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Optimizing systemic therapy for metastatic renal cell carcinoma beyond the first-line setting

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Abstract

Since the approval of sorafenib, an inhibitor of vascular endothelial growth factor receptor (VEGFR), in December 2005, seven drugs have been introduced that have provided a high level of clinical efficacy in patients with mRCC, with a median survival ~30 months in an unselected patient population that generally fits trials eligibility¹. Despite such success, advancements in therapies have reached a plateau: different combinations of targeted agents have not demonstrated additional benefit mainly due to toxicity concerns, and some novel agents have failed to show benefit over approved drugs in clinic.

In this review, we aim to focus on optimizing selection of agents in mRCC after progression on first-line TT. We will also review how new drugs may transform existing guidelines and break through the current plateau reached with approved agents.

Keywords

Sequence; systemic therapy; Renal Cell Carcinoma

1.0 Introduction

Until the development of TT, immunotherapy was the mainstay of treatment in mRCC, with high-dose interleukin-2 (HD-IL2) being the only approved drug. However, in the last decade, the use of TT led to a significant increase in survival, from 9 months in 1995 with interferon alpha² to 28–29 months in 2013¹ with either sunitinib or pazopanib, both VEGFR-tyrosine kinase inhibitors (TKIs). Currently, seven approved agents exist to treat mRCC. Six of these agents were approved by the US Food and Drug Administration (FDA) between 2006 and 2010. Over the past five years however, only one additional agent, axitinib, has become available. Currently, novel drugs targeting the PD-1 /PD-L1 pathway and the discovery of drugs that target mechanisms of resistance to anti-angiogenic therapy seem to hold promise for improving the management of mRCC.

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2.0 Consideration for selection of second-line/Salvage therapy

2.1 Does selection of patients depend on molecular alterations and/or clinical factors?

The identification of potentially targetable molecular alterations in different tumors has affected patient outcomes, but only in a few selected settings in oncology.³ Several genes have been reported to be associated with RCC, including VHL, PBRM1, SETD2 and BAP1.⁴ However, these molecular alterations do not currently guide treatment selection.

Nevertheless, clinical prognostic factors can guide the choice of systemic therapy in pretreated patients, as well as treatment-naïve patients. The International Metastatic Database Consortium (IMDC) prognostic factors have been validated in previously treated patients⁵ and provide a reasonable stratification in patients treated with targeted agents and a glance on the natural biology of disease. A slight modification of the traditional Memorial Sloan Kettering Cancer Center (MSKCC) criteria have been used to selected poor-risk patients for the pivotal trial evaluating temsirolimus in treatment-naïve patients. At present, these criteria represent an appropriate tool to identify patients for first-line temsirolimus therapy, although subset analyses from trials of VEGF-directed agents suggest comparable benefit in patients with poor-risk disease. Eventually, we should be able to integrate a molecular and clinical classification in order to achieve a tailored treatment selection. Currently, IMDC or MSKCC criteria alone are not sufficient to delineate the optimal second- or third-line approach.

2.2 Does intolerance to first-line therapy impact the choice for further line of therapy?

Up to 24% of patients stop receiving standard first-line VEGF-TT due to toxicity concerns.⁶ Whether these patients should switch to different VEGF targeting agents is not yet clear since they may have not acquired resistance to VEGF-TKIs and can subsequently continue to benefit from VEGF inhibition. To date, there are no trials that address this question. However, the efficacy of second-line TT with mammalian target or rapamycin (mTOR) inhibitors in mRCC patients previously treated with VEGF-TKIs was assessed in the RECORD-1 trial, a randomized, placebo-controlled, phase III trial. As the only trial to include patients intolerant to VEGF-TKIs, primarily sunitinib, RECORD-1 shows that treatment with everolimus is associated with a significantly higher PFS than placebo.⁷

