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Original Research

Current status of adjuvant immunotherapy and relapse management in renal cell carcinoma: Insights from a European delphi study

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ABSTRACT

Introduction: Adjuvant immunotherapy has remarkably advanced the management of localized renal cell carcinoma (RCC) in patients at high risk of post-surgery recurrence. This Delphi study aimed to establish expert consensus on its use and subsequent management of relapse.
Methods: Fifteen RCC experts participated in a two-round Delphi process between July and November 2024. The study included 43 core survey items, divided into 67 components for comprehensive evaluation.
Results: Consensus, defined as ≥ 75 % agreement, was achieved for 39 of 67 items (58.2 %). Experts agreed on using the Leibovich score for selecting patients for adjuvant pembrolizumab (79 %), initiating therapy within 90 days post-surgery (86 %), and not restricting treatment to programmed death ligand-1 (PD-L1)-positive tumors (100 %). Plasma kidney injury molecule-1 (KIM-1) was considered by the experts as a potential useful recurrence risk biomarker (93 %). Immune checkpoint inhibitor (ICI)-refractory disease was defined as relapse within 6 months post-adjuvant therapy (80 %). Focal therapies for oligometastatic recurrence (80 %), and targeted therapies or clinical trial enrollment for ICI-refractory patients (87 %) were supported. Belzutifan was recommended for fourth-line or later use after ICI therapy and multiple tyrosine kinase inhibitors (93 %). By contrast, no consensus was reached on ICI salvage therapy in specific subgroups, including patients with clear-cell RCC (60 %), without bone/brain metastases (60 %), good performance status (60 %), low tumor burden (47 %), or papillary RCC (36 %).
Conclusions: This Delphi study provides insights into the evolving role of adjuvant immunotherapy in localized RCC and relapse management. A multidisciplinary approach and periodic review are essential to optimizing treatment strategies.

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1. Introduction

Adjuvant immunotherapy has recently transformed the management of localized renal cell carcinoma (RCC), for patients at high risk of recurrence after surgery [1,2]. Pembrolizumab, an immune checkpoint inhibitor (ICI) used as adjuvant therapy, aims to reduce the risk of local and distant recurrence by targeting minimal residual disease that may persist after nephrectomy or metastasectomy, rendering the patient with no evidence of disease (NED) status [3]. The KEYNOTE-564 trial was the first phase III study to demonstrate the benefits of adjuvant pembrolizumab in patients with resected clear-cell RCC and an intermediate-high or high risk of recurrence, as well as those with stage M1 resected to no NED within 12 months [1]. After a median follow-up of 57.2 months, pembrolizumab was associated with significantly improved disease-free survival (DFS) (hazard ratio [HR], 0.72; 95 % confidence interval [CI], 0.59–0.87) and improved overall survival (OS) (HR, 0.62; 95 % CI, 0.44–0.87) compared to placebo [1].

However, results from other phase III trials, including IMmotion010 [4], Checkmate 914 [5], and PROSPER [6], have failed to demonstrate improvements in DFS, highlighting the importance of individualized evaluation when considering adjuvant therapy. A meta-analysis of KEYNOTE-564 [1], IMmotion010 [4], Checkmate 914 [5], and PROSPER [6] revealed that DFS benefits were most pronounced in patients with programmed death ligand-1 (PD-L1)-positive tumors as well as in patients with sarcomatoid features [7]. Relapse risk assessment, through several published prognostic and risk stratification models such as the Leibovich scoring system or the 16-gene recurrence score, is also important for identifying patients who are at risk of recurrence and may benefit from adjuvant immunotherapy [8,9].

Approximately 40 % of patients will experience relapse within 5 years, despite receiving adjuvant pembrolizumab [10]. For the first-line treatment of metastatic clear-cell RCC, combination regimens involving ICIs and tyrosine kinase inhibitors (TKIs) are recommended. Among these, lenvatinib plus pembrolizumab, axitinib plus pembrolizumab, and cabozantinib plus nivolumab are approved across all International Metastatic RCC Database Consortium (IMDC) risk groups [2]. Additionally, ipilimumab plus nivolumab is recommended for the first-line treatment of IMDC intermediate- and poor-risk disease, and although not approved in Europe, it may be considered for favorable-risk disease [2]. In patients who experience disease progression on first-line therapy with a TKI plus an ICI or dual ICI therapy, treatment options in this setting include previously unused TKIs such as cabozantinib, lenvatinib plus everolimus, and the hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor belzutifan [2,11].

In a previous Delphi study, we reported consensus among experts on the definition, diagnosis, and first-line treatments for metastatic RCC [12]. The current Delphi study seeks to address the clinical uncertainties surrounding the use of adjuvant immunotherapy in localized RCC and the subsequent treatment of relapse. By gathering insights from experts across Europe, this study aims to establish a consensus on the criteria for selecting patients most likely to benefit from adjuvant immunotherapy after surgery and to explore the most appropriate treatment options for RCC that progresses to the metastatic stage despite adjuvant treatment.

