Individualising treatment choices in a crowded treatment algorithm

Rosalie Fisher, James Larkin *

The Royal Marsden Hospital, Department of Medicine, London, UK

1.   Introduction

Metastatic renal-cell cancer (mRCC) is considered incurable, and systemic therapy is the foundation of patient management. Historically, hormonal therapy was used for palliation of symptoms but had little anti-cancer effect [1]; cytotoxic chemotherapy is beneficial for only a small proportion of patients [2–7]. Immunotherapy, generally interferon-alpha (IFNα), was standard treatment until 2005, when it was replaced by the first inhibitor of the vascular endothelial growth factor receptors (VEGFRs), sunitinib [8]. Since then, another six agents which target either the VEGF or the mammalian target of rapamycin (mTOR) pathways have been developed and approved for use in advanced RCC [9–15]. Notably, cytoreductive nephrectomy was proven in two randomised trials to improve survival in combination with IFN, compared with drug treatment alone [16]. Despite a significant change in the systemic agents utilised in mRCC, this has remained an integral aspect of the treatment approach.

The prognosis for patients with mRCC has improved markedly with the introduction of agents targeting cell signalling pathways [17,18]. The expected survival time for an individual patient can be highly variable, but it is standard practice to categorise patients with mRCC into prognostic groups, originally defined by the Memorial Sloan Kettering Cancer Center (MSKCC) in the immunotherapy era of treatment [19]. This model, which uses clinical and pathological factors to group patients into favourable, intermediate and poor-risk groups, has now been updated and validated in patients treated with VEGFR–tyrosine kinase inhibitors (VEGFR–TKIs) [20] and is an important consideration in the current standards of care.

The treatment algorithm for mRCC in 2013 includes seven targeted agents and cytokine therapy, used in a sequential fashion [21]. This algorithm is becoming increasingly complex as clinical trials attempt to define the optimal treatment regimen to improve progression-free and overall survival and response rates, and to preserve quality of life. Combinations of targeted drug therapy remain experimental; to date, no combination has proved to be superior to monotherapy, and it is frequently poorly tolerated [22].

This educational chapter will summarise the treatment algorithm for advanced RCC and will provide details on how treatments may be individualised within the algorithm. The potential impact of new agents, future trial results and developments in translational research in mRCC will also be discussed.

2.   First-line therapies

It has long been recognised that some patients with mRCC have indolent disease biology, and a period of observation is often recommended when metastatic disease is first diagnosed. This approach has clear advantages – it allows assessment of the pace of metastatic disease and can spare patients the chronic toxicities associated with drug therapy, as well as having health economic benefits – but there is only preliminary, retrospective evidence for its safety, and it is not clear for which patients this strategy is most suitable [23]. A deferred drug treatment approach in mRCC is currently being evaluated in a prospective, observational study [24].

Immunotherapy has largely been replaced by targeted therapies, but is considered an acceptable treatment option in patients with low- or intermediate-risk disease; IFN in particular remains a relevant therapy in those countries with restricted or no access to high-cost drugs. A 2005 systematic review of IFN reported modest improvements in disease control rates, 1-year and overall survival compared with non-immunotherapy controls, with approximately 13% of patients achieving a partial or complete response [25]. Notably, high-dose IL-2 (HD IL-2) produces durable response rates in a small proportion of patients with mRCC [26,27]; most recently, the 'SELECT' trial of HD IL-2 found an improved response rate (29%) compared with historical results which was attributed to improved patient selection on clinical and pathological

* *Corresponding author:* Address: Department of Medicine, The Royal Marsden Hospital, Fulham Road, London SW36JJ, UK. Tel.: +44 207 808 8576; fax: +44 207 811 8103.

E-mail address: James.larkin@rmh.nhs.uk (J. Larkin).

grounds [28]. This remains the only systemic therapy associated with long-term remissions in mRCC, but its potential for severe toxicity and efficacy in a restricted, molecularly undefined subgroup of patients has limited its clinical application.

Sunitinib and sorafenib are kinase inhibitors with multiple targets, including the VEGF-receptors [29–31]. They were the first drugs developed in the VEGFR–TKI class of agents; hence they are associated with extensive clinical experience in mRCC. There is a stronger evidence base for sunitinib as first-line therapy. Sunitinib was compared with IFN in a randomised phase III trial and resulted in a statistically superior response rate (47% versus 12%), and progression-free survival (PFS) time (median 11 months versus 5 months) [8]. The median overall survival time was 26.4 months for sunitinib compared to 21.8 months for IFN-treated patients, which only became significant when those patients who crossed over from IFN to sunitinib were excluded from the analysis [32]. The efficacy of sunitinib was confirmed in a large safety study which enrolled a broader population of patients, including elderly patients, those with poor-risk disease as defined by the MSKCC criteria and those with non-clear-cell RCC [33]. Sorafenib was also compared with IFN treatment in 189 untreated mRCC patients in a randomised phase II trial [34]. Although the median PFS times for sorafenib and IFN were similar (approximately 5.7 months), sorafenib was interpreted as having superior clinical benefit because of improved response rates, tolerability and quality-of-life assessments.

Pazopanib was developed as a multi-targeted kinase inhibitor with improved potency against VEGFR-2, thought to have the most biological relevance of the VEGF receptors in clear-cell RCC [35]. It was registered in the first-line treatment setting on the basis of improved progression-free and overall survival in patients who were either treatment-naïve or who had received prior cytokine therapy, in a placebo-controlled trial [36]. Preliminary results of the COMPARZ study, comparing sunitinib and pazopanib in first-line treatment for mRCC, were presented in abstract form at the European Society of Medical Oncology (ESMO) meeting in 2012 [37]. The median PFS for pazopanib was 8.4 months and 9.5 months for sunitinib, and interim OS times were 28.4 months and 29.3 months, respectively. This was a non-inferiority study, and although it has been criticised for its design, it would appear to confirm anecdotal experience that the two drugs are equivalent in efficacy, and this is reflected in current clinical practice guidelines [21,38].

