

Outcome after treatment with axitinib in children, young adults, and adults with renal cell carcinoma: a narrative review

Julia Sprokkerieft^{a,*}, Justine N. van der Beek^a, Filippo Spreafico^b, Barbara Selle^c,
Tanzina Chowdhury^d, Norbert Graf^e, Arnaud C. Verschuur^f, Rana Dandis^a, Axel Bex^{g,h},
James I. Gellerⁱ, Godelieve A.M. Tytgat^a, Marry M. van den Heuvel-Eibrink^a

^a Department of Pediatric Oncology, Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

^b Pediatric Oncology Unit, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy

^c Hopp Children's Cancer Center Heidelberg (KiTZ) & Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany

^d Pediatric Oncology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom

^e Department of Pediatric Oncology and Hematology, Saarland University, Homburg, Germany

^f Department of Pediatric Hematology-Oncology, Hôpital d'Enfants de la Timone, APHM, Marseille, France

^g Department of Urology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam 1066CX, the Netherlands

^h Division of Surgical and Interventional Science, The Royal Free London NHS Foundation Trust and UCL, London, UK

ⁱ Division of Oncology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, USA

ARTICLE INFO

Keywords:

Pediatric
young adult
renal cell carcinoma
axitinib

ABSTRACT

Renal cell carcinoma (RCC) is a very rare type of renal cancer in children and young adults. When metastasized or recurrent, no standards of care are available, and outcome is still poor. The tyrosine kinase inhibitor axitinib is approved for treatment of RCC in adults, but its effects in children and young adults with RCC remains unclear. Due to the histological and biological differences between children and adults, it is difficult to extrapolate knowledge on treatments from the adult to the pediatric and young adult setting. This paper summarizes the clinical characteristics and outcomes of patients with RCC who were treated with axitinib, with the aim to gain insight in the clinical efficacy of this compound in this young patient group.

1. Introduction

Renal tumors account for 5 % of all new cancer diagnoses in children (Nakata et al., 2020). Renal cell carcinoma (RCC) is the most prevalent type of kidney cancer in adults, whereas the disease is very rare in children, only accounting for less than 5 % of all pediatric renal tumors (Spreafico et al., 2010). In 1998, it was suggested that pediatric RCC may be different from adult RCC as children seemed to present with a unique subtype with a translocation involving Xp11.2 (Carcao et al., 1998). This translocation-type RCC (MiT-RCC) is characterized by translocations in the microphthalmia transcription (MiT) factor family, and mainly involves *TFE3* and *TFEB* translocations (Inamura, 2017).

TFE3 translocations have been thoroughly explored and comprise more than 20 different *TFE3*-gene fusions such as *ASPSCR1-TFE3*, *PRCC-TFE3*, *SFPQ-TFE3* and *NONO-TFE3* (Inamura, 2017; Argani et al., 2001; Sun et al., 2021). After inclusion of MiT-RCC into the 2004 WHO classification system, the difference in histological subtypes between adults and children became more evident (Bruder et al., 2004; Eble et al., 2004; Geller et al., 2008; He et al., 2021; Ray et al., 2020). Whereas in children the MiT-RCC subtype seems to occur most frequently (representing approximately 50 % of pediatric RCC), in adults, clear-cell RCC remains the most common histological subtype (van der Beek et al., (2020); van der Beek et al., (2021)). This makes a direct comparison between treatment and outcome of adults and children with RCC challenging

Abbreviations: BID, Twice a day; COG, Children's Oncology Group; ECOG, Eastern Cooperative Oncology group; HR, Hazard ratio; IMDC, International Metastatic Database Consortium; MiT, Microphthalmia transcription; MiT-RCC, Translocation RCC; MSKCC, Memorial Sloan Kettering Center; ORR, Overall response rate; OS, Overall survival; PFS, Progression-free survival; RCC, Renal cell carcinoma; SIOP-RTSG, International Society of Pediatric Oncology – Renal Tumor Study Group; TKI, Tyrosine kinase inhibitor; TTP, Time-to-progression; VEGF, Vascular endothelial growth factor.

* Correspondence to: Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, Utrecht 3584 CS, the Netherlands.

E-mail address: j.sprokkerieft@prinsesmaximacentrum.nl (J. Sprokkerieft).

<https://doi.org/10.1016/j.critrevonc.2024.104523>

Received 3 May 2024; Accepted 21 September 2024

Available online 24 September 2024

1040-8428/© 2024 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

(Hsieh et al., 2017).

For pediatric RCC, upfront surgery is standard of care for localized disease. Advances in metastatic systemic therapy and adjuvant therapy have been much slower than in the adult setting. Systemic treatment is not indicated, and it is generally administered only in patients with unresectable or metastatic disease, or at recurrence. Furthermore, due to its rarity, treatment options are unclear because of limited evidence on agent efficacy. Currently, the International Society of Pediatric Oncology – Renal Tumor Study Group (SIOP-RTSG) 2016 UMBRELLA protocol recommends use of sunitinib in pediatric patients with advanced or metastatic RCC. Upon progression, novel agents such as alternative TKIs or immunotherapy are considered (van den Heuvel-Eibrink et al., 2017). However, the optimal drug or drug combination still needs to be determined for these patients.

The treatment setting for adult RCC is rapidly changing. The KEYNOTE-564 trial recently showed the benefit of adjuvant treatment with pembrolizumab, an immune checkpoint inhibitor (ICI), as an option after resection with curative intent (Choueiri et al., 2021a; Bedke et al., 2022). In the metastatic setting, a wide variety of effective treatment options are available, including combinations of ICI with either anti-CTLA4 or tyrosine kinase inhibitors (TKI) in first line (PDQ Cancer, 2002; Ljungberg et al., 2022). These combinations have superseded treatment with single-agent TKI, which is now restricted to further lines or in situations where ICI are not available or not tolerated (Ljungberg et al., 2022).

Axitinib is a TKI that targets the vascular endothelial growth factor

receptors (VEGFR) 1, 2 and 3, and thereby suppresses VEGF pathway signaling (Fig. 1). Preclinical studies showed that through inhibition of this pathway, angiogenesis and likely tumor progression may be prevented, though tumors can develop resistance to anti-angiogenic therapy (Giuliano and Pagès, 2013; Haibe et al., 2020; Hicklin and Ellis, 2005; Keating, 2015; McIntyre and Harris, 2015; Negrier et al., 2020). First-line cabozantinib is currently recommended for advanced papillary RCC based on the increased progression-free survival (PFS) and response rate of cabozantinib compared to sunitinib in the Southwest Oncology Group (SWOG) phase II PAPMET trial (Pal et al., 2021). The phase II AXIPAP trial showed efficacy of axitinib in adult patients with metastatic papillary RCC but is not recommended as first-line in this setting (Negrier et al., 2020). A single-arm, phase II study provided evidence of clinical activity using axitinib after progression with checkpoint inhibitors in adult patients with metastatic RCC (Ornstein et al., 2019). Axitinib in combination with pembrolizumab has been accepted as first-line treatment for patients with metastatic clear cell RCC (Ljungberg et al., 2022).

Axitinib is currently not approved for treatment of pediatric RCC due to the MiT-RCC histology commonly found in pediatric RCC and limited data in this setting. The low prevalence of pediatric RCC makes clinical trials challenging. However, Geller et al. reported a positive response to axitinib in one pediatric patient with RCC (Geller et al., 2018). The Children's Oncology Groups (COG) phase I trial (ADVK1315) studied axitinib in children with recurrent or refractory solid tumors, and a recommended starting dose was established (Geller et al., 2018).

