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ORIGINAL PAPER

Best treatment options for advanced renal cell carcinoma (RCC) patients: a Delphi consensus study

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Abstract

The introduction of targeted therapy for the treatment of advanced renal cell carcinoma (RCC) has improved the outcome of these patients in the last decade. However, many patients still relapse. The aim of this consensus study was to establish common recommendations about the best treatment options in patients with RCC. A two-round Delphi methodology was used. A total of 25 statements were submitted to a panel of 30 specialists. If consensus was not obtained in the first round a second and last round was performed. Agreement was achieved for 19 of the proposed 25 statements (76%). When making a decision about the treatment option, considering the efficiency and response rate to previous treatment, drug's toxicity and the patients' clinical features are very relevant.

Keywords Renal cell carcinoma · Delphi study · Nivolumab · Cabozantinib · Everolimus · TKI · Immunotherapy

Introduction

Kidney cancer accounts for 3.7% of all new cases of cancer, and it is among the 10 most common cancers in both women and men [1]. From all renal tumors, clear-renal cell carcinoma (RCC) is the most common subtype, comprising 85% of all kidney tumors with approximately 116,000 related deaths per year worldwide [2]. Up to 30% of RCC patients are metastatic at diagnosis and around 20% of patients with initially localized disease experience recurrence [3, 4]. When patients are diagnosed early and the tumor is localized, after a partial or radical nephrectomy the 5-year survival rate is about 93%. But when metastatic, the 5-year survival rate drops sharply to 10–20% [4].

Over the last ten to fifteen years, a better understanding of the underlying biology of the tumor has allowed the identification of relevant molecular pathways implicated in RCC. This has led to the development of targeted therapies that have improved the outcome of RCC patients [5]. One of the main oncogenic events is the inactivation of the von Hippel-Lindau (VHL) gene, which results in the aberrant activation of the vascular endothelial growth factor (VEGF) [6]. Also, mTOR is usually upregulated in this disease [7]. And finally there is the special immune microenvironment that is commonly hyperinfiltrated in these patients. The third therapeutic strategy aims to strengthen patient's immune system to target tumor cells [8]. Molecularly directed therapies have replaced the cytokine-based previous strategies. The most used first-line options are the antiangiogenic tyrosine kinase inhibitors (TKIs) sunitinib and pazopanib [9]. The second-line options available have increased in the past recent years giving the clinicians the possibility of further personalizing the treatment based on the patients features. The options available are cabozantinib, nivolumab, axitinib, and the combination of the antiangiogenic TKI lenvatinib and the mTOR inhibitor everolimus [4, 10, 11].

Therefore, the introduction of antiangiogenic and targeted therapies has gradually improved the outcome of advanced RCC [4]. However, despite this improvement, advanced

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RCC continues to be associated with a relatively poor prognosis and the management of advanced RCC remains a clinical challenge [2, 12]. Members of the Spanish Society of Medical Oncology working in the treatment and care of patients with advanced RCC are aware of this difficulty they face in a daily basis, and therefore, they have decided to perform this Delphi survey. The aim of the current work was to conduct a consensus study on medical decisions regarding the best therapeutic options in patients diagnosed with RCC, providing a tool to select the right treatment option for each patient.

Materials and methods

Expert panel selection

A scientific committee consisting of five experts was formed. These experts are oncologist from Instituto Valenciano de Oncología, Clinica Universidad de Navarra, Hospital Universitario 12 de Octubre, Hospital Universitario Clinic de Barcelona, and Vall d'Hebron University Hospital and Institute of Oncology. To create the expert panel, a total of 30 members were selected by the scientific committee considering their experience and knowledge in the field of RCC. These panelists are medical oncologists from different hospitals in Spain. All the participants have at least 10 years of experience in the management of RCC, and they treat at least 15 new patients per year.

Study design

The goal of the Delphi method is to transform individual opinions into an expert group consensus [13]. In this study, a two-round Delphi method was used as the consensus method, following the RAND/UCLA recommendations [14, 15]. The goals of the study and the consensus design were first discussed face-to-face in a brainstorming exercise. After a bibliographic search 25 items were written down for further evaluation. Each statement reflected the current situation regarding treatment options for advanced RCC. Twenty-five statements were agreed on in 4 differentiated areas: second-line treatment options based on efficacy and response to previous treatment (7 items), second-line treatment options based on toxicity (6 items), treatment options based on patient's clinical features (7 items), and future treatment options (5 items).

