A phase 1/1b study of the theranostic pair RYZ811 (diagnostic) and RYZ801 (therapeutic) in patients with glypican-3-positive (GPC3+) previously treated, unresectable hepatocellular carcinoma

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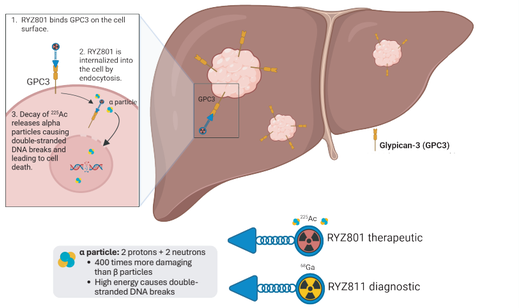
BACKGROUND

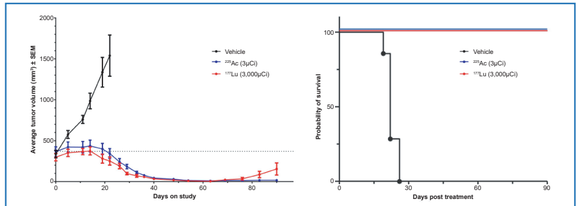
- GPC3 is an oncofetal protein that is selectively expressed in up to 75% of hepatocellular carcinomas (HCCs) and is associated with poor prognosis.[1–3]
- HCC, a radiosensitive cancer, presents both diagnostic and therapeutic unmet needs. Although immunotherapy has changed the therapeutic landscape for patients with HCC, 5-year overall survival is less than 25%.[4] Diagnostically, monitoring treatment response, surveillance, and identification of residual or recurrent disease is challenging with conventional imaging, especially following locoregional therapies.
- The theranostic pair RYZ811/RYZ801 consists of the GPC3 binder RAYZ-8009 radiolabeled with the diagnostic radioisotope ^{68}Ga (RYZ811) or the therapeutic α-emitting radioisotope ^{225}Ac (RYZ801) as shown in Figure 1.

FIGURE 1. RYZ801 and RYZ811: a theranostic pair



- In GPC3-positive (GPC3+) HCC mouse models, single-dose RAYZ-8009 labeled with either ^{177}Lu or ^{225}Ac (RYZ801) significantly inhibited tumor growth, with RYZ801 achieving superior efficacy at 1000-fold lower doses (Figure 2).[5,6]
- Significant tumor growth inhibition and survival benefits were achieved with RYZ801 in GPC3+ HCC xenografts at 37 kBq, 1000- to 3000-fold lower than the required effective dose for ^{177}Lu-RAYZ-8009.[5,6]
- In a study conducted in 24 patients with known or suspected HCC, RYZ811 was used for disease detection and diagnosis in conjunction with high-contrast PET/CT scanning.[7] RYZ811 had a rapid and favorable biodistribution, with high tumor accumulation in HCC and little accumulation in normal and cirrhotic liver, as well as most normal organs.

FIGURE 2. Antitumor activity and survival in GPC3+ HCC xenografts



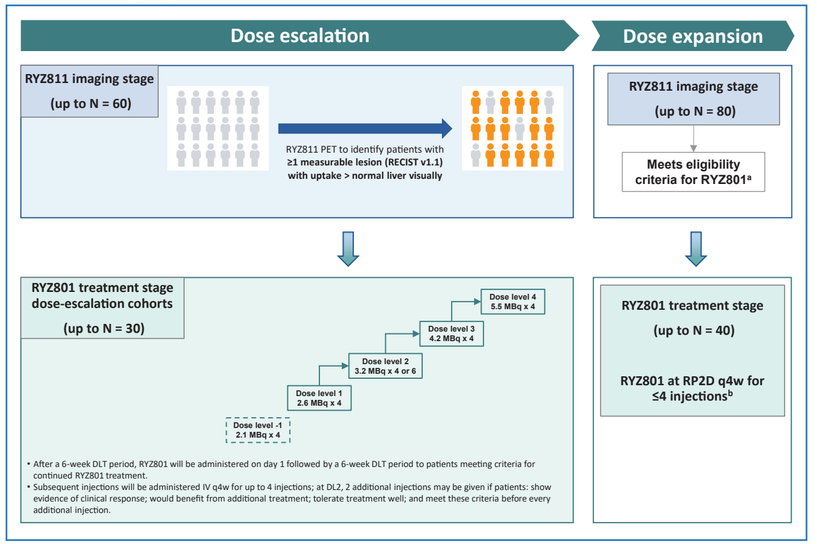
- Here we describe the design of RYZ801-101, a phase 1/1b study of RYZ811 and RYZ801 in previously treated patients with GPC3+ unresectable HCC (NCT06726161).