2. Methods

This modified Delphi study was designed to gather consensus from a panel of 15 experts from across Europe, all with extensive experience in the management of RCC. To enhance the generalizability of the findings, experts were purposively selected to ensure diversity in geographic representation (including Western, Central, and Southern Europe) and professional background (medical oncology, surgical oncology, and urology). Expert panel members were chosen for their scholarly achievements and their contributions to pivotal clinical trials and the development of European clinical guidelines.

A steering committee (A.B., L.A., B.E., V.G.) oversaw the Delphi process, which included the establishment of the Delphi survey, the analysis of results, and the coordination of two consensus-building Delphi rounds. The Delphi survey was conducted in two iterative rounds between July and November 2024. Since this study involved a clinical vignette-based survey of expert opinions, no ethical approval was necessary.

2.1. Delphi survey content

Based on published evidence and practical experience, the steering committee developed a 43-item Delphi online survey structured into three main sections. 1 included a total of 22 items and focused on adjuvant immunotherapy in the treatment of localized RCC. Specifically, this section addressed patient selection criteria, encompassing 12 items centered on the use of adjuvant pembrolizumab therapy based on factors such as pathological staging, biomarkers, gene signatures, and recurrence risk assessment. Additionally, 10 items covered the management of patients who experience relapse post-adjuvant therapy, particularly focusing on ICI-refractory disease and the use of ipilimumab plus nivolumab combination therapy. 2, consisting of 10 items, focused on optimizing first-line treatment strategies for patients with favorable-risk localized RCC, exploring monotherapy versus combination approaches. 3 included 11 items and addressed subsequent treatment following disease progression after first-line therapy with a TKI plus ICI or dual ICI therapy.

2.2. Consensus building and voting process

Each expert was asked to indicate whether they "Agree" or "Disagree" with each survey item. In cases of uncertainty, the experts were instructed to choose the response they believed was more likely based on their clinical judgment. They were asked to assume that all therapeutic options for RCC were accessible at their clinical institutions.

Consensus on any given item was defined as ≥ 75 % agreement among the expert panel members, as previously reported [12]. Results from the first round were summarized, and only items with a consensus level between > 60 % and < 75 % were rephrased in the second round, based on discussions during a face-to-face meeting that brought together the expert panel to analyze first-round results. During this meeting, the steering committee presented anonymized group-level feedback, including summary statistics from the first round, as well as key points raised by the panelists in free-text comments. This allowed for a structured discussion of areas of disagreement, and informed the rewording and refinement of select survey items for the second round. Items reaching a consensus ≥ 75 % or non-consensus ≤ 60 % in the first round were considered final and were not readdressed in the second Delphi round.

3. Results

A total of 15 expert panel members participated in the first Delphi round. Of these, 14 participated in the second round. The results of this Delphi study are presented in Supplementary Table 1, Supplementary Table 2, Supplementary Table 3, and Supplementary Table 4. The Delphi study included 43 core survey items, fragmented into 67 distinct components. Consensus, defined as ≥ 75 % agreement, was achieved for 39 of 67 total items (58.2 %). Table 1 and Table 2 summarize the Delphi study outcomes where consensus was reached, while (Figs. 1–4) present items where consensus was not achieved (<75 % agreement).

3.1. Patient selection for adjuvant pembrolizumab therapy

The Delphi panel achieved consensus on 13 of 18 items (72.2 %) regarding patient selection for adjuvant immunotherapy in localized RCC (Supplementary Table 1). Patients with pathological (p)T3 N0 M0 grade 1 clear-cell RCC and a Leibovich score of 4 should not receive

Table 1
Summary of the delphi study outcomes on adjuvant immunotherapy in the treatment of localized renal cell carcinoma (RCC).

Clinical situation	Consensus
Patient selection for adjuvant pembrolizumab therapy	
Patients with pathological (p)T3 N0 M0 grade 1 clear-cell RCC, < 10 cm in size, no necrosis at pathology, and a Leibovich score of 4, indicating intermediate-high risk	Should not be offered adjuvant therapy
Leibovich score or similar risk scores in patients with pT3 grade 1 tumors	Should be used to assess the risk level before deciding on adjuvant pembrolizumab therapy
Patients who develop recurrence within 1 year after curative-intent surgery	Should undergo an interval CT scan before deciding on further treatments (e.g., metastasectomy and adjuvant pembrolizumab)
Patients with clear-cell RCC who undergo complete resection of a singular bone metastasis and achieve NED	Should be considered for adjuvant pembrolizumab therapy
Patients eligible for adjuvant pembrolizumab therapy	Should adhere to the KEYNOTE−564 trial protocol, i.e., treatment within 90 days of surgery
Prioritize patients with molecular subsets associated with immunotherapy response (clusters 4–6 in IMmotion151 analysis or ccrcc−4 profile) for adjuvant therapy with pembrolizumab	There is insufficient evidence
Plasma KIM−1 to identify patients at increased risk of recurrence who may benefit from adjuvant pembrolizumab therapy	Should be investigated
Adjuvant pembrolizumab therapy	Should not be restricted to patients with a PD-L1 combined positive score ≥ 1
Management of relapse post-adjuvant therapy	
Patients who relapse during or within 6 months of completing adjuvant ICI therapy	Are considered ICI-refractory
Focal therapies with curative intent for patients previously treated with adjuvant ICI therapy and have an oligometastatic recurrence	Should always be considered
Patients with ICI-refractory disease	Should receive targeted therapy without an ICI component; Or be considered for clinical trial inclusion
Patients who experience recurrence more than 12 months after completing adjuvant ICI treatment and are not candidates for focal therapy	Should receive standard-of-care first-line therapy
Ipilimumab combined to nivolumab in patients with sarcomatoid RCC or asymptomatic clear-cell RCC	May be considered after recurrence following adjuvant pembrolizumab
Patients with uncertain radiologic findings suggesting recurrence	Should not receive immediate systemic treatment
In asymptomatic patients with oligometastatic disease	Active surveillance may be offered