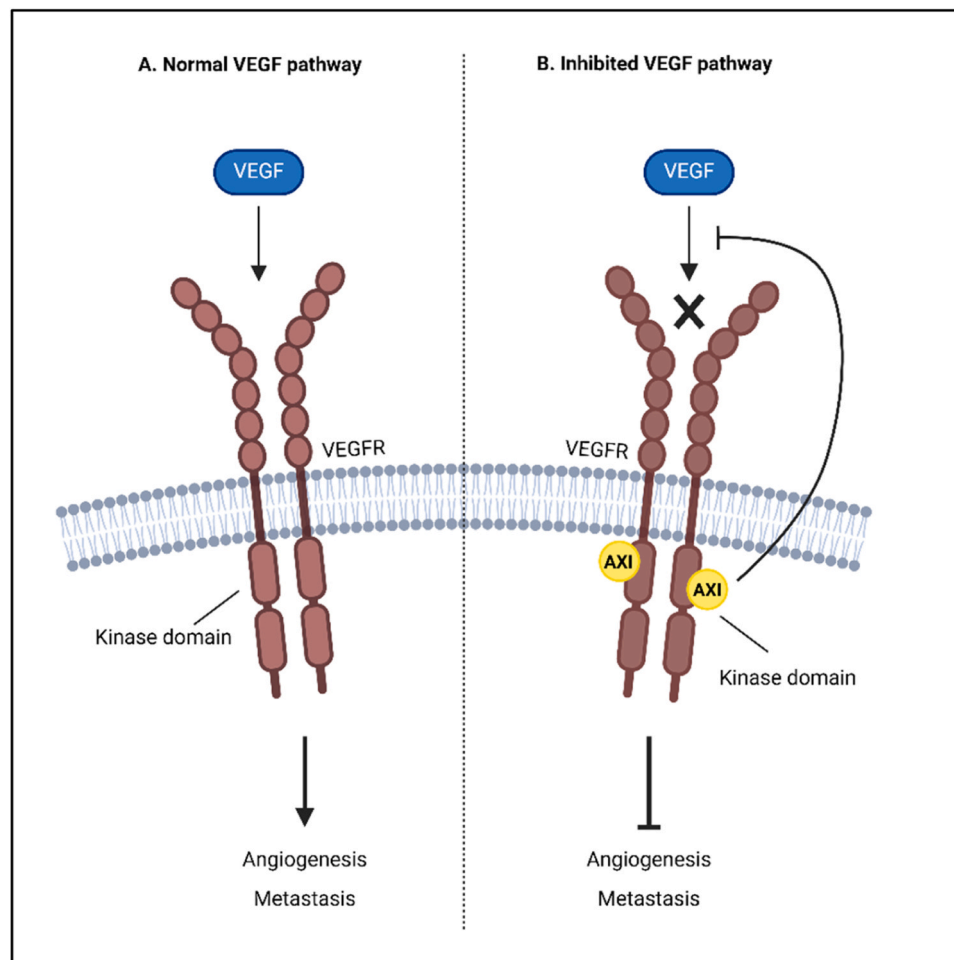


Fig. 1. The normal VEGF pathway versus the VEGF pathway inhibited by axitinib. A. The normal VEGF pathway stimulates angiogenesis and tumor metastasis. B. Upon administration of axitinib (Axi), the drug binds intracellularly to the kinase domain of the VEGF receptor. This indirectly inhibits the binding of VEGF to the VEGF receptor and inhibits angiogenesis and metastasis. Created with BioRender.com.

Following these results, a 3-arm randomized trial for axitinib was initiated for patients with MiT-RCC of all age groups, including children (AREN1721) (Geller, 2020).

This review aims to summarize the clinical effects of axitinib through a literature review of randomized controlled trials in adults, and all available literature concerning pediatric and young adults on axitinib, with the goal to give an overview of its possible application and effects in the described patient settings.

2. Methods

For this review, PubMed, Embase and Cochrane were searched for

relevant articles, using a search comprising the main terms 'renal cell carcinoma' and 'axitinib'. Inclusion criteria for title and abstract screening were histologically confirmed RCC, adult RCC studies with ten or more patients, all available studies including pediatric and young adult RCC cases (≤ 25 years) and treatment with axitinib. Exclusion criteria were animal or *in vitro* studies, case series or cohort studies with less than ten patients in adult studies, or any language other than English or Dutch (Fig. 2). A total of 1851 articles were identified in PubMed ($n = 703$), Embase ($n=1058$) and Cochrane ($n=90$) after a double-blind screening process by two lead investigators. After deduplication, 1463 articles remained for title- and abstract screening. Based on the in- and exclusion criteria, 1295 articles were excluded. Through full-text

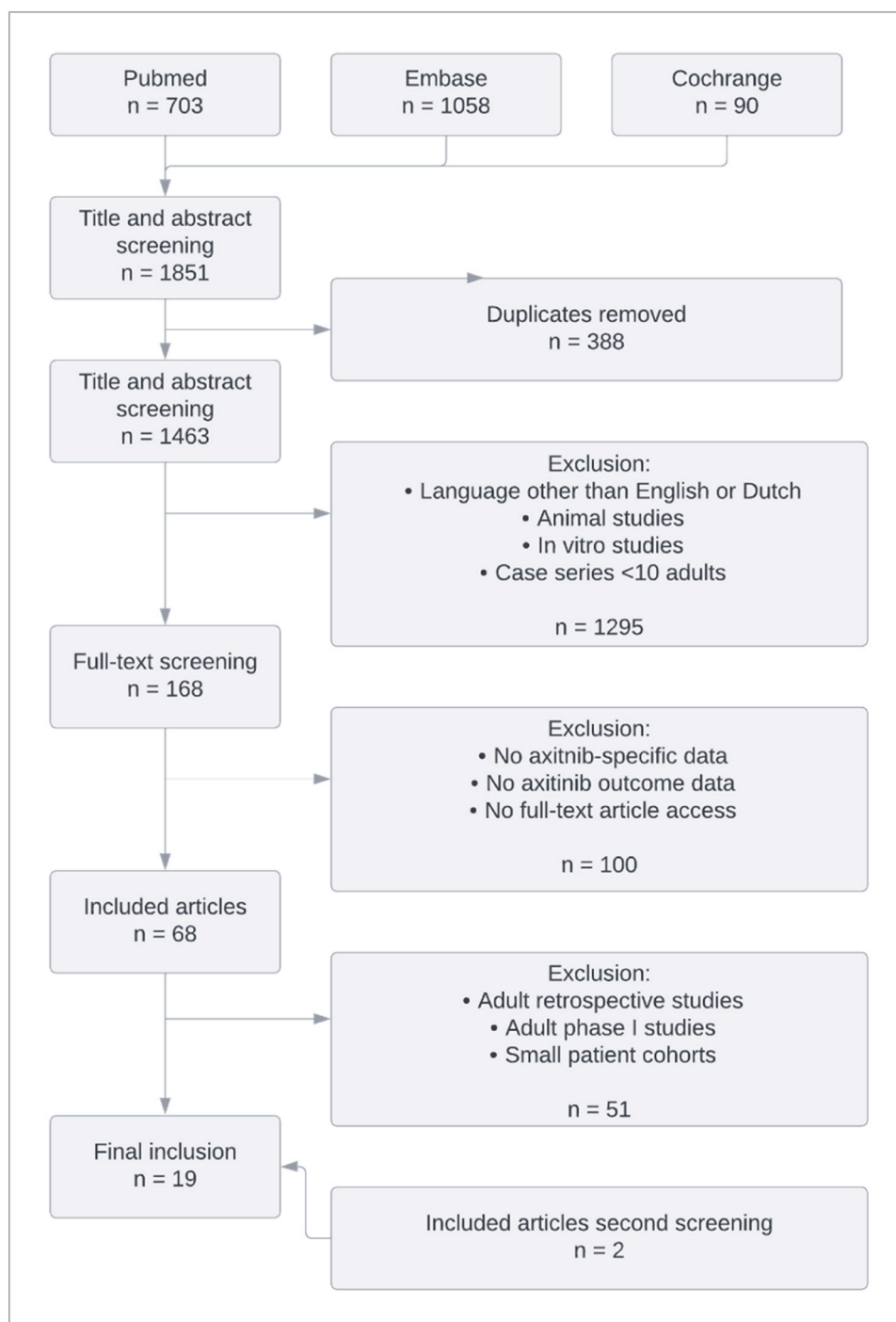


Fig. 2. Flow chart of included studies.

screening, articles were removed when the data were not reported separately for axitinib, and outcome data such as overall survival (OS), PFS, a hazard ratio (HR) or overall response rate (ORR) were not reported. In case more than one report was identified on a clinical trial, the Cochrane article was excluded and the most recently updated article from PubMed or Embase was included. Ultimately, a total of 68 articles were identified but given the large number of articles, it was decided to only include adult randomized controlled trials and all pediatric studies. Finally, 17 articles remained, with 12 randomized controlled trials for adult RCC and five case reports about pediatric RCC. The search was updated in 2023 and led to the further inclusion of one trial, two trial updates and one pediatric case report.

