

Efficacy and safety of SABR/partial-SABR combined with axitinib and toripalimab in recurrent or metastatic renal cell carcinoma: Preliminary results from a prospective phase 2 trial

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Received March 8, 2025; Accepted May 14, 2025

DOI: 10.3892/ol.2025.15122

Abstract. The present study aimed to investigate the safety and efficacy of the combination of axitinib, toripalimab and stereotactic ablative body radiotherapy (SABR) in the treatment of recurrent or metastatic renal cell carcinoma (RCC). The present study was a single-center, prospective study in which all patients received a treatment regimen consisting of axitinib combined with toripalimab and comprehensive multi-lesion SABR. The primary endpoint was progression-free survival (PFS)1 (start of radiotherapy to first disease progression), while secondary endpoints included PFS2 (start of radiotherapy to second-line systemic treatment due to disease progression), overall survival (OS), local control, objective response rate (ORR) and disease control rate (DCR). Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 5.0. A total of 30 patients were enrolled, of whom 21 (70.0%) had clear cell carcinoma and 23 (76.7%) had oligometastatic disease. The median follow-up time was 17.8 months (range, 1.2-47.7 months). The overall ORR was 60.0%, and the DCR was 80.0%, with a DCR of 96.7% for the irradiated lesions and 83.3% for the non-irradiated lesions. The median PFS1 time was 20.3 months (95% CI, 5.2-35.4 months), and the median OS was 44.8 months (95% CI, 20.0-69.6 months), while the median PFS2 time was not reached. As of September 2024, 24 out of 30 patients remained alive, with 15 experiencing disease progression. Subgroup analysis revealed that PFS1 was significantly longer when radiotherapy was administered before treatment failure compared with after (28.6 vs. 6.9 months; $P=0.014$). Regarding adverse events, the most common were diarrhea and fatigue,

with grade ≥ 3 adverse events occurring in 50.0% of patients. In conclusion, mid-term analysis results show that the combination therapy of axitinib, toripalimab and SABR has achieved satisfactory survival outcomes in patients with recurrent or metastatic RCC, with manageable adverse reactions. Long-term follow-up data are still needed for validation. The present trial was retrospectively registered at clinicaltrials.gov (registration no. NCT06889649; 03-03-2025).

Introduction

Renal cell carcinoma (RCC) is a significant malignancy that arises from the epithelial lining of the renal tubules. Within the spectrum of urinary tract malignancies encountered in clinical practice, RCC accounts for 3-5% of all adult cancer diagnoses. Major risk factors include smoking, obesity and hypertension (1). According to data from the Centers for Disease in the United States, patients with localized RCC have a 80-90% 5-year survival rate, contrasting sharply with the rates for recurrent or metastatic disease (10-40%) (2). In China, the incidence of kidney cancer ranks third among urological tumors, following bladder cancer and prostate cancer (3). In patients with kidney cancer, ~30% present with distant metastases at the time of initial diagnosis (4). Therefore, the implementation of effective treatment strategies is critical for improving patient outcomes.

With the success of the CLEAR, KEYNOTE and CheckMate series of studies, the management of recurrent or metastatic RCC has entered an era of combined targeted and immune therapy (target-immunotherapy). In the treatment guidelines for kidney cancer from the National Comprehensive Cancer Network (5), the European Association of Urology (6) and the Chinese Society of Clinical Oncology (7), the combination of axitinib and programmed cell death protein 1 (PD-1) inhibitors is recommended as one of the first-line therapeutic options for recurrent or metastatic RCC. This combination significantly prolongs the median progression-free survival (PFS) time compared with targeted therapy alone (15.4 vs. 11.1 months; $P<0.0001$) (8). Toripalimab, a PD-1 monoclonal antibody developed in China, has demonstrated promising results in the RENOTORCH study (axitinib combined with toripalimab), achieving a median PFS time of 18 months in patients with advanced RCC (9). In April

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Key words: recurrent or metastatic renal cell carcinoma, stereotactic ablative body radiotherapy, axitinib, toripalimab

2024, the combination of axitinib and toripalimab was officially approved by the National Medical Products Administration of China as a first-line treatment for patients with recurrent or metastatic RCC.

Despite these advances, most patients experience disease progression within 1-2 years of initiating combined targeted and immunotherapy (9-13). Extending overall survival (OS) time for patients with advanced RCC remains a notable challenge. The potential of incorporating lesion radiotherapy to improve PFS warrants further exploration.

Previous studies have demonstrated that RCC is not particularly sensitive to conventional fractionated radiotherapy (14,15). However, previous evidence suggests that stereotactic ablative body radiotherapy (SABR), characterized by high single-dose fractions, high biological efficacy and fewer treatment sessions, can markedly enhance the radiosensitivity of RCC (16). SABR has demonstrated notable efficacy and safety in treating recurrent and metastatic RCC lesions (17-19), with reported 1-year local control (LC) rates >90% (20). Higher biological effective dose (BED) values are associated with improved LC rates, with 1-year LC rates reaching 100% when the BED is 117 Gy (21).