The intravenous monoclonal antibody to VEGF, bevacizumab, is an alternative first-line treatment for patients with favourable or intermediate-risk mRCC. Two phase III trials combined bevacizumab with IFN and randomised patients to the combination or to IFN alone [12,13]. Both reported improved response rates (combined analysis 28.4% versus 12.9% [18]) and PFS times (8.5 months versus 5.2 months [12]) and 10.2 months versus 5.4 months [13]) over IFN monotherapy. Overall survival was not significantly improved by bevacizumab in either study, perhaps because of subsequent anti-VEGF systemic treatment in many patients.

Temsirolimus is an inhibitor of the mTOR complex 1 and is the only systemic agent to be studied specifically in a poor-prognosis group of patients with mRCC. A phase III trial of temsirolimus or IFN or the combination enrolled treatment-naïve patients who met three of six adverse risk features: lactate dehydrogenase (LDH) level of more than 1.5 times the upper limit of normal, haemoglobin level below the lower limit of normal, elevated calcium, time from initial diagnosis of RCC to randomisation of less than 1 year, a Karnofsky performance status of 60 or 70, or metastases in multiple organs [15]. Notably, approximately a third of the patients in this study had not had a nephrectomy. Median PFS in the temsirolimus group was 5.5 months and median OS 10.9 months, and temsirolimus is therefore a standard of care in this group.

3. Second-line therapies

Accepted second-line treatments for mRCC are the VEGFR–TKIs sorafenib, sunitinib, pazopanib and axitinib, and the oral mTOR inhibitor everolimus. Frequently, the decision is influenced by which first-line treatment the patient has received; for example, there is evidence that sorafenib, sunitinib, pazopanib and axitinib have clinical activity after prior cytokine therapy [10,11,33,39].

The main controversy exists in the decision between everolimus and axitinib, when patients have been previously treated with a VEGFR–TKI. The RECORD-1 study compared everolimus to placebo in previously treated patients [14,40]. This was not strictly a second-line trial only, but patients were stratified by the number of previous VEGFR–TKI treatments; in patients who had received only one prior VEGFR–TKI, the median PFS for everolimus was 5.4 months, and 1.9 months for placebo [41]. Similar results were reported for the analysis of sunitinib- and sorafenib-treated patients. Two further trials, including the large expanded access study of everolimus (REACT), confirmed that everolimus has meaningful clinical activity in anti-VEGF treatment-refractory patients [42,43].

The phase III AXIS study randomised patients who had received prior sunitinib, cytokine, bevacizumab or temsirolimus to second-line treatment with axitinib or sorafenib [11]; approximately two thirds of the 723 patients enrolled had had first-line anti-VEGF treatment. Overall, PFS was in favour of axitinib, with a median time of 6.7 months, compared to 4.7 months for sorafenib. This difference was less pronounced, however, in patients who had received prior sunitinib or bevacizumab.

Results of the RECORD-3 study were presented in abstract form in 2013, adding further support to the efficacy of a VEGFR–TKI:mTOR inhibitor algorithm [44]. This phase II trial randomised patients to either first-line everolimus, followed by sunitinib on progressive disease, or sunitinib followed by everolimus. It was designed to prove non-inferiority of PFS with first-line everolimus compared to sunitinib, but did not with its primary end-point (median PFS for everolimus 7.85 months and for sunitinib 10.71 months). Preliminary OS results suggest that the current algorithm of sunitinib in the first line followed by everolimus is superior to the opposite sequence. These results do not resolve the issue of whether a VEGFR–TKI or mTOR inhibitor is superior after failure of first-line anti-VEGF treatment, but add to the evidence base regarding optimal sequencing of systemic agents in mRCC. With respect to the former question, the efficacy of temsirolimus and sorafenib were compared in patients previously

treated with sunitinib in the INTORSECT trial, presented at the ESMO meeting in 2012 [45]. Both drugs produced a median PFS of approximately 4 months, but overall survival was significantly better for sorafenib (16.6 months versus 12.4 months for temsirolimus). These results seem to indicate that although VEGF followed by mTOR inhibition is an efficacious strategy, everolimus and temsirolimus are not necessarily interchangeable, perhaps owing to their differing pharmacokinetics [46,47].

4. Factors which guide treatment selection

It is clear that multiple choices now exist for the first- and second-line treatment of patients with mRCC. Currently, the choice of agent is largely determined by the licensed indication for the drug, which in turn depends on the clinical context in which the drug's registration trial took place. However, as the clinical trial portfolio in mRCC has expanded to include more sophisticated trial designs, and eligibility criteria broadened, the decision about optimal treatment has become increasingly complex. To further complicate the issue, there are few direct comparisons between the various agents [11,37,45] and it is therefore difficult to confidently identify a superior drug for a given clinical situation. Nonetheless, there are a number of factors which enable selection of treatment to some degree, and also research initiatives aiming to move the field towards an individualised approach to treatment.

4.1. Disease and patient factors

Clinical risk models such as the MSKCC model provide a formalised assessment of those features which indicate less favourable biology in mRCC [19]. This model, now validated by Heng and colleagues in patients treated with VEGFR–TKIs [20] includes parameters such as haematological, biochemical and performance status to categorise patients into favourable-, intermediate- and poor-risk groups, each with a distinct survival time. However, risk stratification does not predict response to treatment; a nomogram which utilises 11 pre-treatment clinical and pathological variables predicts a 12-month PFS with first-line sunitinib treatment [48]. A more comprehensive model such as this may improve decision-making for individual patients, but it has not been validated. Recently, an analysis of factors influencing survival in sunitinib-treated patients was published, and this confirmed previously published findings but also identified independent predictors of long-term survival, including ethnic origin, bone metastases and adjusted calcium level [49].