3. Results

3.1. Adult randomized clinical trials

3.1.1. Clinical- and tumor characteristics

Thirteen publications described nine unique phase II or phase III trials that provided information on 4087 different patients (Table 1). The median age ranged between 58 and 65 years, and more males (2761/4087 (72.7 %)), than females were included. One trial included two patients of 20 and 22 years old; these patients were not reported in the included pediatric case reports (Rini et al., 2011).

Most trials included patients with metastatic RCC, whereas some studies included patients with advanced RCC. Performance status was determined through Eastern Cooperative Oncology Group (ECOG) performance status and prognosis was assessed by Memorial Sloan Kettering Center (MSKCC) score and the International Metastatic RCC Database Consortium (IMDC) risk model (Table 1). On average, 73.0 % of the patients with ECOG performance status were classified with ECOG grade 0, which indicates patients were not restricted by their disease (Azam et al., 2019; Choueiri et al., 2021b; Gross-Goupil et al., 2018; Kollmannsberger et al., 2021). In another study, where axitinib was compared to sorafenib, 37.1 % of the patients receiving axitinib were classified with intermediate risk and similarly, 35.9 % of patients receiving sorafenib also had intermediate risk (based on MSKCC score) (Rini et al., 2011; Motzer et al., 2013). The four remaining studies applied the IMDC risk model, which is also used for patients with metastatic RCC (Tanaka et al., 2016). Herein, patients were assessed to have primarily favorable - intermediate risk (25.3 % - 64 %) (Motzer et al., 2019; Powles et al., 2020; Rini et al., 2019; Voss et al., 2019). The RENOTORCH study only included patients with intermediate-poor risk (81.5 % and 18.5 %, respectively (Yan et al., 2023)). One study did not specify the risk stage of the patients treated with axitinib or placebo (Rini et al., 2016).

Most studies required presence of clear-cell RCC as an inclusion criterion and therefore, only two studies described different histological subtypes (Table 2). Kollmannsberger et al., included 23 patients with unclassified type or not otherwise specified RCC (Kollmannsberger et al., 2021). In the ATLAS trial, histological subtypes were defined as clear-cell RCC and non-clear-cell RCC with <50 % of the patients being in the latter category (Gross-Goupil et al., 2018).

3.1.2. Outcomes with axitinib monotherapy

The phase III ATLAS trial compared 724 patients with non-metastatic disease in the adjuvant setting, who were at risk of recurrence and had not been previously treated with anti-angiogenic- or systemic treatment (Gross-Goupil et al., 2018). Patients were either treated with axitinib (5 mg BID) or given placebo (Tables 1 and 3). The trial was discontinued due to no significant disease-free survival (DFS) improvement in the axitinib arm (HR 0.87; 95 % CI 0.660–1.147; $p = 0.321$) (Table 1) (Gross-Goupil et al., 2018). Toxicity profiles were similar for both arms except for grade 3/4 adverse events, which were reported more frequently in the axitinib arm (Table 3) (Gross-Goupil et al., 2018).

In a phase II trial, 213 treatment-naïve patients with metastatic

disease were included. (Tables 1 and 4) (Rini et al., 2016). This trial from Rini et al. studied the effect of titration; patients received 5 mg BID axitinib either with axitinib dose titration or with placebo dose titration up to 7 mg BID. Patients who were not eligible for titration were placed in a separate non-randomized arm that received 5 mg axitinib BID. There was no significant difference in PFS (14.5 vs. 15.7 months) and OS (42.7 vs. 30.4 months) (HR 0.850; 95 % CI 0.54–1.35; $p = 0.24$ and HR 0.785; 95 % CI 0.485–1.272; $p = 0.162$) between the axitinib titration and placebo titration arms, respectively (Supplementary figures 1–4) (Rini et al., 2016; Tomita et al., 2019). However, it should be noted that dose reductions and dose interruptions were more frequent in the axitinib titration arm and could account for the lack of an improved PFS. At the same time, an objective response was observed more frequently with axitinib titration and could be of clinical significance. The adverse events were considered manageable but were reported at a higher incidence in the axitinib titration group and mainly consisted of hypertension, hand-foot syndrome and vomiting (Rini et al., 2016).

Axitinib was also compared to sorafenib in two unique phase III trials. Hutson et al. compared axitinib to sorafenib in the first line setting in 288 patients with metastatic RCC. The AXIS trial included 723 patients with metastatic disease and were treated second line, following first line sunitinib, bevacizumab plus interferon-alfa, temsirolimus, or cytokines (Rini et al., 2011; Motzer et al., 2013; Hutson et al., 2017). Both trials adhered to a sorafenib dose of 400 mg twice a day (BID) and an axitinib dose of 5 mg BID. Hutson et al. and Rini et al. allowed dose-titration depending on predefined clinical events or hypertension and adverse events above grade 2, respectively (Rini et al., 2011; Hutson et al., 2017). In the AXIS trial, patients who received axitinib had a significantly better PFS compared to patients treated with sorafenib (8.3 vs. 5.7 months, HR, 0.656; 95 % CI, 0.552–0.779) but the PFS in the smaller trial did not reach significance (10.1 vs. 6.5 months; HR, 0.77; 95 % CI, 0.56–1.05; $p = 0.038$) (Supplementary figures 1 and 2) (Motzer et al., 2013; Hutson et al., 2017). Although the OS did not increase with use of axitinib in either trial, the AXIS trial highlighted the potential of axitinib as a second-line agent in patients with metastatic RCC (AXIS: 20.1 vs. 19.2 months; Hutson et al.: 21.7 vs. 23.3 months) (Table 1; Supplementary figure 3) (Motzer et al., 2013; Hutson et al., 2017).

In a randomized phase II trial, axitinib was compared to a novel drug called AGS-16C3F. The antibody-drug conjugate binds the cell surface marker ectonucleotide pyrophosphatase 3 (ENPP3) and attacks cells with a microtubule disruptive agent (Table 1) (Kollmannsberger et al., 2021). The drugs were given as further-line treatment in 133 patients with metastatic disease. Similar to the previous studies, the axitinib dose was also 5 mg BID (Table 3). Patients who received AGS-16C3F had a lower PFS compared to those who received axitinib (13.1 vs. 15.4 months, HR, 1.676; 95 % CI, 1.107–2.537) (Supplementary figures 1 and 2) (Kollmannsberger et al., 2021). AGS-16C3F caused more ocular toxicities (44 vs. 26 %) whereas axitinib caused more diarrhea (48 % vs. 17 %). The study did not meet its primary endpoint and AGS-16C3F was not further studied. One limitation of the study was the population heterogeneity due to the study's inclusion of non-clear cell RCC. However, the study emphasizes the potential of axitinib as further-line treatment in patients with metastatic disease.

3.1.3. Outcomes with axitinib combination therapy

Axitinib was also administered in combination with other agents in the metastatic setting. Two trials studied whether a combination of axitinib with pembrolizumab (phase III KEYNOTE-426) or axitinib with avelumab (phase III JAVELIN Renal 101) would result in an improved outcome compared to sunitinib (Table 1) (Choueiri et al., 2020; Haanen et al., 2023; Motzer et al., 2019; Plimack et al., 2023; Powles et al., 2020; Rini et al., 2019; Tomita et al., 2022). Both studies prescribed 5 mg axitinib BID and 50 mg sunitinib daily (Table 3). The KEYNOTE-426 trial consisted of 861 treatment-naïve patients with advanced disease. Axitinib combined with pembrolizumab led to an improved PFS compared to sunitinib (16 versus 11 months, HR 0.68; 95 % CI

Table 1Overview of characteristics and outcome of included series (≥ 10 patients) of renal cell carcinoma (RCC) patients treated with an axitinib-monotherapy or axitinib-combination treatment.

