A systematic literature review of comparative efficacy measures in randomized controlled trials of adjuvant treatment in localized renal cell carcinoma

CO33

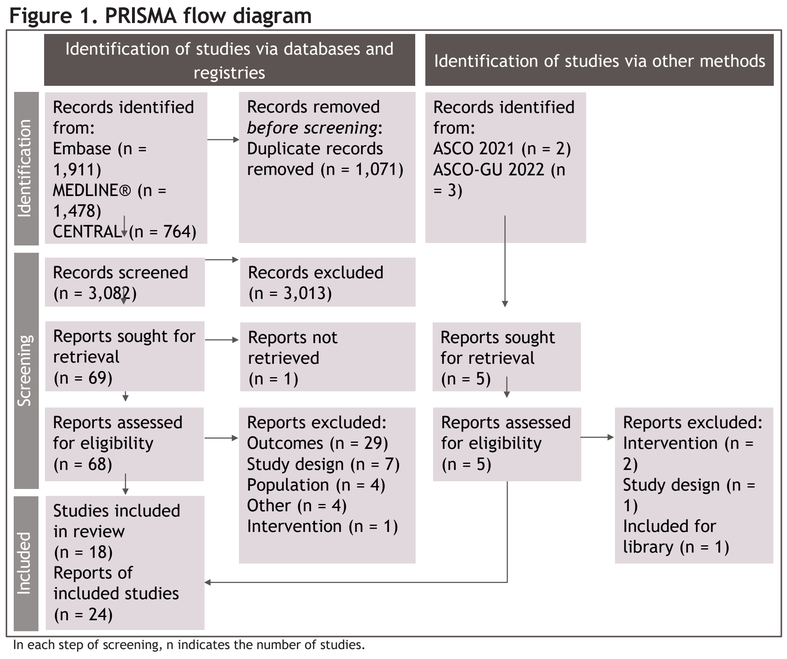
Flavia Ejzykowicz,[1] Murat Kurt,[1] Mathew Dyer,[2] Jessica R May,[2] Walid Shouman,[3] Ellen Kasireddy,[3] Mir-Masoud Pourrahmat[3]

[1]Bristol Myers Squibb, Princeton, NJ, USA; [2]Bristol Myers Squibb, Uxbridge, UK; [3]Evidinno Outcomes Research Inc., Vancouver, BC, Canada

Background and Objectives

- Renal cell carcinoma (RCC) is the most common type of kidney cancer among adults and accounts for an estimated 90% of malignant kidney tumors.[1]
- According to the data from Surveillance, Epidemiology and End Results, survival rates for RCC vary by stage. Specifically, 5-year survival rates are 93% for localized disease, 70% for regional, and 13% for distant stages.[2]
- Surgical resection of localized RCC has a curative intent and may result in favorable long-term survival.[3] Generally, more than 50% of patients with stage I to III localized RCC are cured.[3] However, around 30% of patients experience relapse after surgical resection and develop metastatic RCC. Although treatment of metastatic RCC has evolved positively with the advent of immune-checkpoint inhibitors and their combinations, depending on the local standard of care options, its treatment can lead to poor outcomes for refractory patients after radical resection.[4]
- Current treatment options for localized RCC consist of neoadjuvant therapy to downstage unresectable tumors or to facilitate nephron-sparing approaches,[5] while adjuvant therapy may play an important role to reduce the risk of relapse after surgical intervention.
- Recently, immune checkpoint inhibitor pembrolizumab has been approved by the United States (US) Food and Drug Administration and European Medicines Agency for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. Despite regulatory approvals in the US and Europe, adjuvant treatment with pembrolizumab is cautiously recommended by the European Association of Urology guidelines in high-risk clear cell RCC, while the National Comprehensive Cancer Network guidelines do not support the use of pembrolizumab as an adjuvant therapy for clear cell and non-clear cell stage II and III RCC.
- We aimed to characterize the current adjuvant treatment options for adults with localized RCC using published evidence from clinical trials.

Figure 1. PRISMA flow diagram



In each step of screening, n indicates the number of studies.

