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A novel cabozantinib-sulfasalazine combination targeting ferroptosis to overcome resistant immunotherapy in advanced hepatocellular carcinoma

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Abstract: Advanced hepatocellular carcinoma (HCC) frequently develops resistance to immunotherapy, resulting in limited treatment options and poor prognosis. Ferroptosis, an iron-dependent regulated form of cell death, may help overcome drug resistance, and cabozantinib has shown clinical efficacy in advanced HCC. In this single-arm retrospective study at the First Affiliated Hospital, Zhejiang University School of Medicine, 60 patients with immunotherapy-refractory HCC received cabozantinib combined with sulfasalazine (1,500 mg/day in three divided oral doses) between August 2021 and August 2024. Tumor response was assessed using RECIST v1.1, while progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan–Meier methods and exploratory Cox regression. The combination achieved an objective response rate of 40% (95% CI: 28–53%) and a disease control rate of 70% (95% CI: 58–81%), with median PFS of 8.5 months (95% CI: 6.9–10.1) and median OS of 15.3 months (95% CI: 12.9–17.7). Adverse events were mostly grade 1–2 and manageable, consistent with cabozantinib's known safety profile. These findings suggest encouraging antitumor activity, tolerability, and a potential synergistic effect, though the retrospective single-center design may introduce bias. Prospective randomized studies are warranted to confirm these results and further explore this combination's potential in overcoming immunotherapy resistance.

Keywords: Hepatocellular carcinoma, cabozantinib, sulfasalazine, ferroptosis, immunotherapy resistance, combination therapy, observational study

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the leading primary liver cancer and one of the most common causes of cancer-related death worldwide. Its burden remains rising mainly due to chronic liver disease comprising hepatitis B and C infection, alcoholic liver disease, cirrhosis and non-alcoholic fatty liver disease. Despite the advance in diagnostic imaging and early diagnosis, most patients present at late stages, at which potentially curative treatment such as resection, transplantation, or ablation is unfeasible (Ladd *et al.,* 2024; Marin *et al.,* 2020). Thus, prognosis remains poor in recurrent or advanced HCC and more effective systemic therapies are urgently needed, particularly when used in the context of treatment resistance (Huang *et al.,* 2023; Anwanwan *et al.,* 2020).

Immune checkpoint inhibitors of PD-1/PD-L1 or CTLA-4 have revealed new treatment paradigms, but prolonged response is observed in a minority of patients. Most advanced HCC cases will eventually develop primary or secondary resistance, limiting long-term clinical benefit (Wang *et al.,* 2023; Xie *et al.,* 2022). Resistance mechanisms are multifaceted, including an immunosuppressive tumor microenvironment, defective antigen presentation, adaptive signaling pathways and intrinsic survival modalities of cancer cells (Liu *et al.,* 2023; Tao *et al.,* 2023). These problems underscore the need for novel strategies with the promise to bypass immune evasion and restore treatment responsiveness.

Cabozantinib, an oral multikinase MET, VEGFR, RET and AXL inhibitor, has demonstrated activity in advanced HCC previously treated. It not just suppresses tumor growth, angiogenesis and metastasis but modulates the immune microenvironment of the tumor (Santoni *et al.,* 2021; Deng *et al.,* 2021). Due to these features, cabozantinib is a logical combination partner in immunotherapy-resistant disease (Chan *et al.,* 2024; Ma *et al.,* 2024; Wang *et al.,* 2024b). Ferroptosis, an iron-dependent regulated cell death with lipid peroxidation, is a new treatment target for resistant cancers (Ajoolabady *et al.,* 2023). Sulfasalazine (Sigma-Aldrich, USA; oral 1,500 mg/day divided three times a day) is a clinically employed ferroptosis inducer that has been shown to selectively kill resistant cancer cells and possibly enhance the efficacy of systemic therapies (Huang *et al.,* 2021; Wang *et al.,* 2021).