Consensus was reached with an agreement of ≥ 75 % among experts. Abbreviations: CT, computed tomography; ICI, immune checkpoint inhibitor; KIM-1, kidney injury molecule-1; NED, no evidence of disease; PD-L1, programmed death-ligand 1.

adjuvant therapy (86 % agreement). Consensus was reached (79 %) on using the Leibovich score to guide selection for adjuvant pembrolizumab therapy in this subgroup. Consensus was also reached (93 %) on offering interval imaging prior to adjuvant therapy in patients rendered NED within 12 months post-surgery. Adjuvant pembrolizumab therapy was recommended after resection of singular bone metastases (86 %), but consensus was not reached for those treated with stereotactic ablative radiotherapy (SABR) (71 % agreement). The panel agreed (86 %) that the initiation of adjuvant pembrolizumab should follow the timeline established in KEYNOTE-564 [1], i.e., ≤ 12 weeks of surgery.

Regarding molecular biomarkers, the panel strongly agreed (93 %) that angiogenesis-related molecular subsets (e.g., IMmotion151 clusters 1/2) should not exclude patients from adjuvant pembrolizumab. There was also unanimous agreement (100 %) that current evidence does not justify prioritization based on immunotherapy-associated molecular profiles. Plasma kidney injury molecule-1 (KIM-1) was identified as a potential recurrence biomarker (93 %), while the use of the 16-gene recurrence score did not achieve consensus (53 % agreement). Restricting adjuvant pembrolizumab therapy to patients with PD-L1 combined positive score (CPS) ≥ 1 was unanimously rejected (100 %). Pembrolizumab was not supported for papillary RCC (79 %), and recommendations to offer pembrolizumab to patients with other non-clear-cell subtypes, such as unclassified or chromophobe RCC, received low agreement, ranging from 7 % to 40 %.

Table 2
Summary of the delphi study outcomes on the treatment of localized renal cell carcinoma (RCC) when it progresses to the metastatic stage.

Clinical situation	Consensus
Optimizing first-line therapeutic strategies for favorable-risk patients	
Patients with favorable-risk disease presenting with pancreatic metastases	Good candidates for surveillance
Patients with favorable-risk disease presenting with low tumor burden	Can be considered for surveillance
Patients with favorable-risk disease	ICI and TKI combination therapy is currently the standard of care
Patients with favorable-risk disease	Combination of an ICI with a well-tolerated TKI is the preferred treatment option compared to other combination therapies
Patients with favorable-risk disease	The choice of treatment is influenced by the presence of symptoms
Patients with favorable-risk and asymptomatic disease	TKI monotherapy is a valid treatment option for some
Favorable-risk patients with sarcomatoid features	The combination nivolumab + ipilimumab is a reasonable treatment choice
Subsequent treatment following disease progression after first-line TKI+ ICI or dual ICI therapy	
Patients with disease progression following first-line VEGFR TKI + ICI therapy	Disease-related symptoms and performance status impact the choice of the next VEGFR TKI
After disease progression on first-line dual ICI therapy	Any available VEGFR TKI can be used as the next treatment
Patients who discontinued first-line VEGFR TKI + ICI therapy due to grade 3 immune-mediated toxicity and later experienced disease progression with no residual toxicity	Resuming the same VEGFR TKI alone is appropriate
After ICI + TKI combined therapy and for fourth-line use after ICI and VEGFR TKI therapies	Belzutifan is considered for second-line treatment
Patients treated with first-line dual ICI therapy who achieved response in all metastatic sites and later developed isolated brain progression	Brain-only progression is typically managed with local therapy (radiotherapy or surgery) without changing systemic treatment
Patients who progressed on four prior lines, including ICI therapy	Rechallenging with a previously used VEGFR TKI may be considered if the patient responded to it earlier and remains fit for therapy
Metastatic papillary RCC treated with TKI + ICI combination therapy	The next regimen of choice is typically a single-agent VEGFR TKI not used in the front-line setting

Consensus was reached with an agreement of ≥ 75 % among experts. Abbreviations: ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

