Adjuvant Systemic Treatment for Renal Cancer After Surgery: A Network Meta-Analysis

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Abstract

Background Approximately 15% to 20% of patients will experience disease recurrence following surgical removal of renal cell carcinoma. A range of pharmacological agents is prescribed for metastatic renal cell carcinoma, but there are trials testing whether these have an earlier role in the adjuvant setting. We aim to assess the efficacy of adjuvant systemic treatment following surgery in patients with renal cell carcinoma and to determine the most effective treatment.

Methods The protocol for this review was published in PROSPERO (CRD42021281588). We searched multiple databases up to August 2021. We included only randomized trials of patients with renal cell carcinoma that had been completely resected. We included patients with locoregional nodal disease if it was surgically removed, and excluded all cases of metastatic disease. We included all adjuvant systemic therapies that were commenced within 90 days of renal surgery. A network meta-analysis was performed using a frequentist approach.

Results A total of 13 studies with 8103 patients were included for analysis. Only pembrolizumab (HR 0.74; 95%CI 0.57 to 0.96) and pazopanib (HR 0.80; 95%CI 0.68 to 0.95) improved disease-free survival compared with observation. These 2 treatments were the 2 highest ranked comparisons with a P-score of 0.87 and 0.80. No agent improved overall survival. All agents increased the risk of severe adverse events compared with observation.

Conclusions Pembrolizumab and pazopanib were the only 2 adjuvant agents that improved time to disease recurrence compared with observation, with the former likely being the more efficacious. None of the treatments improved overall survival and almost all increased severe adverse events.

Introduction

There has been an increased incidence of renal cell carcinoma, especially in developed countries[1]. Most of these cancers are localized to the kidney at the time of presentation and are curable by surgery. However, approximately 20% of patients will experience disease recurrence following surgery[2]. Overall prognosis for advanced disease is poor with a median survival time of 21 months after recurrence[3].

Key Words

Renal cancer, immunotherapy, systematic review

Competing Interests

None declared.

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A range of pharmacological agents has been used to treat metastatic renal cell carcinoma (mRCC) with varying efficacy, including chemotherapy, immunotherapy, tyrosine kinase inhibitors, monoclonal antibody against circulating vascular endothelial growth factor, and mTOR inhibitors. A network meta-analysis found that combination immunotherapy likely represents the current best available treatment[4]. The European Association of Urology guidelines support this by suggesting that immunotherapy (including combinations) should be used as first-line treatment in this setting[5]. As immunotherapy has come to the forefront of mRCC management, there has been increasing interest in employing these treatments at earlier stages of disease. Many of the aforementioned treatments have been trialled in the adjuvant setting with varying results, and there are recent reports of use of adjuvant immunotherapy. However, these trials have primarily been conducted using observation or placebo as a comparator arm, which has not permitted direct comparisons of active agents.

We therefore aimed to perform a systematic review and network-meta-analysis of systemic agents used in the adjuvant setting after surgery for kidney cancer.

Methods

We registered the protocol of this systematic review in PROSPERO (CRD42021281588). We searched multiple databases (MEDLINE, EMBASE, ScienceDirect, Cochrane Libraries, HTA database, and Web of Science) up to 20 August 2021, with a range of keywords associated with "renal carcinoma" and "adjuvant therapy." We also searched the abstracts from leading urological and oncological meetings, including those of the European Association of Urology, American Urological Association, American Society of Clinical Oncology, and European Society of Medical Oncology in the last 5 years. We also searched trial registries such as ClinicalTrials.gov. We did not place any restriction on language or date of publication. We included only randomized studies.

Our population of interest was patients with RCC that had been completely resected. Surgical treatment included both radical and partial nephrectomy. We included patients with locoregional nodal disease if they underwent surgical removal at the time of kidney extirpation, ie, N+ cases were eligible. We included all histological subtypes of renal carcinoma. We excluded all patients with distant metastatic disease even if they had undergone metastectomy, ie, M1 cases were not eligible for inclusion.

