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Tislelizumab plus lenvatinib as the first-line therapy in patients with advanced fumarate hydratase-deficient renal cell carcinoma: a single-arm, single-centre, phase 2 trial and metabolic biomarker analysis

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Abstract

Background

Fumarate hydratase-deficient renal cell carcinoma (FH-RCC) is a rare subtype of kidney malignancy with poor prognosis. Standard of care for advanced FH-RCC has not been established, although our prior retrospective study showed encouraging antitumor activity of immune checkpoint inhibitor (ICI) plus tyrosine kinase inhibitor (TKI) combinations.

Objective

We aimed to conduct an investigator-initiated prospective study to assess the efficacy and safety of tislelizumab plus lenvatinib as a first-line treatment for patients with advanced FH-RCC.

Methods

In this single-arm, open-label, phase 2 trial, adult patients with previously untreated, pathologically confirmed, unresectable advanced or metastatic FH-RCC, and at least one measurable lesion per RECIST 1.1 were eligible for enrollment. All enrolled patients received tislelizumab 200 mg intravenously every three weeks plus lenvatinib 20 mg orally once daily until disease progression, intolerable toxicity, or withdrawal of consent. This trial is registered with ClinicalTrials.gov (NCT05877820) and closed enrollment. The primary end point was objective response rate (ORR) as assessed by RECSIT 1.1. Secondary endpoints included progress-free survival, overall survival, disease control rate, duration of response, clinical benefit rate and treatment-related adverse events (TRAEs) assessment. Efficacy and safety were analyzed in all treated patients. Correlation between circulating metabolic biomarker dynamics and clinical response was investigated as an exploratory endpoint.

Results

From September 5, 2023, to December 10, 2024, 25 patients were screened and 20 were eligible to receive treatment. Median age was 41.5 years (IQR: 30–50) and 80% of patients were male. ECOG performance status was 1 or 2 in 40% of patients. Patients were classified as favorable, intermediate, or poor risk group in three (15%), eleven (55%), and six (30%) patients respectively per IMDC categorization. *FH* germline mutation was identified in 15/20 (75%) patients; the remainder were considered to carry biallelic somatic *FH* alterations. As data cutoff, the median follow-up was 17.8 months (IQR: 12.2–23.0). Nineteen patients achieved a confirmed objective response (ORR: 95%; 95% CI: 75.1–99.9), including four (20%) with a complete response and 15 (75%) with a partial response as the best response, with a median duration of response of 19.2 months (95%CI: 16.3-NR). The median PFS was 20.7 months (95%CI: 17.8-NR). Two-year overall survival rate was estimated as 89.7% (95% CI: 77.2–100). Grade ≥ 3

TRAEs occurred in 9/20 (45%) patients; and dose interruption, reduction or discontinuation of any study agent occurred in 14/20 (70%) patients. We found that circulating succinyl-adenosine and succinic-cysteine tracked radiographic tumor burden assessed by RECIST 1.1 in 16/20 (80%) patients. The main limitation is the single-centre and single-arm design, and the sample size is limited.

Conclusions

Tislelizumab plus lenvatinib has favorable antitumor activity in patients with previously untreated advanced FH-RCC, with a safety profile consistent to that of previous reports, which shows potential as a first-line treatment option. Circulating succinate-modifying metabolites may act as potential biomarkers for real-time treatment response monitoring and for the detection of early treatment failure.

1. Introduction

Fumarate hydratase deficient renal cell carcinoma (FH-RCC) is a rare renal malignancy with aggressive biological behavior and a dismal prognosis. FH-RCC is mostly associated with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome characterized by *FH* germline mutations; it is also caused by biallelic somatic *FH* alterations in few cases[1]. Tumorigenesis and progression of FH-RCC are believed to be driven by tricarboxylic acid metabolic rewiring and abnormal accumulation of fumarate in the tumor cell, due to functional deficiency of fumarate hydratase[2].

There is no standard of care for patients with advanced FH-RCC, although the NCCN Guidelines recommend bevacizumab plus erlotinib (Beva/Erlo) based on a phase 2 trial initiated over ten years ago[3,4], the results of which were recently published[5]. During the past decade, combinations of immune checkpoint inhibitor (ICI) and tyrosine kinase inhibitor (TKI) have been shown to provide great benefit for patients with advanced RCC and revolutionized the treatment landscape[6–9]. A real-world multicenter retrospective study showed comparable response rates between ICI/TKI and Beva/Erlo in the front-line treatment for advanced FH-RCC patients, and the former seemed to provide favorable clinical outcomes[10]. However, the retrospective nature and different TKIs used in the study population obscured the advantages of ICI/TKI therapy. Prospective KEYNOTE-B61 study demonstrated that pembrolizumab plus lenvatinib had encouraging antitumor efficacy and acceptable safety for advanced non-clear cell RCC patients, yet without focusing on any specified subtype such as FH-RCC[11]. Here, we report the results of a prospective phase 2 study of tislelizumab plus lenvatinib combination as the first-line therapy for patients with advanced or metastatic FH-RCC. Tislelizumab is an anti-PD-1 monoclonal antibody developed by a Chinese biopharmaceutical company and is approved for the treatment of multiple malignancies across China and western countries.

The disrupted Kreb's cycle caused by FH deficiency occurring in the tumor cell leads to unique metabolic traits and our previous work identified two robust circulating metabolic biomarkers, succinyl-adenosine and succinic-cysteine, which were able to sensitively and specifically reflect genomic alteration status

and tumor burden in FH-RCC. Therefore, as an exploratory endpoint, we also reported dynamic correlation between biomarker change and clinical response per RECIST assessment.