2.3 Can patients' preferences play a role in therapy choice?

There are several available TKIs that have been approved by the FDA for both first- and second-line management of mRCC. Although efficacy and survival are the ultimate endpoints when considering potential second-line treatment options, patients' preferences remain an important factor, especially when one particular therapy may have only a slight efficacy edge over another. Generally, no standardized methodologies are available to evaluate "patients' preferences" and data collection methods are rather heterogeneous.⁹ Escudier et al.¹⁰ completed the first randomized study to evaluate patients' preferences in patients with mRCC, albeit in a first-line setting. The PISCES study enrolled 169 patients with mRCC and randomly assigned them to either 800-mg pazopanib for 10 weeks followed by a 2-week washout and then crossover to 50-mg sunitinib per day for 10 weeks, or the reverse sequence. They found that 70% of patients reported preferring pazopanib compared

to 22% preferring sunitinib ($P < .001$); 8% reported no preference. Less fatigue and a better overall quality of life were the most common reasons for patient preference of pazopanib. The main reason for sunitinib preference was the lower frequency of diarrhea over pazopanib.

2.4 The impact on the type of prior treatment: published evidence

2.4.1 Cytokines—Cytokine therapy, particularly high-dose interleukin-2 (HD-IL2) or interferon- α (IFN- α), was the standard treatment for mRCC until late 2005. However, poor overall response rates and significant toxicities limited their applicability.¹¹ Despite its drawbacks, HD-IL2 remains indicated for a highly selected population of patients in specialized centers.² Several attempts to identify reliable and predictive biomarkers of response to cytokine therapy have failed¹². When HD-IL2 (or IFN- α , mainly outside the US) are given as a first-line treatment, there is evidence supporting the sequence of a VEGF-TT as second-line treatment. Several anti-angiogenic drugs have shown a benefit in cytokine pre-treated patients with mRCC, including sunitinib, pazopanib,¹³ bevacizumab,¹⁴ and tivozanib.¹⁵ In particular, sorafenib¹⁶ has the most extensive supporting data and axitinib has the most remarkable PFS. Escudier et al.¹⁷ reported that sorafenib as a second-line treatment (after IL-2 or IFN- α) achieved better outcomes than placebo (PFS of 5.5 and 2.8 months and overall survival (OS) of 19.3 and 15.9 months in the sorafenib and placebo arms, respectively). In the AXIS trial¹⁸ and when stratified by previous treatment, patients previously treated with cytokines had significantly longer PFS in the axitinib group (12.2 months; 95% CI, 10.2–15.5) than in the sorafenib group (8.2 months; 95% CI, 6.6–9.5; HR: 0.505; 95% CI, 0.373–0.684; $p < 0.0001$). Pazopanib¹⁹ and sunitinib²⁰ showed a PFS of 7.4 and 8.3 months, respectively, in cytokines-pretreated patients.

Little data exist regarding the use of mTOR-inhibitors as a second-line treatment after cytokines. Small studies showed that temsirolimus and everolimus can show some benefits.^{21, 22}

2.4.2 VEGF TT Refractory—Both mTOR and VEGFR inhibitors have enough level of evidence to be used as second-line therapy after progression on VEGF-TT.

2.4.2.1 mTOR inhibitors after VEGF-TT: Everolimus was the first TT to receive approval for second-line treatment after TKIs (sunitinib and/or sorafenib) in mRCC. Cancer guidelines and recommendations across the U.S.²³ and Europe²⁴ include everolimus as a standard second-line therapy after TKI failure. In the RECORD-1 trial,⁷ everolimus had a longer PFS than placebo (4.9 and 1.9 months, respectively; $p < 0.001$; HR 0.30; 95% CI, 0.22–0.40). However, in the RECORD-1 trial, sunitinib was the first line treatment in only 16% of patients enrolled.

Temsirolimus is approved as a first-line therapy in patients with poor prognosis mRCC. The INTORSECT study was the first randomized clinical trial comparing an mTOR-inhibitor – temsirolimus – to a VEGFR TKI – sorafenib – as second-line treatments. The patients were randomized after progression of disease on sunitinib. The primary endpoint did not show any difference in PFS between both arms: 4.28 months for temsirolimus versus 3.91 months for sorafenib ($p = 0.193$).²⁵ Interestingly, median OS favored sorafenib over temsirolimus.

The median OS was 16.64 months with sorafenib compared to 12.27 months with temsirolimus; ($P = 0.01$). The results remain puzzling: baseline characteristics between arms, treatment discontinuation related to toxicity and the receipt of third line therapies were similar between both groups.