We included all adjuvant systematic therapies that were commenced within 90 days of renal surgery. We excluded autologous vaccine-based treatments because they are not widely available in clinical practice. We did not include adjuvant radiotherapy. Control arms eligible for analysis were observation, placebo, and active treatments, although we did not find any studies with the last.

Following our search, titles and abstracts were screened by 2 independent authors according to the inclusion/exclusion criteria. Full texts of relevant abstracts were then reviewed by 2 independent authors to confirm eligibility. Any disagreements were resolved by a third senior author. Data were then extracted independently.

The efficacy outcomes of interest were disease-free survival (DFS), defined as time from randomization to disease recurrence (local or distant) and/or death; and overall survival (OS), defined as time from randomization to death from any cause.

The safety outcome of interest was severe adverse events defined as incidence of grade III to V events per patient.

We also intended to perform subgroup analysis on the efficacy outcome according to histological subtype (clear-cell versus other subtypes) and nodal disease (no nodal disease [N0] versus nodal disease [N1]).

Statistical analysis

We first performed traditional pairwise meta-analysis of the included studies (data not shown). To do this, we applied the model proposed by Woods et al. by extracting hazard rates for DFS and OS and number of severe adverse events from each of the included studies[6].

We then performed a network meta-analysis of all included trials which enables indirect comparisons of treatments based on a common comparator arm. We adopted a frequentist approach and performed a fixed-effect consistency network meta-analysis. As a sensitivity analysis, we used the same approach with a random-effects model. We used P-scores that estimate the extent that one treatment is superior to another, averaged over all competing treatments, to determine which agent is the most efficacious.

All analyses were performed using RJAGS and R (R Foundation for Statistical Computing, Vienna, Austria) version 3.4. Risk of bias was performed according to the Cochrane framework[7].

Results

Our search retrieved 4088 abstracts of which 41 proceeded to full text review. After inclusion/exclusion criteria were applied, 13 studies were eligible and included for analysis (**Online Supplementary Figure 1**). The details of included studies are shown in **Table 1**.

The included trials tested a range of adjuvant treatments: axitinib[8], girentuximab[9], interferon-alpha[10–14], interleukin-2[10, 11], pazopanib[15], pembrolizumab[16], sorafenib[17,18], sunitinib[17,19], and thalidomide[20]. Two of the trials tested combination adjuvant therapies of interleukin-2+interferon-alpha[10] and interleukin-2+interferon-alpha+5-flurouracil[11]. The PROTECT trial that compared pazopanib with placebo included patients who received either 600 mg or 800 mg, and we included both in this analysis[15]. The trials were overall of moderate quality, and the detailed risk of bias classification can be found in **Online Supplementary Table 1**. We also found a further 6 trials in progress (**Table 2**).

Disease-free survival

All eligible studies reported on DFS and were included in this analysis of 8103 patients. Only the 2016 study by Haas et al. reported on direct comparison between active agents[17]. The forest plot of HRs compared with control arm for each agent is shown in **Figure 1A**. Only pembrolizumab (HR 0.74; 95% CI 0.57 to 0.96) and pazopanib (HR 0.80; 95% CI 0.68 to 0.95) prolonged DFS compared with observation. These 2 treatments were the