Afterward the statements were sent to the expert panelists for online evaluation and vote. According to the agreement level, a nine-point ordinal scale was assessed to evaluate each of the items, being 1 full disagreement and 9 full agreement. The responses were organized into three groups: 1–3 were considered as disagreement, 4–6 were considered as neither agreement nor disagreement, and 7–9 were considered as agreement. If a statement did not reach consensus, it was reevaluated in the second and last rounds, rephrasing the statement if needed to avoid ambiguity. Between the two rounds, the panelists were notified with the detailed responses from the first round. Those panelists who did not reply in the first round were not included in the second.

Analytical methodology

Achieving consensus is very important during the Delphi process, even though definitions of consensus vary widely among different studies. In the current study, it was considered that consensus was obtained if the median of the answers was more than 7 and less than 3, if less than a third of the panelists voted out of range and if the interquartile range (IQR) was less than 4.

The results are reflected in Tables 1, 2, 3, and 4, where the median of the responses of the panelists, the IQR, the degree of agreement among the panelists, and the final results are collected. The degree of agreement describes the percentage of panelists who voted within the median range, based on the three categories described in the experimental design: 1–3; 4–6; 7–9.

Results

A total of 30 Spanish medical oncologists with a wide experience in RCC were initially included as panelists to perform the Delphi study. After the first round, 23 (76.7%) panelists voted the statements and therefore they were included in the second round. Finally, 21 (70%) panelists answered the second round.

A total of 25 statements about four well-differentiated topics were evaluated, 7 items regarding second-line treatment options based on efficacy and response to previous treatment, 6 items regarding the best second-line treatment options based on toxicity, 7 items based on the best treatment options depending on patient's clinical features, and 5 items about future treatment options.

In the first round 18 out of 25 statements reached consensus, hence panelists did not agree in 7 items: 2 items related to the first topic, 2 items related to the second topic, and 3 items related to the third topic (Tables 1, 2, 3). The second and last rounds were performed in order to obtain consensus in these 7 statements. After the second round only 1 out of 7 items reached consensus, included in the first topic about the best second-line treatment options based on efficacy and response to previous treatment (Table 1). Therefore, at the end of the study a consensus was obtained for 19 out of 25 statements (76%).

Table 1 Section I results: second-line therapeutic options based on the efficacy and response to previous treatment

Statements	Median (IQR)	Agreement (%)	Final results
1. Nivolumab increases overall survival in patients with advanced RCC previously treated with antiangiogenic drugs and it is considered one of the main therapeutic alternatives to treat these patients	9 (9–9)	100.0	First-round agreement
2. Nivolumab increases overall survival in patients with RCC regardless of the response time to previous treatment with tyrosine kinase inhibitors (TKIs)	9 (8–9)	100.0	First-round agreement
3. Cabozantinib increases overall survival in patients with RCC previously treated with antiangiogenic drugs and it constitutes the other most relevant alternative for the treatment of these patients	9 (9–9)	100.0	First-round agreement
4. Cabozantinib increases overall survival in patients with RCC regardless of the response time to previous treatment with TKIs	8 (8–9)	95.7	First-round agreement
5. The combination of lenvatinib with everolimus increases the overall survival compared to everolimus alone, according to data from a randomized phase II study (vs nivolumab and cabozantinib data from phase III studies). Therefore, the level of evidence of this combination strategy is not comparable to nivolumab or cabozantinib to recommend it in the second line of treatment	7 (6–9)	63.6	No agreement
6. The TKIs axitinib and sorafenib, and the mTOR inhibitor everolimus have not demonstrated to increase overall survival after antiangiogenic therapy; therefore, they are not treatments to be chosen before nivolumab and cabozantinib	8 (7–9)	90.9	Second-round agreement
7. At this time, there is a lack of valid biomarkers to select the most appropriate treatment for each patient. No direct comparisons between PD1 or PDL1 blocking therapy and TKIs that improve overall survival in previously treated RCC patients have been made	9 (9–9)	100.0	First-round agreement

IQR interquartile range

Table 2 Section II results: second-line therapeutic options based on the toxicity

