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First-line immune checkpoint inhibitors in advanced or metastatic renal cell carcinoma with sarcomatoid features

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ABSTRACT

Advanced or metastasized renal cell carcinoma (mRCC) can present with sarcomatoid features, which is considered a poor prognosis marker and a treatment challenge. Several trials in first line mRCC have included immune checkpoint inhibitors (ICI) in combination either with other ICI or tyrosine kinase inhibitors (TKI), that have led to the approval of some of these treatment strategies and their recommendation in international guidelines. The authors review all randomized phase III trials in first-line treatment with ICI for advanced or mRCC and selected prospective phase I-IV trials, that included patients with tumors with sarcomatoid features.

All these trials, in first-line treatment with ICI immunotherapy in combination with another ICI or TKI, included patients with mRCC with sarcomatoid features, corresponding from 5 to 15% of the study population. The efficacy and survival end points were superior in the sarcomatoid features subgroup with ICI in combination vs TKI in monotherapy, achieving overall response rates of 50–60%. A new benchmark has been established by trials reporting over 20 months in median overall survival. Even when considering ICI in monotherapy, the efficacy has been remarkable in patients with sarcomatoid features, demonstrating a striking consistency in these groundbreaking results. No biomarkers predictive of response to ICI were identified. The toxicity profile seems similar to the general study population.

Despite the limitations of the clinical trials design to infer definitive conclusions in the sarcomatoid features patients, the data overwhelmingly support that ICI-based therapy should be the preferred strategy.

Introduction

Sarcomatoid features in metastasized renal cell carcinoma (mRCC) were historically described as a histopathologic pattern consisting of an apparent pleomorphic mixture of malignant elements arising from the connective tissue, smooth muscle tissue or other tissues[1,2]. More recently, it has been characterized by the presence of malignant spindle cells that usually express markers of both epithelial and stromal differentiation[3] (Fig. 1). Any presence of sarcomatoid component is enough to determine the tumor as having sarcomatoid features[4,5]. The relative percentage of the sarcomatoid component within the tumor can be residual or be as high as 100% of the cells[6]. In this specific case, having the totality of the tumor with sarcomatoid component, the recommended labelling is unclassified RCC or World Health Organization (WHO)- International Society of Urological Pathology (ISUP) grade 4 tumor[4]. The relative percentage of the sarcomatoid component has an important prognostic correlation: the higher the percentage, the greater the likelihood of the risk of death, namely at each 10% of increase in the relative percentage of the sarcomatoid component, there's a 6% increase in the risk of death[7].

Although generally considered a rare histological feature - estimated around 5% of cases[8,9] - its incidence can be clinically significant, representing up to 20% of cases in some series[10,11]. Also, sarcomatoid features can be associated with any of the RCC histological subtypes

Abbreviations: AEs, Adverse events; CI, Confidence Interval; CR, Complete responses; DFS, Disease-free survival; EMT, Epithelial–mesenchymal transition; HR, Hazard Ratio; ICI, Immune checkpoint inhibitors; ITT, Intention-to-treat population; IMDC, International mRCC Database Consortium; mRCC, metastasized renal cell carcinoma; MSI-H, Microsatellite Instability-High; NA, Not Available; nccRCC, non-clear cell renal cell carcinoma; NR, Not Reached; ORR, Objective Response Rate; OS, Overall survival; PD-1, Programmed death-1; PD-L1, Programmed death ligand-1; PFS, Progression-free survival; TKI, Tyrosine kinase inhibitors; TME, Tumor microenvironment; TMB, Tumor Mutational Burden; VEGFR, Vascular endothelial growth factor receptor; VHL, Von Hippel-Lindau.

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currently recognized by WHO[12].

The mechanisms originating the sarcomatoid features remain largely undetermined, but the accumulated evidence suggests a common cell-of-origin – this cell loses the epithelial features and gains mesenchymal ones, the process known as epithelial–mesenchymal transition (EMT) [13].

It has been long suggested that there is an association between sarcomatoid features and a worse prognosis or survival in mRCC[14,15]. Of interest, it was considered that the classic International mRCC Database Consortium (IMDC) risk score can be reliably applied to non-clear cell histologies, including sarcomatoid features[16]. In some prognostic nomograms, it was actually an independent poor risk factor in mRCC [7,17].

For decades, there has been no widely accepted standard systemic treatment in mRCC patients with sarcomatoid features. Initial results using chemotherapy were variable, since no or only limited objective responses, very rarely complete responses (CR), were observed in otherwise effective chemotherapy regimens based primarily on doxorubicin[8,13,18,19]. Using vascular endothelial growth factor receptor (VEGFR)–targeted therapy, the standard of care for over a decade in mRCC, has shown limited tumor activity, with partial response (as best response) in only 19% of patients and median progression-free survival (mPFS) of ~5 months and median overall survival (mOS) of 12 months [20]. Even with a multi-target tyrosine kinase inhibitor (TKI) drug such as Cabozantinib, the mOS in the sarcomatoid features subpopulation (real-world data) was about 8 months[21]. This may be explained by loss of Von Hippel-Lindau (*VHL*) gene in only 41% of tumors with sarcomatoid features (vs 76%, or higher, in clear cell tumors)[22]. Actually, having more than 20% of sarcomatoid component within a tumor has been associated with increased resistance to systemic treatments, either VEGF-directed therapy or Interleukin (IL) 2 immunotherapy [9,14,20].