FIGURE 1.
Treatment versus control for (A) DFS and (B) OS

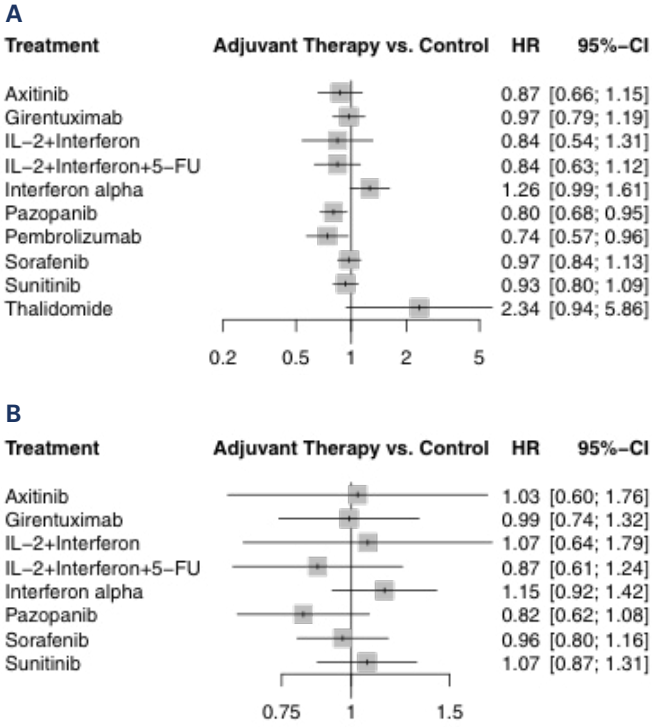

TABLE 1.
Characteristics of included studies, *Cont'd*

Author/Year	Adjuvant treatment	Number of participants	Inclusion criteria	Number of participants with ≤T2 disease, n	Number of participants with clear-cell RCC	Number of participants with nodal disease
Gross-Goupil et al. 2018[8]	Axitinib: 5 mg BD up to 3 years	724	• ≥pT2 and/or N+ • Any Fuhrman grade • ECOG performance status 0/1	80	NR	36
Chamie et al. 2017[9]	Girentuximab: IV 50mg week 1 followed by IV 20 mg week 2–24	864	Histologically confirmed ccRCC pT3/pT4Nx/N0M0 or pTanyN+M0 or pT1b/pT2Nx/N0M0 with nuclear grade 3 or greater	139	834	65
Passalacqua et al. 2014[10]	IL-2 + IFN-a: IL-2 SC 1 mil IU/m2 5 days per week for 4 weeks; INF-a SC 1.8 mil IU/m^2 on day 3 and 5 each week. Cycles repeated every 4 months for 2 years and 6 months for 3 years	310	Partial or radical nephrectomy with no residual disease and free surgical margins: pT2-3b pN0-3 M0	182	254	12

NR: not reported

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TABLE 1.

Characteristics of included studies, *Cont'd*

Author/Year	Adjuvant treatment	Number of participants	Inclusion criteria	Number of participants with ≤T2 disease, n	Number of participants with clear-cell RCC	Number of participants with nodal disease
Aitchison et al.2014[11]	IL-2 + IFN-a + 5-FU: IL-2 SC 20 mil IU/m2 on days 3-5 in weeks 1 and 4 and SC 5 mil IU/m2 on days 1, 3 and 5 in weeks 2 and 3; IFN-a SC 6 mil IU/m^2 in weeks 2 and 3 and increasing to SC 9 mil IU/m2 in weeks 5-8 given on days 1, 3 and 5; 5-FU IV 750mg/m^2 weekly in weeks 5-8	309	Histologically proven stage T3b, T3c, T4 tumour or any pT stage and nodal status pN1 or 2, or any pT stage Clinical N+ disease removed and had no metastatic disease or macroscopic residual disease as confirmed within 2–4 weeks prior to randomization by CT or MRI plus CXR	65	NR	49
Messing et al. 2003[12]	Interferon α-NL: SC 5 days every 3 weeks (3 mil IU/m^2 day 1, 5 mil IU/m2 day 2, 20 mil IU/m2 day 3-5) up to 12 cycles	283	Unilateral, locally advanced (pT3-4a) and/or node-positive renal cancer following radical nephrectomy No disseminated disease	36	176	44
Pizzocaro et al.2001[13]	Interferon α: IM 6 mil IU 3 times per week for 6 months	247	Radical nephrectomy with suggested unilateral para-aortic nodal dissection Patients with pathologic stages II and III RCC (1987 tumour-node-metastasis categories T3aN0M0 and T3bN0M0 or T2/3N1-3M0) were eligible for the study	16	NR	43
Hinotsu et al.2013[14]	Interferon α: IM 3-6 mil IU 3 times per week for 1 year	107	Histopathological diagnosis of renal cell carcinoma resection of the primary tumour by nephrectomy, for which open or laparoscopic surgery could have been selected and lymph node dissection was possible no metastatic disease	40	82	5

NR: not reported

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TABLE 1.

