BERLIN 2025 ESMO congress

2215O

HRS-4642 combined with gemcitabine and nab-paclitaxel in KRAS-G12D mutant advanced pancreatic cancer: A phase Ib/II study

L. Wang[1], K. Jiang[2], W. Li[3], S. Ni[4], H. Zong[5], J. Du[6], Y. He[7], Z. Liu[8], Q. Kong[9], Y. Zhang[10], J. Cui[1], X. Li[11], H. Han[11]

[1] Department of Oncology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, [2] Pancreas Center, Jiangsu Province Hospital, Nanjing, China, [3] Cancer Center, The First Hospital of Jilin University, Changchun, China, [4] Phase I Clinical Research Center, Shandong First Medical University Affiliated Tumor Hospital, Jinan, China, [5] Medical Oncology, First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, [6] Department of Oncology, Affiliated Drum Tower Hospital, Nanjing University, Nanjing, China, [7] Internal Medicine of Digestive Tract Tumors, Anhui Provincial Cancer Hospital, Hefei, China, [8] Hepatobiliary Surgery, Chifeng City Hospital, Chifeng, China, [9] Medical Oncology, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China, [10] Gastroenterology Ward 2, Harbin Medical University Cancer Hospital, Harbin, China[11] Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Background

Combination of gemcitabine and nab-paclitaxel (GA) remains first-line treatment for pancreatic ductal adenocarcinoma (PDAC). *KRAS*-G12D inhibitors, by blocking MEK/ERK phosphorylation, may further improve GA's efficacy in *KRAS*-G12D mutant PDAC. We conducted a phase 1b/2 study to assess HRS-4642, a novel *KRAS*-G12D inhibitor, combined with GA in patients (pts) with advanced *KRAS*-G12D mutant PDAC.

Methods

Eligible pts with advanced *KRAS*-G12D mutant PDAC received HRS-4642 (500 mg on day 1 and 1200 mg on day 8, intravenous infusion [IV] Q3W) in combination with GA (gemcitabine 1000 mg/m^2 on day 1 and day 8, IV Q3W; nab-paclitaxel 125 mg/m^2 on day 1 and day 8, IV Q3W).

Results

As of Apr 10, 2025, a total of 31 pts were enrolled, including 1 previously treated pt and 30 treatment-naïve pts. With a median follow-up of 4.4 months, 26 (83.9%) pts remained on treatment. The previously treated pt achieved stable disease for over 7 months following the study treatment and continued to receive the treatment at the data cutoff. For the treatment-naïve pts, the confirmed objective response rate was 60.0% (95% CI 40.6%-77.3%) (Table). Among the 18 responders, objective responses were still ongoing in 17 pts, and the median duration of response was immature. Three progression events (10.0%) occurred among the 30 treatment-naïve pts, with progression-free survival data remaining immature at the data cutoff. Grade ≥ 3 treatment-related adverse events (TRAEs) occurred in 77.4% (24/31) of pts. The most common grade ≥ 3 TRAEs (incidence ≥ 10%) were decreased neutrophil count (61.3%), decreased white blood cell count (45.2%) and anemia (12.9%). There were no TRAEs leading to treatment discontinuation and no treatment-related deaths.Table: 2215O

Efficacy outcomes

	HRS-4642 + GA Previously untreated pts (n = 30)
ORR, % (95% CI)	60.0 (40.6, 77.3)
DCR, % (95% CI)	93.3 (77.9, 99.2)
BOR, n (%)	
PR	18 (60.0)
SD	10 (33.3)
PD	1 (3.3)
No post-baseline assessment	1 (3.3)

ORR, objective response rate; DCR, disease control rate; BOR, best overall response; PR, partial response; SD, stable disease; PD, progressive disease.

Conclusions

HRS-4642 combined with GA showed encouraging antitumor activity and manageable safety profile in advanced *KRAS*-G12D mutant PDAC. Follow-up is ongoing for long-term efficacy and safety data.

Clinical trial identification

NCT06520488, 2024-07-25.

Legal entity responsible for the study

Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Funding

Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Disclosure

X. Li, H. Han: Financial Interests, Personal, Full or part-time Employment: Jiangsu Hengrui Pharmaceuticals Co., Ltd. All other authors have declared no conflicts of interest.