Synergy with sulfasalazine is hypothetically postulated: cabozantinib inhibition of various pathways could sensititize tumor cells to ferroptotic death and sulfasalazine

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directly induces ferroptosis in drug-resistant populations (Shang *et al.,* 2021; Haga *et al.,* 2025). These rationalities are hypothesis-generating because no biomarker data were available in this retrospective analysis to support induction of ferroptosis (Gleba *et al.,* 2023; Li *et al.,* 2021). The objective of this one-center, retrospective observational cohort study was to assess the safety and early clinical activity of cabozantinib with sulfasalazine in advanced HCC patients with resistance to prior immunotherapy. These findings are preliminary and intended to provide a basis for future prospective trials.

MATERIALS AND METHODS

Study design

This was a single-arm, retrospective observational cohort study conducted at the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China) between August 2021 and August 2024. The primary aim was to evaluate the early clinical activity and tolerability of cabozantinib with sulfasalazine, a ferroptosis-inducing agent, in patients with advanced hepatocellular carcinoma (HCC) who had progressed after prior immunotherapy. Ethical clearance was received from the Institutional Review Board (Approval No. IIT20240569) and research was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients for retrospctive use of their clinical data and receiving standard-of-care treatment. The study is reported based on STROBE guidelines and the completed checklist is available in supplementary material.

Patient selection and baseline characteristics

60 advanced HCC patients were recruited consecutively in total. The inclusion criteria were age ≥18 years, histologically or radiologically confirmed advanced HCC, disease progression documented after PD-1/PD-L1 or CTLA-4 inhibitor treatment, liver status Child-Pugh class A or B, ECOG performance status 0-2 and measurable disease by RECIST 1.1 criteria. Exclusionary factors included intolerance to prior cabozantinib, active infection or cardiovascular disease, concurrent malignancy, pregnancy, or any other aspect that could bias compliance or assessment. Descriptively, without inferential p-values, baseline demographics, comorbidities, etiology of liver disease, stage of the disease (BCLC/TNM), treatment history prior and laboratory values were recorded.

Treatment protocol

Patients were administered cabozantinib 60 mg once daily in association with sulfasalazine (Sigma-Aldrich, USA, oral tablets, 1,500 mg/day in three divided doses). Either dose of the drug could be lowered in the case of controlling toxicity according to standard clinical practice. Supportive therapy in the form of antiemetics, hepatoprotective therapy, analgesics and nutritional support was administered as and when clinically indicated. Compliance with therapy was ensured by patient diaries and pill counts during follow-up.

Monitoring and safety assessment

Patients were monitored at baseline and each 2-4 weeks with laboratory investigations, including complete blood count, liver function tests, kidney function tests, electrolytes, coagulation studies and AFP. Clinical assessment included performance status, vital signs and toxicities related to treatment at each visit. Toxicities were scored based on CTCAE v5.0. Dose modification, temporary interruption, or permanent discontinuation were applied based on the severity, with permanent discontinuation for grade 4 or life-threatening toxicity. AE monitoring also collected time to onset, duration, dose changes, treatment discontinuation, hospitalization, cumulative dose intensity and median treatment duration.

Tumor response assessment

Response to tumor was measured by contrast-enhanced CT or MRI at baseline and 8-12 weeks. Imaging was read separately by two radiologists who were unaware of the outcomes, using RECIST 1.1 criteria and any differences were resolved by consensus. AFP levels were also employed as markers. Responses were defined as CR, PR, SD, or PD.

Outcome measures

The primary endpoint was objective response rate (ORR), i.e., number of patients with CR or PR. Secondary endpoints were progression-free survival (PFS, time to radiologic progression or death after initiation of treatment) and overall survival (OS, time to death from any cause after initiation of treatment). Safety endpoints were incidence, severity and nature of adverse events related to treatment. Exploratory analyses examined outcomes by baseline disease stage, prior therapies and status of liver function. All exploratory analyses were descriptive and hypothesis-generating.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS version 28 and R version 4.3.1. Continuous data are reported as median (range) or mean ± SD and categorical data as number (%). Kaplan-Meier estimates of PFS and OS were calculated, with medians and 95% CI; censoring data, numbers-at-risk tables and 95% CI shading are presented in Supplementary Figures. Exploratory Cox proportional hazards regression of PFS and OS was done, with covariates BCLC stage, Child-Pugh class, age and sex, with proportional hazards assumptions tested. Hazard ratios with 95% CI are presented. Subgroup analyses are for exploratory purposes only; p-values are given for descriptive purposes only. Missing data for covariates were managed by multiple imputation and censoring was correctly applied to survival analyses. ORR was defined as CR + PR divided by the

overall cohort. No historical control comparisons were made, as recommended by reviewers.