Based on these findings, a single-center, prospective study was initiated to evaluate the combination of axitinib and toripalimab with SABR for the treatment of recurrent or metastatic RCC.

Materials and methods

Patient selection. The present prospective, single center, single-arm, phase II trial was reviewed and approved by the Ethics Committee of Peking University First Hospital (Beijing, China; approval no. 2019-345). The patient recruitment commenced on 01-04-2020 and concluded on 31-07-2024. The patients provided written informed consent before treatment. Eligible patients possessed histopathologically confirmed recurrent or metastatic RCC with radiologically evaluable lesions demonstrating either ≤ 5 completely irradiable metastases or > 5 lesions with ≥ 3 amenable to radiotherapy planning, while excluding those with prior anti-PD-1/programmed death-ligand 1 therapy or radiotherapy history. The detailed enrollment protocols are shown in Data S1. The present trial was retrospectively registered at clinicaltrials.gov (registration no. NCT06889649; 03-03-2025).

Treatment protocol. All patients received a combination therapy of targeted therapy and immunotherapy plus radiotherapy. The trial schema and timeline are shown in Fig. 1.

The treatment protocols were as follows: i) Systemic therapy, where patients received 5 mg oral axitinib twice daily and 240 mg intravenous toripalimab every 3 weeks; maintenance therapy continued post-oligoprogression (defined as progression at ≤ 5 sites) with additional local radiotherapy to oligoprogressing lesions, until further treatment modification [inferior-line tyrosine kinase inhibitor (TKI) such as sorafenib, erlotinib and lenvatinib] due to extensive disease progression or intolerance to adverse reactions; and ii) radiotherapy, for primary and metastatic lesions distant from organs at risk, where SABR was administered with peripheral doses of 6-8 Gy/fractions in 5 fractions and tumor doses of 8-10 Gy/fraction in 5

fractions. For lesions adjacent to organs at risk, partial-SABR (p-SABR) was used with edge doses ≥ 2 -2.5 Gy/fraction in 20-25 fractions and central tumor doses of 8-12 Gy/fraction in 3 fractions. If neither SABR nor p-SABR were feasible, moderate hypofractionated radiotherapy (MHFRT) with curative doses was applied. Patients with oligoprogression post-radiotherapy could receive additional radiotherapy to progressing lesions. For patients demonstrating extensive progression who had switched systemic therapy (inferior-line TKI such as sorafenib, erlotinib and lenvatinib), while all-sites radiotherapy was attempted, complete irradiation of all progressing sites could not be ensured due to the high tumor burden characterized by numerous metastatic foci, their widespread anatomical distribution and compromised patient tolerance thresholds. The frequency of radiotherapy (1-3 courses) was determined by the time to disease progression and the tolerance of the patient to treatment.

Endpoints. The primary endpoint was PFS1, defined as the time from the start of radiotherapy to the first disease progression. Secondary endpoints included PFS2 (defined as the time from the start of radiotherapy to the need for a second-line systemic treatment due to disease progression), OS (defined as the time from the start of radiotherapy to death from any cause), LC rate of irradiated lesions, objective response rate (ORR) [complete response (CR) + partial response (PR)] and disease control rate (DCR) [CR + PR + stable disease (SD)]. Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 5.0 (22). Toxicities associated with radiotherapy, targeted therapy and immunotherapy were attributed based on temporal relationships and known toxicity profiles. Serological tests and imaging examinations were also utilized to differentiate the attribution of adverse reactions. The specific standards are shown in Data S1. The evaluation of efficacy and adverse events continued until disease progression, initiation of subsequent antitumor treatments, study completion or patient mortality.

Follow-up. Patients were followed up via outpatient visits and telephone calls every 3 months for 2 years, and then every 6 months beyond 2 years or until tumor progression or mortality. Follow-up evaluations included hematological tests, enhanced chest CT, enhanced abdominal and pelvic CT or MRI and bone scans. Additional brain MRI or positron emission tomography/CT exams were performed as necessary. The follow-up examinations included both the primary tumor and oligometastatic sites.

Statistical analysis. Statistical analyses were performed using SPSS 26.0 software (IBM Corp.). Continuous data are expressed as median (range), and categorical data as frequency and percentage. The Kaplan-Meier method was used to calculate PFS and OS, with group differences assessed by the log-rank test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

General characteristics. The present study included 30 patients with recurrent or metastatic RCC who received combination therapy with axitinib, toripalimab and SABR at Peking