An integrated multi-omics evaluation has identified several molecular subsets, in particular, sarcomatoid tumors exhibited lower prevalence of *PBRM1* mutations and angiogenesis markers (VEGF pathway-related genes), frequent *CDKN2A/B* and *PTEN* alterations, and increased programmed death ligand-1 (PD-L1) expression, revealing a highly proliferative molecular phenotype associated with immune presence[11]. In part, these features support the increased sensitivity of sarcomatoid tumors to ICI-based therapies. Additional research suggests that *NF2, ARID1A* and *BAP1* alterations were mutually exclusive with *TP53* and each other but not with *VHL* mutations[23,24]. It is worth mentioning that the Hippo pathway (of which *NF2* is a potent suppressor) is also considered a feature of sarcomatoid mRCC (most likely a late event in the dedifferentiation process), and a potential therapeutic target[25]. The *FAT* proteins play multiple critical roles in cell adhesion, motility, polarity, signaling, and proliferation, and mutations are implicated in a variety of cancers but rarely found in clear cell RCC - *FAT1/2/3* mutations were all significantly increased (over 35% of cases) in the sarcomatoid tumors[24]. An increased frequency of loss of heterozygosity across the genome has also been described and provides further molecular support to the dedifferention process associated with the sarcomatoid state [24].

In mRCC, an increased programmed death-1 (PD-1) or PD-L1 expression is associated with a worse prognosis[26]. Several studies [9,27,28] have suggested an enrichment of PD-L1 expression (defined either as present in $\geq$ 1%, $\geq$ 5% of tumor cells or PD-L1 H-score $\geq$ 10) in mRCC with sarcomatoid features from 43 to 54% of patients (vs 17% to 21% in non-sarcomatoid cells). Even concurrent PD-1/PD-L1 expression with sarcomatoid differentiation was high, around 50% of cases[9]. Some molecular findings might be useful when considering prediction of response to immunotherapy in this setting, such as the sarcomatoid component having a higher tumor mutational burden (TMB)[24], although not consistently[29], or having increased amplification of *PDL1* and *PDL2* genes[30] than the corresponding epithelial counterpart. An immune-inflamed phenotype characterized by immune activation has been described[28], in particular, the CD8 + T cell infiltration was increased in these tumors. Of note, microsatellite instability high (MSI-H), an United States Food and Drug Administration (FDA) approved therapeutic target for the ICI Pembrolizumab in solid tumors (tumor site–agnostic indication)[31], was estimated to be around only 1% of sarcomatoid tumors[22], a residual value.

An important factor to consider in ICI response is the tumor microenvironment (TME), especially its subtype characterized by extensive immune infiltrate and enrichment in *BAP1* mutations[32].

Epigenetic regulatory mechanisms have been described in renal cell carcinoma in general, but remains an opportunity for research in sarcomatoid tumors [13].

The objective of this article is to review the efficacy and safety data from the trials that use ICI-based therapy in the first line setting in patients with sarcomatoid features tumors and explore potential predictive biomarkers.