#	Author, year	Study type	Treatment approach	Line of treatment	Nr. of patients	Gender (M/F)	Age (years, range) (md)	Surgery	Risk group	Risk stage (nr. of patients)	Evaluation system	PFS (months, 95 %CI)	OS (months, 95 %CI)	Effect axitinib-treatment (95 % CI)
1	(Gross-Goupil et al., 2018)	Phase III (R): ATLAS	Axitinib	First line	363	280/83	md 58 (51–66)	363	ECOG PS	0 (313)	NS	-	-	DFS HR 0.870 (0.660–1.147; $p = 0.321$)
			Placebo		361	250/111	md 58 (51–66)	361		1 (43)				
2	(Rini et al., 2016) (Tomita et al., 2019)	Phase II (R)	Axitinib titration	First line	56	143/70	md 62 (28–87)	183/213	Not studied	0 (314)	NS	md 14.5 (9.2–24.5)	md 42.7 (24.7 – not reached)	PFS HR 0.85 (0.54–1.35) $p = 0.24$ (one-sided)
			Placebo titration		56					1 (44)		md 15.7 (8.3–19.4)	md 30.4 (23.7–45.0)	OS HR 0.785 (0.485–1.272) $p = 0.162$ (one-sided)
			Non-randomized		91							md 16.6 (11.2–22.5)	NS	NS
3	(Rini et al., 2011) (Motzer et al., 2013)	Phase III (R): AXIS	Axitinib	Second line	361	265/96	md 61 (20–82)	658/723	MSKCC	Favorable (100)	RECIST 1.0	md 8.3 (6.7–9.2)	md 20.1 (16.7–23.4)	PFS HR 0.656 (0.552–0.779) $p < 0.0001$
										Intermediate (134)				OS HR 0.969 (0.800–1.174) $p = 0.374$
										Poor (118)				
										Not available (9)				
			Sorafenib		362	258/104	md 61 (22–80)			Favorable (101)		md 5.7 (4.7–6.5)	md 19.2 (17.5–22.3)	
										Intermediate (130)				
										Poor (120)				
										Not available (11)				
4	(Hutson et al., 2017)	Phase III (R)	Axitinib	First line	192	NS	NS	-/288	ECOG PS	0 (NS)	RECIST 1.0	md 10.1	md 21.7 (18.0–31.7)	PFS HR 0.77 (0.56–1.05)
			Sorafenib		96					1 (NS)			ORR 32 %	$p = 0.038$
												md 6.5	md 23.3 (18.1–33.2)	OS HR 0.995 (0.731–1.356)
													ORR 15 %	$p = 0.4883$
														ORR: $p = 0.0006$
5	(Kollmannsberger et al., 2021)	Phase II (R)	AGS–16C3F	$\geq$ Third line	67	49/18	md 63 (33–77)	NS	ECOG PS	0 (19)		md 2.9 (2.0–4.0)	md 13.1 (10.1–23.0)	PFS HR 1.676 (1.107–2.537)
			Axitinib		66	49/17	md 60 (37–88)			1 (48)		md 5.7 (5.3–9.1)	md 15.4 (12.5–21.6)	OS HR 1.079 (0.681–1.707)
6	(Rini et al., 2019) (Powles et al., 2020) (Plimack et al., 2023)	Phase III (R): KEYNOTE–426	Axitinib + pembrolizumab	First line	432	308/124	md 62 (55–68)	357/432	IMDC	1 (47)	RECIST 1.1	md 16.0 (14.0–20.0)	md 46.0	PFS HR 0.68 (0.58–0.80)
										Favorable (138)				OS HR 0.73 (0.60–0.88)
										Intermediate (238)				
										Poor (56)				
			Sunitinib		429	320/109	md 61 (53–68)	358/429		Favorable (131)		md 11.0 (8.9–13.0)	md 41.0	
										Intermediate (246)				
										Poor (52)				

(continued on next page)

Table 1 (continued)

#	Author, year	Study type	Treatment approach	Line of treatment	Nr. of patients	Gender (M/F)	Age (years, range) (md)	Surgery	Risk group	Risk stage (nr. of patients)	Evaluation system	PFS (months, 95 %CI)	OS (months, 95 %CI)	Effect axitinib-treatment (95 % CI)
7	(Choueiri et al., 2020) (Motzer et al., 2019) (Tomita et al., 2022) (Haanen et al., 2023)	Phase III (R): JAVELIN Renal 101	Avelumab + axitinib	First line	442	316/126	md 62.0 (29.0–83.0)	352	IMDC	Favorable (94) Intermediate (271) Poor (72) Not reported (5)	RECIST 1.1	md 13.9 (11.1–16.6)	Median not reached (42.2-NE)	PFS HR 0.67 (0.568–0.785; one-sided $p < 0.0001$) OS HR 0.79 (0.634–0.969; one-sided $p = 0.0116$)
			Sunitinib		444	344/100	md 61.0 (27.0–88.0)	355		Favorable (96) Intermediate (276) Poor (71) Not reported (1)		md 8.5 (8.2–9.7)		
8	(Yan et al., 2023)	Phase III (R): RENOTORCH	Axitinib + toripalimab	First line	210	162/48	md 60 (20.0–78.0)	135	IMDC	Intermediate (169) Poor (41)	RECIST 1.1	md 18.0 (15.0-NE)	md NE (NE-NE)	PFS HR 0.65 (0.49–0.86) $p = 0.0028$ OS HR 0.61 (0.404–0.922)
			Sunitinib		211	157/54	md 60.0 (28–78)	127		Intermediate (174) Poor (37)		md 9.8 (8.3–13.8)		
9	(Voss et al., 2019)	Phase II (R): DART study	Axitinib + dalantercept	≥ Second line	58	38/20	md 63 (37–81)	56	IMDC	Favorable (11) Intermediate (45) Poor (2)	RECIST 1.1	md 6.8 (4.5–9.4)	Median not reached ORR: 19 %	PFS HR 1.11 (0.71–1.73) OS HR 1.39 (0.70–2.77)
			Axitinib + placebo		61	35/26	md 59 (27–75)	52		Favorable (16) Intermediate (43) Poor (2)		md 5.6 (3.3–8.3)		
10	(Choueiri et al., 2021b)	Phase II (R): TRAXAR	Carotuximab + axitinib	Second line	75	49/26	md 63.0	NS	ECOG PS	0 (39) 1 (36)	RECIST 1.1	md 6.7 (5.6–13.1)	NS	PFS HR 1.42 (0.88–2.30)
			Axitinib		75	57/18	md 65.0			0 (38) 1 (37)		md 11.4 (5.8-NE)		

R = randomized; Nr = number; M = male; F = female; md = median; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MSKCC = Memorial Sloan-Kettering Cancer Center score; IMDC = International Metastatic RCC Database Consortium risk score; DFS = disease-free survival; PFS = progression-free survival; OS = overall survival; ORR = objective response rate; HR = hazard ratio; NS = not specified.

Table 2

Distribution of histological subtypes in included studies of axitinib monotherapy and combination therapy in adult, pediatric and/or young adult patients.

#	Author, year	Treatment approach	Clear-cell RCC	MiT-RCC	Other histological subtypes
1	(Gross-Goupil et al., 2018)	Axitinib	>50 %	0	Non-ccRCC (<50 %)
2	(Rini et al., 2016)	Placebo	213	0	0
		Axitinib titration			
		Placebo titration			
		Non-randomized			
3	(Motzer et al., 2013)	Axitinib	723	0	0
	(Rini et al., 2011)	Sorafenib			
4	(Hutson et al., 2017)	Axitinib	288	0	0
		Sorafenib			
5	(Kollmannsberger et al., 2021)	AGS-16C3F	55	0	Unclassified/ NOS (12)
		Axitinib	55		Unclassified/ NOS (11)
6	(Rini et al., 2019)	Axitinib + pembrolizumab	861	0	0
	(Powles et al., 2020)	Sunitinib			
	(Plimack et al., 2023)				
7	(Choueiri et al., 2020)	Avelumab + axitinib	886	0	0
	(Motzer et al., 2019)	Sunitinib			
	(Tomita et al., 2022)				
	(Haanen et al., 2023)				
8	(Yan et al., 2023)	Axitinib + toripalimab	421	0	0
		Sunitinib			
9	(Voss et al., 2019)	Axitinib + dalantercept	119	0	0
		Axitinib + placebo			
10	(Choueiri et al., 2021b)	Carotuximab + Axitinib	75	0	0
		Axitinib	75		
11	(de Oliveira et al., 2019)	Axitinib	0	0	Papillary (1)
12	(Ambalavanan and Geller, 2019)	Axitinib	0	2	0
		Axitinib + denosumab			
13	(Kakoki et al., 2017)	Axitinib	0	1	0
14	(Jiménez et al., 2017)	Axitinib	0	1	0
15	(Sudour-Bonnange et al., 2014)	Axitinib	0	1	0
16	(Gurruchaga Sotes et al., 2021)	Axitinib + pembrolizumab	0	0	Papillary (1)

NOS = not otherwise specified; ccRCC = clear-cell RCC.