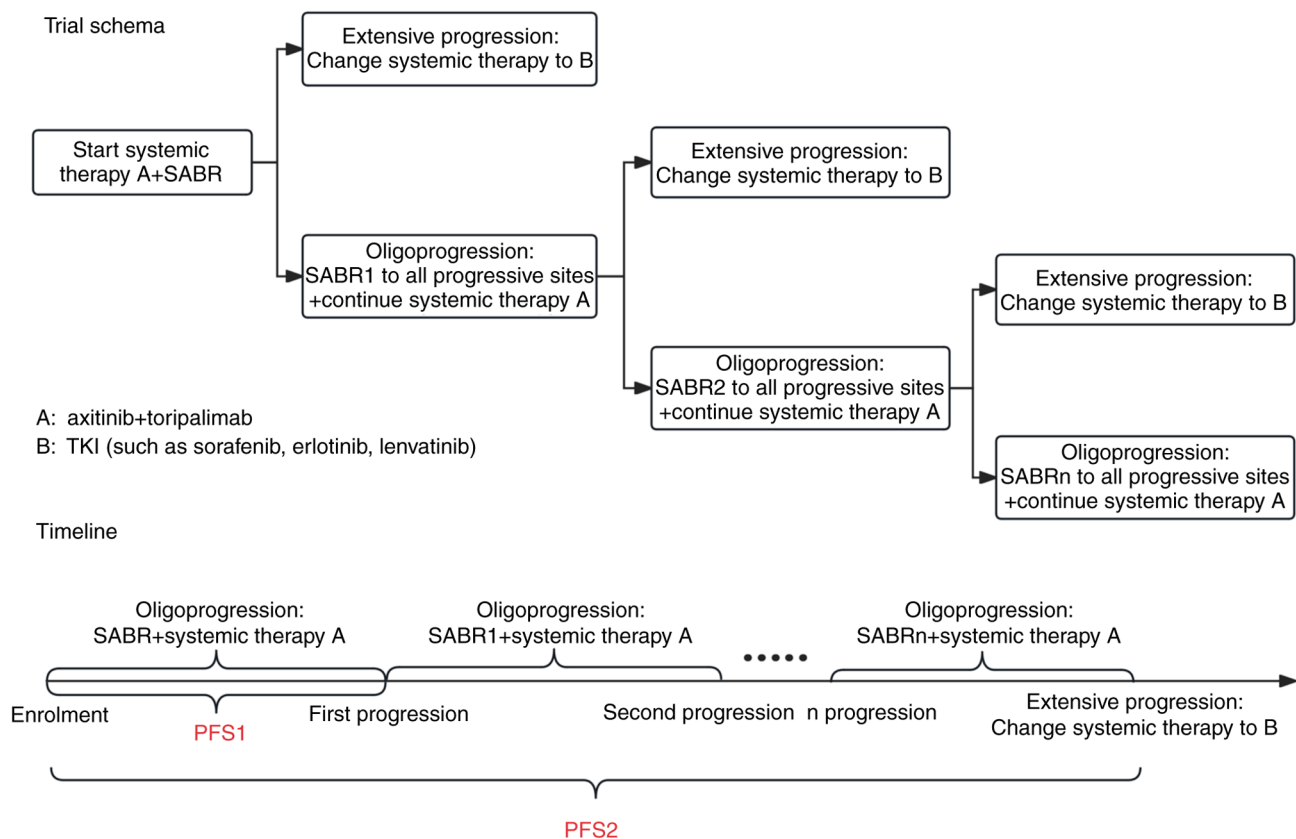


Figure 1. Trial schema and timeline. SABR, stereotactic ablative body radiotherapy; TKI, tyrosine kinase inhibitor; PFS, progression-free survival.

University First Hospital between May 2020 and June 2024. The median age was 57 years, with 66.7% of patients classified as intermediate to high risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (23). Clear cell carcinoma was the predominant histological type, accounting for 70% of the cases. The baseline characteristics of the patients are detailed in Table I.

Treatment details. All 30 patients received combination therapy with axitinib, toripalimab and radiotherapy. Post-radiotherapy, 7 patients (16.7%) developed new oligoprogressive lesions, each of whom completed two or three courses of radiotherapy. A total of 20 patients (66.7%) underwent all-sites radiotherapy (all metastatic sites of the patient were treated with radiotherapy). Among the 30 patients, there were a total of 114 metastatic lesions, 88 of which (77.2%) received radiotherapy. Of these patients, 85% underwent SABR or p-SABR treatment.

As of the follow-up in September 2024, 16 out of 30 patients were still undergoing treatment. The cycles of toripalimab received by these patients are detailed in Table II.

Efficacy. As of September 2024, the clinical efficacy of the treatment was evaluated in 30 patients. The outcomes were as follows: CR in 3 patients, PR in 15 patients, SD in 6 patients and progressive disease (PD) in 6 patients. The ORR rate was 60.0% (18/30) and the disease control rate DCR was 80.0% (24/30). The DCR for irradiated lesions was 96.7% (29/30).

The median follow-up duration for the 30 patients was 17.8 months (range, 1.2–47.7 months). The median PFS1 was 20.3 months (95% CI, 5.2–35.4 months), with 1- and 2-year

PFS1 rates of 67.3 and 46.7%, respectively. The median PFS2 was not reached; the 1 and 2-year PFS2 rates were 74.1 and 56.6%, respectively. The median OS time was 44.8 months (95% CI, 20.0–69.6 months), with 1- and 2-year OS rates of 95.3 and 89.6%, respectively. The 1- and 2-year LC rates were 100.0 and 96.7%, respectively. The survival curves are presented in Fig. 2. By the end of the follow-up period, the LC rate of all irradiated lesions was 96.7%. Only 1 patient experienced local recurrence at the edge of the radiotherapy field 13.8 months after radiotherapy due to the inability to deliver sufficient SABR dose to lesions adjacent to the bowel.