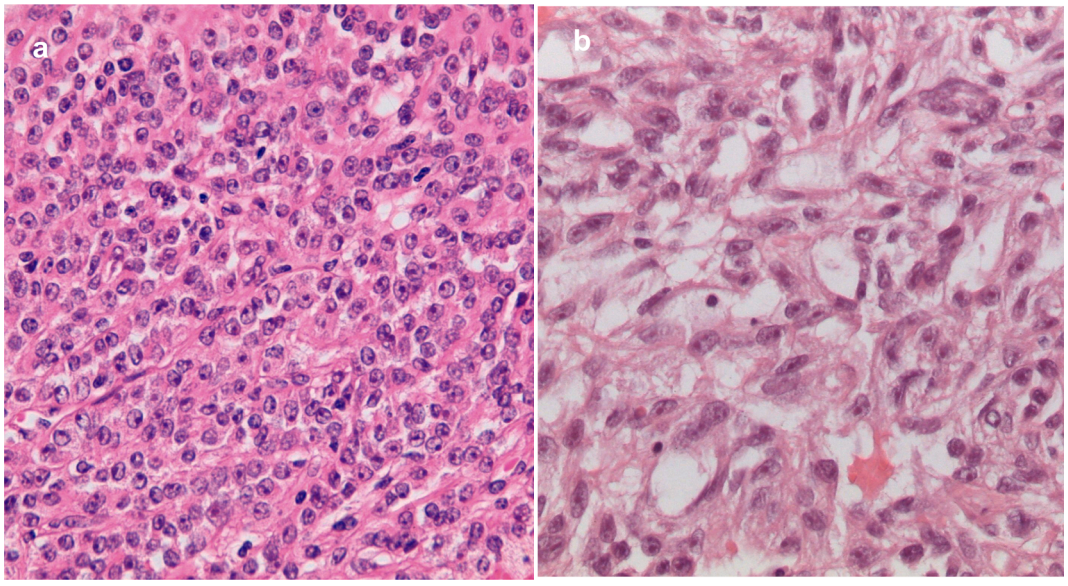

Fig. 1. Example of sarcomatoid features in a renal cell carcinoma (papillary type 2, with *FH* gene germline mutation). a) Hematoxylin and eosin (H&E) staining at 20x magnification b) H&E staining at 40x magnification. Images provided by Raquel Brodbeck Ilgenfritz MD, MSc, Hospital CUF Descobertas (Lisbon).

Methods

All randomized phase III trials in first-line systemic treatment with ICI in combination, for advanced or metastatic renal cell carcinoma (with data regarding sarcomatoid features subpopulation) were included; non-randomized phase I-IV trials with ICI arm were also included upon search in MEDLINE/PubMed, American Society of Medical Oncology (ASCO) Annual Meeting, ASCO's Genitourinary Cancers Symposium and European Society for Medical Oncology (ESMO) Congress abstracts, from January 2018 to February 2022.

Results

Six phase III randomized clinical trials were identified that fulfilled the methodology criteria: CheckMate-214[33–35], KEYNOTE-426 [36–38], JAVELIN Renal 101[39–41], IMmotion 151[42], CheckMate-9ER[43,44] and CLEAR[45]. All of these trials, focused on first-line treatment with ICI immunotherapy in combination, included patients with mRCC with sarcomatoid features (Table 1). Additionally, selected non-randomized phase I-IV trials were also included because of their clinical relevance in using ICI (either monotherapy or combination) in patients with tumors with sarcomatoid features (Table 2).

CheckMate-214 was a phase III trial that randomly assigned patients in a 1:1 ratio to receive either Nivolumab, an anti-PD-L1 drug, [3 mg/kilogram(kg) of body weight] plus Ipilimumab, an anti-CTLA-4 drug, (1 mg/kg) intravenously every 3 weeks for four doses, followed by Nivolumab (3 mg/kg) every 2 weeks, or Sunitinib (50 mg) orally once daily for 4 weeks (6-week cycle)[33], the standard schedule. The coprimary end points were OS, objective response rate (ORR), and PFS, in patients with IMDC intermediate or poor prognostic risk, while the intention-to-treat (ITT) population included IMDC's favorable risk patients. It was the first combination to be approved, and also the first (and only) combination regimen with exclusively ICI drugs thus being anti-VEGF-drugs-free regimen, the mainstay of mRCC treatment over a decade. The combination's approval was based on initial efficacy data: the mOS was not reached with Nivolumab plus Ipilimumab vs 26.0 months with Sunitinib [Hazard Ratio (HR) 0.63; $P < 0.001$); ORR was 42% vs 27% ($P < 0.001$), and CR rate was 9% vs 1%.

On a dedicated subanalysis[35], of the 1096 randomized patients, 139 patients (13%) with sarcomatoid features and IMDC's intermediate/poor-risk disease and six with favorable-risk disease (0.5%) were identified. The analysis included PD-L1 + tumors (PD-L1 expression $\geq$ 1%). The mOS [95% Confidence Interval (CI)] favored Nivolumab plus Ipilimumab [Not reached (NR) (25.2 - Not estimable (NE); n = 74] versus Sunitinib [14.2 months (9.3–22.9); n = 65; HR 0.45 (95% CI, 0.3–0.7; $P = 0.0004$)]. The mPFS was higher with Nivolumab plus Ipilimumab [26.5 vs 5.1 months; HR 0.54 (95% CI, 0.33–0.86; $P = 0.0093$)]. Confirmed ORR was 60.8% with Nivolumab plus Ipilimumab versus 23.1% with Sunitinib. The CR rates were six times higher in the ICI combination arm vs Sunitinib, with 18.9% versus 3.1%, respectively. In the 5-year follow-up[46], the reported ORR was higher (61% vs 23%; $p < 0.0001$), the median duration of response was longer (NR vs 25 months), and more patients had CR (23% vs 6%) with Nivolumab plus Ipilimumab vs Sunitinib, respectively, and regardless of PD-L1 status (Table 1). At this extended follow-up, there was a significant 54% reduction in the risk of death [HR 0.46 (95% CI 0.29–0.71); $p = 0.0004$] [46]. No new safety signals emerged[35,47]. Of note, there was an independent central pathology review of archival tumor tissue or histological classification per local pathology regarding sarcomatoid features [46].