2. Patients and Methods

(1) Study Design and Patient Eligibility

This is an investigator-initiated, single-arm, single-centre, open-label, phase 2 trial (ClinicalTrials.gov identifier: NCT05877820). Eligible patients were aged 18–80 years with pathological confirmed, unresectable advanced or metastatic FH-RCC, which were reviewed by two expert GU pathologists (ZY. Wang, DF. Cao). An archival tumor tissue or newly biopsy was tested for FH and 2-succinocysteine (2-SC) expression via immunohistochemistry, and genetic testing were required for all subjects. FH-RCC was diagnosed based on morphologic features and immunohistochemical result. Morphologically, FH-RCC demonstrates multiple admixed histologic patterns including papillary, tubulopapillary, solid, cystic and cribriform ones and shows focal to extensive eosinophilic macronucleoli with perinucleolar halo[12]. The diagnosis was supported by negative staining for FH and overexpression of 2-SC (diffuse and strong staining). In cases with positive but weak FH staining, the diagnosis was made based on morphologic features with overexpression of 2-SC[13,14]. In one case without tumor tissue pathology (i.e. cystic renal tumor not suitable for puncture biopsy), the diagnosis of HLRCC was based on the finding of *FH* germline mutation. All FH-RCCs were further confirmed with molecular testing which showed pathogenic or likely pathogenic germline or somatic alteration in *FH* gene. All eligible patients were required to have at least one measurable lesion defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1[15], ECOG performance status 0–2, adequate organ function, and no history of prior systemic therapy. Key exclusion criteria included prior therapy with TKI or ICI agents, or clinically significant cardiovascular disease, or untreated brain metastases. This trial was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice and was approved by the institutional ethics review board; all patients provided written informed consents.

(2) Treatment and Assessment

All enrolled patients received concurrent lenvatinib 20mg orally once daily plus tislelizumab 200mg intravenously every three weeks. Treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients with progressive disease were allowed to continue the treatment if the investigator considered them to still be deriving treatment benefit. Interruption of tislelizumab, or delay for no more than 12 weeks, or permanent discontinuation was permitted to manage immune-related adverse events (irAEs), while dose reduction was not allowed. Dose reduction of lenvatinib from 20mg daily to 16mg, 12mg, or 8mg daily gradually in sequence based on the previous dose, or temporal interruption, or discontinuation was implemented to manage lenvatinib-related toxicities, and lenvatinib dose re-escalation was permitted once AE resolved after dose reduction and supportive care measures were applied. Patients who interrupted or discontinued the treatment of either tislelizumab or lenvatinib were permitted to continue the remaining agent in the absence of disease progression.

Abdominal and pelvic contrast-enhanced magnetic resonance imaging (preferred) or contrast-enhanced computed tomography, and chest plain computed tomography were performed at baseline and repeated every six weeks until Week 24, and every three months thereafter. Tumor response was assessed according to RECIST 1.1 by two independent radiologists (GY Wu, GQ Liu). Clinical and laboratory assessments, including complete blood counting, urinalysis, metabolic panel, endocrine panel and electrocardiograph, were performed every three weeks within the initial 24 weeks, and every three months thereafter. Extra imaging and laboratory examinations were allowed if clinically needed. For patients participating exploratory endpoint studies, plasma succinyl-adenosine and succinic-cysteine quantitation as per previously reported protocol [16] were conducted every three weeks within the initial 24 weeks to explore the correlation between metabolic biomarker dynamics and clinical response per RECIST assessment, which was continued among patients able to provide plasma samples in the follow-up period after the initial 24 weeks.

(3) Outcomes

The primary endpoint was objective response rate (ORR) defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR) as the best response according to RECIST 1.1. Secondary endpoints included progress-free survival (PFS), overall survival (OS), disease control rate (DCR), duration of response (DOR), clinical benefit rate and treatment-related adverse events (TRAEs) assessment. PFS and OS were calculated using time-to-events methods to account for censoring. PFS was defined as the interval between treatment initiation and the first occurrence of disease progression or death from any cause. Patients without progression disease (PD) or death during the follow-up period were censored at their last imaging assessment date. OS was defined as time from treatment start to death of any cause. DCR was defined as the combined proportion of patients achieving CR, PR or stable disease (SD). DOR was calculated from the time of first documented response until the first event of PD or death of any cause. The clinical benefit rate was defined as the percentage of patients who achieved sustained disease control for at least 24 weeks. AEs were assessed and graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0[17] and were recorded until 30 days after treatment discontinuation and post-treatment 90 days for serious AEs.

(4) Statistics analysis

We used an exact binomial design with a pre-specified internal futility assessment, analogous to a Simon two-stage approach, to evaluate the antitumor activity of the investigational regimen. In our previous real-world retrospective cohort, first-line ICI/TKI or Beva/Erlo produced an objective response rate (ORR) of approximately 20–30%. We tested H_0: ORR ≤ 30% (p_0=0.30) versus H_1: ORR ≥ 60% (p_1=0.60), representing a clinically meaningful improvement consistent with outcomes reported for lenvatinib plus pembrolizumab or cabozantinib plus nivolumab in advanced renal cell carcinoma. With a one-sided α = 0.05 and 80% statistical power, 17 evaluable patients were required according to the exact binomial calculation; the regimen would be considered promising if ≥ 9 patients achieved an objective response.

To account for an anticipated 10–20% attrition rate and ensure operational feasibility, the target sample size was 20.

The study was initially planned to enroll 10 patients as an exploratory cohort. After completion of the first 10 cases, an interim review of responses was conducted; as predefined, if ≥ 5 confirmed responses (consistent with an expected ORR ≥ 50%) were observed, the sample size would be expanded to 20. Under the final design, the regimen would be considered promising if ≥ 10 of 20 patients achieved an objective response, corresponding to an exact type I error rate of 4.8% and statistical power of 87.3% under p_0=0.30 and p_1=0.60.

Efficacy and safety analyses included all patients who received at least one dose of either study agent. ORR, DCR and clinical benefit rate were summarized with exact Clopper–Pearson 95% CIs. Median PFS, OS, and DOR were estimated using Kaplan-Meier methods, with 95% CIs calculated using the Greenwood's formula. All analyses were performed using R software (version 4.3.3).