Methodology

- A systematic literature review (SLR) was conducted by searching MEDLINE®, Embase, and CENTRAL from database inception to January 17, 2022.
- Additionally, gray literature searches were conducted (via Embase) for the following conferences in 2020 and 2021:
  - American Society of Clinical Oncology (ASCO)
  - American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO-GU)
  - European Society for Medical Oncology (ESMO)
- After exclusion of duplicate records, two investigators reviewed all articles, abstracts and proceedings identified through the searches and assessed eligibility according to the following criteria:
  - Patients were adults with localized (stage I-III) RCC who have undergone partial or radical nephrectomy.
  - Interventions were any adjuvant treatments (including but not limited to systemic treatments, radiotherapy, and chemoradiation).
  - Comparators could be any treatment in the adjuvant setting, placebo, or no treatment beyond surgery.
  - The full-text studies identified for eligibility included overall survival (OS) and either disease-free survival (DFS) or its common analogues such as relapse-free survival (RFS) or progression-free survival (PFS).
  - Study types were limited to randomized controlled trials (RCTs) of any phase.

Results

Study selection

- There were 3,082 non-duplicate records identified in total, of which 24 reports pertaining to 18 unique RCTs were included for the qualitative synthesis (**Figure 1**; **Table 1**).
- Of the 18 included RCTs, 13 were phase III, and 5 were of unknown phase. Seven trials had double-blind, and 11 had open-label enrollment.
- Most trials were conducted in a multinational setting (n = 8). Other solo study locations included Italy (n = 3), the United States (n = 3), Japan (n = 2), the United Kingdom (n = 1), and Germany (n = 1).
- Median follow-up ranged from 24.1 to 164.4 months
- Sample size varied widely from 46 to 1,943 patients (median = 310 patients).

Table 1. Study and intervention characteristics

Reference	Sample Size	Intervention	Comparator	Minimum Follow-up (months)
Galligioni 1996[23]	120	BCG vaccine	Observation	92
Naito 1997[18]	71	UFT	Non-adjuvant control	120
Pizzocaro 2001[22]	264	IFN-alpha	Observation	60
Clark 2003[13]	69	IL-2	Observation	57
Messing 2003[15]	294	IFN-alpha	Observation	168
Atzpodien 2005[20]	203	5-FU + IFN-alpha + IL-2	Observation	117.6
Wood 2008[11]	728	Vitespen	Observation	72.3
Margulis 2009[14]	46	Thalidomide	Observation	NR
Hinotsu 2013[21]	107	IFN-alpha	Observation	84
Aitchison 2014[19]	309	5-FU + IFN-alpha + IL-2	Observation	144
Passalacqua 2014[16]	310	IFN-alpha + IL-2	Observation	144
Ravaud 2016[10]	615	Sunitinib	Placebo	81.6
Haas 2016[8]	1943	Sorafenib	Placebo	104
		Sunitinib	Placebo	98
Chamie 2017[6]	864	Girentuximab	Placebo	84
Motzer 2017[9]	1538	Pazopanib	Placebo	60
Gross-Goupil 2018[7]	724	Axitinib	Placebo	60
Eisen 2020[17]	1711	Sorafenib 1 year	Placebo	132
		Sorafenib 3 years	Placebo	132
Choueiri 2021[12]	994	Pembrolizumab	Placebo	42

Abbreviations - 5-FU: 5-fluorouracil; BCG: Bacillus Calmette-Guerin; IFN-alpha: Interferon-alpha; IL-2: Interleukin-2; NR: Not reported; UFT: Tegafur/uracil.