As of September 2024, 24 patients were still alive, and 6 patients had died. Of these, 5 mortalities were due to tumor progression and 1 mortality was due to an unknown infection leading to systemic inflammatory response syndrome. A total of 15 patients experienced disease progression, with 7 patients exhibiting oligoprogression and 8 patients showing wide progression. Among the 7 patients with oligoprogression, 6 underwent radiotherapy for the progressive lesions without altering the systemic therapy regimen. However, 1 patient did not receive a second course of radiotherapy due to local recurrence at the edge of the radiotherapy field.

Subgroup analysis revealed that patients who received radiotherapy before systemic treatment failure had a significantly longer median PFS1 time compared with those who received radiotherapy after treatment failure (28.6 vs. 6.9 months; $P=0.014$; Fig. 3). However, no significant differences in median PFS1 time were observed, neither based on metastatic burden (≤ 5 vs. >5 lesions, 9.6 vs. 20.3 months; $P=0.978$; Fig. 4) nor IMDC risk categories (low-risk vs.

Table I. Baseline characteristics of patients (n=30).

Characteristic	Value
Median age (range), years	57 (36-81)
Sex, n (%)	
Male	24 (80.0)
Female	6 (20.0)
IMDC risk classification at enrolment, n (%)	
Low risk	10 (33.3)
Intermediate risk	15 (50.0)
High risk	5 (16.7)
Surgical intervention for primary tumor, n (%)	
Radical nephrectomy	20 (66.7)
Partial nephrectomy	4 (13.3)
No surgery	6 (20.0)
Histology, n (%)	
ccRCC	21 (70.0)
Papillary	3 (10.0)
XP11.2 translocation/TFE3 fusion RCC	2 (6.7)
Chromophobe	1 (3.3)
Other	3 (10.0)
Number of metastatic lesions, n (%)	
1-5	23 (76.7)
≥6	7 (23.3)
Sites of metastasis, n (%)	
Lymph nodes	13 (20.0)
Bone	13 (20.0)
Lung	12 (19.1)
Liver	5 (7.5)
Muscle	3 (4.5)
Pancreas	2 (3.0)
Seminal vesicle	1 (1.5)
Vagina	1 (1.5)
Ovary	1 (1.5)
Breast	1 (1.5)
Peritoneum	1 (1.5)
Renal fossa/residual kidney recurrence	6 (9.2)
Primary tumor	6 (9.2)
Prior systemic therapy, n (%)	
None	26 (86.7)
Sorafenib	2 (6.7)
Pazopanib	1 (3.3)
Lenvatinib	1 (3.3)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ccRCC, clear cell renal cell carcinoma; TFE3, transcription-factor binding to IGHM enhancer 3.

intermediate- and high-risk, 20.3 vs. 30.6 months; $P=0.514$; Fig. 5). By contrast, subgroup analysis of OS demonstrated significant disparities across IMDC risk categories (low-risk vs. intermediate-risk vs. high-risk, not reached vs. 47.2 vs. 24.6 months; $P=0.002$; Fig. 6).

Table II. Treatment details (n=30).

Treatment	n (%)
Number of radiotherapy courses	
1	25 (83.3)
2	3 (10.0)
3	2 (6.7)
All sites radiotherapy	
Yes	20 (66.7)
No	10 (33.3)
Radiotherapy technique for metastases	
SABR	54 (61.4)
p-SABR	19 (21.6)
MHFRT	15 (17.0)
Cycles of toripalimab	
1-8	14 (46.7)
9-17	9 (30.0)
18-34	6 (20.0)
≥34	1 (3.3)

SABR, stereotactic ablative body radiotherapy; p, partial; MHFRT, moderate hypofractionated radiotherapy.

Adverse reactions

Targeted therapy and immunotherapy-related adverse reactions. Among the 30 patients, 15 (50.0%) experienced grade 1-2 adverse reactions, while 15 (50.0%) experienced grade 3-4 adverse reactions (Table III). All adverse reactions improved following symptomatic treatment, dose reduction or discontinuation of therapy.

Radiotherapy-related adverse reactions. Among the 30 patients, 9 experienced grade 1-2 adverse reactions (30.0%). The most common reactions included fatigue (16.7%), diarrhea and decreased appetite (16.7%), skin reactions (3.3%), leukopenia (3.3%) and radiation pneumonitis (3.3%) (Table IV). All adverse reactions improved following symptomatic treatment. Notably, there were no occurrences of grade ≥3 radiotherapy-related adverse reactions.

Discussion

The present study explored the application of SABR in conjunction with targeted therapy using axitinib and immunotherapy with toripalimab for patients with recurrent or metastatic RCC. To the best of our knowledge, the present study is the only prospective study to date that integrates targeted therapy, immunotherapy and radiotherapy in a triple-modality approach for recurrent or metastatic RCC, and preliminary results indicate promising efficacy.

