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The Use of Targeted Therapies in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Updated Guideline 2017

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Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

The primary objective of this report is to determine the optimal targeted therapies for locally advanced or metastatic renal cell cancer (mRCC). The secondary objective is to determine whether a combination of targeted agents is better than any single targeted agent.

TARGET POPULATION

Adult patients with inoperable locally advanced or mRCC.

INTENDED USERS

Oncologists who treat patients with RCC.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE - Question 1: What are the optimal targeted therapies for locally advanced or mRCC?

PREVIOUSLY UNTREATED PATIENTS

Recommendation 1
Either of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF TKIs) sunitinib or pazopanib is recommended for previously untreated patients with locally advanced or mRCC.

Qualifying Statements for Recommendation 1

- Pazopanib and sunitinib have been shown to have similar survival benefits. However, sunitinib has been associated with more symptomatic side effects and pazopanib has been more frequently associated with hepatic toxicity.
- The dose used in the initial trial of sunitinib was 50 mg daily by mouth for four weeks, followed by two weeks off drug, in repeated six-week cycles. Alternative schedules of sunitinib (three-week cycles of two weeks on drug [50 mg] followed by one week off therapy) or continuous daily dosing [37.5 mg]) have been shown effective.

Recommendation 2
Although bevacizumab combined with interferon alpha (IFN-α) is superior to IFN-α alone, it is not recommended due to a high rate of side effects. Current data do not support the use of single-agent bevacizumab, and it is not recommended.

Recommendation 3
Temsirolimus is a treatment option for first-line therapy for the subset of patients with poor-risk disease.

Qualifying Statements for Recommendation 3

- The dose used in the trial of temsirolimus was 25 mg intravenously, once per week for patients with poor-risk disease.
- Based on comparative results with another mammalian target of rapamycin inhibitor similar to temsirolimus (everolimus), VEGF TKI therapy is preferred for first- and subsequent-line therapies for all patient types.

PREVIOUSLY TREATED PATIENTS

Recommendation 4
Nivolumab is recommended over everolimus as a treatment for patients with advanced RCC who have progressed on first- or second-line VEGF TKI.

Qualifying Statements for Recommendation

- Nivolumab has been associated with uncommon but severe immune-mediated adverse reactions, with the most common being enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.
- Patients treated with nivolumab showed improved overall survival (OS), less toxicity, and better quality of life compared with everolimus.

Recommendation 5
Cabozantinib is recommended over everolimus as a treatment for patients with advanced or mRCC who have progressed on VEGF therapy.

Qualifying Statements for Recommendation

- Individuals treated with cabozantinib showed significantly improved OS, but with more toxicity, compared with everolimus.

Recommendation 6
Everolimus is a treatment option for locally advanced or mRCC patients previously treated with first- or second-line VEGF TKI.

Qualifying Statements for Recommendation

- The dose used in the trial of everolimus was 10 mg daily by mouth given in four-week cycles.
- Recent studies have found superiority of other agents (e.g., nivolumab, cabozantinib) over everolimus; however, for those who cannot tolerate these agents, everolimus is an option.

Recommendation 7
Axitinib is a treatment option for second-line therapies.

Qualifying Statements for Recommendation

- Two meta-analyses suggest axitinib's superiority over sorafenib and pazopanib for previously treated patients.
- One trial showed significantly improved progression-free survival and overall response rate with axitinib over sorafenib in previously treated patients.

Recommendation 8
Sorafenib is a treatment option in patients with favourable- to intermediate-risk RCC previously treated with cytokine therapies.

Qualifying Statements for Recommendation 8

- The dose used in the trial of sorafenib was 400 mg by mouth twice daily, continuously.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE - Question 2: Is a combination of agents better than any single targeted agent?

Recommendation 9
Current evidence does not support the use of combinations of targeted agents outside of a clinical trial setting. Thus, there are no combinations of targeted therapies that can be recommended at this time.

Qualifying Statements for Recommendation 9

- LENEVE, a phase II randomized controlled trial comparing lenvatinib, everolimus, and a combination of the two, had promising efficacy results with the combination of lenvatinib and everolimus, and lenvatinib alone, over the single administration of everolimus; however, the sample size was small. A phase III randomized trial of the combination in mRCC is planned.

The Use of Targeted Therapies in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Updated Guideline 2017

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

The primary objective of this report is to determine the optimal targeted therapies for locally advanced or metastatic renal cell cancer (mRCC). A secondary objective is to determine whether a combination of agents is better than any single targeted agent.

TARGET POPULATION

Adult patients with inoperable locally advanced or mRCC.

INTENDED USERS

Oncologists who treat patients with RCC.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE - Question 1: What are the optimal targeted therapies for locally advanced or mRCC?

PREVIOUSLY UNTREATED PATIENTS

Recommendation 1
Either of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGF TKIs) sunitinib or pazopanib is recommended for previously untreated patients with locally advanced or mRCC.
Qualifying Statements for Recommendation 1
• Pazopanib and sunitinib have been shown to have similar survival benefits. However, sunitinib has been associated with more symptomatic side effects and pazopanib has been more frequently associated with hepatic toxicity. • The dose used in the initial trial of sunitinib was 50 mg daily by mouth for four weeks, followed by two weeks off drug, in repeated six-week cycles. Alternative schedules of sunitinib (three-week cycles of two weeks on drug [50 mg] followed by one week off therapy) or continuous daily dosing (CDD – 37.5 mg) have been shown effective.
Key Evidence for Recommendation 1
• A network meta-analysis, comparing first-line treatments in the management of advanced RCC, identified 11 randomized controlled trials (RCTs) reporting results for eligible treatments. In the case of progression-free survival (PFS), sunitinib was superior compared with bevacizumab plus interferon alpha (IFN-α) (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.64 to 0.96), everolimus (HR, 0.70; 95% CI, 0.56 to 0.87), sorafenib (HR, 0.56; 95% CI, 0.40 to 0.77) and temsirolimus plus bevacizumab (HR, 0.74; 95% CI, 0.56 to 0.96). There was no significant difference in PFS between sunitinib and axitinib, pazopanib, or tivozanib. Sensitivity analyses confirmed that no treatment was significantly more efficacious than sunitinib [1]. • Median PFS in the EFFECT trial was 8.5 months for scheduled dosing (50 mg/d with 4 weeks on treatment and 2 weeks off) versus 7.0 months for the CDD (37.5 mg/d) (HR, 0.77; 95% CI, 0.58 to 1.02; p=0.070) for previously untreated patients [2]. • The COMPARZ trial found equal efficacy for pazopanib and sunitinib (HR for progression of disease or death from any cause, 1.05; 95% CI, 0.90 to 1.22; HR for death with pazopanib, 0.91; 95% CI, 0.76 to 1.08). Patients treated with sunitinib had a higher

incidence of fatigue (63% vs. 55%), hand-foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%), and patients treated with pazopanib had a higher incidence of increased levels of alanine aminotransferase (ALT) (60% vs. 43%) [3].
- In the PISCES trial, significantly more patients preferred pazopanib (70%) over sunitinib (22%); 8% had no preference (p=0.001). Better overall quality of life (QOL) and less fatigue were the main reasons for preferring pazopanib, with less diarrhea being the most reported reason for preferring sunitinib [4].

Interpretation of Evidence for Recommendation 1

Sunitinib and pazopanib appear equally effective. Oncologists should discuss and assess the different toxicity profiles of the two drugs with their patients.

Recommendation 2

Although bevacizumab combined with IFN-α is superior to IFN-α alone, it is not recommended due to a high rate of side effects. Current data do not support the use of single-agent bevacizumab, and it is not recommended.

Qualifying Statements for Recommendation 2

- None

Key Evidence for Recommendation 2

- The AVOREN trial found that bevacizumab plus IFN-α significantly improved PFS compared with INF-α plus placebo (median, 10.2 vs. 5.5 months; HR, 0.63; 95% CI, 0.52 to 0.75; p=0.0001), with an improved, but not significant, overall survival (OS) (median survival, 23.3 vs. 21.3 months; HR, 0.86; 95% CI, 0.72 to 1.04) among previously untreated patients. However, the proportion of patients who experienced an adverse event (AE) that led to treatment stoppage was higher in the bevacizumab plus IFN-α group than in the control group (28% vs. 12%). Serious AEs were more common in IFN-α plus bevacizumab patients (29% vs. 16% for INF-α alone [5].
- In the CALGB 90206 trial, treatment with bevacizumab plus IFN-α resulted in a significant improvement in PFS (median, 8.5 vs. 5.2 months; HR, 0.71; 95% CI, 0.61 to 0.83; p<0.0001)[6] and a longer, but not significant, OS (median, 18.3 vs. 17.4 months; HR, 0.86; 95% CI 0.73 to 1.01; p=0.07) compared with INF-α alone among previously untreated patients. Overall toxicity was greater for bevacizumab plus IFN-α, with patients having significantly more grade 3 hypertension (9% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%), and proteinuria (13% vs. 0%) [7].

Interpretation of Evidence for Recommendation 2

VEGF TKIs (sunitinib and pazopanib) are efficacious and safer alternatives to the bevacizumab plus INF-α combination.

Recommendation 3

Temsirolimus is a potential treatment option for first-line therapy for the subset of patients with poor-risk disease.

Qualifying Statements for Recommendation 3

- The dose used in the trial of temsirolimus was 25 mg intravenously, once per week for patients with poor-risk disease.
- Based on comparative results with another mammalian target of rapamycin (mTOR) inhibitor similar to temsirolimus (everolimus), VEGF TKI therapy is preferred for first- and subsequent-line therapies for all patient types.

Key Evidence for Recommendation 3

- One large phase III trial (GLOBAL-ARCC, Hudes et al. 2009) studied the efficacy of first-line temsirolimus treatment in patients with poor-risk mRCC. Compared with INF-α (7.3; 95% CI, 6.1 to 8.8), median OS (months) was significantly longer for patients treated with single-agent temsirolimus (10.9; 95% CI, 8.6 to 12.7) (HR, 0.73; 95% CI, 0.58 to 0.92; p=0.008), but not with temsirolimus combined with INF-α (8.4; 95% CI, 6.6 to 10.3). Median PFS (months) was longer in patients treated with temsirolimus alone (3.8; 95% CI, 3.6 to 5.2) and in combination (3.7; 95% CI, 2.9 to 4.4) compared with INF-α alone (1.9; 95% CI, 1.9 to 2.2) (p<0.0001). Temsirolimus-based regimens were associated with significantly more grade 3/4 anemia, neutropenia, and thrombocytopenia [8].

Rationale for recommendation of TKI over mTOR inhibition:

- The RECORD-3 (n=471) trial reported first-line everolimus (mTOR inhibitor similar to temsirolimus) to be inferior to sunitinib, with a worse PFS of 7.9 months compared with 10.7 months (HR, 1.4; 95% CI, 1.2 to 1.8). Overall PFS, after crossover from everolimus to sunitinib, was also inferior to sunitinib followed by everolimus (21.1 months compared with 25.8 months, HR, 1.3; 95% CI, 0.9 to 1.7). The median OS was 22.4 months for sequential everolimus followed by sunitinib and 32.0 months for sequential sunitinib followed by everolimus (HR, 1.2; 95% CI, 0.9 to 1.6) [9].
- A randomized phase II ESPN trial of everolimus (mTOR similar to temsirolimus) versus sunitinib with crossover design in mRCC reported the interim analysis for 68 patients. The median overall response rate (ORR) in first-line therapy was 12% for sunitinib and 0% with everolimus. The median PFS in first-line therapy was 6.1 months with sunitinib and 4.1 months with everolimus (p=0.6). Median PFS in second-line therapy was 1.8 months for sunitinib (95% CI, 1.5 to not estimable) and 4.3 months for everolimus (95% CI, 1.4 to not estimable). Median OS in first-line was 10.5 months for everolimus and was not reached with sunitinib (p=0.01). The trial contained many non-clear cell RCC patients, which may explain the poor results [10].
- The ASPEN trial randomized 108 previously untreated patients with non-clear cell RCC to either sunitinib or everolimus. Sunitinib significantly increased PFS compared with everolimus (8.3 months; 80% CI, 5.8 to 11.4 vs. 5.6 months; 80% CI, 5.5 to 6.0; HR, 1.41; 80% CI, 1.03 to 1.92; p=0.16). OS was similar between the two treatment groups (HR, 1.12; 95% CI, 0.7 to 2.1; p=0.60). Median OS was 31.5 months (95% CI, 14.8 to not reached) in the sunitinib group and 13.2 months (95% CI, 9.7 to 37.9) in the everolimus group [11].

Interpretation of Evidence for Recommendation 3

Temsirolimus or sunitinib are first-line treatment options for patients with poor-prognosis mRCC.

PREVIOUSLY TREATED PATIENTS

Recommendation 4

Nivolumab is recommended over everolimus as a treatment for patients with advanced RCC who have progressed on first- or second-line VEGF TKI.

Qualifying Statements for Recommendation 4

- Nivolumab has been associated with uncommon but severe immune-mediated adverse reactions, with the most common being enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.
- Patients treated with nivolumab showed improved OS, less toxicity, and better QOL compared with everolimus.

Key Evidence for Recommendation 4
The phase II CheckMate 025 trial [12] examined patients with advanced clear cell RCC, who previously received treatment with one or two regimens of VEGF-targeted therapy. Patients were randomly assigned (in a 1:1 ratio) to receive 3 mg of nivolumab per kilogram of body weight intravenously every two weeks or 10 mg everolimus orally once daily. The median OS was 25.0 months (95% CI, 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The HR for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; p=0.002), meeting the pre-specified criterion for superiority (p≤0.0148). The ORR was 25% with nivolumab and 5% with everolimus (odds ratio, 5.98; 95% CI, 3.68 to 9.72; p<0.001). The median PFS was 4.6 months (95% CI, 3.7 to 5.4) with nivolumab and 4.4 months (95% CI, 3.7 to 5.5) with everolimus (HR, 0.88; 95% CI, 0.75 to 1.03; p=0.11). Nineteen percent of patients receiving nivolumab had grade 3 or 4 treatment-related AEs compared with 37% of the patients receiving everolimus [12].
Interpretation of Evidence for Recommendation 4
The Checkmate 025 trial demonstrates superiority of nivolumab over everolimus, with improved survival, a good safety profile, and better QOL.
Recommendation 5
Cabozantinib is recommended over everolimus as a treatment for patients with advanced or mRCC who have progressed on VEGF pathway inhibitor therapy.
Qualifying Statements for Recommendation 5
• Individuals treated with cabozantinib showed significantly improved OS, but with more toxicity, compared with those treated with everolimus.
Key Evidence for Recommendation 5
• The METEOR, phase III RCT [13] compared cabozantinib (60 mg daily) and everolimus (10 mg daily) in patients with advanced or mRCC that progressed after previous VEGF-targeted therapy. Median PFS was 7.4 months with cabozantinib versus 3.8 months for everolimus (HR, 0.58; 95% CI, 0.45 to 0.74; p<0.001). The ORR was 21% with cabozantinib and 5% with everolimus (p<0.001). An interim analysis showed that OS was longer with cabozantinib than with everolimus (HR for death 0.67; 95% CI, 0.51 to 0.89; p=0.005). Dose reductions due to AEs occurred in 60% of the patients who received cabozantinib and in 25% of those who received everolimus. Discontinuation of the study drug due to AEs occurred in 9% of the patients who received cabozantinib and in 10% of those who received everolimus [13].
Interpretation of Evidence for Recommendation 5
Cabozantinib improves OS compared with everolimus. However, AEs were more frequently observed with cabozantinib, compared with everolimus, and patients need to be closely monitored for toxicity and dose modification.
Recommendation 6
Everolimus is a treatment option for locally advanced or mRCC patients previously treated with first- or second-line VEGF TKI.
Qualifying Statements for Recommendation 6
• The dose used in the trial of everolimus was 10 mg daily by mouth given in four-week cycles. • Recent studies have found superiority of other agents (nivolumab and cabozantinib) over everolimus; however, for those who cannot tolerate these agents, everolimus is an option.
Key Evidence for Recommendation 6

- The RECORD-1 trial's [14] final results established the efficacy and safety of everolimus compared with placebo in patients with mRCC after progression on sunitinib and/or sorafenib. The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (HR, 0.33; p<0.001). The median OS was 14.8 months (everolimus) versus 14.4 months (placebo) (HR, 0.87; p=0.162). Eighty percent of patients in the placebo arm crossed over to everolimus and survival corrected for crossover was 1.9-fold longer (95% CI, 0.5 to 8.5) with everolimus compared with placebo only.
- See above recommendations 4 and 5 for details on the CheckMate and METEOR trials

Interpretation of Evidence for Recommendation 6

Patients with contraindications to nivolumab or cabozantinib may still benefit from everolimus.

Recommendation 7

Axitinib is a treatment option for second-line therapies.

Qualifying Statements for Recommendation 7

- Two meta-analyses suggest axitinib's superiority over sorafenib and pazopanib for previously treated patients.
- One trial showed significantly improved PFS and ORR with axitinib over sorafenib in previously treated patients.

Key Evidence for Recommendation 7

- A network meta-analysis compared the clinical efficacy and safety among newer targeted agents for the treatment of mRCC, identifying seven RCTs for inclusion [3,14-19]. The network indirect analysis suggested that axitinib may prolong PFS following failure of first-line therapy and that axitinib exhibits higher efficacy and safety compared with sorafenib (PFS-HR, 0.67; 95% CI, 0.54 to 0.81) and pazopanib (PFS-HR, 0.64; 95% CI, 0.42 to 0.98) in patients who previously received systematic treatment [20] (see Appendix E).
- A network meta-analysis, employing indirect comparative methods to assess the effectiveness and safety of axitinib as second-line treatments for advanced RCC, found that PFS was significantly improved with axitinib compared with placebo (HR, 0.25; 95% CI, 0.17 to 0.38), sorafenib (HR, 0.46; 95% CI, 0.32 to 0.68) and pazopanib (HR, 0.47; 95% CI, 0.26 to 0.85) [21] (see Appendix E).
- The AXIS phase III trial of second-line axitinib resulted in significantly longer PFS compared with sorafenib for mRCC (median, 8 vs. 6 months; HR, 0.66; 95% CI, 0.55 to 0.78). There was a significant increase in ORR with axitinib (23% vs. 12%) [18].

Interpretation of Evidence for Recommendation 7

The value of axitinib as first-line therapy is unclear; however, it may be considered an option for second-line therapy if there is limited access or contraindications to nivolumab or cabozantinib.

Recommendation 8

Sorafenib is a treatment option in patients with favourable- to intermediate-risk RCC previously treated with cytokine therapies.

Qualifying Statements for Recommendation 8

- The dose used in the trial of sorafenib was 400 mg by mouth twice daily, continuously.

Key Evidence for Recommendation 8

- The TARGET trial compared sorafenib and placebo in 903 patients who had progressed on interleukin-2 (IL-2) or IFN-α. Significant increases in median PFS (5.5 vs. 2.8 months; HR, 0.44; 95% CI, 0.35 to 0.55; p<0.001) were observed among previously treated patients receiving sorafenib, compared with placebo. As a result of these findings, sorafenib was offered to all patients in the placebo group. Secondary OS analysis

censoring placebo patients demonstrated a survival benefit for those receiving sorafenib (19.3 vs. 15.9 months, respectively; HR, 0.77; 95% CI, 0.63 to 0.95; p=0.015), although the findings did not meet the pre-specified boundary for statistical significance [19].

- The **SWITCH** study [22] prospectively evaluated sequential use of sorafenib followed by sunitinib (So-Su) versus sunitinib followed by sorafenib (Su-So) in patients with mRCC. In total, 365 patients were randomized (So-Su, n=182; Su-So, n=183). There was no significant difference in total PFS between So-Su and Su-So (median 12.5 vs. 14.9 months; HR, 1.01; 90% CI, 0.81 to 1.27; p=0.5 for superiority). OS was similar for So-Su and Su-So (median 31.5 and 30.2 months; HR, 1.00, 90% CI, 0.77 to 1.30; p=0.5 for superiority). More So-Su patients than Su-So patients reached protocol-defined second-line therapy (57% vs. 42%). Overall, AE rates were generally similar between the treatment arms [22].
- The findings from the network meta-analysis by Leung et al. mentioned above also found sunitinib to be superior to sorafenib (PFS–HR, 1.63; 95% CI, 1.09 to 1.52 – sorafenib vs. sunitinib) [20] (see Appendix E).

Interpretation of Evidence for Recommendation 8

Other therapies are preferred for first and subsequent lines for all patient types.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE - Question 2: Is a combination of agents better than any single targeted agent?

Recommendation 9

Current evidence does not support the use of combinations of targeted agents outside of a clinical trial setting. Thus, there are no combinations of targeted therapies that can be recommended at this time.

Qualifying Statements for Recommendation 9

- LENEVE, a phase II RCT [23] comparing lenvatinib, everolimus, and a combination of the two, had promising efficacy results with the combination of lenvatinib and everolimus, and lenvatinib alone, over the single administration of everolimus; however, the sample size was small. A phase III randomized trial of the combination in mRCC is planned.