2.4.2.2 VEGF-TKIs after initial VEGF-TT: The AXIS trial¹⁸ was the first randomized clinical trial to compare two VEGF-TKIs as second-line therapies. First-line agents included mainly sunitinib and interferon-alpha with a small minority receiving bevacizumab or temsirolimus. The median PFS was significantly longer with axitinib compared to sorafenib (6.7 and 4.7 months, respectively; $p < 0.0001$). In the sunitinib pre-treated population, the PFS for axitinib and sorafenib patients was 4.8 months and 3.4 months, respectively ($p = 0.0107$), modestly favoring axitinib. OS was 15–16 months in both arms.

Data from the SWITCH-I²⁶, another trial assessing the use of VEGF-TKIs as second line treatment following first line VEGF TT, addressed the hypothesis of whether sequential use of sorafenib followed by sunitinib in mRCC would produce longer PFS. This study enrolled 365 treatment-naïve patients and switched over to the alternate therapy (sunitinib-sorafenib versus sorafenib-sunitinib), which the patients received until progression or intolerable toxicity. The trial did not show any difference in either PFS or OS between the two sequences. The median total PFS duration reached 12.5 months in the sorafenib-sunitinib arm and 14.9 months in the sunitinib-sorafenib arm. Median OS showed comparable outcomes, with 31.5 months in the sorafenib-sunitinib arm and 30.2 months in the sunitinib-sorafenib arm.

Most of the studies on second-line therapies are based on sunitinib as a first-line therapy. Results from the COMPARZ trial¹ demonstrate that pazopanib is not inferior to sunitinib. Pazopanib is commonly used in the first-line setting in mRCC, with its sales increasing worldwide by 50% from 2012 to 2013.²⁷ Unfortunately, there are no prospective randomized trials assessing the efficacy of targeted agents following first line treatment of pazopanib. A small retrospective study showed that VEGF-TKIs were more effective than mTOR inhibitors after disease progression on pazopanib, although OS was not significantly different between both groups.²⁸

2.4.3 mTOR inhibitors refractory

2.4.3.1 VEGFR-TKIs after mTOR inhibitors: In clinical practice, the use of mTOR inhibitors as first-line therapy is limited to patients with poor prognosis²⁹ or intolerance to VEGF-TT. In addition, poor-risk patients are unlikely to receive subsequent lines.³⁰

The sequence of everolimus to sunitinib versus sunitinib to everolimus was studied in the RECORD-3 trial³¹. First-line PFS, combined PFS, and OS favored the sequence of sunitinib followed by everolimus. The OS was 22.4 months for everolimus followed by sunitinib versus 32 months for sunitinib followed by everolimus (HR 1.24; 95% CI, 0.94–1.64).³² The sequence of sunitinib to everolimus was also favored in select subsets of patients, such as poor-risk mRCC or non-clear cell RCC. Notably, next generation sequencing (NGS) studies paired to RECORD-3 provide some of the most important insights to date with respect to potential predictors of response to mTOR- versus VEGF-directed therapy. The study

suggested that patients with *PBRM1* alteration may have a prolonged response to everolimus, while patients with *KDM5C* alteration may have a prolonged response to sunitinib.

2.4.3.2 mTOR inhibitors after mTOR inhibitors: The use of a rapalog as a second-line treatment following progression on a first-line rapalog is not currently recommended. Interestingly, a study enrolling only 12 patients showed that this sequence may result in some benefit.³³ However, due to the small cohort size, this sequence should not be recommended unless the patient did not experience real progression on the first rapalog.

3.0 Novel treatment approaches after progression on first-line targeted therapy

3.1 Immune checkpoint inhibition

The immunogenic nature of RCC has led to exploration of several strategies to stimulate an anti-tumor immune response. The promising results and approval of ipilimumab, anti-(cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) blocker, in melanoma revived an interest in immunotherapy, with a particular focus on immune checkpoint inhibition.^{33,34} Central to the concept of tumor immune evasion is the presence of co-inhibitory molecules, such as CTLA-4 and programmed cell death protein-1 (PD-1) receptors expressed on T-lymphocytes' surface.³⁵ The interaction between these receptors and their respective ligands expressed on antigen-presenting cells (APCs) results in an inhibitory signal on activated T cells.³⁶ PD-1 ligand (PD-L1) may be expressed in tumor cells or in the surrounding microenvironment constitutively due to an activated oncogenic pathway or as part of an adaptive immune resistance mechanism. Furthermore, the expression of PD-L1 specifically in RCC has been associated with a more aggressive behavior and a worse survival.³⁷ In mRCC, targeting the PD-1/PD-L1 pathway has thus far been promising.³⁸