The treatment landscape for recurrent or metastatic RCC has entered the era of combined targeted therapy and immunotherapy. Since 2018, multiple large-scale, international, multicenter clinical trials have demonstrated that immunotherapy with PD-1/L1 monoclonal antibodies, when combined with targeted therapy, markedly improves first-line treatment outcomes for advanced RCC compared with the

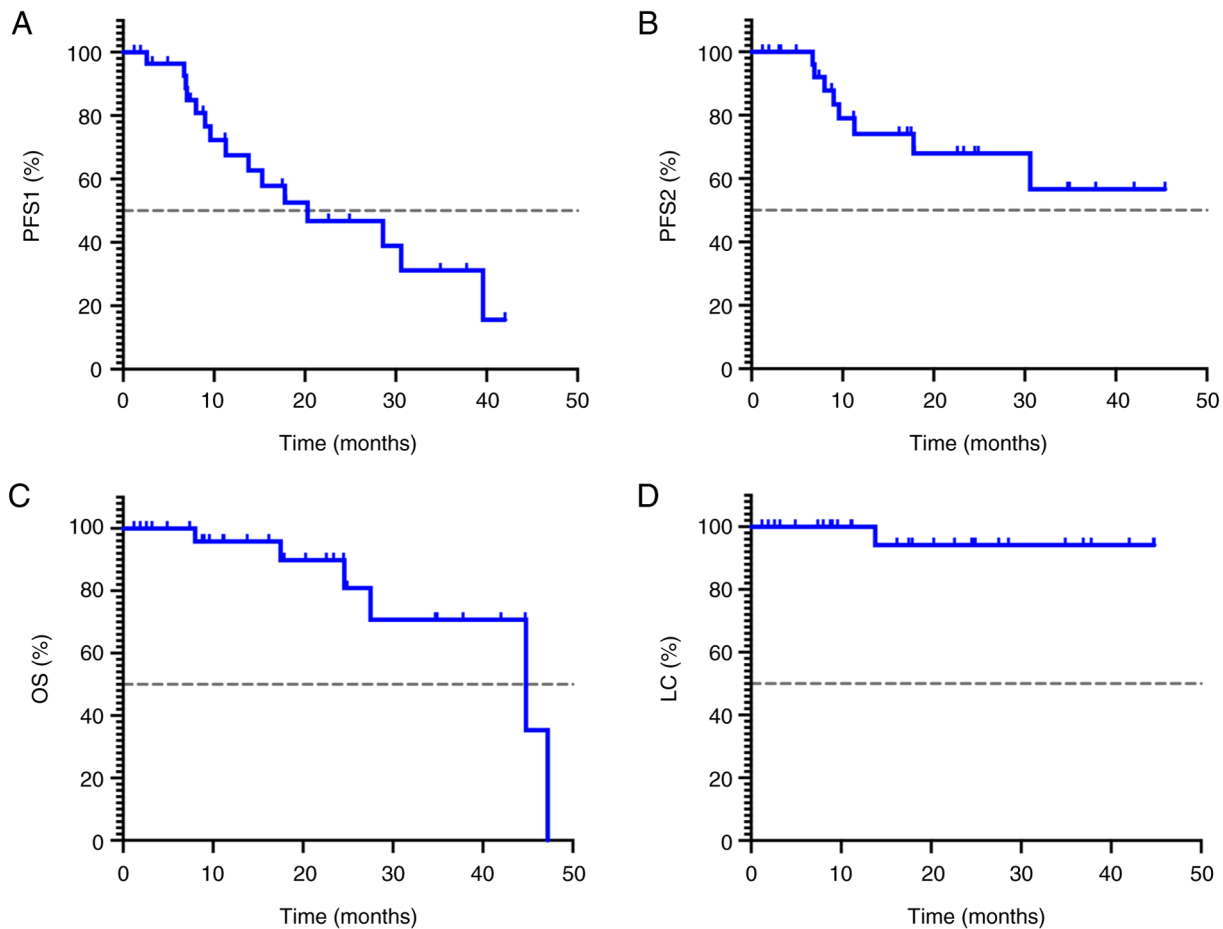


Figure 2. Kaplan-Meier survival curves of (A) PFS1, (B) PFS2, (C) OS and (D) LC. PFS, progression-free survival; OS, overall survival; LC, local control.

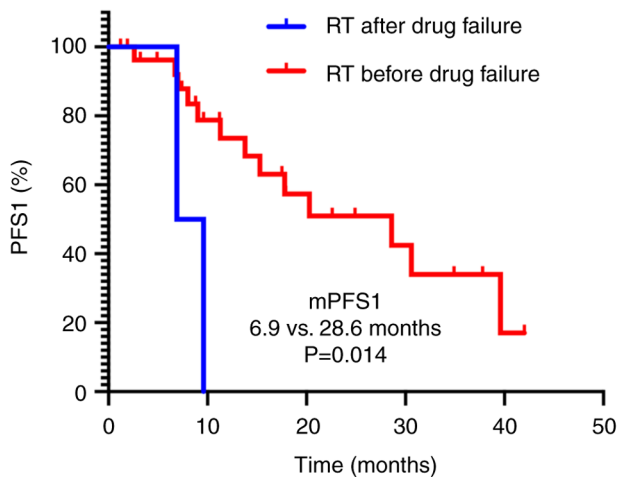


Figure 3. PFS1 curves for RT before vs. after treatment failure. mPFS1, median progression-free survival 1; RT, radiotherapy.