Key Evidence for Recommendation 9

- A meta-analysis comparing four of the trials listed below (RECORD-2, INTORACT, TORAVA, BEST) suggested that there was no benefit from a combination of several targeted drugs versus a single agent in first-line treatment of RCC patients [24].
- The recently published phase II trial (LENEVE) compared lenvatinib (n=52), everolimus (n=50), and the combination of lenvatinib and everolimus (n=51) for patients previously treated with VEGF-targeted therapy or immunotherapy. Median months of PFS was more than doubled for the lenvatinib + everolimus group (14.6; 95% CI, 5.9 to 20.1), compared with the lenvatinib (7.4; 95% CI, 5.6 to 10.2) and everolimus (5.5; 95% CI, 3.5 to 7.1) groups. Lenvatinib + everolimus significantly prolonged PFS versus everolimus (HR, 0.40; 95% CI, 0.24 to 0.68; p<0.001). Lenvatinib alone also significantly prolonged PFS versus everolimus (HR, 0.61; 95% CI, 0.38 to 0.98; p=0.048). Median months of OS were 25.5 (95% CI, 20.8 to 25.5) for the lenvatinib + everolimus group, 18.4 (13.3 to not estimable) for the lenvatinib group, and 17.5 (11.8 to not estimable) for the everolimus group. OS analysis showed significant difference for lenvatinib + everolimus versus everolimus (HR, 0.51; 95% CI, 0.30 to 0.88; p=0.024). Lenvatinib + everolimus significantly improved ORR versus everolimus (p<0.001 and p=0.007, respectively) [23].
- The RECORD-2 study found the efficacy of a combination of everolimus and bevacizumab to be similar to bevacizumab combined with IFN-α for previously untreated patients [25].
- A phase III study (INTORACT) of previously untreated patients found that temsirolimus/bevacizumab combination therapy was not superior to IFN-α/bevacizumab for first-line treatment in clear cell mRCC [26].
- The TORAVA phase II trial concluded that the AEs of the temsirolimus and bevacizumab combination was higher than anticipated. Clinical activity was low compared with the benefit expected from sequential use of each targeted therapy [27].
- The BEST trial found bevacizumab-induced PFS was not enhanced with the addition of either sorafenib or temsirolimus, or by the use of sorafenib plus temsirolimus in previously untreated patients. The median PFS was 7.5 months for bevacizumab alone (90% CI, 5.8 to 10.8 months), 7.6 months for bevacizumab plus temsirolimus (90% CI, 6.7 to 9.2 months), 9.2 months for bevacizumab plus sorafenib (90% CI, 7.5 to 11.4 months), and 7.4 months for sorafenib plus temsirolimus (90% CI, 5.6 to 7.9 months). HRs were 1.01, 0.89, and 1.07 (with respective p values of 0.95, 0.49, and 0.68) for the three combinations, respectively, compared with bevacizumab alone [28].
- A trial examining AMG 386 in combination with sorafenib in treatment-naïve patients with mRCC, found that AMG 386 plus sorafenib was tolerable but did not significantly improve PFS compared with placebo plus sorafenib [29].

Interpretation of Evidence for Recommendation 9

Results are promising for the combination of lenvatinib and everolimus, and lenvatinib alone, over everolimus alone. Further phase III testing is warranted.

The Use of Targeted Therapies in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Updated Guideline 2017

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR UPDATED GUIDELINE

In December 2012, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. The new data supported the existing recommendations; however, there was new evidence that expands on recommendations (e.g., newer agents, further lines of therapy, new trials, and new options). Hence, the Genitourinary Cancer Disease Site Group (DSG) recommended updating the 2009 recommendations on the use of targeted therapies in adult patients with inoperable locally advanced or mRCC.

GUIDELINE DEVELOPERS

This guideline was developed by the Genitourinary GDG Working Group (which was convened at the request of the CCO).

The project was led by a small Working Group of the Genitourinary GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology and health research methodology. Other members of the Genitourinary GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix A, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [30,31] . This process includes a systematic review, interpretation of the evidence by the Working Group and draft

recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the Appraisal of Guidelines for Research and Evaluation (AGREE) II framework [32] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

This search did not yield a guideline that could be endorsed or adapted. A summary of the guideline search results can be found in Appendix D.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason. Of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the

guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

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The Use of Targeted Therapies in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Updated Guideline 2017

Section 4: Systematic Review

INTRODUCTION

The original report for this series was entitled "The use of inhibitors of angiogenesis in patients with inoperable locally advanced or metastatic renal cell cancer (mRCC)". Since the studies addressing this topic are no longer limited to angiogenesis inhibitors, the term "angiogenesis inhibitors" has been changed to "targeted therapies". The targeted therapies that are considered in this evidence-based series (EBS) update are listed in Table 4-1. See the previous version of this report (EBS 3-8-4) for a more detailed introduction to the topic of targeted agents in patients with inoperable locally advanced or mRCC. https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/genito-ebs/

For patients presenting with inoperable or mRCC, cure is rarely possible, and treatment efforts typically centre on effectively controlling symptoms and offering a chance at improved survival. Clinical trials in the metastatic setting have shown mRCC to be largely resistant to conventional chemotherapeutic agents [33]. IFN-α and IL-2 have been evaluated extensively in the setting of inoperable or mRCC using various doses and modes of delivery and in combination with a number of cytotoxic agents. Although these cytokines have shown activity in RCC, they are associated with modest improvements in survival and relatively high levels of acute toxicities [33].

RCC are highly vascular tumours, and VEGF is a crucial regulator of tumour angiogenesis. Hence, VEGF and its receptors (VEGFR) are obvious therapeutic targets, which can be inhibited through a number of mechanisms. Over the past few years, strong enthusiasm regarding this novel class of antiangiogenic anti-cancer agents has permitted rapid accrual to large pivotal clinical trials [34].

In December 2012, the original version of this guideline was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. The new data supported the existing recommendations; however, there was new evidence that expands on recommendations (e.g., newer agents, further lines of therapy, new trials). Hence, the Genitourinary Cancer DSG recommended UPDATING the 2009 recommendations on the use of targeted therapies in adult patients with inoperable locally advanced or mRCC.

The original review identified nine randomized trials that evaluated inhibitors of angiogenesis [6,8,19,35-40]. Across the nine trials, six different inhibitors of angiogenesis were studied: sorafenib, sunitinib, temsirolimus, bevacizumab, everolimus, and thalidomide. These agents were evaluated in the first-line setting in six trials and as second- or third-line treatment in three trials.

However, recent results from randomized trials evaluating inhibitors of angiogenesis show superior clinical benefits over IFN-α-based immunotherapy (and placebo), with an acceptable toxicity profile, making these agents preferred treatment options. Sunitinib and temsirolimus should be offered as first-line treatment for patients with favourable- to intermediate-risk and poor-risk disease, respectively. Sorafenib should be offered as second-line therapy for patients with favourable- to intermediate-risk disease who have failed prior immunotherapy. Everolimus improves PFS in patients who previously received TKIs and is therefore recommended as the standard treatment for that population. The preliminary nature of some of the reports that comprise the evidence base means that this systematic

review and the recommendations will be subject to revision as more mature and additional data become available.

Table 4-1. Targeted therapies covered in this evidence summary

Generic Name (trade name)	Target(s)
Vascular endothelial growth factor (VEGF)/VEGF receptor inhibitors	
Axitinib* (Inlyta®)	KIT, PDGFRß, VEGFR1/2/3
Bevacizumab (Avastin®)	VEGF
Cabozantinib* (Cometriq™)	FLT3, KIT, MET, RET, VEGFR2
Cediranib (Recentin)	VEGF1/2/3, KIT, PDGFR
Dovitinib* (N/A)	FGFR, PDGFR
Lenvatinib* (Lenvima™)	VEGFR2
Nintedanib* (Ofev™)	VEGFR1/2/3, FGFR, PDGFR
Pazopanib* (Votrient®)	VEGFR, PDGFR, KIT
Sorafenib (Nexavar®)	VEGFR1/2/3, PDGFR, KIT, RAF
Sunitinib (Sutent®)	VEGFR, PDGFR,KIT
Tivozanib* (Aveo)	VEGFR1/2/3
Mammalian target of rapamycin (mTOR) inhibitors	
Everolimus (Afinitor®)	mTOR
Temsirolimus (Torisel®)	mTOR
Other	
Naptumomab* (Anyara)	5T4
Nivolumab* (Opdivo®)	PD-1
Trebananib* (N/A)	TIE-2 receptor, Ang1, Ang2
Thalidomide (Thalomid®)	unclear

Abbreviations: Ang - angiopoietin; PDGFR - platelet-derived growth factor receptors; FGFR - fibroblast growth factor receptors; FLT3 - Fms-like tyrosine kinase 3; KIT - v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog; MET - mesenchymal-epithelial transition receptor tyrosine kinase; PD-1 - programmed cell death protein 1; RAF - rapidly accelerated fibrosarcoma kinase; RET - rearranged during transfection receptor; TIE-2 - tyrosine kinase with immunoglobulin-like and EGF-like domains 2; VEGFR - vascular endothelial growth factor receptors; 5T4 – 5T4 antigen.
*New for update; N/A – not applicable.

RESEARCH QUESTIONS

1a: What are the optimal targeted therapies for locally advanced or mRCC? -Previously untreated patients.

1b: What are the optimal targeted therapies for locally advanced or mRCC? -Previously treated patients.

2: Is a combination of agents better than any single targeted agent?

METHODS

This report was developed by a Working Group, consisting of medical oncologists and two research methodologists, at the request of the Genitourinary Cancer DSG. The Working Group was responsible for reviewing the identified evidence and drafting the report. Conflict of interest declarations for all authors are summarized in Appendix A, and were managed in accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest Policy.

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature.

This systematic review is an update of the review described in the previous version of this report (EBS 3-8-4). The body of evidence in this review is primarily comprised of RCTs. This review forms the basis of a clinical practice guideline (Sections 1 and 2) developed by the Genitourinary DSG. This systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the OMHLTC through CCO. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for existing systematic reviews that had been published since 2008. Relevant articles were identified by searches of MEDLINE (2008 – April 2016 week 19), EMBASE (2008 – 2016 week 19), and the Cochrane Library (2016). The complete MEDLINE and EMBASE search strategies are detailed in Appendix B.

The conference proceedings of the annual meetings of the American Society of Clinical Oncology (2008-2016), including the Genitourinary Cancer Symposium (2008-2016), the European Society of Medical Oncology (2008-2016), and the European Cancer Conference (2008-2016) were also searched for relevant trials. Where relevant abstracts were identified, supplementary online resources (i.e., slides from accompanying presentations) were also searched for additional data.

The reference lists of eligible trials were searched for relevant articles, and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) was searched for existing evidence-based practice guidelines. Expert colleagues were also asked to identify any relevant unpublished or published trials not otherwise identified.

Study Selection Criteria

Articles were eligible for inclusion into the systematic review if they met the following criteria:

- They were meta-analyses of RCTs.
- They were RCTs (published or unpublished, full articles or abstracts) with ≥30 patients per study arm comparing:
  - targeted therapy (±IFN-α, or IL-2) vs. placebo, IFN-α, or IL-2
  - targeted therapy versus targeted therapy (alone or in combination)
  - different schedules of targeted therapy
  - sequential administration of targeted therapy
- They reported on at least one of the following outcomes: OS, PFS, QOL, objective tumour response rate (RR), clinical RR, and AEs.
- They were published in English, as translation capabilities were not available.

Data Extraction and Assessment of Study Quality and Potential for Bias

All relevant papers identified by the literature search were assessed against the above selection criteria independently by two of the authors (SH, JB). Discrepancies regarding eligibility were resolved by consensus of all the authors. The methodologic quality of eligible trials was assessed using a modified version of the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [41]; the following seven risk of bias criteria were considered: 1) whether sample size was appropriate (i.e., based on statistical estimation), 2) whether treatment allocation was random, 3) whether allocation was concealed from the participants, 4) whether industry funding was obtained, 5) whether treatment arms were balanced for important baseline characteristics, 6) whether analyses were performed by intention-to-treat, and 7) whether the study was terminated early. Data extraction was performed by one of the

authors (JB), while a second reviewer acted as an independent auditor to verify the accuracy of the data extraction.

If deemed appropriate, the completeness of reporting of the systematic reviews was analyzed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool [42]. The AMSTAR tool was used to assess the reviews' use of the following methodologies: 1) an 'a priori' study design, 2) duplicate study selection and data extraction, 3) a comprehensive literature search, 4) status of publication (i.e., grey literature) used as an inclusion criterion, 5) a list of studies (included and excluded) provided, 6) the characteristics of the included studies provided, 7) the scientific quality of the included studies assessed, 8) scientific quality of the included studies used appropriately in formulating conclusions, 9) the methods used to combine the findings of studies, 10) appropriate likelihood of publication bias assessed, and 11) conflict of interest stated.

Synthesizing the Evidence

A quantitative analysis of the trial data was planned for the outcomes of interest if the authors deemed it appropriate (i.e., clinical homogeneity of the treatment regimens and patient populations). When data were available from two or more trials, a meta-analysis would be performed using Review Manager (RevMan 5.3.1) [43] provided by the Cochrane Collaboration. The HR is the preferred statistic for pooling time-to-event outcomes because it incorporates data from the entire Kaplan-Meier curve and allows for censoring. When available, the HR would be extracted directly from the most recently reported trial results. The variances of the HR estimates would be calculated from the reported CIs or p-values using the methods described by Parmar et al. [44].

RESULTS

Literature Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram summarizing this information is provided in Appendix C.

Articles were retrieved from the following databases: MEDLINE (n=2935), EMBASE (n=1264), and additional records identified through other sources (n=601). After duplicates were removed from the combined search results, 1673 articles were assessed by title and abstract for possible inclusion in the evidence summary. Of these, 1516 articles were rejected at the title level and the remaining 157 were assessed at the level of full text.

Thirty-nine RCTs (60 published reports) were included, with the most recent publication being used where duplicate reports exist [2-5,7-19,23,25,26,28,29,35-38,45-57]. Table 4-2 shows the RCTs from the original literature search (to 2009) and our updated search conducted for this review. The original literature search identified nine RCTs that satisfied the eligibility criteria (Table 4-2 original articles pre-2009). The remaining 30 RCTs were new trials published since the original 2009 report.

Meta-Analysis

Since there were few RCTs directly comparing the same intervention and control arms, direct meta-analysis was not possible for this report. In contrast to conventional pairwise meta-analysis, network meta-analysis can provide estimates of relative efficacy between all interventions, even though some have never been compared head to head [58]. Three [1,20,21] of 14 systematic reviews [1,20,21,24,59-68] with outcomes relevant to this review performed network meta-analysis (or indirect comparisons) for targeted therapies in the treatment of mRCC. Where applicable, the results from these network meta-analyses were used when comparing the targeted therapies in this report. All three network meta-analyses used Bayesian hierarchical models using the Markov chain Monte Carlo software WinBUGS

[69]. One study used a random effects method to calculate the logarithm of the HR and its standard error for each indirect comparison [20]. The other two studies used a fixed-effect model because of the small number of studies available for each treatment pair in the analysis [1,21].

One meta-analysis examined sequencing and combinations of systematic therapy and was used to assess question 2 (Is a combination of agents better than any single targeted agent?) [24].

Of the remaining 10 systematic reviews, four performed network meta-analysis [60,62,64,70] on RCTs already covered by the three studies listed above [1,20,21] and will not be discussed further. As well, six meta-analyses [59,61,63,65,67,68] were excluded because they directly compared one specific targeted therapy of interest (e.g., sunitinib) on the one hand to all other targeted therapies on the other (e.g., pazaponib or axitinib or sorafenib); a comparator too heterogeneous for this report.

Since the network meta-analyses examine only a portion of the network of targeted therapies being assessed in this review, and since these meta-analyses did not evaluate adverse events, all individual RCTs were included and discussed individually in this report.

Trial Characteristics

Table 4-2 shows the included trials by lines of treatment. Four of the 39 RCTs were first-line and second-line trials [9,10,16,46], six were second-line [18,19,23,38,49,54], three were second- and third-line [12-14], and one was third-line [52]; the remaining trials were first-line.

Appendix F shows the histology, prognosis, planned outcomes and target therapies, doses, and schedules used by the studies. Most trials were international, multicentre trials, with the exception of two that were single-centre trials [25,55] and eight that did not specify locations [17,28,36,38,48,53,54,56]. The number of randomized patients ranged from 96 [47] to 1100 [3]. IFN-α was the comparator arm in six trials [5,7,8,35,48,50] and six were placebo-controlled [7,14,16,17,19,29,38]. Four trials examined various doses of the same therapies [2,38,53,56] and 20 examined two or more targeted therapies head to head [3,4,9,10,12,13,15,18,23,25,26,28,45-47,49,51,52,54,57].

One study limited enrollment to non-clear cell mRCC [11] and two [49,55] had a combination of clear and non-clear cell RCC patients. The remaining studies enrolled patients with clear cell RCC. Two studies [25,57] only enrolled patients with favourable Memorial Sloan-Kettering Cancer Center (MSKCC) risk, three [7,19,46] only enrolled poor- and intermediate-risk patients, and four studies did not report disease prognosis [23,28,38,47,48,54,56]. The remaining studies included patients with poor, intermediate, and favourable MSKCC risk RCC. The median age of patients ranged from 53 [38] to 65 years [46], with the majority of patients being male, and studies reporting percentage males ranging from 63% [10] to 77% [14] (see Appendix F).

Study Design and Quality

The eligible RCTs were published between 2003 and 2016. One trial was four-arm [28], four were three-arm trials [8,23,27,38] and the remaining were two-arm. Eleven of the included RCTs were described as phase II studies [2,11,19,25,28,29,45,47,50,55,56], and one was described as a phase II/III study [48]. The remaining studies were phase III (see Appendix F).

Details of the AMSTAR evaluations for the four recent meta-analyses used in this review are also included in Appendix G. The studies had similar results with one study scoring six [21] on the 11-item assessment, two scoring seven [1,20], and one scoring eight [24]. All four reviews duplicated study selection and data extraction, performed a comprehensive

literature search, provided characteristics of the included studies, and used appropriate methods to combine the findings of studies. All but one of the studies provided an 'a priori' design [21] and all but one [1] assessed and documented the scientific quality and used the information appropriately in formulating questions. Only one of the studies used the status of publication as an inclusion criterion [24], only one provided a list of the inclusion and exclusion criteria of the included studies [1], and only one stated conflict of interest [1]. None of the studies assessed the likelihood of publication bias.

Details of the methodological characteristics of the 39 trials are in Appendix G. Forty-five percent of the trials stated that the trials' allocation to study arms was concealed and the remainder (55%) did not report on allocation concealment. Thirty-seven percent of the trials were blinded and 50% were not; the remainder (16%) did not report on whether the study was blinded. Seventy-three percent performed statistical analyses according to intention to treat and 32% did not report on whether this was done. Seventy-four percent of the studies reported that they had received industry funding to conduct the trial, while only 5% stated that they had not; the remainder (26%) did not disclose whether they received industry funding. Seventy-four percent of the studies reported that the baseline characteristics of the study groups were balanced and 84% included a sample size power calculation in the methods section. Two trials were terminated early [10,14].

Table 4-2: Updated eligible randomized controlled trials

Trials examining first-line treatments

Trial	Treatment Groups	Articles
CALGB 90206	BEV+IFN-α vs. IFN-α+placebo	Rini2010, Rini2008*
AVOREN	BEV+IFN-α vs. IFN-α	Escudier2010, Escudier2009*[ab], Escudier2007*
GLOBAL-ARCC	TEM vs. TEM+IFN-α vs. IFN-α	Hudes2007*
SUTENT	SUN vs. IFN-α	Motzer2009*, Motzer2007*
EFFECT	SUN inter. vs. SUN-CDD	Motzer2012
IGR	SOR vs. IFN-α	Escudier2009*,Szcylik2007[ab]*
MDACC-Soraf	SOR vs. SOR+IFN-α	Jonasch2010
ROSORC	SOR + IL-2 vs. SOR	Procopio2013[ab], Procopio2011
	AXI dose titration vs. AXI+placebo	Rini2015[ab], Rini2013[ab], Rini2013[ab]
AZD2171	CED vs. placebo-1st or 1 prior immunotherapy	Mulders 2012
COMPARZ	PAZ vs. SUN	Motzer2013
PISCES	PAZ vs. SUN	Escudier2014
	NIN vs. SUN	Eisen2015, Eisen2013[ab]
CROSS-J-RCC	SUN vs. SOR	Tomita2014[ab]
	AXI vs. SOR	Hutson2013
TIVO-1	TIV vs. SOR	Motzer2013, Motzer2013[ab]
AMG-386	SOR+AMG 386 vs. Placebo	Rini2012
Manchester	NAP+IFN-α vs. IFN-α	Hawkins2013[ab]
TORAVA	TEM+BEV vs. SUN vs. IFN-α+BEV	Bay2012[ab], Negrier2011
INTORACT	TEM+BEV vs. IFN-α+BEV	Rini2014
BEST	BEV vs. BEV+TEM vs. BEV+SOR vs. SOR+TEM	Flaherty2015, McDermott2013[ab]
RECORD-2	EVE+BEV vs. IFN-α+BEV	Ravaud2015, Ravaud2013[ab]
ASPEN	EVE vs. SUN	Armstrong2016
	THA vs. INF-α	Gordon2004 [ab]*

Trials examining first- and second-line treatments

Trial	Groups	Previous treatment	Articles
VEG105192	PAZ vs. placebo	Treatment-naïve or received one prior cytokine-based systemic therapy	Sternberg2013, Sternberg2010, Cella2012
ESPN	EVE vs. SUN	crossover at progression (no prior treatment)	Tannir2014[ab]
RECORD-3	EVE/SUN vs. SUN/EVE	No prior systemic therapy	Motzer2014, Motzer2013[ab],
SWITCH	SOR/SUN vs. SUN/SOR	Unsuitable for cytokine therapy no prior systemic therapy	Eichelberg2015, Michel2014[ab], Fischer2014[ab],

Trials examining second- and/or third-line treatments

Trial (line)	Groups	Previous treatment	Articles
2nd	BEV3mg vs. BEV10mg vs. Placebo	IL-2 (or contraindications to IL-2)	Yang2003*
TARGET (2nd)	SOR vs. placebo	Undergone one prior systemic therapy	Escudier2009*
AXIS (2nd)	AXI vs. SOR	SUN, BEV+IFN-α, TEM, or cytokines	Motzer2013
INTORSECT (2nd)	TEM vs. SOR	4-week cycle of continuous SUN	Hutson2014
LENEVE (2nd) (Q2)	LEN vs. EVE vs. LEN+EVE	1 VEGF-targeted therapy	Motzer2015[ab]
GDC-0980 (2nd)	GDC-0980 vs. EVE	Progressed on or after VEGF	Powles2014[ab]
RECORD-1 (2nd&3rd)	EVE vs. Placebo	SUN and/or SOR, prior cytokines and/or VEGF permitted.	Motzer2010, Motzer2008*
METEOR (2nd&3rd)	CAB vs. EVE	Prior treatment with at least one VEGF	Choueiri2015
CheckMate (2nd&3rd)	NIV vs. EVE	One or two previous regimens of antiangiogenic therapy.	Motzer2015
MSKCC (2nd&3rd)	NIV3 vs. NIV2 vs. NIV10	VEGF therapies	Motzer12015, Motzer2014
GOLD (3rd)	DOV vs. SOR	One previous VEGF or mTOR inhibitor in either sequence.	Motzer2014, Motzer2013[ab]

*Included in 2009 review; ab = abstract; AXI = axitinib; BEV = bevacizumab; CAB = cabozantinib; CED = cediranib; CDD = continuous daily dosing; DOV = dovitinib; EVE = everolimus; IFN-α = interferon-alpha; IL-2 = interleukin; LEN = lenvatinib; mTOR = mammalian target of rapamycin; NAP = naptumomab; NIN = nintedanib; NIV = nivolumab; PAZ = pazopanib; SOR = sorafenib; SUN = sunitinib; TEM = temsirolimus; TIV = tivozanib; VEGF = vascular endothelial growth factor

Studies addressing question 1: What are the optimal targeted therapies for locally advanced or mRCC?