0.58–0.80) (Supplementary figures 1–2) (Rini et al., 2019; Powles et al., 2020; Plimack et al., 2023). The trial also showed an improved OS with the combination of axitinib and pembrolizumab compared to sunitinib (46 versus 41 months, HR 0.73; 95 % CI 0.60–0.88). The JAVELIN Renal 101 included 886 treatment-naïve patients with advanced RCC. Similar to the KEYNOTE-426 trial, the combination of axitinib and avelumab led to a PFS of 13.9 months compared to 8.5 months with sunitinib (HR 0.67; 95 % CI 0.568–0.785; $p < 0.0001$) (Choueiri et al., 2020; Haanen et al., 2023; Motzer et al., 2019; Plimack et al., 2023; Tomita et al., 2022). The RENOTORCH trial also showed an improved PFS with combined axitinib and toripalimab treatment compared to sunitinib treatment (HR 0.651; 95 % CI 0.490–0.864; $p = 0.0028$) (Yan et al., 2023). The OS data for all treatment groups of both the KEYNOTE-426

and RENOTORCH trial are immature and not statistically significant (Yan et al., 2023; Haanen et al., 2023).

Two phase II studies compared axitinib combination treatment to axitinib (Table 1) (Choueiri et al., 2021b; Voss et al., 2019). The TRAXAR trial studied 150 patients with advanced or metastatic RCC who previously progressed on VEGF targeted therapies and studied the combination of carotuximab (TCR105) and axitinib to axitinib (Choueiri et al., 2021b). Patients treated with combination treatment had a 6.7 month PFS and the axitinib arm had a 11.4 month PFS (HR 1.42; 95 % CI 0.88–2.30; $p = 0.15$) (Supplementary figures 1–2). It was concluded that the combination of axitinib and carotuximab did not have added value over axitinib monotherapy and the development of carotuximab was stopped (Choueiri et al., 2021b). Another trial compared the combination of dalantercept and axitinib to axitinib and placebo in 119 patients with advanced RCC who underwent one or more previous treatments (Table 1) (Voss et al., 2019). This trial also showed no improved outcome for patients in the dalantercept arm as there was no improved PFS (6.8 months versus 5.6 months, HR 1.11; 95 % CI 0.71–1.73; $p = 0.670$) (Supplementary figures 1–2) (Voss et al., 2019). Combining dalantercept with axitinib does not seem to improve treatment efficacy. Surprisingly, adverse events ≥ 3 occurred evenly across both the dalantercept combination treatment arm (59 %) and axitinib treatment arm (64 %) (Table 3) (Choueiri et al., 2020; Motzer et al., 2019; Powles et al., 2020; Rini et al., 2019; Tomita et al., 2022; Voss et al., 2019).

3.2. Pediatric and young adult case reports

3.2.1. Clinical and tumor characteristics

No pediatric or young adult cohort studies were available, but seven case reports described the effects of axitinib in children and young adults (Table 4) (Ambalavanan and Geller, 2019; de Oliveira et al., 2019; Jiménez et al., 2017; Kakoki et al., 2017; Sudour-Bonnange et al., 2014). The case reports included one young adult with RCC of 24 years of age (de Oliveira et al., 2019). In total, 4 patients were diagnosed in the first decade of life and three patients were male (Ambalavanan and Geller, 2019; Gurruchaga Sotes et al., 2021; Jiménez et al., 2017; Kakoki et al., 2017; Sudour-Bonnange et al., 2014).

In the 7 pediatric patients, different diagnostic tumor staging systems were used (Table 4) (Ambalavanan and Geller, 2019; de Oliveira et al., 2019; Jiménez et al., 2017; Kakoki et al., 2017; Sudour-Bonnange et al., 2014). The postoperative tumor stage (pTN) was applied for the staging of three patients; pT3a, pT2a pN1 R0 and pT3a pN1 (de Oliveira et al., 2019; Sudour-Bonnange et al., 2014). Two one-year-old patients were diagnosed with T3aN1Mx and T3aN0M0, respectively, according to the tumor node metastasis (TNM) staging (Ambalavanan and Geller, 2019). While the two remaining case reports did not describe a staging system for their respective patient, tumor pathology reported lymph node metastases in one patient and metastatic disease at diagnosis in the other (Kakoki et al., 2017; Jiménez et al., 2017). Overall, all seven patients were diagnosed with advanced or metastatic disease (Ambalavanan and Geller, 2019; de Oliveira et al., 2019; Gurruchaga Sotes et al., 2021; Jiménez et al., 2017; Kakoki et al., 2017; Sudour-Bonnange et al., 2014).

Unlike the predominant clear-cell RCC tumor histology in adults, different RCC subtypes were found in children and young adults (Table 4). The 18- and 24-year-old patients were diagnosed with papillary RCC and five other children (1–15 years old) with MiT-RCC (Ambalavanan and Geller, 2019; de Oliveira et al., 2019; Gurruchaga Sotes et al., 2021; Jiménez et al., 2017; Kakoki et al., 2017; Sudour-Bonnange et al., 2014). The 18-year-old male with papillary RCC had an exon 8 deletion of the *FH* gene and was diagnosed with hereditary leiomyomatosis and renal cell cancer (Gurruchaga Sotes et al., 2021).

3.2.2. Outcome in case reports

The identified patients were treated with a variety of agents, of which one was axitinib (Table 4) (Ambalavanan and Geller, 2019; de

Table 3

Treatment and toxicity overview of adult, pediatric and/or young adult patients.