Features of the disease are frequently used in clinical practice to guide selection of treatment. The most obvious example is the histological subtype of RCC. Most phase IIII trials in mRCC enrolled only patients with the clear-cell subtype, but approximately 25% of patients will have non-clear-cell histology, most commonly papillary or chromophobe subtypes. The optimal treatment for these groups has not yet been defined; on balance it appears that the targeted agents currently in use have activity in non-clear-cell RCC, but that the activity may be reduced compared to that in patients with clear-cell mRCC. However, there is evidence from some large therapeutic series that temsirolimus, everolimus and sunitinib have similar effi-

cacy in patients with clear-cell and non-clear-cell disease [33,50,51]. Considering the papillary subtype alone, the reported range of PFS on VEGF-targeted agents varies considerably (1.6–11.9 months) [52–55], but studies have not always analysed type 1 and type 2 papillary patients (in whom there is clearly distinct biology) separately. Response rates in the range of 12–40% and PFS times from 4 to 14 months have been reported for sunitinib, sorafenib, temsirolimus or everolimus in chromophobe mRCC [52,53,55–59], although not always in the first- or second-line setting. The presence of sarcomatoid differentiation, which can occur in any histological subtype, adds a considerable degree of uncertainty as to the best choice of systemic agent (for a comprehensive review, see [60]), because the molecular driver of sarcomatoid change is unknown, the degree to which it is present is highly variable, and there are limited prospective therapeutic studies. Based on available data, the activity of sorafenib and sunitinib seems to be superior to that of cytotoxic chemotherapy, but outcomes are modest at best with these agents [61–64].

The burden and pattern of metastatic disease further influences treatment choice. Patients who are symptomatic from either a high volume of metastatic disease or disease in critical viscera are probably best served by a multi-targeted kinase inhibitor, because these agents are more likely to cause tumour regression than mTOR inhibitors. Response rates to sunitinib and pazopanib as first-line treatment, and axitinib as second-line treatment, can be as high as 40% [8,10,11], whereas reported response rates for temsirolimus and everolimus monotherapy are ⩽10% [14,15]. Decisions about systemic treatment in those with specific metastatic disease sites such as the brain are complex; frequently, integration of local therapies is required, and there are no prospective data on which to base treatment recommendations. In the example of brain metastases, sunitinib has the strongest evidence of clinical activity [65–68].

Patient factors that should be considered when choosing systemic treatment for mRCC include their co-morbidities, age, expectations of and preferences for treatment and social and pragmatic issues such as their ability to attend the hospital. The VEGFR–TKIs have multiple additional targets, and the relative potency of these agents for different targets results in differing side-effect profiles. The toxicities associated with specific agents are described in detail in a separate educational chapter, but these must be balanced against baseline organ dysfunction – including cardiovascular, endocrine, hepato-biliary and haematological problems – when therapy is chosen.

The effect of advanced age on the safety and efficacy of targeted agents is now under careful evaluation, with the recognition that patients treated in drug development trials are not representative of the mRCC population encountered in the clinic. A combined analysis of 4684 patients treated with sorafenib in six clinical trials and two expanded access programmes was recently published [69], including 599 patients aged over 75 years. The authors reported that tolerability of sorafenib monotherapy was similar between the four age groups analysed, but those in the oldest group had a shorter duration of treatment (median 3.1 months) compared to those aged between 55 and 75 (median 4.0–4.2 months). Notably, 17% of patients aged 65–75 and 8% of those over 75 re-

ceived sorafenib treatment for a duration of more than 12 months. Likewise, pooled retrospective data from approximately 1000 patients treated with sunitinib indicate that its efficacy is similar in those under and over the age of 70 [70]. The overall rate of treatment-related adverse events was also comparable between the two age groups, although particular side-effects – such as fatigue, anorexia and weight loss, cough, peripheral oedema and haematological abnormalities – were noted to be higher in the older age group. The sunitinib expanded access study included a significant proportion of patients over the age of 65 (approximately 1/3 of the study population, 1000 patients); the response rate of 17%, median PFS of 11.3 months and median OS of 18.2 months were the same as in the overall study population [33]. Finally, there is evidence that everolimus has a similar efficacy and safety profile in those over 65 years of age, from a retrospective analysis of the RECORD-1 study [71]. In summary, these data suggest that chronological age alone should not be an influential factor in treatment selection, rather that co-morbidities and geriatric syndromes such as polypharmacy may need more careful assessment and weighting in the older patient.

Preservation of quality of life is an important therapeutic goal in mRCC. This can be difficult to achieve, because all targeted agents are associated with at least some degree of toxicity which is chronic. Arguably, patients are best placed to make decisions about treatment based on toxicity and quality of life, but the latter has not been rigorously studied and/or reported in clinical trials. For this reason, the PISCES (patient preference study between first-line pazopanib and sunitinib) trial, presented in abstract form in 2012 [72], has been commended for its novel design. Patients were randomised to receive either drug for 10 weeks, followed by a 2-week washout period before switching to the second drug. A clear patient preference for pazopanib over sunitinib was displayed, although the different drug schedules and timing of quality of life assessments complicate the analysis and in particular may have disadvantaged the evaluation of sunitinib. A similar study design is employed in the TAURUS trial, a phase II trial evaluating patient preference for the potent VEGFR–TKI tivozanib for 12 weeks followed by sunitinib for 12 weeks, or vice versa (NCT01673386). The phase III SWITCH trial will evaluate sunitinib followed by sorafenib and the opposite sequence, but the primary end-point is PFS (NCT00732914). Both of these trials will be conducted in the first-line treatment setting.