3. Results

(1) Baseline characteristics

From September 5, 2023, to December 10, 2024, 25 patients were screened for eligibility, and 20 patients were enrolled. At the data cutoff on December 22, 2025, the median follow-up was 17.8 months (IQR: 12.2–23.0). Patient characteristics are summarized in Table 1 and individual details are listed in supplemental materials (Supplemental Table S1). Median age at enrollment was 41.5 years (IQR: 30–50), 16 (80%) patients were male and four (20%) were female. Physical status was affected by advanced disease in eight (40%) patients, whose ECOG performance status were 1 or 2. Patients were classified as favorable, intermediate, or poor risk group in three (15%), eleven (55%), and six (30%) patients respectively per International Metastatic RCC Database Consortium (IMDC) risk categorization. Twelve patients (60%) had a history of radical nephrectomy, and three (15%) underwent partial nephrectomy prior to enrollment. For cases with a history of nephrectomy, the median interval from surgery until enrollment was 10.7 months (IQR: 5.7–14.2). The median number of organs or disease sites involved was three (IQR: 1–4). The most common locations of metastases or recurrence were lymph node (14/20, 70%), followed by bone (10/20, 50%), retroperitoneal/renal fossa/peritoneal cavity (10/20, 50%), adrenal gland (6/20, 30%), lung (4/20, 20%), and liver (3/20, 15%). In terms of pathology, tumor tissue from 19 patients was available for immunohistochemical staining, amongst whom 16 were confirmed lack of FH expression, while the remaining three showed FH positivity. In contrast, all tumor tissues demonstrated positive staining of 2-SC. On the molecular level, *FH* germline mutation was identified in 15 out of 20 patients (75%), while the other five (25%) were confirmed carrying somatic biallelic *FH* alterations.

Table 1
Baseline clinical characteristics of enrolled patients

Characteristics	**Cohort (n = 20)**
Age at diagnosis, years-median (range)	41.5 (24–62)
Sex, No. (%)	
Male	16 (80)
Female	4 (20)
ECOG performance status, No. (%)	
0	12 (60)
1	4 (20)
2	4 (20)
IMDC risk classification, No. (%)	
Favorable	3 (15)
Intermediate	11 (55)
Poor	6 (30)
Prior nephrectomy, No. (%)	
Partial nephrectomy	3 (15)
Radical nephrectomy	12 (60)
T stage at enrollment, No. (%)	
Tx	12 (60)
T1-T2	2 (10)
≥T3	6 (30)
No. of disease sites, Median (range)	3 (1–6)
Location of metastasis, No. (%)	
Lymph nodes	14 (70)
Bone	10 (50)
Retroperitoneal/peritoneal space/renal fossa including residual kidney recurrence	10 (50)
Adrenal gland	6 (30)
Lung	4 (20)
Liver	3 (15)

Characteristics	Cohort (n = 20)
Molecular pathology, No. (%)	
Germline	15 (75)
Somatic	5 (25)

(2) Efficacy

Nineteen patients were confirmed to have an objective response (ORR 95%, 95% CI: 75.1–99.9), with four (20%) achieving CR and 15 (75%) showing PR, while one (5%) had SD as the best response, and DCR was 100% accordingly. The clinical benefit rate, defined as durable disease control lasting ≥ 24 weeks, was 85% (Table 2). When stratified by *FH* status, ORR in patients with *FH* germline mutation was comparable with that of patients with *FH* somatic alteration (15/15, 100% vs. 4/5, 80%), which was not statistically different ($p = 0.25$) (Fig. 2). All patients showed measurable tumor shrinkage since treatment started, and no primary progression was observed (Fig. 2).Most patients demonstrated rapid clinical response, for the median time to response was six weeks (IQR: 6–6). The median DOR was 19.2 months (95%CI: 16.3-NR), and the median PFS was 20.7 months (95%CI: 17.8-NR). Median OS was not reached, while the two-year OS rate was estimated as 89.7% (95% CI: 77.2–100) (Fig. 2). Among 19 responders, nine experienced subsequent disease progression; seven underwent surgery or radiotherapy against predefined target lesions; one patient discontinued the treatment due to serious irAE, one patient requested discontinuation after maintenance of CR for 13.4 months, and two patients died. At last follow-up, 16 patients remained on combination therapy; seven were continuing beyond progression per investigator judgment (i.e. after oligoprogression managed with radiotherapy, or limited progression managed with drug re-escalation), four maintained an ongoing response, and five continued treatment as adjuvant therapy after definitive surgery or radiotherapy to target lesions (Fig. 3) Although the response rate was not significantly different between patients with *FH* germline mutation and those with somatic alteration, the duration of disease control appeared to be different. The subgroup with *FH* germline mutation showed favorable median PFS comparing to that carrying somatic alteration (24.8 months *vs.* 8.7month, HR 0.12 (95%CI 0.02–0.73), $p = 0.0214$) and also demonstrated better OS although the medians of both subgroups were not reached (HR 0.01 (95%CI 0.00-0.38), $p = 0.0109$) (Supplemental Figure S1).

Table 2
Treatment efficacy

Response	Cohort (n = 20)
ORR, % (95% CI)	95 (75.1–99.9)
Best response, No. (%)	
CR	4 (20)
PR	15 (75)
SD	1 (5)
PD	0 (0)
Disease control rate, % (95% CI)	100 (80.0-100)
Clinical benefit rate, % (95% CI)	85 (61.1–96.0)
Median TTR, weeks (range)	6 (6–18)
Median DOR, months, (95% CI)	19.2 (16.3-NR)
Median PFS, months, (95% CI)	20.7 (17.8-NR)
Median OS, months	NR
2-year OS rate, % (95% CI)	89.7 (77.2–100)
NOTE. ORR includes patients with CR or PR. DCR includes patients with objective response or SD in the initial 24 weeks. Clinical benefit includes patients with objective response or SD lasting ≥ 24 weeks.	
Abbreviations: TTR, time to response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; NR, not reached.	

