Adverse Events (AE) Management among Advanced Renal Cell Carcinoma (aRCC) Patients Receiving First-Line (1L) Axitinib+Checkpoint Inhibitor (CPI) Therapy

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BACKGROUND

- Renal cell carcinoma (RCC) comprises 2–3% of all adult malignancies with an estimated 63,000 incident cases and 14,000 deaths annually in the United States (US).[1]
- Recent advancements with CPI therapeutic agents have changed the treatment paradigm for aRCC. Axitinib in combination with either pembrolizumab (KEYNOTE 426) or avelumab (JAVELIN Renal 101) in metastatic clear cell RCC have demonstrated significantly better efficacy outcomes when compared single agent sunitinib.[2,3]
- While axitinib has demonstrated a generally favorable tolerability profile in real world studies,[4,5] more safety and efficacy data is needed about axitinib+CPI therapy in similar settings.

OBJECTIVE

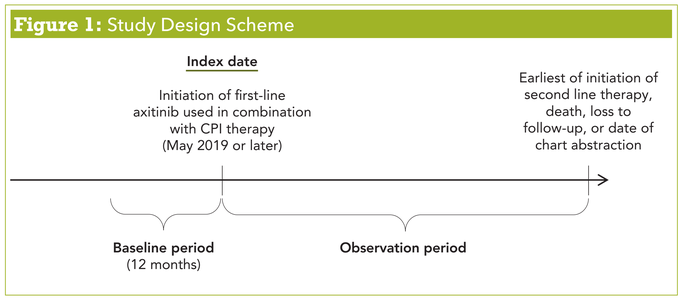
- The objective of this study was to assess the AE profile and management strategies used among US aRCC patients treated with 1L axitinib+CPI therapy.

METHODS

Study design and population

- A retrospective physician-administered chart review of patients with aRCC in the US who were treated with 1L axitinib+CPI (avelumab or pembrolizumab) therapy in US clinical practice.
  - Physicians had to be specialized in oncology and have treated ≥1 patient with aRCC who met the patient eligibility criteria (below) with access to patients' complete medical records.
- Eligible patients were ≥18 years of age at the time of their confirmed aRCC diagnosis who:
  - Were treated with 1L axitinib+CPI combination therapy at or after diagnosis
  - Experienced at least one of the following AEs: diarrhea, fatigue, nausea, hypertension, and palmar plantar erythrodysesthesia (hand-foot syndrome) while treated with axitinib+CPI therapy.
  - Initiated axitinib+CPI therapy (index date) in May 2019 or later and for at least 3 months prior to the start date of medical chart abstraction [**Figure 1**].

Figure 1: Study Design Scheme



Study endpoints

- Type of AEs (i.e., diarrhea, fatigue, nausea, hypertension, and palmar plantar erythrodysesthesia)
- AE characteristics (e.g., severity and seriousness of AE)
- Type of AE management strategies
- AE resolution/improvement (as reported final disposition of AE), described between focal AE management strategies (axitinib modifications [dose reduction and/or treatment interruption] vs. no action)
- Time to AE resolution/improvement, described in two ways:
  - Time from date of AE onset to date of documented AE resolution/improvement
  - Time from date of management strategy initiation (for axitinib modifications) to date of AE resolution/improvement

Statistical analysis

- Baseline patient demographic and clinical characteristics (prior to treatment with axitinib+CPI therapy), AEs characteristics, AE management strategies used, AE resolution/improvement, and time to AE resolution/improvement were described and summarized. Continuous variables were summarized with mean (± standard deviation [SD]) and median (interquartile range [IQR]) values, while categorical variables were summarized with frequency distributions.
- AE resolution/improvement among AEs treated with axitinib modifications vs. no action were described and compared across overall and among severe AEs via Chi-squared test or Fisher's exact test (if any category had <5 patients).

RESULTS

- Patient demographic and clinical characteristics at baseline [**Table 1**]
  - Among 481 patients (median age 63 years, 67% male, 74% White) abstracted by 201 oncologists (67% community-based, 37% academic-based), 131 and 350 patients received axitinib+avelumab and axitinib+pembrolizumab, respectively.
  - 83% of patients remained on 1L at chart abstraction.
  - Among 209 (44%) patients with IMDC risk scores, 11%, 52%, and 37% had favorable, intermediate, and poor risk, respectively.