4.2. Predictive biomarkers in mRCC

Predicting sensitivity to systemic therapy is the fundamental prerequisite for the delivery of personalised treatment in mRCC. Response to first-line targeted agents appears to be an important indicator of longer-term outcome, with a retrospective analysis demonstrating that PFS below and above an arbitrary threshold of 6 months during first-line treatment was an independent predictor of overall survival (median OS 12.1 months versus 46.8 months, respectively, $P < 0.0001$) [73]. However, when anti-VEGF treatments are used in a first- and second-line sequence, response to the first does not predict response to the second [74,75]; this is somewhat counter-intuitive, but is perhaps further evidence that drug response is probably the result of complex interaction between multi-

ple tumoural, pharmacodynamic and pharmacokinetic factors.

Clinical parameters indicative of response to VEGF-targeted treatments may help to limit patients' exposure to the drug in the absence of benefit. Drug-induced hypertension is a compelling example of this. A retrospective, pooled analysis of data from four clinical trials of sunitinib treatment in patients with mRCC found that hypertensive patients, defined by systolic blood pressure and diastolic blood pressure to a lesser degree, had improved clinical outcomes [76]. In the AXIS trial, diastolic blood pressure of $\geqslant 90$ mmHg at 12 weeks was significantly associated with improved overall survival in both the axitinib (20.7 months versus 12.9 months) and sorafenib (20.9 months versus 14.8 months) arms [75], confirming an earlier correlation of axitinib efficacy and diastolic blood pressure in phase II studies [77]. A prospective, randomised assessment of the efficacy of axitinib dose up-titration is currently under way (NCT00835978).

The utility of hypertension in treatment selection for an individual patient is debatable; the identification of a molecular marker that is predictive of response a priori is a key goal of translational research in mRCC. At this time, no such biomarker has been established. In patients treated with anti-VEGF agents, biomarker development efforts based on deficient tumoural von Hippel Lindau (VHL) gene function and resultant angiogenesis, the central abnormalities in clear-cell RCC, have been unsuccessful, perhaps because the pathogenesis involves stromal rather than tumour cells. However, promising discoveries have been made in relation to single-nucleotide polymorphisms (SNPs), inherited variants in DNA sequence, which may influence the biology underlying drug sensitivity. Several retrospective analyses correlated SNPs in VEGF or VEGF-receptors and drug metabolism genes (including CYP3A5, CYP1A1, ABCB1 and 2 and NR1I3) with sunitinib efficacy or toxicity [78–80]; a fourth study found that an SNP in VEGF was associated with the development of sunitinib-induced hypertension, but no single SNP predicted variation in clinical outcome [81]. A prospective observational study in which all patients received sunitinib demonstrated a significant relationship between polymorphisms in VEGFR3 and CYP3A5*1 with reduced sunitinib response and greater toxicity, respectively [82]. Furthermore, SNPs in angiogenesis or drug exposure genes – including IL-8 and HIF1A – may have predictive value; the IL-8 2767TT and the HIF1A 1790AG variant genotypes were associated with reduced PFS times compared to wild-type genotypes, in patients treated with pazopanib compared to placebo [83]. This finding has biological plausibility in that IL-8 has been identified as a potential mediator of an angiogenic escape and thus resistance to anti-VEGF treatment [84]. High plasma concentration of IL-8 has also been shown to predict for shorter PFS in patients treated with pazopanib in a retrospective analysis of the phase III pazopanib-versus-placebo trial, whereas high concentration of IL-6 predicted PFS benefit from pazopanib [85]. The major issue with the studies relating to SNPs is that they have each evaluated non-overlapping sets of SNPs, and no dominant polymorphism or one common to different anti-VEGF treatments has emerged [86]. Additionally, the frequency of identified SNPs is often low, and the biological processes which underpin the relationship between SNPs and clinical out-

comes, such as increased susceptibility of the tumour or normal tissue to the drug or altered drug metabolism, are not described. However, if validated, germline genetic variants may be very useful in drug selection, and may be particularly relevant to efficacy and safety of drugs between different ethnic groups affected by RCC.

Activation of the mTOR signalling pathway is extensively demonstrated across grades, histological subtypes and tumour sites in RCC, and alteration of some of its components has been shown to confer a worse prognosis [87,88]. Furthermore, there is preliminary evidence that somatic mutations in genes such as mTOR, or the tumour suppressor tuberous sclerosis genes (TSC1 and TSC2) causing gain or loss of function, respectively, are associated with long-term response to mTOR inhibitors [89]. Serum LDH may have a prognostic – and possibly predictive – role in patients treated with temsirolimus or everolimus [40,90,91].

Evidently, the biological relationship between tumour and drug response is multifaceted, and recent work using advanced genomic technology has added further layers of complexity to the picture. Exome sequencing of multiple tumour regions from a small number of patients with advanced clear-cell RCC revealed spatially separated somatic mutations in a large number of low-frequency tumour suppressor genes; the identification of only a small number of genes altered ubiquitously throughout tumour regions, and the clonal hierarchy of the mutations, points to early divergent evolution of these tumours [92]. It is therefore contended that a single biopsy will not represent the mutational range of the entire tumour, and that such intra-tumour heterogeneity will hinder biomarker discovery efforts [93,94]. It is widely recognised that there is a critical need to identify biomarkers predictive of response [17,95], and this is reflected by the now considerable number of biomarker development programmes in RCC (reviewed in [96]). Increasingly, therapeutic clinical trial design includes a tissue collection component to facilitate scientific research.

5. Ongoing trials and emerging therapies

The clinical trial portfolio in mRCC continues to expand rapidly, and there are several ongoing trials that may alter the current treatment algorithm. On the other hand, there is debate as to how significantly emerging agents will improve upon current standards. For example, a phase III trial randomising patients to the potent pan-VEGFR inhibitor tivozanib or sorafenib found a PFS benefit in favour of tivozanib (11.9 months versus 9.1 months) but no difference in overall survival between the two drugs [97]. The AGILE study, comparing axitinib and sorafenib in first-line treatment of mRCC, also found improved PFS and response rates for axitinib, but did not meet its statistical primary end-point of PFS [98]. Both of these trials could be criticised for their use of sorafenib as a comparator, and the data are still immature, but in a broader view may suggest that improvements in clinical outcomes with the classes of agents currently available have reached a plateau.