Participant characteristics in the evidence base

- Median/mean baseline age ranged from 49 to 60 years.
- Percentage of males ranged between 52% and 74% (median = 68%).
- In terms of ethnicity, percentage of white patients ranged between 25% and 95% (median = 88%), percentage of Black/African American patients ranged between 0.6% and 4.4% (median = 0.7%), and percentage of Asian patients ranged between 1.2% and 73.3% (median = 7.3%; **Table 2**).
- Performance status was reported in 13 studies, majority of which used the Eastern Cooperative Oncology Group (ECOG) scale. Majority of patients (66-96% across 9 studies) had an ECOG score of 0. ECOG and other performance status measures are depicted in **Table 3**.
- In terms of disease histology, a high percentage of patients (ranging between 46% and 100%, with median = 79%) had clear cell tumors. The percentage of patients with papillary tumors ranged between 1% and 8% (median = 7%), and the percentage of patients with granular tumors ranged between 2% and 8% (median = 3%).

Table 2. Distribution of reported race/ethnicities across studies

Reference	Treatment Subgroup	Sample Size	Ethnicity Distribution (%)				
			White/ Caucasian	Black/ African American	Hispanic	Asian	Other/ Unknown
Wood 2008[11]	Vitespen	361	94.74	0.28	2.49	1.11	1.39
	Observation	367	94.55	1.09	2.72	1.36	0.27
Haas 2016[8]	Sunitinib	647	92.43	4.17	-	1.7	1.7
	Sorafenib	649	90.76	4.16	-	2.62	2.46
	Placebo	647	90.42	4.79	-	2.32	2.47
Ravaud 2016[10]	Sunitinib	309	82.2	0.97	-	13.92	2.91
	Placebo	306	85.95	0.33	-	10.78	2.94
Chamie 2017[6]	Girentuximab	433	93.53	2.31	1.85	2.31	-
	Placebo	431	93.97	1.16	1.86	2.09	0.93
Motzer 2017[9]	Pazopanib	769	83.09	1.04	-	12.87	2.99
	Placebo	769	85.7	0.13	-	12.48	1.69
Gross-Goupil 2018[7]	Axitinib	363	25.07	0.83	-	72.73	1.38
	Placebo	361	24.93	0.28	-	73.96	0.83

Table 3.Distribution of reported performance statuses across studies

Performance Status Scale	Measure	Range	Median
ECOG (9 studies[6-8,10,12-16])	0	66.08% - 95.71%	85.36%
	1	10.10% - 33.22%	14.79%
	2	2.02%	-
	≥ 1	4.29%	-
	≥ 2	0.16%	-
	Unknown	0.49%	-
WHO (3 studies[11,17,18])	0	77.47% - 80.30%	79.66%
	1	18.18% - 22.53%	19.58%
	2	0.06% - 1.52%	0.79%
	Missing data	0.70%	-
Karnofsky Performance Status (1 study[9])	100	68.20%	-
	80-90	31.73%	-
	Unknown	0.07%	-

Abbreviations - ECOG: Eastern Cooperative Oncology Group. WHO: World Health Organization.

DFS and analogue endpoints

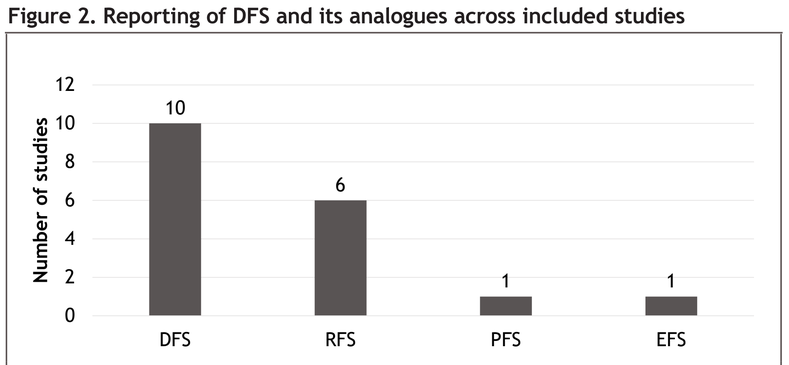
- The distribution of studies reporting data for DFS, and its analogues is presented in **Figure 2**. Proportional hazard models were used in all studies to estimate corresponding hazard ratios (HRs).
- The extent of duration over which DFS was measured varied between 57 and 144 months (median = 84 months).
- Reported HR for DFS (DFS_{HR}) was greater than 1 in four studies, and less than 1 in eight studies.
- The extent of duration over which RFS was measured ranged between 72 months and 168 months (median = 120 months).
- As an analogue of DFS_{HR}, reported HR for RFS (RFS_{HR}) was greater than 1 in four studies and less than 1 in two studies (**Table 4**).
- Three studies reported a statistically significant DFS_{HR}, while no studies reported a statistically significant RFS_{HR}, PFS_{HR}, or EFS_{HR}.