Characteristics of included studies, *Cont'd*

Author/Year	Adjuvant treatment	Number of participants	Inclusion criteria	Number of participants with ≤T2 disease, n	Number of participants with clear-cell RCC	Number of participants with nodal disease
Motzer et al.2017[15]	Pazopanib: 600 mg or 800 mg once daily	1538	Resected non-metastatic (M0) clear-cell or predominant clear-cell RCC histology within the following TNM classification and Fuhrman grades: pT2G3-4N0, pT3-T4 GanyN0, or pTanyGanyN1	235	1057	90
Choueiri et al. 2021[16]	Pembrolizumab: IV 200 mg once every 3 weeks up to 17 cycles	994	Histologically confirmed locoregional renal cell carcinoma with a clear-cell component that is at high risk of recurrence (ie, tumour stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumour stage 3 or higher, regional lymph node metastasis, or stage M1 with NED) Surgery (partial or radical nephrectomy or metastasectomy) with negative surgical margins In those with M1 NED status, M1 disease was present in addition to the primary tumour at diagnosis, and metastases had to be completely resected at the time of nephrectomy or within 1 year after nephrectomy	86	994	62
Eisen et al. 2020[18]	Sorafenib: 400 mg BD PO	1711	Histologically confirmed RCC No evidence of residual macroscopic disease on postoperative CT scan after resection of RCC	604	1455	74

NR: not reported

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TABLE 1.

Characteristics of included studies, *Cont'd*

Author/Year	Adjuvant treatment	Number of participants	Inclusion criteria	Number of participants with ≤T2 disease, n	Number of participants with clear-cell RCC	Number of participants with nodal disease
Haas et al. 2016[17]	Sunitinib: 50 mg PO daily for first 28 days of each 6-week cycle Sorafenib: 400 mg BD PO daily	1943	Histologically proven, completely resected high-risk clear-cell or non-clear-cell RCC within 12 weeks of removal of the primary tumour. High-risk features: pT1b G3–4 N0 (or pNX where clinically N0) M0 to T(any) G(any) N + (fully resected) M0	NR	1541	NR
Ravaud et al. 2016[19]	Sunitinib: 50 mg PO daily 4 weeks on, 2 weeks off schedule for 1 year	615	Locoregional RCC (tumour stage 3 or higher, regional lymph node metastasis, or both) Histologic confirmation of clear-cell RCC The absence of macroscopic residual or metastatic disease after nephrectomy, as confirmed on blinded independent central review of CT images	NR	615	49
Margulis et al. 2009[20]	Thalidomide: 100 mg/day for 2 weeks then 200 mg/day for 2 weeks followed by 300 mg/day	46	Completely resected locally advanced high-risk RCC, as defined by one of the following criteria: pT2 (Fuhrman grade 3 or 4), pT3a-c, T4, or N1–2 disease resected to no evidence of residual disease All tumour subtypes were eligible	7	34	13

NR: not reported

TABLE 2.