Table 1: Baseline Patient Characteristics among Patients with aRCC who Experienced AEs while Treated with 1L Axitinib+CPI Therapy[1,2]

	Overall	First-Line Therapy	
		Axitinib + Avelumab	Axitinib + Pembrolizumab
	N=481	N=131	N=350
Age at index[3] (years)			
Mean ± SD	61.9 ± 9.5	59.4 ± 10.3	62.9 ± 9.1
Median (IQR)	62.6 (56.3, 68.6)	60.1 (53.2, 66.6)	63.4 (58.2, 69.3)
Male, n (%)	320 (66.5)	82 (62.6)	238 (68.0)
Race/Ethnicity,[4] n (%)			
White	358 (74.4)	102 (77.9)	256 (73.1)
Black/African-American	76 (15.8)	18 (13.7)	58 (16.6)
Hispanic/Latino	24 (5.0)	3 (2.3)	21 (6.0)
Other[5]	21 (4.4)	9 (6.9)	12 (3.4)
Unknown	6 (1.2)	0 (0.0)	6 (1.7)
Time from advanced RCC diagnosis to index (months)			
Mean ± SD	1.8 ± 6.2	1.3 ± 2.8	2.0 ± 7.1
Median (IQR)	0.5 (0.2, 1.0)	0.5 (0.1, 1.1)	0.5 (0.3, 1.0)
Nephrectomy prior to index, n (%)			
Yes	154 (32.0)	39 (29.8)	115 (32.9)
No	290 (60.3)	74 (56.5)	216 (61.7)
Unknown	37 (7.7)	18 (13.7)	19 (5.4)
Number of metastases, n (%)			
0	36 (7.5)	16 (12.2)	20 (5.7)
1	126 (26.2)	31 (23.7)	95 (27.1)
>1	319 (66.3)	84 (64.1)	235 (67.1)
Largest primary tumor dimension (cm)			
Mean ± SD	4.0 ± 2.9	3.6 ± 2.1	4.2 ± 3.1
Median (IQR)	4.0 (2.0, 5.0)	3.0 (2.0, 4.0)	4.0 (3.0, 5.0)
Unknown, n (%)	94 (19.5)	27 (20.6)	67 (19.1)
Sarcomatoid differentiation, n (%)			
Yes	60 (12.5)	29 (22.1)	31 (8.9)
No	372 (77.3)	81 (61.8)	291 (83.1)
Unknown	49 (10.2)	21 (16.0)	28 (8.0)
IMDC risk score, n (%)[6]	*209 (43.5)*	*40 (30.5)*	*169 (48.3)*
Favorable	22 (10.5)	5 (12.5)	17 (10.1)
Intermediate	109 (52.2)	21 (52.5)	88 (52.1)
Poor	78 (37.3)	14 (35.0)	64 (37.9)

Abbreviations: aRCC = advanced renal cell carcinoma; CPI = checkpoint inhibitor; IMDC = International Metastatic RCC Database Consortium; IQR = interquartile range; MSKCC = Memorial Sloan-Kettering Cancer Center Score for Metastatic Renal Cell Carcinoma; SD = standard deviation.
Notes:
[1] Only patients with first-line axitinib in combination with avelumab or axitinib in combination with pembrolizumab were included in the study.
[2] Patient characteristics were assessed as of the index date or on the date closest to the index during the baseline period, which was defined as the 12-month period prior to the initiation of first-line axitinib in combination with CPI therapy.
[3] Age was calculated at the index date. As only birth month and year were collected, the 15th of the month was used as a proxy for patient's birth date when calculating age.
[4] More than one category may have been reported.
[5] Other races include Asian, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander.
[6] IMDC prognostic risk scores were provided for 157 patients and computed for 52 patients by adding prognostic risk factor information to calculate the score.

- Types of AEs [**Table 2**]
  - Among patients, AE incidence varied by type: 48% fatigue, 38% diarrhea, 29% nausea, 22% hypertension, 11% PPE.
  - Median time from 1L initiation to AE onset was 1 month.
  - Out of 729 total AEs:
    - 376 (52%), 242 (33%), and 102 (14%), were classified as mild, moderate, and severe AEs, respectively (as defined by the Common Terminology Criteria for Adverse Events [CTCAE] v5).
    - 130 (18%) were classified as serious AEs.
    - 12 (2%) were recurrent AEs (i.e., the second or later distinct episode of AE of the same type for a given patient).