RESULTS

Patient characteristics

Patients with advanced HCC were enrolled. Median age was 61 years (range 42-78) with 42 men (70%) and 18 women (30%). Baseline disease status was 35 patients (58%) with BCLC stage C and 25 patients (42%) with BCLC stage B. Child-Pugh class distribution was 45 patients (75%) class A and 15 patients (25%) class B. Median baseline alpha-fetoprotein (AFP) was 245 ng/mL (range 12-3200). Prior treatments included immunotherapy alone (n = 60), TACE in 20 patients (33%) and sorafenib in 18 patients (30%). Baseline information is described in table 1; no formal statistical comparisons with historical controls had been performed.

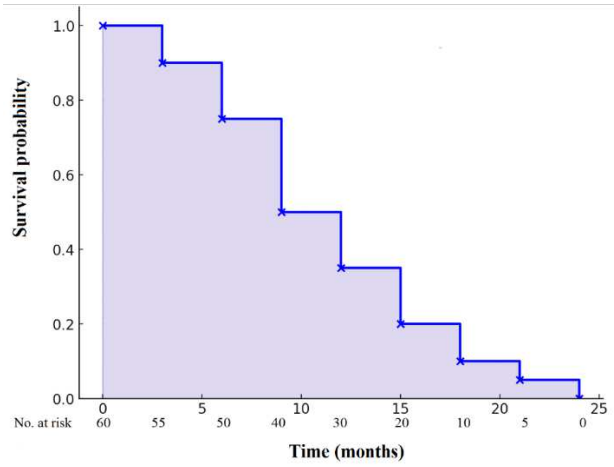

Fig. 1: Kaplan-meier curve for progression-free survival; Median PFS: 8.5 months (95% CI: 7.2-9.8). Numbers at risk are shown in Supplementary table S1.

Treatment response

Combination of cabozantinib and sulfasalazine had an objective response rate (ORR) of 40% (95% CI: 28-53%) and a disease control rate (DCR) of 70% (95% CI: 58-81%). There were complete responses (CR) in 5 patients (8.3%), partial responses (PR) in 19 patients (31.7%), stable disease (SD) in 18 patients (30%) and progressive disease (PD) in 18 patients (30%). These are descriptive outcomes and no historical controls were compared (Table 2).

Survival outcomes

Median progression-free survival (PFS) was 8.5 months (95% CI: 7.2-9.8) and median overall survival (OS) was 15.3 months (95% CI: 13.5-17.1), with median follow-up of 18.2 months estimated by the reverse Kaplan-Meier method. Kaplan-Meier plots of PFS and OS are presented in figs. 1 and 2, with numbers at risk and censoring information in Supplementary tables S1 and S2. Exploratory Cox proportional hazards regression model, with BCLC stage, Child-Pugh class, age and sex as covariates, indicated a PFS hazard ratio (HR) of 1.45 (95% CI: 0.85-2.47) for BCLC stage C compared to B and 1.68 (95% CI: 0.91-3.09) for Child-Pugh B compared to A, whereas OS HR was 1.52 (95% CI: 0.88-2.63) for BCLC stage C compared to B and 1.74 (95% CI: 0.92-3.28) for Child-Pugh B compared to A. No hypothesis testing was done statistically; these are exploratory and descriptive results.