#	Author, year	Treatment protocol	Dose of axitinib	Trial	Surgery	Toxicity Grade ≥ 3 (%)
1	(Gross-Goupil et al., 2018)	Axitinib	5 mg bid	NCT01599754	363	Hypertension (64), diarrhea (47), dysphonia (42), Hand-Foot syndrome (32), proteinuria (23), fatigue (21), hypothyroidism (21), arthralgia (16), nasopharyngitis (16), headache (13), increased blood TSH (13), rash (13), stomatitis (13), back pain (13), decreased appetite (12), asthenia (12), dizziness (12) ^e
		Placebo			361	Hypertension (25), diarrhea (14), dysphonia (6), Hand-Foot syndrome (5), proteinuria (7), fatigue (12) hypothyroidism (5), arthralgia (10), nasopharyngitis (18), headache (11), rash (4), stomatitis (3), back pain (15), asthenia (6), dizziness (10) ^e
2	(Rini et al., 2016)	Axitinib titration	5 mg bid + titration	NCT00835978	183/213	Hypertension (18), diarrhea (13), fatigue (5), decreased appetite (7), nausea (5), Hand-Foot syndrome (4), proteinuria (4) ^b
		Placebo titration				Hypertension (9), diarrhea (5), fatigue (4)
		Non-randomized				Hypertension (49), diarrhea (9), fatigue (8), decreased appetite (5), Hand-Foot syndrome (5)
3	(Motzer et al., 2013) (Rini et al., 2011)	Axitinib titration	5 mg bid	NCT00678392	658/723	Diarrhea (11), hypertension (17), fatigue (10), decreased appetite (4), Hand-Foot syndrome (6), weight decreased (3), asthenia (4), proteinuria (3)
		Sorafenib	400 mg bid			Diarrhea (8), hypertension (12), fatigue (4 %), Hand-Foot syndrome (17), weight decreased (3), rash (4)
4	(Hutson et al., 2017)	Axitinib	5 mg bid + titration	NCT00920816	-/288	PPE (7), diarrhea (10), hypertension (13), weight decrease (11), fatigue (6), asthenia (9)
		Sorafenib	400 mg bid			PPE (16), diarrhea (5), weight decrease (6), asthenia (5)
5	(Kollmannsberger et al., 2021)	AGS-16C3F	1.8 mg/kg every + 3w	NCT02639182	NS	Fatigue (8), dyspnea (3), hypertension (5), abdominal pain (6), anemia (11), arthralgia (3), dry eye (3), asthenia (3) ^e
		Axitinib	5 mg bid			Fatigue (11), diarrhea (9), decreased appetite (5), back pain (3), dyspnea (6), hypertension (25), decreased weight (6), dehydration (6), anemia (3), stomatitis (5) asthenia (3) ^e
6	(Rini et al., 2019) (Powles et al., 2020) (Plimack et al., 2023)	Axitinib + pembrolizumab	5 mg bid + 200 mg i.v. every 3w	NCT02853331	357/432	Diarrhea (10), hypertension (22), fatigue (3), PPE (5), ALT increased (6), AST increased (6), proteinuria (3)
		Sunitinib	50 mg/day		358/429	Diarrhea (5), hypertension (20), fatigue (5), PPE (5), proteinuria (3), asthenia (3), platelet count decreased (6), anemia (4), thrombocytopenia (5), neutropenia (7), neutrophil count decreased (7)
7	(Choueiri et al., 2020) (Motzer et al., 2019) (Tomita et al., 2022) (Haanen et al., 2023)	Avelumab + axitinib	10 mg/kg every 2w + 5 mg bid	NCT02684006	352	Diarrhea (10.4), hypertension (28.6), fatigue (4.1), PPE (6.5), decreased weight (3.9), increased alanine aminotransferase level (6.9) ^e
		Sunitinib	50 mg/day		355	Diarrhea (3.2), hypertension (18.9), fatigue (3.9), nausea (1.8), PPE (4.3)
8	(Yan et al., 2023)	Axitinib + toripalimab	5 mg bid + 240 mg/3w	NCT04394975	421	Hypothyroidism (10.1), hyperthyroidism (6.3), rash (4.8)
9	(Voss et al., 2019)	Sunitinib	50 mg/day		-	-
		Axitinib + dalantercept	5 mg bid (+ titration) + 0.9 mg/kg/3w	NCT01727336	56	Fatigue (3.4), hypertension (10.3), PPE (3.4), anemia (5.2), hypophosphatemia (5.2), lipase increased (5.2) ^g
		Axitinib + placebo	5 mg bid + placebo		52	Fatigue (4.9), diarrhea (8.2), hypertension (19.7), nausea (3.3), weight decreased (3.3), vomiting (3.3), back pain (3.3), hyponatremia (9.8), ejection fraction decreased (4.9), hypophosphatemia (4.9)
10	(Choueiri et al., 2021b)	Carotuximab + axitinib	5 mg bid + 10 mg/kg every week	NCT01806064	NS	Headache (6.9), diarrhea (13.7), fatigue (9.6), hypertension (15.1), weight loss (4.1), anemia (15.1), back pain (4.1)
11	(de Oliveira et al., 2019)	Axitinib	5 mg bid	-	Yes	Diarrhea (9.5), hypertension (23), PPE (6.8), proteinuria (10.8)
12	(Ambalavanan and Geller, 2019)	Axitinib	-	-	No	
		Axitinib + denosumab	-	-	Yes	
13	(Kakoki et al., 2017)	Axitinib	5–10 mg/day	-	Yes	
14	(Jiménez et al., 2017)	Axitinib	5 mg/m ² bid	-	No	
		Axitinib	6.5 mg/m ² bid	-		
15	(Sudour-Bonnange et al., 2014)	Axitinib	3 mg bid	-	Yes	
16	(Gurruchaga Sotes et al., 2021)	Axitinib + pembrolizumab	5 mg bid + 200 mg every 3 weeks	-	Yes	

PPE = Palmar-plantar erythrodysesthesia; ^a hypothyroidism; ^b non-hypothyroidism; ^c carotuximab: anti-endoglin antibody; ^d total nephrectomy or nephron sparing surgery; ^e adverse events that occur in ≥ 10 % in either group; ^f adverse events that occur in ≥ 15 % in either group; ^g adverse events that occur in ≥ 20 % in either group;

^h adverse events that occur in ≥ 30 % of the total population.

Table 4
Overview of characteristics and outcome of included pediatric and/or young adult patients with renal cell carcinoma (RCC) treated with axitinib.

#	Author, year	Country	Type of study	Nr. of patients	Gender (M/F)	Age (md years)	Predisposition syndrome	Treatment approach (treatment line)	Surgery	Staging	Response	TTP (months)	OS (months)
11	(de Oliveira et al., 2019)	NS	CR	1	M	24	-	Axitinib (2nd)	Yes	PTN stage: pT3a TNM: T3aN1Mx (stage IV)	Progressive disease	-	3
12	(Ambalavanan and Geller, 2019)	US	RS	2	F	1	-	Axitinib (2nd)	No	TNM: T3aN1Mx (stage IV)	-	10	-
13	(Kakoki et al., 2017)	Japan	CR	1	M	9	-	Axitinib + denosumab (4th)	Yes	TNM: T3aN0M0 (stage IV) Lymph node metastases but no staging available	-	5.5	5
14	(Jiménez et al., 2017)	France	CR	1	F	2	-	Axitinib (4th)	No	Metastatic and loco-regional	Progressive disease	10	-
15	(Sudour-Bonnange et al., 2014)	France	CR	1	F	15	-	Axitinib (6th) Axitinib (3rd)	Yes	PTN stage: pT2a pN1 R0	Clinical response but progressive disease	-	-
16	(Gurruchaga Sotes et al., 2021)	Spain	CR	1	M	18	HLRCC	Axitinib + pembrolizumab (2nd)	Yes	TNM stage: pT3a pN1 (stage IV) (4/7 lymph nodes affected)	Partial response	-	OS: 20; DFS: 15

CR = case report; RS = retrospective study; Nr. = number; md = median; TTP = time-to-progression; OS = overall survival; DFS = disease-free survival; FISH = fluorescence *in situ* hybridization; Bid. = twice a day; HLRCC = hereditary leiomyomatosis and renal cell cancer.

Oliveira et al., 2019; Gurruchaga Sotes et al., 2021; Jiménez et al., 2017; Kakoki et al., 2017; Sudour-Bonnange et al., 2014). Altogether, the drug was prescribed as monotherapy to five patients as second-line (n = 2), third-line (n = 1), fourth-line (n = 2) or even sixth-line treatment (n = 1). The combination of axitinib plus pembrolizumab and axitinib complemented by denosumab were administered as second-line and fourth-line treatment, respectively (Ambalavanan and Geller, 2019; Gurruchaga Sotes et al., 2021).

Four patients with MIT-RCC were treated with axitinib monotherapy (Table 4). Two patients had a TTP of 10 months, one patient an OS of 5 months and the last patient was reported to have had a clinical response before eventually progressing (Ambalavanan and Geller, 2019; Jiménez et al., 2017; Sudour-Bonnange et al., 2014). A patient with papillary RCC had an OS of 2 months after treatment with axitinib (de Oliveira et al., 2019; Kakoki et al., 2017). The combination of axitinib and denosumab resulted in a time-to-progression (TTP) of 5.5 months (Ambalavanan and Geller, 2019). Further, the combination of axitinib and pembrolizumab induced a partial response and led to a disease-free survival (DFS) of 15 months and an OS of 20 months (Gurruchaga Sotes et al., 2021).

Overall, axitinib treatment dose was variable between patients and ranged between 3 and 10 mg BID (Table 3). The dose was not available in three patients. Adverse events were either not reported or they did not occur, so the relationship between the dose and adverse events was not further studied (Ambalavanan and Geller, 2019; de Oliveira et al., 2019; Gurruchaga Sotes et al., 2021; Jiménez et al., 2017; Kakoki et al., 2017; Sudour-Bonnange et al., 2014).