Table 2: AEs among Patients with aRCC Treated with 1L Axitinib+CPI Therapy, by Type of AE[1]

	Overall	AE				
		Fatigue	Diarrhea	Nausea	Hypertension	Palmar-plantar erythrodysesthesia
	N=729	N=234	N=186	N=146	N=108	N=55
Time from index to AE incidence (months)						
Mean ± SD	1.5 ± 1.6	1.6 ± 1.8	1.4 ± 1.6	1.4 ± 1.7	1.6 ± 1.3	1.4 ± 1.2
Median (IQR)	1.0 (0.3, 2.0)	1.1 (0.4, 2.0)	1.0 (0.3, 1.8)	0.9 (0.2, 1.9)	1.1 (0.5, 2.6)	1.0 (0.4, 1.8)
AE severity, n (%)						
Mild	376 (51.6)	139 (59.4)	87 (46.8)	84 (57.5)	34 (31.5)	32 (58.2)
Moderate	242 (33.2)	69 (29.5)	64 (34.4)	44 (30.1)	48 (44.4)	17 (30.9)
Severe	102 (14.0)	21 (9.0)	34 (18.3)	18 (12.3)	23 (21.3)	6 (10.9)
Unknown	9 (1.2)	5 (2.1)	1 (0.5)	0 (0.0)	3 (2.8)	0 (0.0)
Serious AE, n (%)						
Yes	130 (17.8)	21 (9.0)	51 (27.4)	17 (11.6)	28 (25.9)	13 (23.6)
No	572 (78.5)	203 (86.8)	128 (68.8)	125 (85.6)	75 (69.4)	41 (74.5)
Unknown	27 (3.7)	10 (4.3)	7 (3.8)	4 (2.7)	5 (4.6)	1 (1.8)
Recurrent AE,[2] n (%)	12 (1.6)	2 (0.9)	2 (1.1)	5 (3.4)	2 (1.9)	1 (1.8)

Abbreviations: 1L = first line; AE, adverse event; aRCC = advanced renal cell carcinoma; CPI = checkpoint inhibitor; IQR, interquartile range; SD, standard deviation.
Notes:
[1] Only patients with first-line axitinib in combination with avelumab or axitinib in combination with pembrolizumab were included in the study.
[2] Recurrent AEs were defined as two or more distinct episodes of AE of the same type.

- AE management strategies [**Table 3**]
  - AE management strategies were defined as follows:
    - No action indicates that no modifications to axitinib and/or CPI treatment and no supportive care were reported to address the AE.
    - Axitinib modifications include AEs managed via axitinib dose reduction and/or temporary treatment interruption (with or without additional CPI modifications and/or supportive care).
    - Supportive care includes typical treatments for each type of AE, and primarily consisted of anti-emetics, anti-diarrheals, anti-hypertensives, and topical treatments.
    - CPI modifications include CPI treatment interruptions and/or treatment discontinuation (with or without supportive care).
    - Axitinib discontinuation includes AEs that were ultimately managed via axitinib discontinuation, regardless of whether other management strategies (e.g., axitinib modifications) were used prior to discontinuation.
  - Out of 729 total AEs, 251 (34%) and 198 (27%) were managed with axitinib modifications and no action, respectively.
    - Among severe AEs (N=102), 32 (31%) and 15 (15%) were managed with axitinib modifications and no action, respectively.
  - Of 251 AEs managed with axitinib modifications, 60% dose reduced and 49% stopped temporarily.
    - Of 32 severe AEs managed with axitinib modifications, 47% dose reduced and 59% stopped temporarily.

Table 3: Management Strategies for AEs Experienced Among Patients with aRCC Treated with 1L Axitinib+CPI Therapy, by AE Severity

	Overall	AE Severity[1]		
		Mild	Moderate	Severe
	N=729	N=376	N=242	N=102
No action,[2] n (%)	198 (27.2)	131 (34.8)	43 (17.8)	15 (14.7)
Axitinib modifications,[3] n (%)	251 (34.4)	87 (23.1)	132 (54.5)	32 (31.4)
Dosage reduction	150 (59.8)	50 (57.5)	85 (64.4)	15 (46.9)
Treatment interruption	124 (49.4)	41 (47.1)	64 (48.5)	19 (59.4)
Axitinib modifications with CPI modification,[3] n (%)	96 (38.2)	38 (43.7)	48 (36.4)	10 (31.3)
Axitinib dosage reduction + CPI modification	43 (44.8)	18 (47.4)	22 (45.8)	3 (30.0)
Axitinib treatment interruption + CPI modification	70 (72.9)	23 (60.5)	38 (79.2)	9 (90.0)
Supportive care only,[4] n (%)	202 (27.7)	151 (40.2)	45 (18.6)	6 (5.9)
CPI modification only (with or without supportive care),[3] n (%)	24 (3.3)	7 (1.9)	12 (5.0)	5 (4.9)
Axitinib discontinuation,[5] n (%)	54 (7.4)	0 (0.0)	10 (4.1)	44 (43.1)