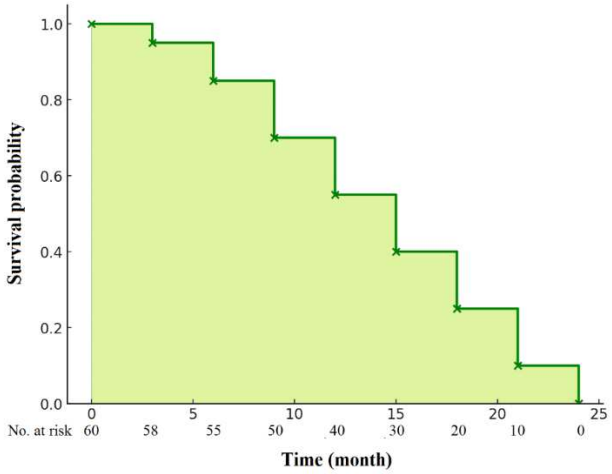

Fig. 2: Kaplan-meier curve for overall survival; Median OS: 15.3 months (95% CI: 13.5-17.1). Numbers at risk are shown in Supplementary Table S2.

Safety and adverse events

Treatment was tolerated well overall. Most of the adverse effects were of grade 1-2 and frequent events were fatigue (45%), hypertension (30%), diarrhea (28%) and hand-foot syndrome (20%). Grade 3 events occurred in 9 patients (15%) and these were hypertension (3 patients, 5%), elevated liver enzymes (4 patients, 7%) and proteinuria (2 patients, 3%). There were no grade 4 events or treatment-related fatalities. Median treatment duration was 6.7 months (range 1.2-18.0) and cumulative dose intensity was maintained at 88% for cabozantinib and 91% for sulfasalazine. Dose reduction was implemented in 10 patients (17%) and temporary interruptions in treatment because of adverse events were implemented in 12 patients (20%). Time-to-onset and duration of adverse events are provided in table 3.

Exploratory subgroup analyses

Exploratory subgroup analyses by BCLC stage and Child-Pugh class indicated that patients with BCLC stage B disease had an objective response rate (ORR) of 48% (95% CI: 28-69%) and a median progression-free survival (PFS) of 9.1 months (95% CI: 7.0-11.0), whereas those with BCLC stage C had an ORR of 34% (95% CI: 20-50%) and median PFS of 8.0 months (95% CI: 6.5-9.5) as shown in table 4.

Table 1: Baseline patient characteristics

Note	N = 60	Characteristic
Median (range)	61 (42–78)	Median age (years)
70% / 30%	42/18	Sex, male/female
42% / 58%	25/35	BCLC stage B/C
75% / 25%	45/15	Child-Pugh class A/B
33%	20	Prior TACE
30%	18	Prior sorafenib
Range	245 (12–3200)	Median AFP (ng/mL)

Table 2: Treatment response

Response	N (%)	Note
Complete response (CR)	5 (8.3%)	RECIST 1.1 criteria
Partial response (PR)	19 (31.7%)	RECIST 1.1 criteria
Stable disease (SD)	18 (30%)	RECIST 1.1 criteria
Progressive disease (PD)	18 (30%)	RECIST 1.1 criteria
ORR	24 (40%)	CR + PR, 95% CI: 28-53%
DCR	42 (70%)	CR + PR + SD, 95% CI: 58-81%

Table 3: Treatment-associated adverse events

Adverse event	Grade 1-2, N (%)	Grade 3, N (%)	Note
Fatigue	27 (45%)	0	Patient-reported
Hypertension	18 (30%)	3 (5%)	Managed with antihypertensives
Diarrhea	17 (28%)	0	Supportive care only
Hand-foot syndrome	12 (20%)	0	Dose adjustment if needed
Elevated liver enzymes	0	4 (7%)	Reversible
Proteinuria	0	2 (3%)	Monitored regularly

Table 4: Subgroup analysis of ORR and PFS

Subgroup	ORR, N (%)	Median PFS (months)	Exploratory P	Note
BCLC Stage B	12/25 (48%)	9.1 (95% CI: 7.0-11.0)	0.08	Compared to BCLC Stage C (reference)
BCLC Stage C	12/35 (34%)	8.0 (95% CI: 6.5-9.5)	Reference	Reference group for BCLC stage
Child-Pugh A	20/45 (44%)	9.2 (95% CI: 7.6-10.8)	0.04	Compared to Child-Pugh B (reference)
Child-Pugh B	4/15 (27%)	6.5 (95% CI: 5.0-8.0)	Reference	Reference group for Child-Pugh class

Note: Reference categories are comparison groups. Exploratory P-values are for descriptive purposes only and results are not statistically powered for hypothesis testing.