VEGF/VEGF Receptor Inhibitors
Sunitinib and Pazopanib

Appendix E show the results from meta-analysis. A network meta-analysis, comparing first-line treatments in the management of advanced RCC, identified 11 RCTs reporting results for eligible treatments. In the case of PFS, sunitinib was superior compared with bevacizumab plus IFN-α (HR, 0.79; 95% CI, 0.64 to 0.96), everolimus (HR, 0.70; 95% CI, 0.56 to 0.87), sorafenib (HR, 0.56; 95% CI, 0.40 to 0.77), and temsirolimus plus bevacizumab (HR, 0.74; 95% CI, 0.56 to 0.96). There was no significant difference in PFS between sunitinib and axitinib, pazopanib or tivozanib. Sensitivity analyses confirmed that no treatment was significantly more efficacious than sunitinib [1]. The network consistency calculations suggested that there was no statistically significant inconsistency between the direct trial results and the indirect treatment paths in the network loop ($p>0.05$). The authors concluded that "the NMA [network meta-analysis] results from both the base case and sensitivity analyses support the findings of previous studies and suggest that no treatments are clinically superior to sunitinib to extend PFS in the management of advanced RCC in the first-line setting." [1].

Appendix H shows the efficacy outcomes for the included trials. In the phase III SUTENT trial, median OS and median PFS was significantly greater among treatment-naïve patients in the sunitinib group compared with the IFN-α group (26.4 vs. 21.8 months, HR, 0.821; 95% CI, 0.673 to 1.001; p=0.051; and 11 vs. 5 months, HR, 0.539; 95% CI, 0.451 to 0.643; $p<0.001$, respectively). A subgroup analysis, performed by the MSKCC, showed a benefit with sunitinib for all risk groups, although the differences in the poor-risk subgroup did not reach statistical significance. Patients on sunitinib experienced a comparative increased frequency in overall AEs to that of the IFN-α group [37].

In the phase II EFFECT trial, median PFS was 8.5 months for scheduled dosing (50 mg/day with 4 weeks on treatment and 2 weeks off) versus 7.0 months for the CDD (37.5 mg/day) (HR, 0.77; 95% CI, 0.58 to 1.02; p=0.070) for previously untreated patients. No significant difference was observed for OS (23.1 vs. 23.5 months; p=0.615), AEs, or patient-reported kidney cancer symptoms. Scheduled dosing was statistically superior to CDD in time to deterioration, a composite end point of death, progression, and disease-related symptoms (p=0.034) [2].

In the phase III double-blind VEG105192 trial, PFS was significantly prolonged with pazopanib compared with placebo in the overall study population (median PFS 9.2 vs. 4.2 months; HR, 0.46; 95% CI, 0.34 to 0.62; $p<0.0001$); the treatment-naïve group (median PFS 11.1 vs. 2.8 months; HR, 0.40; 95%, CI 0.27 to 0.60; $p<0.0001$); and the cytokine-pretreated group (median PFS 7.4 vs. 4.2 months; HR, 0.54; 95% CI, 0.35 to 0.84; $p<0.001$) [71]. The difference in final OS between pazopanib- and placebo-treated patients was not statistically significant (22.9 vs. 20.5 months, respectively; HR, 0.91; 95% CI, 0.71 to 1.16; one-sided p=0.224) There was no evidence of clinically important differences in QOL or AEs for pazopanib versus placebo [16] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

The COMPARZ trial found equal efficacy for pazopanib and sunitinib (HR for progression of disease or death from any cause, 1.05; 95% CI, 0.90 to 1.22; HR for death with pazopanib, 0.91; 95% CI, 0.76 to 1.08). Patients treated with sunitinib had a higher incidence of fatigue (63% vs. 55%), hand-foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%), and patients treated with pazopanib had a higher incidence of increased levels of ALT

(60% vs. 43%) [3]. In the PISCES trial, significantly more patients preferred pazopanib (70%) over sunitinib (22%); 8% had no preference (p=0.001). Better overall QOL and less fatigue were the main reasons for preferring pazopanib, with less diarrhea being the most reported reason for preferring sunitinib [4].

Bevacizumab plus IFN-α

In the CALGB 90206 study, the bevacizumab plus IFN-α group had a significantly improved PFS (median 8.5 vs. 5.2 months; HR, 0.71; 95% CI, 0.61 to 0.83) compared with the IFN-α-alone group [6]. There were no statistically significant differences in OS. However, there was significantly more grade 3 to 4 hypertension, anorexia, fatigue, and proteinuria for bevacizumab plus IFN-α [7]. Likewise, in the AVOREAN trial, IFN-α plus bevacizumab significantly increased PFS compared with IFN-α plus placebo (10.2 months vs. 5.4 months; HR, 0.63; 95% CI, 0.52 to 0.75; p=0.0001) [72]. Again, there were no significant differences in OS. According to the authors, study participants (>55%) in both arms received at least one post-protocol antineoplastic therapy, which may have possibly confounded the OS analysis. The proportion of patients who experienced an adverse event that led to treatment stoppage was higher in the bevacizumab plus IFN-α group than in the control group (28% vs. 12%) [72] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

Axitinib and Sorafenib

A network meta-analysis compared the clinical efficacy and safety among newer targeted agents for the treatment of mRCC, identifying seven RCTs, already included in this review [3,14-19], that included patients that had previously undergone nephrectomy or received a systematic cytokine-based treatment. The direct assessment of the targeted therapies showed better efficacy in terms of longer PFS, but worse safety (more withdrawals due to AEs) The network indirect analysis suggested that axitinib may prolong PFS following failure of first-line therapy and that axitinib exhibits higher efficacy and safety compared with sorafenib (PFS-HR, 0.67; 95% CI, 0.54 to 0.81) and pazopanib (PFS–HR, 0.64; 95% CI, 0.42 to 0.98) in patients who previously received systematic treatment. The findings also suggested that sunitinib was superior to sorafenib (PFS–HR, 1.63; 95% CI, 1.09 to 2.45). The authors concluded that "sunitinib and axitinib may be more clinically efficient and axitinib is associated with a lower risk of AEs compared to sorafenib, pazopanib and temsirolimus" [20] (see Appendix E).

A network meta-analysis also assessing the effectiveness and safety of axitinib as second-line treatments for advanced RCC found 24 RCTs fitting the study's inclusion criteria, with three included in a Bayesian fixed-effect meta-analysis and also included in our list of studies [16,18,19]. In terms of PFS, axitinib was superior compared with placebo (HR, 0.25; 95% credible interval [CrI], 0.17 to 0.38), sorafenib (HR, 0.46; 95% CrI, 0.32 to 0.68), and pazopanib (HR, 0.47; 95% CrI, 0.26 to 0.85). An overall analysis, which included the entire patient population, regardless of previous first-line treatment, reported similar results; namely, there was no significant difference in PFS between sorafenib and pazopanib. The authors concluded that "the results … suggest that axitinib will be an important treatment option to extend PFS in the management of advanced RCC in the second-line setting. Ongoing research will define the optimal treatment algorithm leading to a patient-focused treatment strategy" [21].

In the AXIS (included in direct comparison meta-analysis above) trial, treatment with axitinib resulted in a significant improvement in PFS compared with sorafenib (median, 8 vs. 6 months; HR, 0.66; 95% CI, 0.55 to 0.78) in previously treated patients. The benefit was higher in patients previously treated with either cytokines (12 vs. 8 months; HR, 0.51; 95% CI, 0.37 to 0.68) or sunitinib (6.5 vs. 4.4 months; HR, 0.72; 95% CI, 0.57 to 0.90). There was a

significant increase in ORR with axitinib (23% vs. 12%), but there was no significant difference in OS. Similar patient-reported QOL outcomes were seen between the two treatment groups [18] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In the TARGET trial, median PFS was significantly longer in the sorafenib group, compared with placebo (5.5 vs. 2.8 months; HR, 0.44; 95% CI, 0.35 to 0.55). However, OS was not significantly prolonged with sorafenib compared with placebo, and the authors point out that patients originally assigned to placebo could cross over to sorafenib. In the final analysis, censoring patients at crossover revealed a significant improvement in OS for patients treated with sorafenib [19]. In a separate analysis from the trial, sorafenib significantly improved PFS for patients ≥70 years [73] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

The SWITCH study prospectively evaluated sequential use of sorafenib followed by sunitinib (So-Su) versus sunitinib followed by sorafenib (Su-So) in patients with mRCC. In total, 365 patients were randomized (So-Su, n=182; Su-So, n=183). There was no significant difference in total PFS between So-Su and Su-So (median, 12.5 vs. 14.9 months; HR, 1.01; 90% CI, 0.81 to 1.27; p=0.5 for superiority). OS was similar for So-Su and Su-So (median, 31.5 and 30.2 months; HR, 1.00; 90% CI, 0.77 to 1.30; p=0.5 for superiority). More So-Su patients than Su-So patients reached protocol-defined second-line therapy (57% vs. 42%). Overall, AE rates were generally similar between the treatment arms [22].

Newer VEGFs

Patients in the phase III CheckMate trial [12], with advanced clear cell RCC for which they had received previous treatment with one or two regimens of antiangiogenic therapy, were randomly assigned to receive nivolumab or everolimus. The median OS was 25.0 months (95% CI, 21.8 to not estimable) with nivolumab and 19.6 months (95% CI, 17.6 to 23.1) with everolimus. The HR for death with nivolumab versus everolimus was 0.73 (98.5% CI, 0.57 to 0.93; p=0.002), meeting the pre-specified criterion for superiority (p≤0.0148). The ORR was 25% with nivolumab and 5% with everolimus (odds ratio, 5.98; 95% CI, 3.68 to 9.72; p<0.001). The median PFS was 4.6 months (95% CI, 3.7 to 5.4) with nivolumab and 4.4 months (95% CI, 3.7 to 5.5) with everolimus (HR, 0.88; 95% CI, 0.75 to 1.03; p=0.11). Nineteen percent of patients receiving nivolumab had a grade 3 or 4 treatment-related AEs compared with 37% of the patients receiving everolimus. Nivolumab has been associated with rare but severe immune-mediated adverse reactions, with the most common being enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy [74] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

The recent phase III METEOR study compared cabozantinib (60 mg daily) and everolimus (10 mg daily) in 658 patients with advanced or mRCC that progressed after previous VEGF-targeted therapy. Median PFS was 7.4 months with cabozantinib versus 3.8 months for everolimus (HR, 0.58; 95% CI, 0.45 to 0.75; p<0.001). The ORR was 21% with cabozantinib and 5% with everolimus (p<0.001). The interim analysis showed that OS was longer with cabozantinib than with everolimus (HR death, 0.67; 95% CI, 0.51 to 0.89; p=0.005). Discontinuation of the study drug due to AEs occurred in 9% of the patients who received cabozantinib and in 10% of those who received everolimus [13] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In a phase II study (AZD2171), 71 treatment-naïve patients with advanced cancer were randomized (3:1) to receive cediranib 45 mg/day or placebo. After 12 weeks of therapy, there was a significant difference in mean percentage change from baseline in tumour size between the cediranib (-20%) and placebo (+20%) groups (p<0.0001). Eighteen patients (34%) on cediranib achieved a partial response and 25 (47%) experienced stable disease. The median PFS was 12.1 months for the cediranib group versus 2.8 months for the placebo group (HR,

0.45; 90% CI, 0.26 to 0.76; p=0.017). The most common AEs in patients receiving cediranib were diarrhea (74%), hypertension (64%), fatigue (58%), and dysphonia (58%) [17] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

A phase II trial comparing tivozanib with sorafenib (TIVO-1), as initial targeted therapy in patients with mRCC, demonstrated improved PFS, but not OS, for tivozanib compared with sorafenib, as well as a differentiated safety profile [51]. However, in 2013, the Food and Drug Administration rejected tivozanib for the treatment of RCC, stating that the inconsistent PFS and OS results, as well as the imbalance in post-study treatments, make the TIVO-1 results uninterpretable and inconclusive when making a risk-benefit assessment necessary for drug approval [75]. Tivozanib currently has not received Health Canada approval [76] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

A randomized exploratory trial of 96 patients randomized to either nintedanib or sunitinib found the two drugs comparable for PFS (HR, 1.12; 95% CI, 0.70 to 1.80; p=0.64), median OS (HR, 0.92; 95% CI, 0.54 to 1.56; p=0.76), and overall incidence of any grade AE (48.4% vs. 59.4%). However, the sample size in the nintedanib group was selected to ensure sufficient power to assess the primary safety endpoint and was not powered to detect significant differences in efficacy parameters. The authors conclude that: "further evaluation of nintedanib in advanced RCC may be explored, particularly as second-line therapy after failure of tyrosine kinase inhibitors (TKIs), where there is a continuing unmet clinical need for new therapies that balance efficacy with a manageable safety profile" [47] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In the GOLD multicentre, phase III study, patients with clear cell mRCC who received one previous VEGF-targeted therapy and one previous mTOR inhibitor were randomly assigned to receive open-label dovitinib (500 mg orally according to a 5-days-on and 2-days-off schedule) or sorafenib (400 mg orally twice daily) in a 1:1 ratio. Median PFS was 3.7 months (95% CI, 3.5 to 3.9) in the dovitinib group and 3.6 months (95% CI, 3.5 to 3.7) in the sorafenib group (HR, 0.86; 95% CI, 0.72 to 1.04; one-sided p=0.063). Median OS was 11.1 months (95% CI, 9.5 to 13.4) in the dovitinib group and 11.0 months (95% CI, 8.6 to 13.5) in the sorafenib group (HR, 0.96; 95% CI, 0.75 to 1.22). The most common serious AE was dyspnea (6% in the dovitinib and 5% in the sorafenib groups) (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

mTOR Inhibitors

As reported in the 2009 original report for this series, the phase III GLOBAL-ARCC trial by Hudes et al. [8] studied the efficacy of first-line temsirolimus treatment in patients with poor-risk mRCC. Compared with IFN-α (7.3; 95% CI, 6.1 to 8.8), median months of OS was significantly longer for patients treated with single-agent temsirolimus (10.9; 95% CI, 8.6 to 12.7) (HR, 0.73; 95% CI, 0.58 to 0.92; p=0.008), but not with temsirolimus combined with IFN-α (8.4; 95% CI, 6.6 to 10.3). Median months of PFS was longer in patients treated with temsirolimus alone (3.8; 95% CI, 3.6 to 5.2) and in combination (3.7; 95% CI, 2.9 to 4.4) compared with IFN-α alone (1.9; 95% CI, 1.9 to 2.2) (p<0.0001). The updated HR for death for single-agent temsirolimus versus IFN-α, and combination therapy versus IFN-αwere 0.73 (95% CI, 0.58 to 0.92; p=0.0008) and 0.96 (95% CI, 0.76 to 1.20; p=0.70), respectively. The median survival time of patients in all three groups remained unchanged [8] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

The RECORD-1 trial randomized patients with mRCC to everolimus or placebo plus best supportive care. The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (HR, 0.33; p<0.001). The median OS was 14.8 months (everolimus) versus 14.4 months (placebo) (HR, 0.87; p=0.162). Eighty percent of patients in the placebo arm crossed over to everolimus and survival corrected for crossover was 1.9-fold longer (95% CI, 0.5 to 8.5) with everolimus compared with placebo alone. Independent prognostic factors for shorter OS in

the study included low performance status, high corrected calcium, low hemoglobin, and prior sunitinib (p<0.01) [14] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In a phase III study (GDC-0980), patients with mRCC who progressed on or after VEGF-targeted therapy were randomized (1:1) to GDC-0980 (40 mg once daily) or everolimus (10 mg once daily), stratified by MSKCC score and time to progression on first VEGF-targeted therapy (≤ or >6 months). The median PFS was significantly shorter for GDC-0980 than everolimus (3.7 vs. 6.1 months; HR, 2.04; 95% CI, 1.18 to 3.54; p<0.01) and did not favour GDC-0980 for any stratification subgroup. Median OS was not significantly different but was slightly higher for everolimus (11.9 vs. 14.6 months; HR, 1.73; 95% CI, 0.87 to 3.43; p=0.12). ORR was 7.1% for GDC-0980 and 11.6% for everolimus. Patients treated with GDC-0980 had a greater incidence of grade 3-4 AEs and were more likely to discontinue treatment because of an AE (GDC-0980 31%; everolimus 12%). GDC-0980 was associated with substantially more high-grade hyperglycemia (GDC-0980 40%; everolimus 7%) and rash (GDC-0980 24%; everolimus 5%) [54] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

The RECORD-3 (n=471) trial reported first-line everolimus (mTOR inhibitor similar to temsirolimus) to be inferior to sunitinib, with a worse PFS of 7.9 months compared with 10.7 months (HR, 1.4; 95% CI, 1.2 to 1.8). Overall PFS, after crossover from everolimus to sunitinib, was also inferior to sunitinib followed by everolimus (21.1 months compared with 25.8 months; HR, 1.3; 95% CI, 0.9 to 1.7). The median OS was 22.4 months for sequential everolimus followed by sunitinib and 32.0 months for sequential sunitinib followed by everolimus (HR, 1.2; 95% CI, 0.9 to 1.6) [9].

A randomized phase II ESPN trial of everolimus versus sunitinib with crossover design in mRCC reported the interim analysis for 68 patients. The median ORR in first-line therapy was 12% for sunitinib and 0% for everolimus. The median PFS in first-line therapy was 6.1 months with sunitinib and 4.1 months with everolimus (p=0.6). Median PFS in second-line therapy was 1.8 months for sunitinib (95% CI, 1.5 to not estimable) and 4.3 months for everolimus (95% CI, 1.4 to not estimable). Median OS in first-line therapy was 10.5 months for everolimus and was not reached with sunitinib (p=0.01). The trial contained many non-clear cell RCC patients, which may explain the poor results.[10].

The ASPEN trial randomized 108 previously untreated patients with non-clear cell RCC to either sunitinib or everolimus. Sunitinib significantly increased PFS compared with everolimus (8.3 months [80% CI, 5.8 to 11.4] vs. 5.6 months [80% CI, 5.5 to 6.0]; HR, 1.41 [80% CI, 1.03 to 1.92]; p=0.16). OS was similar between the two treatment groups (HR, 1.12; 95% CI, 0.7 to 2.1; p=0.60). Median OS was 31.5 months (95% CI, 14.8 to not reached) in the sunitinib group and 13.2 months (95% CI, 9.7 to 37.9) in the everolimus group [11].

Studies addressing question 2: Is a combination of agents better than any single targeted agent?

A meta-analysis examining sequencing and combinations of systemic therapy in mRCC identified 24 studies reporting on 9589 patients eligible for inclusion; data from four studies were included in the meta-analysis and included in this review [26,29,77,78]. The meta-analysis compared trials of a single targeted agent versus a combination of several targeted drugs in mRCC, reporting on a total of 1412 patients. No benefit from a combination of therapies approach was observed [24] (see Appendix E).