The KEYNOTE-426 was an open-label, phase III trial, that randomly assigned 861 patients with mRCC in first-line, to receive Pembrolizumab (200 mg intravenously once every 3 weeks) plus Axitinib (starting at 5 mg, up to 10 mg, orally twice daily) or Sunitinib (standard schedule) [36]. The primary end points were OS and PFS in the ITT population. This combination, the first ICI plus TKI regimen to be approved, resulted in significantly longer mOS (initial HR 0.53, the latest 0.68, still statistically significant[38]) and mPFS (15.1 vs 11.1 months), as well as a higher ORR (59.3 vs 35.7%), than with Sunitinib (Table 1). Of the 578 randomized patients with known histological status, 105 (18.2%) had sarcomatoid features: 51 in the Pembrolizumab + Axitinib arm vs 54 in the Sunitinib arm[37]. The mOS, at data cutoff date of Aug 24, 2018, had not been reached in both experimental and control arms. Grade $\geq$ 3 AEs of any cause occurred in 76% of patients in the Pembrolizumab plus Axitinib group and in 71% in the Sunitinib group. The most common AEs related to treatment, in both groups, were diarrhea and hypertension

Table 1
Summary of data on randomized phase III clinical trials with immunotherapy in first line for advanced renal cell carcinoma with sarcomatoid features. Not intended as cross-trial comparison.

Clinical Trials	Experimental arm	Sarcomatoid features subpopulation		
		Trial N (%) in Exp arm vs Control arm*	ORR/CR (95% CI) Experimental vs Control arm*	mPFS/ mOS (months, 95% CI) Experimental vs Control arm*
CheckMate-214 [ref35,46]	Nivolumab + Ipilimumab	I/P risk disease: 74 (8.7%) vs 65 (7.7%) I/P risk disease and PD-L1+: 36 (9.4%) vs 33 (8.4%)	I/P risk disease: 61%/23% vs 23%/6% I/P risk disease and PD-L1+: 69%/25% vs 24%/9%	I/P risk disease: 26.5/NR vs 5.1/14.2 I/P risk disease and PD-L1+: NR/NR vs 4.4/20.9
KEYNOTE-426 [ref36]	Axitinib + Pembrolizumab	51 (12%) vs 54 (13%)	58.8%/11.8% vs 31.5%/0%	NR/NR vs 8.4/NR
JAVELIN Renal 101[ref40]	Axitinib + Avelumab	47 (5.2%) vs 61 (6.8%)	46.8%/4.3% vs 21.3%/0%	7.0/NA vs 4.0/NA
IMmotion 151 [ref10,42]	Atezolizumab + Bevacizumab	ITT: 68 (15%) vs 74 (16%); PD-L1 + 36 (20%) vs 50 (27%)	ITT: 49.0%/10.0% vs 14.0%/3.0% PD-L1+: 56.0%/14.0% vs 12.0%/4.0%	ITT: 8.3/21.7 vs 5.3/15.4 PD-L1+: 8.6/19.3 vs 5.6/15.0
CheckMate-9ER [43,44,48]	Nivolumab + Cabozantinib	34 (10.9%) vs 41 (12.9%)	55.9%/8.8% vs 22.0%/2.4%	10.9/NR vs 4.2/19.7
CLEAR[45,49]	Lenvatinib (L) + Pembrolizumab (P) / L + Everolimus	28 (7.9%) vs 24 (6.7%) vs 21 (5.9%)	L + P: 61%/NA vs 24%/NA	11.1/NR vs 5.5/NR

Abbreviation: CI: Confidence interval; CR: complete responses; Exp: Experimental arm; I/P: intermediate or poor risk disease; ITT: intention-to-treat population; L: Lenvatinib; mPFS: median progression-free survival; mOS: median overall survival; NA: Not available; NR: not reached; ORR: overall response rate. PD-L1: programmed death-ligand 1; P: Pembrolizumab.
* Note: the control arm in all trials was Sunitinib 50 mg orally once daily for 4 weeks (6-week cycle).

[36].

In the JAVELIN Renal 101 phase III trial, patients were randomly assigned in a 1:1 ratio to receive Avelumab (10 mg/kg) intravenously every 2 weeks plus Axitinib (5 mg) orally twice daily or Sunitinib (standard schedule). The two independent primary end points were PFS and OS among patients with PD-L1 + tumors (PD-L1 expression ≥ 1%) [39]. The PFS was significantly longer (13.9 vs 7.2 months) with Avelumab plus Axitinib than with Sunitinib. OS results have not been reported so far.

A subgroup analysis focusing on efficacy and biomarkers of patients with sarcomatoid histology has been published[40]. Of the 886 randomised patients, 108 (12.2%; 47 on Avelumab plus Axitinib and 61 on Sunitinib arm) had sarcomatoid mRCC. The combination improved PFS (median [95% CI], 7.0 [5.3, 13.8] vs 4.0 [2.7, 5.7] months; HR 0.57 [95% CI, 0.325, 1.003]) and ORR [95% CI] (46.8% [32.1, 61.9] vs 21.3% [11.9, 33.7]; CR in 4.3% vs 0%) vs Sunitinib.