Table 4. Summary of efficacy measure in terms of hazard ratios

Reference		OS HR (95% CI)	HR for DFS and its analogues (95% CI)		
			DFS	RFS	Other
Galligioni 1996[23]		1.12 (0.62, 2.00)	1.50 (0.88, 2.54)	-	-
Naito 1997[18]		0.98 (0.28, 3.39)	-	1.17 (0.36, 3.74)	-
Pizzocaro 2001[22]		1.04 (0.67, 1.61)	-	-	EFS: 1.41 (0.93, 2.15)
Clark 2003[13]		0.61 (0.15, 2.45)	1.33 (0.65, 2.73)	-	-
Messing 2003[15]		1.26 (0.95, 1.68)	-	1.15 (0.88, 1.50)	-
Atzpodien 2005[20]		1.45 (0.89, 2.35)	-	1.33 (0.89, 1.97)	-
Wood 2008[11]		0.98 (0.70, 1.36)	-	0.92 (0.73, 1.17)	-
Margulis 2009[14]		1.98 (0.54, 7.22)	-	2.34 (0.94, 5.85)	-
Hinotsu 2013[21]		3.43 (0.94, 12.49)	-	-	PFS: 1.50 (0.79, 2.84)
Aitchison 2014[19]		0.87 (0.61, 1.23)	0.84 (0.63, 1.12)	-	-
Passalacqua 2014[16]		1.07 (0.64, 1.79)	-	0.84 (0.54, 1.31)	-
Ravaud 2016[10]		1.01 (0.72, 1.44)	0.76 (0.59, 0.98)	-	-
Haas 2016[8]	Sorafenib	0.98 (97.5% CI = 0.75, 1.28)	0.97 (97.5% CI = 0.80, 1.17)	-	-
	Sunitinib	1.17 (97.5% CI = 0.90, 1.52)	1.02 (97.5% CI = 0.85, 1.23)	-	-
Chamie 2017[6]		0.99 (0.74, 1.32)	0.97 (0.79, 1.18)	-	-
Motzer 2017[9]		0.82 (0.63, 1.08)	0.80 (0.68, 0.95)	-	-
Gross-Goupil 2018[7]		1.03 (0.60, 1.76)	0.87 (0.66, 1.15)	-	-
Eisen 2020[17]	Sorafenib 1 year	0.92 (0.71, 1.20)	0.94 (0.77, 1.14)	-	-
	Sorafenib 3 years	1.06 (0.82, 1.38)	1.01 (0.82, 1.23)	-	-
Choueiri 2021[12]		0.54 (0.31, 0.86)	0.68 (0.53, 0.87)	-	-

DFS: Disease-free survival; EFS: Event-free survival; OS: Overall survival; PFS: Progression-free survival; RFS: Recurrence-free survival; HR: Hazard ratio. Colored font indicates statistical significance.

Figure 2. Reporting of DFS and its analogues across included studies



Abbreviations - DFS: Disease-free survival; EFS: Event-free survival; PFS: Progression-free survival; RFS: Recurrence-free survival.