3.2. Management of relapse Post-Adjuvant therapy

Consensus was reached on 10 of 21 items (47.6 %) regarding relapse management post-adjuvant ICI therapy (Supplementary Table 2). ICI-refractory relapse was defined as occurring during or within 6 months of therapy (80 % agreement). Focal therapies for oligometastatic recurrence were strongly supported (80 %), as were targeted therapies or clinical trial enrollment for ICI-refractory patients (87 %). Standard-of-care first-line therapy was unanimously recommended (100 %) for

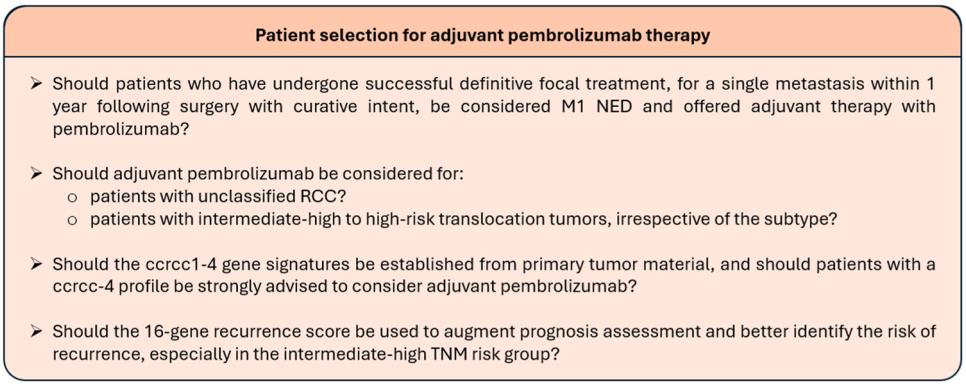

Fig. 1. Questions arising from areas of non-consensus on patient selection for adjuvant pembrolizumab therapy. Abbreviations: NED, no evidence of disease; RCC, renal cell carcinoma; TNM, tumor–node–metastasis.

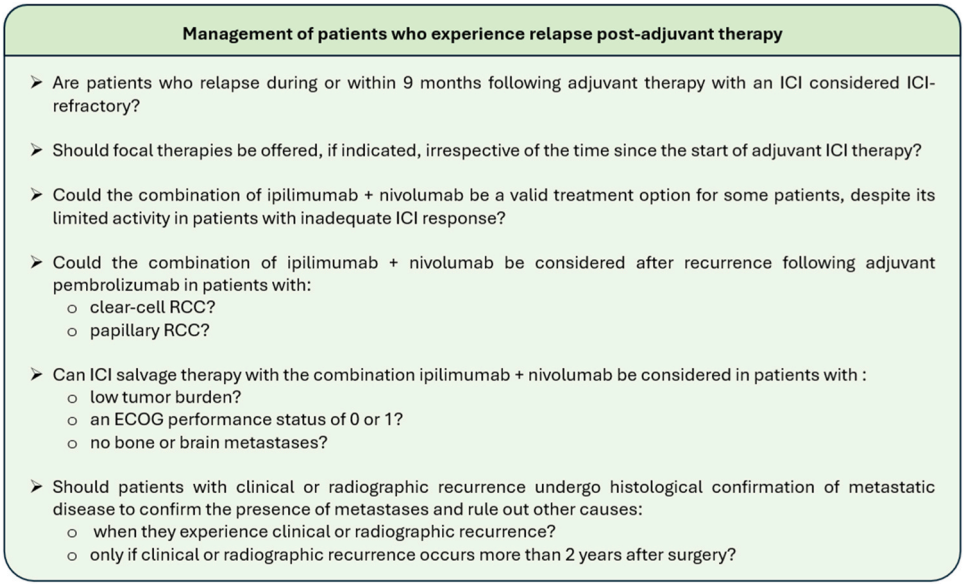

Fig. 2. Questions arising from non-consensus areas on management of relapse after adjuvant therapy. Abbreviations: ECOG, eastern cooperative oncology group; ICI, immune checkpoint inhibitor; RCC, renal cell carcinoma.

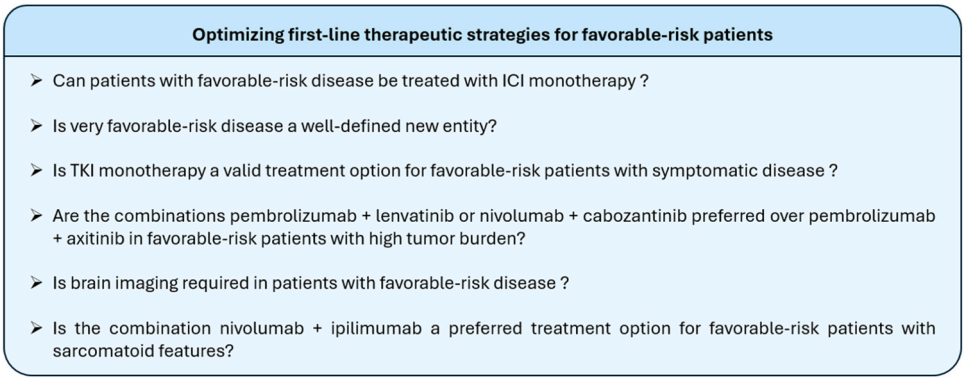

Fig. 3. Questions arising from non-consensus areas on optimizing first-line therapeutic strategies for favorable-risk patients. Abbreviations: ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