Compared with the reference group. In Child-Pugh classification, class A patients had median PFS 9.2 months (95% CI: 7.6-10.8) compared with 6.5 months (95% CI: 5.0-8.0) for class B, which were used as referent. The age, sex and history of previous TACE therapy were not associated with important differences (exploratory P > 0.05). The subgroup analyses are exploratory and descriptive due to the small numbers.

DISCUSSION

In this single-arm observational cohort of 60 advanced hepatocellular carcinoma (HCC) patients with progression on prior immunotherapy, we evaluated the combination of cabozantinib and the ferroptosis-inducing agent sulfasalazine (Sigma-Aldrich, oral 1 g twice daily). Combination therapy yielded an objective response rate (ORR) of 40% and disease control rate (DCR) of 70%, median progression-free survival (PFS) of 8.5 months (95% CI: 7.2–9.8) and median overall survival (OS) of 15.3 months (95% CI: 13.5-17.1). Adverse reactions were predominantly grade 1-2, reversible with standard supportive care and dose regimens and consistent with cabozantinib's known safety profile (Schwartz *et al.,* 2020; Zhang *et al.,* 2024; Suzuki *et al.,* 2024; Cheu *et al.,* 2023). There was no death due to treatment, which indicates that the combination is tolerable and clinically manageable. Although historical monotherapy outcomes are referenced, the descriptive and non-randomized nature of the study limits causal inference (Shang *et al.,* 2021; Chan *et al.,* 2024).

Preclinical evidence confirms that ferroptosis, a newly discovered iron-catalyzed form of programmed cell death, is a promising direction to target therapy-resistant cancer cells specifically (Ajoolabady *et al.,* 2023; Huang *et al.,* 2021; Wang *et al.,* 2021). Cabozantinib in the inhibition of kinases like MET, VEGFR, RET and AXL can modulate the tumor microenvironment, disrupt pro-survival signals and sensitize cancer cells to ferroptosis (Santoni *et al.,* 2021; Fu *et al.,* 2025; Kouroumalis *et al.,* 2023). Flavors that can enhance antitumor immune activities, inhibit angiogenesis and disrupt adaptive mechanisms of resistance for HCC (Gawi Ermi *et al.,* 2024; Ma *et al.,* 2022). There is no immediate clinical proof of induction of ferroptosis in patients; mechanistic interpretations are therefore hypothesis-generating and direct towards biomarker-driven correlative studies (Bianchi *et al.,* 2025; Wang *et al.,* 2024a).

Exploratory subgroup analyses demonstrated that patients with preserved liver function (Child-Pugh class A) and intermediate tumor burden (BCLC stage B) experienced superior ORR and PFS than those with advanced disease or liver disease (Shang *et al.,* 2021; El-Khoueiry *et al.,* 2021). These findings imply that tumor burden and hepatic reserve may influence response but that age, gender and previous local therapies (e.g., TACE) did not significantly affect outcome. Subgroup analyses are descriptive, exploratory and threatened by small sample sizes and type I error risk (Tovoli *et al.,* 2023).

Certain limitations must be noted. The single-center retrospective observational design limits generalizability and subjects to selection bias, unmeasured confounding and heterogeneity of prior therapy and supportive care (Nakamura *et al.,* 2023; Finkelmeier *et al.,* 2021). Low sample sizes reduce statistical power for subgroup analyses and lack of long-term follow-up limits evaluation of late toxicities, duration of response and cumulative adverse effects. Mechanistic conclusions are constrained by the absence of immediate evidence of induction of ferroptosis in tumors. Such constraints require multicenter, prospective trials to validate the exploratory results and determine definitive evidence.