Statements	Median (IQR)	Agreement (%)	Final results
8. In the choice of treatment, it is elementary to consider the toxicity profile of each option	9 (8–9)	100.0	First-round agreement
9. Serious side effects are less frequent in patients treated with nivolumab than in those treated with everolimus or cabozantinib; thus, nivolumab may be the most appropriate option as a second-line treatment in patients with metastatic RCC; especially in patients with prior toxicity to TKI or in patients presenting comorbidities that will determine the continuation with TKIs (previous coronary or thromboembolic events, congestive heart failure)	8 (6–9)	73.9	First-round agreement
10. It is important to be able to reduce the dose of the treatment in order to manage the side effects associated with it	6 (5–7)	40.9	No agreement
11. Treatment with oral TKIs may be more comfortable for the patient than the intravenous administration of the drug	7 (7–9)	87.0	First-round agreement
12. The comfort, knowledge and management of possible side effects associated with TKI treatment comparing to new drugs with immunotherapy could be decisive in the treatment selection by the clinician	6 (4–8)	31.8	No agreement
13. The new treatment options with immunotherapy could present side effects that would suppose the training of the clinician in the handling and use of them	9 (8–9)	95.7	First-round agreement

IQR interquartile range

Discussion

In RCC, the selection of the best therapeutic approach depends on the physician's criteria. Despite the fact that in the recent years immunotherapy and targeted therapy have improved patients' 5-year overall survival the election of the most appropriate treatment remains a challenge [3, 16]. Therefore, it is important to review the best available alternatives and evaluate the grade of agreement the experts committee can reach about them. In order to provide the best treatment options for each patient, the scientific committee created 4 categories to discuss about: (i) second-line therapeutic options based on the efficacy and response to previous treatment; (ii) second-line therapeutic options based on the

Table 3 Section III results: treatment selection based on the clinical features of the patient

Statements	Median (IQR)	Agreement (%)	Final results
14. The medical history or comorbidities of patients with metastatic RCC will determine their treatment selection	8 (7–8)	82.6	First-round agreement
15. Patients with a history of autoimmune disease, active infections (e.g., hepatitis virus or human immunodeficiency virus), organ transplantation, or chronic treatment with corticosteroids are not optimal candidates for nivolumab; thus, cabozantinib may be the best treatment option	9 (8–9)	87.0	First-round agreement
16. In patients with a history of autoimmune disease, active infections (e.g., hepatitis virus or human immunodeficiency virus), organ transplantation, chronic treatment with corticosteroids, and non-candidates for cabozantinib axitinib can be considered the best treatment, although it has not shown benefit in terms of overall survival	8 (7–9)	87.0	First-round agreement
17. In patients with difficult-to-control hypertension, severe prior intolerance to TKI, heart disease, chronic diarrhea, malabsorption, or difficulty in taking oral treatments, nivolumab would be the best treatment option	8 (8–9)	87.0	First-round agreement
18. In patients with difficult-to-control hypertension, severe prior intolerance to TKI, heart disease, chronic diarrhea, malabsorption, or difficulty in taking oral treatments and not candidates to receive nivolumab, everolimus should be considered as the best treatment option	7 (5–8)	59.1	No agreement
19. Age alone is not a factor that allows to select a treatment; however, given the greatest safety profile of nivolumab, this could be a good treatment option in elderly patients	7 (5–8)	54.5	No agreement
20. Patients with liver and/or bone disease appear to benefit more from cabozantinib than from nivolumab; hence, in patients with these characteristics, cabozantinib should be considered	7 (6–8)	63.6	No agreement

IQR interquartile range

Table 4 Section VI results: future treatment directions (líneas futuras de tratamiento)

Statements	Median (IQR)	Agreement (%)	Final results
21. Based on the results of the CHECKMATE-214 study, the combination treatment with nivolumab and ipilimumab is a new first-line treatment option of RCC patients	9 (8–9)	100.0	First-round agreement
22. According to the results of the CHECKMATE-214 study, the combination of nivolumab and ipilimumab appears to be the treatment of choice in patients with PDL-1 + tumors with intermediate and high-risk category tumors, although the results of the overall survival analysis (HR 0.73) show a presumable benefit in the PDL-1 negative group (a longer follow-up is pending to reach the necessary events)	8 (7–9)	91.3	First-round agreement
23. The results of further first-line studies can make the combination of immunotherapy and antiangiogenic agents, the treatment of choice	9 (7–9)	87.0	First-round agreement
24. Based on data from the CHECKMATE-214 study and if different first-line studies with immunotherapy, with or without antiangiogenic agents, are positive, we could consider TKIs as second-line treatment	8 (7–9)	82.6	First-round agreement
25. Performing biopsies after tumor progression would permit to study the appearance of novel resistance mechanisms	9 (7–9)	91.3	First-round agreement

IQR interquartile range

toxicity of the drug; (iii) therapeutic options based on the patient's clinical features; and (iv) future treatment options.