recurrence occurring more than 12 months post-adjuvant therapy, and active surveillance was endorsed for asymptomatic oligometastatic disease (100 %). Experts also agreed (79 %) that immediate systemic treatment should not be initiated for uncertain radiologic findings. No consensus was reached on histological confirmation of metastatic disease (29 %–53 % agreement) or ICI salvage therapy in specific subgroups, including patients with clear-cell RCC (60 %), no bone/brain metastases (60 %), good performance status (60 %), low tumor burden (47 %), or papillary RCC (36 %). However, 87 % agreed that ipilimumab plus nivolumab could be considered for sarcomatoid RCC following recurrence after adjuvant pembrolizumab.

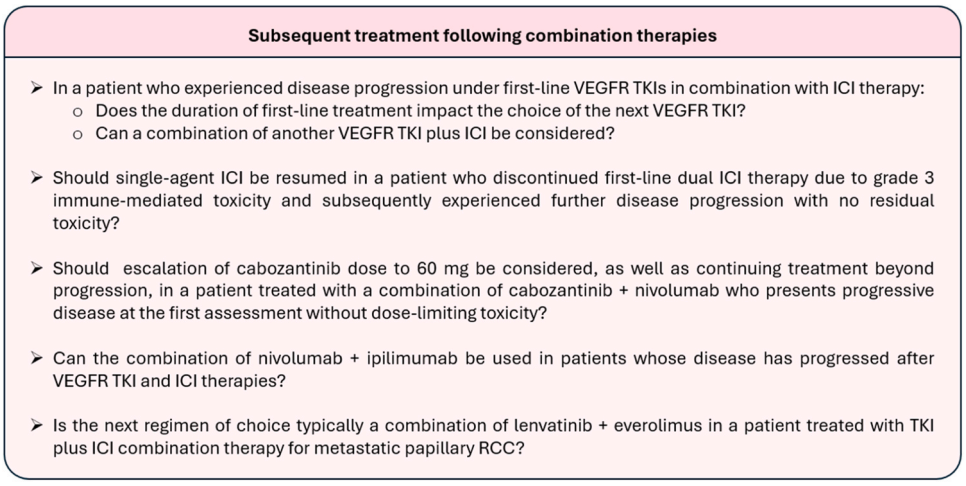

Fig. 4. Questions arising from non-consensus areas on subsequent treatment following combination therapies. Abbreviations: ICI, immune checkpoint inhibitor; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

3.3. First-Line optimization for Favorable-Risk patients

Consensus was reached on 7 of 13 items (53.8 %) related to first-line therapeutic strategies for favorable-risk RCC (Supplementary Table 3). Surveillance was strongly supported for patients with low tumor burden (100 %) or pancreatic metastases (93 %). ICI and TKI combination therapy was confirmed as the standard of care (93 %), with the combination of a well-tolerated TKI and an ICI preferred over other regimens (93 %). Symptom presence influenced treatment choice (86 %), and TKI monotherapy was supported for asymptomatic patients (86 %). Nivolumab–ipilimumab was considered reasonable for sarcomatoid features (87 %). Uncertainties remained around ICI monotherapy (29 % agreement), TKI monotherapy for symptomatic patients (40 %), routine brain imaging (60 %), and the definition of "very favorable-risk disease" (40 %).

3.4. Subsequent treatment following combination therapies

The Delphi panel achieved consensus on 9 of 15 items (60 %) regarding treatment following combination therapies for metastatic RCC (Supplementary Table 4). TKI choice should be guided by symptoms and performance status after progression on first-line TKI plus ICI therapy (87 %). Any available TKI was recommended after dual ICI progression (87 %). Resuming the same TKI alone was also endorsed for patients who discontinued first-line TKI plus ICI therapy due to toxicity but later progressed without residual toxicity (87 %). Belzutifan was supported for second-line use after ICI plus TKI therapy (79 %), and also recommended for fourth-line or later use (93 %). For brain-only progression under dual ICI therapy, radiotherapy or surgery to the brain without systemic therapy change was recommended (87 %). Additionally, rechallenging with a prior TKI was supported after four prior lines if previously effective (93 %). For metastatic papillary RCC, a new single-agent TKI was preferred after prior ICI–TKI therapy (80 %).

4. Discussion

The findings of this Delphi study provide valuable insights into the evolving role of adjuvant immunotherapy in localized RCC and the subsequent management of relapse. Following two consecutive Delphi rounds, consensus was achieved for 39 of a total of 67 survey items (58.2 %), reflecting that regular expert meetings can optimize the clinical management approach of patients with RCC.