In a phase II, open-label RCT (LENEVE), patients were randomized to lenvatinib plus everolimus, lenvatinib monotherapy, or everolimus monotherapy. No crossover was permitted within the context of the study. The combination of lenvatinib and everolimus resulted in a median OS of 25.5 versus 18.4 months for lenvatinib alone and 17.5 for everolimus alone (HR, 0.51; 95% CI, 0.30 to 0.88; p=0.024). The median PFS with the combination was 14.6 months

compared with 7.4 months with lenvatinib alone and 5.5 months with everolimus alone (HR, 0.40; 95% CI, 0.24 to 0.68; p<0.001). The ORR was 43% with the combination, 27% with lenvatinib alone, and 6% with single-agent everolimus (p<0.001). A phase III randomized trial of the combination in mRCC is planned [23] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In a phase II trial, previously untreated patients were randomized to bevacizumab with either everolimus or IFN-α (RECORD-2). Tumour assessments occurred every 12 weeks. The median PFS was 9.3 months in the everolimus/bevacizumab arm and 10.0 months in the IFN-α/bevacizumab arm (p=0.485). The predicted probability of phase III success was 5.05% (HR, 0.91; 95% CI, 0.69 to 1.19). The median duration of exposure was 8.5 and 8.3 months for everolimus/bevacizumab and IFN-α/bevacizumab, respectively. The percentage of patients discontinuing because of AEs was 23.4% for everolimus/bevacizumab and 26.9% for IFN-α/bevacizumab [25] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In a randomized, open-label, multicenter, phase III study (INTORACT), patients with previously untreated predominantly clear cell mRCC were randomly assigned to receive the combination of either temsirolimus or IFN-α with bevacizumab. Median PFS in patients treated with temsirolimus/bevacizumab (n=400) versus IFN-α/bevacizumab (n=391) was 9.1 and 9.3 months, respectively (HR, 1.1; 95% CI, 0.9 to 1.3; p=0.8). There were no significant differences in OS (25.8 vs. 25.5 months; HR, 1.0; p=0.6) or ORR (27.0% vs. 27.4%) with temsirolimus/bevacizumab versus IFN-α/bevacizumab, respectively. Patients receiving temsirolimus/bevacizumab reported significantly higher overall mean scores in the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-15 and FKSI-Disease Related Symptoms subscale compared with IFN-α/bevacizumab (indicating improvement); however, similar global health outcome measures were observed [26] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

TORAVA was an open-label, multicentre, randomized phase II study undertaken in 24 centres in France. One hundred seventy-one patients with untreated mRCC were randomly assigned to receive bevacizumab and temsirolimus in combination (group A), or sunitinib (group B), or the combination of IFN-α and bevacizumab (group C). Median PFS was 8.2 months (95% CI, 7.0 to 9.6) in group A, 8.2 months (95% CI, 5.5 to 11.7) in group B, and 16.8 months (95% CI, 6.0 to 26.0) in group C. Fifty-one percent of patients in group A stopped treatment for reasons other than progression compared with 12% in group B and 38% in group C. Grade 3 or worse AEs were reported in 77% of patients in group A versus 60% in group B and 70% in group C. The authors concluded that “the toxicity of the temsirolimus and bevacizumab combination was much higher than anticipated and higher than limited treatment continuation over time. Clinical activity was low compared with the benefit expected from sequential use of each targeted therapy. This combination cannot be recommended for first-line treatment in patients with metastatic renal cell carcinoma” [27] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In a phase II trial (BEST), 361 patients with metastatic clear cell RCC were randomly assigned to bevacizumab alone (arm A), bevacizumab and temsirolimus (arm B), bevacizumab and sorafenib (arm C), or sorafenib and temsirolimus (arm D). The median PFS was 7.5 months for arm A (90% CI, 5.8 to 10.8 months), 7.6 months for arm B bevacizumab plus temsirolimus (90% CI, 6.7 to 9.2 months), 9.2 months for arm C (90% CI, 7.5 to 11.4 months), and 7.4 months for arm D (90% CI, 5.6 to 7.9 months). AEs did not differ significantly among treatment arms. The authors concluded that “the activity of sorafenib, temsirolimus, and bevacizumab administered in doublet combinations did not significantly improve median progression-free survival in comparison with bevacizumab monotherapy” [28] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

In a phase II double-blinded trial (AMG386), previously untreated patients with good/intermediate risk per MSKCC prognostic classification with mRCC were randomized to receive sorafenib plus AMG 386 at 10 mg/kg (arm A) or 3 mg/kg (arm B) or placebo (arm C) once weekly. Patients in arm C could receive open-label AMG 386 plus sorafenib following disease progression. Median PFS was 9.0, 8.5, and 9.0 months in arms A, B, and C, respectively (HR for arms A and B vs. arm C, 0.88; 95% CI, 0.60 to 1.30; p=0.523). The ORR (95% CI) for arms A, B, and C, respectively, were 38% (25% to 53%), 37% (24% to 52%), and 25% (14% to 40%). The incidence of AEs of any grade was similar in all treatment groups; however, more patients receiving placebo plus sorafenib (group C) had grade ≥3 AEs (66%, 73%, and 86% in arms A, B, and C, respectively) [29] (see Appendix F for study characteristics and Appendix H for efficacy outcomes).

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet https://www.cancer.gov/about-cancer/treatment/clinical-trials/search was searched for reports of new or ongoing trials (see below). The Genitourinary Cancer DSG will monitor the progress of the following trials and review reported results when they become available. See Appendix I for a list of ongoing trials

DISCUSSION

Previous (2009) report

This report updates a previous systematic review evaluating the use of inhibitors of angiogenesis in patients with mRCC. This earlier review identified nine RCTs published between 2001 and 2008. Across the nine trials, six different inhibitors of angiogenesis were studied: sorafenib, sunitinib, temsirolimus, bevacizumab, everolimus, and thalidomide. These agents were evaluated in the first-line setting in six trials and as second- or third-line treatment in three trials.

Based on efficacy data and an acceptable toxicity profile from a trial of 750 patients with favourable- or intermediate-risk mRCC, sunitinib was recommended as a first-line treatment option in patients with inoperable locally advanced or mRCC [79]. Bevacizumab combined with IFN-α reduced the risk of disease progression or death by 35% as first-line therapy in patients with favourable- and intermediate-risk disease. However, the benefit appeared potentially inferior to the benefit associated with sunitinib, and in light of the associated toxicities of IFN-α therapy, bevacizumab combined with IFN-α was not recommended in the previous report [5,7]. Temsirolimus was recommended as first-line therapy for patients with poor-risk disease, based on a 27% reduction in the risk of death [8]. Everolimus was recommended as second- or third-line therapy in patients previously treated with sunitinib, sorafenib, or both, based on a 70% reduction in the risk of disease progression [14]. The initial report also suggested that sorafenib should be considered a treatment option in patients who progress following initial cytokine therapy. This recommendation was based on a 56% reduction in the risk of disease progression or death reported with second-line therapy in patients with favourable- to intermediate risk disease previously treated with immunotherapy [19].

Current Update

The current evidence summary includes 39 RCTs (60 articles): the nine RCTs identified in the original literature search plus 30 new RCTs published since the original 2009 report. The 39 trials studied 15 different targeted therapies: axitinib, bevacizumab, cabozantinib, cediranib, dovitinib, everolimus, lenvatinib, naptumomab, nivolumab, nintedanib, pazopanib, sorafenib, sunitinib, temsirolimus, and tivozanib. Four of the 39 RCTs were first- and second-

line trials [9,10,16,46], six were second-line [18,19,23,38,49,54], four were second- and third-line [12-14], and one was third-line [52]; the remaining 24 trials were first-line.

Question 1: What are the optimal targeted therapies for locally advanced or mRCC?
1a: Previously untreated patients

Based on evidence from a recent network meta-analysis and the SUTENT, EFFECT, PISCES, and COMPARZ trials, either sunitinib or pazopanib is recommended by this report for previously untreated patients with RCC. A network meta-analysis comparing first-line treatments in the management of advanced RCC showed that for PFS, sunitinib was superior compared with bevacizumab plus IFN-α, everolimus, sorafenib and temsirolimus plus bevacizumab. The study found no significant difference in PFS between sunitinib and axitinib, pazopanib, or tivozanib [1]. The EFFECT trial indicated a numerical advantage of three-week cycles of two weeks on sunitinib (50 mg) followed by one week off therapy over CDD in terms of time to tumour progression [2]. The COMPARZ trial found that patients treated with sunitinib had a higher incidence of fatigue (63% vs. 55%), hand-foot syndrome (50% vs. 29%), and thrombocytopenia (78% vs. 41%), and patients treated with pazopanib had a higher incidence of increased levels of ALT (60% vs. 43%) [3]. In the PISCES trial, significantly more patients preferred pazopanib (70%) over sunitinib (22%); 8% had no preference (p=0.001) [4]. However, since the COMPARZ trial was an non-inferiority trial, caution is warranted in interpreting equivalence between the two drugs (sunitinib and pazopanib) specific to this trial.

The benefits of bevacizumab appear similar to sunitinib and pazopanib based on evidence from the AVOREN and CALGB 90206 trials. However, in the AVOREN trial, the proportion of patients who experienced an AE that led to treatment stoppage was higher in the bevacizumab plus IFN-α group than in the control group receiving placebo plus IFN-α (28% vs. 12%). Serious AEs were also more common in IFN-α plus bevacizumab patients (29% vs. 16% for IFN-α alone) [5]. Likewise, in the CALGB 90206 trial, overall toxicity was greater for bevacizumab plus IFN-α, with patients having significantly more grade 3 hypertension (9% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%), and proteinuria (13% vs. 0%) [7]. In light of the associated AEs of IFN-α therapy, as in the original report, bevacizumab combined with IFN-α is not recommended. There is still no evidence to suggest that bevacizumab alone is beneficial.

This report proposes temsirolimus as an option for first-line therapy for the subset of patients with poor-risk disease. The study by Hudes et al. [8] found that compared with IFN-α, median months of OS was significantly longer for patients treated with single-agent temsirolimus (7.3 vs. 10.9 months), but not with temsirolimus combined with IFN-α (7.3 vs. 8.4 months). Median months of PFS was longer in patients treated with temsirolimus alone (3.8; 95% CI, 3.6 to 5.2) and in combination compared to IFN-α alone (3.8 and 3.7 vs. 1.9 months, respectively). However, the RECORD-3 trial found everolimus to be inferior to sunitinib with a worse PFS of 7.9 months compared with 10.7 months [9]. Likewise, the ASPEN trial found that sunitinib significantly increased PFS compared with everolimus among non-clear cell patients (8.3 vs. 5.6 months) [11]. In the ESPN trial, median OS in first-line was 10.5 months for everolimus and was not reached with sunitinib (p=0.01) [10]. Thus, this report recommends that TKIs such as sunitinib be considered as the optimal first-line option for all patients regardless of risk category. The ESPN and ASPEN trials included non-clear cell RCC patients; thus caution is advised when interpreting treatment outcomes for all RCC patients from those trials in relation to mTOR inhibitors. The ESPN trial contained only 20% of clear cell patients but all with an extensive sarcomatoid component, which is biologically different from regular clear cell patients.

1b: Previously treated patients

Nivolumab is recommended by this report as a treatment for patients with mRCC who have progressed on VEGF pathway inhibitor therapy, based on improved OS in those treated with the drug, and less toxicity and better QOL compared with everolimus. The recent CheckMate trial found a significantly longer OS (25.0 vs. 19.6 months) and a significantly higher ORR rate (25% vs. 5%) with nivolumab compared with everolimus. Nineteen percent of patients receiving nivolumab had grade 3 or 4 treatment-related AE compared with 37% of the patients receiving everolimus [12].

Cabozantinib is also recommended over everolimus for previously treated patients with advanced RCC, based on significantly improved OS, but with more toxicity, compared with everolimus. Patients receiving cabozantinib in the METEOR trial had a significantly longer PFS compared with patients receiving everolimus (7.4 vs. 2.8 months). Dose reduction due to AEs occurred in 60% of the patients who received cabozantinib and in 25% of those who received everolimus [13].

Everolimus is proposed by this report as an option for RCC patients previously treated with sunitinib, sorafenib, or both, based on the final results of the RECORD-1 trial establishing the efficacy and safety of everolimus compared with placebo in patients with mRCC (median months PFS 4.9 vs. 1.9) [14]. Thus, some patients with contra-indications to nivolumab (and/or cabozantinib) may still benefit from everolimus. For patients without contraindications, cabozantinib or nivolumab should clearly be considered before everolimus, but the sequence in which they should be administered is not yet defined.

Axitinib is suggested as an option in this report for second-line treatment based on two network meta-analyses showing improved PFS over sorafenib and pazopanib in previously treated patients [20,21]. Likewise, sorafenib was suggested as a treatment option in patients with favourable- to intermediate-risk RCC who progress following initial cytokine therapy. The TARGET trial found significant increases in median PFS (5.5 vs. 2.8 months) among previously treated patients receiving sorafenib, compared with placebo. The SWITCH study found no differences in PFS or OS for patients administered sorafenib followed by sunitinib versus sunitinib followed by sorafenib [22]. The findings from the network meta-analysis by Leung et al. found sunitinib to be superior to sorafenib (PFS–HR 1.63, 95%CI 1.09 to 1.52 – sorafenib vs. sunitinib) [20] (see Appendix E). Thus, other therapies, such as sunitinib, are preferred for first-line for all patient types.

Question 2: Is a combination of agents better than any single targeted agent?

Although a recently published phase II RCT reported significant clinical activity with lenvatinib plus everolimus compared with everolimus or lenvatinib alone, current evidence does not yet support the use of combinations of targeted agents outside of a clinical trial setting. The LENEVE trial compared lenvatinib (n=52), everolimus (n=50), and the combination of lenvatinib + everolimus (n=51) for patients previously treated with VEGF-targeted therapy or cytokine therapy [23]. Median months of PFS was more than doubled for the lenvatinib + everolimus group, compared with the lenvatinib and everolimus (14.6 vs. 7.4 vs. 5.5 months; respectively) groups. OS analysis showed significant difference for lenvatinib + everolimus versus everolimus, and lenvatinib + everolimus significantly improved ORR versus everolimus. However, a recent meta-analysis suggested that there was no benefit from a combination of several targeted drugs versus a single agent in first-line treatment [24]. Thus, the current evidence does not support the use of combinations of targeted agents outside of a clinical trial setting and thus no recommendations could be made regarding question 2.

The Use of Targeted Therapies in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer: Updated Guideline 2017

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix A). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 17 members of the GDG Expert Panel, 13 members cast votes and four abstained, for a total 76% response in January 2017. Of those that cast votes, 13 (100%) approved the document. Of the 13 responders, one member had comments for consideration by the Working Group. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
Could the authors consider combining recommendations for second-line therapy? Having several recommendations are confusing. Why not state that cabozantinib and nivolumab are recommended with everolimus and axitinib as options?	We have combined the recommendations for second- and third-line therapies in a section entitled "previously treated patients"

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in October 2016. The RAP conditionally approved the document October 26, 2016. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
I thought this guideline was really, really, really well written. It was very clear. Things were internally consistent even though certain areas are repeated three times with increasingly deep levels of information. You did a great job of putting the evidence into context, i.e., when to use Bevacizumab or why combination is not approved at this time.	We have removed some repetitive text in the document.
Recommendation 1: Qualifying statements: the third bullet is the most important one and should go first. The other two bullets should be combined into one. Recommendation 2: In what way is the combination superior? Survival? And what line of therapy are we talking about?	We liked this reorganization and have changed the recommendations to make them clearer to the reader.

Recommendation 3: The second bullet is more important and should come first. And I think 'poor-risk disease' should be defined with a bullet Recommendation 4: Again, I would reverse the order. Otherwise, it's surprising at first that you are recommending this toxic drug. Recommendation 5: Stick to 'VEGF TKI' and do not introduce 'VEGF pathway inhibitor therapy', because you're not including bevacizumab here (according to the Table on page 68, METEOR required progression on kinase inhibitor therapy).	
It is a fine document - I have no problem with the recommendations, per se. The most substantive thing - I am not sure why the existing meta-analyses were not used as an evidence base; given that they were not used, I am not sure why meta-analyses were not conducted for this review; there is some reference to network meta-analysis but I see a description of five current meta-analyses and not the network part - which also speaks to - why not use it - if there is one.	The following paragraphs have been added to explain why we did not conduct a meta-analysis but used already published network meta-analysis: Since there were few RCTs directly comparing the same intervention and control arms, direct meta-analysis was not possible for this report. In contrast to conventional pairwise meta-analysis, network meta-analysis can provide estimates of relative efficacy between all interventions, even though some have never been compared head to head [58]. Three [1,20,21] of 14 systematic reviews [1,20,21,24,59-68] with outcomes relevant to this review performed network meta-analysis (or indirect comparisons) for targeted therapies in the treatment of mRCC. Where applicable, the results from these network meta-analyses were used when comparing the targeted therapies in this report.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Five targeted peer reviewers from Ontario, Alberta, Nova Scotia, British Columbia, and the United Kingdom who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix A); three responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	1	2
2. Rate the guideline presentation.	0	0	0	0	3
3. Rate the guideline recommendations.	0	0	0	0	3

4. Rate the completeness of reporting.	0	0	0	0	3
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	1	2
6. Rate the overall quality of the guideline report.	0	0	0	0	3
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	0	3
8. I would recommend this guideline for use in practice.	0	0	0	0	3
9. What are the barriers or enablers to the implementation of this guideline report?	• Funding for each drug in Ontario. • There should not be any major barriers to the implementation of this guideline report. • I do not anticipate any barriers. Most of what is there is already in practice				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. Very well done.	
2a. Page 4 COMPARZ trial discussion: the report states "equal efficacy" between sunitinib and pazopanib. This trial was a non-inferiority trial and I would caution to state equivalence. 2b. Same applies for the interpretation of evidence section on page 5. 2c. Page 6: "rationale for the recommendation of TKI over mTOR in first-line…". The ESPN and ASPEN trials included non-clear cell RCC patients and I would caution against deriving treatment recommendations for all RCC patients from those trials. The ESPN trial contained a small portion (20%) of clear cell patients but all with an extensive sarcomatoid component, which is biologically different from regular clear cell patients. 2d. Page 6 qualifying statement for recommendation 4 nivolumab: one might add that severe autoimmune side effects with nivolumab are rare. 2e. Page 8 interpretation of evidence for recommendation 7 axitinib: Why is axitinib listed as an option only in patients with contraindications for everolimus? I think the current evidence positions axitinib as an equal alternative to everolimus. 2f. Page 14, last paragraph: that paragraph sounds outdated. Should that be revised or am I misunderstanding that paragraph?	2a and 2b. We have added the following to the end of the paragraph discussing sunitinib and pazopanib in the discussion… "However, since the COMPARZ trial was a non-inferiority trial, caution is warranted in interpreting equivalence between the two drugs (sunitinib and pazopanib) specific to this trial. 2c. We have added the reviewer's comment to the discussion as follows: "The ESPN and ASPEN trials included non-clear cell RCC patients; thus, caution is advised when interpreting treatment outcomes for all RCC patients from those trials in relation to mTOR inhibitors. The ESPN trial contained only 20% of clear cell patients but all with an extensive sarcomatoid component, which is biologically different from regular clear cell patients." 2d. We have added that autoimmune side effects are uncommon in the qualifying statement. 2e. We have removed the mention of everolimus from recommendation 7. 2f. This comment was in reference to the results of the previous document in this series.
3. Thorough review, concise, clear. Makes sense of the data in a very fluid and evolving field.	N/A

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All physicians with an interest in genitourinary cancer in the PEBC database were contacted by email to inform them of the survey. A total of 97 individuals were contacted in Canada, of whom six practiced outside of Ontario and the remaining practiced within Ontario. Seven (7.2%) responses were received. None of the non-participants gave reasons why they were unavailable to review this guideline at the time. The results of the feedback survey from seven people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	reviewer rating n=7(%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	1	6
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1	3	3
3. I would recommend this guideline for use in practice.	0	0	0	1	6
4. What are the barriers or enablers to the implementation of this guideline report?	• Reputable source will help adoption. • Really well-written, comprehensive document. Consistent documented evidence throughout. Extensive literature review summarized effectively. • Rapidly changing field. This will need frequent revisiting and updating. Enabler: This has boiled down a complex, large amount of literature and made it digestible. Good quick reference for practice and nice teaching tool as well. • Few barriers. • One of the barriers I would expect would be funding, which may prevent the proper use as per the guideline. I.e., if you can only get funding for one drug, you may use it regardless of the guideline recommendation. • None.				

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	**Responses**
1. This is a very complex area. Great job putting evidence into context.	N/A
2. As long as this gets updated frequently to stay relevant, it will be very useful.	N/A
3. Please note that I've answered 3 in	N/A

Question #2 because as a Radiation Oncologist, this guideline is very useful academically but since I do not (cannot) prescribe the targeted therapies described, I technically cannot make use of this guideline.	

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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77. Ravaud A, Barrios CH, Alekseev BY, Tay MH, Agarwala SS, Yalcin S, et al. Randomized phase II study of first-line everolimus plus bevacizumab (E+B) versus interferon alpha-2a plus bevacizumab (I+B) in patients (pts) with metastatic renal cell carcinoma (mRCC): Record-2 final overall survival (OS) and safety results. Journal of Clinical Oncology. 2013;1).
78. Bukowski RM, Kabbinavar FF, Figlin RA, Flaherty K, Srinivas S, Vaishampayan U, et al. Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. Journal of Clinical Oncology. 2007;25(29):4536-41.
79. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007;356(2):115-24.

Appendix A. List of Authors and Conflict Of Interest (COI) Declarations

Name	Affiliation	Declaration of Interest
Working Group		
Judy Brown Research Methodologist	McMaster University, Department of Oncology, Program in Evidence-Based Care, Hamilton, Ontario	None declared
Christina Canil Medical Oncologist	The Ottawa Hospital/University of Ottawa, Ottawa, Ontario	Attended and received honorarium from advisory boards for Pfizer, Novartis, Amgen, AstraZeneca, Sanofi-Aventis, and Janssen. Received travel grant from Novartis and Pfizer. Was a paid speaker for Janssen and Pfizer.
Urban Emmenegger Medical Oncologist	University of Toronto, Department of Medicine, Division of Medical Oncology; Odette Cancer Centre, Toronto, Ontario	Was paid $5,000 or more in a single year to act in consulting capacity with Amgen, Astellas, Janssen, and Sanofi-Aventis. Received a grant or other research support from Pfizer. Was a co-investigator on an investigator-initiated clinical trial of temsirolimus (funded by Pfizer)
Sebastien Hotte Medical Oncologist	McMaster University, Department of Oncology, Division of Medical Oncology; Juravinski Cancer Centre, Hamilton, Ontario	Received research support from Novartis.