3.2 Anti PD-1/PD-L1 monotherapy

Recent strategies targeting the PD-1/PD-L1 pathway in mRCC showed potential efficacy in early phase clinical trials. Topalian et al.³⁸ conducted a large phase I study of nivolumab (an Ig4 antibody against PD-1) in 296 patients with treatment-refractory advanced solid tumors, including 34 patients with mRCC. A notable objective response rate (ORR) of 27% was reached, and 5 out of 8 patients achieved durable responses of 24 months or more. The long-term follow up results from this cohort of patients showed a median duration of response of 12.9 months. Serious adverse events were 18%, including 9% immune-mediated adverse events.³⁹ In another phase I trial of BMS-936559 enrolling 17 patients with previously treated mRCC, an ORR of 12% was observed⁴⁰.

In a three arm, randomized, phase II clinical trial exploring 3 different doses of nivolumab in 168 TKI-refractory patients with mRCC, the median PFS ranged from 2.7 to 4.2 months. When immune-response PFS was assessed, PFS ranged from 4.3 to 6.9 months. The overall response rate (ORR) ranged from 20% to 22%. The median OS ranged from 18.2 to 25.5 months, raising high expectations considering the acceptable safety profile of nivolumab.⁴⁰ In comparison, expected survival from trials in the same setting (RECORD-1, AXIS) is

around 15–16 months. In another biomarker study of nivolumab including both previously-treated and treatment-naïve patients, efficacy results were similar. Nivolumab also showed an immunomodulatory effect, with a significant increase in the number of effector T cells and their transcripts in sequential biopsies.⁴¹ Notably, response rate was modestly higher in patients with PD-L1 positivity (22% versus 8%), and OS appeared to be prolonged (NR versus 23.4 mos). With these results in mind, PD-L1 expression should be explored as a potential biomarker of response in forthcoming studies. CheckMate 025, a large, phase III clinical trial finished accruing over 800 pre-treated mRCC patients and compares nivolumab monotherapy versus standard of care everolimus (NCT01668784). This trial assumes a median OS of 14.8 months for everolimus compared to 19.5 months for nivolumab.

Alternatively, PD-L1 inhibition with the advantage of sparing PD-1/PD-L2 interaction has been investigated as well. MPDL3280A, a monoclonal antibody against PD-L1, was tested in a phase I trial with 69 mRCC patients, 26% of which were poor prognosis patients by MSKCC criteria and only 13% were treatment-naïve. The median PFS was 24 weeks (95% CI, 38–63 weeks) and the ORR was 15%. ORR for Fuhrman grade 4 or sarcomatoid clear cell RCC (n = 18) was 22%. Treatment-related grade 3 AEs occurred in 11 patients (16%).⁴²

3.3 Combined immune checkpoint strategies

Monoclonal antibodies against CTLA-4 have been widely used in several tumors, mainly melanoma and non small cell lung cancer (NSCLC)⁴³ A phase II trial of ipilimumab was conducted in 61 patients with mRCC.⁴⁴ A partial response rate of 10% was observed, mostly at the higher dose of 3 mg/kg every 3 weeks.⁴⁵ Several trials investigating the combination of PD-1 and CTLA-4 blockade have been conducted as well, following the impressive data seen in metastatic melanoma. Hammers et al.⁴⁵ reported the use of dual immune checkpoint blockade in 44 patients with mRCC, with most patients having received prior systemic therapy. Patients were assigned to receive either nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg (N3+I1), or nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg (N1+I3) then nivolumab at 3 mg/kg every 2 weeks until progression/toxicity. ORRs ranged between 29%–39% in both arms. The toxicity profile favored the lowest dose of ipilimumab (24% of grade 3/4 related AEs in the N3+I1 arm versus 61% in the N1+I3 arm). Currently, multiple studies are assessing the combination of CTLA4 and PD1 blockade. CheckMate214 (NCT02231749) is a phase 3, randomized, open-label trial investigating nivolumab combined with ipilimumab versus sunitinib monotherapy in subjects with previously untreated mRCC. The combination of ipilimumab and pembrolizumab (anti-PD1) is currently being studied in a phase I-II clinical trial (NCT02089685).