(3) Safety

As data cutoff, the median duration of treatment with at least one agent was 16.3 months (IQR: 11.9–21.5). All patients experienced TRAEs; Grade ≥ 3 events occurred in nine (45%). The most common TRAEs of any grade included hypertension (80%), TSH elevation/hypothyroidism (80%), proteinuria (70%), pharyngolaryngeal pain (45%), and hyperuricemia (40%). The most common Grade 3 TRAEs were hypertension (30%) and arthralgia (15%). No Grade ≥ 4 TRAEs occurred (Table 3). Lenvatinib was temporarily held or was reduced with the dosage in 13 patients (65%) for AEs management, and one patient permanently discontinued lenvatinib due to Grade 3 immune-related pneumonitis and tumor complete remission during the following assessment. The most frequent TRAEs causing lenvatinib interruption or dosage reduction were arthralgia (6/20, 30%), pharyngolaryngeal pain (5/20, 25%), palmar-plantar erythrodysesthesia (4/20, 20%), transaminitis or hyperbilirubinemia (4/20, 20%) and thrombocytopenia (2/20, 10%). At the latest follow-up, lenvatinib of 20mg per day remained in four

patients, two kept on 16mg per day, while ten patients reduced to 12 or 8mg per day. Tislelizumab was held in three patients (15%) with immune-related pneumonitis or adrenal insufficiency, with one patient consequently discontinued permanently due to severe immune-related pneumonitis. High-dose steroid (≥ 40mg prednisone equivalent) was required in two patients.

Table 3
Treatment related adverse events

AE	All grades, No (%)	Grade ≥ 3, No (%)
Hypertension	16 (80)	**6 (30)**
TSH elevation/Hypothyroidism	16 (80)	0 (0)
Proteinuria	14 (70)	**1 (5)**
Pharyngolaryngeal pain	9 (45)	**1 (5)**
Hyperuricemia	8 (40)	0 (0)
Diarrhea	7 (35)	0 (0)
Sinus tachycardia	7 (35)	0 (0)
Palmar-plantar erythrodysesthesia	7 (35)	0 (0)
Tooth pain	6 (30)	0 (0)
Nausea	6 (30)	0 (0)
Arthralgia	6 (30)	**3 (15)**
Fatigue	5 (25)	**1 (5)**
Eosinophilia	5 (25)	0 (0)
Electrocardiogram ST-T change	5 (25)	0 (0)
Hyperthyroidism	4 (20)	0 (0)
Rash acneiform	4 (20)	0 (0)
Neutropenia	4 (20)	0 (0)
Nail disorder	3 (15)	0 (0)
Hyperbilirubinemia	3 (15)	0 (0)
Serum creatinine elevation	3 (15)	0 (0)
Thrombocytopenia	3 (15)	0 (0)
Lymphopenia	3 (15)	0 (0)
Insomnia	3 (15)	0 (0)
Transaminitis	3 (15)	0 (0)
Immune-related pneumonitis	2 (10)	**1 (5)**
Fever	2 (10)	0 (0)
Vomiting	2 (10)	0 (0)

AE	All grades, No (%)	Grade ≥ 3, No (%)
Hypertriglyceridemia	2 (10)	0 (0)
Urinary tract infection	2 (10)	0 (0)
Epistaxis	2 (10)	0 (0)
Mucositis oral	1 (5)	0 (0)
Gastroesophageal reflux	1 (5)	0 (0)
Lung infection	1 (5)	0 (0)
Immune-related adrenal insufficiency	1 (5)	0 (0)
Facial nerve disorder	1 (5)	**1 (5)**
Cardiac troponin T elevation	1 (5)	0 (0)
Nail disorder	1 (5)	**1 (5)**
Atrioventricular block	1 (5)	0 (0)

(4) Metabolic biomarker analysis

Our previous work identified two tumor-derived metabolites, succinyl-adenosine and succinic-cysteine, as plasma biomarkers for diagnosis of tumors with FH deficiency, with cutoff values of 12ng/ml and 32ng/ml, respectively. Moreover, strong correlation between these metabolites and tumor burden was observed, supporting their potential significance for monitoring response to systemic therapies [16].

All enrolled patients participated in the exploratory analysis of biomarker dynamics versus response. At baseline, four patients had biomarker levels below the predefined cutoffs and therefore were excluded from longitudinal change analysis. All these four patients carried low tumor burden, as evidenced by the median number of disease sites being one (range 1–2), in contrast to three sites among the entire cohort. Although the median time to clinical response as per imaging assessment was six weeks, the circulating succinyl-adenosine and succinic-cysteine levels showed an even earlier drop after treatment initiation at Week 3 (Fig. 4). In the remaining 16 patients, we observed coordinated change between circulating metabolite levels and tumor size depicted via RECIST assessment. In most responders with CR or PR as the best response, at least one of the two metabolic biomarkers dropped by over 80% within the initial six weeks, suggesting that metabolic response might precede imaging manifestations. Based on available data of metabolic quantification, among four out of nine patients with PD during follow-up, at least one metabolic biomarker showed synchronous or earlier elevation before imaging progression, underlying the significance of these biomarkers as early warning signs for treatment failure (Fig. 5).

4. Discussion

To our knowledge, this is one of the few prospective clinical trials conducted exclusively in patients with advanced FH-RCC, adding new evidence to support the use of ICI/TKI combination therapy in the front-line setting. The first-line therapy with tislelizumab plus lenvatinib demonstrated encouraging antitumor activity, with 95% of patients having an objective response and 20% achieving complete remission. Notably, we did not observe primary progression in any subject, because all patients achieved at least SD during the initial 12 weeks, and all showed some degree of tumor shrinkage. Furthermore, we observed durable treatment efficacy, as the median DOR and median PFS were 19.2 months and 20.7 months, respectively; and the two-year OS rate was estimated as 89.7%. The activity of tislelizumab plus lenvatinib remained consistent across different IMDC risk groups. Although patients with somatic or germline *FH* mutation demonstrated similar response rate, patients carrying germline alteration seemed to have better survival. The safety profile of the regimen was consistent with previous reports for ICI/TKI combinations. AEs of any grade leading to interruption, discontinuation or dosage reduction occurred in 70% of patients. Most AEs were managed and resolved with interruption and dose reduction, except one patient with Grade 3 immune-related pneumonitis who permanently discontinued both agents.