Abbreviations: 1L = first line; AE, adverse event; aRCC = advanced renal cell carcinoma; CPI, checkpoint inhibitor.
Notes:
[1] There were 9 AEs for which the severity was unknown. AE severity was defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 5 for each AE type.
[2] No action indicates that no modifications to axitinib, no modifications to IO therapy, and no supportive care were reported to address the AE.
[3] Axitinib modifications consist of axitinib dose reductions and/or treatment interruptions. CPI modifications consistent of CPI treatment interruptions and/or treatment discontinuation.
[4] Primarily consists of anti-emetics, anti-diarrheals, anti-hypertensives, and topical treatments.
[5] This category also includes AEs that were managed with other management strategies listed above (e.g., axitinib modifications) before axitinib discontinuation.

- Comparison of AE Resolution/Improvement and Time to Resolution/Improvement among AEs treated with Axitinib Modifications vs. No Action [**Table 4**]
  - A significantly higher proportion of AEs treated with axitinib modification were reported as resolved/improved as the final disposition, relative to AEs where no action was taken, both across all AEs (84% vs. 60%; p<0.001) and among severe AEs (81% vs. 7%; p<0.001).
  - Among AEs with reported dates of resolution/improvement, median time to resolution/improvement (from AE onset) was numerically higher for AEs treated with axitinib modification vs. no action, both across all AEs (18 vs. 31 days) and among severe AEs (16 vs. 53 days).
  - Among AEs that resolved/improved, median time from AE management strategy initiation to resolution/improvement was 15 days for all AEs and 13 days for severe AEs treated with axitinib modification.

Table 4: Comparison of AE Resolution/Improvement and Time to Resolution/Improvement among AEs treated with Axitinib Modifications vs. No Action

	All AEs (N=449)			Severe AEs (N=47)		
	Axitinib modification[1] 251 (56%)	No action[2] 198 (44%)	P-value	Axitinib modification[1] 32 (68%)	No action[2] 15 (32%)	P-value
Resolution/improvement,[3] n (%)	208 (84%)	111 (60%)	< 0.001	26 (81%)	1 (7%)	< 0.001
Days to resolution/improvement,[4] median (IQR)						
From AE onset	18 (10, 29)	31 (15, 62)		16 (6, 29)	53 (53, 53)	
From strategy initiation	15 (8, 28)	-		13 (5, 27)	-	

Abbreviations: AE = adverse event; CPI = checkpoint inhibitor; IQR = interquartile range.
Notes:
[1] Includes axitinib dose reduction and/or treatment interruption, with or without any CPI modifications.
[2] Indicates that no interventions of any type were given.
[3] Proportions are among AEs with known outcome. P-values were calculated using Chi-squared test for all AEs and Fisher's exact test for severe AEs (as the latter included categories with <5 patients).
[4] Assessed where dates of AE resolution/improvement were available.

LIMITATIONS

- With an analysis of non-randomized AE management strategy groups, unmeasured confounding and potential biases (e.g., selection bias) could account for observed differences in AE resolution/improvement outcomes.
- In contrast to clinical trials with protocol-specified definitions of clinical events, assessments of AE outcomes in retrospective studies of real-world clinical practice may not be made consistently across patients and across physician practices.
- Missing data may exist, as AEs never reported to a physician (i.e., if they were self-resolved without seeking care) will not be captured. Moreover, actions taken to manage AEs (e.g., axitinib dose reductions) may be underreported if they were not consistently reported by physicians. As such, documented management strategies for AEs would only apply to AEs that require healthcare intervention.

CONCLUSIONS

- **Patients whose AEs were managed with axitinib treatment modifications had numerically higher AE resolution/improvement rates and shorter time to resolution/improvement compared to no action, both across all AEs and among severe AEs.**
- **This real-world study highlights the importance of proactive therapy management strategies to enable optimal axitinib+CPI combination treatment.**

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