Overall survival

- The minimum follow-up period for OS ranged between 42 months and 168 months (median = 100 months).
- HR for OS (OS_{HR}) was reported to be greater than 1 by 11 studies. In 9 of these studies, the reported OS_{HR} was close to 1, where two studies reported an outlier OS_{HR} of 3.43 and 1.98. Nine studies reported OS_{HR} to be less than 1 (**Table 4**).
- Only one study (Choueiri 2021) reported a statistically significant OS_{HR}.
- Seven studies reported both $HR_{DFS\ (or\ DFS\ analogue)} < 1$ and $HR_{OS} < 1$. These trials investigated sorafenib (n = 2), 5-fluorouracil + interferon-alpha + interleukin-2 (5-FU + IFN-alpha + IL-2; n = 1), pazopanib (n = 1), girentuximab (n = 1), pembrolizumab (n = 1), and vitespen (n = 1).
- Eight studies reported both $HR_{DFS\ (or\ DFS\ analogue)} > 1$ and $HR_{OS} > 1$. These trials investigated IFN-alpha (n = 3), 5-FU + IFN-alpha + IL-2 (n = 1), sorafenib (n = 1), sunitinib (n = 1), thalidomide (n = 1), and Bacillus Calmette-Guerin vaccine (n = 1).

Conclusions

- To the best of our knowledge, this study is the most recent SLR characterizing current treatments with their corresponding efficacy measures for the commonly reported endpoints for adults with localized RCC in the adjuvant setting.
- Findings suggest limited intermediate- and long-term efficacy for several interventions with varying mechanisms of actions highlighting the need for the development of novel therapies in the adjuvant setting.
- Future work may expand this SLR to a broader setting by including other early-stage RCC treatments (e.g., neo-adjuvant) that are not exclusive to adjuvant stage.
- This SLR provides a foundation for exploring surrogate endpoints for OS in adjuvant treatment of localized RCC, where the efficacy results can be leveraged to investigate the association between the treatment effects on DFS (and its analogues) and treatment effects on OS.

References

1. Sally Robertson BS. News Medical Life Sciences - Renal Cell Carcinoma Survival Rate. https://www.news-medical.net/health/Renal-Cell-Carcinoma-Survival-Rate.aspx.
2. Wells G, et al. Newcastle-Ottawa quality assessment scale cohort studies. 2014.
3. Kush Sachdeva M. Medscape - Renal Cell Carcinoma Treatment & Management. https://emedicine.medscape.com/article/281340-treatment#d1.
4. Sterne JA, et al. BMJ 2019;366.
5. Borregales LD, et al. Epub 2015 Nov 20. PMID: 27034725; PMCID: PMC4772353.
6. Chamie K, et al. JAMA Oncol 2017;3(7):913-920.
7. Gross-Goupil M, et al. Ann Oncol 2018;29(12):2371-2378.
8. Haas NB, et al. Lancet 2016;387(10032):2008-2016.
9. Motzer RJ, et al. J Clin Oncol 2017;35(35):3916-3923.
10. Ravaud A, et al. N Engl J Med 2016;375(23):2246-2254.
11. Wood C, et al. Lancet 2008;372(9633):145-154.
12. Choueiri TK, et al. N Engl J Med 2021;385(8):683-694.
13. Clark JI, et al. J Clin Oncol 2003;21(16):3133-3140.
14. Margulis V, et al. Urology 2009;73(2):337-341.
15. Messing EM, et al. J Clin Oncol 2003;21(7):1214-1222.
16. Passalacqua R, et al. J Immunother 2014;37(9):440-447.
17. Eisen T, et al. J Clin Oncol 2020;38(34):4064-4075.
18. Naito S, et al. Int J Urol 1997;4(1):8-12.
19. Aitchison M, et al. Eur J Cancer 2014;50(1):70-77.
20. Atzpodien J, et al. Br J Cancer 2005;92(5):843-846.
21. Hinotsu S, et al. Int J Clin Oncol 2013;18(1):68-74.
22. Pizzocaro G, et al. J Clin Oncol 2001;19(2):425-431.
23. Galligioni E, et al. Cancer 1996;77(12):2560-2566.

Acknowledgments

- Bristol Myers Squibb (Princeton, NJ) and Ono Pharmaceutical Company Ltd. (Osaka, Japan).
- All authors contributed to and approved the presentation; writing assistance was provided by Evidinno Outcomes Research Inc., funded by Bristol Myers Squibb.

Presented at ISPOR Europe 2022; November 6-9, 2022; Vienna, Austria, and virtual

Email: mpourrahmat@evidinno.com