Name	Affiliation	Declaration of Interest
Cindy Walker-Dilks Health Research Methodologist	McMaster University, Department of Oncology, Program in Evidence-Based Care, Hamilton, Ontario	None declared
Eric Winquist Medical Oncologist	Western University, Department of Oncology, Division of Medical Oncology; London Health Sciences Centre, London, Ontario	None declared
Genitourinary Cancer Disease Site Group (who reviewed document)		
Jack Barkin Urologist	Humber River Regional Hospital, Toronto, Ontario	None declared
Glenn Bauman Radiation Oncologist	London Health Sciences Centre, London, Ontario	None declared
Rodney Breau Urologist	The Ottawa Hospital/University of Ottawa, Ottawa, Ontario	None declared
Michael Brundage Radiation Oncologist	Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, Ontario	None declared
Charles Catton Radiation Oncologist	Princess Margaret Hospital, Toronto, Ontario	Employed by UHN and on staff at PMCC
Anthony Finelli Urologist	University of Toronto, Department of Surgery, Division of Urology; Princess Margaret Hospital, Toronto, Ontario	None declared
Neil Fleshner Urologist	Princess Margaret Hospital, Toronto, Ontario	$5,000 or more in a single year to act in a consulting capacity for Hybridyne Imaging Technologies. Received grants from Astellas, Bavarian Nordic, Bayer, Ferring, Janssen, Medivation, Nucleix, Progenics, Sanofi, and Spectracure AB.
Michael Lock Radiation Oncologist	London Regional Cancer Program, Schulich School of Medicine and Dentistry, Western University, London, Ontario	None declared
Aamer Mahmud Radiation Oncologist	Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, Ontario	None declared
Scott Morgan* Radiation Oncologist	University of Ottawa, Department of Radiology, Division of Radiation Oncology; The Ottawa Hospital Cancer Centre, Ottawa, Ontario	None declared
Bobby Shayegan Urologist	St. Joseph's Hospital, McMaster University, Hamilton, Ontario	None declared

Name	Affiliation	Declaration of Interest
Tom Short Urologist	Credit Valley Hospital, Mississauga, Ontario	None declared
John Srigley Pathologist	Credit Valley Hospital, Mississauga, Ontario	None declared
Report Approval Panel		
Melissa Brouwers Director	Program in Evidence-Based Care, McMaster University, Hamilton, Ontario	None declared
Laurie Elit	Juravinski Cancer Centre, Hamilton, Ontario	None declared
Craig Earle	Sunnybrook Health Sciences Centre, Toronto, Ontario	None declared
Targeted Peer Reviewers		
George Bjarnason	Sunnybrook Health Sciences Centre, Toronto, Ontario	$5,000 or more in a single year to act in a consulting capacity for Pfizer, Novartis, BMS Received grants or other research support, either as principal or co-investigator, in any amount, from a relevant business entity (Pfizer, Merck grant for investigator initiated clinical trials)
Christian Kollmannsberger	BC Cancer Agency, BCCA Vancouver Cancer Centre, Vancouver, BC	Served on the PCODR Clinical Guidance committee for pazopanib, axitinib, nivolumab
Scott North	Department of Oncology – University of Alberta	Served on the National AdvisoryB with Astellas and Janssen (over $5,000). Per-case funding for clinical trials has been received but all funds are paid to Alberta Heath Services and not to the Investigator. Was a site PI for the RECORD-1 trial (everolimus in RCC)

Appendix B. Literature Search

Search Strategy: MEDLINE

Methods Terms	1 meta-analysis as topic/ (13223)
	2 meta-analysis.pt. (44218)
	3 (meta analy$ or metaanaly$).tw. (59419)
	4 (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview:).tw. (53495)
	5 (systematic adj (review$ or overview?)).tw. (49997)
	6 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw. (52872)
	7 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or medline).ab. (86014)
	8 (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab. (24420)
	9 or/1-8 (177922)
	10 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (38146)
	11 (stud: adj select:).ab. (9864)
	12 10 or 11 (42019)
	13 12 and review.pt. (23305)
	14 9 or 13 (180766)
	15 exp randomized controlled trials/ or exp clinical trials, phase II/ or exp clinical trials, phase III/ or exp clinical trials, phase IV/ (94187)
	16 (randomized controlled trial or clinical trial, phase II or clinical trial, phase III or clinical trial, phase IV).pt. (381062)
	17 random allocation/ or placebos/ or double blind method/ or single blind method/ (229325)
	18 (random: or placebo: or rct or phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).tw. (801518)
	19 or/14-18 (1109277)
	20 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt. (1468138)
	21 19 not 20 (1075082)
Renal cell carcinoma terms	22 exp kidney neoplasms/ (57060)
	23 exp carcinoma, renal cell/ (21819)
	24 rcc.mp. (8115)
	25 (renal adj cell).mp. (30405)
	26 (cancer: or tumor: or tumour: or carcinoma: or malignan:).mp. (2355976)
	27 25 and 26 (29247)
	28 22 or 23 or 24 or 27 (62648)
Drug terms	29 angiogenesis inhibitors/ (15077)
	30 exp antineoplastic agents/ (810798)
	31 protein kinase inhibitors/ (22577)
	32 (bevacizumab or avastin or everolimus or afinitor).mp. (11440)

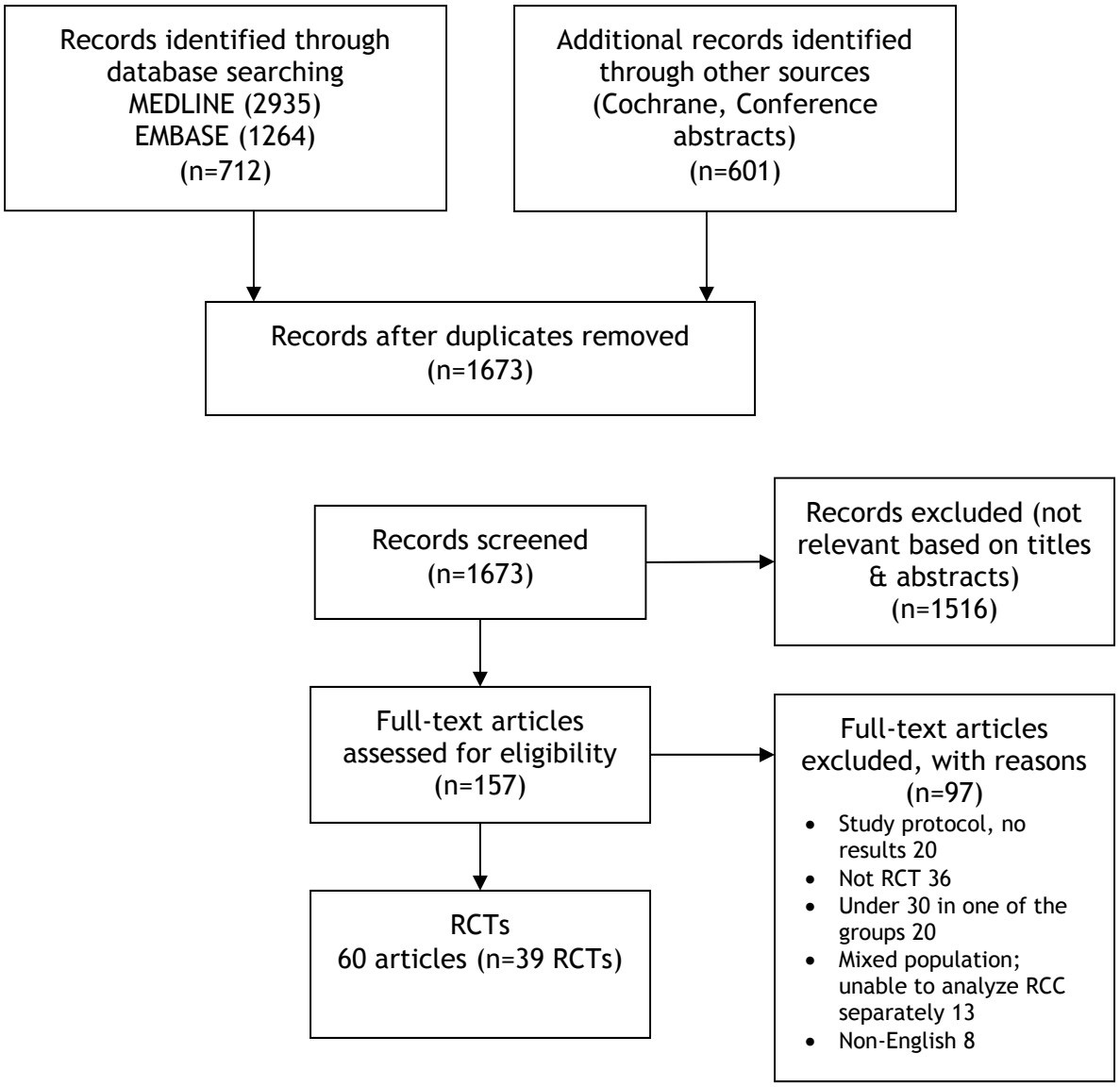
	33	(sorafenib or nexavar or bay 43-9006).mp. (3634)
	34	(sunitinib or sutent or su11248).mp. (3080)
	35	(temsirolimus or torisel or cci-779).mp. (990)
	36	thalidomide/ (6398)
	37	thalidomide.tw. (6068)
	38	(neovastat or ae-941 or (shark adj cartilage)).mp. (209)
	39	(axitinib or inlyta).mp. (288)
	40	(pazopanib or votrient).mp. (484)
	41	(tivozanib or av-951).mp. (40)
	42	or/29-41 (832018)
Methods & renal cell carcinoma & drugs	43	21 and 28 and 42 (1837)
Further limits	44	limit 43 to yr="2008 -Current" (799)
	45	limit 44 to english language (747)

Search Strategy: EMBASE

Methods terms	1	exp meta analysis/ (76710)
	2	exp systematic review/ (70658)
	3	(meta analy$ or metaanaly$).tw. (78175)
	4	(systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview:).tw. (70100)
	5	(systematic adj (review$ or overview?)).tw. (64839)
	6	exp review/ or review.pt. (1568187)
	7	(systematic or selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab. (186586)
	8	(stud: adj select:).ab. (11584)
	9	6 and (7 or 8) (61233)
	10	1 or 2 or 3 or 4 or 5 or 9 (192738)
	11	(cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or medline).ab. (105641)
	12	(reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab. (28348)
	13	10 or 11 or 12 (240999)
	14	"randomized controlled trial (topic)"/ (47710)
	15	single blind procedure/ or double blind procedure/ (110060)
	16	randomization/ or placebo/ (239143)
	17	(random: or placebo: or rct or phase II or phase 2 or phase III or phase 3 or phase IV or phase 4).tw. (872334)
	18	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw. (114100)
	19	randomized controlled trial/ (317421)
	20	or/14-19 (1051641)
	21	(editorial or note or letter or erratum or short survey).pt. or case study/ (1785048)
	22	13 or 20 (1203866)

	23	22 not 21 (1137686)
Renal cell carcinoma terms	24	exp kidney tumor/ (63149)
	25	rcc.mp. (12164)
	26	(renal adj cell).mp. (29782)
	27	(cancer: or tumor: or tumour: or carcinoma: or malignan:).mp. (2448325)
	28	26 and 27 (28778)
	29	24 or 25 or 28 (66649)
Drug terms	30	exp angiogenesis inhibitor/ (79437)
	31	exp protein kinase inhibitor/ (227520)
	32	(bevacizumab or avastin).mp. (31577)
	33	(everolimus or afinitor).mp. (12741)
	34	(sorafenib or nexavar or bay 43-9006).mp. (14976)
	35	(sunitinib or sutent or su11248).mp. (12897)
	36	(temsirolimus or torisel or cci-779).mp. (5397)
	37	thalidomide.mp. (18863)
	38	(neovastat or ae-941 or (shark adj cartilage)).mp. (652)
	39	(axitinib or inlyta).mp. (1855)
	40	(pazopanib or votrient).mp. (2812)
	41	(tivozanib or av-951).mp. (285)
	42	or/30-41 (284182)
Methods & renal cell carcinoma & drugs	43	23 and 29 and 42 (3393)
Further Limits	44	limit 43 to yr="2008 -Current" (2774)
	45	limit 44 to english language (2686)

Appendix C. PRISMA Flow Diagram



Appendix D. Existing Guidelines

Study	Focus
Guidelines	
Bazarbashi S, Al Othman K, Al Otaibi M, Abusamra A, Rabah D, Aljubran A, Murshid E, Al Oraifi I, El-Naghi M, Bahader Y, Soudy H, Rehman A. Saudi Oncology Society clinical management guidelines for renal cell carcinoma. Urol Ann. 2011 Mar;3 Suppl:S3-5. doi: 10.4103/0974-7796.78548. PubMed PMID: 21673849	Consensus based – broad topic, very brief. Non-systematic review – methods for search for evidence not included
Bracarda S, Ruggeri EM, Monti M, Merlano M, D'Angelo A, Ferraù F, Cortesi E, Santoro A; Sorafenib Working Group. Early detection, prevention and management of cutaneous adverse events due to sorafenib: recommendations from the Sorafenib Working Group. Crit Rev Oncol Hematol. 2012 Jun;82(3):378-86. doi: 10.1016/j.critrevonc.2011.08.005. Epub 2011 Sep 23. Review. PubMed PMID: 21944842	Consensus based – mixed, no focus on specific cancers. Methods for search for evidence not included. Adverse effects
Chiong E, Tay MH, Tan MH, Kumar S, Sim HG, Teh BT, Umbas R, Chau NM. Management of kidney cancer in Asia: resource-stratified guidelines from the Asian Oncology Summit 2012. Lancet Oncol. 2012 Nov;13(11):e482-91. doi: 10.1016/S1470-2045(12)70433-3. Review. PubMed PMID: 23117003.	Consensus based – broad topic. Discusses VEGF TKIs (sunitinib, pazopanib, bevacizumab, sorafenib, axitinib trials) & mTOR inhibitors (temsirolimus, everolimus trials). Includes search strategy. No specific recommendations
Escudier B, Eisen T, Porta C, Patard JJ, Khoo V, Algaba F, Mulders P, Kataja V; ESMO Guidelines Working Group. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct;23 Suppl 7:vii65-71. PubMed PMID: 22997456	Consensus based – broad topic. Discusses 1st & 2nd line treatment. Nonsystematic review, methods for search for evidence not included. Levels of evidence – specific recommendations.
Fujioka T, Obara W; Committee for Establishment of the Clinical Practice Guideline for the Management of Renal Cell Carcinoma and the Japanese Urological Association. Evidence-based clinical practice guideline for renal cell carcinoma: the Japanese Urological Association 2011 update. Int J Urol. 2012 Jun;19(6):496-503. doi: 10.1111/j.1442-2042.2012.03031.x. Review. PubMed PMID: 22621218	Consensus based – broad topic, Q&A format. Nonsystematic review – methods for search for evidence not included. Specific recommendations with grades in response to questions

Study	Focus
García Del Muro X, Gallardo E, García Carbonero I, Laínez N, José Méndez M, Maroto P, Ochoa de Olza M, Puente J, Reynes G, Rubio J, Santander C, Suárez C, Vázquez Estévez S, Castellano D. Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with renal cell carcinoma. Cancer Chemother Pharmacol. 2014 Feb 16. [Epub ahead of print] PubMed PMID: 24531612 Calvo E, Maroto P, del Muro XG, Climent MA, González-Larriba JL, Esteban E, López R, Paz-Ares L, Bellmunt J, Castellano D. Updated Recommendations from the Spanish Oncology Genitourinary Group on the treatment of advanced renal cell carcinoma. Cancer Metastasis Rev. 2010 Aug;29 Suppl 1:1-10. doi: 10.1007/s10555-010-9231-6. PubMed PMID: 20640589 Bellmunt J, Calvo E, Castellano D, Climent MA, Esteban E, García del Muro X, González-Larriba JL, Maroto P, Trigo JM. Recommendations from the Spanish Oncology Genitourinary Group for the treatment of metastatic renal cancer. Cancer Chemother Pharmacol. 2009 Mar;63 Suppl 1:S1-13. doi: 10.1007/s00280-009-0955-3. PubMed PMID: 19259675.	Consensus based – includes sections and discussion of evidence on 1st & 2nd line treatment of mRCC. Nonsystematic review – methods for search for evidence not included. Levels of evidence – grades, specific recommendations
Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, Patard JJ, Mulders PF, Sinescu IC; European Association of Urology Guideline Group. EAU guidelines on renal cell carcinoma: the 2010 update. Eur Urol. 2010 Sep;58(3):398-406. doi: 10.1016/j.eururo.2010.06.032. Epub 2010 Jul 12. PubMed PMID: 20633979	Literature search details not provided in paper. Section on targeted agents for mRCC. Table with algorithm for 1st/2nd line, risk or prior treatment, and recommended agent. No specific recommendations.
Molina AM, Motzer RJ. Clinical practice guidelines for the treatment of metastatic renal cell carcinoma: today and tomorrow. Oncologist. 2011;16 Suppl 2:45-50. doi: 10.1634/theoncologist.2011-S2-45. Review. PubMed PMID: 21346039	Nonsystematic review – summarizes update to NCCN and EAU guidelines. Discusses targeted agents for mRCC. Table with agent, clinical trial data (not referenced), & recommendations from NCCN & EAU.
Motzer RJ, Jonasch E, Agarwal N, Beard C, Bhayani S, Bolger GB, Chang SS, Choueiri TK, Derweesh IH, Gupta S, Hancock	NCCN guideline, discusses mTOR inhibirors and TKIs for non-clear cell RCC.

Study	Focus
SL, Kim JJ, Kuzel TM, Lam ET, Lau C, Levine EG, Lin DW, Margolin KA, Michaelson MD, Olencki T, Pili R, Plimack ER, Rampersaud EN, Redman BG, Ryan CJ, Sheinfeld J, Sircar K, Somer B, Wang J, Wilder RB, Dwyer MA, Kumar R. Kidney cancer, version 2.2014. J Natl Compr Canc Netw. 2014 Feb 1;12(2):175-82. PubMed PMID: 24586079 Motzer RJ, Agarwal N, Beard C, Bhayani S, Bolger GB, Carducci MA, Chang SS, Choueiri TK, Hancock SL, Hudes GR, Jonasch E, Josephson D, Kuzel TM, Levine EG, Lin DW, Margolin KA, Michaelson MD, Olencki T, Pili R, Ratliff TW, Redman BG, Robertson CN, Ryan CJ, Sheinfeld J, Spiess PE, Wang J, Wilder RB; National Comprehensive Cancer Network. Kidney cancer. J Natl Compr Canc Netw. 2011 Sep 1;9(9):960-77. Erratum in: J Natl Compr Canc Netw. 2011 Nov 1;9(11):xlv. PubMed PMID: 21917622	Nonsystematic review – methods for search for evidence not included. Algorithm for 1st line & subsequent treatment with levels of evidence & consensus.
Patard JJ, Pignot G, Escudier B, Eisen T, Bex A, Sternberg C, Rini B, Roigas J, Choueiri T, Bukowski R, Motzer R, Kirkali Z, Mulders P, Bellmunt J. ICUD-EAU International Consultation on Kidney Cancer 2010: treatment of metastatic disease. Eur Urol. 2011 Oct;60(4):684-90. doi: 10.1016/j.eururo.2011.06.017. Epub 2011 Jun 24. Review. PubMed PMID: 21704448	Review methods included. Focus on current targeted therapies for mRCC (1st & 2nd line). No specific recommendations.
Plimack ER, Hudes GR. Selecting targeted therapies for patients with renal cell carcinoma. J Natl Compr Canc Netw. 2011 Sep 1;9(9):997-1006; quiz 1007. PubMed PMID: 21917624	NCCN – methods for search for evidence not included. No specific recommendations.