Due to the low incidence and challenges in obtaining a timely diagnosis, standard of care for patients with advanced FH-RCC has not been established until now. The AVATAR study evaluated the efficacy of Beva/Erlo in patients with advanced HLRCC-associated or sporadic papillary RCC and results were recently published. Seventy-two percent of patients with HLRCC-associated RCC exhibited an objective response. The median PFS was 21.1 months, and the median OS was 44.6 months [4,5]. This study was initiated a decade ago and had over ten years of follow-up, during which molecular pathology of RCC developed rapidly, and the therapeutic landscape was completely revolutionized by immunotherapy. The combination of cabozantinib and nivolumab was reported to demonstrate evident superiority over previously reported regimens for advanced non-clear cell RCC, in which ORR for the cohort of papillary, unclassified, and translocation-associated RCC was 47.5% and median PFS was 12.5 months. Interestingly, this study found that 10 out of 12 patients with either *FH* or *NF2* mutations showed a clinical response, with an ORR significantly higher than the average [18,19]. Similarly, KEYNOTE-B61 study consolidated the status of ICI/TKI combination in advanced non-clear cell RCC, in which the front-line treatment with pembrolizumab plus lenvatinib showed an ORR of 49%, and a median PFS of 18 months[11].

Histopathological examination of FH-RCC revealed prominent lymphocytic infiltration and PD-L1 positivity within the tumor microenvironment, suggesting that FH-RCC was a highly immunogenic tumor, and these patients were likely to benefit from immunotherapy[10,20,21]. We performed a retrospective multicenter study across China, and for the first time compared the clinical activity of ICI/TKI versus Bev/Erlo combination for advanced FH-RCC patients in the first-line setting. A comparable response rate was observed between ICI/TKI and Bev/Erlo cohort (27% versus 25%), while ICI/TKI seemed to have favorable median PFS compared to the Beva/Erlo group (18.0 months versus 10.0 months) [10]. However, some other retrospective studies showed conflicting results, in which mTOR/VEGF combination or TKI monotherapy had superior efficacy[22 23]. Thus, this prospective study was designed to resolve concerns

about the limitations of retrospective analysis and heterogeneity of TKI choice in our prior work[24]. Coincidentally, another ICI/TKI combination, sintilimab plus axitinib, showed similar antitumor efficacy for advanced FH-RCC patients in the another recently published study, in which ORR was 56% with a median duration of response not reached and a median PFS of 19.8 months [25]. Combined with our results, ICI/TKI combination therapy is potentially another option in first-line treatment for FH-RCC patients. Interestingly, the response rate was numerically superior in our study, probably attributable to the distinct mechanism of action of specific targeted therapies. Lenvatinib not only has broader activity to block tumor angiogenesis but also acts directly on tumor cells and modulates the tumor microenvironment by inhibiting pathways such as FGFR, which might translate to a favorable response rate especially in patients with non-clear cell RCC [26,27].

For decades, oncological evaluation in clinical research has relied on the RECIST, which is primarily based on measurement of target lesions on contrast-enhanced cross-sectional imaging [15]. Taking advantage of the robust metabolic rewiring occurring in FH-deficient tumor cells, our collaborators identified succinyl-adenosine and succinic-cysteine as specific biomarkers for FH-RCC patients in the previous work [16]. Theoretically, all FH-deficient lesions, either measurable or not on imaging, have abnormal fumarate accumulation and persistently release succinate-modifying metabolites into circulation. Therefore, circulating level of succinyl-adenosine and succinic-cysteine would be ideal surrogate markers for tumor burden, and their fluctuation would mirror tumor remission or progression, which would be potential complements for RECIST-based imaging assessment. By synchronously monitoring the circulating levels of succinyl-adenosine and succinic-cysteine along with the preset imaging evaluations, we found that circulating biomarker dynamics paralleled the tumor burden change quantified by RECIST in the majority of cases. In most responders, at least one of the two biomarkers dropped rapidly as the treatment started, which happened earlier than the first post-treatment imaging assessment and usually demonstrated a greater decline. Among patients initially responding to treatment but progressing later, we could find rebound from nadir of at least one biomarker (Fig. 5: P01, P10, P11, P12). Notably, in two patients with progression in non-measurable bone metastasis (Fig. 5: P01, P12), a sustained rise in circulating succinyl-adenosine and succinic-cysteine predated imaging-confirmed PD by nine weeks. The above findings indicate that circulating metabolic biomarkers could be used for real-time treatment response monitoring and to detect early treatment failure, possibly providing a critical window for treatment modification. However, four patients in our cohort were found to have both circulating succinyl-adenosine and succinic-cysteine below the predefined cutoff value, thereby excluded from the exploratory analysis. These patients were characterized by low disease burden, mainly presenting with local recurrence. In addition, these biomarkers in female patients with treatment-naïve uterine leiomyomas should be interpretated with caution. We found deviations of circulating succinyl-adenosine or succinic-cysteine from the imaging-assessed tumor burden (Fig. 5: P06, P15), which might attribute to metabolic rewiring occurring within uterine leiomyoma cells and disturbance to circulating level of succinate-modifying metabolites. Furthermore, the limited sample size precluded the development of a robust model correlating metabolic biomarker levels with radiographic

measurements. Whether other liquid biopsy biomarkers, such as ctDNA, can guide treatment for patients with FH-RCC, similar to its role in urothelial carcinoma, remains an area requiring further exploration.

5. Conclusions

In summary, tislelizumab plus lenvatinib demonstrated encouraging antitumor efficacy with toxicities aligned with those of previous studies in patients with advanced FH-RCC in the first-line setting. Our results, together with other similar studies, support the front-line use of ICI/TKI as an alternative to Beva/Erlo. However, a limitation of this study is its single-arm, single-centre design and small sample size. Although it is challenging to conduct randomized controlled trials in rare malignancies like FH-RCC, prospectively comparing the efficacy and safety of ICI/TKI and Beva/Erlo and identifying molecular subtypes benefiting from different treatments are becoming critically important. We also found that longitudinal monitoring of circulating succinate-modifying metabolites might offer a valuable complementary dimension to routine imaging assessment particularly for advanced FH-RCC patients.

Declarations

Contributors

Dr. Jin Zhang had full access to all the study data and took responsibility for integrity and accuracy.

W.K., Y.X., and G.L. contributed equally to this work.

J.Z., W.X., L.Z., and G.W. contributed equally and share senior authorship.