METHODS

STUDY DESIGN

- RYZ801-101 consists of two parts (Figure 3): dose escalation (part 1) and dose expansion (part 2). Each part has two stages:
  - **Imaging (RYZ811):** Aims to determine if RYZ811 safely and adequately identifies patients with GPC3+ HCC. RYZ811 dosimetry substudy will be conducted to estimate the absorbed dose (AD) of RYZ811 in organs and tissues, as well as the effective dose in ≥10 evaluable patients.
  - **Treatment (RYZ801):** Aims to determine the safety, pharmacokinetics (PK), recommended phase 2 dose (RP2D; part 1), and preliminary antitumor activity of RYZ801 (part 2). RYZ801 dosimetry substudy will be conducted within the treatment stage to determine the RYZ801 ADs to critical organs and tumors in ≥10 evaluable patients.

FIGURE 3. Study design



[a]All lesions >1 cm must be GPC3+ (uptake > normal liver) on RYZ811 PET imaging; [b]≤6 injections if the RP2D includes additional injections.
Abbreviations: DL, dose level; DLT, dose-limiting toxicity; GPC3+, glypican-3-positive; IV, intravenously; PET, positron emission tomography; q4w, every 4 weeks; RECIST 1.1, Response Evaluation Criteria for Solid Tumours, version 1.1; RP2D, recommended phase 2 dose.

KEY ELIGIBILITY CRITERIA

Key inclusion criteria

- Aged ≥18 years
- Histologically/cytologically/radiographically confirmed diagnosis of HCC
- BCLC stage C (or BCLC stage B not amenable/refractory to locoregional therapy)
- Child-Pugh A
- ECOG performance status 0 or 1
- Measurable disease per RECIST v1.1
- Adequate organ function
- Dose escalation: disease progression after ≥1 prior systemic therapy for unresectable HCC OR patient considered not suitable for other available systemic therapies
- Dose expansion: disease progression after 1 prior systemic therapy

Key exclusion criteria

- Fibrolamellar carcinoma, sarcomatoid HCC, or combined hepatocellular cholangiocarcinoma
- Prior liver transplantation or candidate for liver transplant
- Known hypersensitivity to ^{68}Ga, ^{225}Ac, or excipients of RYZ801 or RYZ811
- Portal vein thrombosis (Vp4)
- Hepatic encephalopathy within 6 months before enrollment
- Prior liver radioembolization

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; EBRT, external beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

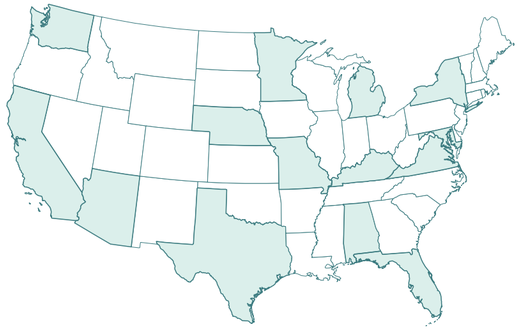
PRIMARY STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Imaging stage – RYZ811	
• Assess safety and tolerability of RYZ811	• Incidence and severity of AEs (NCI-CTCAE v5)
• Evaluate biodistribution of RYZ811	• SUV_{mean}, SUV_{max}, SUV_{peak} of organs and tumors; volume of RYZ811 avid uptake in tumor lesions; tumor-to-normal tracer uptake ratios
Treatment stage – RYZ801	
• Determine RP2D of RYZ801 (dose escalation only)	• Rate of DLTs during first 42 days
• Assess safety and tolerability of RYZ801	• Incidence and severity of AEs (NCI-CTCAE v5)

Abbreviations: AE, adverse event; DLT, dose-limiting toxicity; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RP2D, recommended phase 2 dose; SUV_{max}, maximum standard uptake value; SUV_{mean}, mean standard uptake value; SUV_{peak}, peak standard uptake value.

CURRENT STATUS

- Enrollment for part 1 is ongoing in the USA.



ACKNOWLEDGMENTS

The RYZ801-101 study is sponsored by RayzeBio Inc., San Diego, CA, USA. The study sponsor also funded medical writing and layout support for this poster, which was provided by Miller Medical Communications Ltd.

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DISCLOSURES

Dr Brandon Mancini declares the following conflicts of interest:

Employment: BAMF Health; **consulting or advisory role:** RubiconMD, GoodRx; MCG Health; Lantheus Medical Imaging; **speakers' bureau:** GE Healthcare; **travel, accommodations, expenses:** BAMF Health; **stock and other ownership interests:** BAMF Health.

For information about this clinical trial please scan the QR code

Presented at the ASCO Gastrointestinal Cancers Symposium, January 8–10, 2026, San Francisco, CA, USA

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