Notably, consensus (79 %) was reached on using the Leibovich score to guide patient selection for adjuvant pembrolizumab therapy, particularly in patients with pT3 grade 1 clear-cell RCC. Indeed, a recent national Danish cohort study further supported this approach, identifying a high Leibovich score as a recurrence risk factor [13]. However, the KEYNOTE-564 trial [1], which established pembrolizumab as an adjuvant treatment option for patients with clear-cell RCC at increased risk for recurrence after surgery, included pT3 any grade clear-cell RCC and did not incorporate the Leibovich score in its design, while the RAMPART (NCT03288532) [14] and SORCE [15] studies did. Thus, individualized shared decision-making remains paramount in selecting patients who are eligible by TNM for adjuvant therapy with pembrolizumab. This decision should balance potential survival benefits against the risks of immune-related adverse events and the possibility of overtreatment [16,17].

Panelists agreed (93 %) that additional biomarkers, such as post-nephrectomy plasma KIM-1, should be investigated to identify patients with minimal residual disease who may derive the greatest benefit from adjuvant pembrolizumab therapy. Post-hoc analyses from phase III trials such as ASSURE [18], CheckMate 914 [19], and IMmotion010 [20] indicate that elevated plasma KIM-1 levels post-nephrectomy are linked to worse DFS and OS among patients with localized RCC. However, KIM-1 has not been prospectively validated for patient stratification in adjuvant pembrolizumab therapy. Circulating KIM-1 may serve as a non-invasive marker of minimal residual disease and disease recurrence, and has been associated with improved clinical outcomes with atezolizumab versus placebo in adjuvant RCC, though its predictive value for pembrolizumab remains uncertain and requires further validation [20]. Likewise, the ccrcc1–4 gene signatures, IMmotion151 gene clusters, and the 16-gene recurrence score lack prospective validation for adjuvant pembrolizumab. Consequently, 100 % of panelists agreed that there is insufficient evidence to prioritize patients with molecular subsets, such as IMmotion151 clusters 4–6 or the ccrcc-4 profile, for adjuvant pembrolizumab therapy.

In KEYNOTE-564, survival benefits were observed in both patients with a PD-L1 CPS ≥ 1 and < 1 [1]. Accordingly, the panel unanimously disagreed (100 %) with the notion of limiting adjuvant pembrolizumab to patients with a PD-L1 CPS ≥ 1. The panel also expressed caution regarding the use of pembrolizumab in non-clear-cell RCC subtypes, such as papillary RCC, unclassified RCC, or chromophobe RCC. Recommendations to extend adjuvant pembrolizumab to these populations received low agreement, ranging from 7 % to 40 %, with 79 % disagreement for papillary RCC. The absence of clinical data for these subtypes underscores the importance of enrolling patients in randomized controlled trials, such as RAMPART (NCT03288532) [14], to better understand the efficacy and safety of adjuvant immunotherapy in non-clear-cell RCC populations. This lack of data also explains the absence of consensus on using adjuvant pembrolizumab after SABR.

Adjuvant immunotherapy was introduced relatively recently, either simultaneously with or after the regimens currently used for metastatic RCC. Consequently, data to guide the management of patients relapsing after adjuvant immunotherapy remain limited and are mostly retrospective. As a result, treatment decisions rely on expert opinion or recommendations. The present Delphi study mirrors this uncertainty in the management of relapse after adjuvant immunotherapy, particularly regarding the use of ipilimumab plus nivolumab as salvage therapy. Current evidence is limited, with modest efficacy demonstrated in trials like HCRN-GU16–260 [21]. HCRN-GU16–260, a single-arm, phase II study, investigated nivolumab plus ipilimumab in 35 patients with clear-cell RCC who had tumors unresponsive to nivolumab monotherapy, showing an objective response rate of 11.4 % [21]. Prospective data from phase III studies (CONTACT-03 and TiNivo-2), although conducted in the metastatic setting, do not support ICI use after prior ICI exposure [22,23]. Further prospective studies are needed to explore optimal therapy sequencing and strategies for managing relapse after adjuvant immunotherapy in RCC.

A point of debate among panelists concerned the need for histological confirmation of metastatic disease such as biopsy in patients with clinical or radiographic recurrence. Percutaneous tumor biopsies are increasingly used in patients with RCC for histological diagnosis to avoid unnecessary surgery and to obtain histology before ablative and systemic treatment [24]. However, only 29 % of panelists agreed that histological confirmation should be routinely performed to confirm the presence of metastases and rule out other causes. Overall, decisions regarding biopsy should be made on a case-by-case basis, with discussions held in multidisciplinary meetings to assess the necessity of biopsy. The time from primary tumor resection to metastatic relapse should be considered, and biopsies should also account for the potential of a second cancer.