4. Discussion

This systematic review presents an overview of the clinical characteristics and outcome of patients who received axitinib in adult randomized controlled trials and case reports on children and young adults. The purpose was to gain insight to the feasibility and efficacy of axitinib in a pediatric RCC setting. So far, knowledge on the value of axitinib for pediatric- and young adult patients with RCC is still limited due to the lack of available trials.

In the recent years, multiple new treatment options for clear-cell RCC have become available for adults but it is not possible to directly compare and implement these treatments in the pediatric RCC setting (Ray et al., 2020). Based on available evidence, the European Association of Urology advises the use of axitinib as further-line treatment for adults with metastatic clear cell RCC, as an alternative to the standard of care and after prior use of a TKI (Ljungberg et al., 2022). Moreover, the European Association of Urology advises axitinib combined with pembrolizumab to be administered first-line in patients with metastatic clear cell RCC, in all IMDC risk groups (Ljungberg et al., 2022). This review confirms that combining axitinib with PD1 immune checkpoint inhibitors such as pembrolizumab or avelumab in adult patients with metastatic clear-cell RCC is beneficial, as is reflected by the superior PFS and OS in the KEYNOTE-426 and JAVELIN Renal 101 trials (Choueiri et al., 2021b; Rini et al., 2019; Powles et al., 2020; Plimack et al., 2023). Altogether, the RCTs that studied axitinib as adjuvant or first-line treatment did not perform better than placebo or sorafenib in terms of DFS or OS (Ljungberg et al., 2022; Gross-Goupil et al., 2018; Rini et al., 2016; Tomita et al., 2019). However, as second-line treatment axitinib resulted in an improved PFS compared to sorafenib and therefore seems more promising than sorafenib.

Evidence for axitinib monotherapy in adults seems unconvincing, so there might be little incentive from the adult setting to start treating children and young adults with axitinib. Considering the differences in RCC histology, biology and genetics between adults and children, there is a possibility that axitinib will induce a different outcome in children (Ray et al., 2020). The case reports on RCC in children and young adults that are currently available do not have enough power to draw strong conclusions on treatment with axitinib, especially considering not all

outcome details were described. The type of outcome data across the patients varied and should preferably be compared to sunitinib, which is recommended by the SIOP-RTSG 2016 UMBRELLA protocol as first-line agent for adjuvant treatment (van den Heuvel-Eibrink et al., 2017). Next to the insufficient outcome data, patients were treated with axitinib in a further-line setting so previous treatments might have affected the response to axitinib. Although trials are the preferred method for studying treatments, in pediatrics, trials are a challenge due to the rarity of pediatric cancer, especially RCC. However, the efficacy of axitinib is currently being tested in a COG phase II trial for patients with MiT-RCC (Geller, 2020). Until new evidence is reported, the SIOP-RTSG 2016 UMBRELLA protocol advises sunitinib as first-line treatment in children with metastatic disease (Ljungberg et al., 2022; van den Heuvel-Eibrink et al., 2017).

This review creates a novel overview of the clinical characteristics and current outcome of pediatric-, young adult- and adult patients with RCC after treatment with the targeted therapy axitinib. Numbers were too few and histology between patient groups too disparate to compare adult survival to the pediatric and young adult setting. In addition, recommendations for the use of axitinib in different disease contexts, adjuvant or in presence of evident disease, do not share a common vision between adult and pediatric patients. Nonetheless, there is an ongoing interest in axitinib in children, as is evident by the axitinib trial set up by the COG that recently closed to accrual (NCT03595124) (Geller, 2020). Collaborative efforts are needed to study axitinib and other agents in larger pediatric settings. Within the SIOP-RTSG 2016 UMBRELLA protocol, the effects of sunitinib will be prospectively evaluated, which might lead to future international studies to further explore the possibilities for treatment of advanced RCC in the pediatric setting.

Author contributions

The work reported in the paper has been performed by authors, unless clearly specified in the text. Conceptualization: JS, JNvdB, GAMT, MMvdHE, AV, FS, NG, TC, BS; Methodology: JS, JNvdB, GAMT, MMvdHE; Formal analysis: JS, RD; Investigation: JS, JNvdB, GAMT, MMvdHE; Writing – original draft preparation: JS, JNvdB, GAMT, MMvdHE; Writing – review & editing: JS, JNvdB, GAMT, MMvdHE, JG, AB, ACV, FS, NG, TC, BS, RD; Visualization: JS, JNvdB, GAMT, MMvdHE; Supervision: JNvdB, GAMT, MMvdHE; Project administration: JS, JNvdB, GAMT, MMvdHE.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2024.104523.