W.K., Y.X., W.L., G.W., L.Z., W.X., and J.Z. proposed the concept and designed the study.

W.K., Y.X., G.L., Z.W., Xiaoyu.W, D.C., F.J., Jiong.H., Jiwei.H., Y.C., W.Z, Xiaorong.W., J.P., Y.H., G.W., L.Z., W.X., and J.Z. contributed to data acquisition, analysis and interpretation.

W.K., Y.X., G.L., and G.W. drafted the manuscript.

W.K., G.W., L.Z., W.X., and J.Z. provided critical revision of the manuscript.

W.L. was responsible for statistical analysis.

Y.X., G.W., L.Z., and J.Z. provided the funding support.

Declaration of interests:

All authors declare no competing interests.

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Figures

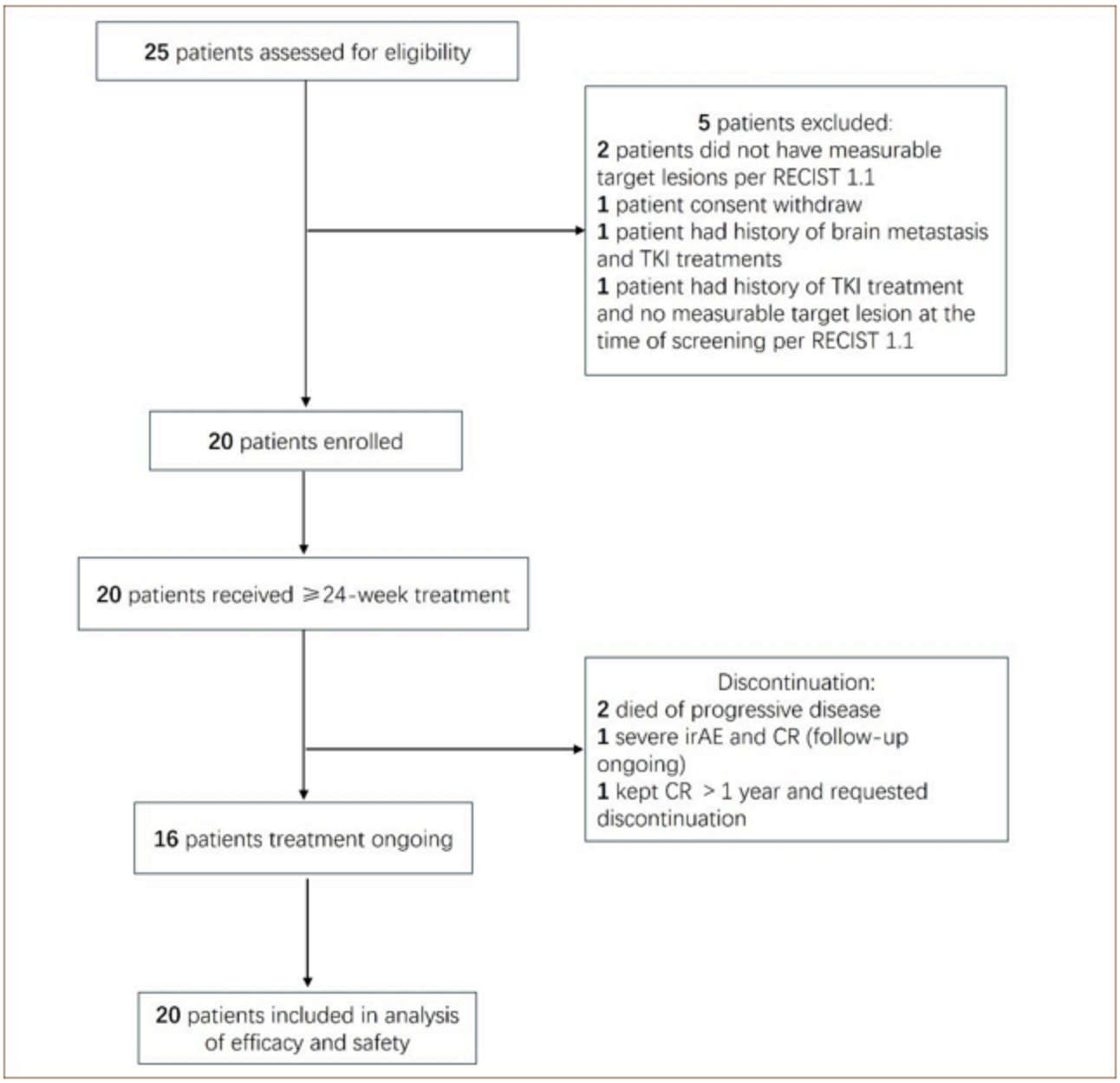


Figure 1

Trial profile. Data cutoff: December 22, 2025.