The IMmotion 151 trial[42] was a randomized controlled phase III trial comparing Atezolizumab (anti-PD-L1) plus Bevacizumab (anti-VEGF) versus Sunitinib (standard schedule) in patients with previously untreated metastatic renal cell carcinoma. Although the combination strategy significantly prolonged mPFS versus Sunitinib, it failed to show a benefit in mOS so far (co-primary end points). The trial comprised two populations: PD-L1+ (PD-L1 expression ≥ 1%) N = 362 and ITT N = 915. The trial allowed the enrollment patients with mRCC and any component of high-grade malignant spindle cells consistent with sarcomatoid histology per local pathology review. A prespecified subgroup analysis on the sarcomatoid features population has been published[10]. Patients whose tumour had any component of sarcomatoid features were included: N = 68 in Atezolizumab plus Bevacizumab arm vs N = 74 in Sunitinib arm. The mPFS was significantly longer in the group receiving Atezolizumab plus Bevacizumab: in the overall population (8.3 vs 5.3 months; HR 0.52 95% CI 0.34–0.79) and in the subset of patients with PD-L1 + tumours (8.6 vs 5.6 months; HR 0.45, 95% CI 0.26–0.77). More patients receiving combination treatment achieved an objective response (49% vs 14%), including CR (10% vs 3%). Also, there was greater symptom improvements versus Sunitinib. No new safety concerns were reported.

The CheckMate 9ER trial[44] was a randomized controlled phase III trial comparing Nivolumab (240 mg intravenously every 2 weeks) plus Cabozantinib (anti-VEGF, at the dose of 40 mg, once daily) versus Sunitinib (standard schedule) in patients with previously untreated metastatic renal cell carcinoma. The primary endpoint was PFS in all randomized patients. Nivolumab plus Cabozantinib had a superior PFS benefit over sunitinib, with a HR for disease progression or death of 0.51 (95% CI, 0.41 to 0.64; P < 0.001). The combination also had superior OS benefit: HR for death 0.60; 98.89% CI, 0.40 to 0.89; P = 0.001, while the mOS was not reached in either group (median follow-up 18.1 months). Also, objective responses were superior in the combination arm with 55.7% (95% CI, 50.1 to 61.2) vs 27.1% (95% CI, 22.4 to 32.3) with sunitinib (P < 0.001). In the combination arm, 34/313 (10.9%) patients had sarcomatoid features (Table 1). PD-L1 expression was considered positive if ≥ 1%. Response, PFS and OS data in the sarcomatoid features subgroup has been reported for the CheckMate 9ER trial[48], after a minimum follow-up of 16 months. The ORR (95% CI) was 55.9% (37.9–72.8) in the sarcomatoid group (Table 1), that was similar to the non-sarcomatoid group treated with Nivolumab + Cabozantinib (54.7%), but patients with sarcomatoid features had the lowest ORR (22.0%) when treated with Sunitinib (non-sarcomatoid patients treated with Sunitib had ORR of 29.3%)[48]. Treatment-related AEs lead to discontinuation with either Nivolumab, Cabozantinib or both in 23.4% vs 9.1% with Sunitinib.

The CLEAR trial[45] was a randomized controlled phase III trial comparing Lenvatinib (anti-VEGF; 18 mg orally, once daily) plus Pembrolizumab 200 mg intravenously once every 3 weeks or Everolimus (mTOR inhibitor; 5 mg orally, once daily) versus Sunitinib (standard schedule) in patients with previously untreated mRCC. The primary endpoint was PFS, which was significantly longer with Lenvatinib (L) plus Pembrolizumab (P) vs Sunitinib [median, 23.9 months (95% CI, 20.8 to 27.7) vs. 9.2 months (95% CI, 6.0 to 11.0)] with an HR for disease progression or death, 0.39; 95% CI, 0.32 to 0.49; P < 0.001). Survival was also significantly longer with L plus P than with Sunitinib (HR for death, 0.66; 95% CI, 0.49 to 0.88; P = 0.005). PFS was also superior in the L + Everolimus (E) vs Sunitinib, but the OS was not significantly longer. Objective responses, with L + P were 71.0% vs 36.1% with Sunitinib. The trial included patients with tumor with sarcomatoid features: 28/355 (7.9%) in L + P, 24/357 (6.7%) in L + E and 21/357 (5.9%) in Sunitinib arm (Table 1). PD-L1 + was defined as PD-L1 combined positive score ≥ 1).

Data regarding the sarcomatoid features subpopulation from the CLEAR trial were reported[49]. The ORR was greater with the combination arm (L + P) vs Sunitinib for the subgroup with sarcomatoid histology [61% vs 24%; odds ratio: 8.9 (95% CI 2.1, 37.8)]. The most frequent immune-mediated AEs treated with high-dose corticosteroids were pneumonitis (3.7%) and hypothyroidism (2.8%), among others.