TKI sunitinib. Notable randomized controlled trials such as JAVELIN Renal 101, KEYNOTE-426, CheckMate 9ER and CLEAR have reported median PFS times ranging from 13.3 to 23.3 months, which is markedly superior to those for sunitinib monotherapy (10-13). However, the application of combined targeted therapy and immunotherapies remains limited in China due to the lack of regulatory approval.

Toripalimab, the first approved fully human monoclonal antibody targeting the PD-1 receptor in China, exhibits higher affinity for PD-1 compared with pembrolizumab and nivolumab, and possesses a unique IgG4 binding site that does not rely on glycosylation modifications (24). Clinical studies across various disease areas have demonstrated its efficacy (25-27), and it is currently approved for the treatment of advanced melanoma, nasopharyngeal carcinoma and urothelial carcinoma. Phase I clinical trials have reported effective treatment responses in patients with advanced RCC (28). The results of the randomized controlled phase III trial, RENOTORCH, presented at the 2023 European Society for Medical Oncology Congress, indicated a median PFS time of 18.0 months for patients with advanced RCC treated with the combination of axitinib and toripalimab compared with sunitinib, with a favorable safety profile (9). Notably, the patients included in the RENOTORCH study were categorized as intermediate- to high-risk, and comparisons with high-risk cohorts from the JAVELIN Renal 101, KEYNOTE-426, CheckMate 9ER and CLEAR studies revealed longer median PFS times for the axitinib plus toripalimab combination compared with sunitinib, with PFS remaining a critical focus in the comprehensive treatment of advanced RCC.

SABR has emerged as a principal non-surgical treatment modality for patients with recurrent or metastatic RCC in conjunction with targeted therapy and immunotherapy, gaining increasing recognition in current clinical guidelines (5,6).

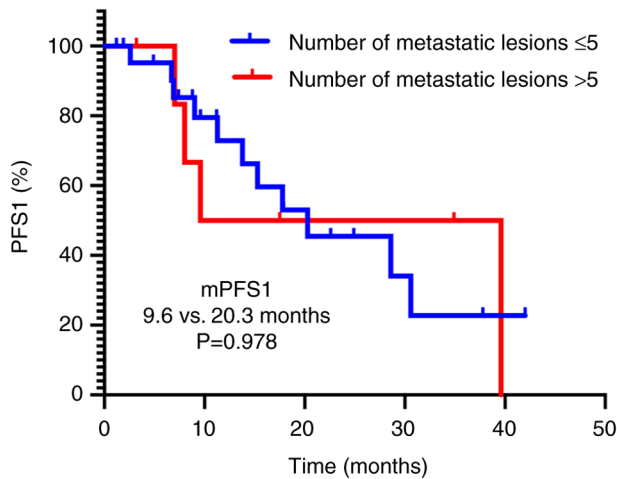


Figure 4. PFS1 curves for number of metastatic lesions (≤ 5 vs. > 5). PFS, progression-free survival.

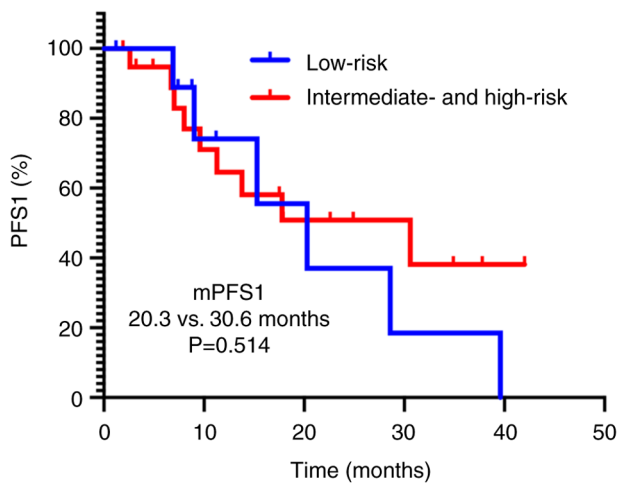


Figure 5. PFS1 curves for International Metastatic Renal Cell Carcinoma Database Consortium low-risk vs. intermediate- and high-risk. PFS, progression-free survival.

However, the current guidelines primarily position SABR as a means to enhance LC rates, without fully acknowledging its potential role in improving OS as part of a combination treatment strategy.