Trials in progress

Trial name/ number	Interventions	Inclusion criteria	Current progress	Estimated completion date
EVEREST NCT01120249	Everolimus	Histologically or cytologically confirmed renal cell carcinoma Considered pathologically either intermediate high-risk or very high-risk disease No history of distant metastases Have undergone a full surgical resection (radical nephrectomy or partial nephrectomy) including removal of all clinically positive nodes No evidence of residual or metastatic renal cell cancer on CT scan of the chest, abdomen, and pelvis (all with oral and IV contrast) performed after nephrectomy	Active, not recruiting	October 2021
SPARC-1 NCT04028245	Spartalizumab and Canakinumab	Histologically confirmed clear-cell or predominantly clear-cell RCC Non-metastatic (localized) RCC that is clinical stage T2 and above, or clinical N1 disease with any T stage Scheduled to undergo either radical or partial nephrectomy	Recruiting	December 2022
PROSPER NCT03055013	Nivolumab – neo-adjuvant and adjuvant	Patients must have a renal mass consistent with a clinical stage ≥T2Nx renal cell carcinoma (RCC) or TanyN+ RCC for which radical or partial nephrectomy is planned Patients must have no clinical or radiological evidence of distant metastases (M0) unless the presumed M1 disease is planned to be resected/definitively treated (eg, thermal ablation, stereotactic radiation)	Active, not recruiting	November 2023
IMmotion010 NCT03024996	Atezolizumab	Pathologically confirmed RCC with a component of either clear-cell histology or sarcomatoid histology that has not been previously treated in the adjuvant or neoadjuvant setting and classified as being at high risk of RCC recurrence Radical or partial nephrectomy with lymphadenectomy in select participants Absence of residual disease and absence of metastasis, as confirmed by a negative baseline CT of the pelvis, abdomen, and chest Absence of brain metastasis, as confirmed by a negative CT with contrast or MRI scan of the brain	Active, not recruiting	February 2024

NR: not reported

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TABLE 2.

Trials in progress, *Cont'd*

Trial name/ number	Interventions	Inclusion criteria	Current progress	Estimated completion date
CheckMate 914 NCT03138512	Nivolumab Nivolumab + ipilimumab	Kidney tumour has been completely resected with negative surgical margins obtained Pathologic TNM staging meeting one of the following: pT2a, G3 or G4, N0 M0; pT2b, G any, N0 M0; pT3, (a, b, c), G any, N0 M0; pT4, G any, N0 M0; pT any, G any, N1 M0 Post-nephrectomy tumour shows RCC with a predominantly clear-cell histology, including participants with sarcomatoid features Participants must have no clinical or radiological evidence of macroscopic residual disease or distant metastases after nephrectomy	Recruiting	July 2025
RAMPART NCT03288532	Durvalumab Durvalumab + Tremelimumab	Histologically proven RCC (all cell types of RCC are eligible, except for pure oncocytoma, collecting duct, medullary and transitional cell cancer [TCC]); no evidence of residual macroscopic disease on postoperative CT scan after resection of RCC Patients with microscopically positive resection margins after radical nephrectomy at the nephrectomy bed, renal vein, or inferior vena cava are eligible provided the postoperative CT scan shows no evidence of residual macroscopic disease	Recruiting	December 2034

NR: not reported

2 highest ranked comparisons with a P-score of 0.87 and 0.80, respectively. Thalidomide was the lowest ranked treatment with a P-score of 0.03. Interferon-alpha was inferior to axitinib, pazopanib, pembrolizumab and sunitinib. Comparisons of all treatments are shown in Table 3. These findings were the same in the sensitivity analysis when using a random-effects model (data not shown).

Overall survival

The OS analysis included 7063 patients from all the studies from above except Margulis et al. (thalidomide, 2009)[20] and Choueiri et al. (pembrolizumab, 2021) [16]. The forest plot of HRs compared with the control arm for each agent is shown in Figure 1B. None of the agents demonstrated a survival benefit compared with observation. Pazopanib was the highest ranked treatment with a P-score of 0.83. Comparisons of all treatments are shown in Online Supplementary Table 2. There was no difference between any of the treatment comparisons. These findings were the same in the sensitivity analysis when using a random-effects model (data not shown).

Severe adverse events

Data from 8 trials using the following interventions were included in the safety analysis: axitinib, girentuximab, interferon-alpha, pazopanib, pembrolizumab, sorafenib, sunitinib, and thalidomide[8,9,12,15–17,19,20]. The forest plots of ORs compared with control are shown in Online Supplementary Figure 2. All of the active treatments except girentuximab significantly increased the likelihood of severe adverse events compared with observation. These findings were the same in the sensitivity analysis when using a random-effects model.

Subgroup analyses

There were insufficient data to perform a network meta-analysis on the planned subgroups.