ICI-based combinations, either dual ICI or ICI plus TKI, are the standard frontline therapy for metastatic RCC [2,24]. For patients with favorable-risk metastatic RCC, ICI plus TKI combination therapy is widely recognized as the standard of care, supported by 93 % agreement among the expert panel [2,24]. However, 86 % of the panel also acknowledged that TKI monotherapy remains a valid treatment option for select patients with favorable-risk disease, particularly those with asymptomatic disease. While current clinical guidelines emphasize combination therapy for the first-line treatment of patients with favorable-risk metastatic RCC, there is a need for a nuanced, patient-centered approach in clinical decision-making [2,24]. TKI monotherapy may be prioritized for patients unable to tolerate ICIs or those ineligible due to active autoimmune disease, prior organ transplantation, or chronic immunosuppressive therapy, to avoid the risk of autoimmune flare or other complications related to immune activation [24,25]. Importantly, recommendations for favorable-risk patients should be interpreted with caution, as high-level evidence in this group is limited.

The combination of nivolumab and ipilimumab was considered a reasonable off-label treatment choice for favorable-risk patients with sarcomatoid features, with 87 % agreement among the expert panel. Similarly, 87 % of panelists agreed that the combination of ipilimumab and nivolumab after recurrence following adjuvant pembrolizumab could be considered in patients with sarcomatoid RCC, irrespective of the time of recurrence. Sarcomatoid differentiation, which can be found in all RCC subtypes, denotes high-grade and very aggressive tumors with a distinct biology [24]. Evidence suggests that sarcomatoid features are associated with a highly immunogenic tumor microenvironment, making dual ICI therapy a viable therapeutic option for patients with sarcomatoid RCC [26,27]. In the phase III CheckMate 214 trial, nivolumab plus ipilimumab demonstrated durable responses, even in favorable-risk patients, who had a 13 % complete response rate [28].

After progression on prior ICI therapy, whether as part of a TKI plus ICI combination or a dual ICI regimen, ICI rechallenge remains a highly disputed strategy. In this study, only 36 % of the panel agreed that a combination of another TKI plus ICI could be considered in this scenario, reflecting a lack of consensus. Recent data from the CONTACT-03 and TiNivo-2 phase III trials demonstrated no clinical benefit of ICI rechallenge after progression on ICI-based combinations, with potentially increased toxicity [22,23]. This underscores the need to carefully select alternative therapeutic options after progression on first-line ICI-based combinations, such as TKI monotherapy, which is recommended by the authors of TiNivo-2 in the post-ICI setting [23] and supported by 87 % of our panel in the present study.

The use of belzutifan in the second-line setting after first-line ICI plus TKI therapy also received support from 79 % of the panel. The LITESPARK-005 phase III trial demonstrated clinical activity of belzutifan in patients with stage IV clear-cell RCC who had received a median of 2 prior therapies (range, 1–4) [29]. Consequently, in February 2025, the European Medicines Agency approved belzutifan for adult patients with advanced clear-cell RCC whose disease has progressed after at least two prior lines of therapy, including an ICI and at least two VEGF-targeted therapies [30]. While belzutifan presents a promising treatment option for advanced RCC, further studies are needed to determine its optimal sequencing, particularly as 93 % of the panel also agreed that belzutifan could be considered for fourth-line and later use after ICI therapy and multiple TKI therapies.

Our study has limitations. The dual role of the steering committee in both developing the Delphi survey and interpreting the results may introduce interpretative bias. Moreover, the present results are based on the input of specific individual expert panelists, and the limited number of experts involved restricts the representativeness of the consensus achieved. Additionally, the opinions of the panel may not fully reflect broader clinical practices, especially considering the evolving nature of treatment guidelines and patient populations as well as differences in drug availability among different countries. While several consensus items reaffirm current clinical guidelines [2,31], such as the use of pembrolizumab regardless of PD-L1 status and the application of the Leibovich score, these results underscore how expert practice is shaped by existing recommendations [2,31] and reinforce their real-world relevance. Notably, many non-consensus items focused on areas not yet addressed by guidelines, including the definition of very favorable-risk disease, the use of ICI monotherapy and imaging strategies in favorable-risk disease, optimal ICI salvage therapy approaches, and adjuvant pembrolizumab use in different non-clear-cell RCC subtypes [2,31]. These findings highlight key evidence gaps and suggest that clinical practice may be evolving ahead of available guidance. Overall, this Delphi study advances the collective understanding of RCC treatment paradigms by providing both confirmation of current standards and expert insights into unresolved areas of care.

5. Conclusions

The current Delphi study provides useful direction on the use of adjuvant immunotherapy for localized RCC and the subsequent management of relapse. The present work has highlighted key knowledge gaps, including the absence of robust evidence to guide adjuvant treatment decisions for non-clear-cell RCC, the need for biomarker integration in clinical practice, histological confirmation of recurrence, and the optimal use of salvage ICI therapy. These gaps should be addressed in future prospective studies to facilitate consensus among experts in upcoming consensus meetings. A multidisciplinary approach and periodic review will be essential in addressing these gaps and optimizing treatment strategies for patients with RCC, as well as identifying further opportunities for clinical trials to bridge the existing knowledge gaps.