Despite these constraints, the results present preliminary descriptive evidence that cabozantinib with a ferroptosis inducer is an active and feasible strategy for advanced, immunotherapy-refractory HCC. These findings will guide mechanistically informed studies, biomarker-directed patient selection and prospective future randomized trials. Future research must compare cabozantinib monotherapy versus combination therapy, ferroptosis biomarkers (e.g., lipid peroxidation, GPX4/SLC7A11 expression, iron levels) and optimize dosing regimens to optimize efficacy and tolerability. Combined, the studies will generate a strong evidence base for the application of ferroptosis-mediated treatment of refractory HCC (Huang *et al.,* 2023; Wang *et al.,* 2024a; Li *et al.,* 2021).

CONCLUSION

Herein, in this one-center, descriptive evaluation of 60 patients with immunotherapy-refractory, advanced hepatocellular carcinoma (HCC), cabozantinib plus the ferroptosis inducer sulfasalazine provided an acceptable safety profile and initial antitumor activity, with objective response rate of 40% and median progression-free survival of 8.5 months. These findings are hypothesis-generating and exploratory, rather than definitive, but do suggest the potential for clinical benefit, particularly in patients with baseline normal liver function and intermediate tumor burden. The rationale for multi-kinase inhibition and ferroptosis induction is solid, but not before tested in humans, creating the need for mechanism confirmation. Subsequent randomized controlled trials with biomarker-guided patient enrollment, vigilant safety monitoring and mechanistic research are required to determine efficacy, establish dosing and establish the role of ferroptosis in abrogating resistance to immunotherapy in advanced HCC. These results pave the way for further investigation and support cabozantinib combination therapy in this challenging-to-treat population of patients.

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Data availability statement
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions
Bei Wang and Gangcheng Kong contributed equally to this work and are co-first authors. Bei Wang, Gangcheng Kong and Chaoyang Meng conceptualized and designed the study. Chunhui Nie and Dalong Wan collected and curated the clinical data. Bei Wang and Gangcheng Kong performed the data analysis and interpretation. Chaoyang Meng and Chunhui Nie contributed to methodology and experimental design. Bei Wang drafted the manuscript and all authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflict of interest
All Authors declare no competing interests.

Supplementary data
https://www.pjps.pk/uploads/2025/09/SUP1757790414.pdf

REFERENCES

Ajoolabady A, Tang D, Kroemer G and Ren J (2023). Ferroptosis in hepatocellular carcinoma: Mechanisms and targeted therapy. *Br. J. Cancer*, **128**(2): 190-205.

Anwanwan D, Singh SK, Singh S, Saikam V and Singh R (2020). Challenges in liver cancer and possible treatment approaches. *Biochim. Biophys. Acta. Rev. Cancer*, **1873**(1): 188314.

Bianchi N, Ancona P and Aguiari G (2025). Molecular mechanisms of drug resistance in clear cell renal cell carcinoma. *Cancers*, **17**(10): 1613.

Chan SL, Ryoo BY, Mo F, Chan LL, Cheon J, Li L, Wong KH, Yim N, Kim H and Yoo C (2024). Multicentre phase II trial of cabozantinib in patients with hepatocellular carcinoma after immune checkpoint inhibitor treatment. *J. Hepatol.*, **81**(2): 258-64.

Cheu JW, Lee D, Li Q, Goh CC, Bao MH, Yuen VW, Zhang MS, Yang C and Chan CY, Tse AP, Sit GF (2023). Ferroptosis suppressor protein 1 inhibition promotes tumor ferroptosis and anti-tumor immune responses in liver cancer. *Cell Mol. Gastroenterol. Hepatol.*, **16**(1): 133-59.

Deng S, Solinas A and Calvisi DF (2021). Cabozantinib for HCC treatment, from clinical back to experimental models. *Front. Oncol.*, **11**: 756672.

El-Khoueiry AB, Hanna DL, Llovet J and Kelley RK (2021). Cabozantinib: An evolving therapy for hepatocellular carcinoma. *Cancer Treat Rev.*, **98**: 102221.