Second-line therapeutic options depending on the effectiveness and response to previous treatment

Regarding this Sect. 100% of the panelists agreed on that nivolumab increases overall survival in patients with advanced RCC previously treated with antiangiogenic drugs, being considered one of the best alternatives to treat these patients. Furthermore, the highest overall survival in patients with nivolumab treatment was maintained regardless of the duration of the first-line therapy [11, 17]. Hence, the benefit in overall survival is not dependent on duration of response to the previous treatment with TKIs. Nivolumab is a human IgG4 monoclonal antibody that acts like a Programmed death-1 (PD-1) immune checkpoint inhibitor [16].

PD-1 receptor, expressed on activated T-cells, binds to the ligands PD-L1 and PD-L2 inhibiting T-cell activation and suppressing the antitumor immune response [16, 18]. PD-L1 is upregulated in different tumors, including RCC where its expression is associated with a poor prognosis [16, 19]. Motzer et al. performed a randomized phase III study including 821 patients with advanced RCC, previously treated with one or two regimens of antiangiogenic therapy, where they compared nivolumab with everolimus, an oral protein kinase inhibitor of mTOR approved by the FDA and the EMA for the treatment of different tumors, including advanced RCC [11, 20]. Indeed nivolumab entailed a 5.4-month benefit in overall survival (25.0 months vs 19.6 months, $p=0.002$) and an increase in the response rate (25% vs 5%, $p<0.001$) even though these results were found to be independent of the PD-L1 expression [11].

The panelists also agreed on that cabozantinib increases overall survival in patients with advanced RCC previously treated with antiangiogenic drugs (100%), independently of the time of response to the previous TKI therapy (95.7%). Cabozantinib is a small-molecule TKI targeting VEGFR along with MET and AXL [21]. A phase III trial performed by Choueri et al. compared the use of cabozantinib and the use of everolimus in 658 patients diagnosed with advanced RCC and previously treated with antiangiogenic therapy [22]. Cabozantinib produced an increase in the median event-free survival (7.4 months vs 3.8 months) and in the objective response rate compared to everolimus (21% vs 5%, $p<0.001$). The final analysis confirmed that cabozantinib increases overall survival compared to everolimus in a statistically significant manner (21.4 months vs 16.5 months, $p=0.00026$) [10].

In 2015 Motzer et al. published the data of a randomized phase II study where everolimus, lenvatinib, and the combination of everolimus and lenvatinib were compared [23]. Lenvatinib is an oral TKI that targets VEGFR1-3 together with FGFR, PDGFRα, RET, and KIT [23]. The study included 153 patients diagnosed with advanced or metastatic RCC previously treated with antiangiogenic therapy. The objective response rate for the combination of everolimus and lenvatinib was 43% compared to 6% for everolimus alone ($p<0.001$) and 27% for lenvatinib alone ($p=0.0067$). The median event-free survival was 14.6 months in the patients treated with the combination therapy compared to 5.5 months when using everolimus alone ($p=0.005$) or to 7.4 when using lenvatinib alone (not statistically significant). The median overall survival was 25.5 months when using the combination of everolimus and lenvatinib, 15.4% when treating with everolimus as a single agent ($p=0.024$) and 19.1% when treating with lenvatinib as a single agent (not statistically significant) [23]. In 2016 Motzer and collaborators updated the data of this study performing an independent radiologic review [24]. Regarding the objective responses, these were achieved by 35% of the patients treated with the combination of lenvatinib and everolimus [95% CI 22–50] and by 39% of the patients treated with lenvatinib alone [95% CI 25–53; $p<0{\cdot}0001$]). None of the patients treated with everolimus alone achieved the objective responses [95% CI 0–7; $p<0{\cdot}0001$] [24]. When updated, the median progression-free survival in the group treated with the combination of lenvatinib and everolimus was 12·8 months (95% CI 7·4–17·5) compared to 5·6 months (3·6–9·3) when treating with everolimus, and 9·0 months (5·6–10·2) when using lenvatinib [24]. Despite the promising results, this is a phase II study, whereas the results for nivolumab and cabozantinib were originated from phase III clinical studies. However, the panelists did not agree on the related statement and consensus was not reached after two rounds. The TKIs axitinib and sorafenib and the mTOR inhibitor everolimus have not demonstrated to improve overall survival after previous antiangiogenic therapy. Therefore, unless tolerance issues appear, nivolumab or cabozantinib has been proposed to be the preferred treatment options [25–29].