Appendix E. Meta-Analysis Coverage Of Five Recent Meta-Analyses

Citation	Outcome	Intervention	Line	Study	Result
Albiges2015	Combined vs. Single agent	Erlotinib + BEV vs. BEV alone	NA	Bukowsi2007	HR 1.05 (0.91-1.21)
		EVE + BEV vs. BEV + IFN-α		Ravaud2012	
		AMG 386 SOR vs. placebo		Rini2012	
		TEM + BEV vs. BEV + IFN-α		Rini2013	
Larkin2013	PFS	PAZ vs. placebo	1st & 2nd line	Sternberg2010 (VEG105192)	Indirect comp.: HR (95% CrI) AXI vs. pl 0.25 (0.17 to 0.38) AXI vs. PAZ 0.47 (0.26 to 0.85) AXI vs. SOR 0.46 (0.32 to 0.68) SOR vs. PAZ 1.00 (0.63 to 1.61)
		SOR vs. placebo	2nd line	Escudier2009a (TARGET) Updates Escudier2007b	
		AXI vs. SOR		Rini2011 (AXIS)	
		EVE vs. placebo	2nd & 3rd line	Motzer2008 (RECORD-1)	
Larkin2015	PFS	SOR vs. IFN-α	1st line	Escudier2009	Indirect comp.: mean HR (95% CrI) SUN vs. PAZ 0.94 (0.80 to 1.08) SUN vs. AXI 0.75 (0.46 to 1.15) SUN vs. BEV+IFN-*α* 0.79 (0.64 to 0.96) SUN vs. EVE 0.70 (0.56 to 0.87) SUN vs. SOR 0.57 (0.40 to 0.78) SUN vs. TIV 0.76 (0.48 to 1.13) SUN vs. TEM+BEV 0.74 (0.56 to 0.96)
		AXI vs. SOR		Hutson2013	
		BEV + IFN-α vs. placebo + IFN-α		Escudier2010 (AVOREN)	
		SUN vs. IFN-α		Motzer2009	
		TIV vs. SOR		Motzer2013 (TIVO-1)	
		PAZ vs. SUN		MOTZER2013 (COMPARZ)	
		EVE vs. SUN		Motzer2013 (RECORD-3)	
		SOR vs. placebo	2nd line	Negrier2009 (TARGET)	
		BEV + IFN-α vs. IFN-α		Rini2008 (CALB)	
		TEM + BEV vs. BEV = IFN-α		Rini2014 (INTORACT)	
		PAZ vs. placebo		Sternberg2010 (VEG105192	
		SUN vs. IFN-α		Motzer2009,2007 (SUTENT)	
		PAZ vs. placebo	1st & 2nd line	Sternberg2010 (VEG105192)	
		SOR vs. placebo	2nd line	Escudier2007b (TARGET)	
Leung2014	PFS	TAs vs. placebo (direct comp.)	1st & 2nd line	TARGET, RECORD-1, AZD2171, VEG105192	HR 0.41 (0.35-0.48)
	Safety	TAs vs. placebo (direct comp.)	1st & 2nd line	TARGET, RECORD-1, AZD2171, VEG105192	OR 2.61 (0.84 to 8.17)
	PFS PFS PFS	AXI vs. other TAs (PAN) (indirect comp.)	1st & 2nd line 1st & 2nd line 1st & 2nd line	TARGET, RECORD-1, AZD2171, VEG105192, AXIS, INTORSECT, Motzer 2010)	HR 0.64(0.42 to 0.98)
	PFS PFS PFS	AXI vs. other TAs (SOR) (indirect comp.)	1st & 2nd line 1st & 2nd line 1st & 2nd line	TARGET, RECORD-1, AZD2171, VEG105192, AXIS, INTORSECT, Motzer 2010)	HR 0.67(0.54 to 0.81)
	PFS	CED vs. other TAs	1st & 2nd line	TARGET, RECORD-1, AZD2171,	NS

Citation	Outcome	Intervention	Line	Study	Result
		(indirect comp.)		VEG105192, AXIS, INTORSECT, Motzer 2010)	
		EVE vs. other TAs (indirect comp.)		TARGET, RECORD-1, AZD2171, VEG105192, AXIS, INTORSECT, Motzer 2010)	NS
		PAZ vs. other TAs (indirect comp.)		TARGET, RECORD-1, AZD2171, VEG105192, AXIS, INTORSECT, Motzer 2010)	NS
		SOR vs. other TAs (SUN) (indirect comp.)		TARGET, RECORD-1, AZD2171, VEG105192, AXIS, INTORSECT, Motzer 2010)	HR 1.63 (1.09 to 1.52)
		SUN vs. other TAs (TEM) (indirect comp.)		TARGET, RECORD-1, AZD2171, VEG105192, AXIS, INTORSECT, Motzer 2010)	HR 0.73 (0.56 to 0.96)

AXI=axitinib; BEV=bevacizumab; CED=cediranib; CI=confidence interval; comp =comparison; CrI=credible interval; D-L= DerSimonian and Laird method; EVE=everolimus; HR=hazard ratio; IFN-α=interferon-alpha; M-H=Mantel-Haenszel method; NA=not available; NS=not significant; OR=odds ratio; ORR=objective response rate; OS=overall survival; PAZ=pazopanib; PFS=progression-free survival; pl=placebo; RR= Response Rate; SOR = sorafenib; SUN=sunitinib; TAs=targeted agents; TEM=temsirolimus; TIV=tivozanib

Appendix F. Study Characteristics

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
First-line treatment					
Escudier2010 **AVOREN** Phase III/multi See also Escudier2009ab **(updates Escudier2007 in 3-8-4 orig)**	61 yr / 70%	mRCC - All predominantly clear cell (>50%) Favourable 93 (29%) Intermediate 180 (56%) Poor 25 (8%) NA 24 (7%)	BEV+ IFN-α (327)	BEV 10 mg/kg IV every 2 wk plus IFN-α 9 MU SC 3×/wk	**OS** PFS (independent & investigator assessment of radiographs) TTP TTF ORR Adverse effects
Rini2010 **CALGB 90206** Phase III/multi **(updates Rini2008 in 3-8-4 orig)**	61 yr / 69%	mRCC - All clear cell Favourable 97 (26%) Intermediate 234 (64%) Poor 38 (10%)	BEV+ IFN-α (369)	BEV10 mg/kg IV every 2 wk plus IFN-α 9 MU SC 3×/wk	**OS** PFS (investigator assessment of radiographs) ORR Adverse effects
		Favourable 95 (26%) Intermediate 231 (64%) Poor 37 (10%) NA 28 (9%)	IFN-α (363)	IFN-α 9 MU SC 3×/wk	
Hudes2007 **Global-ARCC** Phase III/multi **(3-8-4 orig)**	59 yr / 69%	mRCC - Clear cell 169 (81%) Other 40 (19%) Intermediate 64 (31%) Poor 145 (69%)	TEM(209)	25 mg IV once/wk	**OS** PFS (independent & investigator assessment of radiographs) ORR Clinical benefit rate Adverse effects
		Clear cell 163 (78%) Other 47 (22%) Intermediate 50 (24%) Poor 160 (76%)	TEM+ IFN-α (210)	TEM15 mg IV once/wk plus IFN-α 3 MU→6 MU SC 3×/wk	
		Clear cell 170 (82%) Other 37 (18%) Intermediate 50 (24%) Poor 157 (76%)	IFN-α (207)	3 MU→18 MU SC 3×/wk	
Motzer2009 **SUTENT** Phase III/multi **(updates Motzer2007 in 3-8-4 orig)**	60 yr / 71%	mRCC - All clear cell Favourable 143 (38%) Intermediate 209 (56%) Poor 23 (6%)	SUN (375)	50 mg/day PO, 4 wk, then 2 wk off	**PFS** (independent assessment of radiographs) ORR OS Adverse effects
		Favourable 121 (34%) Intermediate 212 (59%) Poor 25 (7%)	IFN-α (375)	3 MU →9 MU SC 3×/wk	
Escudier2009b **IGR** Phase II/multi	62 yr / 62%	mRCC - All clear cell Low 52 (53.6%) Intermediate 44 (45.4%) High 1 (1%)	SOR (97)	400 mg→600 mg PO 2 x/day continuous	**PFS** (independent assessment of radiographs) OR DCR

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
(updates Szcylik2007ab) in 3-8-4 orig)		NA 0			PR CR Adverse effects
		Low 47 (51.1%) Intermediate 44 (47.8%) High 0 (0%) NA 1 (1.1%)	IFN-α (92)	9 MU SC 3 x/wk (with option to switch to SOR)	
Gordon2004ab Phase III/ **(3-8-4 orig)**	59 yr / 66%	Histology, prognosis not reported	Thalidomide + IFN-α (NR)	Thalidomide 200 mg/day PO for 2 wk→weekly escalation 400 mg/d→1000 mg/day maximum plus IFN-α 1 MU SC 2×/day	**PFS** ORR OS QOL
			IFN-α (NR)	1 MU SC 2 x/day	
Procopio2013 ab **ROSORC** Phase II/single See also Procopio2011 **(new)**	64 yr / 74%	Clear cell 58 (88%) Nonclear cell 8 (12%) Low 36 (55%) Intermediate 27 (41%) High 3 (5%)	SOR + IL-2 (66)	SOR 400 mg 2 x/day PO plus IL-2 4.5 MU SC 5×/wk; later amended to 3 MU 5×/wk, 2 wk then 2 wk off	**PFS** ORR OS Adverse effects
		Clear cell 56 (90%) Nonclear cell 6 (10%) Low 34 (55%) Intermediate 24 (39%) High 4 (6%)	SOR (62)	400 mg 2×/day PO	
Negrier2011 Bay2012ab **TORAVA** Phase II/multi **(new)**	62 yr / 73%	Clear cell 84 (95%) Good 25 (32%) Intermediate 41 (53%) Poor 11 (14%)	BEV+ TEM(88)	BEV10 mg/kg IV every 2 weeks plus TEM25 mg/wk IV	**48-wk PFS** ORR PFS (independent assessment of radiographs) OS Adverse effects
		Clear cell 40 (95%) Good 12 (31%) Intermediate 23 (59%) Poor 4 (10%)	SUN (42)	50 mg/day PO 4 wk then 2 wk off	
		Clear cell 40 (98%) Good 14 (39%) Intermediate 16 (44%) Poor 6 (17%)	BEV+ IFN-α (41)	BEV10 mg/kg IV every 2 weeks plus IFN-α 9 MU SC 3×/wk	
Motzer2012 **EFFECT** Phase II**/multi** **(new)**	62 yr / 65%	All clear cell or component of clear cell Favourable 43 (29%) Intermediate 91 (62%) Poor 12 (8%)	SUN 4 wk then 2 wk off (146)	50 mg/day PO 4 wk then 2 wk off	**TTP** ORR OS Adverse effects
		Favourable 38 (26%) Intermediate 88 (60%) Poor 20 (14%)	SUN continuous daily dosing (CDD) (146)	37.5 mg/day PO CDD schedule	
Jonasch2010	Mean 61 yr	All clear cell	SOR + IFN-α	400 mg 2×/day PO plus IFN-α 0.5	ORR

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
MDACC-Soraf Phase II/multi **(new)**	/ 76%	Low 20 (50%) Intermediate 18 (45%) Poor 2 (5%)	(40)	MU SC 2×/day	Adverse effects PFS OS
		Low 21 (52.5%) Intermediate 19 (47.5%) Poor 0	SOR (40)	400 mg orally 2×/day	
Flaherty2015, **BEST** Phase II/unclear See also McDermott2013ab **(new)**	NA / NA	All clear cell component Prognosis not reported	BEV (99)	10 mg/kg every 2 wk	PFS ORR OS Adverse effects
			TEM + BEV (91)	TEM25 mg/wk plus BEV10 mg/kg	
			BEV + SOR (90)	BEV5 mg/kg every 2 wk plus SOR 200 mg PO 5 days then 2 days off	
			SOR + TEM (91)	SOR 200 mg/day plus TEM25 mg/wk	
Motzer2013 **TIVO-1** Phase III/multi See also Motzer2013ab **(new)**	59 yr / 72%	All clear cell component Favourable 70 (27%) Intermediate 173 (67%) Poor 17 (7%)	TIV (260)	1.5 mg/day PO 3 days then 1 day off	PFS (independent assessment of radiographs) OS ORR Kidney-specific symptoms HRQoL Adverse effects
		Favourable 87 (34%) Intermediate 160 (62%) Poor 10 (4%)	SOR (257)	400 mg 2×/day PO	
Hutson2013 Phase III/multi **(new)**	58 yr / 72%	All clear cell component Favourable 94 (49%) Intermediate 84 (44%) Poor 7 (4%) NA 7 (4%)	AXI(192)	5 mg→10 mg 2×/day PO	PFS (independent assessment of radiographs) ORR Response duration OS Adverse effects
		Favourable 53 (55%) Intermediate 40 (42%) Poor 2 (2%) NA 1 (1%)	SOR (96)	400 mg 2×/day PO	
Motzer2013b COMPARZ Phase III/unclear Noninferiority **(new)**	61 yr / 73%	All clear cell component Favourable 151 (27%) Intermediate 322 (58%) Poor 67 (12%) NA 17 (3%)	PAZ (557)	800 mg/day PO	PFS (investigator assessment of radiographs) ORR OS HRQOL Medical resource utilization Adverse effects
		Favourable 152 (27%) Intermediate 328 (59%) Poor 52 (9%) NA 21 (4%)	SUN (553)	50 mg/day PO 4 wk then 2 wk off	
Ravaud2013ab **RECORD-2** Phase II/unclear	60 yr / 74%	All clear cell All favourable (93%)	BEV+ EVE (182)	BEV 10 mg/kg every 2 wk plus EVE 10 mg/day	**PFS** (independent assessment of radiographs) OS
			BEV + IFN-α	BEV 10 mg/kg every 2 wk plus	

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
(new)			(183)	IFN-α 9 MU SC 3×/wk	Adverse effects
Rini2015ab **Cleveland** Phase II/unclear See also; Rini2013ab Rini2013ab **(new)**	61 yr / 73%	All clear cell component Prognosis not reported	AXI titration (56)	5 mg 2×/day PO titrated to 10 mg	ORR PFS OS Response duration Adverse effects AXI plasma pharmacokinetics Blood pressure Biomarker/pharmacogenomics analysis
			Placebo titration (56)	N/A	
Eisen2013ab **Cambridge** Phase II/unclear **(new)**	NA / NA	All clear cell component Prognosis not reported	NIN(64)	200 mg 2×/day PO	PFS at 9 months QTc interval change PFS ORR OS TTP TTF Adverse effects
			SUN (32)	50 mg/day 4 wk then 2 wk off	
Hawkins2013ab **Manchester** Phase II/III/unclear **(new)**	NA / NA	All clear cell component Prognosis not reported	NAP + IFN-α (253)	NAP 10-15 mcg/kg IV 4 consecutive days/wk plus IFN-α 3→9 MU SC or IM 3×/wk (Data from clinicaltrials.gov)	OS PFS ORR Adverse effects
			IFN-α (260)	IFN-α 3→9 MU SC or IM 3×/wk	
Tomita2014ab **CROSS-J-RCC** Phase III/multi **(new)**	NA / NA	All clear cell Favourable 21%	SUN (57)	50 mg/day PO 4 wk then 2 wk off	PFS ORR OS Adverse events
		Favourable 22%	SOR (63)	400 mg PO 2×/day	
Rini2014 **INTORACT** Phase III/multi **(new)**	59 yr / 70%	All majority clear cell component Favourable 123 (31%) Intermediate 230 (58%) Poor 47 (12%)	TEM + BEV (400)	TEM25 mg/wk IV plus BEV10 mg/kg IV every 2 wk	PFS (independent & investigator assessment of radiographs) ORR OS Adverse effects
		Favourable 114 (29%) Intermediate 237 (61%) Poor 40 (10%)	BEV + IFN-α (391)	BEV10 mg/kg IV every 2 weeks plus IFN-α 9 MU SC 3×/wk	
Rini2012 **AMG386** Phase II/multi **(new)**	59 yr / 75%	All clear cell component Favourable 40% Intermediate 60% Poor 0%	AMG 386 10 mg + SOR (50)	AMG 386 10 mg/kg IV every wk plus SOR 400 mg 2×/day PO	PFS (independent assessment of radiographs) OS ORR Adverse effects
		Favourable 39%	AMG 386 3	AMG 386 3 mg/kg IV every wk	

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
		Intermediate 61% Poor 0%	mg + SOR (51)	plus SOR 400 mg 2×/day PO	
		Favourable 37% Intermediate 61% Poor 2%	SOR (51)	SOR 400 mg 2×/day PO	
Armstrong2016 **Phase II/ multi** **(new)**	59 yr and 64 yr /27% and 23%	All non-clear cell Good 29% Intermediate 63% Poor 8%	SUN (51)	50 mg/dy; 6-week cycles of 4 wk with treatment followed by 2 wk w/o treatment	PFS Safety
		Good 25% Intermediate 56% Poor 19%	EVE(57)	(10 mg/day)	
First- and second-line treatment					
Sternberg2013 **VEG105192** Phase III/multi See also Sternberg2010; Cella2012 **(new)**	59 yr / 71%	Clear cell 264 (91%) Predominantly clear cell 25 (9%) Favourable 113 (39%) Intermediate 159 (55%) Poor 9 (3%) NA 9 (3%)	PAZ (290)	800 mg/day PO	PFS (independent assessment of radiographs) OS ORR Duration of response Adverse effects
		Clear cell 129 (89%) Predominantly clear cell 16 (11%) Favourable 57 (39%) Intermediate 77 (53%) Poor 5 (3%) NA 6 (4%)	Placebo (145)	Patients who progressed had option to receive PAZ via open-label study VEG107769	
Motzer2014ab **RECORD-3** Phase II/multi See also Motzer2013ab **(new)**	62 yr / 73%	Clear cell 85.4% Favourable 30% Intermediate 56% Poor 14%	Everolimus/SUN (238)	EVE10 mg/day followed by SUN 50 mg/day 4 wk then 2 wk off	PFS (1st line EVE vs. 1st line SUN) OS (interim) Combined 1st/2nd line PFS Adverse effects
			SUN/EVE (233)	SUN 50 mg/day 4 wk then 2 wk off followed by EVE10 mg/day	
Eichelberg2015 **SWITCH** **Phase III/multi** see also Michel2014ab & Fischer2014ab	65 yr / NA	Clear cell 90% Intermediate 59% Low 39%	SOR/SUN (182)	SOR 400 mg 2×/day followed by SUN 50 mg/day 4 wk then 2 wk off	PFS OS Adverse effects
		Clear cell 84% Intermediate 51% Low 45%	SUN/SOR (183)	SUN 50 mg/day 4 wk then 2 wk off followed by SOR 400 mg 2×/day	

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
(new)					
Tannir2014 **ESPN**(ongoing) Phase II/multi Abstract Crossover design	59 yr / 63%	Metastatic non-clear cell Papillary 40% other 60% Good risk 11% Intermediate risk 83% Poor risk 6%	EVE (35)	10 mg by mouth once a day.	PFS in first-line PFS in second line OS Safety
		Good risk 12% Intermediate risk 88%	SUN (33)	50 mg by mouth daily for 4 weeks on / 2 weeks off.	
Second-line treatment					
Yang2003 Phase II/unclear **(3-8-4 orig)**	53 yr / 75%	All clear cell Prognosis not reported	BEV 3 mg (37)	3 mg/kg IV every 2 wk	TTP ORR OS Adverse effects
			BEV 10 mg (39)	10 mg/kg IV every 2 wk	
			Placebo (40)	Patients who progressed had option to crossover to 3 mg BEV± thalidomide	
Escudier2009 **TARGET** Phase III/multi See also Negrier2010 (**updates Escudier2007 in 3-8-4 orig)**	59 yr / 73%	Clear cell 99% Low 233 (52%) Intermediate 218 (48%) NA 0	SOR (451)	400 mg 2×/day	OS PFS (independent assessment of radiographs) ORR Adverse effects
		Low 228 (50%) Intermediate 223 (49%) NA 1 (<1%)	Placebo (452)	Cross over to SOR was permitted following planned PFS analysis	
Motzer2013 **AXIS** Phase III/multi **(new)**	61 yr / 72%	All clear cell component Favourable 100 (28%) Intermediate 236 (65%) Poor 37 (10%) NA 22 (6%)	AXI(361)	5 mg 2×/day increased to 7 and 10 mg 2×/day if tolerated	PFS (investigator assessment of radiographs) OS ORR Adverse effects
		Favourable 79 (22%) Intermediate 225 (62%) Poor 34 (9%) NA 24 (7%)	SOR (362)	400 mg 2×/day	
Hutson2014 **INTORSECT** Phase III/multi **(new)**	60 yr / 75%	Clear cell 214 (83%) Non-clear cell 45 (17%) Favourable 50 (19%) Intermediate 178 (69%) Poor 31 (12%)	TEM(259)	25 mg/wk IV	PFS (independent & investigator assessment of radiographs) ORR OS Adverse effects
		Clear cell 208 (82%) Non-clear cell 45 (18%) Favourable 44 (17%) Intermediate 177 (70%) Poor 32 (13%)	SOR (253)	400 mg 2×/day PO	

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
			EVE (14)	EVE PO on days 1 to 28	
Powles2014 ab **GDC-098** **Phase II/unclear** **(new)**	NR	Clear cell metastatic RCC Prognosis not reported	GDC-0980 (42)	40 mg QD	PFS OS ORR PK
			EVE (43)	10 mg QD	
Motzer2015 ab **LENEVE** **Phase II/multi** **(new)**	NR	Metastatic RCC Prognosis not reported	Lenvatinib (52)	24 mg/d	PFS OS ORR Safety
			EVE (50)	10 mg/d	
			Lenvatinib + EVE (51)	18 = 5 mg/d in 28 d cycles	
Second and third-line treatment					
Motzer2010 **RECORD-1** Phase III/multi **(updates Motzer2008 in 3-8-4 orig)**	61 yr / 77%	All clear cell component Favourable 81 (29%) Intermediate 156 (56%) Poor 40 (14%)	EVE (277)	10 mg/day PO plus best supportive care	PFS (independent assessment of radiographs) OS ORR QOL Adverse effects
		Favourable 39 (28%) Intermediate 79 (57%) Poor 21 (15%)	Placebo (139)	Best supportive care; patients who progressed were offered open-label EVE	
Motzer2015 **MSKCC** Phase II/unclear See also Motzer2014 ab **(new)**		All metastatic RCC Favourable 20 (33%) Intermediate 26 (43%) Poor 14 (23%)	Nivolumab (60)	0.3 mg/kg administered intravenously every 3 wk until disease progression , intolerance, or other	PFS ORR OS Safety
		Favourable 18 (33%) Intermediate 22 (42%) Poor 14 (26%)	Nivolumab (54)	2 mg/kg	
		Favourable 18 (33%) Intermediate 22 (41%) Poor 14 (26%)	Nivolumab (54)	10 mg/kg	
Motzer2015 2nd to 4th line **CheckMate** **Phase II/multi** **(new)**		All clear cell Favourable 145 (35%) Intermediate 201(49%) Poor 64 (16%)	Nivolumab (410)	3 mg per kilo of body weight intravenously 2 wk	OS ORR Safety
		Favourable 148 (36%) Intermediate 203 (49%) Poor 60 (15%)	EVE (411)	10 mg orally once daily	
Choueiri2015 **METEOR** **Phase III/mutli** **(new)**		All clear cell Favourable 150 (45 %) Intermediate 139 (42%) Poor 41 (12%)	Cabozantinib (330)	60 mg orally administered once daily	PFS OS ORR
		Favourable 150 (46%) Intermediate 135 (41%)	EVE (328)	10 mg orally administered once daily	

Trial	Median age/% Male	Histology and prognosis	Comparison	Dose and schedule	Planned outcomes
		Poor 43 (13%)			
Third-line treatment					
Motzer2014a **GOLD** Phase III/multi (new) See also Motzer2013ab	62 yr / 76%	All clear cell or clear cell component Favourable 58 (20%) Intermediate 164 (58%) Poor 62 (22%)	DOV (284)	500 mg PO 5 days then 2 days off	PFS (independent & investigator assessment of radiographs) OS ORR Time to definitive worsening of Karnofsky performance status Adverse effects
		Favourable 59 (21%) Intermediate 162 (57%) Poor 65 (23%)	SOR (286)	400 mg 2×/day PO	

AXI=axitinib; BEV=bevacizumab; CAB=cabozantinib; CED=cediranib; DOV=dovitinib; DCR=disease control rate; d=day; EVE=everolimus; HRQOL=health-related quality of life; IFN-α=interferon-alpha; IL=interleukin; IM=intramuscular; IV=intravenous; LEN=lenvatinib; mRCC=metastatic renal cell carcinoma; MU=million units; NA=not applicable; NAP=naptumomab; NIN=nintedanib; NIV=nivolumab; NR=not reported; ORR=objective response rate; OS=overall survival; PAZ=pazopanib; PFS=progression-free survival; PO=per oral; QD=daily; QOL=quality of life; RCC=renal cell carcinoma; SC=subcutaneous; SOR=sorafenib; SUN=sunitinib; TEM=temsirolimus; TIV=tivozanib; TTF=time to treatment failure; TTp=time to progression; wk=week; yr=years.