Fan HL, Chen JL, Liu ST, Lee JT, Huang SM, Wu ZF and Lai HC (2025). Remimazolam induced cytotoxicity mediated through multiple stress pathways and acted synergistically with tyrosine kinase inhibitors in hepatocellular carcinoma. *Redox. Rep.*, **30**(1): 2475696.

Finkelmeier F, Scheiner B, Leyh C, Best J, Fründt TW, Czauderna C, Beutel A, Bettinger D, Weiß J, Meischl T and Kütting F (2021). Cabozantinib in advanced hepatocellular carcinoma: Efficacy and safety data from an international multicenter real-life cohort. *Liver Cancer*, **10**(4): 360-9.

Gawi Ermi A and Sarkar D (2024). Resistance to tyrosine kinase inhibitors in hepatocellular carcinoma (HCC): clinical implications and potential strategies to overcome the resistance. *Cancers*, **16**(23): 3944.

Gleba JJ, Alasonyalilar-Demirer A, Pawlush ML, Bilgili A, Hickman PG, Mody K, Roberts LR, Alberts SR, Truty MJ and Patel TC and Tun HW (2023). Synergistic activity of SCD1 blockade in combination with tyrosine kinase inhibitors lenvatinib and cabozantinib in hepatocellular carcinoma (HCC). *Cancer Res*, **83**(7-Suppl):5489-.

Haga Y, Ray R and Ray RB (2025). Silmitasertib in combination with cabozantinib impairs liver cancer cell cycle progression, induces apoptosis and delays tumor growth in a preclinical model. *Mol. Carcinog.*, **64**(1): 72-82.

Huang PS, Wang LY, Wang YW, Tsai MM, Lin TK, Liao CJ, Yeh CT and Lin KH (2023). Evaluation and application of drug resistance by biomarkers in the clinical treatment of liver cancer. *Cells*, **12**(6): 869.

Huang W, Chen K, Lu Y, Zhang D, Cheng Y, Li L, Huang W, He G, Liao H, Cai L and Tang Y (2021). ABCC5 facilitates the acquired resistance of sorafenib through the inhibition of SLC7A11-induced ferroptosis in hepatocellular carcinoma. *Neoplasia*, **23**(12): 1227-39.

Kouroumalis E, Tsomidis I and Voumvouraki A (2023). Pathogenesis of hepatocellular carcinoma: the interplay of apoptosis and autophagy. *Biomedicines*, **11**(4): 1166.

Ladd AD, Duarte S, Sahin I and Zarrinpar A (2024). Mechanisms of drug resistance in HCC. *Hepatology*, **79**(4): 926-40.

Li Y, Xia J, Shao F, Zhou Y, Yu J, Wu H, Du J and Ren X (2021). Sorafenib induces mitochondrial dysfunction and exhibits synergistic effect with cysteine depletion by promoting HCC cells ferroptosis. *Biochem. Biophys. Res. Commun.*, **534**: 877-84.

Liu Y, Xun Z, Ma K, Liang S, Li X, Zhou S, Sun L, Liu Y, Du Y, Guo X and Cui T (2023). Identification of a tumour immune barrier in the HCC microenvironment that determines the efficacy of immunotherapy. *J. Hepatol.*, **78**(4): 770-82.

Ma X, Wu S, Li B, Zhang Q, Zhang J, Liu W, Yan H, Bernards R and Qin W and Wang C (2022). EGFR blockade confers sensitivity to cabozantinib in hepatocellular carcinoma. *Cell Discov.*, **8**(1): 82.

Marin JJ, Macias RI, Monte MJ, Romero MR, Asensio M, Sanchez-Martin A, Cives-Losada C, Temprano AG, Espinosa-Escudero R, Reviejo M and Bohorquez LH (2020). Molecular bases of drug resistance in hepatocellular carcinoma. *Cancers*, **12**(6): 1663.