3.4 Dual Immune checkpoint and VEGF blockade

1.1.1 VEGF may play a role in the immune response through the induction of myeloid-derived suppressor cells that suppress both T-cell and dendritic cell functions⁴⁷. VEGF inhibition also regulates the immune response by increasing cytokines and tumor-infiltrating T cells, increasing T cell access into tumors⁴⁸ and developing CD8⁺ and CD4⁺ central memory T cells⁴⁹. Despite achieving notable results, immune checkpoint inhibitors are effective only in a subgroup of patients. Therefore, the combination of both approaches

targeting VEGF and PD-1/PD-L1 together, although still under investigation, is promising and exciting.

The combination of nivolumab with either sunitinib or pazopanib showed an ORR that is higher than expected with either nivolumab or VEGF-TKIs in monotherapy (52% and 45% with sunitinib and pazopanib respectively, both started at full dose) in predominantly pre-treated patients. However, grade 3–4 related adverse events were observed in 73% and 60% with sunitinib and pazopanib respectively⁵⁰.

Results of the dual VEGF and PD-L1 blockade has been reported with the combination of bevacizumab and MPDL3280 in 10 patients with mRCC enrolled in a phase I trial.⁵² Among these 10 patients, 4 experienced a partial response and only 1 patient experienced a high-grade adverse event related to MPDL3280. A prospective phase II study of 300 treatment naive mRCC patients compares this combination with single-agent MPDL3280 and standard-of-care sunitinib (NCT01984242) and just finished accrual.

3.5 Dual MET and VEGF blockade: Reverting resistance to VEGF-targeted agents?

The Majority of patients eventually develop resistance to VEGF TKIs. While heterogeneity may play an important role, unexpectedly acquired mutations are uncommon causes of resistance.^{52–54} Mechanisms of resistance to VEGF inhibition remain under investigation. The upregulation of alternative pro-angiogenic and pro-invasive signaling pathways is thought to play a major role. For example, MET activation was shown to be upregulated following VEGFR inhibition in several tumor models⁵⁴, as a mechanism of resistance. Moreover, high MET expression levels have been associated with a worse outcome.⁵⁶ Therefore, the combined inhibition of the VEGF and MET might overcome resistance to VEGF inhibition, thus increasing the efficacy achieved by VEGF inhibition alone. Cabozantinib is a new TKI with potent activity against MET and VEGFR2, as well as other receptor tyrosine kinases including RET, KIT, AXL, and FLT.⁵⁷ It was first studied in mRCC in a Phase I trial with 25 patients who had at least one prior systemic therapy including VEGF and mTOR inhibitors. Single agent cabozantinib treatment showed antitumor activity with PFS of 12.9 months and response rate of 28%.⁵⁸ METEOR is a randomized phase III trial that compares cabozantinib to standard everolimus in patients with VEGF-TKI refractory mRCC (NCT01865747).

4.0 Future directions

Existing guidelines suggest that everolimus and axitinib are reasonable choices for second-line treatment, based on results of previously described phase III trials. In the absence of head-to-head trials comparing axitinib and everolimus, it is challenging to be dogmatic about which agent should be used first. Based on the data cited from INTORSECT, we propose that VEGF-directed therapy may be preferred second-line in patients with a prolonged response to VEGF-directed therapy in the front-line setting. However, the choice of VEGF versus mTOR inhibition in the second-line setting may become antiquated with the emergence of several phase III studies. Drugs targeting PD-1/PD-L1 pathways and mechanisms of resistance to VEGF-inhibitors may represent the next milestone in the management of mRCC. Checkmate 025 and METEOR, two randomized, phase III clinical

trials assessing the efficacy of nivolumab and cabozantinib respectively, have recently had press releases to show positive results. CheckMate 025 has stopped prematurely because the study has met the primary endpoint demonstrating increased overall survival compared to the control arm – everolimus – in patients with previously-treated mRCC.⁵⁹ METEOR has also met primary endpoint, showing that cabozantinib reduces the risk of disease progression or death by 42% (HR 0.58, [p < 0.0001] compared to everolimus).⁶⁰ Moreover, the interim analysis of overall survival has shown a trend favoring cabozantinib (HR 0.67, [p = 0.005] compared to everolimus). Mature results are awaited to make further conclusions regarding therapeutic sequencing.