Previous studies have reported positive outcomes for the combination of targeted therapy and SABR in patients with oligometastatic RCC. Preliminary results from a prospective phase II clinical trial presented at the 2023 American Society of Clinical Oncology meeting indicated that the combination of sunitinib and SABR in treatment-naïve patients with oligometastatic RCC achieved a significantly longer median PFS time of 18.6 months compared with the sunitinib monotherapy group (7.1 months; $P=0.003$), with no notable difference in the incidence of treatment-related adverse events between the two groups (29). A retrospective analysis by Ma *et al* (30) of patients receiving TKI therapy combined with SABR for oligometastatic RCC from 2015 to 2020, involving 100 lesions with 90% classified as intermediate to high-risk, indicated a median PFS time of 22 months for those receiving combined treatment during first-line therapy. Notably, preclinical evidence

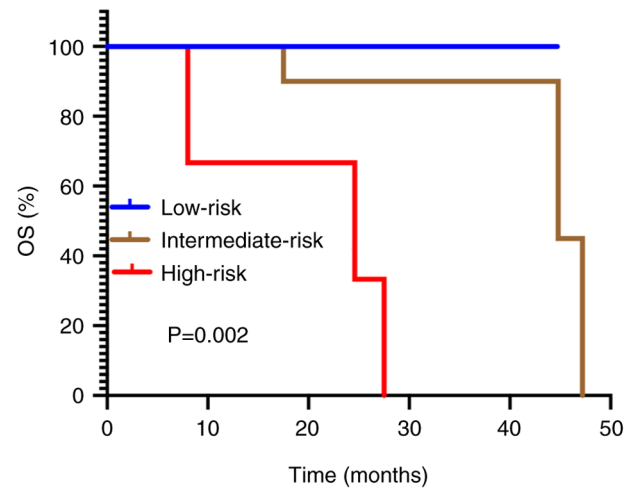


Figure 6. OS curves for International Metastatic Renal Cell Carcinoma Database Consortium low-risk vs. intermediate-risk vs. high-risk. OS, overall survival.

suggests that SABR can synergistically enhance the sensitivity of associated pathways inhibited by targeted therapy, including AKT and mTOR pathways, which provides a further biological basis for clinical research (31-33). Additionally, accumulating evidence has demonstrated that SABR-induced immunogenic cell death facilitates the release of tumor-associated antigens, which subsequently triggers dendritic cell maturation and initiates systemic cytotoxic T-cell responses, thereby remodeling the immunosuppressive tumor microenvironment (34,35). Based on these research outcomes, previous studies have investigated the efficacy of immunotherapy combined with SABR; however, the median PFS time reported (5.6 to 15.6 months) has not been optimal, possibly related to insufficient radiation dose and delayed treatment lines (36-38).

The present study preliminarily explored the efficacy and safety of combining axitinib with toripalimab, an anti-PD-1 monoclonal antibody developed in China, and SABR for patients with recurrent or metastatic RCC. The present study included patients who had received second-line or subsequent therapies, with a high proportion of intermediate to high-risk patients (66.7%) and 30.0% being non-clear cell RCC. Preliminary results indicated a median PFS1 time of 20.3 months, with patients receiving first-line targeted therapy and immunotherapy combined with radiotherapy achieving a PFS1 time of 28.6 months. This outcome surpasses data from studies that utilized axitinib combined solely with immunotherapy (median PFS time ranging from 13.8 to 18.0 months) (9,11,13). The median OS time reached 44.8 months, showing no notable difference compared with previous studies (9,11,13), potentially due to insufficient follow-up duration.

Subgroup analyses revealed that PFS1 time was significantly longer for patients who received radiotherapy before treatment failure compared with those who received it afterward. Early radiotherapy intervention before first-line treatment failure may lead to better PFS due to lower tumor burden, a more favorable immune microenvironment and the opportunity to proactively control disease progression (20,31). The OS subgroup analysis revealed a significant survival gradient across IMDC risk strata: Median OS was not reached

Table III. Incidence of targeted therapy- and immunotherapy-related adverse reactions (n=30).

Adverse reaction	Grade 1-2, n (%)	Grade 3-4, n (%)
Diarrhea	12 (40.0)	7 (23.3)
Fatigue	8 (26.7)	9 (30.0)
Hypertension	13 (43.3)	4 (13.3)
Liver dysfunction	11 (36.7)	5 (16.7)
Rash or hand-foot syndrome	15 (50.0)	1 (3.3)
Kidney dysfunction	12 (40.0)	1 (3.3)
Decreased appetite	11 (36.7)	1 (3.3)
Hypothyroidism	12 (40.0)	0 (0.0)
Esophageal or throat pain, hoarseness	11 (36.7)	0 (0.0)
Proteinuria	10 (33.3)	0 (0.0)
Pain	3 (10.0)	6 (20.0)
Nausea and vomiting	9 (30.0)	0 (0.0)
Pneumonia or respiratory distress	6 (20.0)	3 (10.0)
Anemia	9 (30.0)	0 (0.0)
Leukopenia or neutropenia	7 (23.3)	0 (0.0)
Thrombocytopenia	6 (20.0)	0 (0.0)
Myositis	5 (16.7)	0 (0.0)
Myocarditis	4 (13.3)	0 (0.0)
Infection	3 (10.0)	0 (0.0)
Edema	3 (10.0)	0 (0.0)
Pancreatitis	1 (3.3)	0 (0.0)

Table IV. Incidence of radiotherapy-related adverse reactions (n=30).