Nakamura Y, Hirooka M, Hiraoka A, Koizumi Y, Yano R, Morita M, Okazaki Y, Imai Y, Ohama H, Hirooka K and Watanabe T (2023). Survival improvements in advanced hepatocellular carcinoma with sequential therapy by era. *Cancers*, **15**(21): 5298.

Santoni M, Iacovelli R, Colonna V, Klinz S, Mauri G, Nuti M (2021). Antitumor effects of the multi-target tyrosine kinase inhibitor cabozantinib: A comprehensive review of the preclinical evidence. *Expert Rev. Anticancer Ther.*, **21**(9): 1029-54.

Schwartz G, Darling JO and Mindo M and Damicis L (2020). Management of adverse events associated with cabozantinib treatment in patients with advanced hepatocellular carcinoma. *Target Oncol.*, **15**(4): 549-65.

Shang R, Song X, Wang P, Zhou Y, Lu X, Wang J, Xu M, Chen X, Utpatel K, Che L and Liang B (2021). Cabozantinib-based combination therapy for the treatment of hepatocellular carcinoma. *Gut.*, **70**(9): 1746-57.

Smith EA, Belote RL, Cruz NM, Moustafa TE, Becker CA, Jiang A, Alizada S, Prokofyeva A, Chan TY, Seasor TA and Balatico M (2024). Receptor tyrosine kinase inhibition leads to regression of acral melanoma by targeting the tumor microenvironment. *J. Exp. Clin. Cancer Res.*, **43**(1): 317.

Suzuki H, Iwamoto H, Tanaka T, Sakaue T, Imamura Y, Masuda A, Nakamura T, Koga H, Hoshida Y and

Kawaguchi T (2024). Fibroblast growth factor inhibition by molecular-targeted agents mitigates immunosuppressive tissue microenvironment in hepatocellular carcinoma. *Hepatol. Int.*, **18**(2): 610-22.

Tao S, Liang S, Zeng T and Yin D (2023). Epigenetic modification-related mechanisms of hepatocellular carcinoma resistance to immune checkpoint inhibition. *Front. Immunol.*, **13**: 1043667.

Tovoli F, Pallotta DP, Sansone V, Iavarone M, De Giorgio M, Ielasi L, Di Costanzo GG, Giuffrida P, Sacco R, Pressiani T and Di Donato MF (2023). Outcomes of sorafenib for recurrent hepatocellular carcinoma after liver transplantation in the era of combined and sequential treatments. *Transplantation*, **107**(1): 156-61.

Wang Q, Bin C, Xue Q, Gao Q, Huang A, Wang K and Tang N (2021). GSTZ1 sensitizes hepatocellular carcinoma cells to sorafenib-induced ferroptosis via inhibition of NRF2/GPX4 axis. *Cell Death Dis.*, **12**(5): 426.

Wang Y, Wu Y, Zhang H, Wang J, Song A, Qiu H, Yuan X, Xiong H and Zou Y (2024a). Exploring combination therapy centered on targeted immunotherapy for advanced hepatocellular carcinoma: A beacon of hope. *Oncol. Transl. Med.*, **10**(6): 292-9.

Wang Z, Wang Y, Gao P and Ding J (2023). Immune checkpoint inhibitor resistance in hepatocellular carcinoma. *Cancer Lett.*, **555**: 216038.

Wang Z, Jiang L, Lv X, Yin H, Wang Z, Li W and Liu Y (2024b). Higher risk of hepatotoxicity associated with cabozantinib in cancer patients. *Crit. Rev. Oncol. Hematol.*, **196**: 104298.

Xie Q, Zhang P, Wang Y, Mei W and Zeng C (2022). Overcoming resistance to immune checkpoint inhibitors in hepatocellular carcinoma: Challenges and opportunities. *Front. Oncol.*, **12**: 958720.

Zhang C, Xu T, Ji K, Cao S, Ai J, Pan J, Cao Y, Yang Y, Jing L and Sun JH (2024). Development and experimental validation of a machine learning-based disulfidptosis-related ferroptosis score for hepatocellular carcinoma. *Apoptosis*, **29**(1): 103-20.