For this reason there is much interest in a new class of systemic agents, the immune checkpoint inhibitors. An immune checkpoint is an inhibitory mechanism whose role is to regulate T-cell response to pathogens and to limit autoimmunity. Tumours can exploit these pathways to evade destruction by the immune system, and two immune checkpoint molecules have therapeutic relevance: the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and the programmed death-1 (PD-1) receptors. Ipilimumab is a monoclonal antibody inhibiting the CTLA-4 receptor that improves survival in metastatic melanoma [99,100]. In RCC, the most highly developed of the checkpoint inhibitors is nivolumab (BMS-936558, MDX-1106), a monoclonal antibody against the PD-1 receptor. PD-1 is an inhibitory co-receptor that is expressed on activated T cells, particularly regulatory T cells, as well as activated B cells and natural killer cells [101]. Its two ligands, PD-L1 and PD-L2, are up-regulated widely in response to inflammation; along with activated B, T, myeloid and dendritic cells, PD-L1 is expressed on a range of endothelial and epithelial cells [102]. As such, the function of the PD-1 pathway appears to be in limiting the activity of T cells in peripheral tissues during an inflammatory response [102]. The rationale for inhibition of this pathway as anti-cancer therapy is strengthened by the observations that the PD-1:PD-L1 pathway is up-regulated abundantly in human cancers, and that PD-1 is expressed on a significant proportion of tumour-infiltrating lymphocytes [103]. Expression of PD-1 in resected RCC appears to have prognostic significance [104].

In 2012, a large phase I trial of nivolumab reported its efficacy and safety results in patients with a range of previously treated, solid tumour types [105]. Among 34 patients with RCC, objective responses occurred in four of 17 patients (24%) treated with a dose of 1 mg/kg and in five of 16 patients (31%) treated with 10 mg/kg. At the time of publication, five of eight evaluable patients had an objective response that lasted 1 year of more, and stable disease lasting at least 24 weeks was observed in an additional nine patients (27%). Common treatment-related adverse effects were fatigue, rash, diarrhoea, pruritis, anorexia and nausea, but these were usually low-grade; however, drug-induced pneumonitis occurred in 3% of patients and was fatal in three patients (1%). Nivolumab is currently being assessed in a phase III trial as second-line treatment against everolimus, in patients with mRCC previously treated with one or two anti-VEGF systemic treatments (NCT01668784), and similar anti-PD-1 antibodies are in development.

These encouraging early results come with the promise of a predictive biomarker. In the phase I study described, PD-L1 tumour expression was assessed by immunohistochemistry on pre-treatment tumour specimens from 42 patients; of 17 patients with PD-L1-negative tumours, none had an objective response, and nine of 25 patients (36%) with PD-L1-positive tumours experienced an objective response ($P = 0.006$). However, these results require reproduction and validation in other clinical settings. For example, as PD-L1 expression appears to be closely associated with the presence of tumour-infiltrating lymphocytes and secretion of IFN-gamma [106], the effect of multiple prior treatments is uncertain, and the prognostic versus the predictive power of PD-L1 expression must be determined [101].

Anti-PD-L1 agents target the same axis, and there are now two early reports of their efficacy. Theoretically, blockade of

the PD-1:PD-L1 but not the PD-1:PD-L2 interaction may improve the safety and tolerability profile compared with anti-PD-1 antibodies. In a phase I study, 17 patients with mRCC were treated with the anti-PD-L1 antibody BMS 93-6559 [107]. Two patients (12%) had an objective response, one of which lasted 17 months, and a further seven patients (41%) remained stable for more than 24 weeks. A second phase I trial enrolled a larger cohort of RCC patients and preliminary results were presented at the American Society of Clinical Oncology (ASCO) meeting in 2013 [108]; 53 patients with mRCC, the majority of whom had received previous systemic treatment, received MPDL3280A, an engineered human monoclonal antibody to PD-L1. Notably, both rapid responses and prolonged stability were observed: the response rate was 13%, and 32% of patients achieved stable disease lasting longer than 24 weeks. This treatment was reportedly well tolerated and differed in its side-effect profile from the anti-PD-1 antibodies; in particular, grade 3 or higher pneumonitis did not occur.

6. Conclusions

There are now multiple systemic agents available for use in mRCC, which, particularly when used sequentially, extend the lives of patients and frequently provide effective palliative care. The ever-increasing repertoire of drugs for this condition make decision-making for the individual patient complex. In the absence of a predictive molecular biomarker, treatments are selected using a combination of variables, including the licensed indication of the drug, which in turn can influence funding arrangements, and clinico-pathological factors relating to the patient and the disease biology. The algorithm will be further refined as research into the optimal sequence of treatment, and treatments for smaller patient groups such as those with non-clear-cell mRCC, is completed. Statistically, the currently available drugs result in clinical benefit for approximately 1 year at best, but clinical experience suggests that the outcome for each patient is highly variable. This emphasises the need for improved understanding of mechanisms of resistance and, furthermore, prediction of drug sensitivity or resistance on an individual level. A large number of biomarker initiatives have received high-level funding, and clinical trial design is adapting to address translational questions. The development of novel agents, such as immunostimulatory antibodies, is a further reason for optimism, with drugs such as anti-PD-1 antibodies offering the possibility of long-term disease control.

7. Conflict of interest statement

8. Role of the funding source

REFERENCES

[1] Harris DT. Hormonal therapy and chemotherapy of renal-cell carcinoma. Semin Oncol 1983;10:422–30.

[2] Waters JS, Moss C, Pyle L, et al. Phase II clinical trial of capecitabine and gemcitabine chemotherapy in patients with metastatic renal carcinoma. Br J Cancer 2004;91:1763–8.