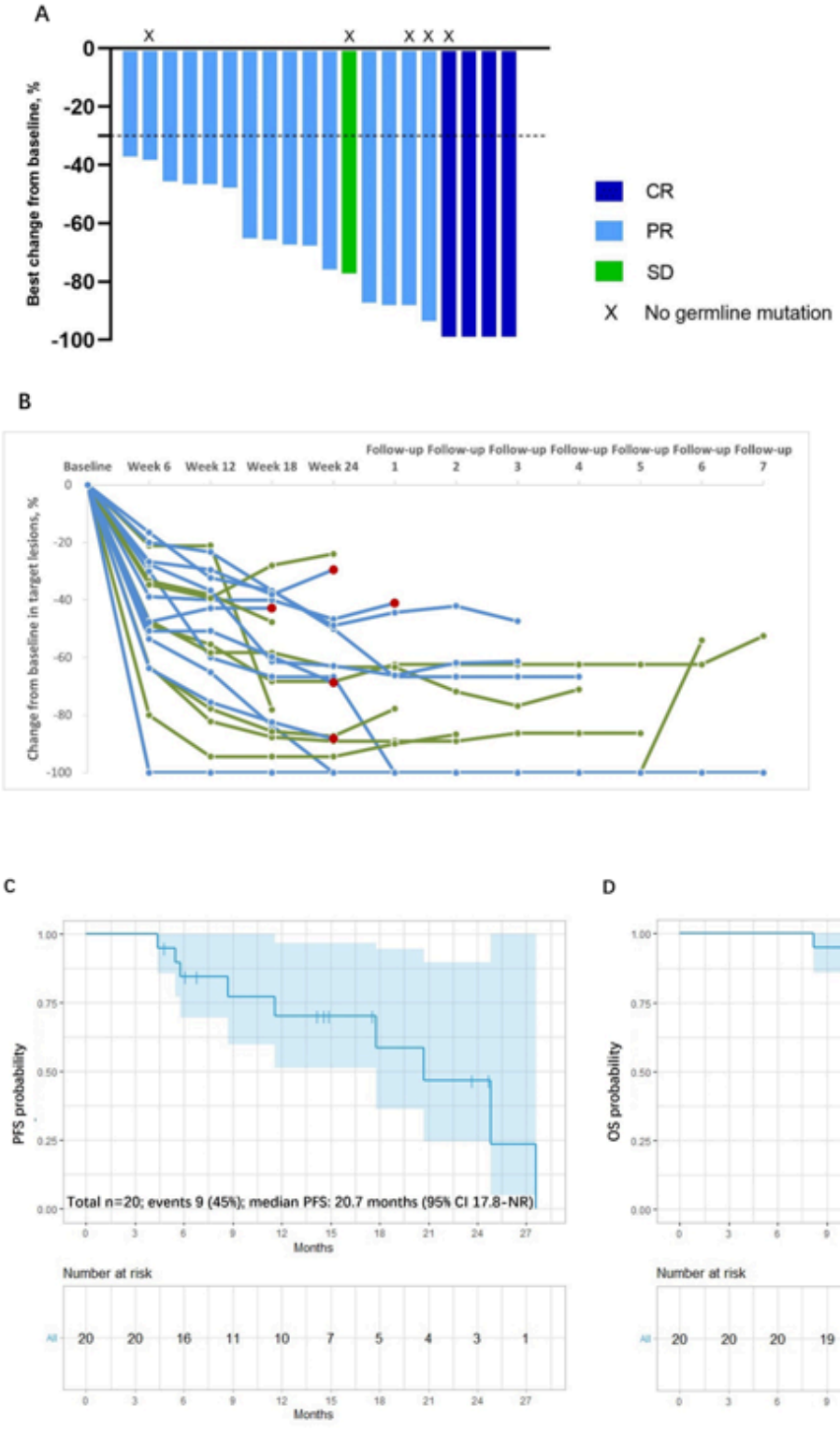


Figure 2

Treatment efficacy in the full analysis set.

(A) Waterfall plot of maximal change from baseline in target lesions and best response according to RECIST 1.1.

(B) Percentage change of target lesions in individual patients from start of treatment. In the initial 24 weeks, imaging evaluations were performed every six weeks. In the subsequent follow-up period, imaging evaluations were performed every three months or specified by investigators' judgement (Green line: PD at the last assessment as per RECIST 1.1; Blue line: continuing response; Red dot: surgery or radiotherapy against the target lesion in the duration of clinical response).

(C) Median PFS was 20.7 months (95% CI:17.8 months to NR).

(D) Median OS was not reached (95% CI, NR to NR). OS estimates were 89.7% (95% CI: 77.2-100) at 18 and 24 months.

Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival.

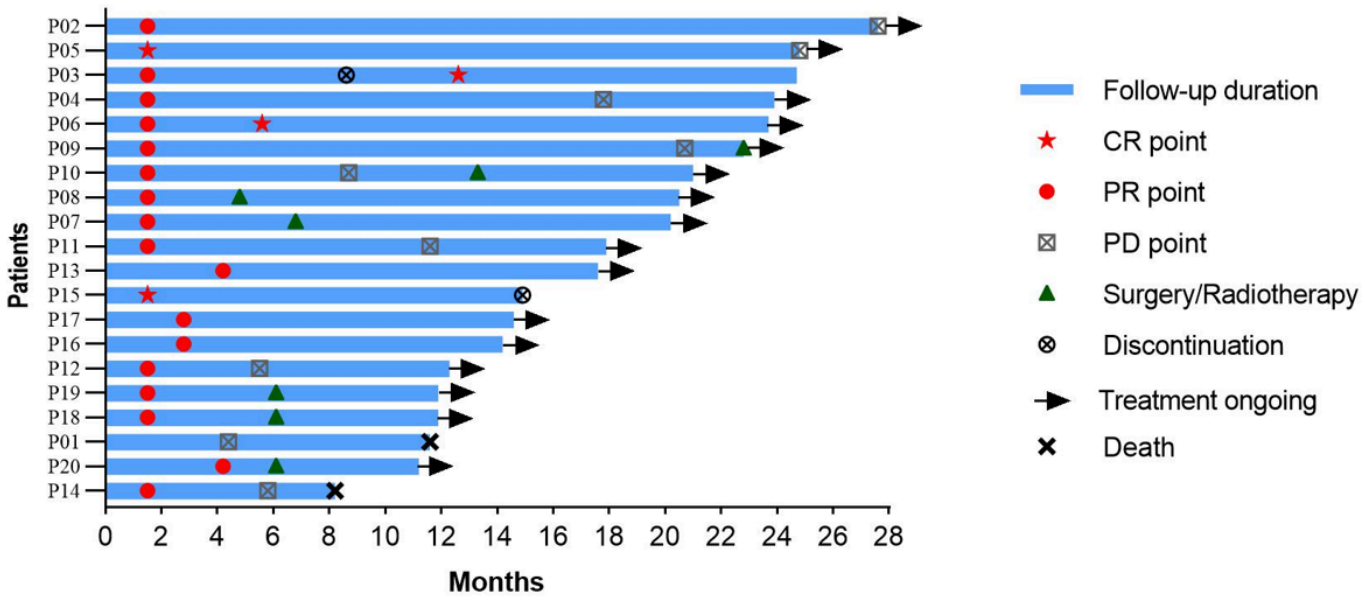


Figure 3

Duration of treatment by patient, and points in time of response, interventions and survival status.