Discussion

Our network meta-analysis report found that pembrolizumab is likely the most efficacious adjuvant agent in prolonging time to disease recurrence compared with other tyrosine kinase inhibitors, monoclonal antibody against circulating vascular endothelial growth factor, and/or chemotherapies. The only other therapy that was shown to improve DFS compared with observation was pazopanib. However, the absolute difference in recurrence-free survival at 3 years was only 3% between pazopanib and placebo[15]. We used data from patients who received both 600 mg and 800 mg where there were discrepancies in the results related to dose. Although patients receiving the lower dose did not experience improved DFS, those receiving the higher dose were noted to have a prolonged disease-free survival. Therefore, it is likely that the benefit of pazopanib 800 mg is greater than the overall estimates in this review. It should also be noted that the sunitinib did show an improvement in DFS in the S-TRAC trial, although the estimates from this meta-analysis were not significant when including the ECOG trial. The results from this network meta-analysis are consistent with those of previously published meta-analyses on the topic[21, 22]. Despite these positive findings in delaying disease recurrence, none of the treatments improved overall survival. We acknowledge that the overall survival data have not matured for most of the recent studies and that there may still be a benefit with adjuvant therapy. Importantly, there was an increased risk of severe adverse events with adjuvant treatment compared with observation.

It should be considered that there are several factors that impact the use of adjuvant treatment and choice of agent. This review represented a population of patients with locoregional renal cancer who had undergone surgery, but there are sub-populations within this group in whom treatment effect may differ. For example, we believed there may have been differences based on histological subtype and nodal status but were unable to perform the pre-planned subgroup analyses due to a lack of data. The POLAR-01 trial reported that patients with N0 disease had better outcomes with combination IL-2 and IFN-alpha treatment than did those with N+ disease[10]. In contrast, the ATLAS trial demonstrated that patients with highest risk (pT3 with grade ≥ 3 or pT4 and/or N+, any T, any grade) benefitted with axitinib treatment compared with those with low risk (pT2 or pT3 with grade ≤ 2) who had no difference in outcomes with axitinib[8]. The wider literature, especially in the metastatic setting, highlights the increasing use of molecular biomarkers to tailor treatment choices[23]. This will increase in importance as immunotherapies are used more in this setting. Therefore, patient selection is key in determining the benefit of adjuvant therapy and the choice of agent.

The findings of this meta-analysis should be contextualised within its limitations. As mentioned above, there is heterogeneity within the populations of the included studies, and we were unable to perform the pre-planned subgroup analyses. There were also individual study limitations, especially with respect to blinding, that may have introduced bias into the estimates. Additionally, we did not assess patient-reported outcomes, which is critical in determining whether adjuvant treatment improves quality in life[24]. Future studies will need to assess the cost-effectiveness of these treatments because immunotherapies are expensive and thus may not be cost-effective[25]. Health economics studies of advanced RCC have reported that a significant decrease in the cost of immunotherapy is required for it to be cost-effective at generally accepted thresholds[26]. It is likely that these would be generalizable to the use of immunotherapy in the adjuvant setting as the absolute benefits of treatment are small, albeit statistically significant, and come at significant cost. Furthermore, this study will need to be updated following the publication of trials in progress.

Conclusions

Pembrolizumab and pazopanib were the only 2 adjuvant agents that improved time to disease recurrence compared with observation, with the former likely being the more efficacious. None of the treatments improved overall survival, and almost all increased severe adverse events. While it is promising to see these agents show efficacy in this setting, the duration and cost of treatment also need to be considered when determining utility.

TABLE 3.

Matrix comparing hazard ratios [confidence intervals] for DFS between all therapies