[3] Yagoda A, Abi-Rached B, Petrylak D. Chemotherapy for advanced renal-cell carcinoma: 1983–1993. Semin Oncol 1995;22:42–60.

[4] Rini BI, Vogelzang NJ, Dumas MC, et al. Phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil in patients with metastatic renal cell cancer. J Clin Oncol 2000;18:2419–26.

[5] Stadler WM, Halabi S, Rini B, et al. A phase II study of gemcitabine and capecitabine in metastatic renal cancer: a report of cancer and leukemia group B protocol 90008. Cancer 2006;107:1273–9.

[6] Tannir NM, Thall PF, Ng CS, et al. A phase II trial of gemcitabine plus capecitabine for metastatic renal cell cancer previously treated with immunotherapy and targeted agents. J Urol 2008;180:867–72 [Discussion 72].

[7] Van Veldhuizen PJ, Hussey M, Lara Jr PN, et al. A phase II study of gemcitabine and capecitabine in patients with advanced renal cell cancer: southwest oncology group study S0312. Am J Clin Oncol 2009;32:453–9.

[8] Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.

[9] Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125–34.

[10] Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061–8.

[11] Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011;378:1931–9.

[12] Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26:5422–8.

[13] Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103–11.

[14] Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372:449–56.

[15] Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271–81.

[16] Flanigan RC, Mickisch G, Sylvester R, et al. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004;171:1071–6.

[17] Gore ME, Larkin JM. Challenges and opportunities for converting renal cell carcinoma into a chronic disease with targeted therapies. Br J Cancer 2011;104:399–406.

[18] Coppin C, Kollmannsberger C, Le L, Porzsolt F, Wilt TJ. Targeted therapy for advanced renal cell cancer (RCC): a Cochrane systematic review of published randomised trials. BJU Int 2011;108:1556–63.

[19] Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials

of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289–96.

[20] Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794–9.

[21] Escudier B, Eisen T, Porta C, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl. 7):65–71.

[22] Pal SK, Vogelzang NJ. Sequential treatment strategies and combination therapy regimens in metastatic renal cell carcinoma. Clin Adv Hematol Oncol 2013;11:146–55.

[23] Fisher RA, Pender A, Thillai K, et al. Observation as a treatment strategy for advanced renal cell carcinoma – a call for prospective validation. Front Oncol 2012;2:155.

[24] Plimack ER, Nemec C, Elson P, et al. An observational study of metastatic renal cell carcinoma patients prior to initiation of initial systemic therapy. J Clin Oncol 2012;30(Suppl.) [abstr. TPS4679].

[25] Coppin C, Porzsolt F, Awa A, et al. Immunotherapy for advanced renal cell cancer. Cochrane Database Syst Rev 2005:CD001425.

[26] Fyfe G, Fisher RI, Rosenberg SA, et al. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. J Clin Oncol 1995;13:688–96.

[27] Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am 2000;6(Suppl. 1):S55–7.

[28] McDermott DF, Ghebremicahel MS, Signoretti S, et al. The high-dose aldesleukin (HD IL-2) "SELECT" trial in patients with metastatic renal cell carcinoma (mRCC). J Clin Oncol 2010;28(Suppl. 15) [abstr. 4514].

[29] O'Farrell AM, Abrams TJ, Yuen HA, et al. SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood 2003;101:3597–605.

[30] Abrams TJ, Lee LB, Murray LJ, Pryer NK, Cherrington JM. SU11248 inhibits KIT and platelet-derived growth factor receptor beta in preclinical models of human small cell lung cancer. Mol Cancer Ther 2003;2:471–8.

[31] Wilhelm SM, Carter C, Tang L, et al. BAY 43–9006 exhibits broad spectrum oral antitumor activity and targets the RAF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004;64:7099–109.

[32] Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584–90.

[33] Gore ME, Szczylik C, Porta C, et al. Safety and efficacy of sunitinib for metastatic renal-cell carcinoma: an expanded-access trial. Lancet Oncol 2009;10:757–63.

[34] Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:1280–9.

[35] Castaneda CA, Gomez HL. Pazopanib: an antiangiogenic drug in perspective. Future Oncol 2009;5:1335–48.

[36] Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013;49:1287–96.

[37] Motzer R, Hutson TE, Reeves J, et al. Randomized, open-label, phase III trial of pazopanib versus sunitinib in first-line treatment of patients with metastatic renal cell carcinoma (mRCC): results of the COMPARZ trial. Ann Oncol 2012;23(Suppl. 9) [abstr. LBA8_PR].

[38] NCCN. G. NCCN Clinical practice guidelines in oncology kidney cancer. Available from: http://www nccn org/professionals/physician gls/pdf/kidney pdf 2013 [accessed July 2013].

[39] Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312–8.

[40] Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma: final results and analysis of prognostic factors. Cancer 2010;116:4256–65.

[41] Calvo E, Escudier B, Motzer RJ, et al. Everolimus in metastatic renal cell carcinoma: subgroup analysis of patients with 1 or 2 previous vascular endothelial growth factor receptor–tyrosine kinase inhibitor therapies enrolled in the phase III RECORD-1 study. Eur J Cancer 2012;48:333–9.

[42] Grunwald V, Karakiewicz PI, Bavbek SE, et al. An international expanded-access programme of everolimus: addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor–tyrosine kinase inhibitor therapy. Eur J Cancer 2012;48:324–32.

[43] Bergmann L, Goebell PJ, Kube U, et al. Everolimus in metastatic renal cell carcinoma after failure of initial vascular endothelial growth factor receptor–tyrosine kinase inhibitor (VEGFr–TKI) therapy: results of an interim analysis of a non-interventional study. Onkologie 2013;36:95–100.

[44] Motzer RJ, Barrios CH, Kim TM, et al. Record-3: phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. J Clin Oncol 2013;31(Suppl.) [abstr. 4504].