Some phase I/II trials also provide important insights. KEYNOTE-427 was an open-label, single-arm trial in first-line in mRCC patients, treated with Pembrolizumab monotherapy 200 mg every 3 weeks for ≤ 24 months[50,51]. Two cohorts were reported according to histology: cohort A (clear cell)[50] and cohort B (non-clear cell)[51]. In both cohorts patients with tumors with sarcomatoid features were included (Table 2). The primary endpoint was ORR by RECIST v 1.1. In the cohort A, the median time from enrollment to data cutoff was ~ 36 months and ORR 36.4%, while for the sarcomatoid features subpopulation ORR was 63.6%. Grade 3–5 treatment-related adverse events (AEs) occurred in 30% of patients, predominantly gastrointestinal (colitis and diarrhea most frequently). In cohort B, the median time from enrollment to data cutoff was ~ 32 months and ORR 26.7%, while for the sarcomatoid features subpopulation ORR was 42.1%. Grade 3–5 treatment-related AEs occurred in 17% of patients, predominantly gastrointestinal (colitis, diarrhea, and hepatitis most frequently).

A smaller phase Ia trial[52] reported single agent Atezolizumab in a non-clear cell population, that included patients with Fuhrman grade 4 and/or sarcomatoid histology tumors. The ORR was 22% (95% CI, 6% to 48%) for patients with high Fuhrman grade and/or sarcomatoid features (n = 18; 26%). The ORR for 16 patients with grade 4 tumors was 25% (95% CI, 7.3% to 52%), and it was 33% (95% CI, 4.3% to 78%) for six patients who had sarcomatoid features. Regarding safety, 17% of patients experienced treatment-related grade 3 AEs, while the most common immune-mediated AE of any grade was rash (20%).

The COSMIC-021 trial is a phase Ib trial that evaluated Atezolizumab plus Cabozantinib in patients with solid tumors and the results from patients with advanced clear cell (with two Cabozantinib posologies: 40 or 60 mg, once daily) and non–clear cell RCC has been reported[53]. Patients with sarcomatoid features tumors were included: 9/34 (26.5%) in the ccRCC Cabozantinib 40 mg, 2/36 (5.6%) in the ccRCC Cabozantinib 60 mg and 4/32 (12.5%) in in the nccRCC group. The reported ORR was remarkably high, around 73% (Table 2). Treatment-related AEs of any grade were experienced by ≥ 97% patients in both cohorts, but there were no grade 5 events[53].

A phase II study evaluated Atezolizumab + Bevacizumab in patients with mRCC with variant histology and/or sarcomatoid features (with ≥ 20% sarcomatoid differentiation)[54]. The primary end point was ORR by RECIST version 1.1 and 60 patients were included, 26 (43%) of them with sarcomatoid features (18 clear cell + 8 variant histology, such as papillary or chromophobe, among others). The ORR was 50% in patients with clear cell with sarcomatoid differentiation and 26% in patients with variant histology RCC (Table 2), but there was no significant association between histology and response. The most reported AEs (any grade) were fatigue (83%) and musculoskeletal pain (82%), among others.

The CheckMate-920 is a phase IIIb/IV trial in patients with no previous systemic treatment with four cohorts but so far only cohort 2 data have been reported[55]. In this cohort, the therapeutic regimen is the

Table 2
Summary of data from prospective clinical trials with immunotherapy in first line for advanced renal cell carcinoma with sarcomatoid features, either in monotherapy or combination, with no comparator arm. Not intended as cross-trial comparison.

Trials	Total pts (N)	Sarcomatoid features subpopulation				
		N (%)	ORR (%)	mPFS (months)	mOS (months)	CR (N/%) *
KEYNOTE-427						
phase II trial						
Agent: Pembrolizumab						
Cohort A (clear-cell)[50]	110	11 (10%)	63.6% (95% CI, 30.8–89.1)	16.3 (95% CI, 3.0–21.6)	32.2 (95% CI, 11.8-NR)	0 / 0%
Cohort B (non-clear cell)[51]	165	38 (23%)	42.1% (95% CI, 26.3–59.2)	6.9 (95% CI, 2.8–15.4)	25.5 (95% CI 13.1–30.0)	4 / 10.5%
McDermott at al.[52]						
phase Ia trial	70	18 (26%) **	22% (95% CI 6–48)	4.2 (95% CI, 1.4–8.4)	26.2 (95% CI, 17.2-NR)	NA
Agent: Atezolizumab (clear and non-clear cell)						
COSMIC-021[ref53]						
phase Ib trial						
Agents: Atezolizumab + Cabozantinib						
ccRCC*** cohort	70	11 (16%)	72.7% (NA)	NA	NA	1 / 9.1%
nccRCC cohort	32	4 (13%)	NA	NA	NA	NA
McGregor et al.[54]						
*phase II trial****	60	26 (43%)	50% (clear cell RCC),38% (non-clear cell RCC)	8.3 (95% CI, 5.7–10.9) for whole population	NA	NA
Agents: Atezolizumab + Bevacizumab						
CheckMate-920						
phase IIIb/IV trial						
Agents: Nivolumab + Ipilimumab						
nccRCC cohort (or cohort 2)[ref55]	46	14 (30.4%)	35.7% (CI 12.8–64.9)	NA	NA	NA