Adverse reaction	Grade 1-2, n (%)	Grade 3-4, n (%)
Fatigue	5 (16.7)	0 (0.0)
Diarrhea and decreased appetite	5 (16.7)	0 (0.0)
Skin reactions	1 (3.3)	0 (0.0)
Leukopenia	1 (3.3)	0 (0.0)
Radiation pneumonitis	1 (3.3)	0 (0.0)

in the low-risk group, while median OS time was 47.2 months in the intermediate-risk group and declined to 24.6 months in the high-risk group, which implies that combining radiation with systemic therapy may amplify benefits in less aggressive disease states, while high-risk tumors likely harbor intrinsic resistance mechanisms that diminish therapeutic impact.

In terms of safety, the observed 50.0% incidence of grade ≥ 3 adverse events with the axitinib-toripalimab-SABR triple-modality therapy were below the rates reported in contemporary TKI/immune-checkpoint inhibitor combinations (67-70% in CheckMate 9ER/KEYNOTE-426) (10,13). There were no occurrences of grade ≥ 3 radiotherapy-associated

adverse reactions, suggesting that the triple-modality regimen may not inherently exacerbate the toxicity profile of the underlying targeted therapy-immunotherapy combination. The most common reasons for discontinuation of targeted therapy and immunotherapy were hepatic dysfunction, diarrhea and gastrointestinal bleeding. These findings indicate the need for heightened vigilance regarding liver function and gastrointestinal responses when administering the axitinib and toripalimab combination.

Furthermore, challenges arose in administering adequate SABR doses due to the presence of large metastatic lesions or their proximity to critical organs. The present study introduced the p-SABR technique, which allowed for dose escalation at the tumor center while maintaining a total dose of 50-60 Gy, thereby optimizing tumor targeting while protecting adjacent critical structures. The institutional protocol prioritizes SABR as the primary radiotherapy modality. The p-SABR approach (combining SABR for tumor core with MHFRT for peripheral regions) is reserved for larger tumors with notable adjacent normal tissue involvement, while MHFRT is typically employed for smaller tumors surrounded by critical structures. For example, in the present study cohort, one patient's tumor was located in the abdominal wall and near the bowel, but the patient chose SABR technology for personal reasons. A controlled dose compromise was strategically accepted in the peripheral target area to maximize SABR coverage of the predominant tumor volume while maintaining bowel sparing. However, the patient experienced a recurrence due to marginal underdosage in the tumor target area. This outcome indicated that choosing p-SABR technology for suitable patients may provide greater benefits compared with traditional SABR technology.

The limitations of the present study include its single-arm design, small sample size and short follow-up for OS endpoints. Due to the exploratory trial design and the ongoing nature of this research, the present publication presents preliminary findings based on a limited sample size (n=30), which inherently restricts the statistical power of the analyses. To enhance the validity of these observations, patient enrollment is actively being expanded and extended follow-up protocols will be implemented in subsequent phases of the investigation. The single-arm design introduces potential confounding factors such as heterogeneous disease burden, variability in prior therapies and IMDC risk stratification, which may compromise outcome interpretation. While propensity score weighting could theoretically mitigate some confounding factors, its applicability remains limited in small single-arm cohorts (n<100). Future randomized trials stratified by confounding factors are warranted to validate the present findings. Future studies will also investigate potential biomarkers associated with the immune-activating effects of SABR in metastatic RCC, such as circulating free DNA and microRNAs, which have been identified as predictors of immunotherapy response in patients with oligoprogressive lung cancer receiving combined SABR and immunotherapy (39). These investigations will aim to further evaluate the efficacy of the triple combination therapeutic regimen.

In conclusion, the combination of axitinib, toripalimab and SABR for the treatment of recurrent or metastatic RCC demonstrates manageable adverse effects and shows

preliminary efficacy in clinical practice. Whether this combination ultimately improves PFS and OS will require further validation through long-term follow-up results. In the future, a two-arm randomized trial of axitinib and toripalimab vs. the triple-modality of axitinib, toripalimab and SABR will be performed, to confirm the efficacy and safety of the triple combination therapy and explore the correlative biomarkers.

Acknowledgements

Not applicable.

Funding

The present study was funded by Capital's Funds for Health Improvement and Research (grant no. 2024-4-40710), National High Level Hospital Clinical Research Funding (High Quality Clinical Research Project of Peking University First Hospital; grant no. 2023HQ11) and National High-Level Hospital Clinical Research Funding (Interdepartmental Clinical Research Project of Peking University First Hospital; grant no. 2022CR29).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KH wrote the original manuscript and contributed to methodology design, data curation, formal analysis and investigation. MWM participated in methodology design, conceptualization, data validation, formal analysis, software development and revision of the manuscript. XSG was responsible for project administration, methodology design, funding acquisition and supervision, and participated in the review and editing of the manuscript. HZL was responsible for supervision and methodology design. JYC participated in data curation and visualization. XYL participated in formal analysis, data validation and resource provision. SBQ participated in formal analysis and validation. XYR participated in data validation and software development. KH and XSG confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study received ethics approval from the Ethics Committee of Peking University First Hospital (Beijing, China; approval no. 2019-345). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Peking University First Hospital and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The patients provided written informed consent before treatment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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