CRediT authorship contribution statement

Laurence Albiges: Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Jens Bedke:** Writing – review & editing, Data curation. **Bohuslav Melichar:** Writing

– review & editing, Data curation. **Mário Fontes-Sousa:** Writing – review & editing, Data curation. **Lisa Pickering:** Writing – review & editing, Data curation. **Aristotelis Bamias:** Writing – review & editing, Data curation. **Viktor Grünwald:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Manuela Schmidinger:** Writing – review & editing, Data curation. **Camillo Porta:** Writing – review & editing, Data curation. **Sylvie Rottey:** Writing – review & editing, Data curation. **Marine Gross-Goupil:** Writing – review & editing, Data curation. **Axel Bex:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Bernard Escudier:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization. **Giuseppe Procopio:** Writing – review & editing, Data curation. **Philippe Barthélémy:** Writing – review & editing, Data curation. **Cristina Suárez:** Writing – review & editing, Data curation. **Guillermo Velasco:** Writing – review & editing, Data curation.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Viktor Grünwald acted as a compensated consultant and/or speaker for Arcus, Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, and Pierre Fabre. Axel Bex has received an educational grant from Pfizer for a neoadjuvant trial paid to his institution and acted as a steering committee member for BMS and Roche, as well as a consultant for Ipsen. Sylvie Rottey declares no conflicts of interest. Cristina Suárez has received consulting or advisory fees and/or speakers' bureau honoraria from Astellas, Bayer, BMS, Roche, Ipsen, MSD, Novartis, Pfizer, and Sanofi. Giuseppe Procopio has received research grants from Janssen, Ipsen, MSD, and Gilead, and honoraria for consulting or advisory roles from Abbott, AstraZeneca, Astellas, Bayer, BMS, Eisai, Ipsen, Janssen, Lilly, Merck, MSD, Novartis, Pfizer, Roche, and Recordati. Guillermo Velasco acted as a compensated consultant and/or speaker for Arcus, Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, Janssen, Merck, MSD, Novartis, Pfizer, and Pierre Fabre. Bohuslav Melichar received honoraria for lectures and advisory boards from Roche, Pfizer, BMS, Astellas, Novartis, MSD, Merck Serono, Servier, AstraZeneca, Eisai, E. Lilly, and Pierre Fabre, and travel support from AstraZeneca, BMS, MSD, and Merck Serono. Jens Bedke has served in a consulting or advisory role for AstraZeneca, BMS, Eisai, EUSA Pharma, Ipsen, Merck KGaA, MSD, Pfizer, and Roche; has participated in the speakers' bureau for Astellas Pharma, Apogepha, BMS, Ipsen, Merck KGaA, MSD, Pfizer, and Seattle Genetics; and has received institutional research funding from Astellas Pharma, BMS, Exelixis, Ipsen, MSD, Novartis, Pfizer, Roche, and Seattle Genetics. Lisa Pickering received honoraria from BMS, Eisai, Ipsen, MSD, and Pfizer. Mário Fontes-Sousa reports personal fees for advisory board participation or lectures in the past two years from Astellas, AstraZeneca, Bayer, BMS, Daiichi-Sankyo, Gilead, Ipsen, Lilly, Merck, MSD, Novartis, Palex, Roche, and Pfizer. Manuela Schmidinger acted as a compensated consultant and/or speaker for BMS, Merck, MSD, Ipsen, Exelixis, Eisai, EUSA, Pfizer, AstraZeneca, and Janssen, and has received travel grants from Ipsen and MSD. Aristotelis Bamias received honoraria for advisory roles or speaking engagements from BMS, Ipsen, Merck, and MSD; research support from Roche, Pfizer, Ipsen, AstraZeneca, and BMS; and acted as a member of the Steering Committee for Roche and MSD, as well as the Data Safety Monitoring Board for Sensorion. Marine Gross-Goupil acted as a compensated consultant and/or speaker for BMS, Ipsen, Merck Serono, MSD, Pfizer, Janssen Cilag, Eisai, AstraZeneca, Astellas, Bayer Novartis, and Gilead. Camillo Porta has served as a consultant and/or speaker for Angelini Pharma, AstraZeneca, BMS, Eisai, Exelixis, Genenta, Genmab, Ipsen, Merck Serono, and MSD; a protocol steering committee member for Eisai and MSD; and a Data Monitoring Committee member for Genenta. Philippe Barthélémy is a member of the advisory board, served as a consultant and/or speaker, and received honoraria from BMS, Pfizer, Merck, Ipsen, AstraZeneca, Janssen-Cilag, Astellas, Bayer, MSD, Advanced Accelerator Applications, and Gilead. Bernard Escudier has received honoraria from Pfizer and BMS, and travel support from BMS, Ipsen, and MSD. Laurence Albiges received honoraria from Astellas Pharma, Eisai, Ipsen, F. Hoffmann-La Roche, BMS, Janssen Pharmaceuticals, and Merck Sharp and Dohme, as well as travel support from MSD and BMS.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115569.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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