Abbreviation: ccRCC: clear cell renal cell carcinoma; CI: Confidence Interval; CR: complete responses; mPFS: median progression-free survival; mOS: median overall survival; NA: Not available; nccRCC: non-clear cell renal cell carcinoma; NR: Not reached; ORR: objective response rate.
* Best response.
** Fuhrman grade 4 and/or sarcomatoid histology.
*** Included 2 groups: Cabozantinib 40 mg (N = 34) and Cabozantinib 60 mg (N = 36).
**** Most patients (94%) treatment-naïve; all patients in sarcomatoid subgroup with ≥ 20% sarcomatoid differentiation.

same as Checkmate-214 (Nivolumab + Ipilimumab, followed by maintenance Nivolumab), but the patient population is non-clear cell renal carcinoma (CheckMate-214 included only clear-cell) with Karnofsky performance status ≥ 70%, that allowed the inclusion of sarcomatoid features. The number of response-evaluable patients was 46, of them, 14 (30%) had sarcomatoid features – of note, the confirmed objective response was the highest of all subgroups, with 35.7% (Table 2). No new safety signals were reported.

Discussion

The inclusion of patients with mRCC with (any) sarcomatoid features in first line systemic treatment phase III trials is a welcomed departure from previous mainstream trials that almost systematically excluded these patients. The percentage of patients that were included with tumors with sarcomatoid features varied across trials ranging, in the experimental arm, as low as 5% up to 15% in unselected populations (and ascending to 20% in PD-L1 + subpopulation). Actually, the PD-L1 expression was always higher in the sarcomatoid subpopulation when compared to the overall population in every phase III trial that made these results available: CheckMate 214 (47% vs 26%)[33], KEYNOTE-426 (74.5% vs 59.3%)[36], Javelin Renal 101 (72.3% vs 61.1%)[39], IMmotion 151 (63% vs 39%)[56] and CheckMate 9ER (47.2% vs 25.5%) [48]. Although previous research (see Introduction) and current trials show higher than the overall population PD-L1 expression in tumors with sarcomatoid features, no significant differences in relevant endpoints were noted between PD-L1+ and PD-L1- subpopulations.

Over 300 patients with tumors with sarcomatoid features were included in these trials that were treated with ICI in combination in first-line (Table 1). An additional 114 patients were treated in prospective single-arm phase I-IV trials that included ICI, either in monotherapy or in combinations (Table 2), thus surpassing 400 patients with sarcomatoid features treated with ICI, when considering all trials. It is important to understand that mRCC patients with sarcomatoid features tumors seldom survived more than 12 months in the literature previous to ICI-based treatment trials[3,57,58]. In the randomized phase III trial that has already reached the median OS (IMmotion 151), it has surpassed 20 months, while more follow-up is still needed for the other trials. For the phase I/II trials the reported mOS has consistently surpassed 24 months (in one even reaching 32 months, the KEYNOTE-427 cohort A), which is a groundbreaking benchmark for sarcomatoid tumors, although one must understand that these are small trials and consequently, the results must be interpreted with caution. The impact in survival and progression was evaluated in a *meta*-analysis[59] based on initial data from randomized phase III trials: a non-significant reduction in the mortality risk of 34% vs Sunitinib [HR 0.66 (95% CI, 0.52–0.84, P = 0.55)], based on 3 trials (CheckMate 214, KEYNOTE-426 and IMmotion 151), but a significant reduction in disease progression or mortality risk of 27% vs Sunitinib [HR 0.73 (95% CI, 0.66–0.83, P = 0.02)] was observed, based on 4 trials (previous trials plus JAVELIN Renal 101)[59]. Of relevance, although within the sarcomatoid group the mPFS benefit favors ICI in combination vs TKI monotherapy in all trials, the results are superior in the non-sarcomatoid clear-cell group[59], stressing the worse prognosis associated with sarcomatoid features. Other systematic reviews have validated the beneficial impact of ICI-based therapy in sarcomatoid features patients[60–62].

In the randomized phase III trials, the ORR has been strikingly different between the ICI-based vs TKI monotherapy: in the combination arms the reported ORR in unselected populations was high, ranging from 47% up to 60%, while in the control arm it has been between 14 and 32%. The highest ORR recorded, 69%, occurred in the PD-L1 + subpopulation in the CheckMate-214 trial[35,46]. When considering ICI

monotherapy, the ORR was variable according to the study population, ranging from 22 to 64% (with mOS above 25 months), suggesting that in selected patients, ICI monotherapy could be a strategy to consider. In smaller trials, using immunotherapy in combination, ORR was reported to have surpassed 70%[53].

Related to the ORR is the percentage of patients with CR (a suggested indicator of improved long-term prognosis[63]) which was essentially non-existent or minimal (0–6%) in the TKI monotherapy arm while in the combination arm, it varied between 4 and up to 25% (Tables 1 and 2). Taken together, these efficacy results lead to international guidelines to strongly recommend ICI-based therapy above single-agent VEGFR TKI [II, A][64].