[45] Hutson T, Escudier B, Esteban E, et al. Temsirolimus vs sorafenib as second line therapy in metastatic renal cell carcinoma: results from the INTORSECT trial. Ann Oncol 2012;23(Suppl. 9) [abstr LBA22_PR].

[46] Buckner JC, Forouzesh B, Erlichman C, et al. Phase I, pharmacokinetic study of temsirolimus administered orally to patients with advanced cancer. Invest New Drugs 2010;28:334–42.

[47] O'Donnell A, Faivre S, Burris 3rd HA, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. J Clin Oncol 2008;26:1588–95.

[48] Motzer RJ, Bukowski RM, Figlin RA, et al. Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma. Cancer 2008;113:1552–8.

[49] Motzer RJ, Escudier B, Bukowski R, et al. Prognostic factors for survival in 1059 patients treated with sunitinib for metastatic renal cell carcinoma. Br J Cancer 2013;108:2470–7.

[50] Dutcher JP, de Souza P, McDermott D, et al. Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies. Med Oncol 2009;26:202–9.

[51] Blank C, Bono P, Larkin J, Kim D, Panneerselvam A, Grunwald V. Safety and efficacy of everolimus in patients with non-clear cell renal cell carcinoma refractory to VEGF-targeted therapy – a subgroup analysis of the REACT expanded-access program. Eur J Cancer 2011;47(Suppl. 1):S516.

[52] Stadler WM, Figlin RA, McDermott DF, et al. Safety and efficacy results of the advanced renal cell carcinoma sorafenib expanded access program in North America. Cancer 2010;116:1272–80.

[53] Tannir NM, Plimack E, Ng C, et al. A phase 2 trial of sunitinib in patients with advanced non-clear cell renal cell carcinoma. Eur Urol 2012;62:1013–9.

[54] Molina AM, Feldman DR, Ginsberg MS, et al. Phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma. Invest New Drugs 2012;30:335–40.

[55] Choueiri TK, Plantade A, Elson P, et al. Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma. J Clin Oncol 2008;26:127–31.

[56] Koh Y, Lim HY, Ahn JH, et al. Phase II trial of everolimus for the treatment of nonclear-cell renal cell carcinoma. Ann Oncol 2013;24:1026–31.

[57] Lee JL, Ahn JH, Lim HY, et al. Multicenter phase II study of sunitinib in patients with non-clear cell renal cell carcinoma. Ann Oncol 2012;23:2108–14.

[58] Zardavas D, Meisel A, Samaras P, et al. Temsirolimus is highly effective as third-line treatment in chromophobe renal cell cancer. Case Rep Oncol 2011;4:16–8.

[59] Paule B, Brion N. Temsirolimus in metastatic chromophobe renal cell carcinoma after interferon and sorafenib therapy. Anticancer Res 2011;31:331–3.

[60] Shuch B, Bratslavsky G, Linehan WM, Srinivasan R. Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. Oncologist 2012;17:46–54.

[61] Molina AM, Tickoo SK, Ishill N, et al. Sarcomatoid-variant renal cell carcinoma: treatment outcome and survival in advanced disease. Am J Clin Oncol 2011;34:454–9.

[62] Staehler M, Haseke N, Roosen A, et al. Sorafenib after combination therapy with gemcitabine plus doxorubicin in patients with sarcomatoid renal cell carcinoma: a prospective evaluation. Eur J Med Res 2010;15:287–91.

[63] Golshayan AR, George S, Heng DY, et al. Metastatic sarcomatoid renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. J Clin Oncol 2009;27:235–41.

[64] Michaelson D, McDermott DF, Atkins MB, et al. Phase II trial of sunitinib and gemcitabine in patients with sarcomatoid and/or poor-risk metastatic renal cell carcinoma. ASCO genitourinary cancers symposium 20102010 [abstract 340].

[65] Gore ME, Hariharan S, Porta C, et al. Sunitinib in metastatic renal cell carcinoma patients with brain metastases. Cancer 2011;117:501–9.

[66] Lim ZD, Mahajan A, Weinberg J, Tannir NM. Outcome of patients with renal cell carcinoma metastatic to the brain treated with sunitinib without local therapy. Am J Clin Oncol 2013;36:258–60.

[67] Medioni J, Cojocarasu O, Belcaceres JL, Halimi P, Oudard S. Complete cerebral response with sunitinib for metastatic renal cell carcinoma. Ann Oncol 2007;18:1282–3.

[68] Helgason HH, Mallo HA, Droogendijk H, et al. Brain metastases in patients with renal cell cancer receiving new targeted treatment. J Clin Oncol 2008;26:152–4.

[69] Procopio G, Bellmunt J, Dutcher J, et al. Sorafenib tolerability in elderly patients with advanced renal cell carcinoma: results from a large pooled analysis. Br J Cancer 2013;108:311–8.

[70] Hutson TE, Bukowski RM, Rini BI, et al. A pooled analysis of the efficacy and safety of sunitinib in elderly patients with metastatic renal cell carcinoma. J Clin Oncol 2011;20(Suppl. 20) [abstr. 4604].

[71] Porta C, Calvo E, Climent MA, et al. Efficacy and safety of everolimus in elderly patients with metastatic renal cell carcinoma: an exploratory analysis of the outcomes of elderly patients in the RECORD-1 trial. Eur Urol 2012;61:826–33.

[72] Escudier BJ, Porta C, Bono P, et al. Patient preference between pazopanib and sunitinib: results of a randomized double-blind, placebo-controlled, cross-over study in patients with metastatic renal cell carcinoma – PISCES study. J Clin Oncol 2012;30(Suppl.) [abstr. CRA4502].

[73] Seidel C, Busch J, Weikert S, et al. Progression free survival of first line vascular endothelial growth factor-targeted therapy is an important prognostic parameter in patients with metastatic renal cell carcinoma. Eur J Cancer 2012;48:1023–30.

