-line setting should be assessed with respect to life years gained. (Molina & Motzer, 2011) For example, Benedict and colleagues utilized a Markov model simulating disease progression, adverse events and survival to assess economic value of first-line treatments in the US and Sweden. Their analyses suggested sunitinib is cost-effective compared with sorafenib, or bevacizumab plus IFN-α for first line metastatic RCC treatment. (Benedict *et al*, 2011) In 2011 NICE, the UK National Institute for Health and Clinical Effectiveness, was unable to approve everolimus for second-line metastatic RCC as it was too expensive for the benefit provided. (http://guidance.nice.org.uk/TA219/Guidance/pdf/English accessed August 1st 2011)

14. Conclusion

The treatment landscape for metastatic RCC has dramatically changed with the development of targeted therapy. Metastatic RCC, once considered a dismal disease to treat has been transformed into a treatable cancer in the era of targeted therapy. These agents are now being investigated either in a sequential or combination fashion in an attempt to search for improved clinical efficacy. The side-effects profile is unique to each agent although there are some common class adverse effects. Careful monitoring and management of side-effects are warranted for patients on these agents to ensure good adherence and effective therapy. Further understanding and insight into the intracellular molecular signaling pathways to both clear-cell and non-clear cell RCC will hopefully lead to the discovery of agents that would confer more durable response and improved prognosis.

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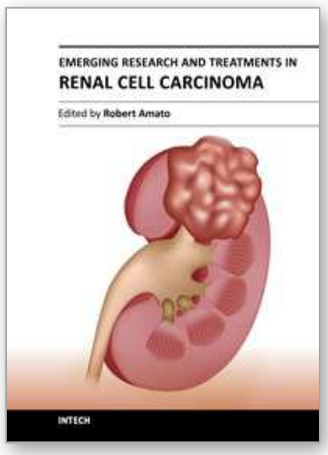

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The field of renal cell cancer has undergone a significant resurgence. This book summarizes up-to-date research and innovative ideas for the future in this rapidly changing field, which encompasses medicine, surgery, radiation oncology, basic science, pathology, radiology, and supportive care. This book is aimed at the clinician or scientist who has an interest in renal cell cancer, whether they are academic or nonacademic. The book covers tumor biology, molecular biology, surgery techniques, radiation therapy, personal testimonies, and present and future treatments of the disease that are on the horizon. The goal was to produce a textbook that would act as an authoritative source for scientists and clinicians and interpret the field for trainees in surgery, medicine, radiation oncology, and pathology.

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