Finally, there is a lack of direct comparisons between the PD-1 immune checkpoint inhibitors and the oral TKIs that increase overall survival in previously treated RCC patients. Currently there are no valid biomarkers available to select the most appropriate treatment for each patient. Therefore, it would be recommended that the decisions to select the appropriate second-line therapeutic option should be guided by the toxicity of the drug and the clinical characteristics of the patients.

Second-line therapeutic options depending on the toxicity of the drug

In order to decide the second-line therapeutic strategy of patients with metastatic RCC, the expert panelists agreed on the importance of considering the toxicity and the associated side effects of the drug when making a decision about the drug to use in each case (100%). Also, the distinct administration procedures of the drugs could be a decisive factor for the clinician to decide the treatment option considering the age of the patient, the distance between home and the hospital, different comorbidities, etc. Thus, 87% of the panelists agreed on the consideration that the oral treatment is more comfortable for the patient than intravenous administration of the drug. Nevertheless, the development of new schedules, in which nivolumab is administered every four weeks, may improve the convenience of the administration of this drug [30].

Nivolumab and cabozantinib show different toxicity profiles [10, 11], which should be taken in consideration for treatment selection. This is especially relevant in patients with prior toxicity to TKI or in patients presenting comorbidities that will determine the continuation with

TKIs (previous coronary or thromboembolic events, congestive heart failure). Consensus about this statement was obtained with the agreement of 73.9% of the panelists. In the METEOR study, there was a need to reduce the dose of cabozantinib in 62% of the patients [10, 22]. Immunotherapy does not allow dose reductions, whereas this is possible with TKI therapy. Therefore, if a side effect appears during immunotherapy the suspension of the treatment would be mandatory, at least until the problem is solved. This could lead clinicians to consider the importance of being able to reduce the doses of the treatment to help manage the side effects associated with it. However, less than 41% of the panelists agreed on this statement and consensus was not reached after two rounds. Related to this, almost 96% of the experts agreed on that immunotherapy could present side effects making necessary the training of the clinician in the handling and use of them. The comfort and knowledge in the management of possible side effects associated with TKI treatment could be decisive to prioritize them to the immunotherapy; however, an agreement was not reached regarding this item (31.8%).

Therapeutic options depending on the patient's clinical characteristics

The medical history or comorbidities of patients with metastatic RCC will determine their treatment selection (agreement achieved by 100% of the panelists). Occasionally patients present comorbidities such as heart problems, hypertension, the need for anticoagulant treatment, or a deteriorated general condition (EGOG 2). In these cases, immunotherapy offers a better risk/benefit profile than oral TKIs. In the randomized phase III trial of nivolumab versus everolimus, less than 6% of the patients treated with nivolumab had an ECOG > 1 or a Karnofsky performance-status score of less than 80%, both characteristics that measure the decay state of the patient [11]. The study analyzing the effectiveness of cabozantinib did not include patients with ECOG 2, all the patients had ECOG 0–1 (a Karnofsky performance-status score between 80–100%) [10]. In patients with ECOG 0–1 both nivolumab and cabozantinib demonstrated a clear benefit in survival. Since patients with ECOG 2 were not represented in the METEOR study, nivolumab could be considered an adequate option for them. Patients with hepatitis virus or human immunodeficiency virus were excluded from the clinical study with nivolumab, nevertheless clinical practice has demonstrated its safety in this population. Patients with a history of autoimmune disease, active infections, organ transplantation, or chronic treatment with corticosteroids are not optimal candidates for nivolumab, and thus, cabozantinib could be the preferred option. If these patients are non-candidates for cabozantinib (e.g., ECOG2 patients), axitinib could be considered an alternative, even though there is no evidence of increased overall survival. Severe prior intolerance to TKI, patient intolerance to oral medication and/or the presence of gastrointestinal symptoms such as nausea or vomiting could favor the use of nivolumab. Also, certain patient comorbidities like poorly controlled cardiovascular disease could determine the use of nivolumab as the first option, e.g., uncontrolled hypertension. If patients with these characteristic are not candidates for nivolumab, everolimus was proposed as a suitable alternative. However, panelists did not agree on this issue, and therefore consensus was not achieved regarding the best treatment option for these cases (59.1%).