When analyzing the epithelial histology associated to the sarcomatoid features in the tumor when ICI monotherapy was evaluated, the efficacy seems to be inferior when associated to nccRCC than with clear cell, although this is exploratory considering the low number and the heterogeneity of the populations in the trials. It is interesting to note that this improved responses with sarcomatoid features present within clear cell histology tumors was also suggested in the earlier days of VEGFR-targeted therapy[20]. There's evidence supporting a molecular profile associated to each histology: prevalence of *BAP1* mutations was highest in clear cell carcinoma with sarcomatoid features whereas non-clear cell carcinoma with sarcomatoid features showed enrichment in *TP53* and *RB1* alterations[11]. Interestingly, both components seem to largely contain the same genomic features[23].

For some trials, data regarding safety and survival endpoints in patients with tumors with sarcomatoid features are pending at this time (Tables 1 and 2) and are eagerly awaited. The AEs pattern in the sarcomatoid features subpopulation seems to be similar to the overall population of the trials.

ICI monotherapy (Pembrolizumab 1 year vs placebo) has also been evaluated in the adjuvant setting for M0 intermediate-to-high risk and in M1 post-metastasectomy rendering no-evidence of disease patients in the KEYNOTE-564 trial[65]. There was a significant improvement in disease-free survival (DFS) in the initial report, at 24 months (HR for recurrence or death 0.68; 95% CI, 0.53–0.87) and later updated at 30 months (HR for recurrence or death 0.63; 95% CI, 0.50–0.80, $p < 0.0001$). Grade 3 or higher AEs occurred in 32% of patients in pembrolizumab arm (vs 18% in placebo arm). This trial included $N = 52$ (10.5%) patients with clear cell histology with sarcomatoid features, and the results for this subpopulation have been made available[66], revealing an impressive HR 0.54 (95% CI 0.29–1.0). These results provide support for the worse prognosis by the presence of sarcomatoid features: 24-month DFS rate in placebo arms of 69.4% in sarcomatoid features absent vs 52.0% in sarcomatoid features present (a 17.4% difference). Remarkably, the 24-month DFS rate in Pembrolizumab arms of 79.5% in sarcomatoid features absent vs 71.8% in sarcomatoid features present (a 7.7% difference) underscores the benefit of immunotherapy in this subpopulation (here in the absence of metastatic disease). OS data is immature.

One of the limitations of interpreting the data is that the relative percentage of the sarcomatoid component has not been made available for most trials, and it could be clinically useful to understand how that variable relates to efficacy endpoints, such as prognosis and survival[7]. Additional molecular studies are critically needed to understand the connection between sarcomatoid features and increased immunotherapy response. PD-L1 immunoexpression, in general, is considered the most widely validated, used and accepted biomarker to guide the selection of patients to receive anti-PD-1 or anti-PD-L1 antibodies[67]. Indeed, some studies have focused on these subjects and showed higher median expression levels of key immune markers, not only PD-L1 but also Interferon gamma (IFNγ)[40] in tumors with sarcomatoid features. Notwithstanding, in mRCC, PD-L1 expression should not guide treatment decision since, in general and so far, no significant differences were reported between PD-L1 + or PD-L1- patients. Conversely, there is also a need for understanding the molecular drivers of ICI resistance in clinical practice [32].

Conclusions

Metastatic RCC with sarcomatoid features is a rare entity with historically poor prognosis and considered difficult to treat. The available exploratory analyses of all the randomized phase III trials (and selected prospective phase I-IV trials) in previously untreated advanced or mRCC that allowed the inclusion of these patients, suggest that ICI-based therapy has a clinically meaningful effect on these tumors, when compared with TKI monotherapy, therefore a paradigm shift. The data that reflects tumor responses (ORR/CR) and PFS are particularly convincing, establishing new benchmarks for this disease, while mature OS data are still awaited in most trials. These benefits have been independent of PD-L1 status, thus there is a need for predictive biomarkers in clinical practice. The AEs pattern in the sarcomatoid features subpopulation seems to be similar to the overall population of the trials.

Once all the data are made available, more *meta*-analysis will be quite useful, and regular updates with extended follow-up from these trials should be expected. Despite the limitations of trial design to infer definitive conclusions, the magnitude of benefit is substantial in every relevant clinical oncological end points, therefore ICI-based therapy should be considered preferential in patients with tumors with sarcomatoid features, which is in accordance with recommendations from current international guidelines.

CRediT authorship contribution statement

Mário Fontes-Sousa: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Emiliano Calvo:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MFS has been contracted as a consultant/speaker for Astellas, Bristol Myers Squibb, Merck Sharp & Dohme (MSD), Novartis, Pfizer and Roche. EC declares Consulting or Advisory Role for Adcendo, Alkermes, Amcure, Amunix, Anaveon, AstraZeneca/MedImmune, BeiGene, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharma, Janssen-Cilag, MSD Oncology, Nanobiotix, Novartis, Roche/Genentech, PharmaMar, PsiOxus Therapeutics, Sanofi, Seattle Genetics, Servier and TarhImmune Therapeutics.

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