Swimmer plot of time to response and response duration of patients treated with tislelizumab plus lenvatinib. Each bar depicts treatment duration, with labels on each bar indicating the best tumor response, drug administration, interventions and survival status for individual patients.

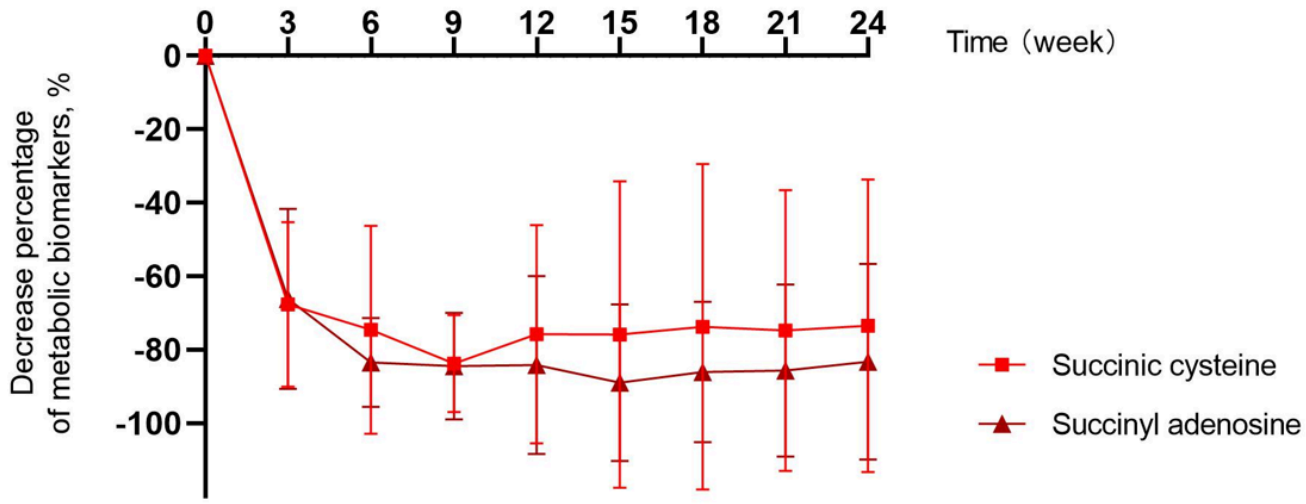


Figure 4

Dynamics of circulating succinate-modifying metabolites during the initial 24 weeks in the qualified set.

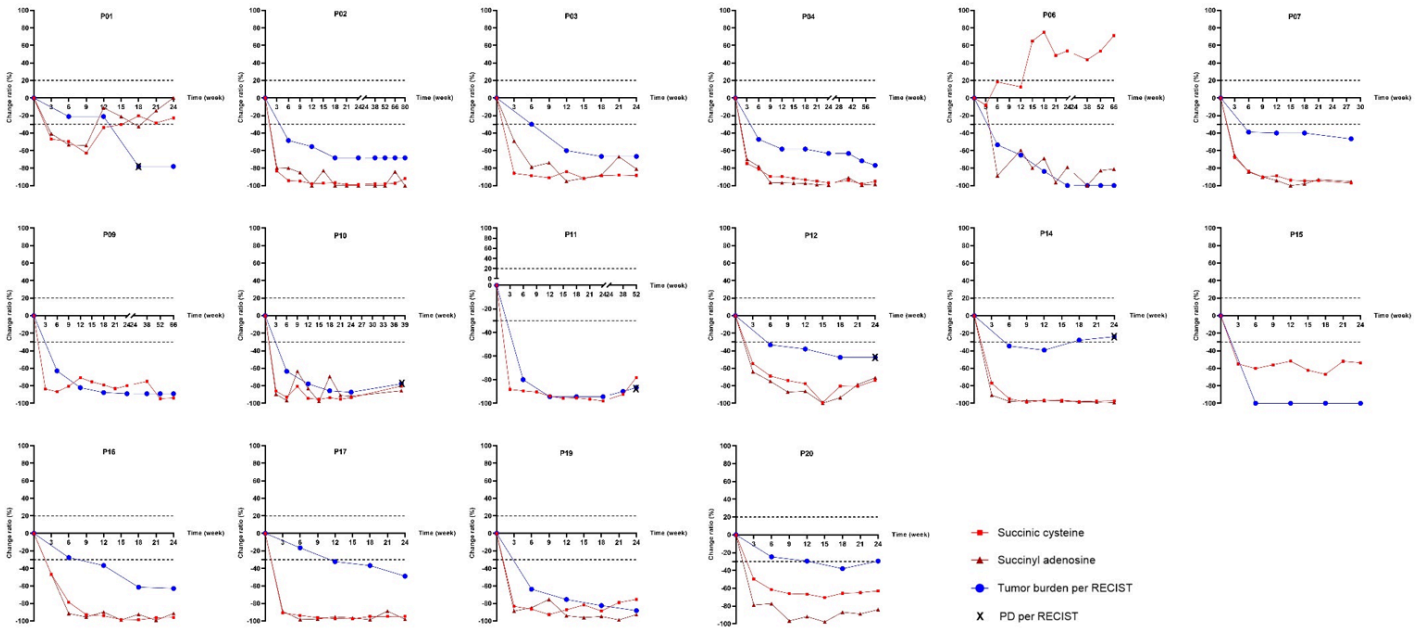


Figure 5

Percentage change of circulating succinate-modifying metabolites and tumor burdens for each patient, according to RECIST assessment.

The blue plot depicts the longitudinal change percentage of RECIST target lesions from the baseline at every time point of imaging assessment. The light and dark red plots depict the longitudinal change percentage of circulating succinic cysteine and succinyl adenosine from the baseline at every time point of follow-up. The dark cross depicts the first documented disease progression per RECIST assessment (For patients P01, P10, P11, P12 and P14, PD was recorded along with available circulating metabolites quantitation results; For patient P02, P04, P05 and P09, PD were recorded at the time when metabolic biomarker data were not available).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTableS1Baselineclinicalinfo.xlsx
- SupplementalTableS2Tumorassessment.xlsx
- SupplementalFigureS1202621.docx
- Protocol2025108.docx