In the CheckMate 025 phase III randomized trial analyzing nivolumab versus everolimus in patients with advanced RCC the age cutoff line was 65 years [11, 17]. Median overall survival for patients < 65 years was 26.7 months with nivolumab and 19.9 months with everolimus. In patients ≥ 65 years median overall survival was 23.6 months with nivolumab and 18.5 months with everolimus [17]. When classifying in three age groups, < 65 years; ≥ 65 to < 75 years; and ≥ 75 years, a survival benefit was observed in the first two groups when treating with nivolumab. However, in patients older than 75 years nivolumab did not show any survival benefit [11]. In the METEOR study, comparing the use of cabozantinib and everolimus in patients with advanced RCC, the age cutoff was again 65 years and both groups of patients presented benefit in terms of overall survival and event-free survival [10, 22]. More clinical information is needed in patients > 75 years of age treated with both therapies. Similarly, there is no data that favors the use of other treatment options (e.g., everolimus or axitinib) based on the age of the patient. Accordingly, age alone is not a factor that allows selecting a treatment, but, given the greatest safety profile of nivolumab, the preferred use of nivolumab in elderly patients has been proposed as a statement to be voted in this Delphi study. Panelists did not agree in this statement (54.5%), and therefore, the choice of the best therapeutic option in elderly patients remains depending on the physician's criteria, who would take into consideration all the patient's features to select the most appropriate therapeutic option.

In the METEOR trial, 23% of the patients treated with cabozantinib presented bone metastases, 27% presented liver metastases, 62% presented lung metastases, 62% presented lymph node metastases, and < 1% brain metastases [10]. In the CheckMate 025 study, the number of bone and liver metastases was smaller. Of the patients treated with nivolumab 19% presented bone metastases, 24% presented liver metastases and 68% presented lung metastases [11, 17]. Subgroup analysis in both studies showed benefit in overall survival for all patients when treated with nivolumab or cabozantinib, as compared to everolimus. However, in patients with visceral and/or bone metastases, the overall

survival benefit appeared to be higher with cabozantinib than with nivolumab. Even though apparently patients with liver and/or bone disease would benefit more from cabozantinib than from nivolumab a direct comparison of both drugs as second-line therapy is missing. Also, since all patients showed benefit from both treatments, the subgroup analyses are only hypothesis-generating and panelists did not achieve agreement on this issue (63.6%).

Future treatment options

A total of 5 statements were written down in this section and the panelists achieved consensus in all 5 of them in the first round. The recent CHECKMATE-214 phase III study has demonstrated that the combination of nivolumab and ipilimumab in patients with previously untreated intermediate and poor prognosis advanced RCC improves clinical outcome when compared to sunitinib, the current standard drug reference [31]. Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody. It blocks the CTLA-4, a negative T-cell regulator, and thus, it increases the immune response to tumor cells [32]. Based on these results, the combination treatment with nivolumab and ipilimumab should be a new first-line treatment option of advanced RCC patients with intermediate and poor prognosis and 100% of the panelists agreed on this statement. According to the results of the CHECKMATE-214 study, the combination of nivolumab and ipilimumab appears to be the treatment of choice in patients with PDL-1 + tumors with intermediate and high-risk category tumors. Moreover, the results of the overall survival analysis (HR 0.73) also show a presumable benefit in the PDL-1 negative group [31]. Probably there will be a need to consider additional combination therapies. The results of further first-line phase III studies can make the combination of immunotherapy and antiangiogenic agents the treatment of choice. Based on data from the CHECKMATE-214 study and if different first-line studies with immunotherapy, with or without antiangiogenic agents, are positive, TKIs could be considered as second-line treatment. Yet, a recent phase II study showed that cabozantinib was superior to sunitinib as first-line treatment of advanced RCC [33].

Conclusions

In summary, the results of this Delphi survey about the treatment of RCC seek an agreement on the available first and second line therapeutic protocols. This study has analyzed the different options based on the efficiency and response rate to previous treatment, the toxicity of the drug and the clinical characteristics of the patients. There are new studies with promising results, and the approval of new therapies is to be expected. To establish general criteria that allow the selection of the right drug to the right patient at the right time obtaining a biopsy of each tumor progression will be necessary to further investigate the underlying biology of the tumor at each stage.

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Compliance with ethical standards

Conflict of interest Authors declare no conflicts of interest regarding this study.

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