Careful selections of patients, toxicity profiles, and long-term survival data, as well as identification of predictive biomarkers, remain critical keys to guides therapeutic decision making. Many patients will still progress and require further systemic therapy after novel agents. One study⁶¹ retrospectively reviewed the data on 56 patients who received subsequent TT after anti-PD-1/PD-L1 therapies. Overall median time to treatment failure (TTF) was 6.6 months after progression on PD1/PD-L1 inhibitors. Median TTF was 6.9 and 5.7 months in patients treated with VEGF and mTOR inhibitors, respectively. Median OS after the initiation of subsequent therapy was 17.5 months. A further retrospective study with 63 patients reached similar results.⁶² This data suggests that targeting PD-1/PD-L1 should not affect the efficacy of further VEGF-TT.

In summary and despite no new approved therapies in mRCC since 2011, pending large phase 3 pivotal trials in the refractory setting with novel agents may finally lead to new options for our mRCC patients.

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Summary

The introduction of molecularly targeted therapies (TT) has transformed the management of metastatic renal cell carcinoma (mRCC). Within a relatively short period of time, systemic treatment of mRCC has evolved from a disease only treated by cytokines to a disease where TT is the cornerstone of patient management.

Table 1

Phase III second-line trials conducted in patients with mRCC.

Agent	Comparator	N	1° EP	Comments
Everolimus	Placebo	410	PFS	<ul style="list-style-type: none"> • Patients received prior sunitinib and/or sorafenib • 2:1 randomization schema • Improvement in PFS with everolimus (4.0 v 1.9 mos; HR 0.30, 95% CI 0.22–0.40, p<0.0001) • Everolimus led to higher rates of stomatitis, rash and fatigue • No OS benefit
Axitinib	Sorafenib	723	PFS	<ul style="list-style-type: none"> • Patients received 1 prior cytokine or 1 prior targeted therapy (either sunitinib, bevacizumab, or temsirolimus) • Improvement in PFS with axitinib (6.7 v 4.7 mos; HR 0.665, 95% CI 0.544–0.812; 1-sided P<0.0001) • Axitinib led to higher rates of diarrhea, fatigue and hypertension • No OS benefit
Cabozantinib	Everolimus	658	PFS	<ul style="list-style-type: none"> • Patients received at least 1 prior VEGF-directed therapy • Preliminary data reported in press release • Improvement in PFS with cabozantinib in the first 375 randomized patients (HR 0.58, 95%CI 0.45–0.75; P<0.0001) • Trend towards improvement in OS with cabozantinib in overall study population (HR 0.67, 95% CI 0.51 – 0.89; p=0.005)
Nivolumab	Everolimus	821	OS	<ul style="list-style-type: none"> • Patients received 1 or 2 prior anti-angiogenic therapies, but no more than 3 prior systemic therapies • Press release suggested that study met primary endpoint of improvement in OS

Table 2

Selected potential combination approaches undergoing clinical evaluation include dual T-cell checkpoint inhibition and combinations with VEGF targeted agents.

Combination regimen	Treatment groups	Phase	Trial number
PD-1 and VEGF inhibition	Pembrolizumab with axitinib	I	NCT02133742
	Pembrolizumab with Pazopanib	I/II	NCT02014636
	Nivolumab with sunitinib vs. nivolumab with pazopanib	I	NCT01472081
PD-1 and CTLA4 inhibition	Pembrolizumab vs. pembrolizumab with ipilimumab vs. pembrolizumab with pegylated IFN- α 2b	I/II	NCDT02089685
	Nivolumab vs. nivolumab with bevacizumab vs. nivolumab with ipilimumab	II	NCT02210117
	Nivolumab with ipilimumab vs. sunitinib	II	NCT02231749
PD-L1 and VEGF inhibition	MPDL3280A vs. MPDL3280A with bevacizumab vs. MPDL3280A with sunitinib	II	NCT01984242