Appendix G. Quality Assessment

AMSTAR Quality Assessment of meta-analyses used in review

AMSTAR items	Albiges 2015	Larkin 2013	Larkin 2015	Leung 2014
1. Was an 'a priori' design provided?	Yes	No	Yes	Yes
2. Was there duplicate study selection & data extraction?	Yes	Yes	Yes	Yes
3. Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Yes	No	No	No
5. Was a list of studies (included & excluded) provided?	No	No	Yes	No
6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes
7. Was the scientific quality of the included studies assessed & documented?	Yes	Yes	No	Yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes	Yes	No	Yes
9. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes
10. Was the likelihood of publication bias assessed?	No	No	No	No
11. Was the conflict of interest stated?	No	No	Yes	No
Total AMSTAR points	8	6	7	7

Methodological Quality Assessment of RCTs

Study reference	Allocation concealment	Blinding	Intention to treat	Industry funding	Baseline characteristics balanced	Statistical power and target sample size	Terminated early
First-line treatment							
Rini2010 CALGB 90206 Phase III	NR	No	Yes	No	Yes	Yes	No
Escudier2010 AVOREN Phase III	Yes	Yes	Yes	Yes	Yes	Yes	No
Hudes2007 Global-ARCC Phase III (3-8-4 orig)	NR	Yes	Yes	Yes	Yes	Yes	No
Motzer2009 SUTENT Phase III	NR	No	Yes	Yes	Yes	Yes	No
Escudier2009b IGR Phase II	NR	No	Yes	Yes	Yes	NR	No
Gordon2004ab Phase III (3-8-4 orig)	NR	No	NR	Yes	NR	Yes	No
Procopio2013 ROSORC Phase II	Yes	No	Yes	Yes	Yes	Yes	No
Negrier2011 Bay2012ab TORAVA Phase II	Yes	No	Yes	Yes	Yes	Yes	No
Motzer2012 EFFECT Phase II	Yes	No	Yes	Yes	Yes	Yes	No
Jonasch2010 MDACC-Soraf Phase II	NR	No	Yes	No	Yes	Yes	No
Mulder 2012 AZD2171 Phase II	Yes	Yes	Yes	Yes	Yes	Yes	No
Flarherty2015, McDermott2013ab BEST Phase II	NR	NR	NR	NR	NR	Yes	No
Motzer2013c TIVO-1 Phase III	NR	No	Yes	Yes	No*	Yes	No
Hutson2013 Phase III	Yes	No	Yes	Yes	Yes	Yes	No
Motzer2013b COMPARZ Phase III	NR	No	Yes	Yes	Yes	Yes	No
Escudier 2014 PISCES	Yes	Yes	Yes	Yes	Yes	Yes	No
Ravaud2013ab RECORD-2 Phase II	NR	NR	NR	NR	NR	NR	No

Study reference	Allocation concealment	Blinding	Intention to treat	Industry funding	Baseline characteristics balanced	Statistical power and target sample size	Terminated early
Rini 2015 [ab] Rini2013 Cleveland Phase II	Yes	Yes	Yes	Yes	Yes	Yes	No
Eisen2013ab Cambridge Phase II	NR	NR	NR	NR	NR	NR	No
Hawkins2013ab Manchester Phase II/III	NR	No	NR	Yes	NR	NR	No
Tomita2014ab CROSS-J-RCC Phase III	NR	No	NR	NR	NR	Yes	No
Rini2014 INTORACT Phase III	Yes	No	Yes	Yes	Yes	Yes	No
Rini2012 AMG386 Phase II	Yes	Yes	Yes	Yes	Yes	Yes	No
Armstrong2016 ASPEN Phase II	Yes	Yes	Yes	Yes	Yes	Yes	No
First- and second-line treatment							
Sternberg2013 VEG105192 Phase III	Yes	Yes	Yes	Yes	Yes	Yes	No
Motzer2013ab RECORD-3 Phase II	NR	No	NR	NR	NR	NR	No
Michel2014ab SWITCH	NR	No	NR	NR	Yes	Yes	No
Tannir2014 ESPN (ongoing)	NR	NR	NR	NR	NR	Yes	Yes
Second-line treatment							
Yang2003 Phase II	NR	Yes	Yes	No	Yes	Yes	No
Escudier2009a TARGET Phase III	NR	Yes	Yes	Yes	Yes	Yes	No
Motzer2013a Rini2011 AXIS Phase III	Yes	No	Yes	Yes	Yes	Yes	No
Hutson2014 INTORSECT Phase III	Yes	No	Yes	Yes	Yes	Yes	No
Jonasch2013ab UCDCCC Phase II	NR	NR	NR	NR	NR	NR	No
Powles2014 GDG-0980	NR	NR	NR	NR	NR	NR	NR
Motzer2015 LENEVE	NR	No	NR	NR	NR	NR	NR
Second- and third-line treatment							
Motzer2010 RECORD-1	NR	Yes	Yes	Yes	Yes	Yes	Yes

Study reference	Allocation concealment	Blinding	Intention to treat	Industry funding	Baseline characteristics balanced	Statistical power and target sample size	Terminated early
Phase III							
Motzer2015 Phase II	Yes	Yes	Yes	Yes	Yes	Yes	No
Motzer2015 2nd to 4th line Check Mate	Yes	Yes	Yes	Yes	Yes	Yes	No
Choueiri2015 METEOR	Yes	Yes	Yes	Yes	Yes	Yes	No
Third-line treatment							
Motzer2014 GOLD Phase III	Yes	No	Yes	Yes	Yes	Yes	No

NR = Not Reported

APPENDIX H. EFFICACY RESULTS (Data according to prior treatment are coloured sections)

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
First-line treatment											
Rini2010 Rini2008 CALGB 90206	46.2	BEV + IFN-α	8.5 (CI 7.5 to 9.7)	Stratified 0.67 (CI 0.57 to 0.79) p<0.0001	18.3 (CI 16.5 to 22.5)	Stratified 0.86 (CI 0.73 to 1.01) p=0.069	25.5% (CI 20.9 to 30.6)	NR	NR	NR	NR
		IFN-α	5.2 (CI 3.1 to 5.6)		17.4 (CI 14.4 to 20.0)		13.1% (CI 9.5 to 17.3)	NR	NR	NR	NR
							p<0.0001				NR
Escudier 2010 AVOREN	23	BEV + IFN-α	10.2	Unstratified 0.63 (CI 0.52 to 0.75) p=0.0001 Stratified 0.61 (CI 0.51 to 0.73) p<0.001	23.3	Unstratified 0.91 (CI 0.76 to 1.10) p=0.3360 Stratified 0.86 (CI 0.72 to 1.04) p=0.1291	31%	4	92	141	NR
	21	IFN-α	5.4		21.3		13%	6	31	144	NR
							p=0.0001			NR	NR
Hudes 2007 Global-ARCC	NR	TEM	5.5 (CI 3.9 to 7.0)	NR	10.9 (CI 8.6 to 12.7)	TEM vs. IFN 0.73 (CI 0.58 to 0.92) p=0.008	8.6% (CI 4.8 to 12.4)	NR	NR	NR	32.1% (CI 25.7 to 38.4)
		TEM + IFN-α	4.7 (CI 3.9 to 5.8)	NR	8.4 (CI 6.6 to 10.3)	TEM + IFN vs. IFN 0.96 (CI 0.76 to 1.20) p=0.070	8.1% (CI 4.4 to 11.8)	NR	NR	NR	28.1% (CI 22.0 to 34.2)
		IFN-α	3.1 (CI 2.2 to 3.8)	NR	7.3 (CI 6.1 to 8.8)	NR	4.8% (CI 1.9 to 7.8)	NR	NR	NR	15.5% (CI 10.5 to 20.4)
Motzer 2009 SUTENT	NR	SUN	11 (CI 11 to 13)	0.54 (CI 0.45 to 0.64) p<0.001	26.4 (CI 23.0 to 32.9)	Unstratified[a] 0.82 (CI 0.67 to 1.001) p=0.051 Stratified 0.82 (CI 0.67 to 0.999) p=0.049	47% (CI 42 to 52)	11	165	150	NR
		IFN-α	5 (CI 4 to 6)		21.8 (CI 17.9 to 26.9)		12% (CI 9 to 16)	4	42	202	NR
							p<0.001				
Escudier 2009b IGR Szcylik 2007ab	NR	SOR	5.7 (CI 5.0 to 7.4)	Stratified 0.88 (CI 0.61 to 1.27) p=0.50	NR	NR	5.2%	0	5	72	NR
		IFN-α	5.6 (CI 3.7 to 7.4)				8.7%	1	7	51	NR
Gordon 2004ab	NR	Thalidomide + IFN-α	3.8	HR NR p=0.04	10.8	HR NR p=0.93	6.5%	3	6		NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
		IFN-α	2.8		12.2		2.2%	0	3		NR
							p=NS				
Procopio 2013 Procopio 2011 ROSORC	58	SOR + IL-2	8.25[a]	HR NR p=0.109	38 (CI 18 to 50)	0.91 (CI 0.59 to 1.41) p=0.667	NR	NR	18	35	NR
		SOR	7.5[a]		33 (CI 16 to 43)		NR	NR	9	37	NR
Negrier 2011 Bay2012ab TORAVA	35.1	BEV + TEM	8.2 (CI 7.0 to 9.6)	NR	NR	NR	27%	2	22	46	NR
		SUN	8.2 (CI 5.5 to 11.7)	NR	NR	TEM+BEV vs. SUN 0.67 (CI 0.40 to 1.12)	29%	0	12	20	NR
		BEV + IFN-α	16.8 (CI 6.0 to 26.0)	NR	NR	TEM+BEV vs. BEV+IFN 0.48 (CI 0.27 to 0.86)[c]	43%	0	17	13	NR
Motzer 2012 EFFECT	NR	SUN 4/2 schedule	8.5 (CI 6.9 to 11.1)	Unstratified 0.77 (CI 0.58 to 1.02) p=0.07	23.1 (CI 17.4 to 25.4)	Unstratified 1.09 (CI 0.78 to 1.50) p=0.615	32% (CI 24.7 to 40.4)	0	47	63	NR
		SUN CDD schedule	7.0 (CI 6.0 to 8.7)		23.5 (CI 17.5 to not reached)		28% (CI 21.0 to 36.1)	1	40	71	NR
							p=0.444				
Jonasch 2010 MDACC-Soraf	19.7	SOR + IFN-α	7.6 (CI 5.2 to 11.1)	0.85 (CI 0.51 to 1.42) p=0.526	27.0 (CI 22.3 to not reached)	2.17 (CI 0.92 to 5.12) p=0.076	25% (CI 12.7 to 41.2)	0	10	20	NR
		SOR	7.4 (CI 5.5 to 9.2)		Not reached		30% (CI 16.6 to 46.5)	1	11	17	NR
							p=NS				
Flaherty 2015 McDermott 2013ab BEST	NR	BEV	7.5 (90% CI 5.8 to 10.8)	NR	28.6	NR	CR+PR 13.2%	1	10	42	NR
		BEV + TEM	7.6 (90% CI 6.7 to 9.2)	vs. BEV 0.91 (CI 0.68 to 1.23) 1.01 p=0.95	24.7	NR	CR+PR 31.6% vs. BEV p=0.008	0	25	41	NR
		BEV + SOR	9.2 (90% CI 7.5 to 11.4)	vs. BEV 0.84 (CI 0.62 to 1.13) 0.89 p=0.49	27.5	NR	CR+PR 30.4% vs. BEV p=0.009	2	23	36	NR
		SOR + TEM	7.4 (90%	vs. BEV1.11	24.3	NR	CR+PR 20.2%	0	17	43	NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
			CI 5.6 to 7.9)	(CI 0.83 to 1.49) 1.07 p=0.68			vs. BEV p=0.30				
Motzer 2013c TIVO-1	NR	Tivozanib	11.9 (CI 9.3 to 14.7)	Stratified 0.80 (CI 0.64 to 0.99) p=0.042	NR	NR	33.1%	3	83	134	NR
		SOR	9.1 (CI 7.3 to 9.5)		NR	NR	23.3%	2	58	168	NR
Hutson 2013	NR	AXI	10.1 (CI 7.2 to 12.1)	Stratified 0.77 (CI 0.56 to 1.05) p=0.038	NR	NR	32%	0	62	83	NR
		SOR	6.5 (CI 4.7 to 8.3)		NR	NR	15%	0	14	51	NR
					NR	NR	RR 2.21 (CI 1.31 to 3.75) p=0.0006				
Motzer 2013b COMPARZ Noninferiority	NR	PAZ	8.4 (CI 8.3 to 10.9)	Stratified 1.05 (CI 0.90 to 1.22) (met criteria for noninferiority)	28.4 (CI 26.2 to 35.6)	Stratified 0.91 (CI 0.76 to 1.08) p=0.28	31%	1	170	216	NR
		SUN	9.5 (CI 8.3 to 11.1)		29.3 (CI 25.3 to 32.5)		25%	3	134	242	NR
							p=0.03				
Ravaud 2013ab RECORD-2	33	BEV + EVE	9.3	0.91 (CI 0.69 to 1.19) p=0.485	27.1 (CI 19.9 to 35.3)	HR NR	NR	NR	NR	NR	NR
		BEV + IFN-α	10.0		27.1 (CI 20.4 to 30.8)		NR	NR	NR	NR	NR
Rini 2015ab Rini2013 Cleveland	26.5	AXI titration	14.5 (CI 9.2 to 24.5)	Stratified 0.85 (CI 0.54 to 1.35) p=0.24	42.7 (CI 24.7 to NE)	0.79 (0.49 to 1.27)	54% (CI 40 to 67)	1	29	13	NR
	26.4	Placebo titration	15.7 (CI 8.3 to 19.4)		30.4 (23.7 to 45.0)		34% (CI 22 to 48)	0	19	24	NR
							RR 1.58 (CI 1.02 to 2.45) p=0.019				
Eisen2013 ab Cambridge	NR	Nintedanib	8.44	1.16 (CI 0.71 to 1.89) p=0.56	20.4	p=0.63	18.8%	NR	NR	NR	NR
		SUN	8.38		21.2		31.3%	NR	NR	NR	NR
							p=0.19	NR	NR	NR	NR
Hawkins 2013ab	43	NAP+ IFN-α	5.8	0.92 (CI 0.77 to 1.11)	17.1	1.08 (CI 0.88 to 1.33)	14%	NR	NR	NR	NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
Manchester		IFN-α	5.8		17.5		15%	NR	NR	NR	NR
Tomita2014ab CROSS-J-RCC	NR	SUN	8.7	0.67 (CI 0.42 to 1.08) p=0.095	Not reached	NR	35.3%	NR	NR	NR	NR
		SOR	7.0				27.8%	NR	NR	NR	NR
							p=0.407	NR	NR	NR	NR
Rini2014 INTORACT	NR	TEM + BEV	9.1 (CI 8.1 to 10.2)	1.1 (CI 0.9 to 1.3) p=0.8	25.8 (CI 21.1 to 30.7)	1.0 (CI 0.9 to 1.3) p=0.6	27.0% (CI 22.7 to 31.6)	2	106	218	NR
		BEV + IFN-α	9.3 (CI 9.0 to 11.2)		25.5 (CI 22.4 to 30.8)		27.4% (CI 223.0 to 32.1)	6	101	184	NR
							p=1.0				
Rini2012 AMG386	NR	AMG386 10 mg + SOR	9.0 (CI 5.6 to 13.1)	vs. SOR 0.80 (CI 0.50 to 1.28) p=0.350	Not reached (CI 24.3 to not estimable)	HR NR	38% (CI 25 to 53)	0	38	48	NR
		AMG386 3 mg + SOR	8.5 (CI 5.3 to 10.9)	vs. SOR 0.96 (CI 0.61 to 1.50) p=0.841	29.2 (CI 22.2 to not estimable)		37% (CI 24 to 52)	2	35	45	NR
		SOR	9.0 (5.5 to 10.9)	NR	27.1 (CI 19.7 to not estimable)		25% (CI 14 to 40)	2	24	59	NR
				NR			CI for 10 mg vs. plac -6.9 to 30.8 CI for 3 mg vs. plac -7.5 to 30.0				
Armstrong 2016 ASPEN	24	SUN 50 mg/dy 4 wk on, 2 wk off	8.3 (80% CI 5.8 to 11.4)	1.41 (80% CI 1.03 to 1.92) p=0.16)	31.5 (14.8 to not reached)	1·12 (CI 0.7 to 2.1) p=0·60	NR	NR	NR	NR	NR
		EVE 10mg dy	5·6 months (5·5 to 6.0)		13.2 (CI 9.7 to 37.9)		NR	NR	NR	NR	NR
First and second-line treatment											
Sternberg 2010 Sternberg 2013 VEG105192	NR	PAZ	9.2	Stratified 0.46 (CI 0.34 to 0.62) p<0.0001	22.9	Stratified 0.91 (CI 0.71 to 1.16) p=0.224	30% (CI 25.1 to 35.6)	1	87	110	NR
		Placebo	4.2		20.5		3% (CI 0.5 to 6.4)	0	5	59	NR
							p<0.001			NR	NR
Treatment naive	NR	PAZ (n=155)	11.1	0.40 (CI 0.27 to 0.60)	22.9 (CI 17.6 to 25.4)	1.01 (CI 0.72 to 1.42)	NR			NR	NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
	NR	Placebo (n=78)	2.8	p<0.0001	23.5 (CI 12.0 to 34.3)		NR			NR	NR
Prior cytokine	NR	PAZ (n=135 [PFS]) (n=53 [OS])	7.4	0.54 (CI 0.35 to 0.84) P<0.001	22.7 (CI 19.3 to 28.3)	0.82 (CI 0.57 to 1.16)	NR			NR	NR
	NR	Placebo (n=67 [PFS]) (n=54 [OS])	4.2		18.7 (CI 14.2 to 26.3)		NR			NR	NR
Motzer 2014b RECORD-3 Non-inferiority	22.7	1st line EVE	7.9 (range 5.6 to 8.2)	1.4 (CI 1.2 to 1.8)	NR	NR	8%	1	18	137	NR
		1st line SUN	10.7 (range 8.2 to 11.5)				27%	3	59	121	NR
		EVE→SUN	21.1 (range 15.0 to 25.9)	1.3 (CI 0.9 to 1.7)	22.4 (CI 19.7 to not reached)	1.2 (CI 0.9 to 1.6)	NR	NR	NR	NR	NR
		SUN→EVE	25.8 (range16.0 to not reached)		32.0 (CI 20.5 to not reached)		NR	NR	NR	NR	NR
Michel 2014ab SWITCH	NR	SOR →SUN		1.01 p=0.54	NR	0.997 p=0.49	NR	NR	NR	NR	NR
		SUN→SOR						NR	NR	NR	NR
Tannir 2014 ESPN (ongoing) Abstract Crossover design	NR	1st line EVE (35)	4.1 (CI 2.7 to 7.4)	p=0.25	10.5 (CI 7.4 to NA)	NR	0%	NR	NR	NR	NR
		1st line SUN (33)	6.1 (CI 4.7 to 10.8		Not reached p=0.01	NR	12%	NR	NR	NR	NR
		2st line EVE (19)	4.3 (CI 1.4 to NA)	NR	NR	NR	NR	NR	NR	NR	NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
		2st line SUN (19)	1.8 (CI 1.5 to NA)	NR	NR	NR	NR	NR	NR	NR	NR
Second-line treatment											
Yang2003	27	BEV 3 mg	3.0	vs. pl 1.26 p=0.053	14.8[c]	HR NR p=NS	0%	0	0	NR	NR
		BEV 10 mg	4.8	vs. pl 2.55 P<0.001	15.2[c]		10% (CI 2.9 to 24.2)	0	4	NR	NR
		Placebo	2.5		12.9[c]		0%	0	0	NR	NR
Escudier 2009a Escudier 2007 Negrier 2010 TARGET	NR	SOR	5.5	Stratified 0.44 (CI 0.35 to 0.55) P<0.001	17.8	Stratified 0.88 (CI 0.74 to 1.04) p=0.146	10%	1	43	333	NR
		Placebo	2.8		15.2		2%	0	8	239	NR
Prior cytokine	NR	AXI	5.5	0.54 (CI 0.45 to 0.64)	NR	NR	NR	NR	NR	NR	NR
	NR	SOR	2.7		NR	NR	NR	NR	NR	NR	NR
Motzer 2013a Rini2011 AXIS	NR	AXI	8.3 (CI 6.7 to 9.2)	Stratified 0.66 (CI 0.55 to 0.78) P<0.0001	20.1 (CI 16.7 to 23.4)	Stratified 0.97 (CI 0.80 to 1.17) p=0.374	23%	NR	NR	NR	NR
		SOR	5.7 (CI 4.7 to 6.5)		19.2 (CI 17.5 to 22.3)		12%	NR	NR	NR	NR
							p=0.0001			NR	NR
Prior cytokine	NR	AXI (n=126)	12.2 (CI 10.2 to 15.5)	0.51 (CI 0.37 to 0.68) P<0.0001	29.4 (CI 24.5 to not estimable)	0.81 (CI 0.56 to 1.19) p=0.144	NR			NR	NR
	NR	SOR (n=125)	8.2 (CI 6.6 to 9.5)		27.8 (CI 23.1 to 34.5)		NR			NR	NR
Prior SUN	NR	AXI (n=194)	6.5 (CI 5.7 to 7.9)	0.72 (CI 0.57 to 0.90) p=0.002	15.2 (CI 12.8 to 18.3)	0.997 (CI 0.78 to 1.27) p=0.490	NR			NR	NR
	NR	SOR (n=195)	4.4 (CI 2.9 to 4.7)		16.5 (CI 13.7 to 19.2)		NR			NR	NR
Prior BEV+ IFN-α	NR	AXI (n=29)	8.3 (CI 2.8 to	0.82 (CI 0.43 to 1.55)	14.7 (CI 9.2 to 20.0)	1.83 (CI 0.94 to 3.54) p=0.965	NR			NR	NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
			10.5)	p=0.266							
	NR	SOR (n=30)	4.5 (CI 3.0 to 6.5)		19.8 (CI 13.1 to not estimable)		NR			NR	NR
Prior TEM	NR	AXI (n=12)	2.6 (CI 1.5 to 17.1)	1.21 (CI 0.43 to 3.38) p=0.634	14.0 (CI 3.8 to not estimable)	0.46 (CI 0.17 to 1.28) p=0.064	NR			NR	NR
	NR	SOR (n=12)	5.7 (CI 2.6 to 8.3)		8.5 (CI 5.7 to 13.5)		NR			NR	NR
Hutson 2014 INTORSECT	9.2	TEM	4.3	Stratified 0.87 (CI 0.71 to 1.07) p=0.19	12.3 (CI 10.1 to 14.8)	Stratified 1.31 (CI 1.05 to 1.63) p=0.01 In favour of SOR	8%	0	20	157	NR
		SOR	3.9		16.6 (CI 13.6 to 18.7)		8%	1	19	153	NR
Prior SUN ≤180 days	NR	TEM (n=97)	NR	0.91 (CI 0.65 to 1.27)	11.4	1.30 (CI 0.94 to 1.81 p=0.11	NR	NR	NR	NR	NR
	NR	SOR (n=92)	NR		10.1		NR	NR	NR	NR	NR
Prior SUN >180 days	NR	TEM (n=162)	NR	0.83 (CI 0.65 to 1.07)	14.4	1.37 (CI 1.04 to 1.80) p=0.02	NR	NR	NR	NR	NR
	NR	SOR (n=161)	NR		17.8		NR	NR	NR	NR	NR
Jonasch 2013ab UCDCCC	NR	MK-2206	3.65 (CI 1.77 to 5.52)	p=0.979	NR	NR	NR	NR	NR	NR	NR
		EVE	7.43 (CI 1.84 to 13.27)		NR	NR	NR	NR	NR	NR	NR
Powles 2014	NR	GDC-0980	3.7	2.04 (CI 1.18 to 3.54)	11.9	1.73 (CI 0.8 to 3.43)	7.1%	NR	NR	NR	NR
		EVE	6.1		14.6		11.6%	NR	NR	NR	NR
Motzer 2015 [ab]	NR	Lenvatinub + EVE	14.6 (CI 0.9 to 20.1)	vs. EVE 0.40 (CI 0.24 to 0.68) p<0.001	25.5 (CI 20.8 to 25.5)	vs. EVE 0.51 (CI 0.30 to 0.88) p=0.024	22 (43%) vs. EVE p<0.001	NR	NR	NR	NR
		Lenvatinub	7.4 (CI 5.6 to 10.2)	vs. EVE 0.61 (CI 0.38 to 0.98) p=0.048	18.4 (CI 13.3 to NE)	NR	14 (27%) vs. EVE p=0.007	NR	NR	NR	NR
		EVE	5.5 (3.5-		17.5 (CI 11.8 to NE)	NR	3 (6%)	NR	NR	NR	NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
			7.1)								
Second and third-line treatment											
Motzer 2010 RECORD-1	NR	EVE	4.9 (CI 4.0 to 5.5)	Stratified 0.33 (CI 0.25 to 0.43) P<0.001	14.8	Stratified 0.87 (CI 0.65 to 1.15) p=0.162	1.8%	0	5	185	NR
		Placebo	1.9 (CI 1.8 to 1.9)		14.4		0	0	0	45	NR
Prior SUN	NR	EVE (n=124)	3.9	0.34 (CI 0.23 to 0.51)	NR	NR	NR	NR	NR	NR	NR
	NR	Placebo (n=60)	1.8		NR	NR	NR	NR	NR	NR	NR
Prior SOR	NR	EVE (n=81)	5.9	0.25 (CI 0.16 to 0.42)	NR	NR	NR	NR	NR	NR	NR
	NR	Placebo (n=43)	2.8		NR	NR	NR	NR	NR	NR	NR
Prior SUN + SOR	NR	EVE (n=72)	4.0	0.32 (CI 0.19 to 0.54)	NR	NR	NR	NR	NR	NR	NR
	NR	Placebo (n=36)	1.8		NR	NR	NR	NR	NR	NR	NR
Motzer 2015	NR	NIV 0.3	2.7 (80%CI 1.9 to 3.0)	NR	18.2 (80% CI 16.2 to24.0),	NR	12 (20%)	1 (2%)	11 (18%)	22 (37%)	NR
	NR	NIV 2	4.0 (80%CI 2.8 to 4.2)	vs. 0.3 1.0 (80%CI 0.7 to 1.3)	25.5 (80% CI 19.8 to 28.8)	NR	12 (22%)	1 (2%)	11 (20%)	23 (43%)	NR
	NR	NIV 10	4.2 (80%CI 2.8 to 5.5)	vs. 0.3 1.0 (80%CI 0.8 to 1.3) vs. 2 1.0 (80%CI 0.8 to 1.3); trend test 0.9	24.7 (80% CI 15.3 to 26.0)	NR	11 (20%)	0	11 (20%)	24 (44%)	NR
Motzer 2015 CheckMate	NR	NIV	4.6 (CI 3.7 to 5.4)	0.88 (CI 0.75 to 1.03) p=0.11	25.0 CI (21.8 to NE)	0.73 (98.5% CI 0.57 to 0.93) p=0.002	25%	4 (1%)	99 (24%)	NR	NR
		EVE	4.4 (CI		19.6 (CI 17.6 to		5% OR=5.98 (CI	2	20 (5%)	NR	NR

