The Introduction of Nivolumab Plus Ipilimumab in the Treatment of aRCC Patients: Differences Between Low- and High-Volume Centers in Germany

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Abstract

In November 2018 the European Medicines Agency approved Nivolumab plus Ipilimumab as first-line therapy in intermediate- or poor-risk Advanced Renal Cell Carcinoma (aRCC) patients. This made it mandatory to stratify patients according to their risk group before starting a therapy. Concomitantly, facility case volume was suggested to influence the quality of aRCC treatment. To this end, we retrospectively analyzed aRCC patient data for those who received first-line therapy in low- or high-volume centres in 2016 vs. 2019. Data from 5 urological and 6 oncological clinics from 95 patients showed that stratification according to the IMDC score was more frequent in high- as compared to low-volume centres in Germany in 2021 (46 vs. 13%, p =0.022). Nevertheless, Nivolumab plus Ipilimumab was used similarly in low- and high-volume centres (31 vs. 29%). However, high-volume centers had a higher clinical benefit rate of first-line therapy compared to low-volume centers (82 vs. 50%, respectively, p =0.025). Moreover, more patients were still on first-line therapy from 2019 in high-volume centers (31 vs. 9%, p =0.033). These findings suggest that case volume and patient stratification according to the IMDC risk score positively affect treatment outcomes in aRCC.

Keywords: Advanced renal cell carcinoma • aRCC • Facility case volume • Ipilimumab • Metastasized renal cell carcinoma • mRCC • Nivolumab

Main Report

Renal Cell Carcinoma (RCC) is the most common type of renal cancer and constitutes 2.2% of all adult malignancies [1]. It presents with primary metastases (synchronous disease) in 35% of newly diagnosed RCC patients or recurrent metastases (metachronous disease) in 20%-40% of cases after local treatment [2,3]. The management of metastatic disease changed fundamentally after the Checkmate 214 study (NCT02231749) introduced the Immunotherapy (IO) consisting of the Programmed Cell Death 1 (PD-1) antibody nivolumab plus the Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA-4) antibody ipilimumab as first-line therapy for intermediate- or poor-risk aRCC patients. The European Medicines Agency (EMA) approved its use accordingly in November 2018 [4]. Thus, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic score model gained significant importance by being utilized for the patients' risk stratification. The variables of this score include time to systemic treatment (less than 1 year from the time of diagnosis to systemic therapy), performance status <80% (based on Karnofsky Performance Status), haemoglobin (<lower limit of normal), corrected serum calcium (>upper limit of normal [ULN]), neutrophil count (>ULN) and platelet count (>ULN). Patients with 0 factors are defined as favourable risk, with 1-2 factors as intermediate risk and with 3-6 factors as poor risk [5].

Concurrently, higher facility case volume was suggested to improve oncologic outcomes in aRCC patients due to the abundance of more experience from daily practice [6]. Joshi reinforced this assumption and defined high aRCC-volume facilities as treating ≥4.8 patients per year [7].

Our study aimed to investigate the effect of the introduction of nivolumab plus ipilimumab on the diagnosis and treatment of aRCC patients receiving first-line therapy in low- and high-volume centres. High volume was defined as treating ≥5 patients per year (Table 1).

Table 1. Clinical parameters of aRCC patients in German low- or high-volume outpatient clinics receiving first-line therapy in 2016 vs. 2019

Variables	2016	2019	*P* value

	(n =51)	(n = 44)	
Age, median	65.3	67.5	
Male sex, n	29	32	0.11
Patients treated in, n			0.99
Low-volume centres (≤4 pat. p. a.)	17	16	
High-volume centres (≥5 pat. p. a.)	34	28	
ECOG performance status, n			0.52
0	7	10	
1	15	15	
>2	6	3	
Unknown	23	16	
Histology, n			0.37
Clear cell	40	28	
Non-clear cell	4	5	
Unclassified	7	11	
Type of metastasis, n			0.56
Synchronous	31	22	
Metachronous	15	16	
Locally advanced	5	6	
Number of metastases, n			0.2
1 metastasis	10	3	
2-5 metastases	17	18	
>5 metastases	19	17	
Comorbidities, n			
Cardiovascular	6	4	0.64
Pulmonary	10	7	0.18
Endocrine	2	0	0.41
Hepatic	6	3	0.23
Neurological	4	1	0.18
Autoimmune	2	0	0.35

In a retrospective descriptive analysis data of 95 patients being treated in urological or oncological centers in Germany in 2016 vs. 2019 was collected in the year 2021 (data cut off December 2021). Of those 33 were treated in low-volume and 62 in high-volume centers.

We showed that after the approval of nivolumab plus ipilimumab, high-volume centres assessed the IMDC risk score significantly more often for their aRCC patients than low-volume centres (Figure 1A; 46 vs. 12%, p =0.022). The rate of risk assessment increased from 2016 to 2019 regardless of case volume but without reaching significance (high-volume: 26% to 46%, p =0.087; low-volume: 0 to 13%, p =0.133).