Axitinib	1.15 [0.87; 1.52]	1.11 [0.79; 1.57]	0.97 [0.57; 1.63]	0.97 [0.65; 1.44]	
0.87 [0.66; 1.15]	**Control**	0.97 [0.79; 1.19]	0.84 [0.54; 1.31]	0.84 [0.63; 1.12]	
0.90 [0.64; 1.26]	1.03 [0.84; 1.26]	**Girentuximab**	0.87 [0.53; 1.41]	0.87 [0.61; 1.23]	
1.04 [0.61; 1.75]	1.19 [0.76; 1.85]	1.15 [0.71; 1.88]	**IL-2 + Interferon**	1.00 [0.59; 1.70]	
1.04 [0.70; 1.54]	1.19 [0.89; 1.59]	1.15 [0.81; 1.64]	1.00 [0.59; 1.70]	**IL-2 + Interferon +5-FU**	
0.69 [0.48; 1.00]	0.79 [0.62; 1.01]	0.77 [0.56; 1.06]	0.67 [0.40; 1.11]	0.67 [0.46; 0.97]	
1.09 [0.79; 1.50]	1.25 [1.06; 1.48]	1.21 [0.93; 1.57]	1.05 [0.65; 1.69]	1.05 [0.75; 1.46]	
1.18 [0.80; 1.72]	1.35 [1.04; 1.75]	1.31 [0.94; 1.82]	1.14 [0.68; 1.90]	1.14 [0.77; 1.67]	
0.89 [0.65; 1.22]	1.03 [0.89; 1.19]	1.00 [0.78; 1.28]	0.86 [0.54; 1.37]	0.86 [0.62; 1.19]	
0.93 [0.68; 1.28]	1.07 [0.92; 1.26]	1.04 [0.81; 1.34]	0.90 [0.56; 1.44]	0.90 [0.65; 1.25]	
0.37 [0.14; 0.97]	0.43 [0.17; 1.07]	0.41 [0.16; 1.06]	0.36 [0.13; 0.99]	0.36 [0.14; 0.94]	

Light blue shading shows superiority, and dark blue shading shows inferiority of the row compared with the column.

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	1.45 [1.00; 2.10]	0.92 [0.67; 1.27]	0.85 [0.58; 1.24]	1.12 [0.82; 1.53]	1.07 [0.78; 1.47]	2.69 [1.04; 7.01]
	1.26 [0.99; 1.61]	0.80 [0.68; 0.95]	0.74 [0.57; 0.96]	0.97 [0.84; 1.13]	0.93 [0.80; 1.09]	2.34 [0.94; 5.86]
	1.30 [0.95; 1.79]	0.82 [0.64; 1.07]	0.76 [0.55; 1.06]	1.00 [0.78; 1.29]	0.96 [0.74; 1.24]	2.42 [0.95; 6.17]
	1.50 [0.90; 2.49]	0.95 [0.59; 1.53]	0.88 [0.53; 1.47]	1.16 [0.73; 1.85]	1.11 [0.69; 1.77]	2.79 [1.01; 7.72]
	1.50 [1.03; 2.19]	0.95 [0.68; 1.33]	0.88 [0.60; 1.30]	1.16 [0.84; 1.60]	1.11 [0.80; 1.54]	2.79 [1.07; 7.28]
	Interferon-alpha	0.63 [0.47; 0.85]	0.59 [0.41; 0.84]	0.77 [0.58; 1.03]	0.74 [0.55; 0.99]	1.86 [0.72; 4.80]
	1.58 [1.17; 2.12]	**Pazopanib**	0.92 [0.68; 1.26]	1.22 [0.98; 1.52]	1.16 [0.93; 1.46]	2.93 [1.16; 7.43]
	1.70 [1.19; 2.44]	1.08 [0.79; 1.47]	**Pembrolizumab**	1.32 [0.98; 1.77]	1.26 [0.93; 1.71]	3.17 [1.22; 8.21]
	1.29 [0.97; 1.72]	0.82 [0.66; 1.02]	0.76 [0.56; 1.02]	**Sorafenib**	0.96 [0.77; 1.18]	2.41 [0.95; 6.08]
	1.35 [1.01; 1.81]	0.86 [0.68; 1.08]	0.79 [0.59; 1.08]	1.05 [0.85; 1.29]	**Sunitinib**	2.52 [0.99; 6.37]
	0.54 [0.21; 1.39]	0.34 [0.13; 0.87]	0.32 [0.12; 0.82]	0.42 [0.16; 1.05]	0.40 [0.16; 1.01]	**Thalidomide**

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