References

- Ambalavanan, M., Geller, J.I., 2019. Treatment of advanced pediatric renal cell carcinoma. *Pedia Blood Cancer* 66 (8), e27766.
- Argani, P., Antonescu, C.R., Illei, P.B., et al., 2001. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. *Am. J. Pathol.* 159 (1), 179–192.
- Azam, F., Latif, M.F., Farooq, A., et al., 2019. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. *Case Rep. Oncol.* 12 (3), 728–736.
- Bedke, J., Albiges, L., Capitanio, U., et al., 2022. 2021 updated European association of urology guidelines on the use of adjuvant pembrolizumab for renal cell carcinoma. *Eur. Urol.* 81 (2), 134–137.
- van der Beek, J.N., Geller, J.I., de Krijger, R.R., et al., 2020. Characteristics and Outcome of Children with Renal Cell Carcinoma: A Narrative Review. *Cancers (Basel)* 12 (7), 104523.
- van der Beek, J.N., Hol, J.A., Coulomb-L'Hermine, A., et al., 2021. Characteristics and outcome of Pediatric Renal Cell Carcinoma patients registered in the International Society of Pediatric Oncology (SIOP) 93-01, 2001, and UK-IMPACT database: a report of the SIOP-Renal Tumor Study Group. *Int. J. Cancer.*
- Bruder, E., Passera, O., Harms, D., et al., 2004. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. *Am. J. Surg. Pathol.* 28 (9), 1117–1132.
- Carcao, M.D., Taylor, G.P., Greenberg, M.L., et al., 1998. Renal-cell carcinoma in children: a different disorder from its adult counterpart? *Med Pediatr Oncol.* 31 (3), 153–158.
- Choueiri, T.K., Motzer, R.J., Rini, B.I., et al., 2020. Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann. Oncol.* 31 (8), 1030–1039.
- Choueiri, T.K., Tomczak, P., Park, S.H., et al., 2021a. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N. Engl. J. Med* 385 (8), 683–694.
- Choueiri, T.K., Zakharia, Y., Pal, S., et al., 2021b. Clinical results and biomarker analyses of axitinib and TRC105 versus axitinib alone in patients with advanced or metastatic renal cell carcinoma (TRAXAR). *Oncologist* 26 (7), 560–e1103.
- Eble, J., Sauter, G., Epstein, J., Sesterhenn, I., 2004. World Health Organization classification of tumours. Pathology and genetics of tumours of the urinary system and male genital organs ed. IARC Press.
- Geller, J.I., Argani, P., Adeniran, A., et al., 2008. Translocation renal cell carcinoma: lack of negative impact due to lymph node spread. *Cancer* 112 (7), 1607–1616.
- Geller, J.I., Fox, E., Turpin, B.K., et al., 2018. A study of axitinib, a VEGF receptor tyrosine kinase inhibitor, in children and adolescents with recurrent or refractory solid tumors: a children's oncology group phase 1 and pilot consortium trial (ADVL1315). *Cancer* 124 (23), 4548–4555.
- Geller J.I. AREN1721: A Randomized Phase 2 Trial of Axitinib/Nivolumab Combination Therapy vs. Single Agent Axitinib or Nivolumab for the Treatment of TFE/Translocation Renal Cell Carcinoma (tRCC) Across All Age Groups. (<https://childrensoncologygroup.org/aren1721>). Published 2020. Accessed2023.
- Geller J. A Randomized Phase 2 Trial of Axitinib/Nivolumab Combination Therapy vs. Single Agent Axitinib or Nivolumab for the Treatment of TFE/Translocation Renal Cell Carcinoma (tRCC) Across All Age Groups. Published 2020. Accessed.
- Giuliano, S., Pagès, G., 2013. Mechanisms of resistance to anti-angiogenesis therapies. *Biochimie* 95 (6), 1110–1119.
- Gross-Goupil, M., Kwon, T.G., Eto, M., et al., 2018. Axitinib versus placebo as an adjuvant treatment of renal cell carcinoma: results from the phase III, randomized ATLAS trial. *Ann. Oncol.* 29 (12), 2371–2378.
- Gurruchaga Sotes, I., Alves, A.N., Arregui, S.V., Santander Lobera, C., 2021. Response to combination of pembrolizumab and axitinib in hereditary leiomyomatosis and renal cell cancer (HLRCC). *Curr. Oncol.* 28 (4), 2346–2350.
- Haanen, J., Larkin, J., Choueiri, T.K., et al., 2023. Extended follow-up from JAVELIN Renal 101: subgroup analysis of avelumab plus axitinib versus sunitinib by the International Metastatic Renal Cell Carcinoma Database Consortium risk group in patients with advanced renal cell carcinoma. *ESMO Open* 8 (3), 101210.
- Haibe, Y., Kreidieh, M., El Hajj, H., et al., 2020. Resistance Mechanisms to Anti-angiogenic Therapies in Cancer. *Front Oncol.* 10, 221.
- van den Heuvel-Eibrink, M.M., Hol, J.A., Pritchard-Jones, K., et al., 2017. Position paper: Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. *Nat. Rev. Urol.* 14 (12), 743–752.
- He, M., Cai, J., Zhu, K., et al., 2021. Renal cell carcinoma in children and adolescents: single-center experience and literature review. *Med. (Baltim.)* 100 (2), e23717.
- Hicklin, D.J., Ellis, L.M., 2005. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J. Clin. Oncol.* 23 (5), 1011–1027.
- Hsieh, J.J., Purdue, M.P., Signoretti, S., et al., 2017. Renal cell carcinoma. *Nat. Rev. Dis. Prim.* 3, 17009.
- Hutson, T.E., Al-Shukri, S., Stus, V.P., et al., 2017. Axitinib versus sorafenib in first-line metastatic renal cell carcinoma: overall survival from a randomized phase iii trial. *Clin. Genitourin. Cancer* 15 (1), 72–76.
- Inamura, K., 2017. Translocation renal cell carcinoma: an update on clinicopathological and molecular features. *Cancers (Basel)* 9 (9).
- Jiménez, I., Brisse, H.J., Fréneau, P., et al., 2017. Pediatric patient with renal cell carcinoma treated by successive antiangiogenics drugs: a case report and review of the literature. *J. Pedia Hematol. Oncol.* 39 (5), e279–e284.
- Kakoki, K., Miyata, Y., Mochizuki, Y., et al., 2017. Long-term treatment with sequential molecular targeted therapy for Xp11.2 translocation renal cell carcinoma: a case report and review of the literature. *Clin. Genitourin. Cancer* 15 (3), e503–e506.
- Keating, G.M., 2015. Axitinib: a review in advanced renal cell carcinoma. *Drugs* 75 (16), 1903–1913.
- Kollmannsberger, C., Choueiri, T.K., Heng, D.Y.C., et al., 2021. A randomized phase ii study of AGS-16C3F versus axitinib in previously treated patients with metastatic renal cell carcinoma. *Oncologist* 26 (3), 182–e361.
- Ljungberg, B., Albiges, L., Abu-Ghanem, Y., et al., 2022. European association of urology guidelines on renal cell carcinoma: the 2022 update. *Eur. Urol.*
- McIntyre, A., Harris, A.L., 2015. Metabolic and hypoxic adaptation to anti-angiogenic therapy: a target for induced essentiality. *EMBO Mol. Med* 7 (4), 368–379.
- Motzer, R.J., Escudier, B., Tomczak, P., et al., 2013. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol.* 14 (6), 552–562.
- Motzer, R.J., Penkov, K., Haanen, J., et al., 2019. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N. Engl. J. Med* 380 (12), 1103–1115.
- Nakata, K., Colombet, M., Stiller, C.A., Pritchard-Jones, K., Steliarova-Foucher, E., 2020. Contributors I-. Incidence of childhood renal tumours: an international population-based study. *Int. J. Cancer* 147 (12), 3313–3327.

- Negrier, S., Rioux-Leclercq, N., Ferlay, C., et al., 2020. Axitinib in first-line for patients with metastatic papillary renal cell carcinoma: results of the multicentre, open-label, single-arm, phase II AXIPAP trial. *Eur. J. Cancer* 129, 107–116.
- de Oliveira, T.R., Ouattara, A., Everaerts, W., De Meerleer, G., Joniau, S., 2019. Nine-year survival after iterative metastasectomies for renal cell carcinoma. *Urol. Ann.* 11 (2), 219–221.
- Ornstein, M.C., Pal, S.K., Wood, L.S., et al., 2019. Individualised axitinib regimen for patients with metastatic renal cell carcinoma after treatment with checkpoint inhibitors: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 20 (10), 1386–1394.
- Pal, S.K., Tangen, C., Thompson, I.M., Jr, et al., 2021. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet* 397 (10275), 695–703.
- PDQ Cancer Information Summaries. In:2002.**
- Plimack, E.R., Powles, T., Stus, V., et al., 2023. Pembrolizumab plus axitinib versus sunitinib as first-line treatment of advanced renal cell carcinoma: 43-month follow-up of the phase 3 KEYNOTE-426 study. *Eur. Urol.* 84 (5), 449–454.
- Powles, T., Plimack, E.R., Soulières, D., et al., 2020. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 21 (12), 1563–1573.
- Ray, S., Jones, R., Pritchard-Jones, K., et al., 2020. Pediatric and young adult renal cell carcinoma. *Pedia Blood Cancer* 67 (11), e28675.
- Rini, B.I., Escudier, B., Tomczak, P., et al., 2011. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 378 (9807), 1931–1939.
- Rini, B.I., Plimack, E.R., Stus, V., et al., 2019. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N. Engl. J. Med* 380 (12), 1116–1127.
- Rini, B.I., Tomita, Y., Melichar, B., et al., 2016. Overall survival analysis from a randomized phase ii study of axitinib with or without dose titration in first-line metastatic renal cell carcinoma. *Clin. Genitourin. Cancer* 14 (6), 499–503.
- Spreafico, F., Collini, P., Terenziani, M., Marchianò, A., Piva, L., 2010. Renal cell carcinoma in children and adolescents. *Expert Rev. Anticancer Ther.* 10 (12), 1967–1978.
- Sudour-Bonnange, H., Leroy, X., Chauvet, M.P., Classe, M., Robin, P.M., Leblond, P., 2014. Cutaneous metastases during an aggressive course of Xp11.2 translocation renal cell carcinoma in a teenager. *Pedia Blood Cancer* 61 (9), 1698–1700.
- Sun, G., Chen, J., Liang, J., et al., 2021. Integrated exome and RNA sequencing of TFE3-translocation renal cell carcinoma. *Nat. Commun.* 12 (1), 5262.
- Tanaka, N., Mizuno, R., Ito, K., et al., 2016. External validation of the MSKCC and IMDC risk models in patients treated with targeted therapy as a first-line and subsequent second-line treatment: a Japanese multi-institutional study. *Eur. Urol. Focus* 2 (3), 303–309.
- Tomita, Y., Motzer, R.J., Choueiri, T.K., et al., 2022. Efficacy and safety of avelumab plus axitinib in elderly patients with advanced renal cell carcinoma: extended follow-up results from JAVELIN Renal 101. *ESMO Open* 7 (2), 100450.
- Tomita, Y., Uemura, H., Oya, M., et al., 2019. Patients with metastatic renal cell carcinoma who benefit from axitinib dose titration: analysis from a randomised, double-blind phase II study. *BMC Cancer* 19 (1), 17.
- Voss, M.H., Bhatt, R.S., Vogelzang, N.J., et al., 2019. A phase 2, randomized trial evaluating the combination of dalantercept plus axitinib in patients with advanced clear cell renal cell carcinoma. *Cancer* 125 (14), 2400–2408.
- Yan, X.Q., Ye, M.J., Zou, Q., et al., 2023. Toripalimab plus axitinib versus sunitinib as first-line treatment for advanced renal cell carcinoma: RENOTORCH, a randomized, open-label, phase III study. *Ann. Oncol.*