Tyrosine Kinase Inhibitor (TKI) monotherapy was the main choice of first-line therapy for both low- and high-volume centres in 2016 with 82 and 88 %, respectively. In 2019 it was still used in approximately 50% of both groups (Figure 1B), even though favourable-risk patients, for which it was solely recommended at that point, constituted only 7% of all aRCC patients in high-volume and none in low-volume centres. Even when assuming that a fraction of the undocumented IMDC risk scores in 2019 (88% in low-volume and 54% in high-volume centres) may have been favourable risk scores, this finding suggests that TKI monotherapy was still given to patients with intermediate- and poor-risk scores in 2019 (Figure 1A). The newly approved combination of nivolumab plus ipilimumab was used in approximately 30% of cases in both groups in 2019 (Figure 1B). Of note, the combination of a checkpoint inhibitor and tyrosine kinase inhibitor - pembrolizumab plus axitinib - was already in use after its approval by the EMA in September 2019 [8]. High-volume centres used this regimen in 17% of their patients, whereas low-volume centres utilized it in 6% (Figure 1B).

The main treatment outcomes in low- and high-volume centres were similar in 2016 (complete remission: 0 vs. 3%; partial remission: 29 vs. 32%; stable disease: 53 vs. 41%; progression: 18 vs. 24%). This changed in 2019, as the clinical benefit rate between low- and high-volume centres became significantly different at 50 vs. 82% (χ^2 (1, N =44) = 5.0, p =0.025). This was mainly driven by an increase in partial remission rates in high-volume centers from 32% to 50% (Figure 1C). Of note, ECOG values of aRCC patients were comparable in both centres in 2019 with a median of 1 in each centre.

When comparing 2019 with 2016, the survival status of patients revealed that high-volume centres had fewer patients who passed away (67% vs. 76%) and more patients still receiving therapy (32% vs. 24%) compared to low-volume centres in 2016 (Figure 1D). For low-volume centres, these numbers remained nearly unchanged in 2019 (69% and 25%, respectively). In comparison a significant change in high-volume centers was noted: the number of patients who passed away dropped from 67% to 31% (χ^2 (1, N =59) =7.5, p =0.006). Moreover, patients in high-volume centres were more often still receiving first-line therapy in 2019 compared with low-volume centres with 31 vs. 9% (χ^2 (1, N =59) =4.5, p =0.034).

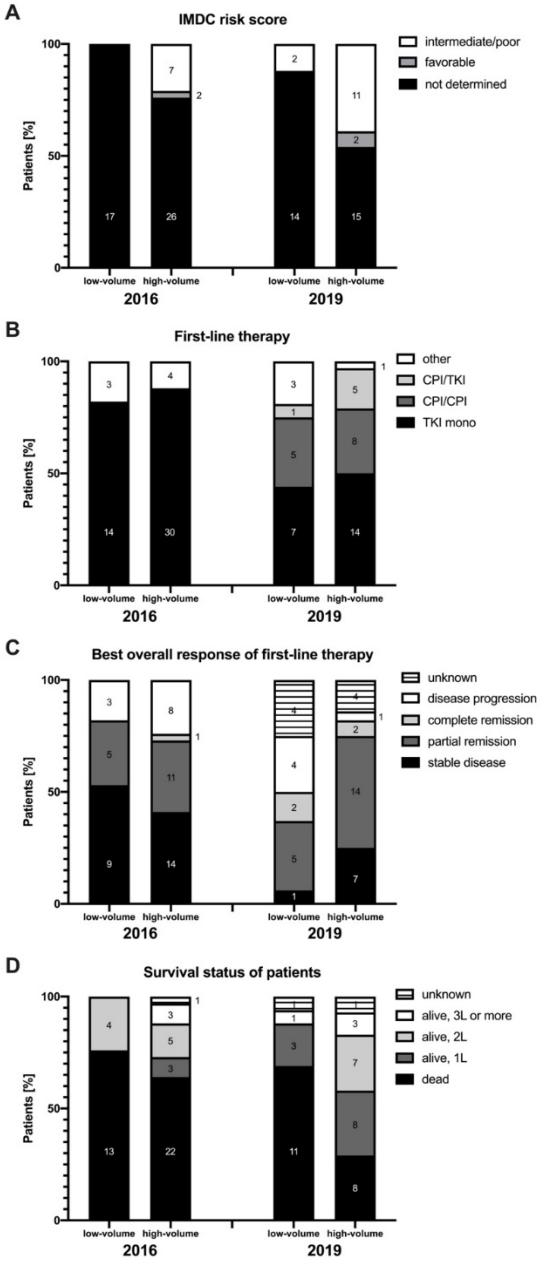

Figure 1. Diagnostic measures, choice of treatment and treatment outcome of aRCC patients in 2016 vs. 2019. The bars represent the percentage of patients from each group. The numbers in the bars represent actual patient numbers. (A) IMDC risk score. (B) First-line therapy. (C) The best overall response of first-line therapy. (D) Survival status of patients. CPI =checkpoint inhibitor; TKI =tyrosine kinase inhibitor; 1/2/3L =1st/2nd/3rd line of therapy

Our results suggest better treatment outcomes for aRCC patients in high-volume centres compared with low-volume centres in 2019. One possible reason might be the more prevalent patient risk stratification according to the IMDC score. Future studies should address how a facility's case volume affects the treatment quality of aRCC patients.

Role of the sponsor

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