[74] Al-Marrawi MY, Rini BI, Harshman LC, et al. The association of clinical outcome to first-line VEGF-targeted therapy with clinical outcome to second-line VEGF-targeted therapy in metastatic renal cell carcinoma patients. Target Oncol 2013; Jan 9 [Epub ahead of print].

[75] Motzer RJ, Escudier B, Tomczak P, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. Lancet Oncol 2013;14:552–62.

[76] Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 2011;103:763–73.

[77] Rini BI, Schiller JH, Fruehauf JP, et al. Diastolic blood pressure as a biomarker of axitinib efficacy in solid tumors. Clin Cancer Res 2011;17:3841–9.

[78] Beuselinck B, Karadimou A, Lambrechts D, et al. VEGFR1 single nucleotide polymorphisms associated with outcome in patients with metastatic renal cell carcinoma treated with sunitinib – a multicentric retrospective analysis. Acta Oncol 2013; Feb 20 [Epub ahead of print].

[79] van der Veldt AA, Eechoute K, Gelderblom H, et al. Genetic polymorphisms associated with a prolonged progression-free survival in patients with metastatic renal cell cancer treated with sunitinib. Clin Cancer Res 2011;17:620–9.

[80] van Erp NP, Eechoute K, van der Veldt AA, et al. Pharmacogenetic pathway analysis for determination of sunitinib-induced toxicity. J Clin Oncol 2009;27:4406–12.

[81] Kim JJ, Vaziri SA, Rini BI, et al. Association of VEGF and VEGFR2 single nucleotide polymorphisms with hypertension and clinical outcome in metastatic clear cell renal cell carcinoma patients treated with sunitinib. Cancer 2012;118:1946–54.

[82] Garcia-Donas J, Esteban E, Leandro-Garcia LJ, et al. Single nucleotide polymorphism associations with response and toxic effects in patients with advanced renal-cell carcinoma treated with first-line sunitinib: a multicentre, observational, prospective study. Lancet Oncol 2011;12:1143–50.

[83] Xu CF, Bing NX, Ball HA, et al. Pazopanib efficacy in renal cell carcinoma: evidence for predictive genetic markers in angiogenesis-related and exposure-related genes. J Clin Oncol 2011;29:2557–64.

[84] Huang D, Ding Y, Zhou M, et al. Interleukin-8 mediates resistance to antiangiogenic agent sunitinib in renal cell carcinoma. Cancer Res 2010;70:1063–71.

[85] Tran HT, Liu Y, Zurita AJ, et al. Prognostic or predictive plasma cytokines and angiogenic factors for patients treated with pazopanib for metastatic renal-cell cancer: a retrospective analysis of phase 2 and phase 3 trials. Lancet Oncol 2012;13:827–37.

[86] Rini BI. Targeted therapy for patients with renal-cell carcinoma. Lancet Oncol. 2011;12:1085–7.

[87] Pantuck AJ, Seligson DB, Klatte T, et al. Prognostic relevance of the mTOR pathway in renal cell carcinoma: implications for molecular patient selection for targeted therapy. Cancer 2007;109:2257–67.

[88] Abou Youssif T, Fahmy MA, Koumakpayi IH, et al. The mammalian target of rapamycin pathway is widely

activated without PTEN deletion in renal cell carcinoma metastases. Cancer 2010;117:290–300.

[89] Voss MH, Hakimi AA, Scott SN, et al. Genetic determinants of long-term response to rapalog therapy in advanced renal cell carcinoma. J Clin Oncol 2012;30(Suppl.) [abstr. 4604].

[90] Armstrong AJ, George DJ, Halabi S. Serum lactate dehydrogenase predicts for overall survival benefit in patients with metastatic renal cell carcinoma treated with inhibition of mammalian target of rapamycin. J Clin Oncol 2012;30:3402–7.

[91] Khattak MA, Bakr F, Krzystanek M, et al. Prognostic and predictive markers in metastatic renal cell carcinoma. J Clin Oncol 2013;31:971–2.

[92] Gerlinger M, Rowan A, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med 2012;366:883–93.

[93] Yap TA, Gerlinger M, Futreal PA, Pusztai L, Swanton C. Intratumor heterogeneity: seeing the wood for the trees. Sci Transl Med 2012;4:127ps10.

[94] Gerlinger M, Swanton C. How Darwinian models inform therapeutic failure initiated by clonal heterogeneity in cancer medicine. Br J Cancer 2010;103:1139–43.

[95] Swanton C, Larkin JM, Gerlinger M, et al. Predictive biomarker discovery through the parallel integration of clinical trial and functional genomics datasets. Genome Med 2010;2:53–63.

[96] Vasudev NS, Selby PJ, Banks RE. Renal cancer biomarkers: the promise of personalized care. BMC Med 2012;10:112.

[97] Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a phase III, randomized, open-label, multicenter trial. J Clin Oncol 2012;30(Suppl.) [abstr. 4501].

[98] Hutson TE, Gallardo J, Lesovoy V, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal cell carcinoma. J Clin Oncol 2013;31(Suppl. 6) [abstr. LBA348].

[99] Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

[100] Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26.

[101] Peggs KS, Quezada SA. PD-1 blockade: promoting endogenous anti-tumor immunity. Expert Rev Anticancer Ther 2012;12:1279–82.

[102] Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity. Curr Opin Immunol 2012 Apr;24(2):207–12.

[103] Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7–H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8:793–800.

[104] Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7–H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res 2006;66:3381–5.

[105] Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443–54.

[106] Taube JM, Anders RA, Young GD, et al. Colocalization of inflammatory response with B7–h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med 2012;4:127ra37.

[107] Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455–65.

[108] Cho DC, Sosman JA, Sznol M, et al. Clinical activity, safety and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with metastatic renal cell carcinoma. J Clin Oncol 2013;31(Suppl.) [abstr. 4505].