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
			3.7 to 5.5)		23.1)		3.68 to 9.72; p=<.001	(<1%)			
	1 prior anti-angiogenic regimens	NIV (n=128)	NR	NR	NR	0.71 (CI 0.56 to 0.90)	NR	NR	NR	NR	NR
		EVE (n=158)	NR	NR	NR		NR	NR	NR	NR	NR
	2 prior antiangiogenic regimens	NIV (n=55)	NR	NR	NR	0.89 (CI 0.61 to 1.29)	NR	NR	NR	NR	NR
		EVE (n=57)	NR	NR	NR		NR	NR	NR	NR	NR
Choueiri 2015 METEOR	NR	CAR	7.4 (CI 5.6 to 9.1)	0.58 (CI 0.45 to 0.75) p<0.001	NR	0.67 (CI 0.51 to 0.89); p=0.005[d]	NR	NR	NR	NR	NR
		EVE	3.8 (CI 3.7 to 5.4)		NR		NR	NR	NR	NR	NR
	1 prior VEGFR	CAR (n=87)	NR	0.56(CI 0.42 to 0.75)	NR	NR	NR	NR	NR	NR	NR
		EVE (n=95)	NR		NR	NR	NR	NR	NR	NR	NR
	≥ 2 prior VEGFR	CAR (n=34)	NR	0.67(CI 0.41to 1.10)	NR	NR	NR	NR	NR	NR	NR
		EVE (n=31)	NR		NR	NR	NR	NR	NR	NR	NR
Third-line treatment											
Motzer 2014a GOLD	11.3	Dovitinib	3.7 (CI 3.5 to 3.9)	Stratified 0.86 (CI 0.72 to 1.04) p=0.063	11.1 (CI 9.5 to 13.4)	Stratified 0.96 (CI 0.75 to 1.22)	3.9%	0	11	147	NR
		SOR	3.6 (CI 3.5 to 3.7)		11.0 (CI 8.6 to 13.5)		3.8%	0	11	149	NR

AXI=axitinib; BEV=bevacizumab; CAR=carbozantinib; CI=confidence interval; CR=complete response; CRR=clinical response rate; EVE=everolimus; HR=hazard ratio; IFN-α=interferon-alpha; IL=interleukin; mo=month; NA=not applicable; NE=not evaluable; NIV=nivolumab; NR=not reported; NS=not significant; ORR=objective response rate; OS=overall survival; PAZ=pazopanib; PFS=progression-free survival; pl=placebo; PR=partial response; RR=relative risk; TEM=temsirolimus; SD=standard deviation; SOR=sorafenib; SUN=sunitinib; VEGFR=vascular

Trial	Median follow-up (mo)	Treatment groups	Outcomes								
			PFS		OS		Response rate				
			Median (mo)	HR (95% CI)	Median (mo)	HR (95% CI)	ORR (%)	CR (n)	PR (n)	SD	CRR
endothelial growth factor receptor; wk=weeks. [a] 33 wk = 8.25 mo (33÷4) [b] 30 wk = 7.5 mo (30÷4) [c] Estimated from Kaplan-Meier graph [d] did not cross p value of ≤0.0019 required to achieve statistical significance at time of interim analysis											

Appendix I. Ongoing Trials

Protocol ID(s)	Title and details of trial
NCT00081614	A Phase II, Multicenter, Randomized, Double-Blind Clinical Trial to Evaluate the Efficacy and Safety of Tarceva (Erlotinib Hydrochloride) in Combination With Avastin (Bevacizumab) Versus Avastin Alone for Treatment of Metastatic Renal Cell Carcinoma Phase (line): Ib & II – (1st) Treatment Groups: Tarceva in combination With Avastin Versus Avastin Alone Target accrual: 100 Start date: March 2004 Date trial summary last modified: May 14, 2014 Estimated primary completion date: not provided Status: study completed, but no results yet Preliminary results reported: none
NCT00873236 MTVERNHOSP-RD2007-114, CDR0000637812, ENH-RD2007-114, EUDRACT-2008-006414-19, EU-20917	Dynamic Contrast Enhanced MRI (DCE-MRI) Assessment of the Vascular Changes Induced With BEVAlone and in Combination With Interferon-α in Patients With Advanced Renal Cell Carcinoma Phase (line): II (1st) Treatment Groups: BEV vs. BEV + IFN-α (low dose) vs. BEV + IFN-α (standard dose) Target accrual: 30 Start date: Apr, 2008 Date trial summary last modified: Aug 9, 2013 Estimated primary completion date: Not provided Status: unknown Preliminary results reported: none
NCT01136733 LENEVE E7080-G000-205	An Open-Label, Multicenter, Phase 1b/2 Study of E7080 Alone, and in Combination With EVE in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment Phase (line): II (2nd) Treatment Groups: Lenvatinib alone and in combination with everolimus Target accrual: 153 Start date: Aug 2010 Date trial summary last modified: Nov 18, 2015 Estimated primary completion date: Jun 2014 Status: Ongoing, but not recruiting patients Preliminary results reported: none
NCT01392183 2011-0358, NCI-2011-01277	A Randomized Phase 2 Trial of PAZ Versus TEM in Poor-Risk Clear-Cell Renal Cell Carcinoma Phase (line): II (1st) Treatment Groups: PAZ vs. TEM Target accrual: 90 Start date: Oct, 2012 Date trial summary last modified: Mar 16, 2016 Estimated primary completion date: Oct, 2018 Status: currently recruiting patients Preliminary results reported: no
NCT01481870 CROSS-J-RCC, UMIN000003040	Randomized Comparison of Sequential Therapies With SUN and SOR in Advanced Renal Cell Carcinoma Phase (line): III (1st) Treatment Groups: SOR/SUN vs. SUN/SOR Target accrual: 120 Start date: Jan, 2010 Date trial summary last modified: Feb 21, 2013 Estimated primary completion date: Jul, 2013 Status: status unknown Preliminary results reported: yes (Tomita2014)

Protocol ID(s)	Title and details of trial
NCT01613846 SWITCH-II 16037 / AN 33/11, 2011-004396-36	Phase III Randomized Sequential Open-label Study to Evaluate the Efficacy and Safety of SOR Followed by PAZ versus PAZ Followed by SOR in the Treatment of Advanced / Metastatic Renal Cell Carcinoma Phase (line): III (1^{st} and 2^{nd}) Treatment Groups: SOR/PAZ vs. PAZ/SOR Target accrual: 544 Start date: May, 2012 Date trial summary last modified: Mar 16, 2016 Estimated primary completion date: Jun, 2016 Status: ongoing but not recruiting patients Preliminary results reported: No
NCT01664182 NCI-2012-01289, NCI-2012-01289, P9048_A12PAMDREVW01, CDR0000738785, PHII-122, 9048, N01CM00038, P30CA033572	A Randomized Phase 2 Study of AMG 386 With or Without Continued Anti-vascular Endothelial Growth Factor (VEGF) Therapy in Patients With Renal Cell Carcinoma Who Have Progressed on Bevacizumab, Pazopanib, SOR, or SUN Phase (line): II (2^{nd}) Treatment Groups: TRE vs. TRE + VEGF-therapy (BEV or PAZ or SOR or SUN) Target accrual: 78 Start date: Aug, 2012 Date trial summary last modified: Mar 23, 2016 Estimated primary completion date: May, 2016 Status: ongoing, but not recruiting Preliminary results reported: no
NCT01727089 CI-2012-02206, NCI-2012-02206, PHII-121, PhII-121, 9144	A Phase II Study of BEV Alone or in Combination With TRC105 for Advanced Renal Cell Cancer Phase (line): II (2^{nd},3^{rd}) Treatment Groups: BEV vs. bevacizumab, anti-endoglin monoclonal antibody TRC105 Target accrual: 88 Start date: Nov, 2012 Date trial summary last modified: May 3, 2016 Estimated primary completion date: Sep, 2016 Status: Ongoing, but no recruiting patients Preliminary results reported: no
NCT01727336 DART study - A041-04, ACE-041	A Phase 2 Randomized, Double-Blind Study of Dalantercept and AXI Compared to Placebo and AXI in Patients With Advanced Renal Cell Carcinoma Phase (line): II (up to 3 previous therapies) Treatment Groups: DAL + AXI vs. Placebo + AXI Target accrual: 174 Start date: Dec, 2012 Date trial summary last modified: Mar 24, 2016 Estimated primary completion date: Dec, 2017 Status: currently recruiting patients Preliminary results reported: no
NCT01731158 BERAT study C-II-008, 2011-005939-78	A Prospective, Open-label, Multicenter, Randomized Phase II Trial: Sequential Therapy With Bevacizumab, Rad001 (Everolimus) and Tyrosine Kinase Inhibitors (TKI) in Metastatic Renal Cell Carcinoma (mRCC) (BERAT Study) Phase (line): II (1^{st},2^{nd},3^{rd}) Treatment Groups: sequential therapy with approved drugs Avastin in combination with Roferon-A (first-line), Afinitor (second-line) and a TKI (third-line) sequential therapy with approved drugs Avastin in combination with Roferon-A (first-line), a TKI (second-line) and Afinitor (third-line) Target accrual: 100 Start date: Oct, 2012 Date trial summary last modified: Jan 26, 2016 Estimated primary completion date: May, 2016 Status: Ongoing, but no recruiting patients Preliminary results reported: none

Protocol ID(s)	Title and details of trial
NCT01784978 SUNRISES (CRAD001LIC34T)	Randomized ph. II Study to Explore Efficacy and Feasibility of Upfront Rotations Between SUN and EVE vs. Sequential Treatment of 1st line SUN & 2nd Line EVE Until Progression in Pats Met. Clear Cell Renal Cancer Phase (line): II (1st) Treatment Groups: SUN + EVE (rotational) vs. SUN + EVE (sequential) Target accrual: 115 Start date: Oct, 2012 Date trial summary last modified: Mar 26, 2014 Estimated primary completion date: Aug, 2014 Status: unknown Preliminary results reported: none
NCT01806064 105RC101	A Randomized Phase 2 Trial of AXI and TRC105 Versus AXI Alone (Including a lead-in Phase 1B Dose Escalation Portion) in Patients With Advanced or Metastatic Renal Cell Carcinoma Phase (line): I and II (2nd) Treatment Groups: TRC105 + AXI vs. AXI Target accrual: 168 Start date: Mar, 2013 Date trial summary last modified: Apr 19, 2016 Estimated primary completion date: Jul, 2016 Status: currently recruiting patients Preliminary results reported: none
NCT01865747 METEOR	A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) vs. EVE in Subjects With Metastatic Renal Cell Carcinoma That Has Progressed After Prior VEGFR Tyrosine Kinase Inhibitor Therapy Phase (line): III (2nd and 3rd) Treatment Groups: CAB tablets vs. EVE Target accrual: 650 Start date: Jun, 2013 Date trial summary last modified: Apr 13, 2015 Estimated primary completion date: Sep, 2015 Status: ongoing, but not recruiting patients Preliminary results reported: yes
NCT01984242	A Phase II, Randomized Study of Atezolizumab Administered as Monotherapy or In Combination With BEV versus SUN In Patients With Untreated Advanced Renal Cell Carcinoma Phase (line): II (1st) Treatment Groups: atezolizumab + Avastin vs. atezolizumab; following PD: atezolizumab + Avastin vs. SUN; following PD: atezolizumab + Avastin Target accrual: 305 Start date: Jan, 2014 Date trial summary last modified: May 4, 2016 Estimated primary completion date: Aug 2019 Status: active, not recruiting Preliminary results reported: no
NCT02072031 ALTN-06-IIA	A Randomized, Positive-controlled, Multicenter, Phase II Study of Anlotinib (AL3818) in Patients With Advanced Renal Cell Carcinoma (RCC) Phase (line): II (1st) Treatment Groups: Anlotinib vs. SUN Target accrual: 133 Start date: Dec, 2013 Date trial summary last modified: Apr 25, 2016 Estimated primary completion date: Dec, 2016 Status: Ongoing, but no recruiting patients Preliminary results reported: no

Protocol ID(s)	Title and details of trial
NCT02089334 RX-0201-P2-A-09	A Multicenter, Open-label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of RX-0201 in Combination With EVE to Treat Subjects With Advanced Renal Cell Carcinoma Phase (line): 1b/2 (2^{nd}, 3^{rd}) Treatment Groups: RX-0201 + EVE vs. EVE alone Target accrual: 39 Start date: Aug, 2014 Date trial summary last modified: Mar 14, 2016 Estimated primary completion date: Dec, 2016 Status: currently recruiting patients Preliminary results reported: no
NCT02187302 CRLX101-208	A Randomized, Phase 2 Study to Assess the Safety and Efficacy of CRLX101 in Combination With BEV in Patients With Metastatic Renal Cell Carcinoma (RCC) Versus Standard of Care (SOC) (Investigator's Choice) Phase (line): II (3/4) Treatment Groups: CRLX101 + BEV vs. SOC Target accrual: 110 Start date: Jul, 2014 Date trial summary last modified: Jan 5, 2016 Estimated primary completion date: Jan, 2016 Status: ongoing, but not recruiting Preliminary results reported: no
NCT02210117 2013-0715, NCI-2014-01857	A Pilot Randomized Tissue-based Study Evaluating Anti-PD1 Antibody or Anti-PD1 + BEVor Anti-PD1 + Anti-CTLA-4 in Patients With Metastatic Renal Cell Carcinoma Who Are Eligible for Cytoreductive Nephrectomy, Metastasectomy or Post-treatment Biopsy. Phase (line): II (unclear) Treatment Groups: NIV vs. NIV + BEV vs. NIV + IPIL Target accrual: 60 Start date: Nov, 2014 Date trial summary last modified: Apr 5, 2016 Estimated primary completion date: Nov, 2018 Status: currently recruiting patients Preliminary results reported: no
NCT02231749 CheckMate 214 - CA209-214, 2014-001750-42	A Phase 3, Randomized, Open-Label Study of Nivolumab Combined With Ipilimumab Versus SUN Monotherapy in Subjects With Previously Untreated, Advanced or Metastatic Renal Cell Carcinoma Phase (line): III (1^{st}) Treatment Groups: VIN + IPIL vs. SUN Target accrual: 1070 Start date: Oct, 2014 Date trial summary last modified: Apr 26, 2016 Estimated primary completion date: June, 2019 Status: active, but not recruiting Preliminary results reported: no
NCT02330783 BCH-RCC-141201	A Randomized, Open-label, Multi-center Phase II Study to Compare BEV Plus SOR Versus SOR for the Third-line Treatment of Patients With Metastatic Renal Cell Carcinoma Phase (line): II (3^{rd}) Treatment Groups: BEV + SOR vs. SOR Target accrual: 106 Start date: Dec, 2014 Date trial summary last modified: Feb 27, 2016 Estimated primary completion date: Dec 2016 Status: currently recruiting patients Preliminary results reported: no

Protocol ID(s)	Title and details of trial
NCT02398552 BCH-RCC-150212	A Randomized Phase II Trial of SUN Four-weeks On/Two-weeks Off Versus Two-weeks On/One-week Off as First Line Therapy in Metastatic Renal Cell Carcinoma. Phase (line): II (1st) Treatment Groups: SUN schedule 4/2 vs. SUN schedule 2/1 Target accrual: 80 Start date: Mar, 2015 Date trial summary last modified: Feb 27, 2016 Estimated primary completion date: Mar, 2017 Status: currently recruiting patients Preliminary results reported: no
NCT02420821 WO29637, 2014-004684-20	A Phase III, Open-Label, Randomized Study of Atezolizumab in Combination With BEVVersus SUN in Patients With Untreated Advance Renal Cell Carcinoma [IMmotion151] Phase (line): III (1st) Treatment Groups: ATE + BEV vs. SUN Target accrual: 550 Start date: May, 2015 Date trial summary last modified: May 4, 2016 Estimated primary completion date: June, 2019 Status: currently recruiting patients Preliminary results reported: no
AXI=axitinib; ATE=atezolizumab; BEV=bevacizumab; CAB=cabozantinib; CDD=continuous daily dosing; DAL=dalantercept; DOV=dovitinib; EVE=everolimus; IFN=interferon; IPIL=ipelimumab; LEN=lenvatinib; NAp=NAPestafenatox/ANYARA; NIN=nintedanib; NIV=nivolumab; PAZ=pazopanib; PD=progressive disease; SOR=sorafenib; SUN=sunitinib; TEM=temsirolimus; THA=thalidomide; TIV=tivozanib; TKI=tyrosine kinase inhibitor; TRE=trebananib; VEGF=vascular endothelial growth factor	